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(54) **COMPOUNDS AND USES THEREOF**

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(57) **ABSTRACT**

The present invention relates to compositions and methods for the treatment of BAF-related disorders, such as cancers and viral infections.

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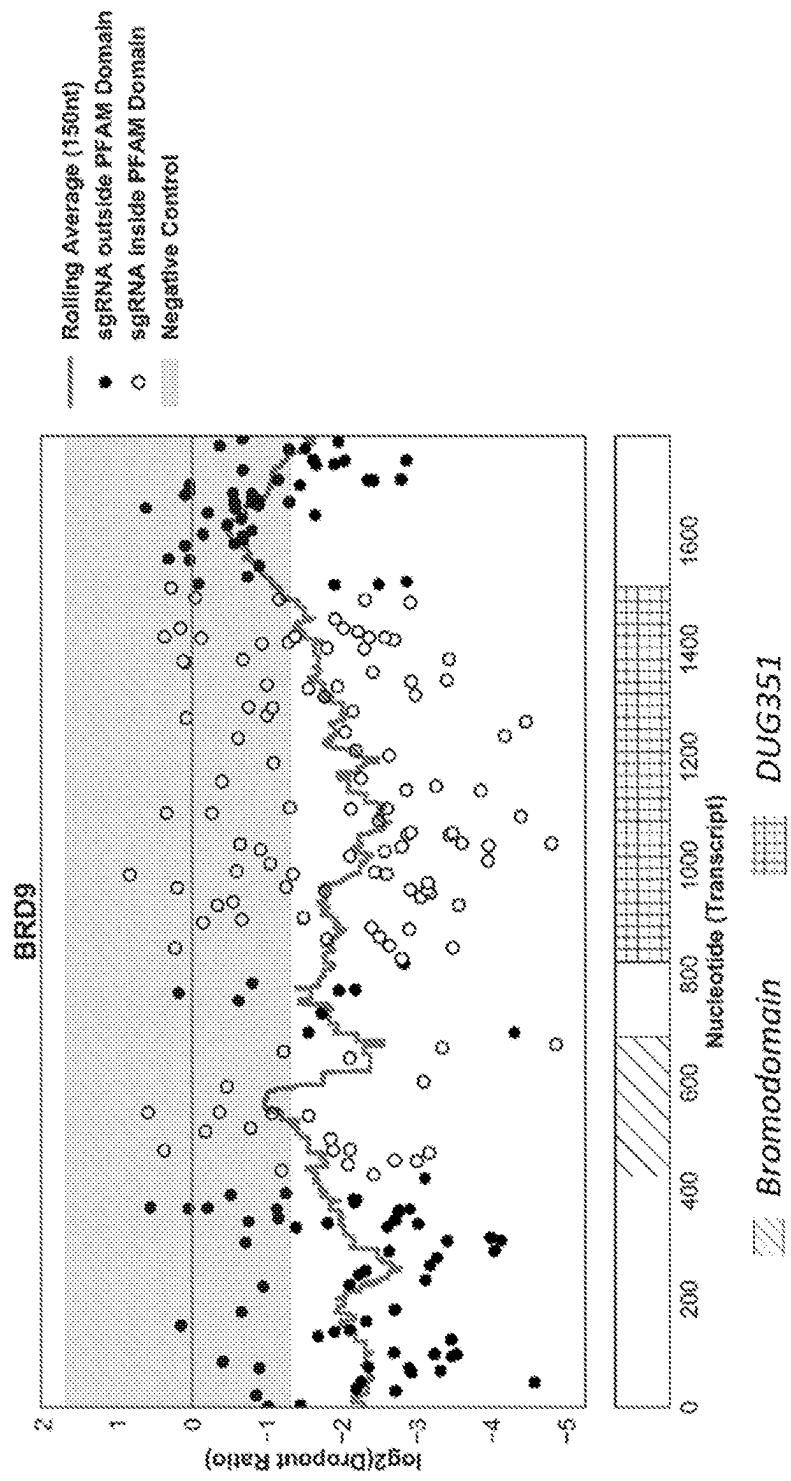
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FIG. 1

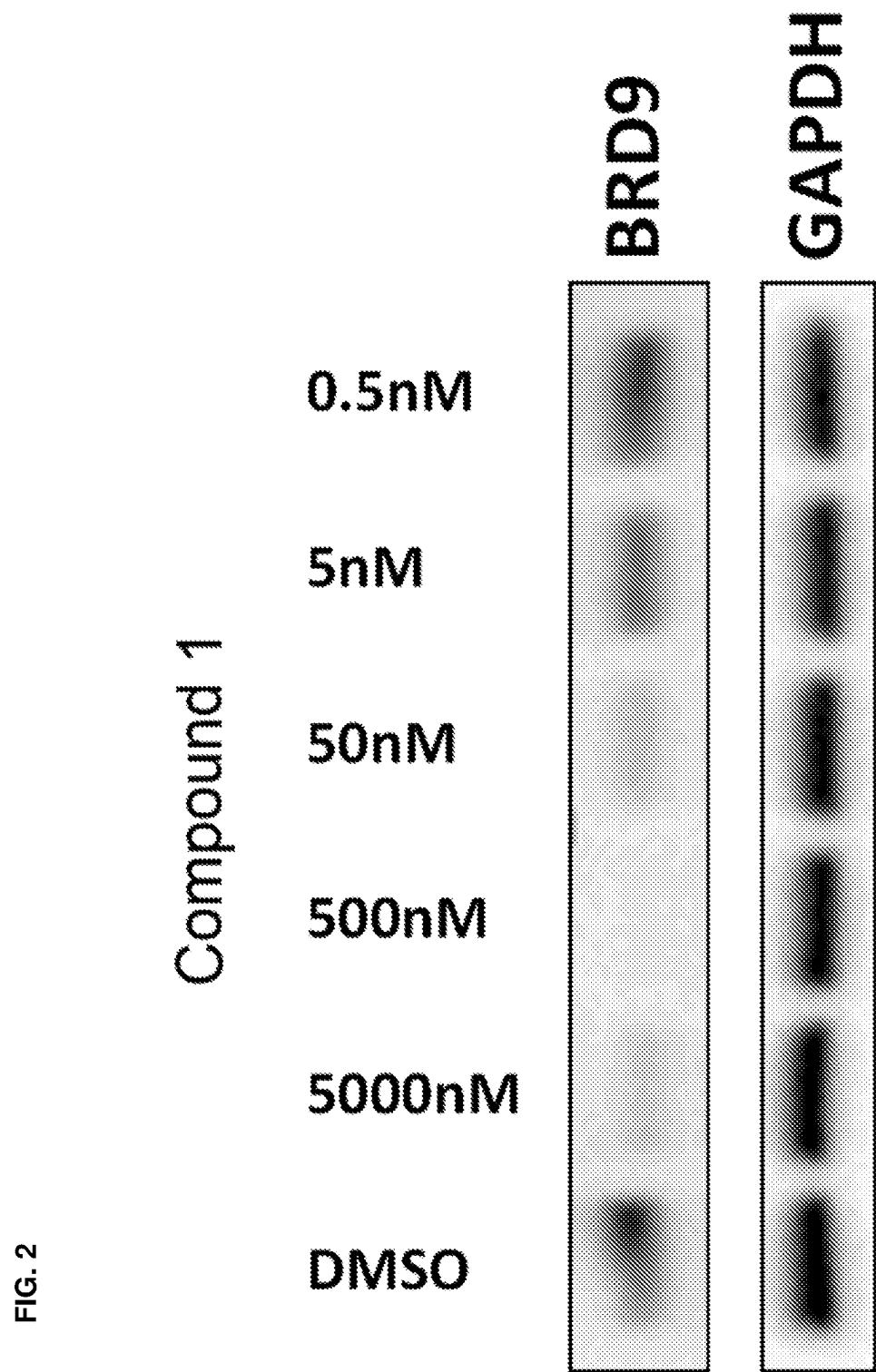
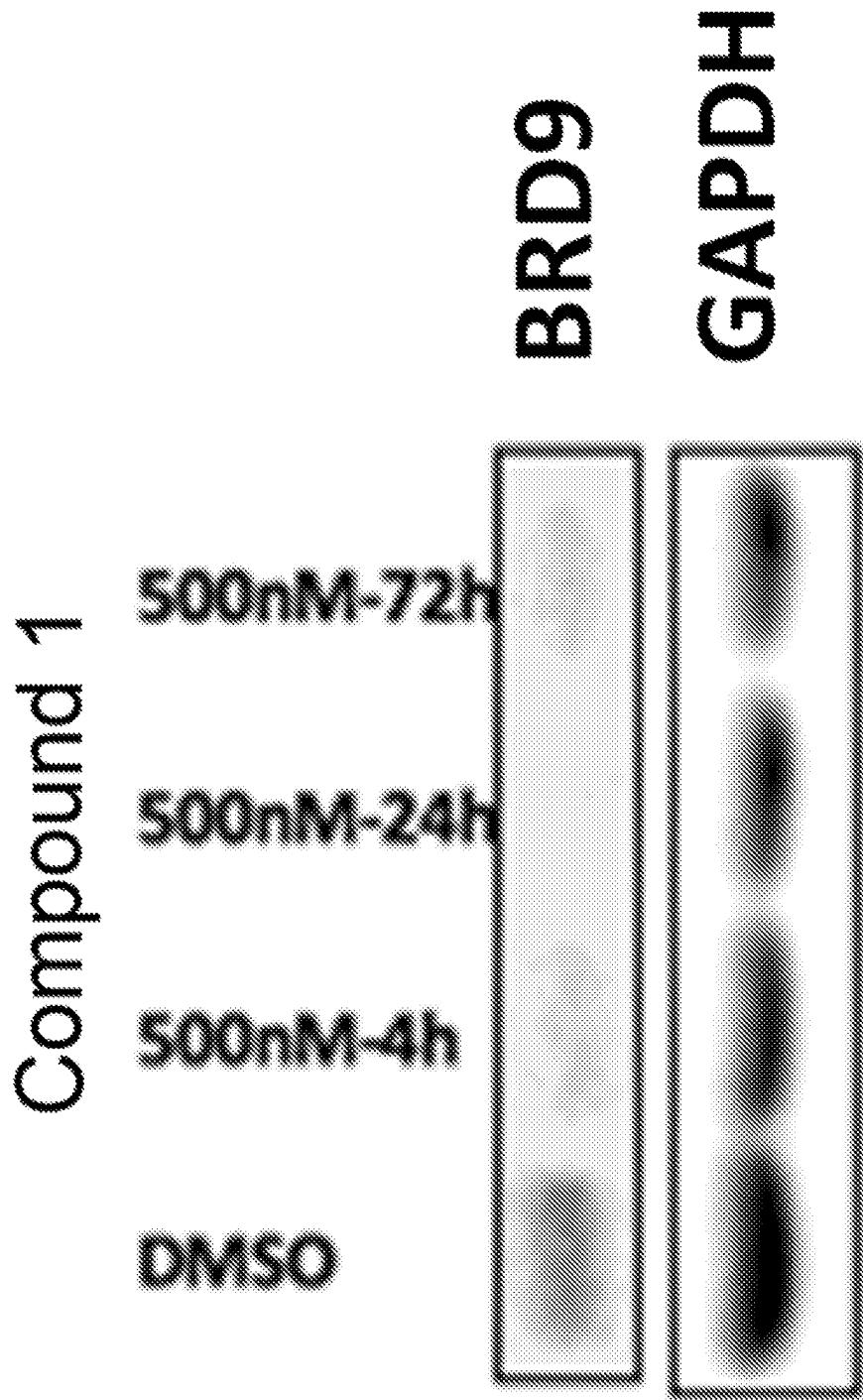


FIG. 3



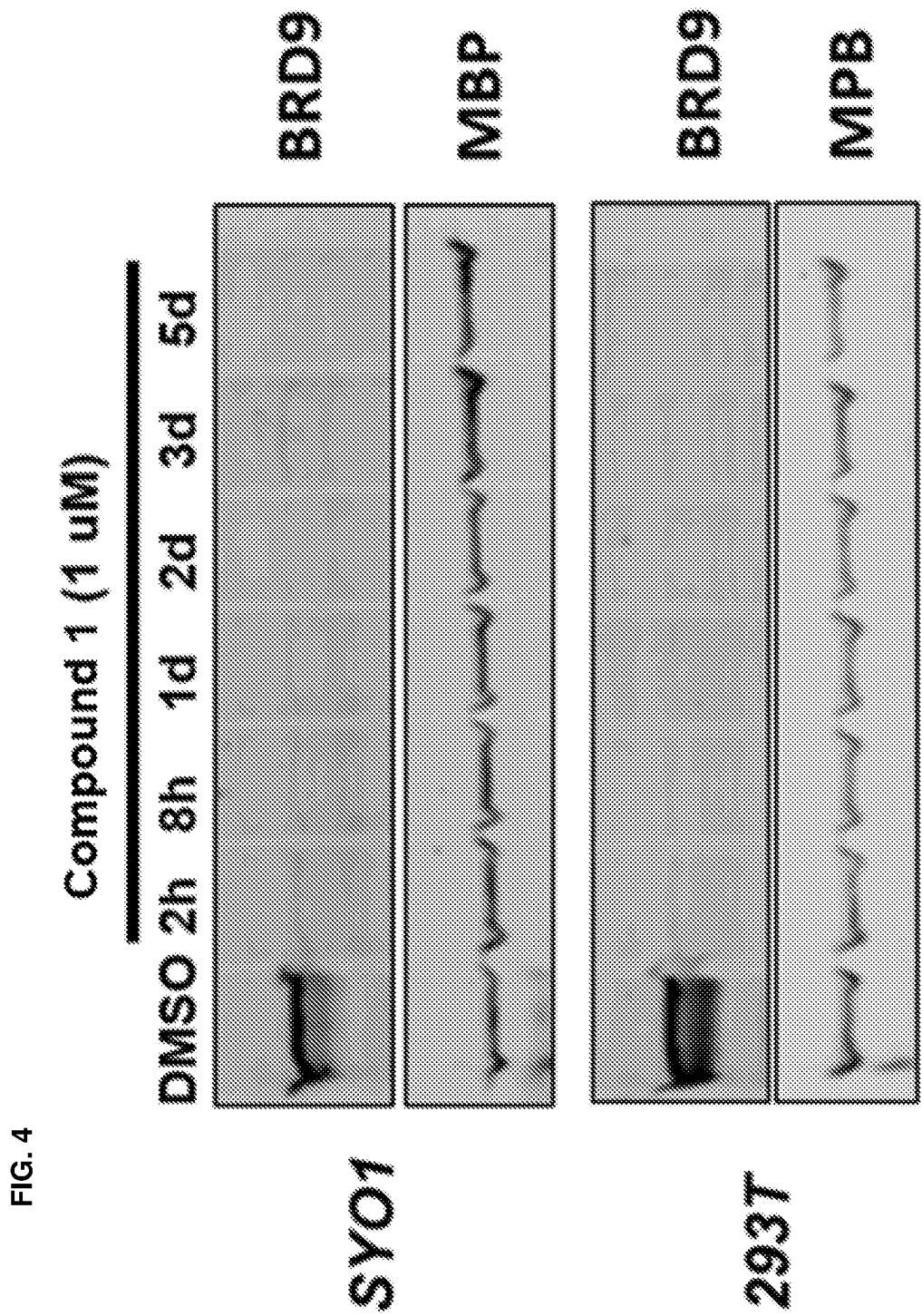
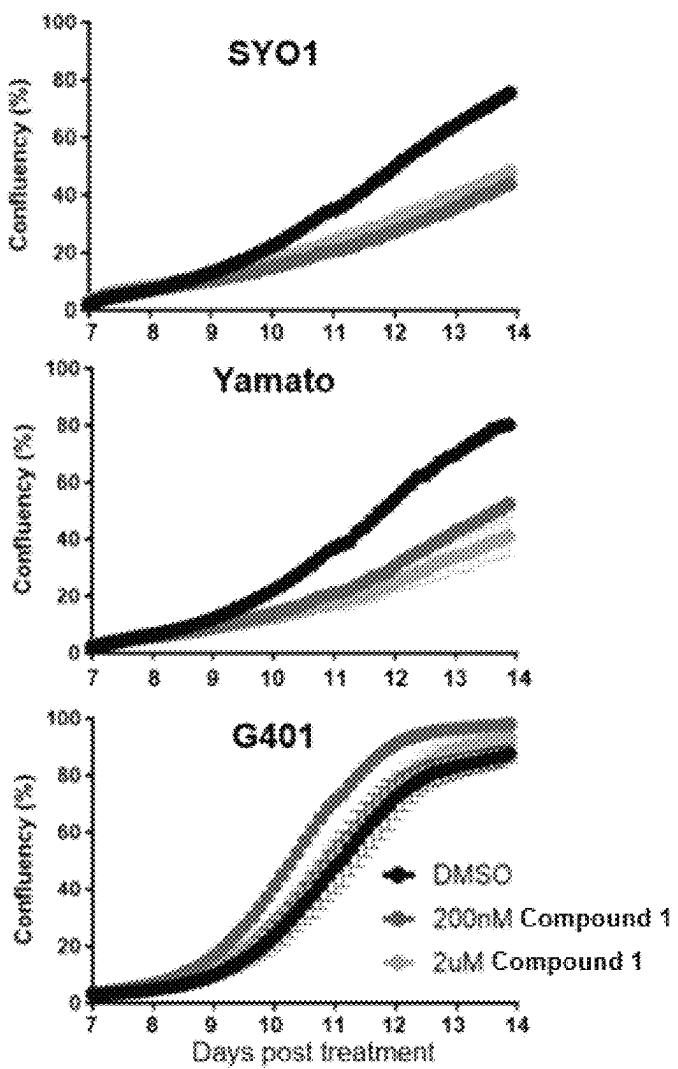


FIG. 5



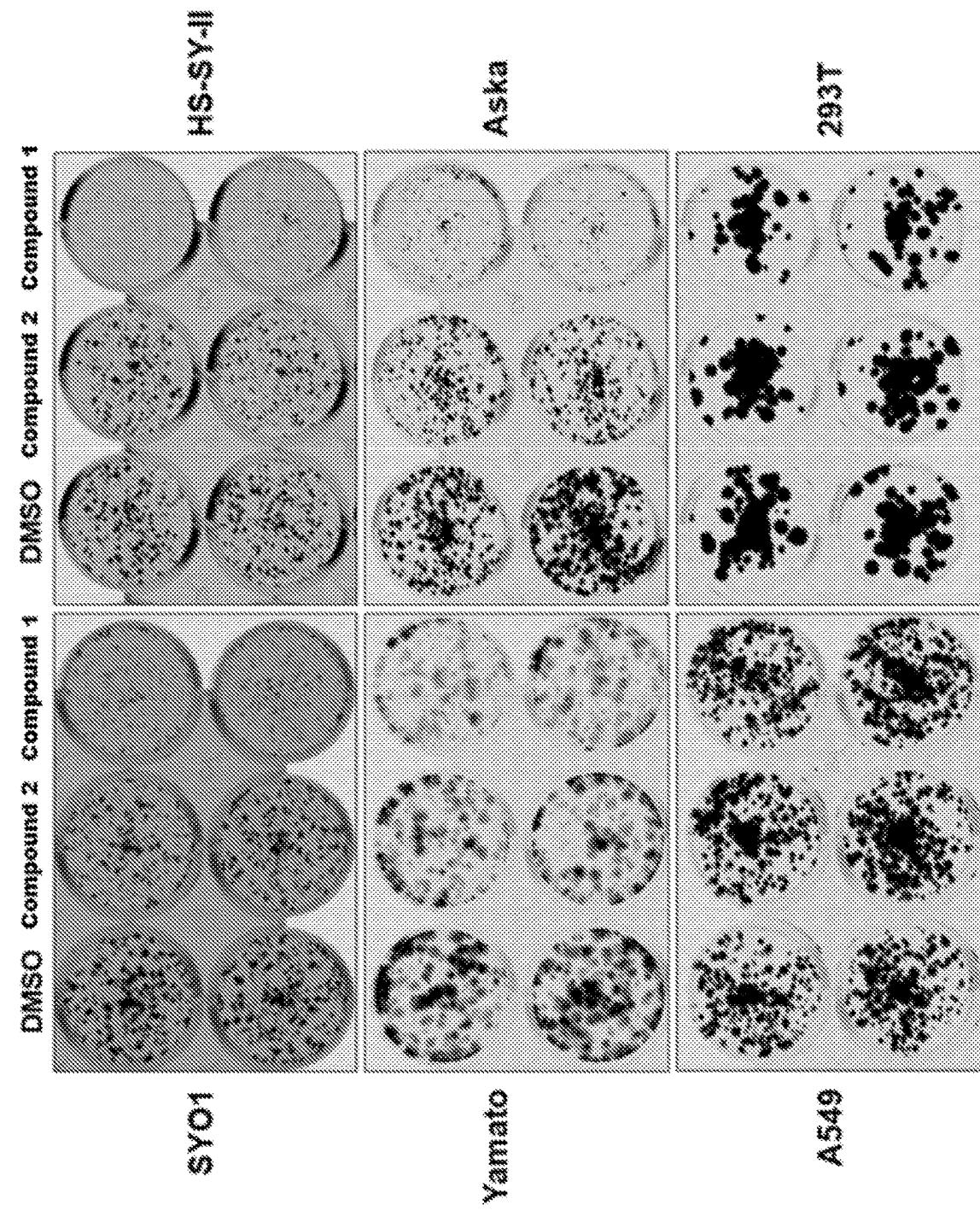


FIG. 6

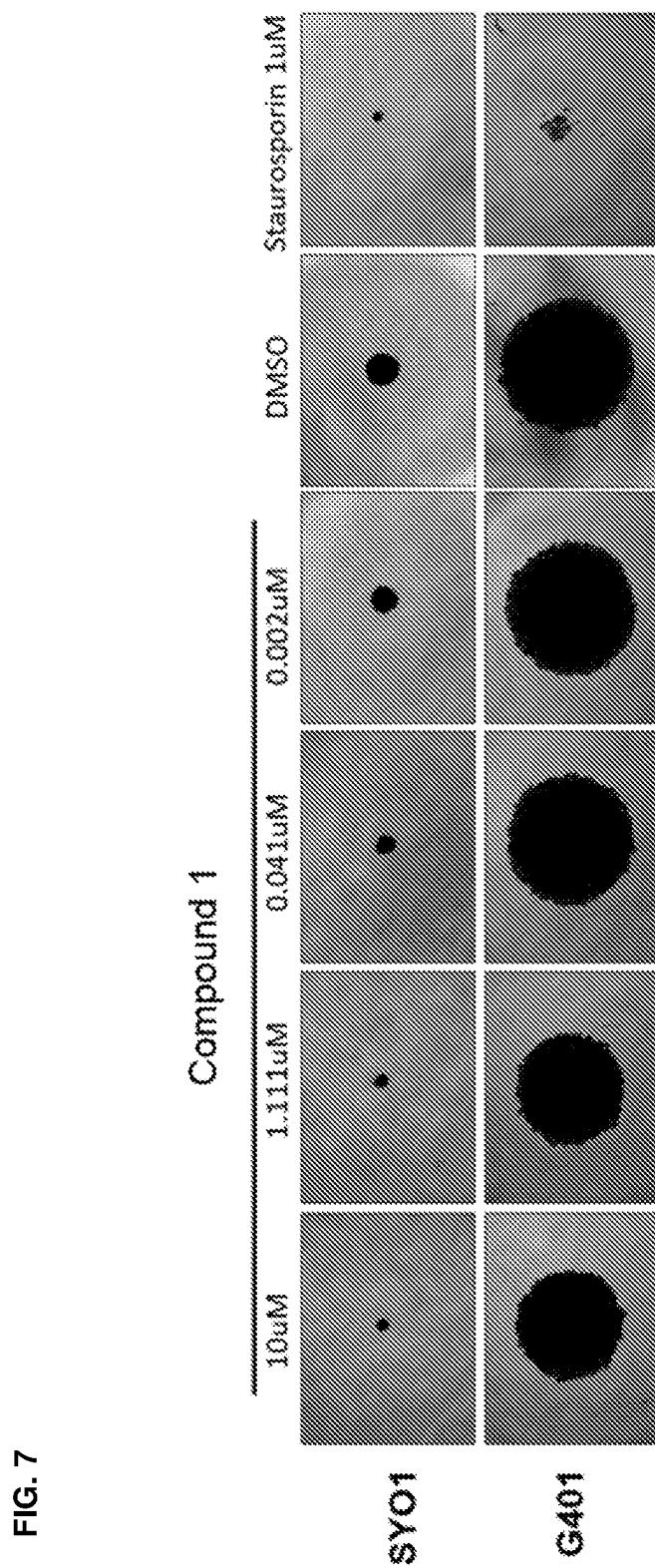
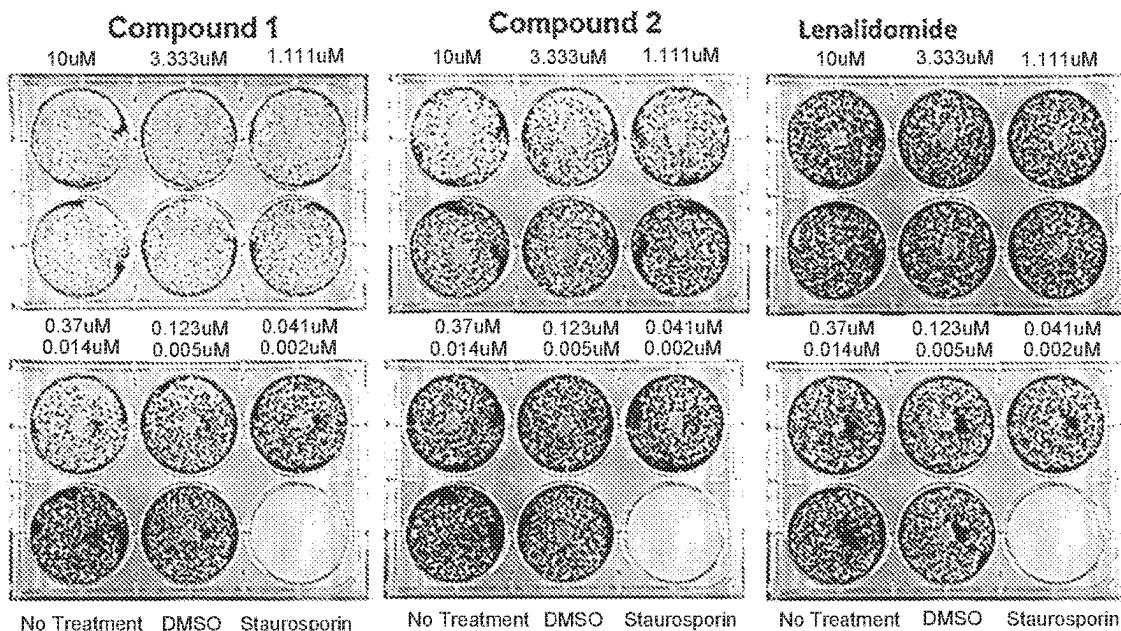
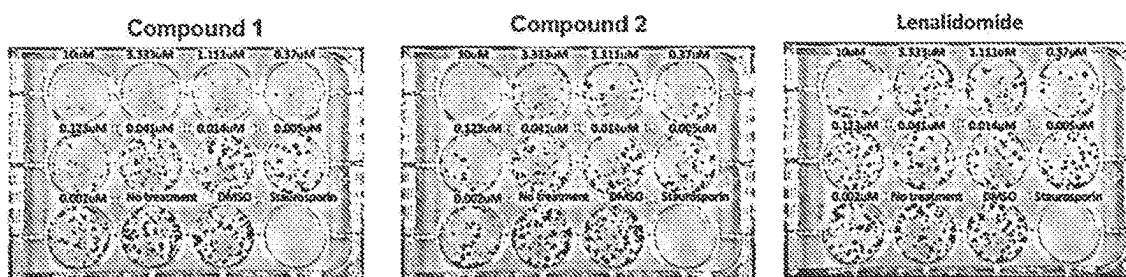


FIG. 8

SYO1



HS-SY-II



ASKA

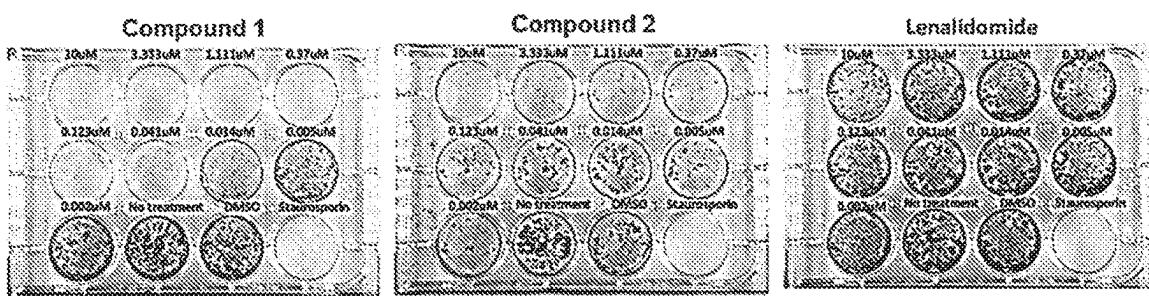
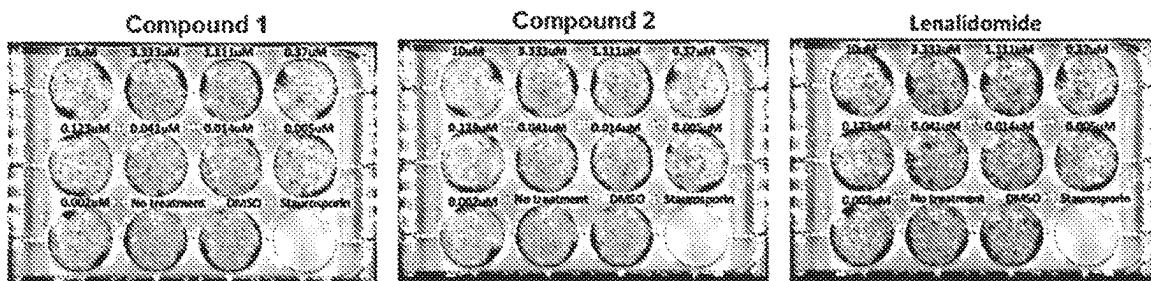
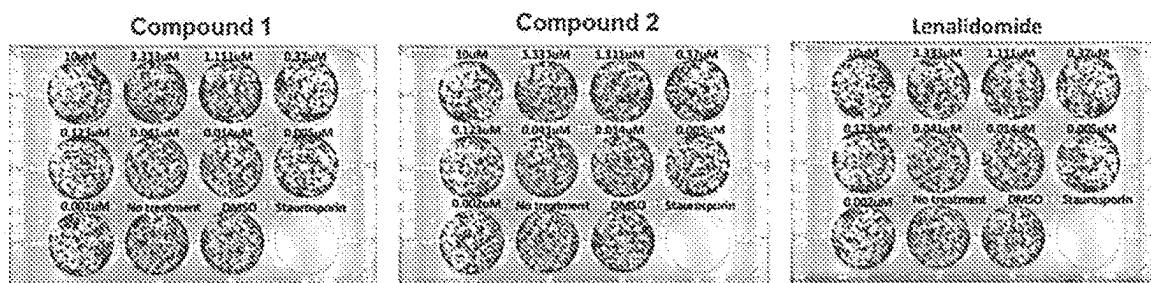


FIG. 9

RD



HCT116



Calu6

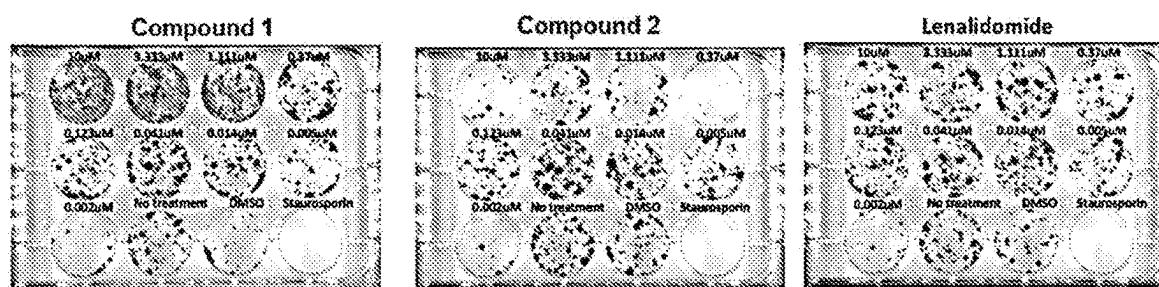


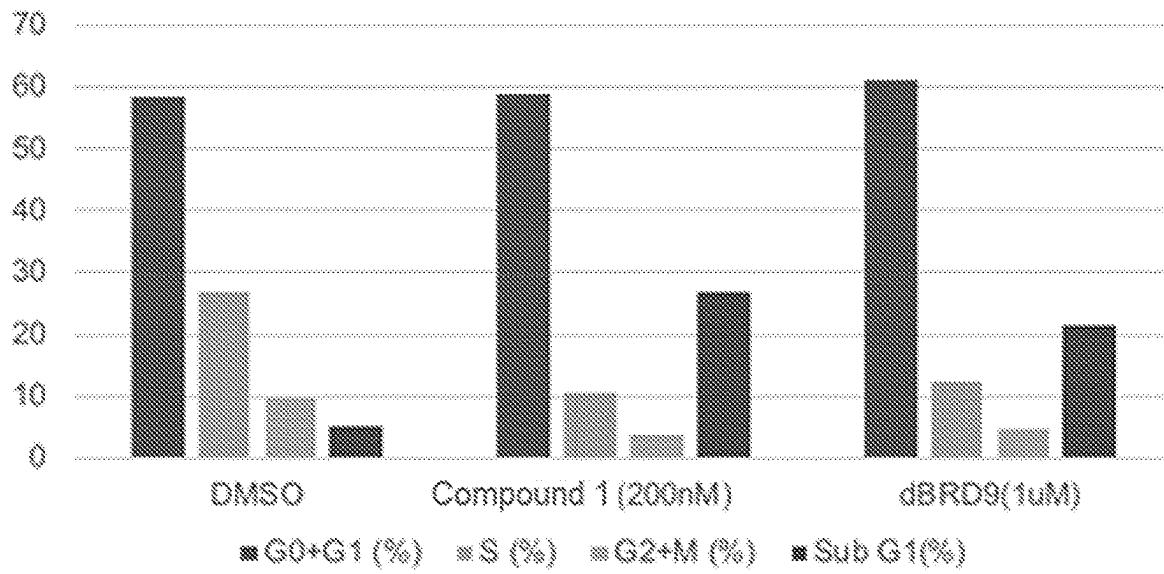
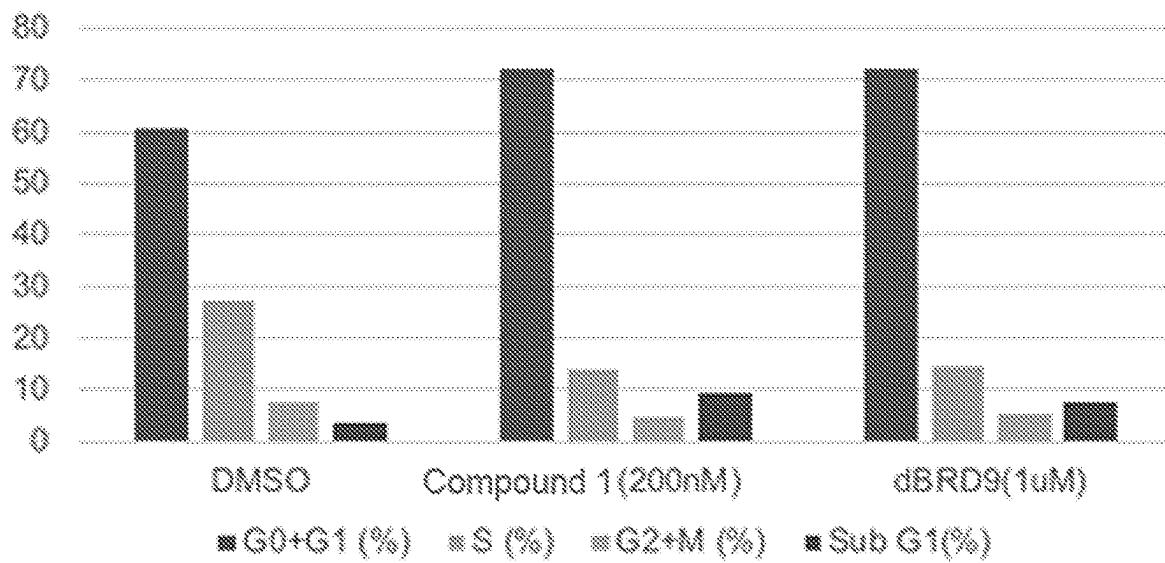
FIG. 10**Cell Cycle Analysis (day 8)****Cell Cycle Analysis (day 13)**

FIG. 11

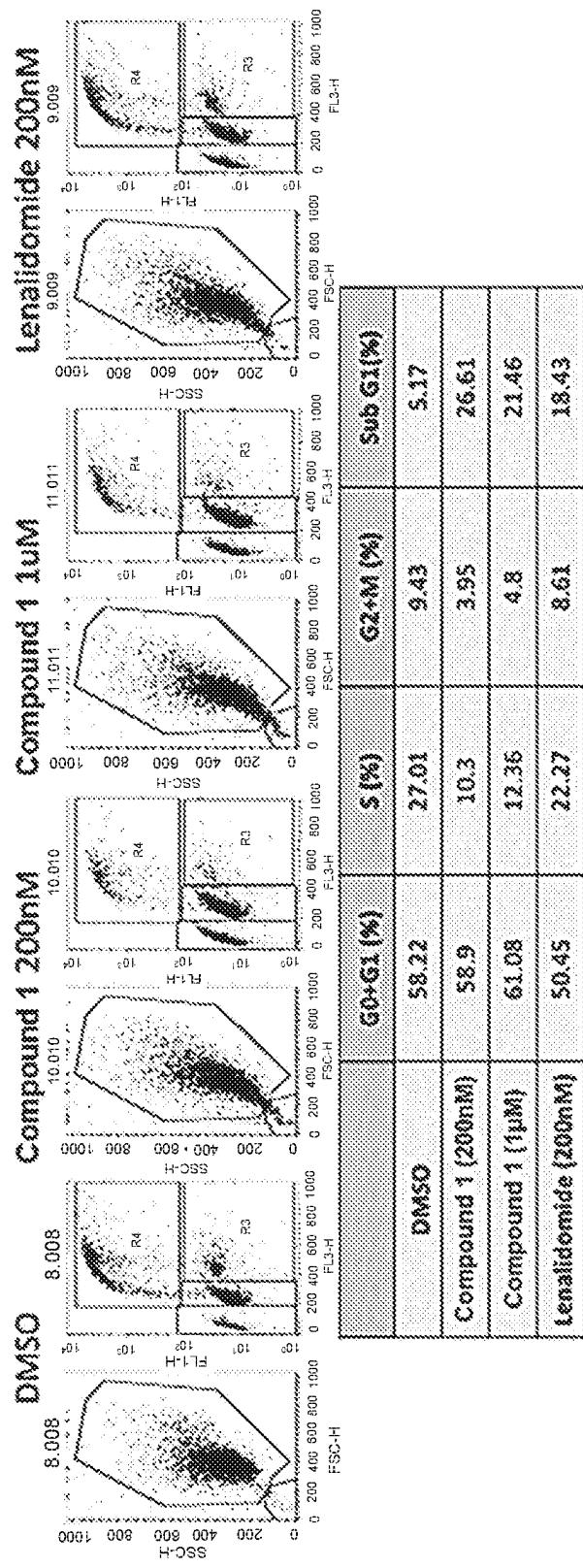


FIG. 12

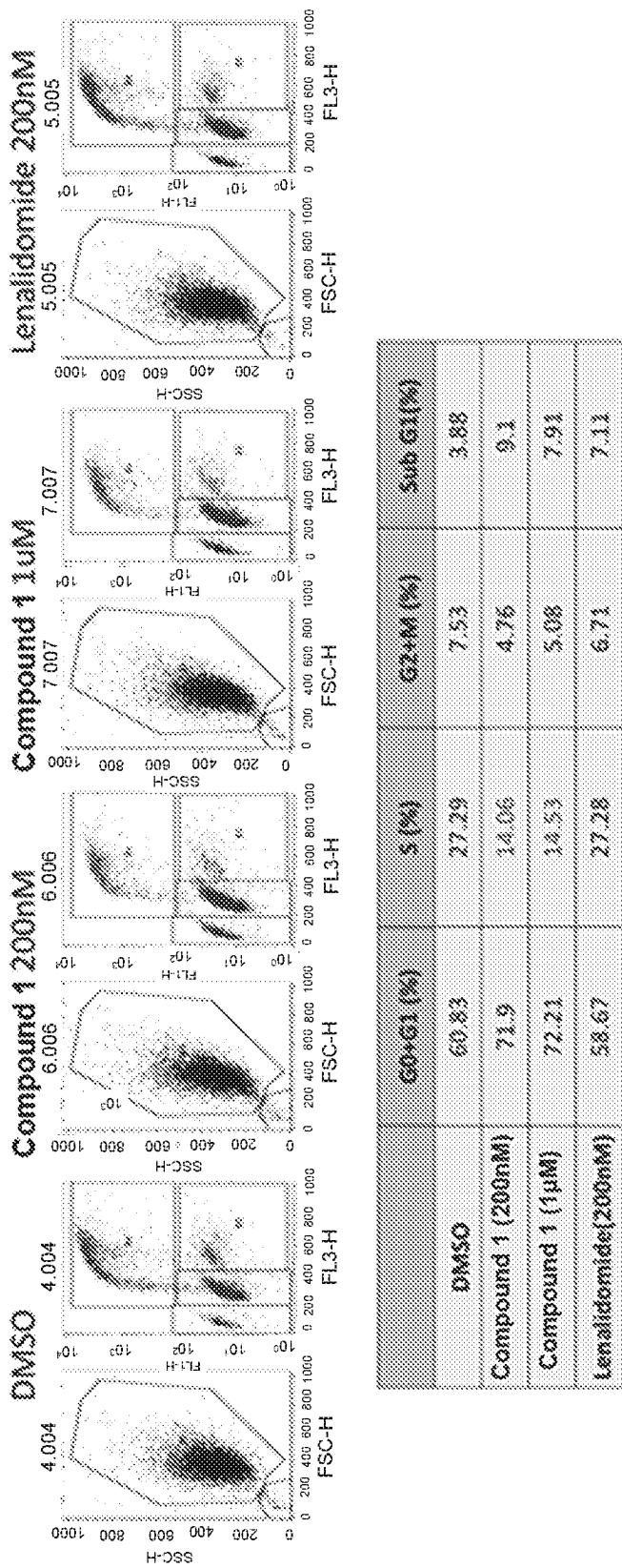
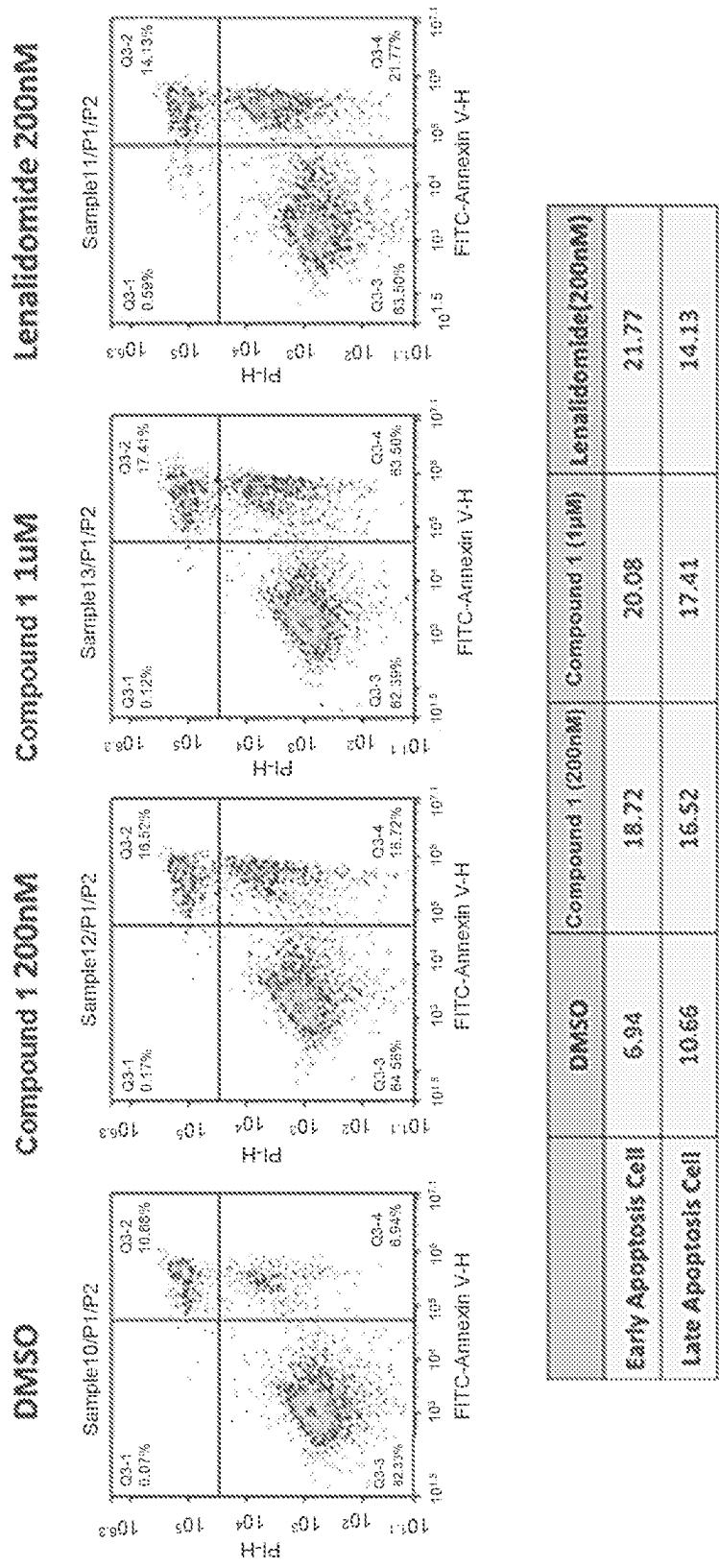
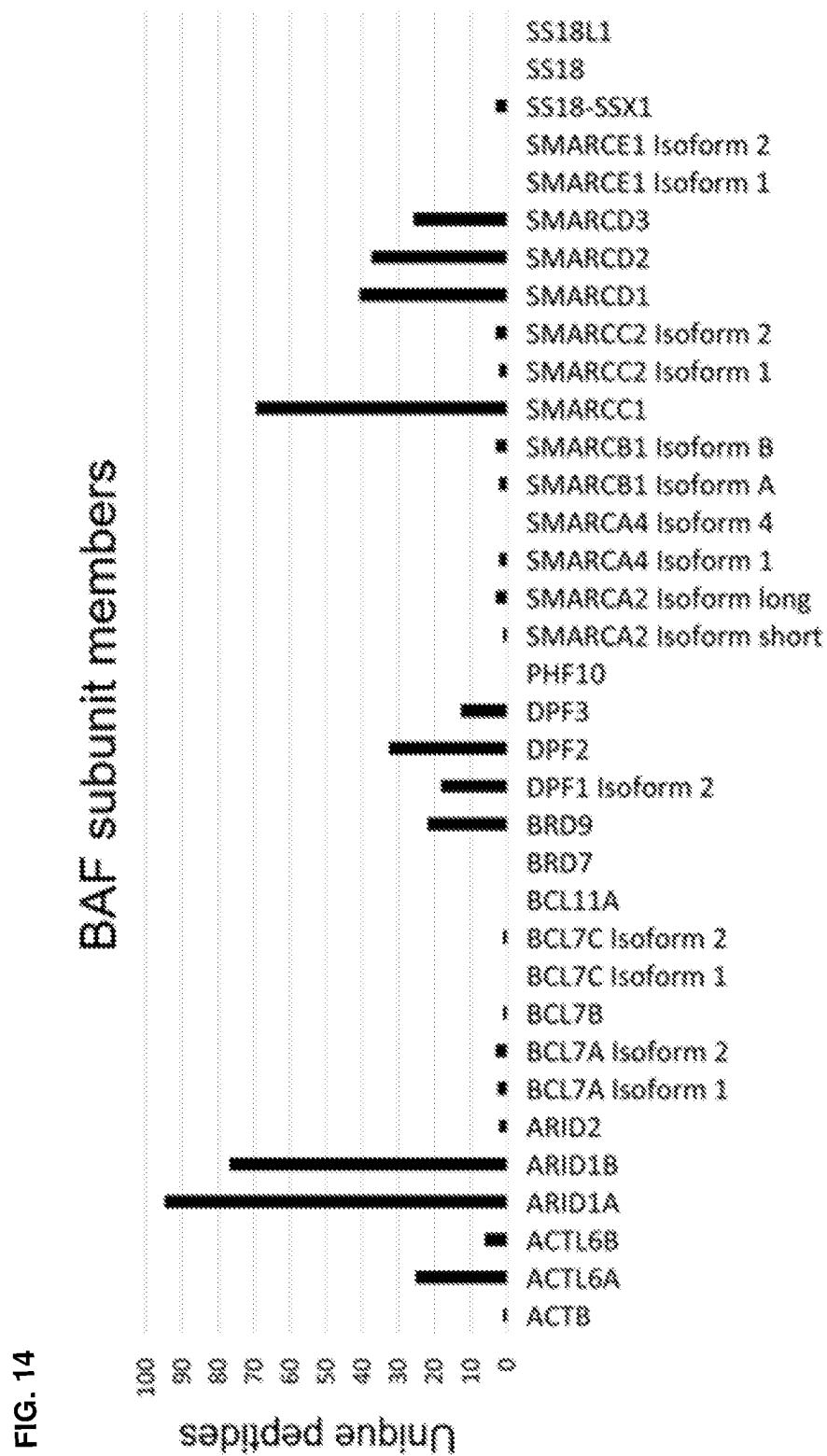


FIG. 13





1
COMPOUNDS AND USES THEREOF

BACKGROUND

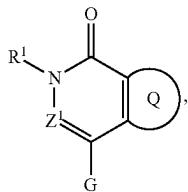
Disorders can be affected by the BAF complex. BRD9 is a component of the BAF complex. The present invention relates to useful compositions and methods for the treatment of BAF complex-related disorders, such as cancer and infection.

SUMMARY

Bromodomain-containing protein 9 (BRD9) is a protein encoded by the BRD9 gene on chromosome 5. BRD9 is a component of the BAF (BRG1- or BRM-associated factors) complex, a SWI/SNF ATPase chromatin remodeling complex, and belongs to family IV of the bromodomain-containing proteins. BRD9 is present in several SWI/SNF ATPase chromatin remodeling complexes and is upregulated in multiple cancer cell lines. Accordingly, agents that reduce the levels and/or activity of BRD9 may provide new methods for the treatment of disease and disorders, such as cancer and infection. The inventors have found that depleting BRD9 in cells results in the depletion of the SS18-SSX fusion protein in those cells. The SS18-SSX fusion protein has been detected in more than 95% of synovial sarcoma tumors and is often the only cytogenetic abnormality in synovial sarcoma. Additionally, evidence suggests that the BAF complex is involved in cellular antiviral activities. Thus, agents that degrade BRD9 (e.g., compounds) are useful in the treatment of disorders (e.g., cancers or infections) related to BAF, BRD9, and/or SS18-SSX.

The present disclosure features compounds and methods useful for treating BAF-related disorders (e.g., cancer or infection).

In an aspect, the disclosure features a compound having the structure of Formula I:

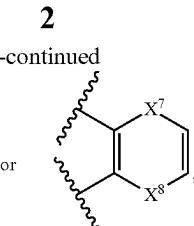
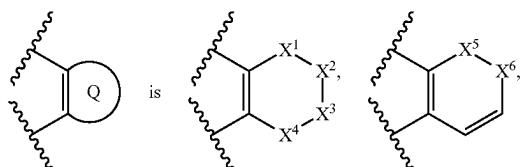


where

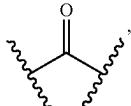
R¹ is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₁₀ carbocyclyl;

Z¹ is CR² or N;

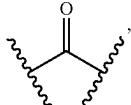
R² is H, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, or optionally substituted C₂-C₉ heteroaryl;



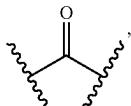
10 X¹ is a bond, O, NR^{3a},



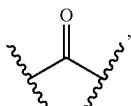
or CR^{4a}R^{5a};
X² is O, NR^{3b},



or CR^{4b}R^{5b};
X³ is O, NR^{3c},



or CR^{4c}R^{5c};
X⁴ is a bond, O, NR^{3d},



or CR^{4d}R^{5d};

X⁵ is O or NR^{3e} and X⁶ is CR^{4f}R^{5f}, or X⁵ is CR^{4e}R^{5e} and X⁶ is O or NR^{3f};

X⁷ is O, NR^{3g}, or CR^{4g}R^{5g};

X⁸ is O, NR^{3h}, or CR^{4h}R^{5h};

each of R^{3a}, R^{3b}, R^{3c}, and R^{3d} is, independently, H, halogen, hydroxyl, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, optionally substituted C₁-C₆ acyl, thiol, optionally substituted sulfone, optionally substituted sulfonamide, or optionally substituted amino, or R^{3a} and R^{4b}, R^{4a} and R^{3b}, R^{4b} and R^{4a}, R^{3b} and R^{4c}, R^{4b} and R^{4c}, R^{3c} and R^{4b}, R^{3c} and R^{4d}, R^{4c} and R^{4d}, and/or R^{3d} and R^{4c}, together with the atoms to which each is attached, combine to form optionally substituted C₂-C₉ heterocyclyl;

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each of R^{4a} , R^{4b} , R^{4c} , and R^{4d} is, independently, H, halogen, hydroxyl, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heterocyclyl, optionally substituted C_6 - C_{10} aryl, 5 optionally substituted C_2 - C_9 heteroaryl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 heteroalkenyl, optionally substituted C_1 - C_6 acyl, thiol, optionally substituted sulfone, or optionally substituted amino, or R^{3a} and R^{4b} , R^{4a} and R^{3b} , R^{4b} and R^{4a} , R^{3b} and R^{4c} , R^{4b} and R^{4c} , R^{3c} and R^{4b} , R^{3c} and R^{4d} , R^{4c} and R^{4d} , and/or R^{3d} and R^{4c} , together with the atoms to which each is attached, combine to form optionally substituted C_2 - C_9 heterocyclyl;

each of R^{5a} , R^{5b} , R^{5c} , and R^{5d} is, independently, H, halogen, hydroxyl, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heterocyclyl, optionally substituted C_6 - C_{10} aryl, 20 optionally substituted C_2 - C_9 heteroaryl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 heteroalkenyl, hydroxyl, thiol, or optionally substituted amino;

each of R^{3e} , R^{3f} , R^{3g} , and R^{3h} is, independently, H, halogen, hydroxyl, optionally substituted C_1 - C_6 alkyl, 25 optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heterocyclyl, optionally substituted C_6 - C_{10} aryl, 30 optionally substituted C_2 - C_9 heteroaryl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 heteroalkenyl, optionally substituted C_1 - C_6 acyl, thiol, optionally substituted sulfone, optionally substituted sulfonamide, or optionally substituted amino, or R^{3e} 35 and R^{4f} or R^{4e} and R^{3f} , together with the atoms to which each is attached, combine to form optionally substituted heterocyclyl;

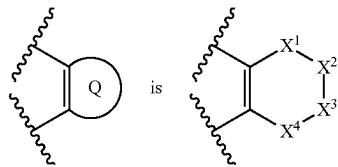
each of R^{4e} , R^{4f} , R^{4g} , and R^{4h} is, independently, H, 40 halogen, hydroxyl, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heterocyclyl, optionally substituted C_6 - C_{10} aryl, 45 optionally substituted C_2 - C_9 heteroaryl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 heteroalkenyl, optionally substituted C_1 - C_6 acyl, thiol, 50 optionally substituted sulfone, optionally substituted sulfonamide, or optionally substituted amino, or R^{3e} and R^{4f} or R^{4e} and R^{3f} , together with the atoms to which each is attached, combine to form optionally substituted heterocyclyl;

each of R^{5e} , R^{5f} , R^{5g} , and R^{5h} is, independently, H, 55 halogen, hydroxyl, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heterocyclyl, optionally substituted C_6 - C_{10} aryl, 60 optionally substituted C_2 - C_9 heteroaryl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 heteroalkenyl, hydroxyl, thiol, or optionally substituted amino; and

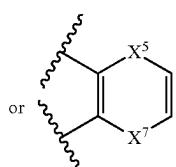
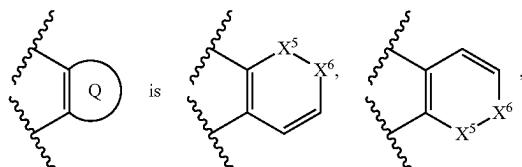
G is optionally substituted C_6 - C_{10} aryl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heteroaryl, or C_2 - C_9 heterocyclyl, or a pharmaceutically acceptable salt thereof.

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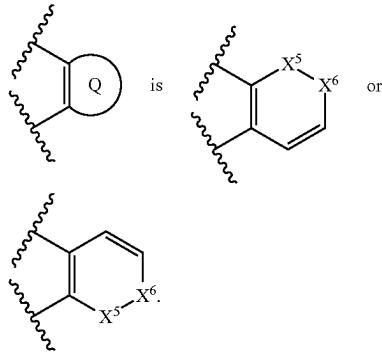
In some embodiments,



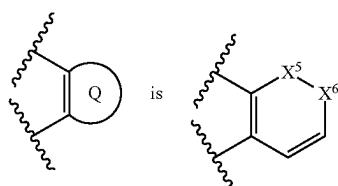
In some embodiments,



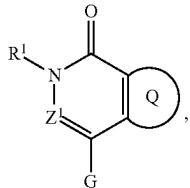
In some embodiments,



In some embodiments, is



In another aspect, the disclosure features a compound having the structure of Formula I:



Formula I 5

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where

R^1 is H, optionally substituted $C_1\text{-}C_6$ alkyl, optionally substituted $C_2\text{-}C_6$ alkenyl, optionally substituted $C_1\text{-}C_6$ heteroalkyl, or optionally substituted $C_3\text{-}C_{10}$ carbocyclyl;

Z^1 is CR^2 or N;

R^2 is H, halogen, optionally substituted $C_1\text{-}C_6$ alkyl, optionally substituted $C_1\text{-}C_6$ heteroalkyl, optionally substituted $C_3\text{-}C_{10}$ carbocyclyl, optionally substituted $C_2\text{-}C_9$ heterocyclyl, optionally substituted $C_6\text{-}C_{10}$ aryl, or optionally substituted $C_2\text{-}C_9$ heteroaryl;

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X^1 is a bond, O, NR^{3a} , or $CR^{4a}R^{5a}$;
 X^2 is O, NR^{3b} , or $CR^{4b}R^{5b}$;
 X^3 is O, NR^{3c} , or $CR^{4c}R^{5c}$;
 X^4 is a bond, O, NR^{3d} , or $CR^{4d}R^{5d}$;
each of R^{3a} , R^{3b} , R^{3c} , and R^{3d} is, independently, H, 40
halogen, hydroxyl, optionally substituted $C_1\text{-}C_6$ alkyl, 45
optionally substituted $C_1\text{-}C_6$ heteroalkyl, optionally substituted
 $C_3\text{-}C_{10}$ carbocyclyl, optionally substituted
 $C_2\text{-}C_9$ heterocyclyl, optionally substituted $C_6\text{-}C_{10}$ aryl,
optionally substituted $C_2\text{-}C_9$ heteroaryl, optionally substituted
 $C_2\text{-}C_6$ alkenyl, optionally substituted $C_2\text{-}C_6$ 50
heteroalkenyl, optionally substituted $C_1\text{-}C_6$ acyl, thiol,
optionally substituted sulfone, optionally substituted
sulfonamide, or optionally substituted amino, or R^{3a}
and R^{4b} , R^{4a} and R^{3b} , R^{4b} and R^{4a} , R^{3b} and R^{4c} , R^{4b} and
 R^{4c} , R^{3c} and R^{4b} , R^{3c} and R^{4d} , R^{4c} and R^{4d} , and/or R^{3d}
and R^{4c} , together with the atoms to which each is
attached, combine to form optionally substituted $C_2\text{-}C_9$
heterocyclyl;
each of R^{4a} , R^{4b} , R^{4c} , and R^{4d} is, independently, H, 55
halogen, hydroxyl, optionally substituted $C_1\text{-}C_6$ alkyl,
optionally substituted $C_1\text{-}C_6$ heteroalkyl, optionally substituted
 $C_3\text{-}C_{10}$ carbocyclyl, optionally substituted
 $C_2\text{-}C_9$ heterocyclyl, optionally substituted $C_6\text{-}C_{10}$ aryl,
optionally substituted $C_2\text{-}C_9$ heteroaryl, optionally substituted
 $C_2\text{-}C_6$ alkenyl, optionally substituted $C_2\text{-}C_6$ 60
heteroalkenyl, optionally substituted $C_1\text{-}C_6$ acyl, thiol,
optionally substituted sulfone, or optionally substituted
amino, or R^{3a} and R^{4b} , R^{4a} and R^{3b} , R^{4b} and R^{4a} , R^{3b}
and R^{4c} , R^{4b} and R^{4c} , R^{3c} and R^{4b} , R^{3c} and R^{4d} , R^{4c} and
 R^{4d} , and/or R^{3d} and R^{4c} , together with the atoms to

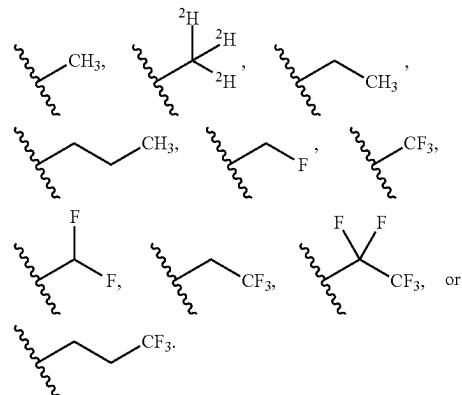
which each is attached, combine to form optionally substituted $C_2\text{-}C_9$ heterocyclyl;
each of R^{5a} , R^{5b} , R^{5c} , and R^{5d} is, independently, H, 10
halogen, hydroxyl, optionally substituted $C_1\text{-}C_6$ alkyl,
optionally substituted $C_1\text{-}C_6$ heteroalkyl, optionally substituted
 $C_3\text{-}C_{10}$ carbocyclyl, optionally substituted $C_2\text{-}C_9$ heterocyclyl,
optionally substituted $C_6\text{-}C_{10}$ aryl, optionally substituted
 $C_2\text{-}C_6$ alkenyl, optionally substituted $C_2\text{-}C_6$ 15
heteroalkenyl, hydroxyl, thiol, or optionally substituted
amino; and G is optionally substituted $C_6\text{-}C_{10}$ aryl,
optionally substituted $C_3\text{-}C_{10}$ carbocyclyl, optionally substituted
 $C_2\text{-}C_9$ heteroaryl, or $C_2\text{-}C_9$ heterocyclyl, or
a pharmaceutically acceptable salt thereof.

In some embodiments, R^1 is H, optionally substituted $C_1\text{-}C_6$ alkyl, optionally substituted $C_1\text{-}C_6$ heteroalkyl, or optionally substituted $C_3\text{-}C_{10}$ carbocyclyl. In some embodiments, R^1 is H, optionally substituted $C_1\text{-}C_6$ alkyl, optionally substituted $C_2\text{-}C_6$ alkenyl, or optionally substituted $C_3\text{-}C_{10}$ carbocyclyl. In some embodiments, R^1 is H, optionally substituted $C_1\text{-}C_6$ alkyl, or optionally substituted $C_3\text{-}C_{10}$ carbocyclyl.

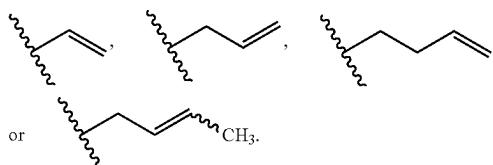
In some embodiments, R^1 is H. In some embodiments, R^1 is optionally substituted $C_1\text{-}C_6$ alkyl. In some embodiments, R^1 is optionally substituted $C_2\text{-}C_6$ alkenyl. In some embodiments, R^1 is optionally substituted $C_3\text{-}C_{10}$ carbocyclyl.

In some embodiments, optionally substituted $C_1\text{-}C_6$ alkyl is $C_1\text{-}C_6$ perfluoroalkyl.

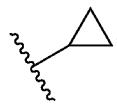
In some embodiments, R^1 is



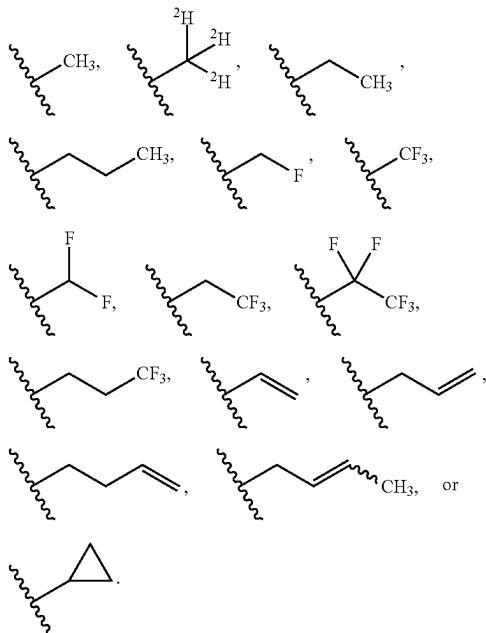
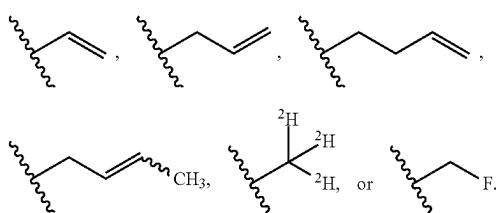
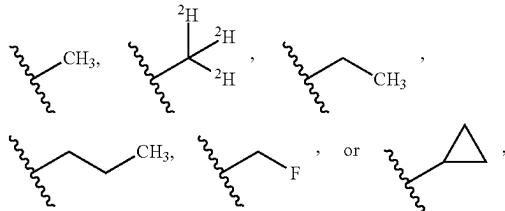
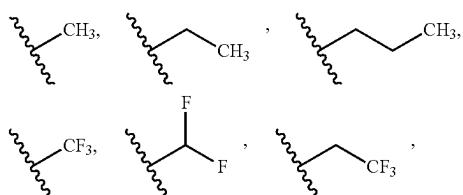
In some embodiments, R^1 is



In some embodiments, R^1 is

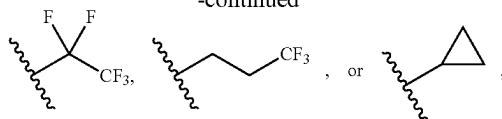
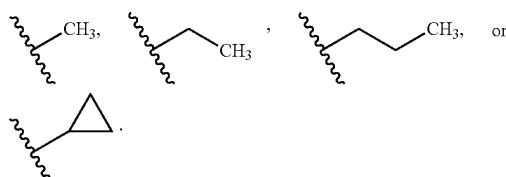


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In some embodiments, R¹ is H,In some embodiments, R¹ isIn some embodiments, R¹ is H,In some embodiments, R¹ is H,

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-continued

In some embodiments, R¹ is H,In some embodiments, R¹ is H orIn some embodiments, R¹ is H. In some embodiments, R¹ isIn some embodiments, Z¹ is CR². In some embodiments, Z¹ is N.In some embodiments, R² is H, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₁₀ carbocycliclyl, or optionally substituted C₆-C₁₀ aryl.In some embodiments, R² is H, halogen, or optionally substituted C₁-C₆ alkyl.In some embodiments, R² is H, F, orIn some embodiments, R² is H. In some embodiments, R² is F. In some embodiments, R² isIn some embodiments, X¹ is a bond, O, NR^{3a}, or CR^{4a}R^{5a}; X² is O, NR^{3b}, or CR^{4b}R^{5b}; X³ is O, NR^{3c}, or CR^{4c}R^{5c}; and X⁴ is a bond, O, NR^{3d}, or CR^{4d}R^{5d}.In some embodiments, X¹ is a bond. In some embodiments, X¹ is O, NR^{3a}, or CR^{4a}R^{5a}. In some embodiments, X¹ is O or NR^{3a}. In some embodiments, X¹ is NR^{3a} or CR^{4a}R^{5a}. In some embodiments, X² is O or NR^{3b}. In some embodiments, X² is CR^{4b}R^{5b}. In some embodiments, X² is NR^{3b} or CR^{4b}R^{5b}.

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In some embodiments, X^3 is O or NR^{3c} . In some embodiments, X^3 is $CR^{4c}R^{5c}$. In some embodiments, X^3 is NR^{3c} or $CR^{4c}R^{5c}$.

In some embodiments, X^4 is a bond. In some embodiments, X^4 is O, NR^{3d} , or $CR^{4d}R^{5d}$. In some embodiments, X^4 is O or NR^{3d} . In some embodiments, X^4 is NR^{3d} or $CR^{4d}R^{5d}$.

In some embodiments, X^1 is O, NR^{3a} , or $CR^{4a}R^{5a}$; X^2 is O, NR^{3b} , or $CR^{4b}R^{5b}$; X^3 is O, NR^{3c} , or $CR^{4c}R^{5c}$; and X^4 is O, NR^{3d} , or $CR^{4d}R^{5d}$.

In some embodiments, X^1 is $CR^{4a}R^{5a}$; X^2 is NR^{3b} ; X^3 is $CR^{4c}R^{5c}$; and X^4 is $CR^{4d}R^{5d}$. In some embodiments, X^1 is $CR^{4a}R^{5a}$; X^2 is $CR^{4b}R^{5b}$; X^3 is NR^{3c} ; and X^4 is $CR^{4d}R^{5d}$. In some embodiments, X^1 is O or NR^{3a} ; X^2 is $CR^{4b}R^{5b}$; X^3 is $CR^{4c}R^{5c}$; and X^4 is O or NR^{3d} . In some embodiments, X^1 is a bond; X^2 is $CR^{4b}R^{5b}$; X^3 is O or NR^{3c} ; and X^4 is $CR^{4d}R^{5d}$. In some embodiments, X^1 is $CR^{4a}R^{5a}$; X^2 is $CR^{4b}R^{5b}$; X^3 is $CR^{4c}R^{5c}$; and X^4 is $CR^{4d}R^{5d}$. In some embodiments, X^5 is NR^{3e} and X^6 is $CR^{4f}R^{5f}$.

In some embodiments, each of R^{3a} , R^{3b} , R^{3c} , and R^{3d} is, independently, H, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_1 - C_6 acyl, optionally substituted sulfone, or optionally substituted sulfonamide. In some embodiments, each of R^{3a} , R^{3b} , R^{3c} , and R^{3d} is, independently, H, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted sulfone, or optionally substituted sulfonamide. In some embodiments, each of R^{3a} , R^{3b} , R^{3c} , and R^{3d} is, independently, H, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 acyl, optionally substituted sulfone, or optionally substituted sulfonamide. In some embodiments, each of R^{3a} , R^{3b} , R^{3c} , and R^{3d} is, independently, H, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 acyl, optionally substituted sulfone, or optionally substituted sulfonamide.

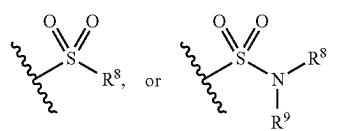
In some embodiments, each of R^{3a} , R^{3b} , R^{3c} , and R^{3d} is, independently, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_1 - C_6 acyl, optionally substituted sulfone, or optionally substituted sulfonamide. In some embodiments, each of R^{3a} , R^{3b} , R^{3c} , and R^{3d} is, independently, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 acyl, optionally substituted sulfone, or optionally substituted sulfonamide.

In some embodiments, each of R^{3a} , R^{3b} , R^{3c} , and R^{3d} is, independently, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, or optionally substituted C_1 - C_6 acyl. In some embodiments, each of R^{3a} , R^{3b} , R^{3c} , and R^{3d} is, independently, optionally substituted C_1 - C_6 alkyl or optionally substituted C_1 - C_6 heteroalkyl. In some embodiments, each of R^{3a} , R^{3b} , R^{3c} , and R^{3d} is, independently, optionally substituted C_1 - C_6 acyl or optionally substituted C_1 - C_6 heteroalkyl. In some embodiments, each of R^{3a} , R^{3b} , R^{3c} , and R^{3d} is, independently, optionally substituted C_1 - C_6 acyl. In some embodiments, each of R^{3a} , R^{3b} , R^{3c} , and R^{3d} is, independently, optionally substituted C_1 - C_6 acyl. In some embodiments, each of R^{3a} , R^{3b} , R^{3c} , and R^{3d} is, independently, optionally substituted sulfone or optionally substituted sulfonamide.

In some embodiments, each of R^{3a} , R^{3b} , R^{3c} , and R^{3d} is, independently, H, optionally substituted C_1 - C_6 alkyl,

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-continued



where

R^5 is H, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_3 - C_{10} carbocyclyl, or optionally substituted C_6 - C_{10} aryl;

W^1 is O or S;

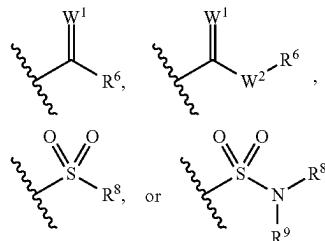
W^2 is NR^7 or O;

R^7 is H, optionally substituted C_1 - C_6 alkyl, or optionally substituted C_1 - C_6 heteroalkyl;

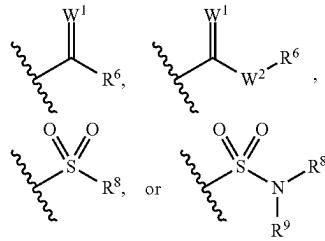
R^8 is optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_3 - C_{10} carbocyclyl, or optionally substituted C_6 - C_{10} aryl; and

R^9 is H, optionally substituted C_1 - C_6 alkyl, or optionally substituted C_1 - C_6 heteroalkyl.

In some embodiments, each of R^{3a} , R^{3b} , R^{3c} , and R^{3d} is, independently, C_1 - C_6 alkyl,

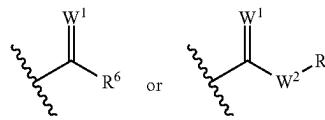


In some embodiments, each of R^{3a} , R^{3b} , R^{3c} , and R^{3d} is, independently, C_1 - C_6 alkyl. In some embodiments, each of R^{3a} , R^{3b} , R^{3c} , and R^{3d} is, independently,



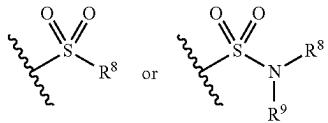
In some embodiments, each of R^{3a} , R^{3b} , R^{3c} , and R^{3d} is, independently,

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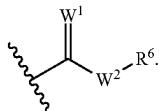


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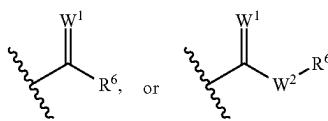
In some embodiments, each of R^{3a} , R^{3b} , R^{3c} , and R^{3d} is, independently,



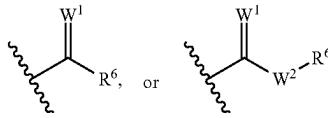
In some embodiments, each of R^{3a} , R^{3b} , R^{3c} , and R^{3d} is, independently,



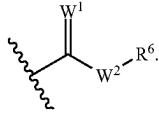
In some embodiments, each of R^{3a} , R^{3b} , R^{3c} , and R^{3d} is, independently, H, optionally substituted C_1 - C_6 alkyl,



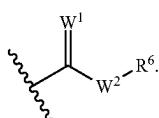
In some embodiments, each of R^{3a} , R^{3b} , R^{3c} , and R^{3d} is, independently, H, C_1 - C_6 alkyl,



In some embodiments, each of R^{3a} , R^{3b} , R^{3c} , and R^{3d} is, independently, H, C_1 - C_6 alkyl, or

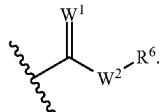


In some embodiments, each of R^{3a} , R^{3b} , R^{3c} , and R^{3d} is, independently, C_1 - C_6 alkyl



In some embodiments, each of R^{3a} , R^{3b} , R^{3c} , and R^{3d} is, independently, H, methyl, or

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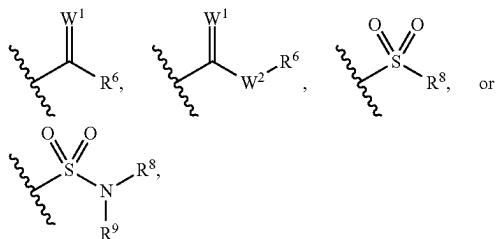


In some embodiments, each of R^{3a} , R^{3b} , R^{3c} , and R^{3d} is, independently, optionally substituted C_1 - C_6 alkyl.

10 In some embodiments, each of R^{4a} , R^{4b} , R^{4c} , and R^{4d} is, independently, H, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_1 - C_6 acyl, optionally substituted sulfone, or optionally substituted sulfonamide. In some embodiments, each of R^{4a} , R^{4b} , R^{4c} , and R^{4d} is, independently, H, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted sulfone, or optionally substituted sulfonamide. In some embodiments, each of R^{4a} , R^{4b} , R^{4c} , and R^{4d} is H. In some embodiments, each of R^{4a} , R^{4b} , R^{4c} , and R^{4d} is, independently, H, optionally substituted C_1 - C_6 alkyl, or optionally substituted C_1 - C_6 acyl.

15 20 In some embodiments, each of R^{4a} , R^{4b} , R^{4c} , and R^{4d} is, independently substituted C_1 - C_6 acyl, optionally substituted sulfone, or optionally substituted sulfonamide. In some embodiments, each of R^{4a} , R^{4b} , R^{4c} , and R^{4d} is, independently, H, optionally substituted C_1 - C_6 alkyl, or optionally substituted C_1 - C_6 acyl.

25 In some embodiments, each of R^{4a} , R^{4b} , R^{4c} , and R^{4d} is, independently, H, optionally substituted C_1 - C_6 alkyl,



30 where

R^6 is H, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_3 - C_{10} carbocyclyl, or optionally substituted C_6 - C_{10} aryl;

W^1 is O or S;

W^2 is NR^7 or O;

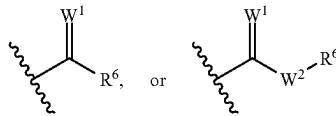
R^7 is H, optionally substituted C_1 - C_6 alkyl, or optionally substituted C_1 - C_6 heteroalkyl;

R^8 is optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_3 - C_{10} carbocyclyl, or optionally substituted C_6 - C_{10} aryl; and

R^9 is H, optionally substituted C_1 - C_6 alkyl, or optionally substituted C_1 - C_6 heteroalkyl.

35 40 45 In some embodiments, each of R^{4a} , R^{4b} , R^{4c} , and R^{4d} is, independently, H, optionally substituted C_1 - C_6 alkyl,

50 55 In some embodiments, each of R^{4a} , R^{4b} , R^{4c} , and R^{4d} is, independently, H or optionally substituted C_1 - C_6 alkyl.



60 In some embodiments, each of R^{4a} , R^{4b} , R^{4c} , and R^{4d} is, independently, H or optionally substituted C_1 - C_6 alkyl. In some embodiments, each of R^{4a} , R^{4b} , R^{4c} , and R^{4d} is, independently, H.

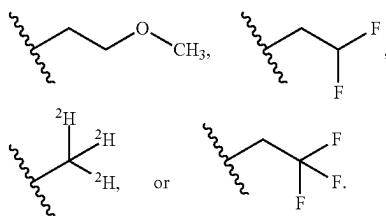
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In some embodiments, W¹ is O. In some embodiments, W¹ is S.

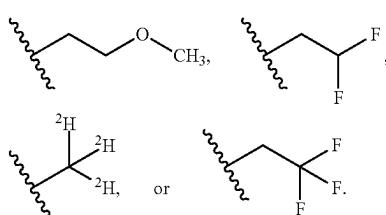
In some embodiments, W² is O. In some embodiments, W² is NR⁷.

In some embodiments, R⁶ is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₁₀ carbocyclyl. In some embodiments, R⁶ is H, optionally substituted C₁-C₆ alkyl, or optionally substituted C₁-C₆ heteroalkyl. In some embodiments, R⁶ is H, optionally substituted C₃-C₁₀ carbocyclyl, or optionally substituted C₆-C₁₀ aryl. In some embodiments, R⁶ is optionally substituted C₁-C₆ alkyl or optionally substituted C₁-C₆ heteroalkyl. In some embodiments, R⁶ is optionally substituted C₃-C₁₀ carbocyclyl or optionally substituted C₆-C₁₀ aryl.

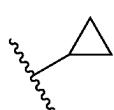
In some embodiments, R⁶ is H, methyl, ethyl



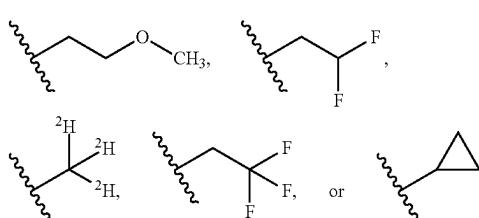
In some embodiments, R⁶ is H. In some embodiments, R⁶ is methyl, ethyl,



In some embodiments, R⁶ is



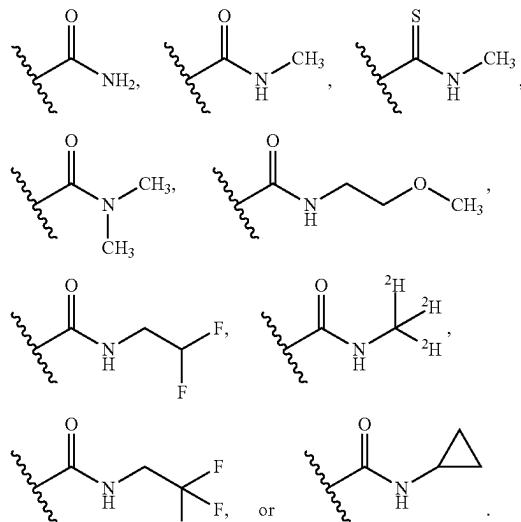
In some embodiments, R⁶ is H, methyl, ethyl,



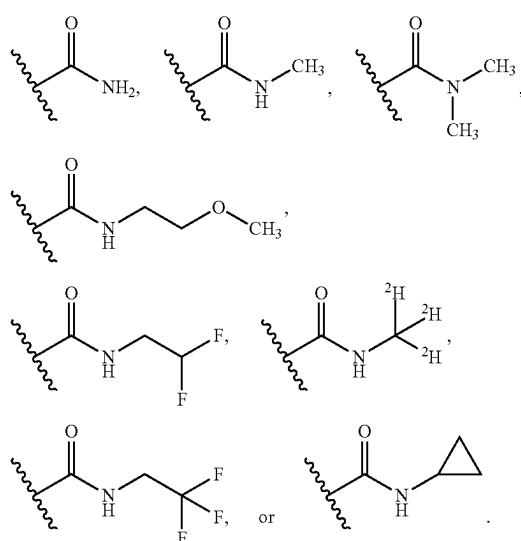
In some embodiments, R⁷ is H or optionally substituted C₁-C₆ alkyl. In some embodiments, R⁷ is H or methyl.

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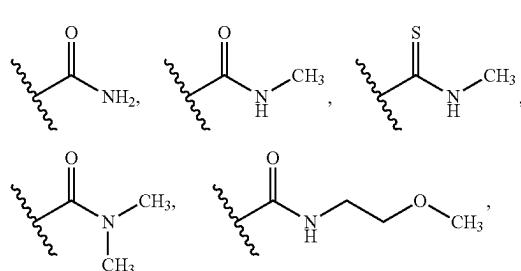
In some embodiments, each of R^{3a}, R^{3b}, R^{3c}, and R^{3d} is, independently, H, methyl,



In some embodiments, each of R^{3a}, R^{3b}, R^{3c}, and R^{3d} is, independently, H, methyl,

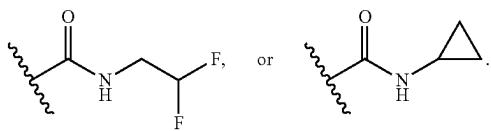
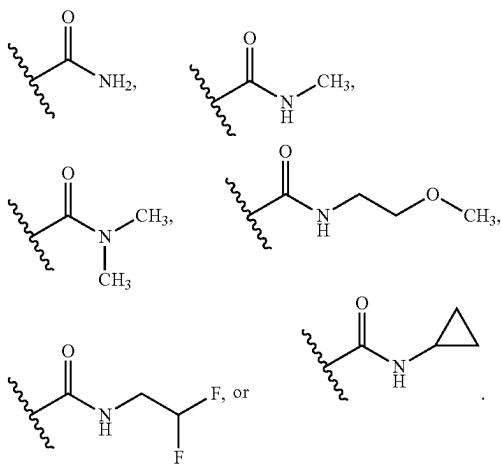
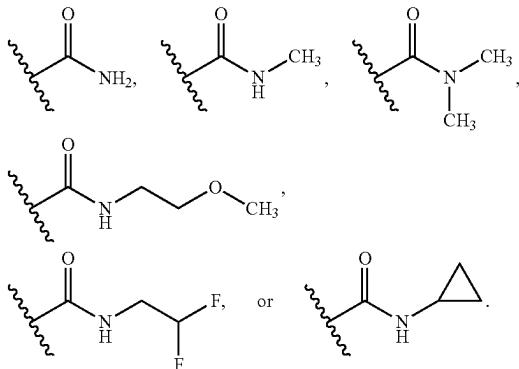
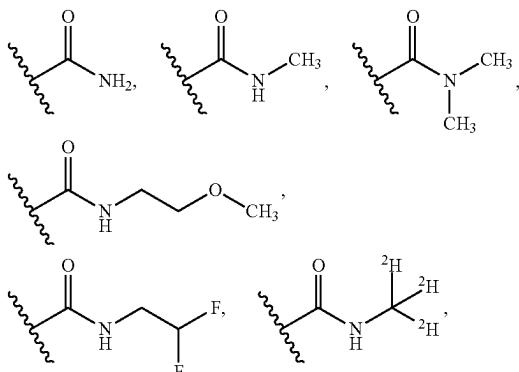


In some embodiments, R^{3a} is H, methyl,

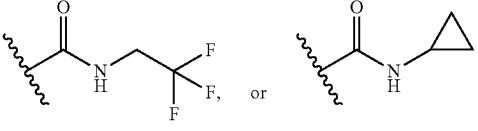


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In some embodiments, R^{3b} is H, methyl,In some embodiments, R^{3c} is H, methyl,In some embodiments, R^{3d} is H, methyl,**16**

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In some embodiments, R^{3a} and R^{4b}, R^{4a} and R^{3b}, R^{4b} and R^{4a}, R^{3b} and R^{4c}, R^{4b} and R^{4c}, R^{3c} and R^{4d}, R^{4c} and R^{4d}, and/or R^{3d} and R^{4c}, together with the atoms to which each is attached, combine to form optionally substituted C₂-C₉ heterocycl.

In some embodiments, R^{3a} and R^{4b}, R^{4b} and R^{4a}, R^{4b} and R^{4c}, R^{3c} and R^{4b}, R^{3c} and R^{4d}, and/or R^{3d} and R^{4c}, together with the atoms to which each is attached, combine to form optionally substituted C₂-C₉ heterocycl.

In some embodiments, each of R^{5a}, R^{5b}, R^{5c}, and R^{5d} is, independently, H, optionally substituted C₁-C₆ alkyl, or optionally substituted C₁-C₆ heteroalkyl. In some embodiments, each of R^{5a}, R^{5b}, R^{5c}, and R^{5d} is H.

In some embodiments, each of R^{3e}, R^{3f}, R^{3g}, and R^{3h} is, independently, H, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₁-C₆ acyl, optionally substituted sulfone, or optionally substituted sulfonamide.

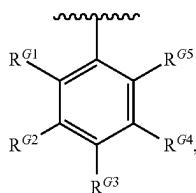
In some embodiments, each of R^{4e}, R^{4f}, R^{4g}, and R^{4h} is, independently, H, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₁-C₆ acyl, optionally substituted sulfone, or optionally substituted sulfonamide.

In some embodiments, each of R^{5e}, R^{5f}, R^{5g}, and R^{5h} is, independently, H, optionally substituted C₁-C₆ alkyl, or optionally substituted C₁-C₆ heteroalkyl. In some embodiments, each of R^{5e}, R^{5f}, R^{5g}, and R^{5h} is H.

In some embodiments, G is optionally substituted C₃-C₁₀ carbocycl or optionally substituted C₂-C₉ heterocycl. In some embodiments, G is optionally substituted C₆-C₁₀ aryl or optionally substituted C₂-C₉ heteroaryl.

In some embodiments, G is optionally substituted C₃-C₁₀ carbocycl. In some embodiments, G is optionally substituted C₆-C₁₀ aryl. In some embodiments, G is optionally substituted C₂-C₉ heterocycl. In some embodiments, G is optionally substituted C₂-C₉ heteroaryl.

In some embodiments, G is



where

each of R^{G1}, R^{G2}, R^{G3}, R^{G4}, and R^{G5} is, independently, H, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocycl, optionally substituted C₂-C₉ heterocycl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, optionally substituted —O—C₃-C₆ carbocycl, optionally substituted —C₁-C₃ alkyl-C₃-C₆ carbocycl, optionally substituted —C₁-C₃ alkyl-C₂-C₅ heterocycl, hydroxyl, thiol, or optionally substituted

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amino; or R^{G1} and R^{G2} , R^{G2} and R^{G3} , R^{G3} and R^{G4} , and/or R^{G4} and R^{G5} , together with the carbon atoms to which each is attached, combine to form optionally substituted C_6 - C_{10} aryl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heteroaryl, or optionally substituted C_2 - C_9 heterocyclyl.

In some embodiments, each of R^{G1} , R^{G2} , R^{G3} , R^{G4} , and R^{G5} is, independently, H, halogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heterocyclyl, optionally substituted C_6 - C_{10} aryl, optionally substituted C_2 - C_9 heteroaryl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 heteroalkenyl, optionally substituted $-O-C_3-C_6-$ carbocyclyl, optionally substituted $-C_1-C_3$ alkyl- C_3-C_6- carbocyclyl, optionally substituted $-C_1-C_3$ alkyl- C_2-C_5 heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R^{G1} and R^{G2} , R^{G2} and R^{G3} , R^{G3} and R^{G4} , and/or R^{G4} and R^{G5} , together with the carbon atoms to which each is attached, combine to form optionally substituted C_6 - C_{10} aryl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heteroaryl, or optionally substituted C_2 - C_9 heterocyclyl.

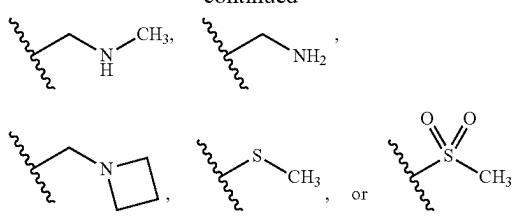
In some embodiments, each of R^{G1} , R^{G2} , R^{G3} , R^{G4} , and R^{G5} is, independently, H, halogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, 25
optionally substituted $—O—C_3-C_6$ carbocyclyl, or optionally substituted $—C_1-C_3$ alkyl- C_2-C_5 heterocyclyl; or R^{G1} and R^{G2} , R^{G2} and R^{G3} , R^{G3} and R^{G4} , and/or R^{G4} and R^{G5} , together with the carbon atoms to which each is attached, 30 combine to form optionally substituted C_2 - C_9 heteroaryl or optionally substituted C_2 - C_9 heterocyclyl.

In some embodiments, each of R^{G1} , R^{G2} , R^{G3} , R^{G4} , and R^{G5} is, independently, H, halogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted $—O—C_3-C_6$ carbocyclyl, or optionally substituted $—C_1-C_6$ alkyl- C_1-C_6 heterocyclyl.

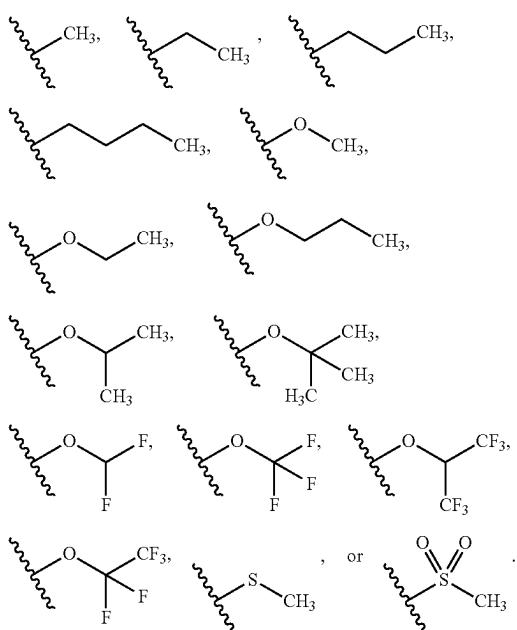
In some embodiments, each of R^{G1} , R^{G2} , R^{G3} , R^{G4} , and R^{G5} is, independently, H, F, Cl,

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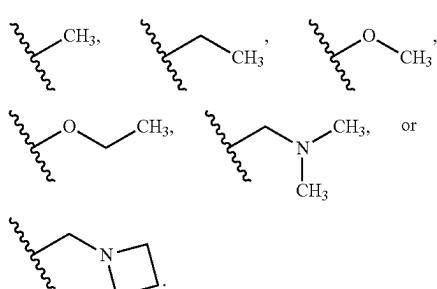
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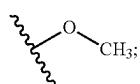
In some embodiments, each of R^{G1} , R^{G2} , R^{G3} , R^{G4} , and R^{G5} is, independently, H, F,



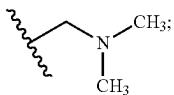
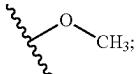
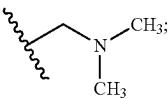
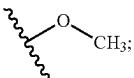
In some embodiments, each of R^{G1}, R^{G2}, R^{G3}, R^{G4}, and R^{G5} is, independently, H, F, Cl,



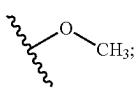
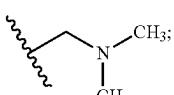
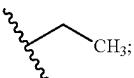
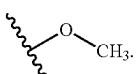
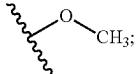
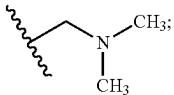
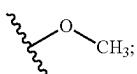
In some embodiments, R^{G1} is H; R^{G2} is



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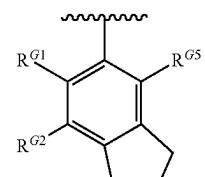
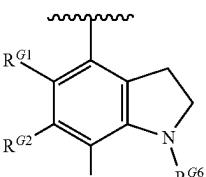
 R^{G3} is R^{G4} isand R^{G5} is H. In some embodiments, R^{G1} is H; R^{G2} is R^{G3} is10 R^{G4} is H; and R^{G5} is H. In some embodiments, R^{G1} is H; R^{G2} is15 R^{G3} isand R^{G5} is H. In some embodiments, R^{G1} is H; R^{G2} is

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 R^{G3} is25 R^{G4} is R^{G4} is H; and R^{G5} is35 and R^{G5} is H.In some embodiments, R^{G1} is H; R^{G2} is R^{G3} is R^{G4} is Cl or F; and R^{G5} is H. In some embodiments, R^{G1} is H; R^{G2} is

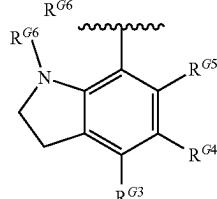
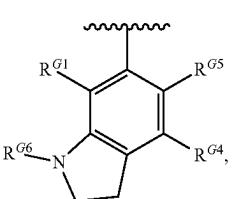
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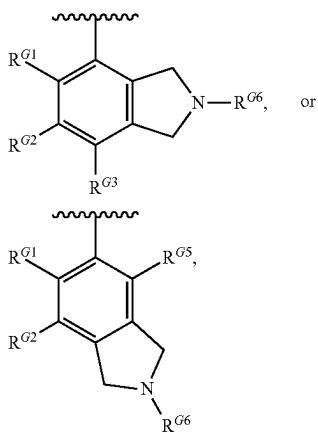
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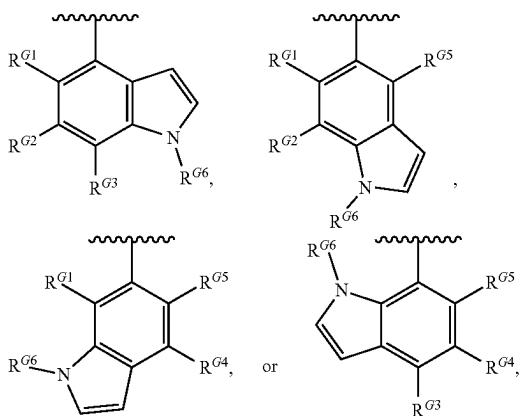


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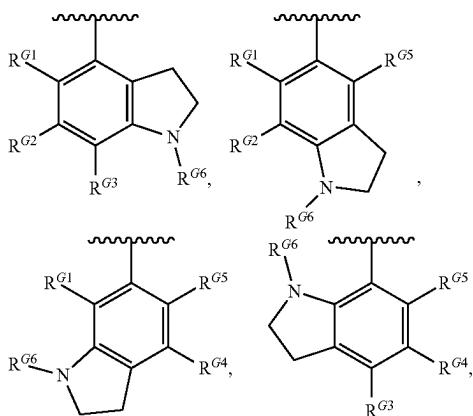
where R^{G6} is H or optionally substituted C₁-C₆ alkyl. In some embodiments, G is



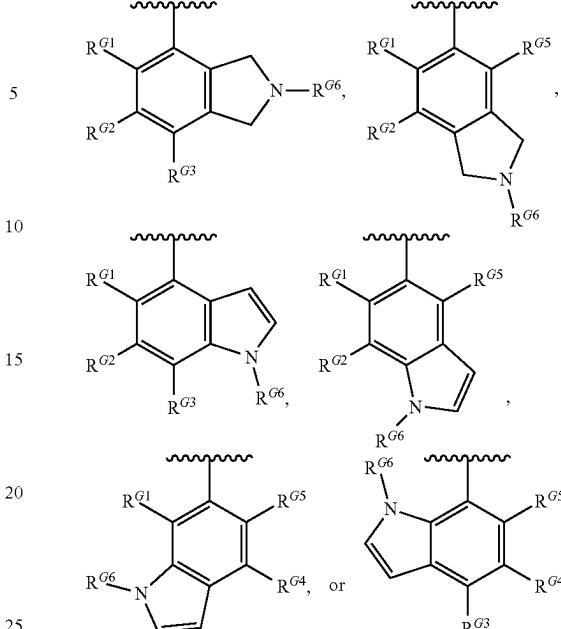
where R^{G6} is H or optionally substituted C₁-C₆ alkyl.

In some embodiments, R^{G1} and R^{G2}, R^{G2} and R^{G3}, R^{G3} and R^{G4}, and/or R^{G4} and R^{G5}, together with the carbon atoms to which each is attached, combine to form optionally substituted C₂-C₉ heterocyclol or optionally substituted C₂-C₉ heteroaryl.

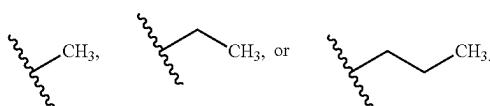
In some embodiments, G is

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where R^{G6} is H or optionally substituted C₁-C₆ alkyl.
In some embodiments, R^{G6} is H,

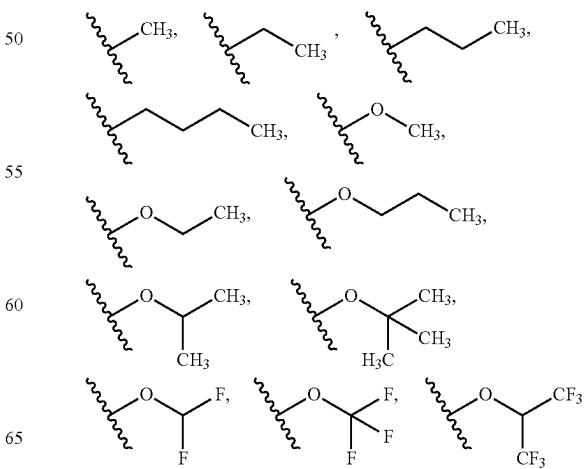


In some embodiments, R^{G6} is H or



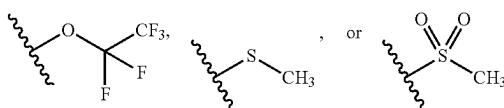
In some embodiments, R^{G6} is H.

In some embodiments, R^{G1} is H, F,



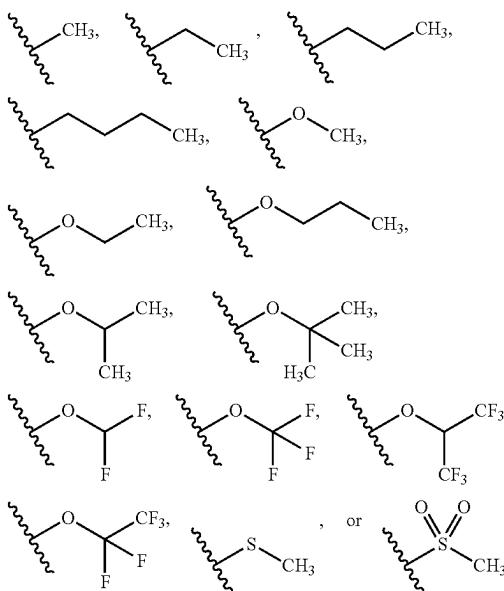
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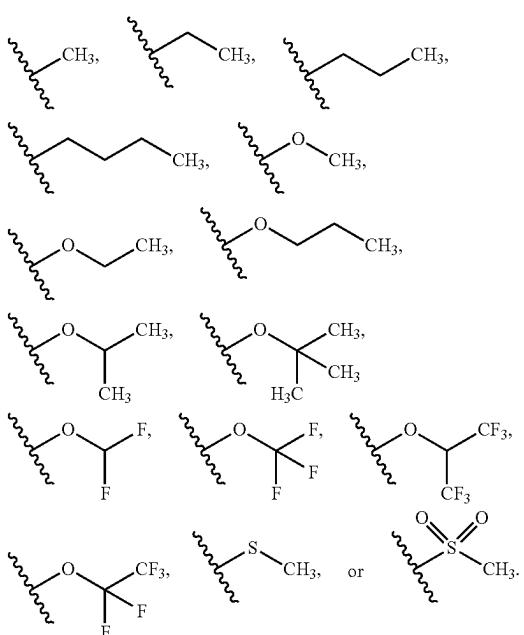
In some embodiments, R^{G1} is H.

In some embodiments, R^{G2} is H, F,



In some embodiments, R^{G2} is H.

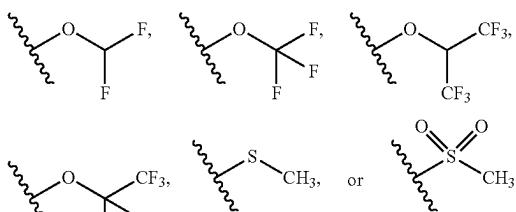
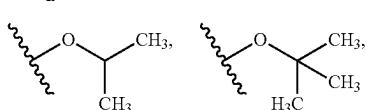
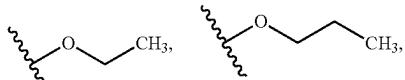
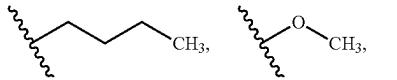
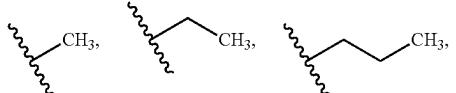
In some embodiments, R^{G3} is H, F,



In some embodiments, R^{G3} is H.

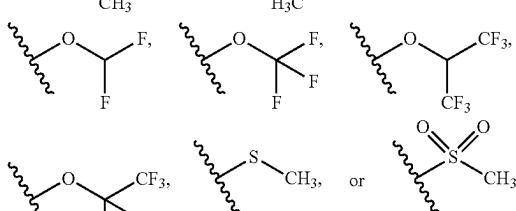
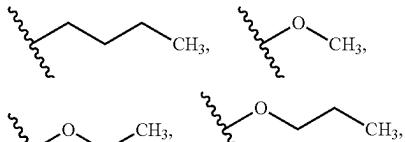
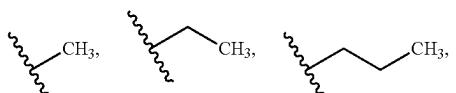
24

In some embodiments, R^{G4} is H, F,



In some embodiments, R^{G4} is H.

In some embodiments, R^{G5} is H, F,

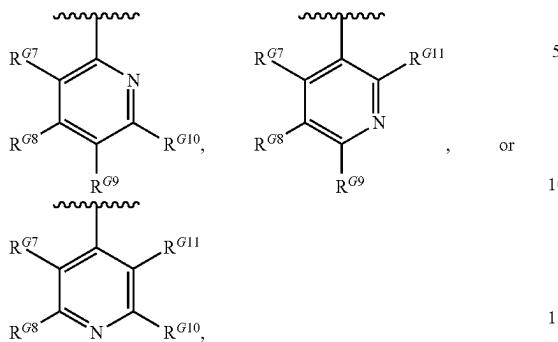


In some embodiments, R^{G5} is H.

In some embodiments, one or more of R^{G1} , R^{G2} , R^{G3} , R^{G4} , and R^{G5} is H. In some embodiments, two or more of R^{G1} , R^{G2} , R^{G3} , R^{G4} , and R^{G5} is H. In some embodiments, three or more of R^{G1} , R^{G2} , R^{G3} , R^{G4} , and R^{G5} is H. In some embodiments, each of R^{G1} , R^{G2} , R^{G3} , R^{G4} , and R^{G5} is H.

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In some embodiments, G is



where

each of R^{G7}, R^{G8}, R^{G9}, R^{G10}, and R^{G11} is, independently, H, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, optionally substituted —O—C₃-C₆ carbocyclyl, optionally substituted —C₁-C₃ alkyl-C₃-C₆ carbocyclyl, optionally substituted —C₁-C₃ alkyl-C₂-C₅ heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R^{G7} and R^{G8}, R^{G8} and R^{G9}, R^{G9} and R^{G10}, and/or R^{G10} and R^{G11}, together with the carbon atoms to which each is attached, combine to form optionally substituted C₆-C₁₀ aryl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heteroaryl, or C₂-C₉ heterocyclyl.

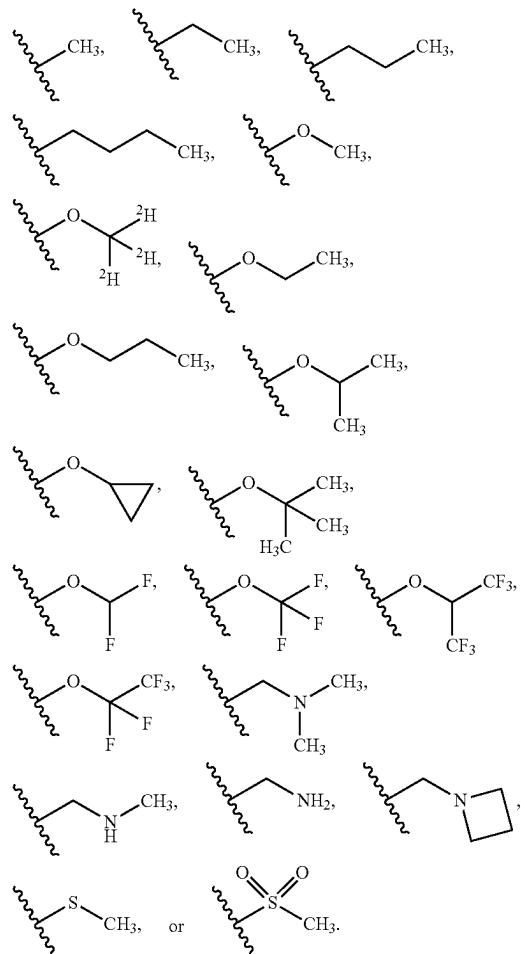
In some embodiments, each of R^{G7} , R^{G8} , R^{G9} , R^{G10} , and R^{G11} is, independently, H, halogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heterocyclyl, optionally substituted C_6 - C_{10} aryl, optionally substituted C_2 - C_9 heteroaryl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 heteroalkenyl, hydroxyl, thiol, or optionally substituted amino; or R^{G7} and R^{G8} , R^{G8} and R^{G9} , R^{G9} and R^{G10} , and/or R^{G10} and R^{G11} , together with the carbon atoms to which each is attached, combine to form optionally substituted C_6 - C_{10} aryl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heteroaryl, or C_2 - C_9 heterocyclyl.

In some embodiments, each of R^{G7} , R^{G8} , R^{G9} , R^{G10} , and R^{G11} is, independently, H, halogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted $-O-C_3-C_6$ carbocyclyl, or optionally substituted $-C_1-C_3$ alkyl- C_2-C_5 heterocyclyl; or R^{G7} and R^{G8} , R^{G8} and R^{G9} , R^{G9} and R^{G10} , and/or R^{G10} and R^{G11} , together with the carbon atoms to which each is attached, combine to form optionally substituted C_6 - C_{10} aryl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heteroaryl, or C_2 - C_9 heterocyclyl.

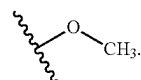
In some embodiments, each of R^{G7} , R^{G8} , R^{G9} , R^{G10} , and R^{G11} is, independently, H, halogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted $—O—C_3$ - C_6 carbocyclyl, or optionally substituted $—C_1$ - C_3 alkyl- C_2 - C_5 heterocyclyl.

In some embodiments, each of R^{G7} , R^{G8} , R^{G9} , R^{G10} , and R^{G11} is, independently, H, F, Cl,

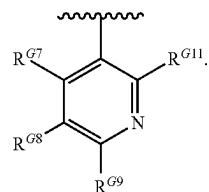
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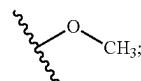
40 In some embodiments, R^{G8} is



In some embodiments, G is

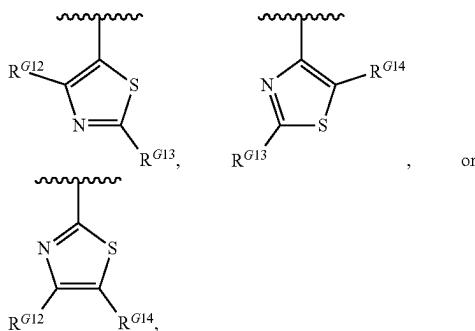


In some embodiments, R^{G7} is H; R^{G8} is



R^{G9} is H; and R^{G11} is H.

In some embodiments, G is

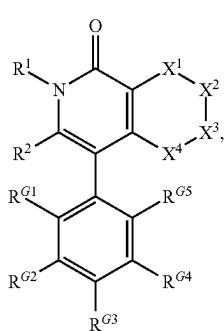


where

each of R^{G12}, R^{G13}, and R^{G14} is, independently, H, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, optionally substituted —O—C₃-C₆ carbocyclyl, optionally substituted —C₁-C₃ alkyl-C₃-C₆ carbocyclyl, optionally substituted —C₁-C₃ alkyl-C₂-C₅ heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R^{G12} and R^{G14}, together with the carbon atoms to which each is attached, combine to form optionally substituted C₆-C₁₀ aryl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heteroaryl, or optionally substituted C₂-C₉ heterocyclyl.

In some embodiments, each of R^{G12}, R^{G13}, and R^{G14} is, independently, H, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, hydroxyl, thiol, or optionally substituted amino; or R^{G12} and R^{G14}, together with the carbon atoms to which each is attached, combine to form optionally substituted C₆-C₁₀ aryl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heteroaryl, or optionally substituted C₂-C₉ heterocyclyl.

In some embodiments, the structure of Formula I has the structure of Formula Ia:

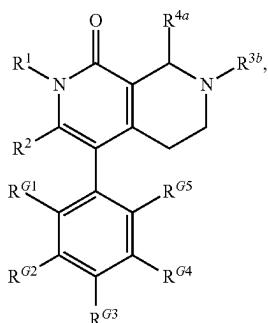


Formula Ia

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In some embodiments, the structure of Formula I has the structure of Formula Ib:



Formula Ib

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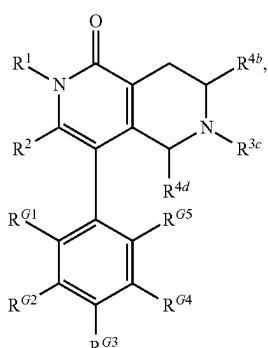
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45

50

or a pharmaceutically acceptable salt thereof.

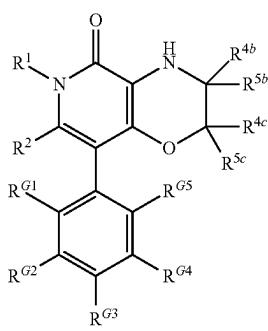
In some embodiments, the structure of Formula I has the structure of Formula Ic:



Formula Ic

or a pharmaceutically acceptable salt thereof.

In some embodiments, the structure of Formula I has the structure of Formula Id:



Formula Id

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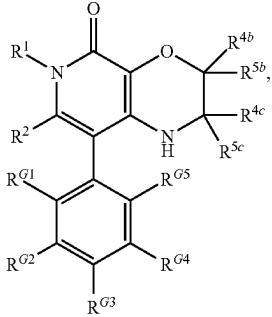
65

or a pharmaceutically acceptable salt thereof.

or a pharmaceutically acceptable salt thereof.

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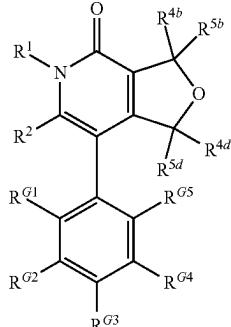
In some embodiments, the structure of Formula I has the structure of Formula Ie:



Formula Ie 5

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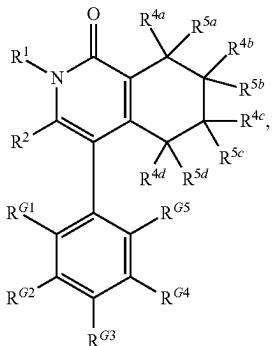
In some embodiments, the structure of Formula I has the structure of Formula Ih:



Formula Ih

or a pharmaceutically acceptable salt thereof.

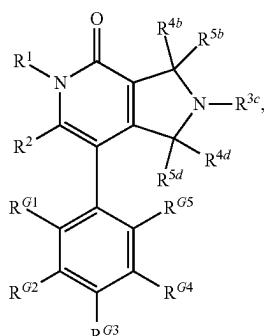
In some embodiments, the structure of Formula I has the structure of Formula If:



Formula If

20 or a pharmaceutically acceptable salt thereof.

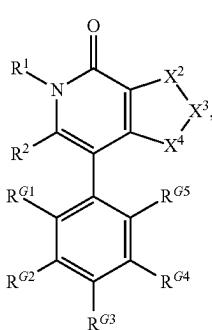
In some embodiments, the structure of Formula I has the structure of Formula II:



Formula II

40 or a pharmaceutically acceptable salt thereof.

In some embodiments, the structure of Formula I has the structure of Formula Ig:



Formula Ig

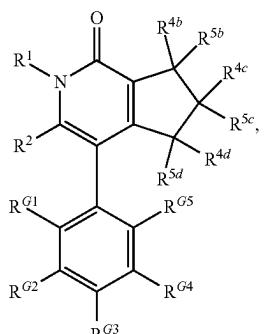
45

Formula Ig

or a pharmaceutically acceptable salt thereof.

In some embodiments, the structure of Formula I has the structure of Formula Ij:

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or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound has the structure of any one of compounds B1-B21 in Table 1A, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound has the structure of any one of compounds B22-B24 in Table 1B, or a pharmaceutically acceptable salt thereof.

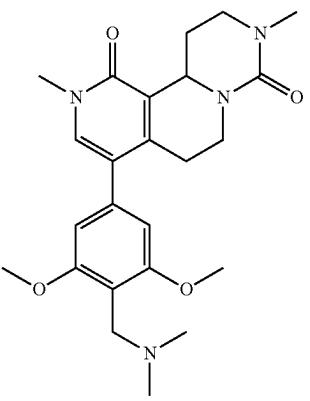
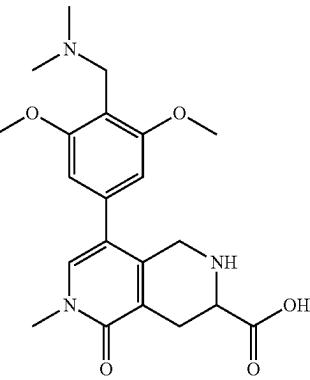
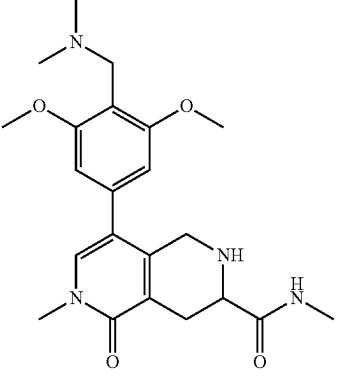
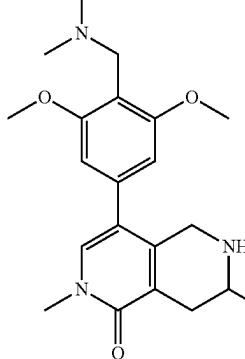
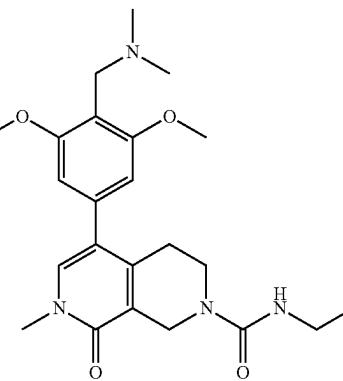
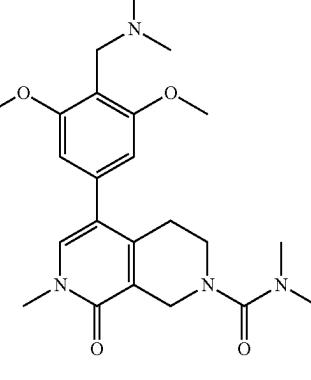
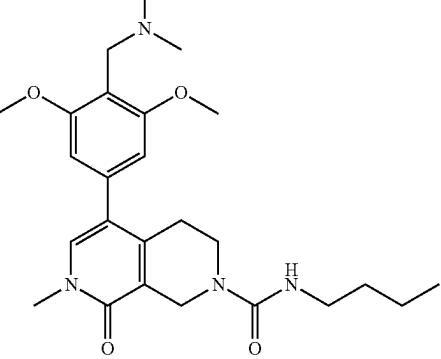
or a pharmaceutically acceptable salt thereof.

31

In an aspect, the disclosure features a compound having the structure of any one of compounds B1-B21 in Table 1A, or a pharmaceutically acceptable salt thereof.

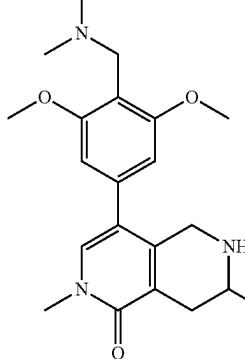
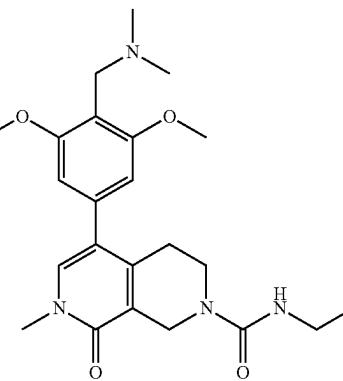
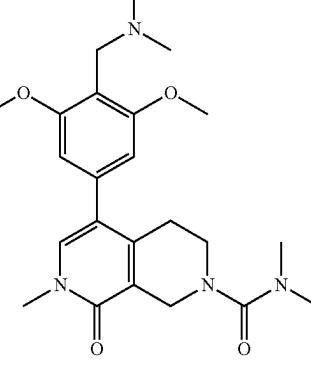
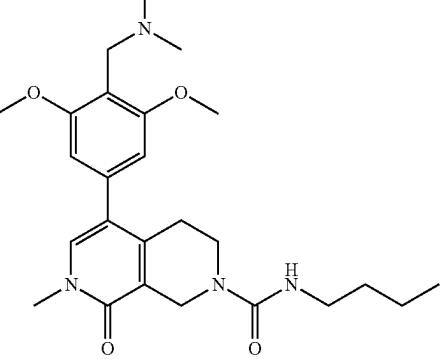
In another aspect, the disclosure features a compound having the structure of any one of compounds B22-B24 in Table 1B, or a pharmaceutically acceptable salt thereof.

TABLE 1A

Compounds B1-B21 of the Disclosure	
Compound No.	Structure
B1	
B2	
B3	
B4	
B5	
B6	
B7	

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TABLE 1A-continued

Compounds B1-B21 of the Disclosure	
Compound No.	Structure
B4	
B5	
B6	
B7	

33

TABLE 1A-continued

Compounds B1-B21 of the Disclosure	
Compound No.	Structure

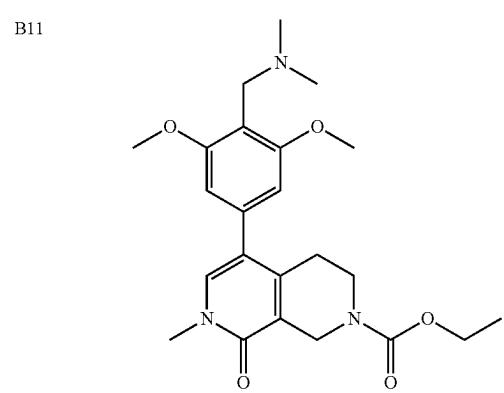
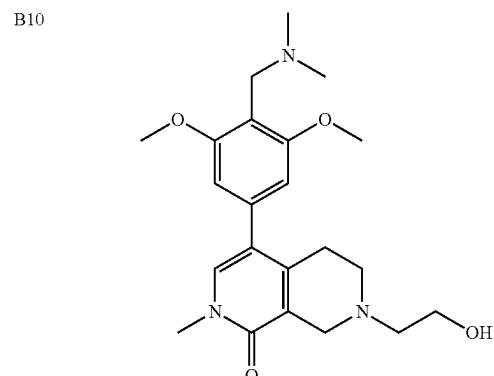
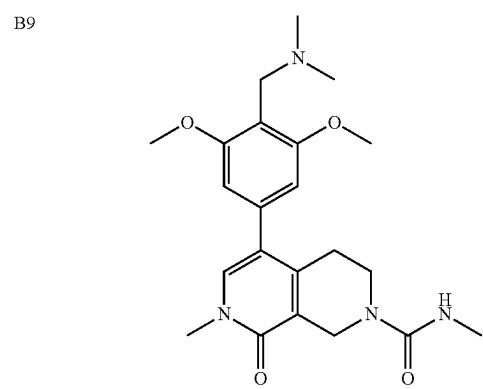
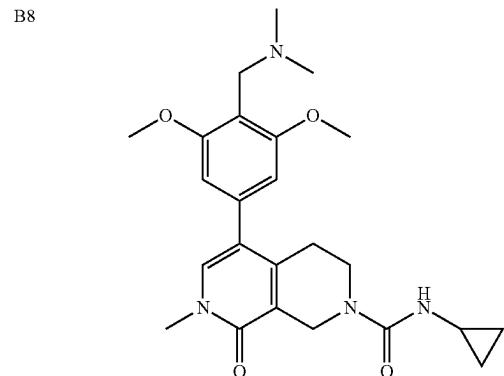
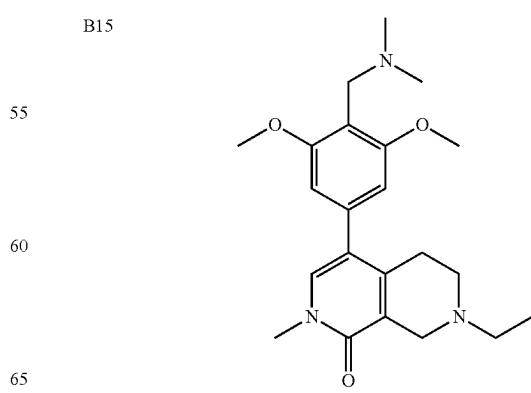
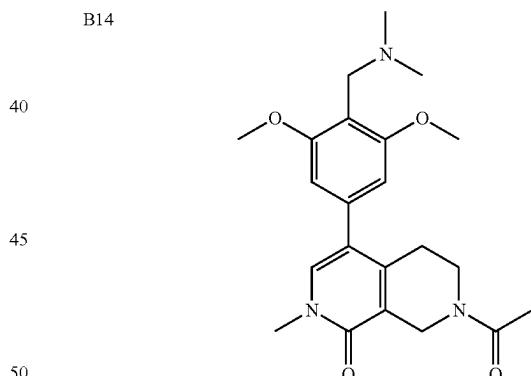
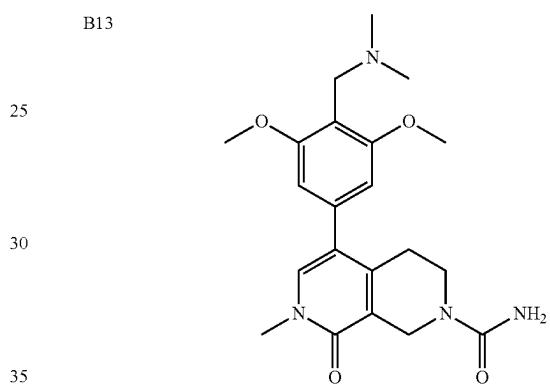
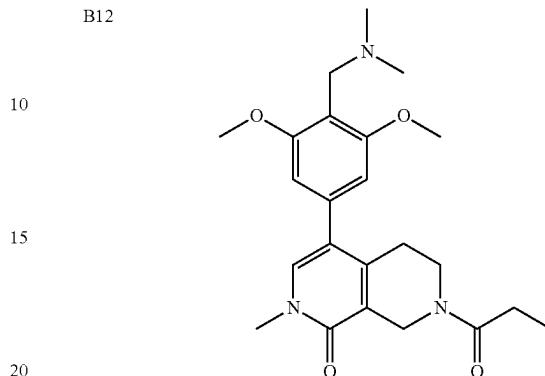
**34**

TABLE 1A-continued

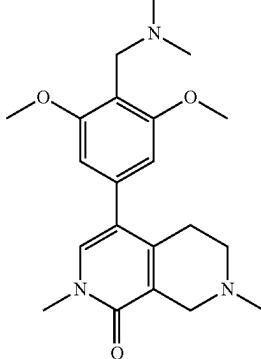
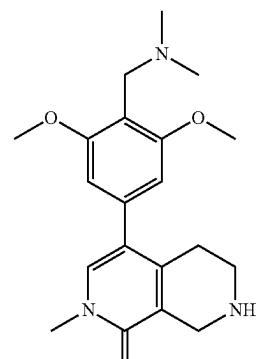
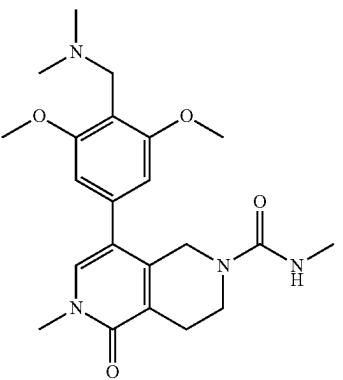
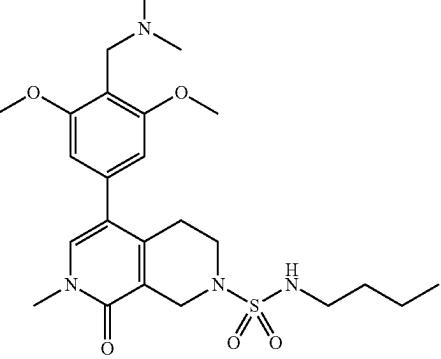
Compounds B1-B21 of the Disclosure	
Compound No.	Structure



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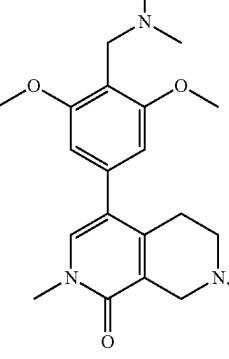
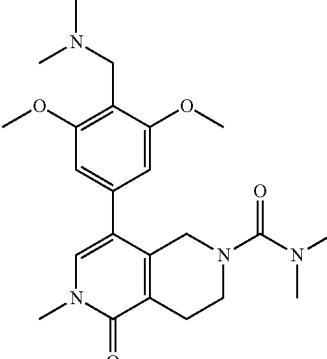
35

TABLE 1A-continued

Compounds B1-B21 of the Disclosure	
Compound No.	Structure
B16	
B17	
B18	
B19	

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TABLE 1A-continued

Compounds B1-B21 of the Disclosure	
Compound No.	Structure
B20	
B21	

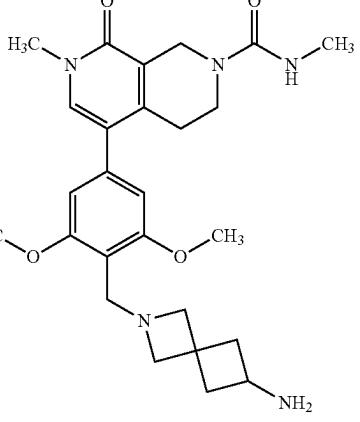
Compounds B22-B24 of the Disclosure	
Compound No.	Structure
B22	

TABLE 1B

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TABLE 1B-continued

Compounds B22-B24 of the Disclosure

Compound No.	Structure	
B23		5 10 15
B24		20 25 30 35

In another aspect, the disclosure features a compound having the structure of Formula II:

A-L-B

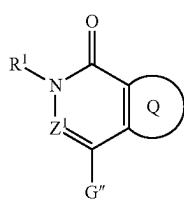
Formula II,

where

B is a degradation moiety,

L is a linker, and

A has the structure of Formula III:



where

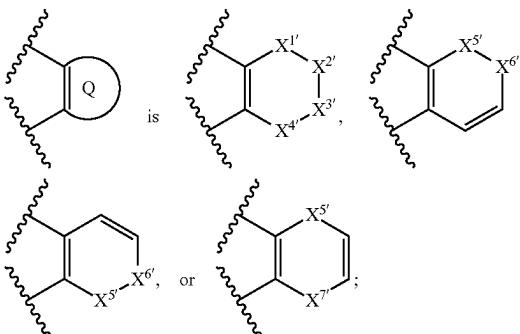
R¹ is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₁₀ carbocyclyl;

Z¹ is CR² or N;

R² is H, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally

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substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, or optionally substituted C₂-C₉ heteroaryl;



X¹' is a bond, O, NR^{3a1}, or CR^{4a1}R^{5a1};
 X²' is O, NR^{3b1}, or CR^{4b1}R^{5b1};
 X³' is O, NR^{3c1}, or CR^{4c1}R^{5c1};
 X⁴' is a bond, O, NR^{3d1}, or CR^{4d1}R^{5d1};
 X⁵' is O, NR^{3e1}, or CR^{4e1}R^{5e1};
 X⁶' is O, NR^{3f1}, or CR^{4f1}R^{5f1};
 X⁷' is O, NR^{3g1}, or CR^{4g1}R^{5g1};
 each of R^{3a1}, R^{3b1}, R^{3c1}, and R^{3d1} is, independently, H,



halogen, hydroxyl, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, optionally substituted C₁-C₆ acyl, thiol, optionally substituted sulfone, optionally substituted sulfonamide, or optionally substituted amino, or R^{3a1} and R^{4b1}, R^{4a1} and R^{3b1}, R^{4b1} and R^{4a1}, R^{3b1} and R^{4c1}, R^{4b1} and R^{4c1}, R^{3c1} and R^{4b1}, R^{3c1} and R^{4d1}, R^{4c1} and R^{4d1}, and/or R^{3d1} and R^{4c1}, together with the atoms to which each is attached, combine to form optionally substituted C₂-C₉ heterocyclyl;

R³' is absent, optionally substituted C₁-C₆ alkylene, optionally substituted C₁-C₆ heteroalkylene, optionally substituted C₃-C₁₀ carbocyclylene, optionally substituted C₂-C₉ heterocyclylene, optionally substituted C₆-C₁₀ arylene, optionally substituted C₂-C₉ heteroarylene, optionally substituted C₂-C₆ alkenylene, optionally substituted C₂-C₆ heteroalkenylene, optionally substituted sulfone, optionally substituted sulfonamide, or optionally substituted amino;

each of R^{4a1}, R^{4b1}, R^{4c1}, and R^{4d1} is, independently, H, halogen, hydroxyl, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, thiol, optionally substituted sulfone, or optionally substituted amino, or R^{3a1} and R^{4b1}, R^{4a1} and

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R^{3b_1} , R^{4b_1} and R^{4a_1} , R^{3b_1} and R^{4c_1} , R^{4b_1} and R^{4c_1} , R^{3c_1} and R^{4b_1} , R^{3c_1} and R^{4d_1} , R^{4c_1} and R^{4d_1} , and/or R^{3d_1} and R^{4c_1} , together with the atoms to which each is attached, combine to form optionally substituted C_2 - C_9 heterocyclyl;

each of R^{5a_1} , R^{5b_1} , R^{5c_1} , and R^{5d_1} is, independently, H, halogen, hydroxyl, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heterocyclyl, optionally substituted C_6 - C_{10} aryl, optionally substituted C_2 - C_9 heteroaryl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 heteroalkenyl, hydroxyl, thiol, or optionally substituted amino;

each of R^{3e_1} , R^{3f_1} , and R^{3g_1} is, independently, H,



halogen, hydroxyl, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heterocyclyl, optionally substituted C_6 - C_{10} aryl, optionally substituted C_2 - C_9 heteroaryl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 heteroalkenyl, optionally substituted C_1 - C_6 acyl, thiol, optionally substituted sulfone, optionally substituted sulfonamide, or optionally substituted amino, or R^{3e} and R^{4f} or R^{4e} and R^{3f} , together with the atoms to which each is attached, combine to form optionally substituted heterocyclyl;

each of R^{4e_1} , R^{4f_1} , and R^{4g_1} is, independently, H, halogen, hydroxyl, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heterocyclyl, optionally substituted C_6 - C_{10} aryl, optionally substituted C_2 - C_9 heteroaryl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 heteroalkenyl, optionally substituted C_1 - C_6 acyl, thiol, optionally substituted sulfone, optionally substituted sulfonamide, or optionally substituted amino, or R^{3e_1} and R^{4f_1} or R^{4e_1} and R^{3f_1} , together with the atoms to which each is attached, combine to form optionally substituted heterocyclyl;

each of R^{5e_1} , R^{5f_1} , and R^{5g_1} is, independently, H, halogen, hydroxyl, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heterocyclyl, optionally substituted C_6 - C_{10} aryl, optionally substituted C_2 - C_9 heteroaryl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 heteroalkenyl, hydroxyl, thiol, or optionally substituted amino;

G'' is

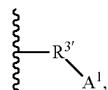


optionally substituted C_6 - C_{10} aryl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heteroaryl, or C_2 - C_9 heterocyclyl;

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G' is optionally substituted C_3 - C_{10} carbocyclene, C_2 - C_9 heterocyclene, optionally substituted C_6 - C_{10} arylene, or optionally substituted C_2 - C_9 heteroarylene; and

A^1 is a bond between A and the linker, where one of R^{3a_1} , R^{3b_1} , R^{3c_1} , R^{3d_1} , R^{3e_1} , R^{3f_1} , and R^{3g_1} is

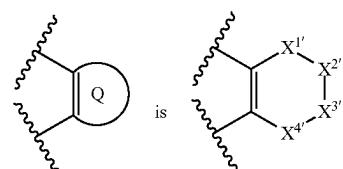


or G is

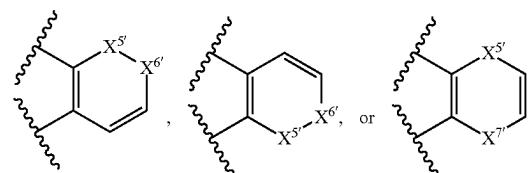
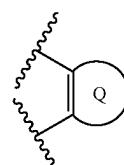


or a pharmaceutically acceptable salt thereof.

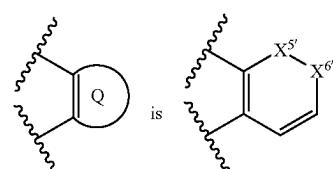
In some embodiments,



In some embodiments,



In some embodiments,



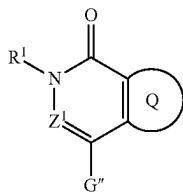
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In another aspect, the disclosure features a compound having the structure of Formula II:

A-L-B

where

B is a degradation moiety,
L is a linker, and
A has the structure of Formula III:



Formula II,

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Formula III

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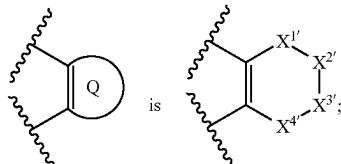
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G'' is

R¹ is, independently, H, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₁₀ carbocyclyl;

Z¹ is CR² or N;

R² is H, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, or optionally substituted C₂-C₉ heteroaryl;



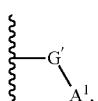
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X^{1t} is a bond, O, NR^{3a}, or CR^{4a}R^{5a};
X^{2t} is O, NR^{3b}, or CR^{4b}R^{5b};
X^{3t} is O, NR^{3c}, or CR^{4c}R^{5c};
X^{4t} is a bond, O, NR^{3d}, or CR^{4d}R^{5d};
each of R^{3a}, R^{3b}, R^{3c}, and R^{3d} is, independently, H,



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A¹ is a bond between A and the linker,
where one of R^{3a}, R^{3b}, R^{3c}, and R^{3d} is

optionally substituted C₆-C₁₀ aryl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heteroaryl, or C₂-C₉ heterocyclyl;

G' is optionally substituted C₃-C₁₀ carbocyclene, C₂-C₉ heterocyclene, optionally substituted C₆-C₁₀ arylene, or optionally substituted C₂-C₉ heteroarylene; and

A¹ is a bond between A and the linker,
where one of R^{3a}, R^{3b}, R^{3c}, and R^{3d} is



or G is



or a pharmaceutically acceptable salt thereof.

halogen, hydroxyl, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, optionally substituted C₁-C₆ acyl, thiol, optionally substituted sulfone, optionally substituted sulfonamide, or optionally substituted amino, or R^{3a} and R^{4a}, R^{4a} and R^{3b}, R^{4b} and R^{4a}, R^{4b} and R^{3b}, R^{4c} and R^{4b}, R^{4c} and R^{3c}, and/or R^{3d} and R^{4c}, together with the atoms to which each is attached, combine to form optionally substituted C₂-C₉ heterocyclyl;

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R^{3t} is absent, optionally substituted C₁-C₆ alkylene, optionally substituted C₁-C₆ heteroalkylene, optionally substituted C₃-C₁₀ carbocyclylene, optionally substituted C₂-C₉ heterocyclylene, optionally substituted C₆-C₁₀ arylene, optionally substituted C₂-C₉ heteroarylene, optionally substituted C₂-C₆ alkenylene, optionally substituted C₂-C₆ heteroalkenylene, optionally substituted sulfone, optionally substituted sulfonamide, or optionally substituted amino;

each of R^{4a}, R^{4b}, R^{4c}, and R^{4d} is, independently, H, halogen, hydroxyl, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, thiol, optionally substituted sulfone, or optionally substituted amino, or R^{3a} and R^{4b}, R^{4a} and R^{3b}, R^{4c} and R^{4b}, R^{3c} and R^{4b}, R^{3b} and R^{4a}, R^{3b} and R^{4c}, and/or R^{3d} and R^{4c}, together with the atoms to which each is attached, combine to form optionally substituted C₂-C₉ heterocyclyl;

each of R^{5a}, R^{5b}, R^{5c}, and R^{5d} is, independently, H, halogen, hydroxyl, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, hydroxyl, thiol, or optionally substituted amino;

G'' is

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C is optionally substituted C₃-C₁₀ carbocyclene, C₂-C₉ heterocyclene, optionally substituted C₆-C₁₀ arylene, or optionally substituted C₂-C₉ heteroarylene; and

A¹ is a bond between A and the linker,
where one of R^{3a}, R^{3b}, R^{3c}, and R^{3d} is

or G is

or a pharmaceutically acceptable salt thereof.

In some embodiments, R¹ is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₁₀ carbocyclyl. In some embodiments, R¹ is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, or optionally substituted C₃-C₁₀

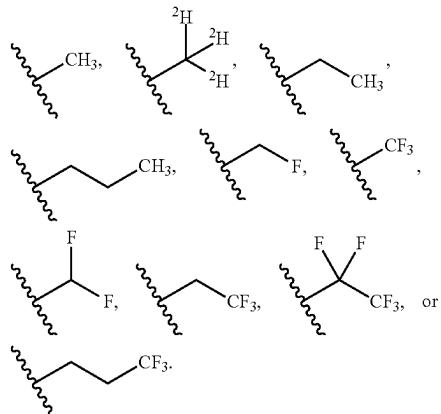
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carbocyclyl. In some embodiments, R¹ is H, optionally substituted C₁-C₆ alkyl, or optionally substituted C₃-C₁₀ carbocyclyl.

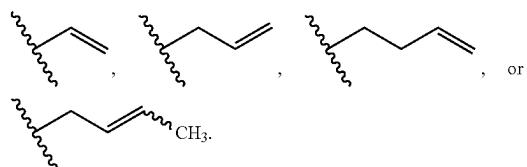
In some embodiments, R¹ is H. In some embodiments, R¹ is optionally substituted C₁-C₆ alkyl. In some embodiments, R¹ is optionally substituted C₂-C₆ alkenyl. In some embodiments, R¹ is optionally substituted C₃-C₁₀ carbocyclyl.

In some embodiments, optionally substituted C₁-C₆ alkyl is C₁-C₆ perfluoroalkyl.

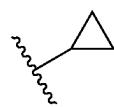
In some embodiments, R¹ is



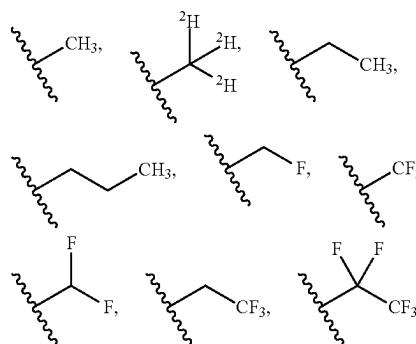
In some embodiments, R¹ is



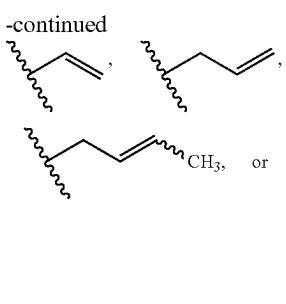
In some embodiments, R¹ is



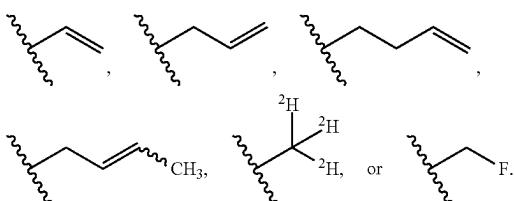
In some embodiments, R¹ is H,



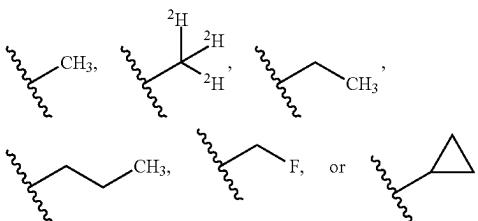
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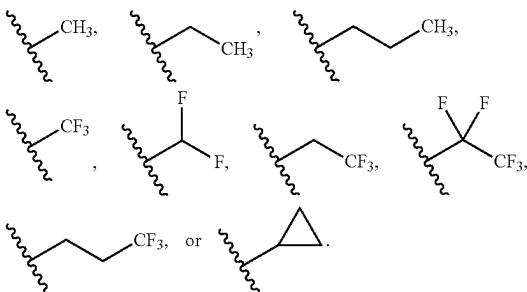
In some embodiments, R¹ is



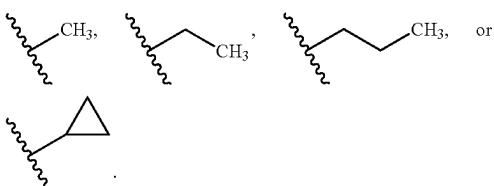
In some embodiments, R¹ is H,



In some embodiments, R¹ is H,



In some embodiments, R¹ is H,



45In some embodiments, R¹ is H or

In some embodiments, R¹ is H. In some embodiments, R¹ is
is



In some embodiments, Z¹ is CR². In some embodiments,
Z¹ is N.

In some embodiments, R² is H, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₁₀ carbocyclic, or optionally substituted C₆-C₁₀ aryl.

In some embodiments, R² is H, halogen, or optionally substituted C₁-C₆ alkyl.

In some embodiments, R² is H, F, or

In some embodiments, R² is H. In some embodiments, R² is
is F. In some embodiments, R² is



In some embodiments, X^{1t} is a bond. In some embodiments, X^{1t} is O, NR^{3a1}, or CR^{4a1}R^{5a1}. In some embodiments, X^{1t} is O or NR^{3a1}. In some embodiments, X^{1t} is NR^{3a1} or CR^{4a1}R^{5a1}.

In some embodiments, X^{2t} is O or NR^{3b1}. In some embodiments, X^{2t} is CR^{4b1}R^{5b1}. In some embodiments, X^{2t} is NR^{3b1} or CR^{4b1}R^{5b1}.

In some embodiments, X^{3t} is O or NR^{3c1}. In some embodiments, X^{3t} is CR^{4c1}R^{5c1}. In some embodiments, X^{3t} is NR^{3c1} or CR^{4c1}R^{5c1}.

In some embodiments, X^{4t} is a bond. In some embodiments, X^{4t} is O, NR^{3d1}, or CR^{4d1}R^{5d1}. In some embodiments, X^{4t} is O or NR^{3d1}. In some embodiments, X^{4t} is NR^{3d1} or CR^{4d1}R^{5d1}.

In some embodiments, X^{1t} is O, NR^{3a1}, or CR^{4a1}R^{5a1}; X^{2t} is O, NR^{3b1}, or CR^{4b1}R^{5b1}; X^{3t} is O, NR^{3c1}, or CR^{4c1}R^{5c1}; and X^{4t} is O, NR^{3d1}, or CR^{4d1}R^{5d1}.

In some embodiments, X^{1t} is CR^{4a1}R^{5a1}; X^{2t} is NR^{3b1}; X^{3t} is CR^{4c1}R^{5c1}; and X^{4t} is CR^{4d1}R^{5d1}.

In some embodiments, X^{1t} is CR^{4a1}R^{5a1}; X^{2t} is CR^{4b1}R^{5b1}; X^{3t} is NR^{3c1}; and X^{4t} is CR^{4d1}R^{5d1}.

In some embodiments, X^{1t} is O or NR^{3a1}; X^{2t} is CR^{4b1}R^{5b1}; X^{3t} is CR^{4c1}R^{5c1}; and X^{4t} is O or NR^{3d1}.

In some embodiments, X^{1t} is a bond; X^{2t} is CR^{4b1}R^{5b1}; X^{3t} is O or NR^{3c1}; and X^{4t} is CR^{4d1}R^{5d1}.

In some embodiments, X^{1t} is CR^{4a1}R^{5a1}; X^{2t} is CR^{4b1}R^{5b1}; X^{3t} is CR^{4c1}R^{5c1}; and X^{4t} is CR^{4d1}R^{5d1}.

46In some embodiments, X^{5t} is CR^{4et}R^{5et} and X^{6t} is NR^{3f}.In some embodiments, each of R^{3a1}, R^{3b1}, R^{3c1}, and R^{3d1} is, independently, H,

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optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₁-C₆ acyl, optionally substituted sulfone, or optionally substituted sulfonamide. In some embodiments, each of R^{3a1}, R^{3b1}, R^{3c1}, and R^{3d1} is, independently, H,



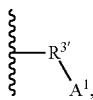
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optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted sulfone, or optionally substituted sulfonamide. In some embodiments, each of R^{3a1}, R^{3b1}, R^{3c1}, and R^{3d1} is, independently, H,



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optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ acyl, optionally substituted sulfone, or optionally substituted sulfonamide. In some embodiments, each of R^{3a1}, R^{3b1}, R^{3c1}, and R^{3d1} is, independently, H,



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optionally substituted C₁-C₆ alkyl, or optionally substituted C₁-C₆ acyl.

In some embodiments, each of R^{3a1}, R^{3b1}, R^{3c1}, and R^{3d1} is, independently,



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optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₁-C₆ acyl, optionally substituted sulfone, or optionally substituted sulfonamide. In some embodiments, each of R^{3a1}, R^{3b1}, R^{3c1}, and R^{3d1} is, independently,



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optionally substituted C₁-C₆ alkyl, or optionally substituted C₁-C₆ acyl.

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optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ acyl, optionally substituted sulfone, or optionally substituted sulfonamide.

In some embodiments, each of R^{3a1}, R^{3b1}, R^{3c1}, and R^{3d1} is, independently,



optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₁-C₆ acyl. In some embodiments, each of R^{3a1}, R^{3b1}, R^{3c1}, and R^{3d1} is, independently,



optionally substituted C₁-C₆ alkyl or optionally substituted C₁-C₆ heteroalkyl. In some embodiments, each of R^{3a1}, R^{3b1}, R^{3c1}, and R^{3d1} is, independently,



optionally substituted C₁-C₆ alkyl or optionally substituted C₁-C₆ acyl. In some embodiments, each of R^{3a1}, R^{3b1}, R^{3c1}, and R^{3d1} is, independently,



or optionally substituted C₁-C₆ acyl. In some embodiments, each of R^{3a1}, R^{3c1}, R^{3d1}, and R^{3d1} is, independently,

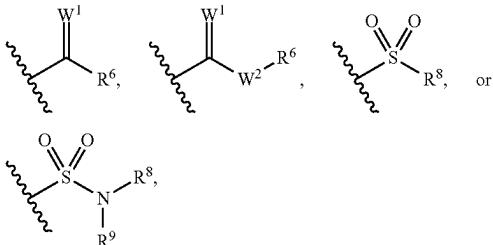


optionally substituted sulfone, or optionally substituted sulfonamide.

In some embodiments, each of R^{3a1}, R^{3b1}, R^{3c1}, and R^{3d1} is, independently, H,

**48**

optionally substituted C₁-C₆ alkyl,



where

R⁶ is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, or optionally substituted C₆-C₁₀ aryl;

W¹ is O or S;

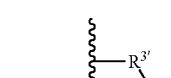
W² is NR⁷ or O;

R⁷ is H, optionally substituted C₁-C₆ alkyl, or optionally substituted C₁-C₆ heteroalkyl;

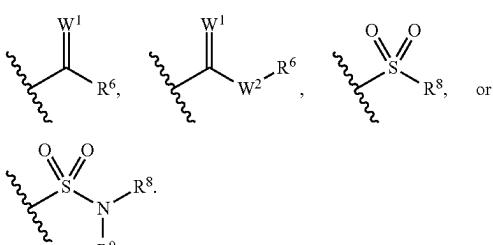
R⁸ is optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, or optionally substituted C₆-C₁₀ aryl; and

R⁹ is H, optionally substituted C₁-C₆ alkyl, or optionally substituted C₁-C₆ heteroalkyl.

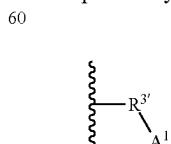
In some embodiments, each of R^{3a1}, R^{3b1}, R^{3c1}, and R^{3d1} is, independently,



C₁-C₆ alkyl,

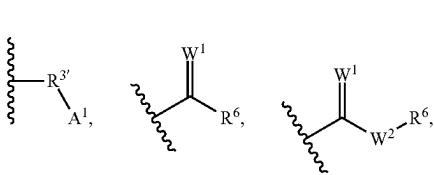


In some embodiments, each of R^{3a1}, R^{3b1}, R^{3c1}, and R^{3d1} is, independently,

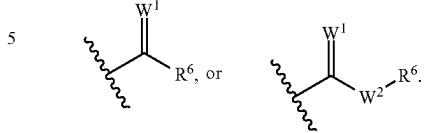


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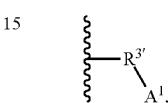
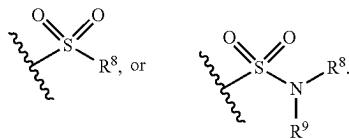
or C₁-C₆ alkyl. In some embodiments, each of R^{3a1}, R^{3b1}, R^{3c1}, and R^{3d1} is, independently



optionally substituted C₁-C₆ alkyl,

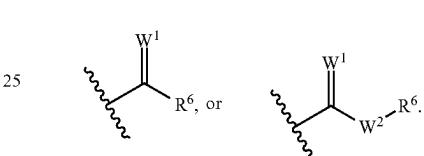
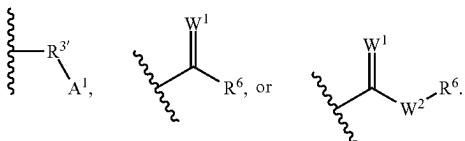
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In some embodiments, each of R^{3a1}, R^{3b1}, R^{3c1}, and R^{3d1} is, independently, H,



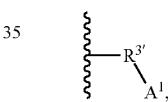
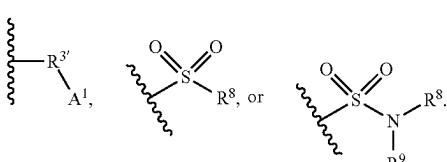
In some embodiments, each of R^{3a1}, R^{3b1}, R^{3c1}, and R^{3d1} is, independently,

C₁-C₆ alkyl,



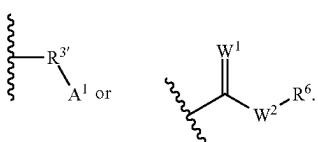
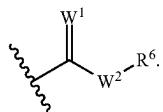
In some embodiments, each of R^{3a1}, R^{3b1}, R^{3c1}, and R^{3d1} is, independently,

In some embodiments, each of R^{3a1}, R^{3b1}, R^{3c1}, and R^{3d1} is, independently, H,

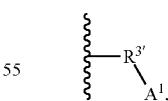


In some embodiments, each of R^{3a1}, R^{3b1}, R^{3c1}, and R^{3d1} is, independently,

C₁-C₆ alkyl, or



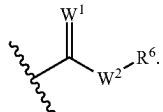
In some embodiments, each of R^{3a1}, R^{3b1}, R^{3c1}, and R^{3d1} is, independently,



In some embodiments, each of R^{3a1}, R^{3b1}, R^{3c1}, and R^{3d1} is, independently, H,

C₁-C₆ alkyl, or

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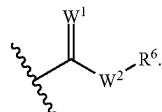
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In some embodiments, each of R^{3a} , R^{3b} , R^{3c} , and R^{3d} is, independently, H,



methyl, or



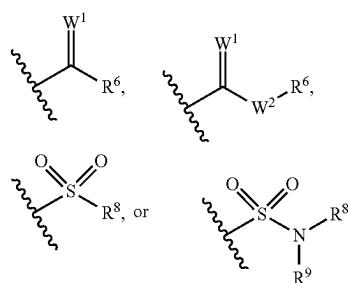
In some embodiments, each of R^{3a} , R^{3b} , R^{3c} , and R^{3d} is, independently



or optionally substituted C_1 - C_6 alkyl.

In some embodiments, each of R^{4a} , R^{4b} , R^{4c} , and R^{4d} is, independently, H, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_1 - C_6 acyl, optionally substituted sulfone, or optionally substituted sulfonamide. In some embodiments, each of R^{4a} , R^{4b} , R^{4c} , and R^{4d} is, independently, H, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted sulfone, or optionally substituted sulfonamide. In some embodiments, each of R^{4a} , R^{4b} , R^{4c} , and R^{4d} is H. In some embodiments, each of R^{4a} , R^{4b} , R^{4c} , and R^{4d} is, independently, H, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 acyl, optionally substituted sulfone, or optionally substituted sulfonamide. In some embodiments, each of R^{4a} , R^{4b} , R^{4c} , and R^{4d} is, independently, H, optionally substituted C_1 - C_6 alkyl, or optionally substituted C_1 - C_6 acyl.

In some embodiments, each of R^{4a} , R^{4b} , R^{4c} , and R^{4d} is, independently, H, optionally substituted C_1 - C_6 alkyl,



where

R^6 is H, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_3 - C_{10} carbocyclyl, or optionally substituted C_6 - C_{10} aryl;

W^1 is O or S;

W^2 is NR^7 or O;

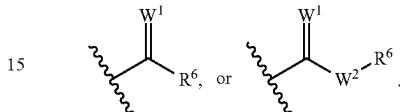
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R^7 is H, optionally substituted C_1 - C_6 alkyl, or optionally substituted C_1 - C_6 heteroalkyl;

R^8 is optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_3 - C_{10} carbocyclyl, or optionally substituted C_6 - C_{10} aryl; and

R^9 is H, optionally substituted C_1 - C_6 alkyl, or optionally substituted C_1 - C_6 heteroalkyl.

In some embodiments, each of R^{4a} , R^{4b} , R^{4c} , and R^{4d} is, independently, H, optionally substituted C_1 - C_6 alkyl,



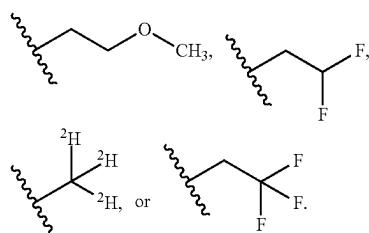
In some embodiments, each of R^{4a} , R^{4b} , R^{4c} , and R^{4d} is, independently, H or optionally substituted C_1 - C_6 alkyl. In some embodiments, each of R^{4a} , R^{4b} , R^{4c} , and R^{4d} is, independently, H.

In some embodiments, W^1 is O. In some embodiments, W^1 is S.

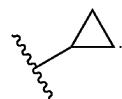
In some embodiments, W^2 is O. In some embodiments, W^2 is NR^7 .

In some embodiments, R^6 is H, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, or optionally substituted C_3 - C_{10} carbocyclyl. In some embodiments, R^6 is H, optionally substituted C_1 - C_6 alkyl, or optionally substituted C_1 - C_6 heteroalkyl. In some embodiments, R^6 is H, optionally substituted C_3 - C_{10} carbocyclyl, or optionally substituted C_6 - C_{10} aryl. In some embodiments, R^6 is optionally substituted C_1 - C_6 alkyl or optionally substituted C_1 - C_6 heteroalkyl. In some embodiments, R^6 is optionally substituted C_3 - C_{10} carbocyclyl or optionally substituted C_6 - C_{10} aryl

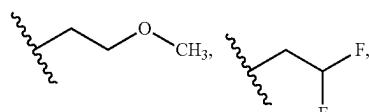
In some embodiments, R^6 is H, methyl, ethyl,



In some embodiments, R^6 is H or

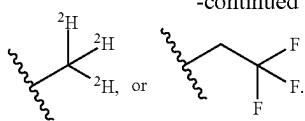
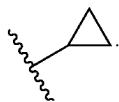
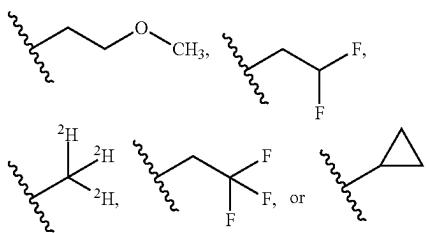


In some embodiments, R^6 is methyl, ethyl,



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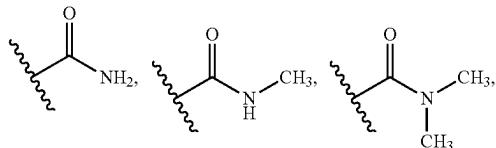
-continued

In some embodiments, R⁶ is orIn some embodiments, R⁶ is H. In some embodiments, R⁶ is H, methyl, ethyl,In some embodiments, R⁷ is H or optionally substituted C₁-C₆ alkyl. In some embodiments, R⁷ is H or methyl.In some embodiments, each of R^{3a1}, R^{3b1}, R^{3c1}, and R^{3d1} is, independently, H,

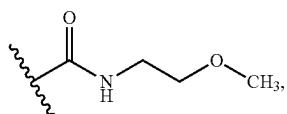
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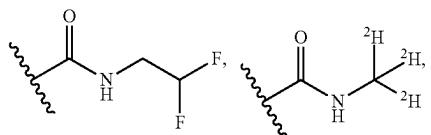
10 methyl,



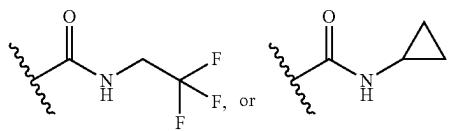
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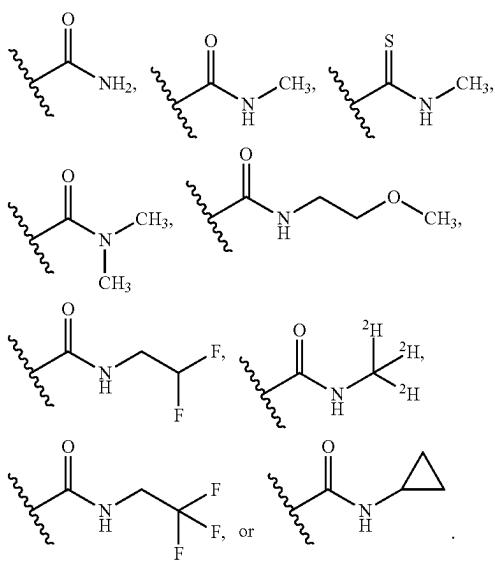
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In some embodiments, R⁷ is H or optionally substituted C₁-C₆ alkyl. In some embodiments, R⁷ is H or methyl.In some embodiments, each of R^{3a1}, R^{3b1}, R^{3c1}, and R^{3d1} is, independently, H,

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In some embodiments, R^{3a1} is H,

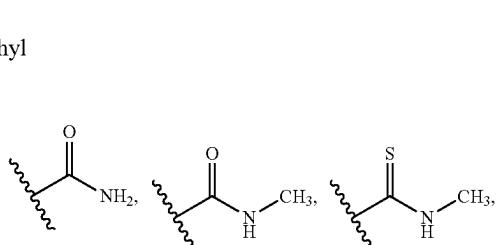
methyl,



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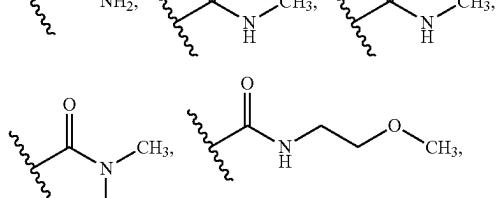


45 methyl



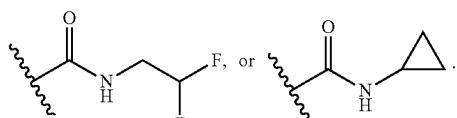
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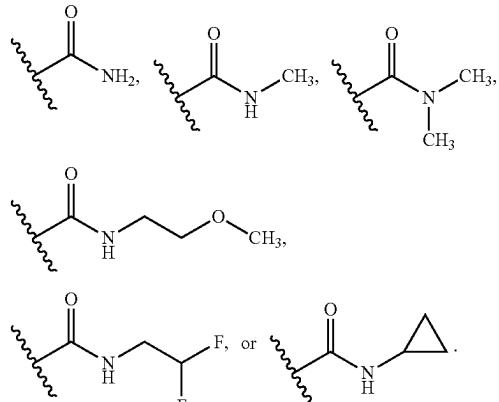
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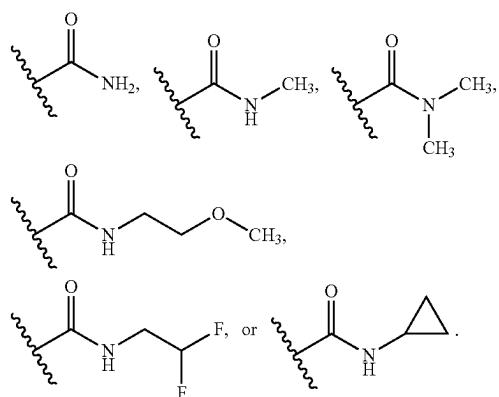


55In some embodiments, R^{3b1} is H,

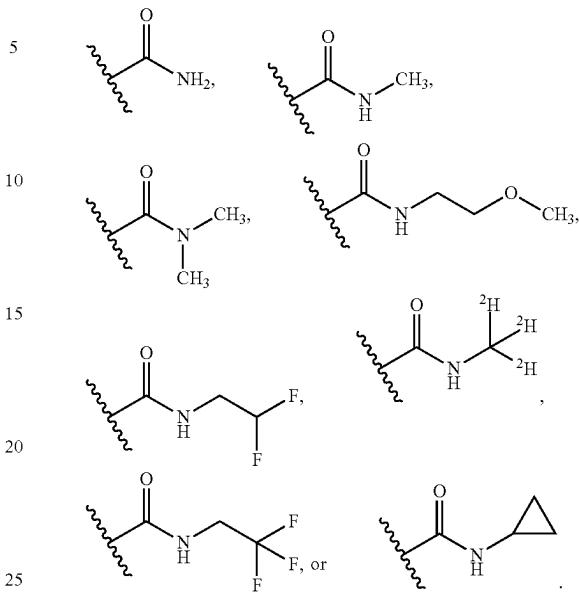
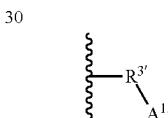
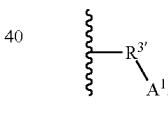
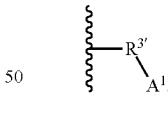
methyl,

In some embodiments, R^{3c1} is H

methyl,

In some embodiments, R^{3d1} is H,**56**

methyl,

In some embodiments, one of R^{3a1}, R^{3b1}, R^{3c1}, and R^{3d1} isIn some embodiments, R^{3b1} isIn some embodiments, R^{3c1} isIn some embodiments, R³ⁱ is absent.

In some embodiments, R^{3a1} and R^{4b1}, R^{4a1} and R^{3b1}, R^{3b1} and R^{4b1}, R^{4a1} and R^{4c1}, R^{3b1} and R^{4c1}, R^{3c1} and R^{4b1}, R^{3c1} and R^{4d1}, R^{4c1} and R^{4d1}, and/or R^{3d1} and R^{4c1}, together with the atoms to which each is attached, combine to form optionally substituted C₂-C₉ heterocyclyl.

In some embodiments, R^{3a1} and R^{4b1}, R^{4a1} and R^{3b1}, R^{3b1} and R^{4b1}, R^{4a1} and R^{3c1}, R^{3c1} and R^{4d1}, and/or R^{4c1} and R^{3d1}, together with the atoms to which each is attached, combine to form optionally substituted C₂-C₉ heterocyclyl.

In some embodiments, each of R^{5a}, R^{5b}, R^{5c}, and R^{5d} is, independently, H, optionally substituted C₁-C₆ alkyl, or optionally substituted C₁-C₆ heteroalkyl. In some embodiments, each of R^{5a}, R^{5b}, R^{5c}, and R^{5d} is H.

In some embodiments, each of R^{3e1} , R^{3f1} , and R^{3g1} is, independently H,



optionally substituted $C_1\text{-}C_6$ alkyl, optionally substituted $C_1\text{-}C_6$ heteroalkyl, optionally substituted $C_1\text{-}C_6$ acyl, optionally substituted sulfone, or optionally substituted sulfonamide.

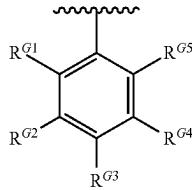
In some embodiments, each of R^{4e1} , R^{4f1} , and R^{4g1} is, independently H, optionally substituted $C_1\text{-}C_6$ alkyl, optionally substituted $C_1\text{-}C_6$ heteroalkyl, optionally substituted $C_1\text{-}C_6$ acyl, optionally substituted sulfone, or optionally substituted sulfonamide.

In some embodiments, each of R^{5e1} , R^{5f1} , and R^{5g1} is, independently H, optionally substituted $C_1\text{-}C_6$ alkyl, or optionally substituted $C_1\text{-}C_6$ heteroalkyl. In some embodiments, each of R^{5e1} , R^{5f1} , and R^{5g1} is H.

In some embodiments, G'' is optionally substituted $C_3\text{-}C_{10}$ carbocycl or optionally substituted $C_2\text{-}C_9$ heterocycl. In some embodiments, G'' is optionally substituted $C_6\text{-}C_{10}$ aryl or optionally substituted $C_2\text{-}C_9$ heteroaryl.

In some embodiments, G'' is optionally substituted $C_3\text{-}C_{10}$ carbocycl. In some embodiments, G is optionally substituted $C_6\text{-}C_{10}$ aryl. In some embodiments, G is optionally substituted $C_2\text{-}C_9$ heterocycl. In some embodiments, G'' is optionally substituted $C_2\text{-}C_9$ heteroaryl.

In some embodiments, G'' is



where

each of R^{G1} , R^{G2} , R^{G3} , R^{G4} , and R^{G5} is, independently H, halogen, optionally substituted $C_1\text{-}C_6$ alkyl, optionally substituted $C_1\text{-}C_6$ heteroalkyl, optionally substituted $C_3\text{-}C_{10}$ carbocycl, optionally substituted $C_2\text{-}C_9$ heterocycl, optionally substituted $C_6\text{-}C_{10}$ aryl, optionally substituted $C_2\text{-}C_9$ heteroaryl, optionally substituted $C_2\text{-}C_6$ alkenyl, optionally substituted $C_2\text{-}C_6$ heteroalkenyl, optionally substituted $O\text{-}C_3\text{-}C_6$ carbocycl, optionally substituted $C_1\text{-}C_3$ alkyl- $C_3\text{-}C_6$ carbocycl, optionally substituted $C_1\text{-}C_3$ alkyl- $C_2\text{-}C_5$ heterocycl, hydroxyl, thiol, or optionally substituted amino; or R^{G1} and R^{G2} , R^{G2} and R^{G3} , R^{G3} and R^{G4} , and/or R^{G4} and R^{G5} , together with the carbon atoms to which each is attached, combine to form optionally substituted $C_6\text{-}C_{10}$ aryl, optionally substituted $C_3\text{-}C_{10}$ carbocycl, optionally substituted $C_2\text{-}C_9$ heteroaryl, or optionally substituted $C_2\text{-}C_9$ heterocycl.

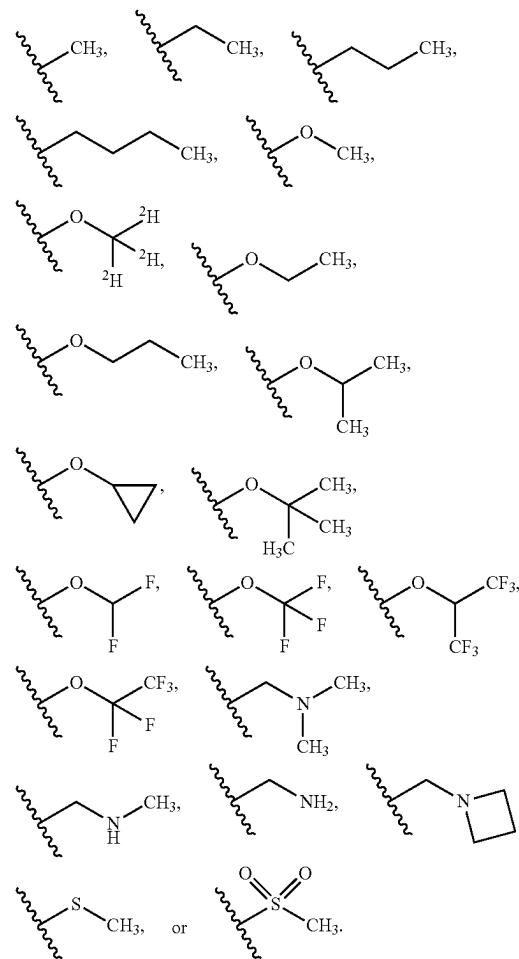
In some embodiments, each of R^{G1} , R^{G2} , R^{G3} , R^{G4} , and R^{G5} is, independently H, halogen, optionally substituted $C_1\text{-}C_6$ alkyl, optionally substituted $C_1\text{-}C_6$ heteroalkyl, optionally substituted $C_3\text{-}C_{10}$ carbocycl, optionally substituted $C_2\text{-}C_9$ heterocycl, optionally substituted $C_6\text{-}C_{10}$ aryl, optionally substituted $C_2\text{-}C_9$ heteroaryl, optionally substi-

tuted $C_2\text{-}C_6$ alkenyl, optionally substituted $C_2\text{-}C_6$ heteroalkenyl, optionally substituted $O\text{-}C_3\text{-}C_6$ carbocycl, optionally substituted $C_1\text{-}C_3$ alkyl- $C_3\text{-}C_6$ carbocycl, optionally substituted $C_1\text{-}C_3$ alkyl- $C_2\text{-}C_5$ heterocycl, hydroxyl, thiol, or optionally substituted amino; or R^{G1} and R^{G2} , R^{G2} and R^{G3} , R^{G3} and R^{G4} , and/or R^{G4} and R^{G5} , together with the carbon atoms to which each is attached, combine to form optionally substituted $C_6\text{-}C_{10}$ aryl, optionally substituted $C_3\text{-}C_{10}$ carbocycl, optionally substituted $C_2\text{-}C_9$ heteroaryl, or optionally substituted $C_2\text{-}C_9$ heterocycl.

In some embodiments, each of R^{G1} , R^{G2} , R^{G3} , R^{G4} , and R^{G5} is, independently H, halogen, optionally substituted $C_1\text{-}C_6$ alkyl, optionally substituted $C_1\text{-}C_6$ heteroalkyl, optionally substituted $O\text{-}C_3\text{-}C_6$ carbocycl, or optionally substituted $C_1\text{-}C_3$ alkyl- $C_2\text{-}C_5$ heterocycl; or R^{G1} and R^{G2} , R^{G2} and R^{G3} , R^{G3} and R^{G4} , and/or R^{G4} and R^{G5} , together with the carbon atoms to which each is attached, combine to form optionally substituted $C_2\text{-}C_9$ heteroaryl or optionally substituted $C_2\text{-}C_9$ heterocycl.

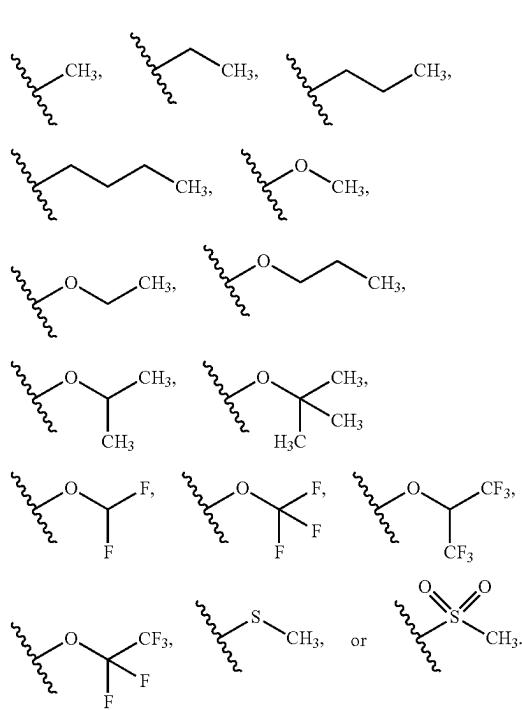
In some embodiments, each of R^{G1} , R^{G2} , R^{G3} , R^{G4} , and R^{G5} is, independently H, halogen, optionally substituted $C_1\text{-}C_6$ alkyl, optionally substituted $C_1\text{-}C_6$ heteroalkyl, optionally substituted $O\text{-}C_3\text{-}C_6$ carbocycl, or optionally substituted $C_1\text{-}C_3$ alkyl- $C_2\text{-}C_5$ heterocycl.

In some embodiments, each of R^{G1} , R^{G2} , R^{G3} , R^{G4} , and R^{G5} is, independently H, F, Cl,

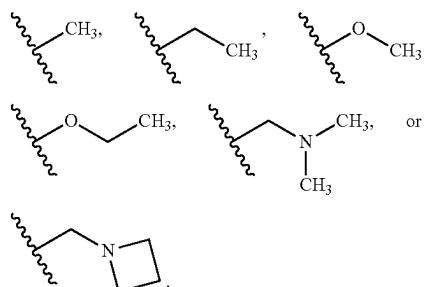


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In some embodiments, each of R^{G1} , R^{G2} , R^{G3} , R^{G4} and R^{G5} is, independently, H, F

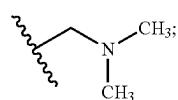


In some embodiments, each of R^{G1} , R^{G2} , R^{G3} , R^{G4} , and R^{G5} is, independently, H, F, Cl,

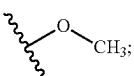


In some embodiments, R^{G1} is H; R^{G2} is

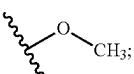
R^{G3} is

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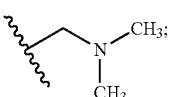
R^{G4} is



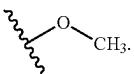
and R^{G5} is H. In some embodiments, R^{G1} is H; R^{G2} is



R^{G3} is

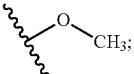


R^{G4} is H; and R^{G5} is

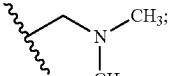


In some embodiments, R^{G1} is H; R^{G2} is

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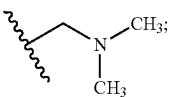
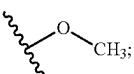
R^{G3} is



50 R^{G4} is Cl or F; and R^{G5} is H. In some embodiments, R^{G1} is H; R^{G2} is

R^{G3} is

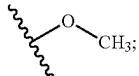
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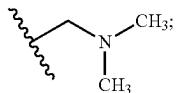
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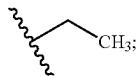
R^{G4} is H; and R^{G5} is H. In some embodiments, R^{G1} is H; R^{G2} is is



R^{G3} is



R^{G4} is



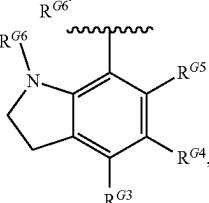
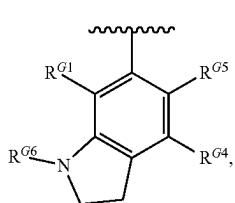
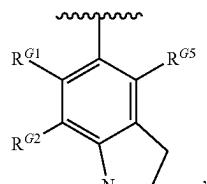
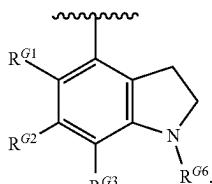
and R^{G5} is H.

In some embodiments, R^{G1} and R^{G2} , R^{G2} and R^{G3} , R^{G3} and R^{G4} , and/or R^{G4} and R^{G5} , together with the carbon atoms to which each is attached, combine to form optionally substituted C_2 - C_9 heteroaryl or optionally substituted C_2 - C_9 heterocyclyl.

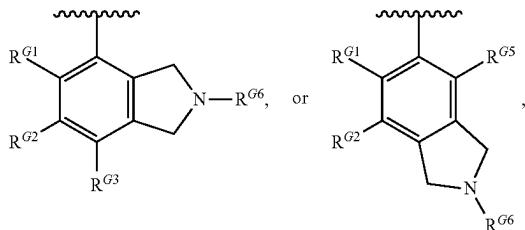
In some embodiments, R^{G1} and R^{G2} , R^{G2} and R^{G3} , R^{G3} and R^{G4} , and/or R^{G4} and R^{G5} , together with the carbon atoms to which each is attached, combine to form optionally substituted C_2 - C_9 heterocyclyl. In some embodiments, R^{G1} and R^{G2} , R^{G2} and R^{G3} , R^{G3} and R^{G4} , and/or R^{G4} and R^{G5} , together with the carbon atoms to which each is attached, combine to form optionally substituted C_2 - C_9 heteroaryl.

In some embodiments, R^{G1} and R^{G2} , R^{G2} and R^{G3} , R^{G3} and R^{G4} , and/or R^{G4} and R^{G5} , together with the carbon atoms to which each is attached, combine to form optionally substituted C_2 - C_9 heterocyclyl. In some embodiments, R^{G1} and R^{G2} , R^{G2} and R^{G3} , R^{G3} and R^{G4} , and/or R^{G4} and R^{G5} , together with the carbon atoms to which each is attached, combine to form optionally substituted C_2 - C_9 heteroaryl.

In some embodiments, G'' is

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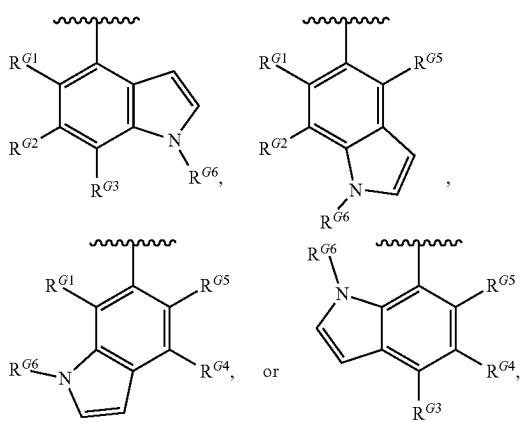
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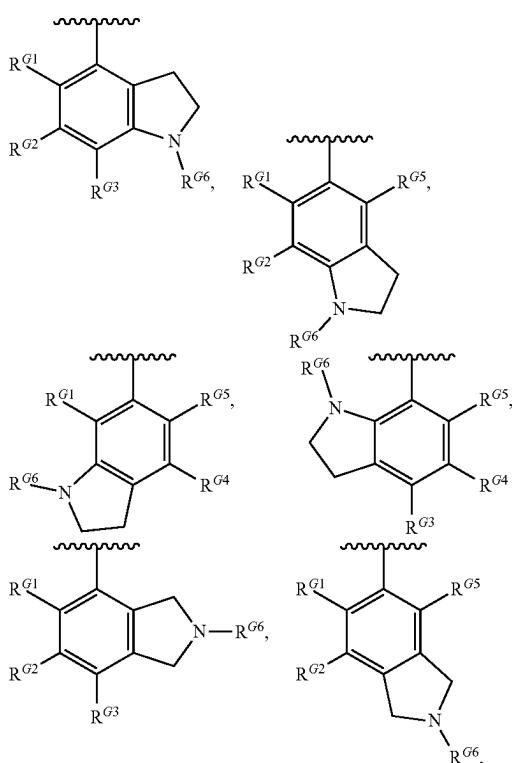
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where R^{G6} is H or optionally substituted C_1 - C_6 alkyl. In some embodiments, G'' is



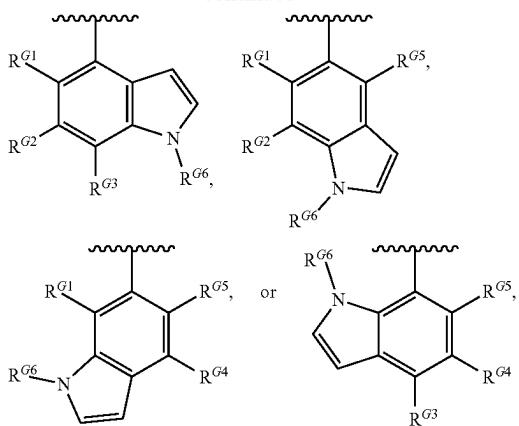
where R^{G6} is H or optionally substituted C_1 - C_6 alkyl.

In some embodiments, G'' is



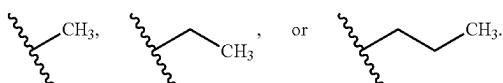
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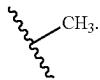


where R<sup>G6</sup> is H or optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl.

In some embodiments, R<sup>G6</sup> is H,

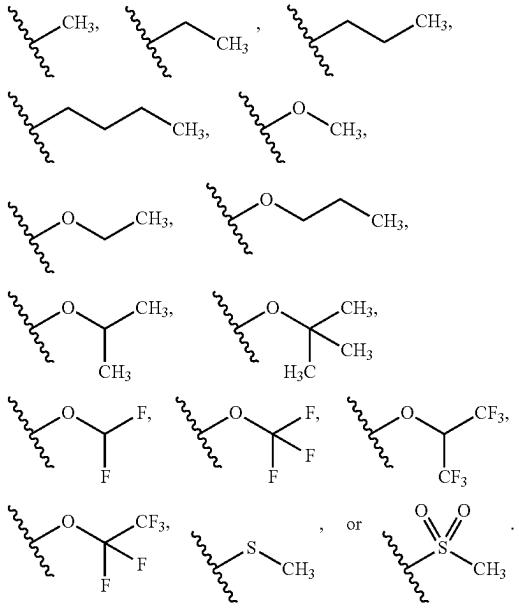


In some embodiments, R<sup>G6</sup> is H or



In some embodiments, R<sup>G6</sup> is H.

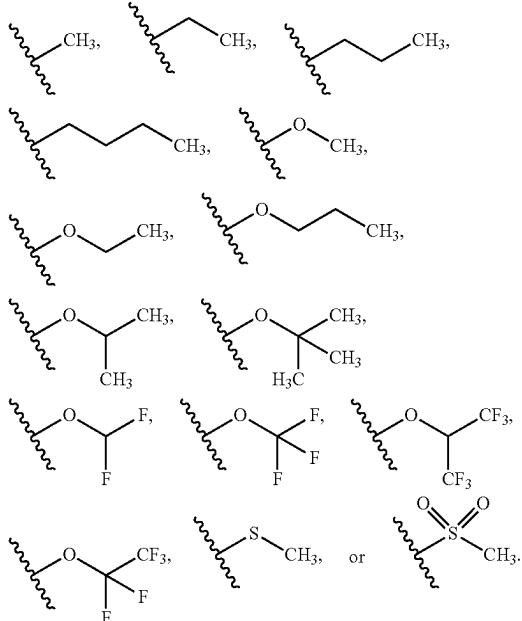
In some embodiments, R<sup>G1</sup> is H, F,



In some embodiments, R<sup>G1</sup> is H.

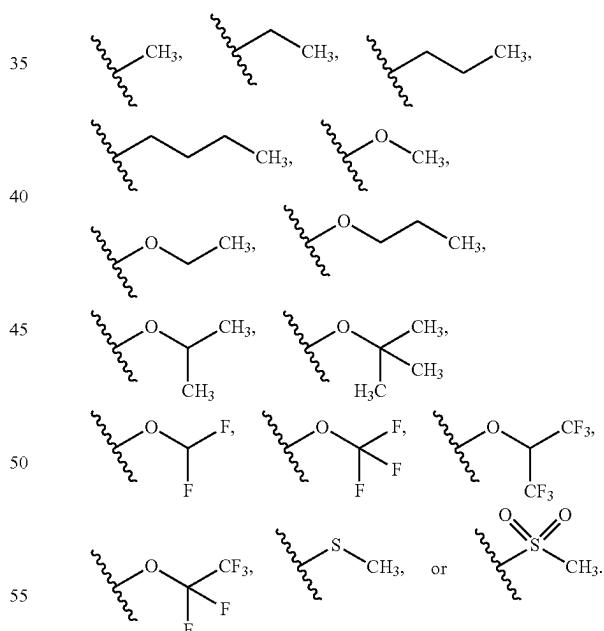
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In some embodiments, R<sup>G2</sup> is H, F,



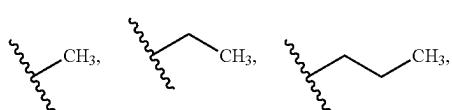
In some embodiments, R<sup>G2</sup> is H.

In some embodiments, R<sup>G3</sup> is H, F,



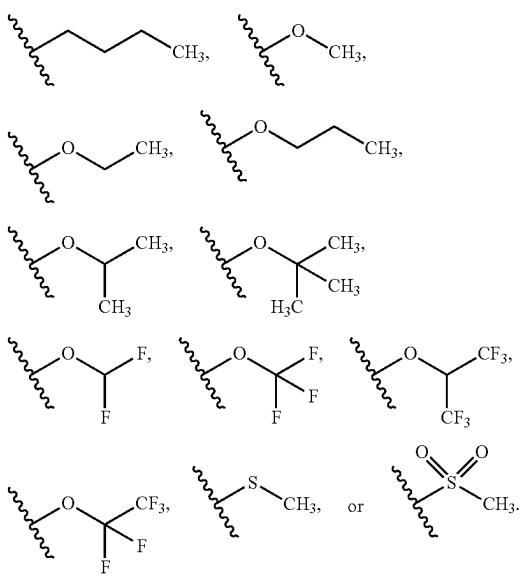
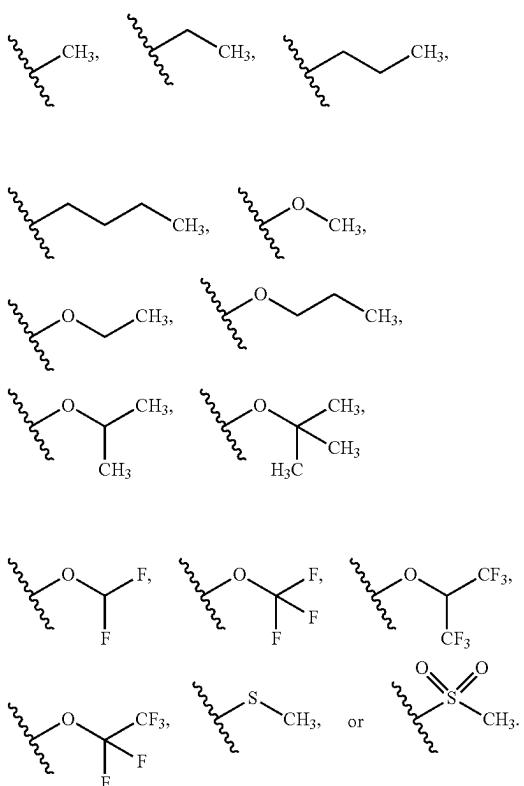
In some embodiments, R<sup>G3</sup> is H.

In some embodiments, R<sup>G4</sup> is H, F,

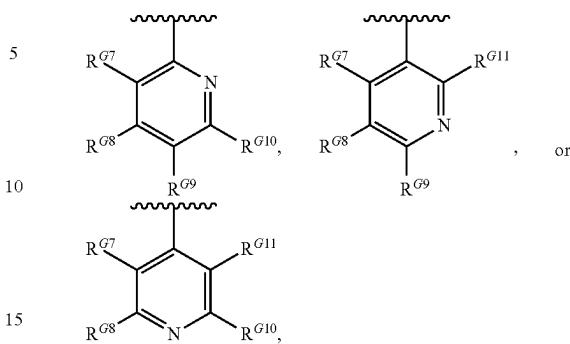


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In some embodiments, R^{G4} is H.In some embodiments, R^{G5} is H, F,In some embodiments, R^{G5} is H.

In some embodiments, one or more of R^{G1} , R^{G2} , R^{G3} , R^{G4} , and R^{G5} is H. In some embodiments, two or more of R^{G1} , R^{G2} , R^{G3} , R^{G4} , and R^{G5} is H. In some embodiments, three or more of R^{G1} , R^{G2} , R^{G3} , R^{G4} , and R^{G5} is H. In some embodiments, each of R^{G1} , R^{G2} , R^{G3} , R^{G4} , and R^{G5} is H.

66In some embodiments, G'' is

where

each of R^{G7} , R^{G8} , R^{G9} , R^{G10} , and R^{G11} is, independently, H, halogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heterocyclyl, optionally substituted C_6 - C_{10} aryl, optionally substituted C_2 - C_9 heteroaryl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 heteroalkenyl, optionally substituted —O— C_3 - C_6 carbocyclyl, optionally substituted — C_1 - C_3 alkyl- C_3 - C_6 carbocyclyl, optionally substituted — C_1 - C_3 alkyl- C_2 - C_5 heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R^{G7} and R^{G8} , R^{G8} and R^{G9} , R^{G9} and R^{G10} , and/or R^{G10} and R^{G11} , together with the carbon atoms to which each is attached, combine to form optionally substituted C_6 - C_{10} aryl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heteroaryl, or C_2 - C_9 heterocyclyl.

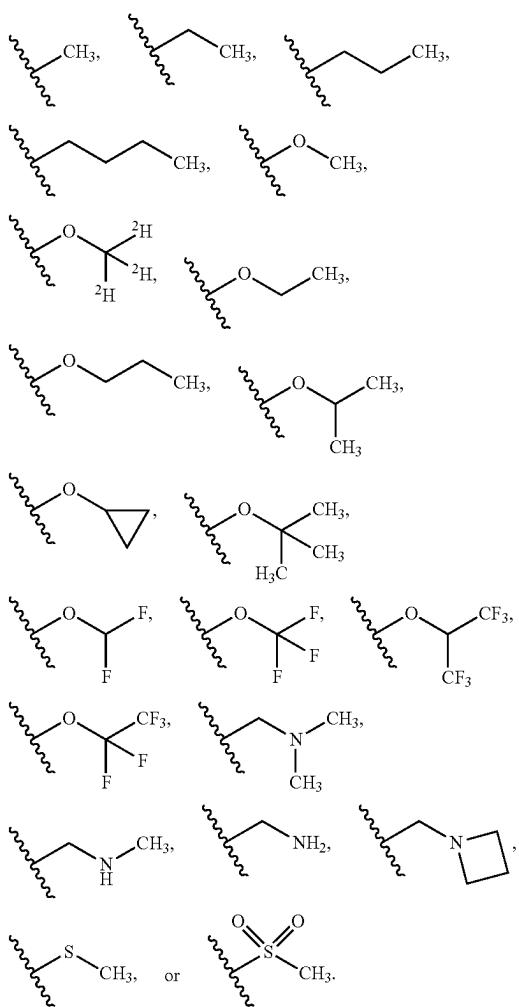
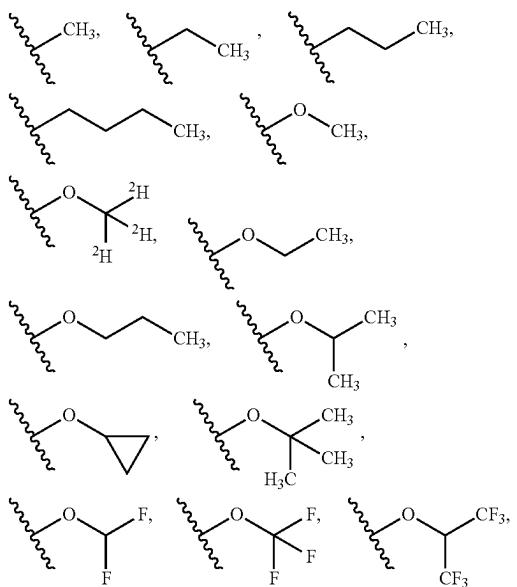
In some embodiments, each of R^{G7} , R^{G8} , R^{G9} , R^{G10} , and R^{G11} is, independently, H, halogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heterocyclyl, optionally substituted C_6 - C_{10} aryl, optionally substituted C_2 - C_9 heteroaryl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 heteroalkenyl, hydroxyl, thiol, or optionally substituted amino; or R^{G7} and R^{G8} , R^{G8} and R^{G9} , R^{G9} and R^{G10} , and/or R^{G10} and R^{G11} , together with the carbon atoms to which each is attached, combine to form optionally substituted C_6 - C_{10} aryl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heteroaryl, or C_2 - C_9 heterocyclyl.

In some embodiments, each of R^{G7} , R^{G8} , R^{G9} , R^{G10} , and R^{G11} is, independently, H, halogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted —O— C_3 - C_6 carbocyclyl, or optionally substituted — C_1 - C_3 alkyl- C_2 - C_5 heterocyclyl; or R^{G7} and R^{G8} , R^{G8} and R^{G9} , R^{G9} and R^{G10} , and/or R^{G10} and R^{G11} , together with the carbon atoms to which each is attached, combine to form optionally substituted C_6 - C_{10} aryl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heteroaryl, or C_2 - C_9 heterocyclyl.

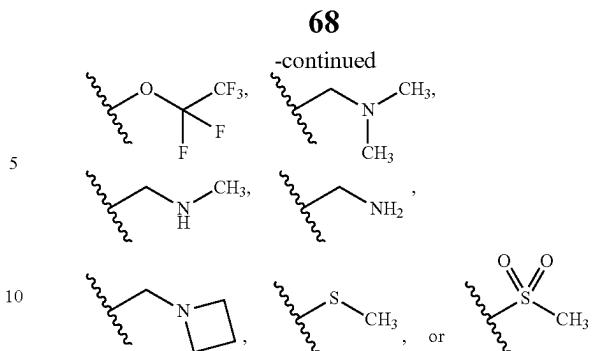
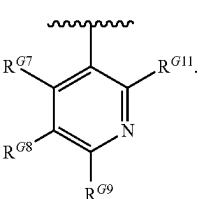
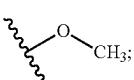
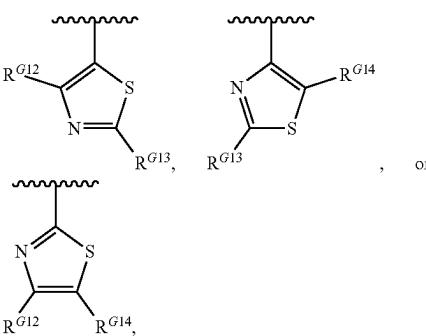
In some embodiments, each of R^{G7} , R^{G8} , R^{G9} , R^{G10} , and R^{G11} is, independently, H, halogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted —O— C_3 - C_6 carbocyclyl, or optionally substituted — C_1 - C_3 alkyl- C_2 - C_5 heterocyclyl.

In some embodiments, each of R^{G7} , R^{G8} , R^{G9} , R^{G10} , and R^{G11} is, independently, H, F, Cl,

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In some embodiments, R^{G8} is

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In some embodiments, G¹¹ isIn some embodiments, R^{G7} is H; R^{G8} isR^{G9} is H; and R^{G11} is H.In some embodiments, G¹¹ is

where

each of R^{G12}, R^{G13}, and R^{G14} is, independently, H, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, optionally substituted —O—C₃-C₆ carbocyclyl, optionally substituted —C₁-C₃ alkyl-C₃-C₆ carbocyclyl, optionally substituted —C₁-C₃ alkyl-C₂-C₅ heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R^{G12} and R^{G14}, together with the carbon atoms to which each is attached, combine to form optionally substituted C₆-C₁₀ aryl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heteroaryl, or optionally substituted C₂-C₉ heterocyclyl.

In some embodiments, each of R^{G12} , R^{G13} , and R^{G14} is, independently, H, halogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heterocyclyl, optionally substituted C_6 - C_{10} aryl, optionally substituted C_2 - C_9 heteroaryl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 heteroalkenyl, hydroxyl, thiol, or optionally substituted amino; or R^{G12} and R^{G14} , together with the carbon atoms to which each is attached, combine to form optionally substituted C_6 - C_{10} aryl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heteroaryl, or optionally substituted C_2 - C_9 heterocyclyl.

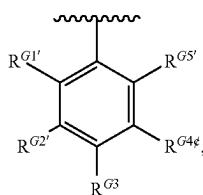
In some embodiments, G'' is



In some embodiments, G' is optionally substituted C₃-C₁₀ carbocyclene or optionally substituted C₂-C₉ heterocyclycene. In some embodiments, G' is optionally substituted C₆-C₁₀ arylene or optionally substituted C₂-C₉ heteroarylene.

In some embodiments, G' is optionally substituted C₃-C₁₀ carbocyclyene. In some embodiments, G' is optionally substituted C₆-C₁₀ arylene. In some embodiments, G' is optionally substituted C₂-C₉ heterocyclylene. In some embodiments, G' is optionally substituted C₂-C₉ heteroarylene.

In some embodiments, G' is



where

each of R^{G1} , R^{G2} , R^{G3} , R^{G4} , and R^{G5} is, independently,

H, A¹, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, optionally substituted —O—C₃-C₆ carbocyclyl, optionally substituted —C₁-C₃ alkyl-C₃-C₆ carbocyclyl, optionally substituted —C₁-C₃ alkyl-C₂-C₅ heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R^{G1} and R^{G2}, R^{G2} and R^{G3}, R^{G3} and R^{G4}, and/or R^{G4} and R^{G5}, together with the carbon atoms to which each is attached, combine to form

(M); and (M) is optionally substituted C₆-C₁₀ aryl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heteroaryl, or optionally substituted C₂-C₉ heterocyclyl, any of which is optionally substituted with A¹, where one of R^{G1}, R^{G2}, R^{G3}, R^{G4}, and

R^{G5} is A^1 , or M is substituted with A^1 .

In some embodiments, each of R^{G1} , R^{G2} , R^{G3} , R^{G4} , and R^{G5} is, independently, H, A¹, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, optionally substituted —O—C₃-C₆ carbocyclyl, optionally substituted —C₁-C₃ alkyl-C₃-C₆ carbocyclyl, 10 optionally substituted —C₁-C₃ alkyl-C₂-C₅ heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R^{G1} and R^{G2}, R^{G2} and R^{G3}, R^{G3} and R^{G4}, and/or R^{G4} and R^{G5}, together with the carbon atoms to which each is attached,

15 combine to form M_1 ; and M_2 is optionally substituted $\text{C}_6\text{-C}_{10}$ aryl, optionally substituted $\text{C}_3\text{-C}_{10}$ carbocyclyl, optionally substituted $\text{C}_2\text{-C}_9$ heteroaryl, or optionally substituted $\text{C}_2\text{-C}_9$ heterocyclyl, any of which is optionally substituted with A^1 , where one of $\text{R}^{G1}, \text{R}^{G2}, \text{R}^{G3}, \text{R}^{G4}$, and

R^{G5t} is A^1 , or  is substituted with A^1 .

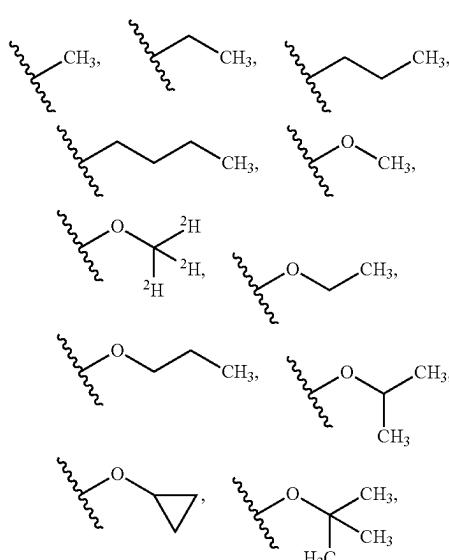
In some embodiments, each of R^{G1} , R^{G2} , R^{G3} , R^{G4} , and R^{G5} is, independently, H, A¹, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted —O—C₃-C₆ carbocyclyl, or optionally substituted —C₁-C₃ alkyl-C₂-C₅ heterocyclyl; or R^{G1} and R^{G2} , R^{G2} and R^{G3} , R^{G3} and R^{G4} , and/or R^{G4} and R^{G5} , together with the carbon atoms to which each is

30 attached, combine to form ; and  is optionally substituted C₂-C₉ heteroaryl or optionally substituted C₂-C₉ heterocycl, any of which is optionally substituted with A¹, where one of R^{G11}, R^{G21}, R^{G31}, R^{G41}, and R^{G51} is A¹, or

35 M is substituted with A¹.

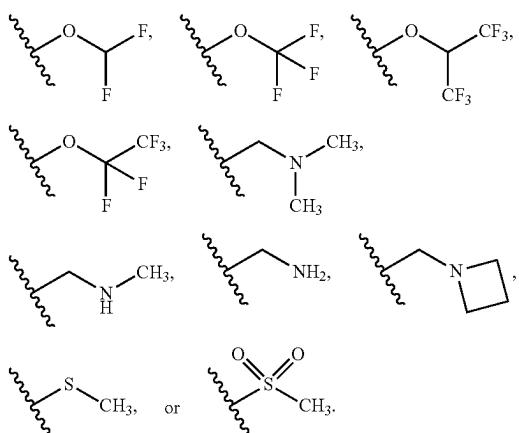
In some embodiments, each of R^{G1} , R^{G2} , R^{G3} , R^{G4} , and R^{G5} is, independently, H, A¹, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, 40 optionally substituted —O—C₃-C₆ carbocyclyl, or optionally substituted —C₁-C₂ alkyl-C₂-C₅ heterocyclyl.

In some embodiments, each of R^{G1} , R^{G2} , R^{G3} , R^{G4} , and R^{G5} is, independently, H , A^1 , F , Cl ,



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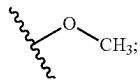
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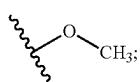
In some embodiments, each of R^{G1t} , R^{G2t} , R^{G3t} , R^{G4t} , and R^{G5t} is, independently, H, A¹, F,

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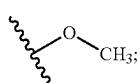
In some embodiments, R^{G1t} is H; R^{G2t} is



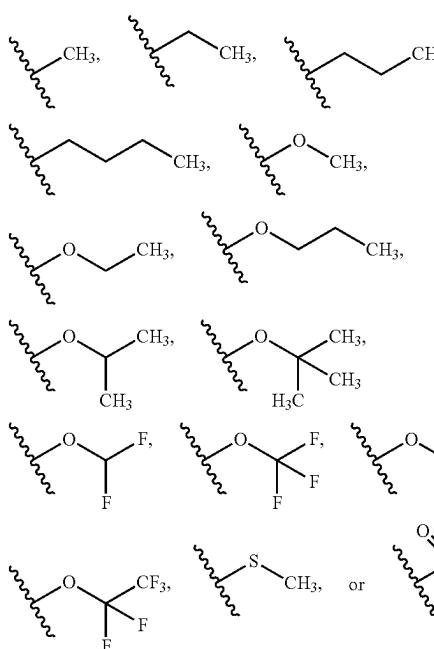
R^{G3} , is A^1 ; R^{G4} , is



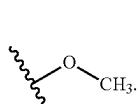
¹⁵ and R^{G5t} is H. In some embodiments, R^{G1t} is H; R^{G2t} is



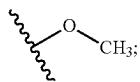
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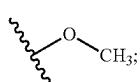
In some embodiments, each of R^{G1t} , R^{G2t} , R^{G3t} , R^{G4t} , and R^{G5t} is, independently, H, A¹, F, Cl,



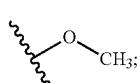
In some embodiments, R^{G1t} is H; R^{G2t} is



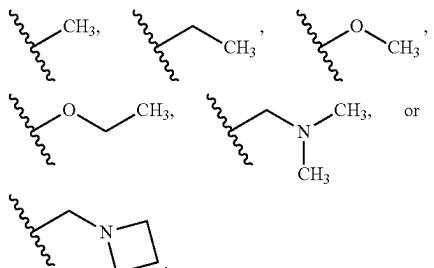
R^{G3t} is A¹; R^{G4t} is Cl or F; and R^{G5t} is H. In some embodiments, R^{G1t} is H; R^{G2t} is



⁴⁵ R^{G3t} is A¹; R^{G4t} is H; and R^{G5t} is H. In some embodiments, R^{G1t} is H; R^{G2t} is



R^{G3} , is A^1 ; R^{G4} , is



In some embodiments, R^{G3} is A^1 .

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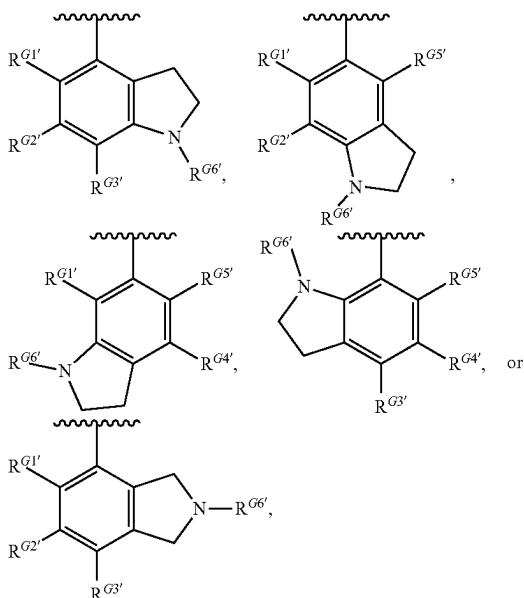
optionally substituted with A¹, where one of R^{G1}, R^{G2},

R^{G3}, R^{G4}, and R^{G5} is A¹, or is substituted with A¹. In some embodiments, R^{G1} and R^{G2}, R^{G2} and R^{G3}, R^{G3}, and R^{G4}, and/or R^{G4} and R^{G5}, together with the carbon atoms

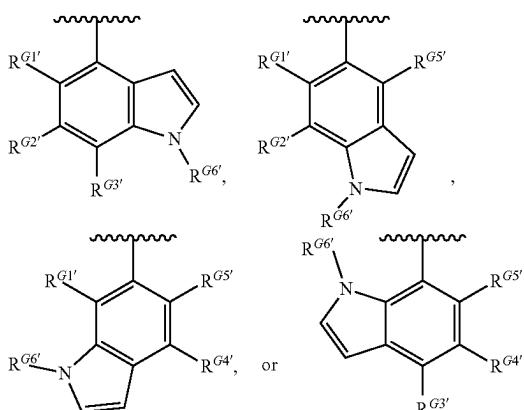
to which each is attached, combine to form ; and

is optionally substituted C₂-C₉ heteroaryl, which is optionally substituted with A¹, where one of R^{G1}, R^{G2},

R^{G3}, R^{G4}, and R^{G5} is A¹, or is substituted with A¹. In some embodiments, G' is



where R^{G6} is H, A¹, or optionally substituted C₁-C₆ alkyl. In some embodiments, G' is



where R^{G6} is H, A¹, or optionally substituted C₁-C₆ alkyl.

In some embodiments, R^{G1} and R^{G2}, R^{G2} and R^{G3}, R^{G3}, and R^{G4}, and/or R^{G4} and R^{G5}, together with the carbon

atoms to which each is attached, combine to form ; and

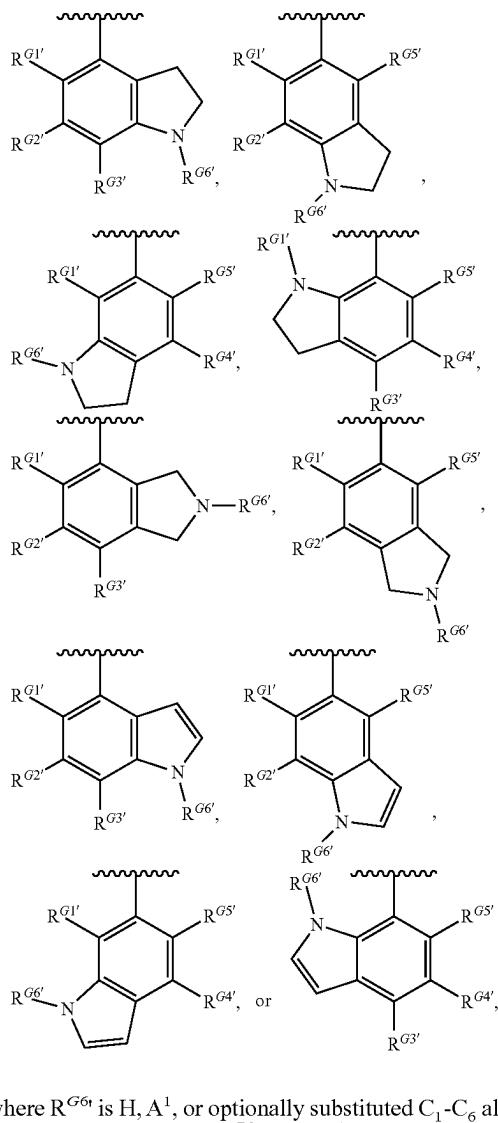
is optionally substituted C₂-C₉ heterocycl or option-

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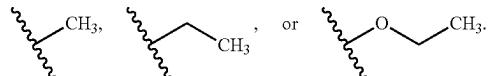
ally substituted C₂-C₉ heteroaryl, any of which is optionally substituted with A¹, where one of R^{G1}, R^{G2}, R^{G3}, R^{G4}, and

R^{G5} is A¹, or is substituted with A¹.

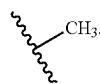
In some embodiments, G' is



where R^{G6} is H, A¹, or optionally substituted C₁-C₆ alkyl. In some embodiments, R^{G6} is H, A¹,

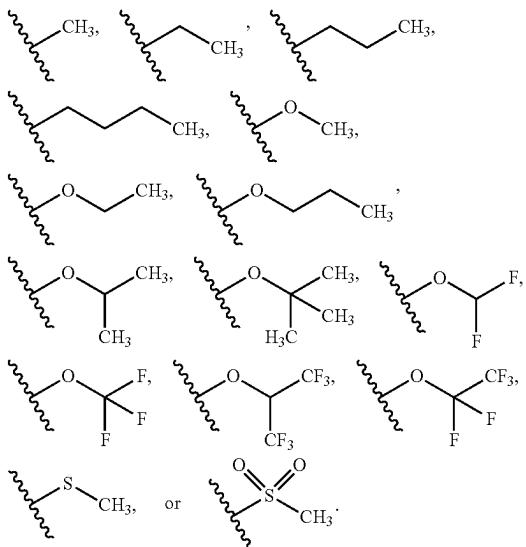
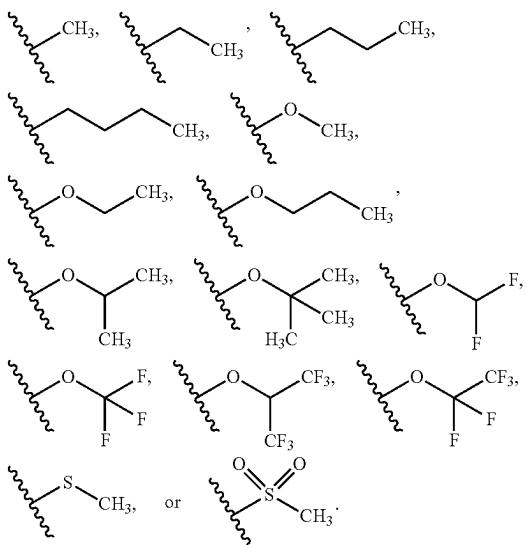
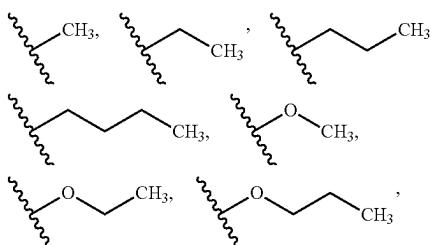


In some embodiments, R^{G6} is H, A¹, or

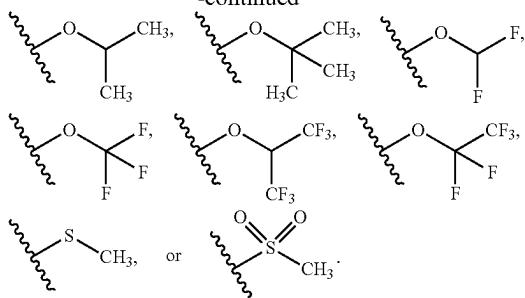
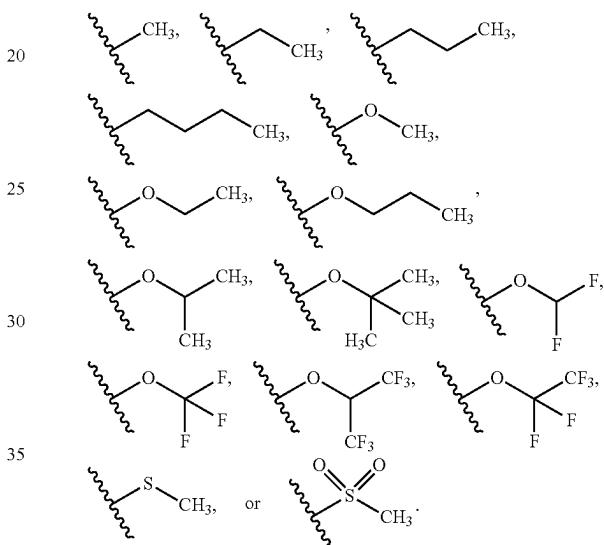
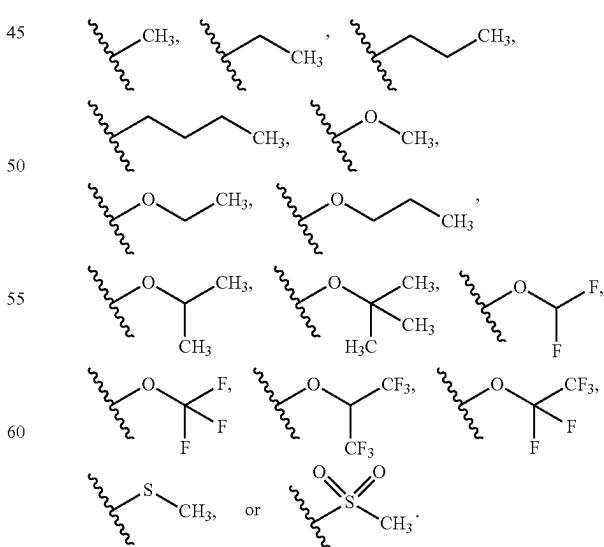


In some embodiments, R^{G6} is H or A¹.

In some embodiments, R^{G6} is H. In some embodiments, R^{G6} is A¹.

75In some embodiments, R^{G1t} is H, A¹, F,In some embodiments, R^{G1t} is H.In some embodiments, R^{G2t} is H, A¹, F,In some embodiments, R^{G2t} is H.In some embodiments, R^{G3t} is H, A¹, F,**76**

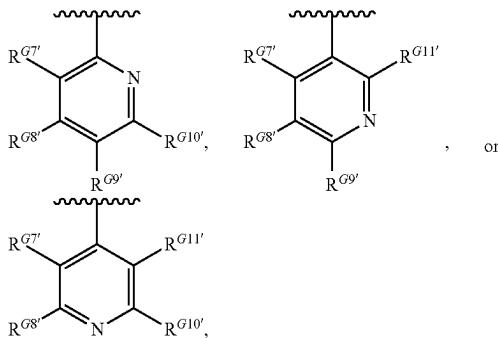
-continued

15 In some embodiments, R^{G3t} is H.
In some embodiments, R^{G4t} is H, A¹, F,40 In some embodiments, R^{G4t} is H.
In some embodiments, R^{G5t} is H, A¹, F,65 In some embodiments, R^{G5t} is H.

In some embodiments, one or more of R^{G1} , R^{G2} , R^{G3} , R^{G4} , and R^{G5} is H. In some embodiments, two or more of R^{G1} , R^{G2} , R^{G3} , R^{G4} , and R^{G5} is H. In some embodiments, three or more of R^{G1} , R^{G2} , R^{G3} , R^{G4} , and R^{G5} is H.

In some embodiments, R^{G1} is A^1 . In some embodiments, R^{G2} is A^1 . In some embodiments, R^{G3} is A^1 . In some embodiments, R^{G4} is A^1 . In some embodiments, R^{G5} is A^1 .

In some embodiments, \textcircled{M} is substituted with A^1 .
In some embodiments, G' is



where

each of R^{G7} , R^{G8} , R^{G9} , R^{G10} , and R^{G11} is, independently, H, A^1 , halogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heterocyclyl, optionally substituted C_6 - C_{10} aryl, optionally substituted C_2 - C_9 heteroaryl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 heteroalkenyl, optionally substituted $O-C_3-C_6$ carbocyclyl, optionally substituted C_1 - C_3 alkyl- C_3 - C_6 carbocyclyl, optionally substituted C_1 - C_3 alkyl- C_2 - C_5 heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R^{G7} and R^{G8} , R^{G8} and R^{G9} , R^{G9} and R^{G10} , and/or R^{G10} and R^{G11} , together with the carbon atoms to which each is attached, combine to form

\textcircled{M} ; and \textcircled{M} is optionally substituted C_6 - C_{10} aryl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heteroaryl, or C_2 - C_9 heterocyclyl, any of which is optionally substituted with A^1 , where one of R^{G7} , R^{G8} , R^{G9} , R^{G10} , and R^{G11} is A^1 ; or

\textcircled{M} is substituted with A^1 .

In some embodiments, each of R^{G7} , R^{G8} , R^{G9} , R^{G10} , and R^{G11} is, independently, H, A^1 , halogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heterocyclyl, optionally substituted C_6 - C_{10} aryl, optionally substituted C_2 - C_9 heteroaryl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 heteroalkenyl, optionally substituted $O-C_3-C_6$ carbocyclyl, optionally substituted C_1 - C_3 alkyl- C_3 - C_6 carbocyclyl, optionally substituted C_1 - C_3 alkyl- C_2 - C_5 heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R^{G7} and R^{G8} , R^{G8} and R^{G9} , R^{G9} and R^{G10} , and/or R^{G10} and R^{G11} , together with the carbon atoms to which each is attached, combine to form

attached, combine to form \textcircled{M} ; and \textcircled{M} is optionally substituted C_6 - C_{10} aryl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heteroaryl, or C_2 - C_9

heterocyclyl, any of which is optionally substituted with A^1 , where one of R^{G7} , R^{G8} , R^{G9} , R^{G10} , and R^{G11} is A^1 ; or

\textcircled{M} is substituted with A^1 .

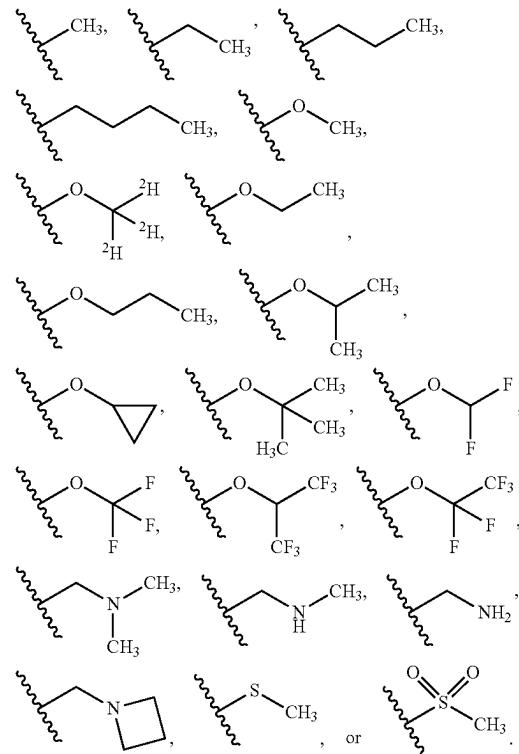
In some embodiments, each of R^{G7} , R^{G8} , R^{G9} , R^{G10} , and R^{G11} is, independently, H, A^1 , halogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted $O-C_3-C_6$ carbocyclyl, or optionally substituted C_1 - C_3 alkyl- C_2 - C_5 heterocyclyl; or R^{G7} and R^{G8} , R^{G8} and R^{G9} , R^{G9} and R^{G10} , and/or R^{G10} and R^{G11} , together with the carbon atoms to which each is

attached, combine to form \textcircled{M} ; and \textcircled{M} is optionally substituted C_6 - C_{10} aryl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heteroaryl, or C_2 - C_9 heterocyclyl, any of which is optionally substituted with A^1 , where one of R^{G7} , R^{G8} , R^{G9} , R^{G10} , and R^{G11} is A^1 ; or

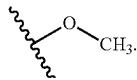
\textcircled{M} is substituted with A^1 .

In some embodiments, each of R^{G7} , R^{G8} , R^{G9} , R^{G10} , and R^{G11} is, independently, H, A^1 , halogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted $O-C_3-C_6$ carbocyclyl, or optionally substituted C_1 - C_3 alkyl- C_2 - C_5 heterocyclyl.

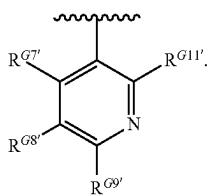
In some embodiments, each of R^{G7} , R^{G8} , R^{G9} , R^{G10} , and R^{G11} is, independently, H, A^1 , F, Cl,



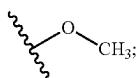
In some embodiments, R^{G8} is



In some embodiments, G' is

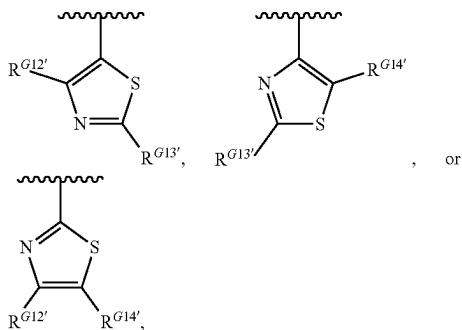


In some embodiments, R^{G7t} is H; R^{G8t} is



R^{G9} is A^1 ; and R^{G11} is H .

In some embodiments, G' is



where

each of R^{G12_1} , R^{G13_1} , and R^{G14_1} is, independently, H, A¹, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, optionally substituted —O—C₃-C₆ carbocyclyl, optionally substituted —C₁-C₃ alkyl-C₃-C₆ carbocyclyl, optionally substituted —C₁-C₃ alkyl-C₂-C₅ heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R^{G12_1} and R^{G14_1} together with the carbon atoms to which each is attached, combine to form

(M); and (M) is optionally substituted C₆-C₁₀ aryl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heteroaryl, or optionally substituted C₂-C₉ heterocyclyl, any of which is optionally substituted with A¹, where one of R^{G12i}, R^{G13i}, and R^{G14i} is

A^1 ; or is substituted with A^1 .

In some embodiments, each of R^{G12t} , R^{G13t} , and R^{G14t} is, independently, H, A^1 , halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, option-

ally substituted —O—C₃-C₆ carbocyclyl, optionally substituted —C₁-C₃ alkyl-C₃-C₆ carbocyclyl, optionally substituted —C₁-C₃ alkyl-C₂-C₅ heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R^{G12t} and R^{G14t}, together with the carbon atoms to which each is attached, combine to

form M; and M is optionally substituted C₆-C₁₀ aryl, optionally substituted C₃-C₁₀ carbocycl, optionally substituted C₂-C₉ heteroaryl, or optionally substituted C₂-C₉ heterocycl, any of which is optionally substituted with A¹,

where one of R^{G12t} , R^{G13t} , and R^{G14t} is A^1 ; or M is substituted with A^1 .

In some embodiments, each of R^{3a} , R^{3b_1} , R^{3c_1} , and R^{3d_1} is, independently, H, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_1 - C_6 acyl, optionally substituted sulfone, or optionally substituted C_1 - C_6 acylidene.

20 substituted sulfonamide. In some embodiments, each of R^{3a_1} , R^{3b_1} , R^{3c_1} , and R^{3d_1} is, independently, H, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted sulfone, or optionally substituted sulfonamide. In some embodiments, each of R^{3a_1}

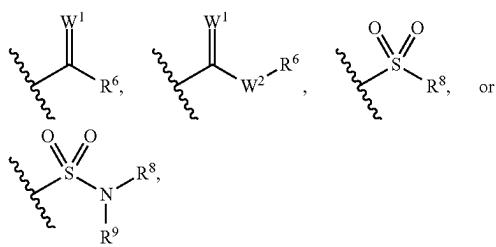
R^{3b_1} , R^{3c_1} , and R^{3d_1} is, independently, H, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 acyl, optionally substituted sulfone, or optionally substituted sulfonamide. In some embodiments, each of R^{3a_1} , R^{3b_1} , R^{3c_1} , and R^{3d_1} is, independently, H, optionally substituted C_1 - C_6 alkyl, or optionally substituted C_1 - C_6 acyl.

In some embodiments, each of R^{3a} , R^{3b_1} , R^{3c_1} , and R^{3d_1} is, independently, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_1 - C_6 acyl, optionally substituted sulfone, or optionally substituted sulfonamide. In some embodiments, each of R^{3a_1} , R^{3b_1} , R^{3c_1} , and R^{3d_1} is, independently, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 acyl, optionally substi-

tuted sulfone, or optionally substituted sulfonamide. In some embodiments, each of R^{3a_1} , R^{3b_1} , R^{3c_1} , and R^{3d_1} is, independently, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, or optionally substituted C_1 - C_6 acyl. In some embodiments, each of R^{3a_1} , R^{3b_1} , R^{3c_1} , and R^{3d_1}

is, independently, optionally substituted C_1 - C_6 alkyl or optionally substituted C_1 - C_6 heteroalkyl. In some embodiments, each of R^{3a} , R^{3b} , R^{3c} , and R^{3d} is, independently, optionally substituted C_1 - C_6 alkyl or optionally substituted C_1 - C_6 acyl. In some embodiments, each of R^{3a} , R^{3b} , R^{3c} , and R^{3d} is, independently, or optionally substituted C_1 - C_6 acyl. In some embodiments, each of R^{3a} , R^{3b} , R^{3c} , and R^{3d} is, independently, optionally substituted sulfone, or optionally substituted sulfonyl amide.

In some embodiments, each of R^{3a1} , R^{3b1} , R^{3c1} , and R^{3d1} is, independently, H, optionally substituted C_1 - C_6 alkyl.



where

R⁶ is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, or optionally substituted C₆-C₁₀ aryl;

W¹ is O or S;

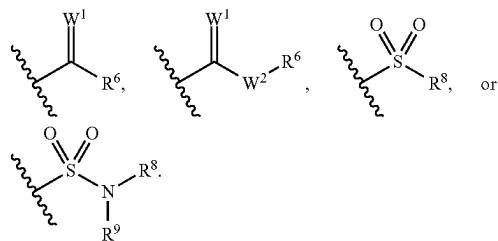
W² is NR⁷ or O;

R⁷ is H, optionally substituted C₁-C₆ alkyl, or optionally substituted C₁-C₆ heteroalkyl;

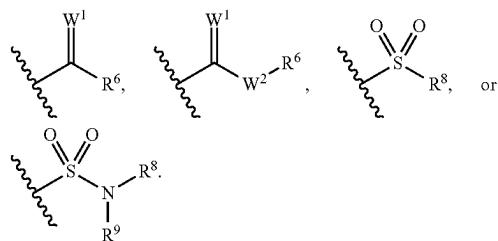
R⁸ is optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, or optionally substituted C₆-C₁₀ aryl; and

R⁹ is H, optionally substituted C₁-C₆ alkyl, or optionally substituted C₁-C₆ heteroalkyl.

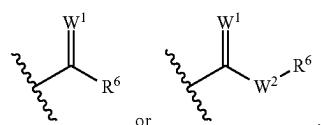
In some embodiments, each of R^{3a1}, R^{3b1}, R^{3c1}, and R^{3d1} is, independently, C₁-C₆ alkyl,



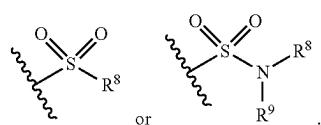
In some embodiments, each of R^{3a1}, R^{3b1}, R^{3c1}, and R^{3d1} is, independently, or C₁-C₆ alkyl. In some embodiments, each of R^{3a1}, R^{3b1}, R^{3c1}, and R^{3d1} is, independently,



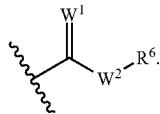
In some embodiments, each of R^{3a1}, R^{3b1}, R^{3c1}, and R^{3d1} is, independently,



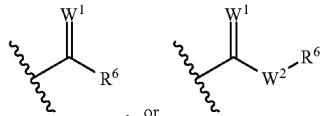
In some embodiments, each of R^{3a1}, R^{3b1}, R^{3c1}, and R^{3d1} is, independently,



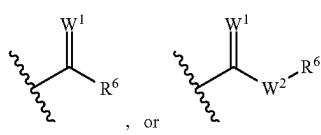
In some embodiments, each of R^{3a1}, R^{3b1}, R^{3c1}, and R^{3d1} is, independently,



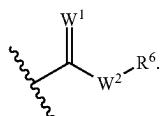
5 In some embodiments, each of R^{3a1}, R^{3b1}, R^{3c1}, and R^{3d1} is, independently, H, optionally substituted C₁-C₆ alkyl,



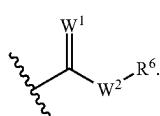
10 In some embodiments, each of R^{3a1}, R^{3b1}, R^{3c1}, and R^{3d1} is, independently, H, C₁-C₆ alkyl,



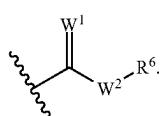
15 In some embodiments, each of R^{3a1}, R^{3b1}, R^{3c1}, and R^{3d1} is, independently, H, C₁-C₆ alkyl, or



20 In some embodiments, each of R^{3a1}, R^{3b1}, R^{3c1}, and R^{3d1} is, independently, C₁-C₆ alkyl or



25 In some embodiments, each of R^{3a1}, R^{3b1}, R^{3c1}, and R^{3d1} is, independently, H, methyl, or



30 In some embodiments, each of R^{3a1}, R^{3b1}, R^{3c1}, and R^{3d1} is, independently, optionally substituted C₁-C₆ alkyl.

In some embodiments, W¹ is O. In some embodiments, W¹ is S.

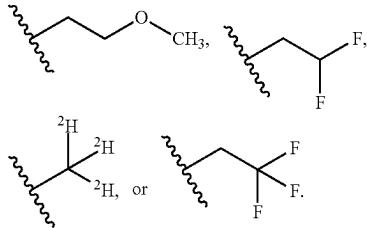
In some embodiments, W² is O. In some embodiments, W² is NR⁷.

35 In some embodiments, R⁶ is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, or

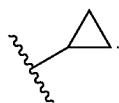
83

optionally substituted C₃-C₁₀ carbocyclyl. In some embodiments, R⁶ is H, optionally substituted C₁-C₆ alkyl, or optionally substituted C₁-C₆ heteroalkyl. In some embodiments, R⁶ is H, optionally substituted C₃-C₁₀ carbocyclyl, or optionally substituted C₆-C₁₀ aryl. In some embodiments, R⁶ is optionally substituted C₁-C₆ alkyl or optionally substituted C₁-C₆ heteroalkyl. In some embodiments, R⁶ is optionally substituted C₃-C₁₀ carbocyclyl or optionally substituted C₆-C₁₀ aryl.

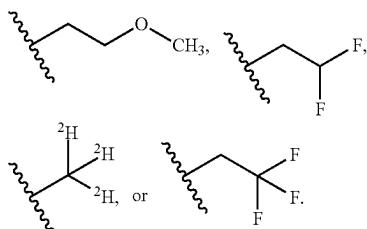
In some embodiments, R⁶ is H, methyl, ethyl,



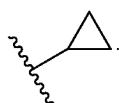
In some embodiments, R⁶ is H or



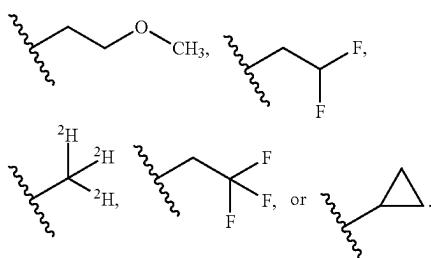
In some embodiments, R⁶ is methyl, ethyl,



In some embodiments, R⁶ is or



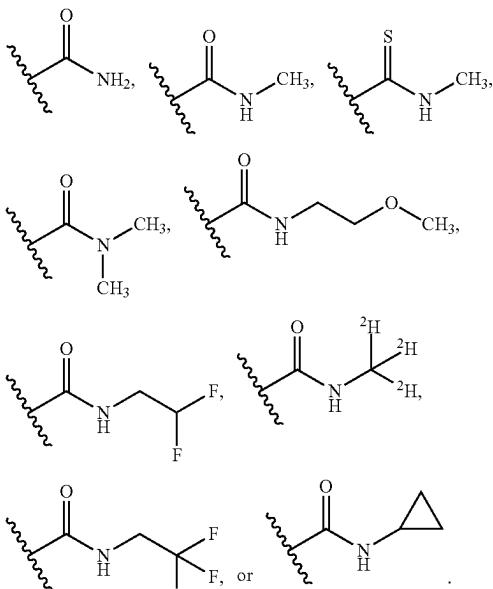
In some embodiments, R⁶ is H. In some embodiments, R⁶ is H, methyl, ethyl,



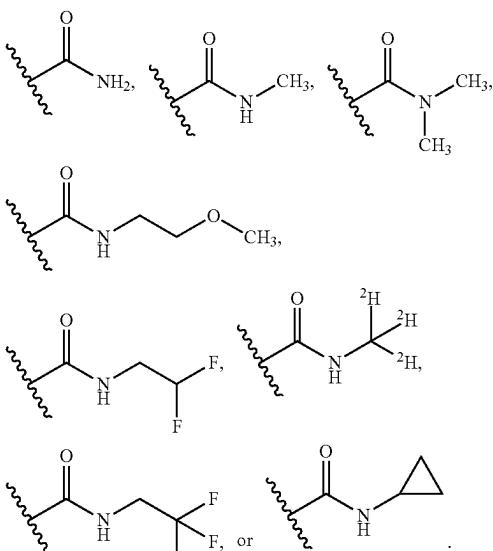
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In some embodiments, R⁷ is H or optionally substituted C₁-C₆ alkyl. In some embodiments, R⁷ is H or methyl.

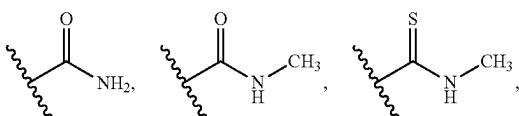
In some embodiments, each of R^{3a1}, R^{3b1}, R^{3c1}, and R^{3d1} is, independently, H, methyl,



In some embodiments, each of R^{3a1}, R^{3b1}, R^{3c1}, and R^{3d1} is, independently, H, methyl,

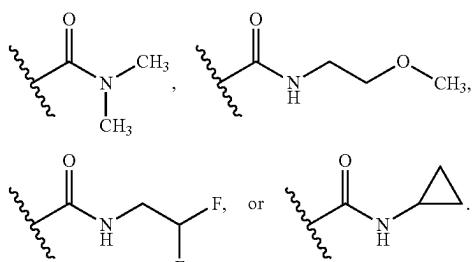


In some embodiments, R^{3a1} is H, methyl,

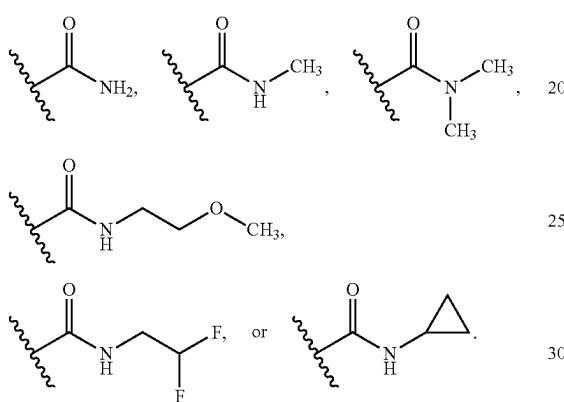


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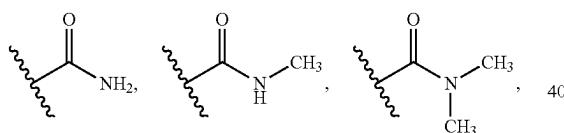
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In some embodiments, R^{3b1} is H, methyl,

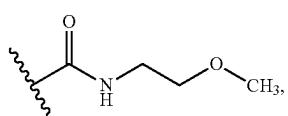
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In some embodiments, R^{3c1} is H, methyl,

30



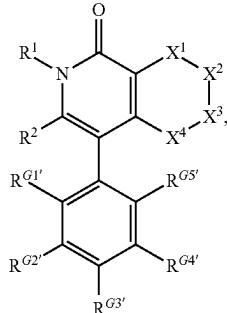
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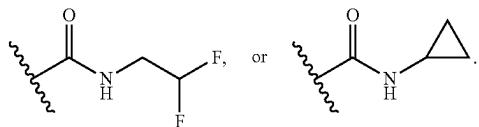
or a pharmaceutically acceptable salt thereof.

45 In some embodiments, A has the structure of Formula IIIa:

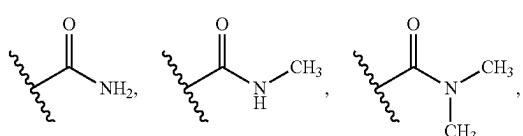
Formula IIIa

In some embodiments, R^{3d1} is H, methyl,

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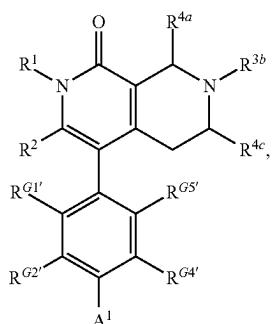
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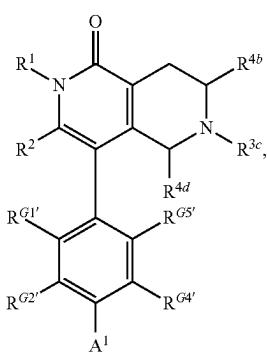
or a pharmaceutically acceptable salt thereof.

Formula IIIb



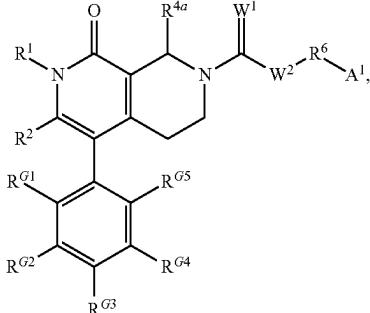
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In some embodiments, A has the structure of Formula IIIc:



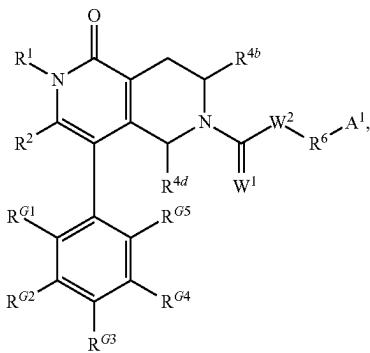
or a pharmaceutically acceptable salt thereof.

In some embodiments, A has the structure of Formula IIId:



or a pharmaceutically acceptable salt thereof.

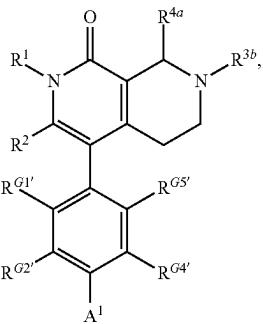
In some embodiments, A has the structure of Formula IIIe:



or a pharmaceutically acceptable salt thereof.

Formula IIIc

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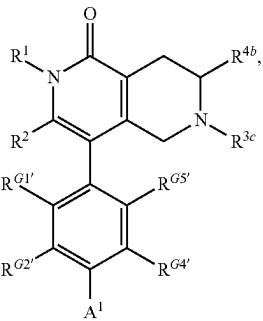
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or a pharmaceutically acceptable salt thereof.

In some embodiments, A has the structure of Formula IIIg:

Formula IIId

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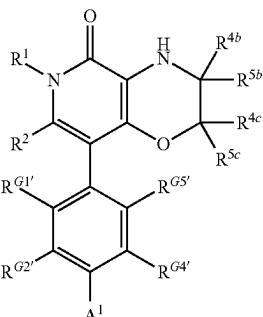
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or a pharmaceutically acceptable salt thereof.

In some embodiments, A has the structure of Formula IIIh:

Formula IIIe

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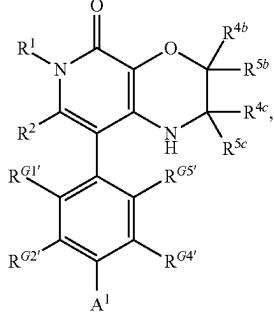
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or a pharmaceutically acceptable salt thereof.

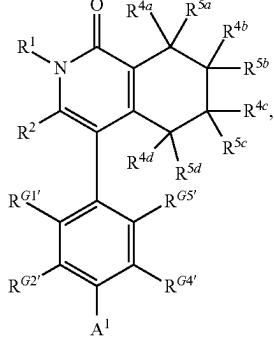
89

In some embodiments, A has the structure of Formula IIIi:



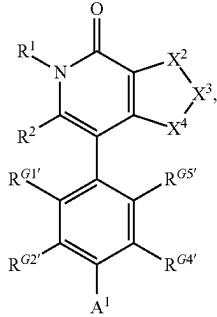
or a pharmaceutically acceptable salt thereof.

In some embodiments, A has the structure of Formula IIIj:



or a pharmaceutically acceptable salt thereof.

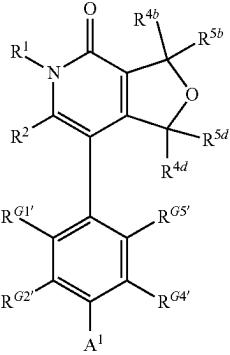
In some embodiments, A has the structure of Formula IIIk:



or a pharmaceutically acceptable salt thereof.

Formula IIIi

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Formula IIIm

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n,

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or a pharmaceutically acceptable salt thereof.

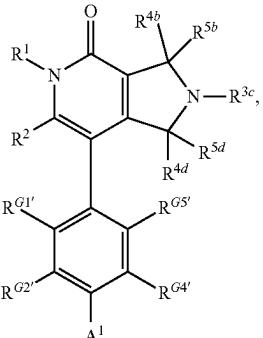
In some embodiments, A has the structure of Formula IIIIn:

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Formula IIIIn

Formula IIIj

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or a pharmaceutically acceptable salt thereof.

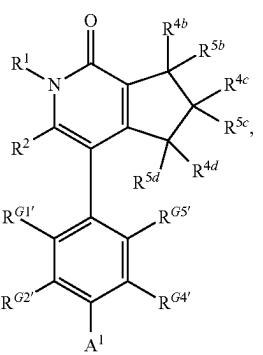
In some embodiments, A has the structure of Formula IIIlo:

45

Formula IIIk

55

Formula IIIo



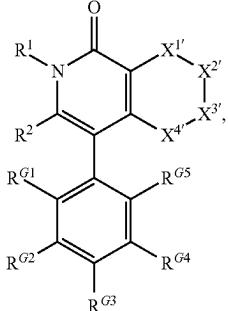
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or a pharmaceutically acceptable salt thereof.

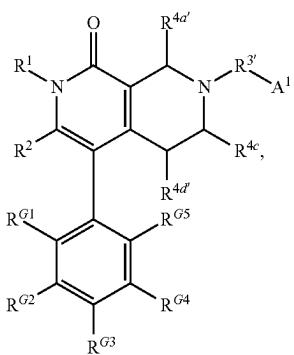
91

In some embodiments, A has the structure of Formula IIIp:



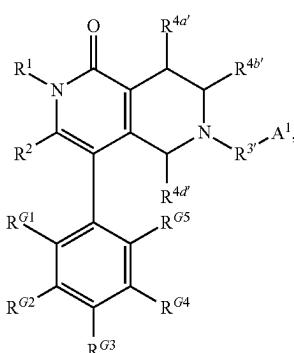
or a pharmaceutically acceptable salt thereof.

In some embodiments, A has the structure of Formula IIIq:



or a pharmaceutically acceptable salt thereof.

In some embodiments, A has the structure of Formula IIIr:

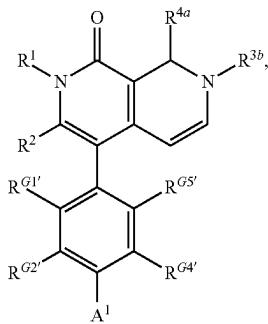


or a pharmaceutically acceptable salt thereof.

92

In some embodiments, A has the structure of Formula IIIs:

Formula IIIp 5

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Formula IIIs

or a pharmaceutically acceptable salt thereof.

In some embodiments, the degradation moiety is a ubiquitin ligase binding moiety.

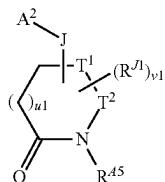
In some embodiments, the ubiquitin ligase binding moiety comprises Cereblon ligands, IAP (Inhibitors of Apoptosis) ligands, mouse double minute 2 homolog (MDM2), or von Hippel-Lindau (VHL) ligands, or derivatives or analogs thereof.

In some embodiments, the degradation moiety is a ubiquitin ligase binding moiety.

In some embodiments, the ubiquitin ligase binding moiety comprises Cereblon ligands, IAP (Inhibitors of Apoptosis) ligands, mouse double minute 2 homolog (MDM2), or von Hippel-Lindau (VHL) ligands, or derivatives or analogs thereof.

In some embodiments, the degradation moiety includes the structure of Formula Y:

Formula IIIq

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35
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Formula Y

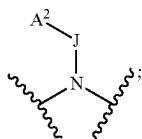
where

A² is a bond between the degradation moiety and the linker;

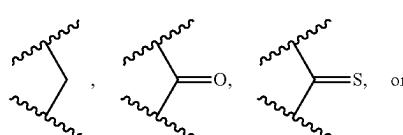
v1 is 0, 1, 2, 3, 4, or 5;

u1 is 1, 2, or 3;

T¹ is a bond or

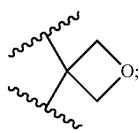


T² is



93

-continued

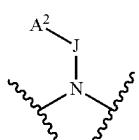


R^{54} is H, optionally substituted C_1 - C_6 alkyl, or optionally substituted C_1 - C_6 heteroalkyl;

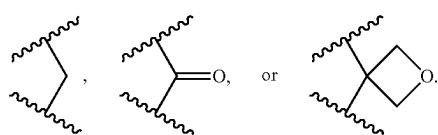
each R^{J1} is, independently, halogen, optionally substituted C_1 - C_6 alkyl, or optionally substituted C_1 - C_6 heteroalkyl; and

J is absent, optionally substituted C_3 - C_{10} carbocyclylene, optionally substituted C_6 - C_{10} arylene, optionally substituted C_2 - C_9 heterocyclylene, or optionally substituted C_2 - C_9 heteroarylene, or a pharmaceutically acceptable salt thereof.

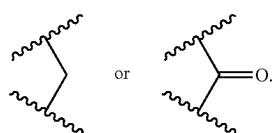
In some embodiments, T^1 is a bond. In some embodiments, T^1 is



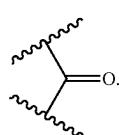
In some embodiments, T^2 is



In some embodiments, T^2 is or

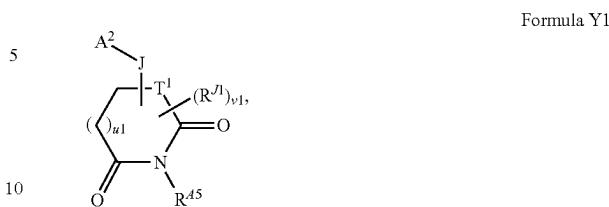


In some embodiments, T^2 is



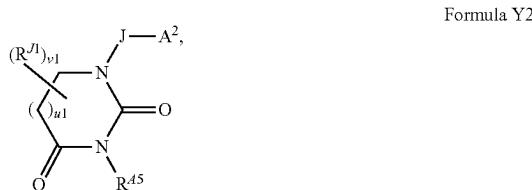
94

In some embodiments, the structure of Formula Y has the structure of Formula Y1:



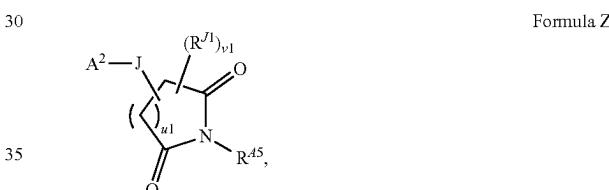
or a pharmaceutically acceptable salt thereof.

In some embodiments, the structure of Formula Y has the structure of Formula Y2:



25 or a pharmaceutically acceptable salt thereof.

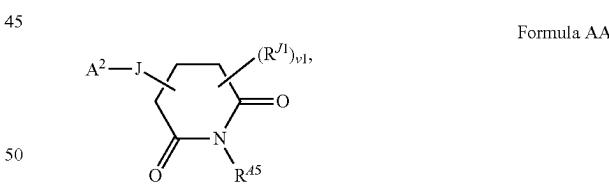
In some embodiments, the structure of Formula Y has the structure of Formula Z:



or a pharmaceutically acceptable salt thereof.

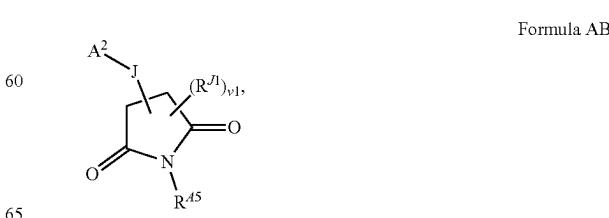
40 In some embodiments, $v1$ is 1. In some embodiments, $u1$ is 2. In some embodiments $u1$ is 3.

In some embodiments, the structure of Formula Z has the structure of Formula AA:



or a pharmaceutically acceptable salt thereof.

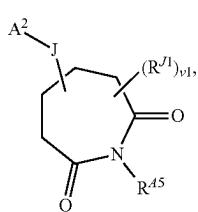
55 In some embodiments, the structure of Formula Z has the structure of Formula AB:



or a pharmaceutically acceptable salt thereof.

95

In some embodiments, the structure of Formula Z has the structure of Formula AC:

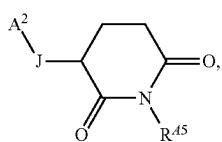


Formula AC 5

or a pharmaceutically acceptable salt thereof.

In some embodiments, v₁ is 0, 1, 2, or 3. In some embodiments, v₁ is 0. In some embodiments, v₁ is 1. In some embodiments, v₁ is 2. In some embodiments, v₁ is 3.

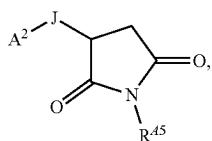
In some embodiments, the structure of Formula AA has the structure of Formula AA1:



Formula AA1

or a pharmaceutically acceptable salt thereof.

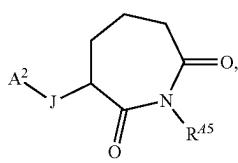
In some embodiments, the structure of Formula AB has the structure of Formula AB1:



Formula AB1

or a pharmaceutically acceptable salt thereof.

In some embodiments, the structure of Formula AC has the structure of Formula AC1:



Formula AC1 50

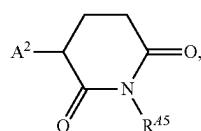
or a pharmaceutically acceptable salt thereof.

In some embodiments, J is absent. In some embodiments, J is optionally substituted C₃-C₁₀ carbocyclylene or optionally substituted C₆-C₁₀ arylene. In some embodiments, J is optionally substituted C₂-C₉ heterocyclylene or optionally substituted C₂-C₉ heteroarylene.

In some embodiments, J is optionally substituted heterocyclylene. In some embodiments, J is optionally substituted C₆-C₁₀ arylene.

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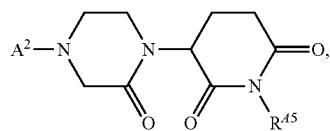
In some embodiments, the structure of Formula AA has the structure of Formula AA2:



Formula AA1

or a pharmaceutically acceptable salt thereof.

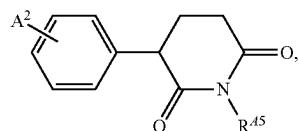
In some embodiments, the structure of Formula AA has the structure of Formula AA3:



Formula AA3

or a pharmaceutically acceptable salt thereof.

In some embodiments, the structure of Formula AA has the structure of Formula AA4:

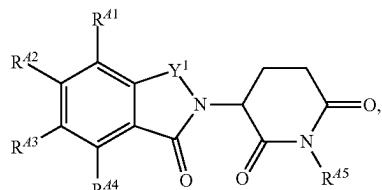


Formula AA4

or a pharmaceutically acceptable salt thereof.

In some embodiments, R⁴⁵S is H or optionally substituted C₁-C₆ alkyl. In some embodiments, R⁴⁵ is H or methyl. In some embodiments, R⁴⁵ is H. In some embodiments, R⁴⁵ is methyl.

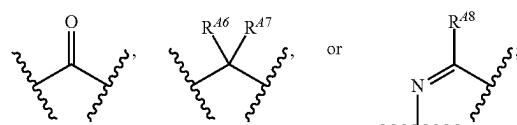
In some embodiments, the structure of Formula AA has the structure of Formula A:



Formula A

where

Y¹ is



R⁴⁵ is H, optionally substituted C₁-C₆ alkyl, or optionally substituted C₁-C₆ heteroalkyl;

R⁴⁶ is H or optionally substituted C₁-C₆ alkyl; and R⁴⁷ is H or optionally substituted C₁-C₆ alkyl; or R⁴⁶ and R⁴⁷,

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together with the carbon atom to which each is bound, combine to form optionally substituted C_3 - C_6 carbocyclyl or optionally substituted C_2 - C_5 heterocyclyl; or R^{46} and R^{47} , together with the carbon atom to which each is bound, combine to form optionally substituted C_3 - C_6 carbocyclyl or optionally substituted C_2 - C_5 heterocyclyl;

R^{48} is H, optionally substituted C_1 - C_6 alkyl, or optionally substituted C_4 - C_6 heteroalkyl; each of R^{41} , R^{42} , R^{43} , and R^{44} is, independently, H, A^2 , halogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heterocyclyl, optionally substituted C_6 - C_{10} aryl, optionally substituted C_2 - C_9 heteroaryl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 heteroalkenyl, optionally substituted $O-C_3-C_6$ carbocyclyl, hydroxyl, thiol, or optionally substituted amino; or R^{41} and R^{42} , R^{42} and R^{43} , and/or R^{43} and R^{44} , together with the carbon atoms to which each is attached,

combine to form \textcircled{N} ; and \textcircled{N} is optionally substituted C_6 - C_{10} aryl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heteroaryl, or C_2 - C_9 heterocyclyl, any of which is optionally substituted with A^2 , where one of R^{41} , R^{42} , R^{43} , and R^{44} is

A^2 , or \textcircled{N} is substituted with A^2 , or a pharmaceutically acceptable salt thereof.

In some embodiments, each of R^{41} , R^{42} , R^{43} , and R^{44} is, independently, H, A^2 , halogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heterocyclyl, optionally substituted C_6 - C_{10} aryl, optionally substituted C_2 - C_9 heteroaryl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 heteroalkenyl, hydroxyl, thiol, or optionally substituted amino; or R^{41} and R^{42} , R^{42} and R^{43} , and/or R^{43} and R^{44} , together with the carbon atoms to which each is attached, combine to form

\textcircled{N} ; and \textcircled{N} is optionally substituted C_6 - C_{10} aryl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heteroaryl, or C_2 - C_9 heterocyclyl, any of which is optionally substituted with A^2 , where one of R^{41} , R^{42} ,

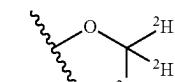
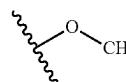
R^{43} , and R^{44} is A^2 , or \textcircled{N} is substituted with A^2 , or a pharmaceutically acceptable salt thereof.

In some embodiments, each of R^{41} , R^{42} , R^{43} , and R^{44} is, H, A^2 , halogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted $O-C_3-C_6$ carbocyclyl, hydroxyl, optionally substituted amino; or R^{41} and R^{42} , R^{42} and R^{43} , or R^{43} and R^{44} , together with the carbon atoms to which each is attached,

combine to form \textcircled{N} ; and \textcircled{N} is optionally substituted C_2 - C_9 heterocyclyl, which is optionally substituted with A^2 ,

where one of R^{41} , R^{42} , R^{43} , and R^{44} is A^2 , or \textcircled{N} is substituted with A^2 .

In some embodiments, each of R^{41} , R^{42} , R^{43} , and R^{44} is, independently, H, A^2 , F,

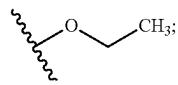


or

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-continued



or R^{41} and R^{42} , R^{42} and R^{43} , or R^{43} and R^{44} , together with the carbon atoms to which each is attached,

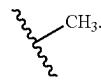
combine to form \textcircled{N} ; and \textcircled{N} is optionally substituted C_2 - C_9 heterocyclyl, which is optionally substituted with A^2 , where one of R^{41} , R^{42} , R^{43} , and R^{44} is

A^2 , or \textcircled{N} is substituted with A^2 .

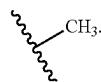
In some embodiments, R^{41} is A^2 . In some embodiments, R^{42} is A^2 . In some embodiments, R^{43} is A^2 . In some embodiments, R^{44} is A^2 . In some embodiments, R^{45} is A^2 .

20 In some embodiments, R^{45} is H or optionally substituted C_1 - C_6 alkyl.

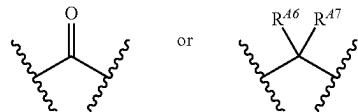
In some embodiments, R^{45} is H or



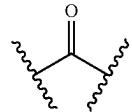
25 In some embodiments, R^{45} is H. In some embodiments, R^{45} is



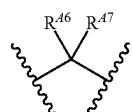
30 In some embodiments, Y^1 is



35 In some embodiments, Y^1 is



40 In some embodiments, Y^1 is

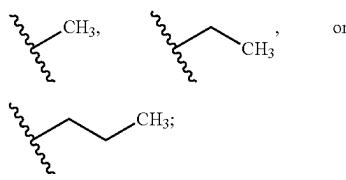


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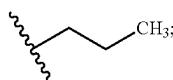
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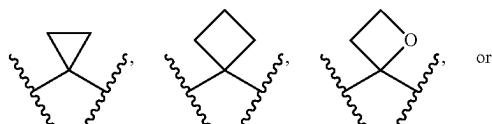
In some embodiments, each of R^{A6} and R^{A7} is, independently, H, F,



or

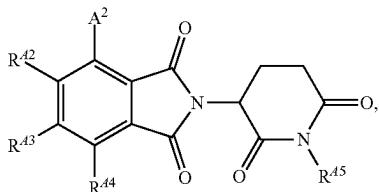


or R^{A6} and R^{A7}, together with the carbon atom to which each is bound, combine to form



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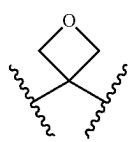


Formula A2

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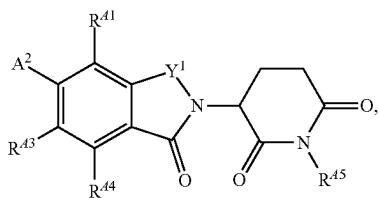
or a pharmaceutically acceptable salt thereof.

In some embodiments, the structure of Formula A has the structure of Formula A3:



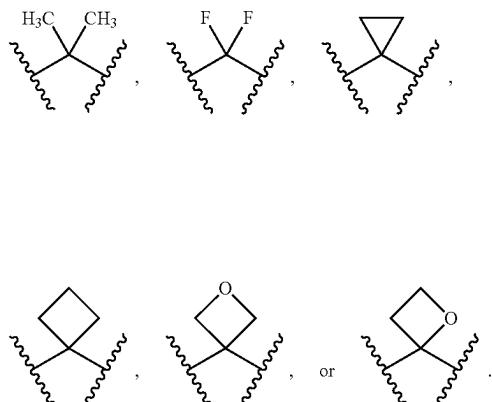
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Formula A3

In some embodiments, Y¹ is



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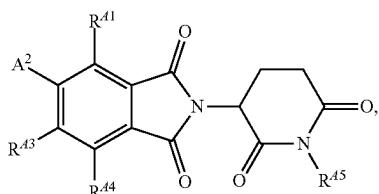
35

In some embodiments, the structure of Formula A has the structure of Formula A4:

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Formula A4

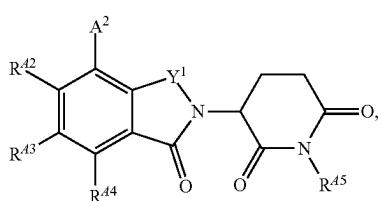
or a pharmaceutically acceptable salt thereof.

In some embodiments, the structure of Formula A has the structure of Formula A5:

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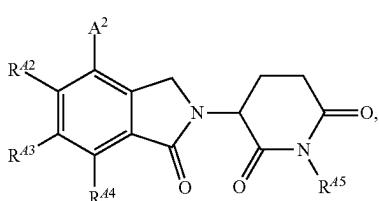
In some embodiments, the structure of Formula A has the structure of Formula A1:

Formula A1



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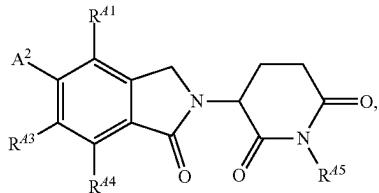
Formula A5

or a pharmaceutically acceptable salt thereof.

or a pharmaceutically acceptable salt thereof.

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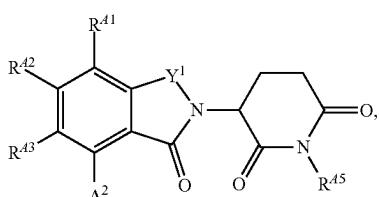
In some embodiments, the structure of Formula A has the structure of Formula A6:



Formula A6

or a pharmaceutically acceptable salt thereof.

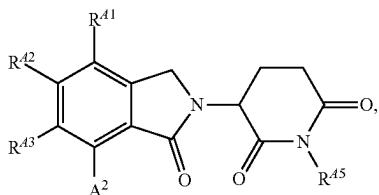
In some embodiments, the structure of Formula A has the structure of Formula A7:



Formula A7

or a pharmaceutically acceptable salt thereof.

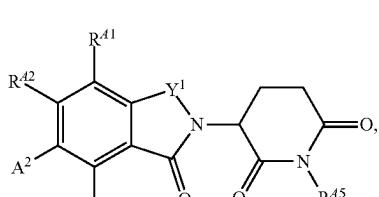
In some embodiments, the structure of Formula A has the structure of Formula A8:



Formula A8

or a pharmaceutically acceptable salt thereof.

In some embodiments, the structure of Formula A has the structure of Formula A9:

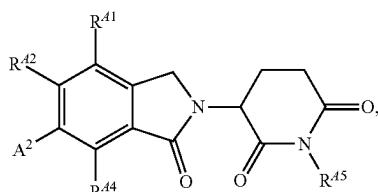


Formula A9

or a pharmaceutically acceptable salt thereof.

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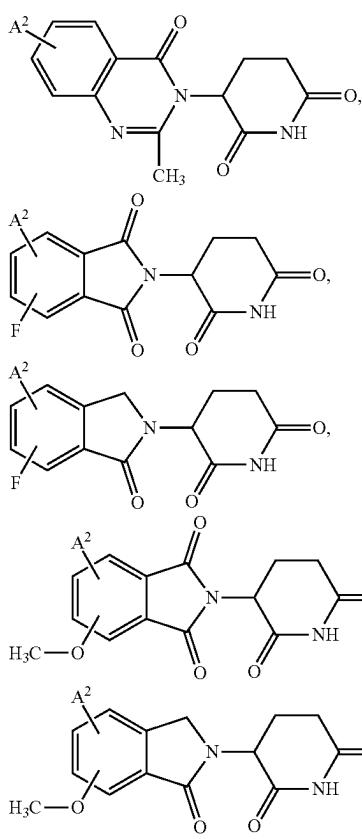
In some embodiments, the structure of Formula A has the structure of Formula A10:



Formula A10

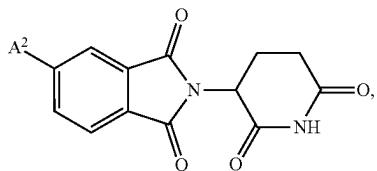
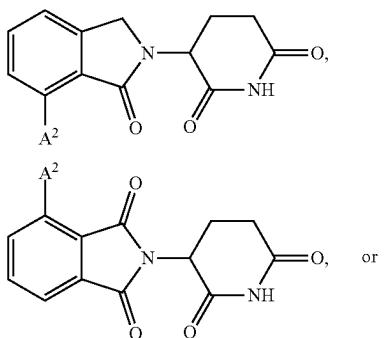
or a pharmaceutically acceptable salt thereof.

In some embodiments, wherein the structure of Formula A is



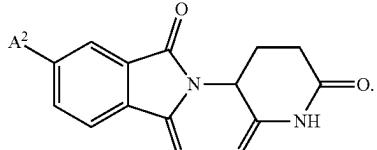
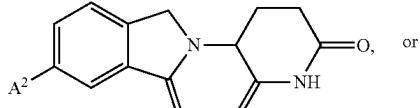
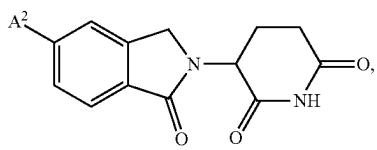
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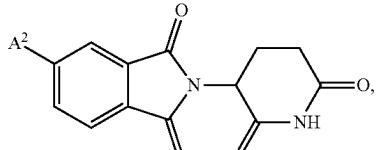
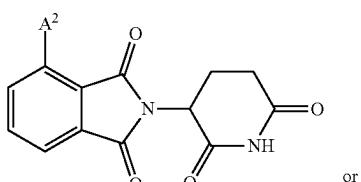


or derivative or analog thereof.

In some embodiments, the structure of Formula A is



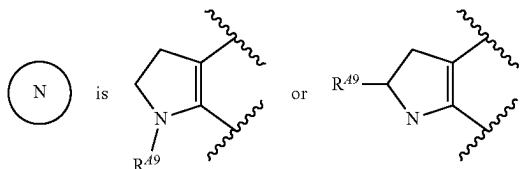
In some embodiments, the structure of Formula A is



or derivative or analog thereof.

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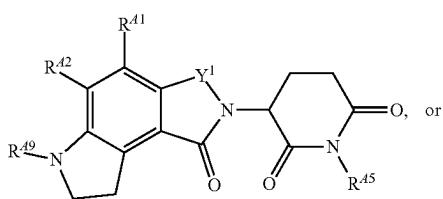
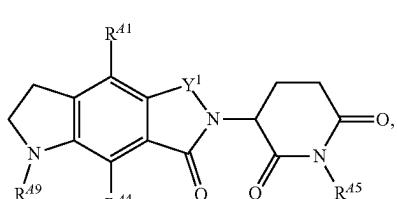
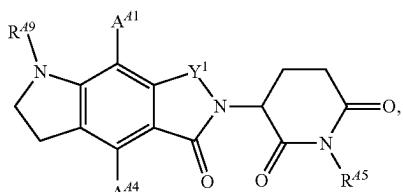
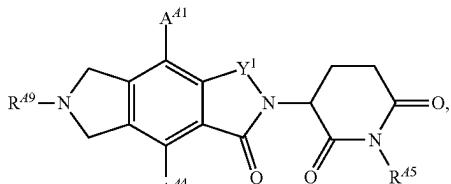
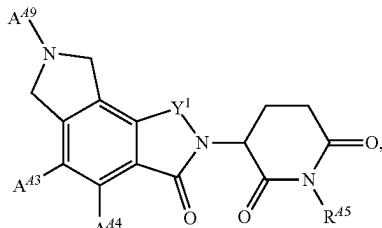
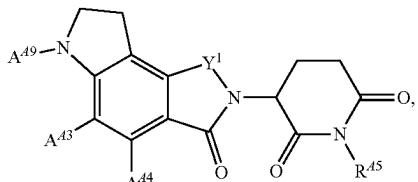
In some embodiments,



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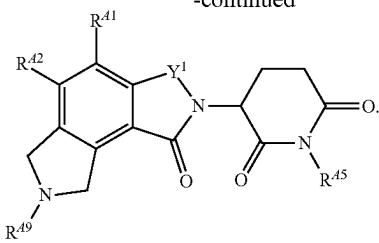
where R⁴⁹ is H, A², optionally substituted C₁-C₆ alkyl, or optionally substituted C₁-C₆ heteroalkyl.

In some embodiments, the structure of Formula A is



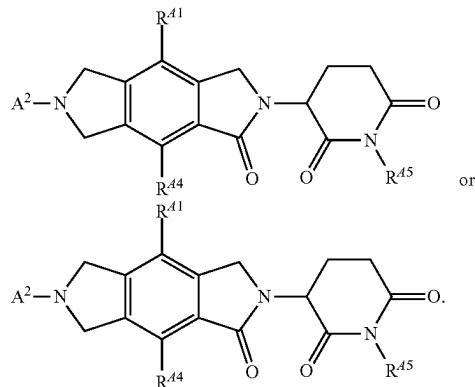
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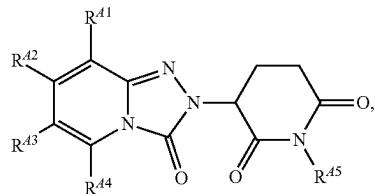
In some embodiments, R⁴⁹ is H, A², or optionally substituted C₁-C₆ alkyl. In some embodiments, R⁴⁹ is H, A², or methyl. In some embodiments, R^{9A} is H. In some embodiments, R^{9A} is methyl. In some embodiments, R⁴⁹ is A².

In some embodiments, the structure of Formula A is



In some embodiments, the structure of Formula AA has the structure of Formula B:

Formula B 40



where

R⁴⁵ is H, optionally substituted C₁-C₆ alkyl, or optionally substituted C₁-C₆ heteroalkyl; each of R⁴¹, R⁴², R⁴³, and R⁴⁴ is, independently, H, A², halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, optionally substituted —O—C₃-C₆ carbocyclyl, hydroxyl, thiol, or optionally substituted amino; or R⁴¹ and R⁴², R⁴² and R⁴³, and/or R⁴³ and R⁴⁴, together with the carbon atoms to which each is attached,

combine to form \textcircled{N} ; and \textcircled{N} is optionally substituted C₆-C₁₀ aryl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heteroaryl, or

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C₂-C₉ heterocyclyl, any of which is optionally substituted with A², where one of R⁴¹, R⁴², R⁴³, and R⁴⁴ is

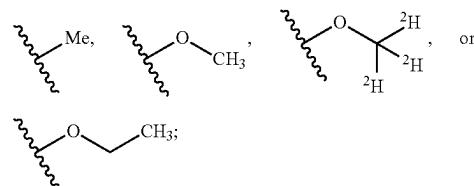
A², or \textcircled{N} is substituted with A², or a pharmaceutically acceptable salt thereof.

In some embodiments, each of R⁴¹, R⁴², R⁴³, and R⁴⁴ is, H, A², halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted —O—C₃-C₆ carbocyclyl, hydroxyl, optionally substituted amino; or R⁴¹ and R⁴², R⁴² and R⁴³, or R⁴³ and R⁴⁴, together with the carbon atoms to which each is attached,

combine to form \textcircled{N} ; and \textcircled{N} is optionally substituted C₂-C₉ heterocyclyl, which is optionally substituted with A²,

where one of R⁴¹, R⁴², R⁴³, and R⁴⁴ is A², or \textcircled{N} is substituted with A².

In some embodiments, each of R⁴¹, R⁴², R⁴³, and R⁴⁴ is, independently, H, A², F,



or R⁴¹ and R⁴², R⁴² and R⁴³, or R⁴³ and R⁴⁴, together with the carbon atoms to which each is attached,

combine to form \textcircled{N} ; and \textcircled{N} is optionally substituted C₂-C₉ heterocyclyl, which is optionally substituted with A², where one of R⁴¹, R⁴², R⁴³, and R⁴⁴ is

A², or \textcircled{N} is substituted with A².

In some embodiments, R⁴¹ is A². In some embodiments, R⁴² is A². In some embodiments, R⁴³ is A². In some embodiments, R⁴⁴ is A². In some embodiments, R⁴⁵ is A².

In some embodiments, R⁴⁵ is H or optionally substituted C₁-C₆ alkyl.

In some embodiments, R⁴⁵ is H or

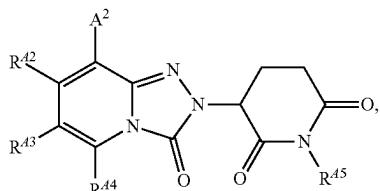


In some embodiments, R⁴⁵ is H. In some embodiments, R⁴⁵ is



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In some embodiments, the structure of Formula B has the structure of Formula B1:

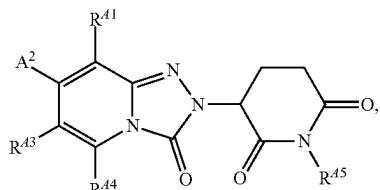


Formula B1

5

or a pharmaceutically acceptable salt thereof.

In some embodiments, the structure of Formula B has the structure of Formula B2:

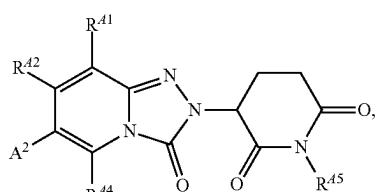


Formula B2

20

or a pharmaceutically acceptable salt thereof.

In some embodiments, the structure of Formula B has the structure of Formula B3:

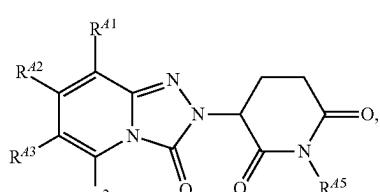


Formula B3

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or a pharmaceutically acceptable salt thereof.

In some embodiments, the structure of Formula B has the structure of Formula B4:



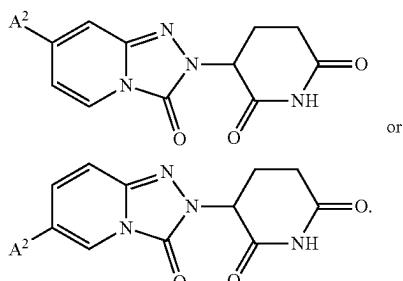
Formula B4

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or a pharmaceutically acceptable salt thereof.

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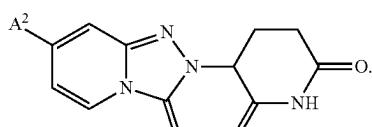
In some embodiments, the structure of Formula B is



or

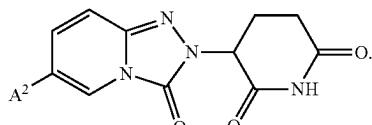
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In some embodiments, the structure of Formula B is



In some embodiments, the structure of Formula B is

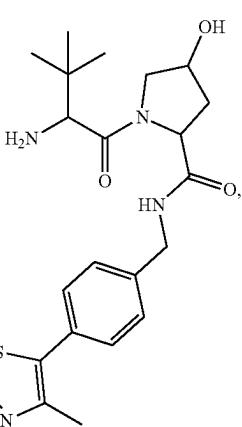
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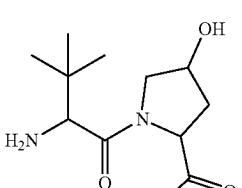
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In some embodiments, the ubiquitin ligase binding moiety comprises a von Hippel-Lindau ligand.

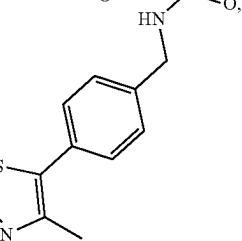
In some embodiments, the von Hippel-Lindau ligand has the structure of



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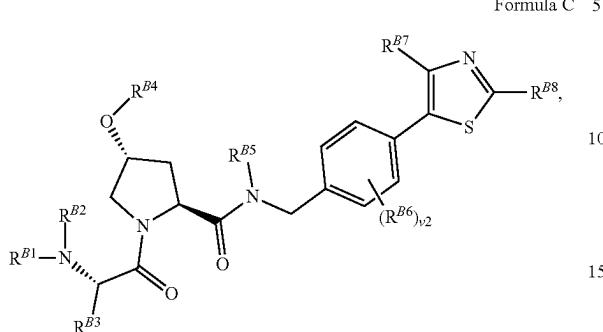
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or derivative or analog thereof.

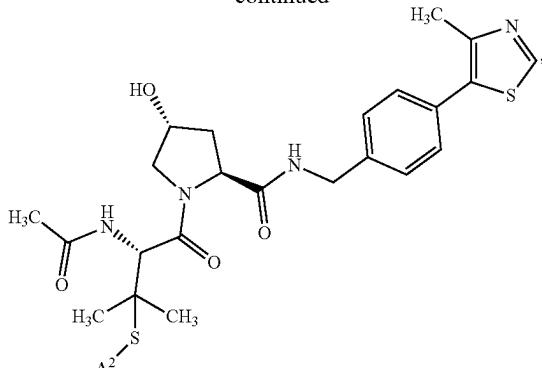
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In some embodiments, the degradation moiety includes the structure of Formula C:

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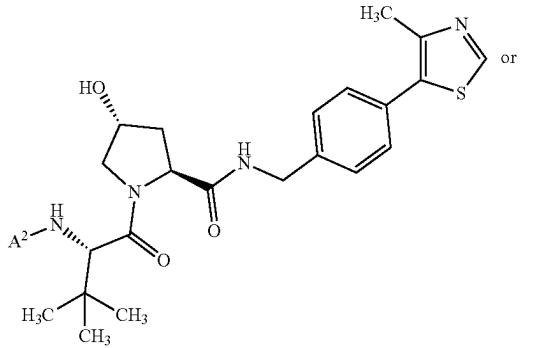
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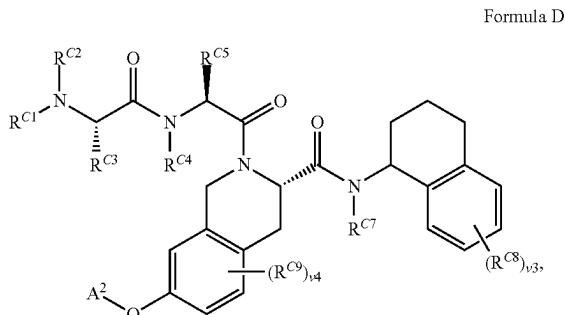
or derivative or analog thereof.
In some embodiments, the structure of Formula C is

where
 R^{B1} is H, A^2 , optionally substituted C_1 - C_6 alkyl, or optionally substituted C_1 - C_6 heteroalkyl;
 R^{B2} is H, optionally substituted C_1 - C_6 alkyl, or optionally substituted C_1 - C_6 heteroalkyl;
 R^{B3} is A^2 , optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_6 - C_{10} aryl, optionally substituted C_1 - C_6 alkyl C_3 - C_{10} carbocyclyl, or optionally substituted C_1 - C_6 alkyl C_6 - C_{10} aryl;
 R^{B4} is H, optionally substituted C_1 - C_6 alkyl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_6 - C_{10} aryl, optionally substituted C_1 - C_6 alkyl C_3 - C_{10} carbocyclyl, or optionally substituted C_1 - C_6 alkyl C_6 - C_{10} aryl;
 R^{B5} is H, optionally substituted C_1 - C_6 alkyl, or optionally substituted C_1 - C_6 heteroalkyl;
 $v2$ is 0, 1, 2, 3, or 4;
each R^{B6} is, independently, halogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heterocyclyl, optionally substituted C_6 - C_{10} aryl, optionally substituted C_2 - C_9 heteroaryl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino; and
each of R^{B7} and R^{B8} is, independently, H, halogen, optionally substituted C_1 - C_6 alkyl, or optionally substituted C_6 - C_{10} aryl,
where one of R^{B1} and R^{B3} is A^2 , or a pharmaceutically acceptable salt thereof.

In some embodiments, the structure of Formula C is

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In some embodiments, the degrader moiety includes the structure of Formula D:



where
 A^2 is a bond between B and the linker;
each of R^{C1} , R^{C2} , and R^{C7} is, independently, H, optionally substituted C_1 - C_6 alkyl, or optionally substituted C_1 - C_6 heteroalkyl;
 R^{C3} is optionally substituted C_1 - C_6 alkyl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_6 - C_{10} aryl, optionally substituted C_1 - C_6 alkyl C_3 - C_{10} carbocyclyl, or optionally substituted C_1 - C_6 alkyl C_6 - C_{10} aryl;
 R^{C5} is optionally substituted C_1 - C_6 alkyl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_6 - C_{10} aryl, optionally substituted C_1 - C_6 alkyl C_3 - C_{10} carbocyclyl, or optionally substituted C_1 - C_6 alkyl C_6 - C_{10} aryl;

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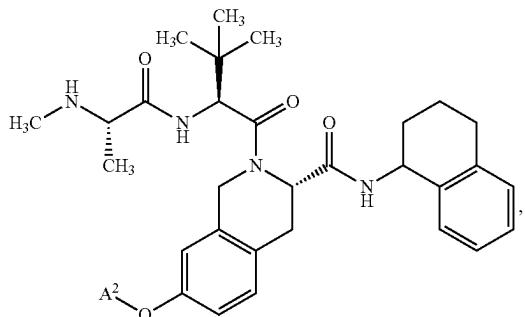
v3 is 0, 1, 2, 3, or 4;

each R^{C8} is, independently, halogen, optionally substituted $C_1\text{-}C_6$ alkyl, optionally substituted $C_1\text{-}C_6$ heteroalkyl, optionally substituted $C_3\text{-}C_{10}$ carbocyclyl, optionally substituted $C_2\text{-}C_9$ heterocyclyl, optionally substituted $C_6\text{-}C_{10}$ aryl, optionally substituted $C_2\text{-}C_9$ heteroaryl, optionally substituted $C_2\text{-}C_6$ alkenyl, optionally substituted $C_2\text{-}C_6$ heteroalkenyl, hydroxy, thiol, or optionally substituted amino;

v4 is 0, 1, 2, 3, or 4; and

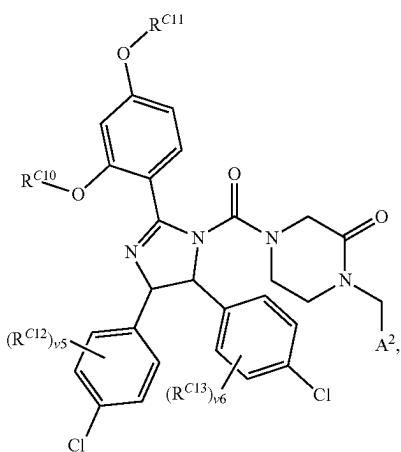
each R^{C9} is, independently, halogen, optionally substituted $C_1\text{-}C_6$ alkyl, optionally substituted $C_1\text{-}C_6$ heteroalkyl, optionally substituted $C_3\text{-}C_{10}$ carbocyclyl, optionally substituted $C_2\text{-}C_9$ heterocyclyl, optionally substituted $C_6\text{-}C_{10}$ aryl, optionally substituted $C_2\text{-}C_9$ heteroaryl, optionally substituted $C_2\text{-}C_6$ alkenyl, optionally substituted $C_2\text{-}C_6$ heteroalkenyl, hydroxy, thiol, or optionally substituted amino, or a pharmaceutically acceptable salt thereof.

In some embodiments, the structure of Formula D is



or derivative or analog thereof.

In some embodiments, the degrader moiety includes the structure of Formula E:



where

 A^2 is a bond between B and the linker;

each of R^{C10} and R^{C11} is, independently, H, optionally substituted $C_1\text{-}C_6$ alkyl, optionally substituted $C_3\text{-}C_{10}$ carbocyclyl, optionally substituted $C_6\text{-}C_{10}$ aryl, optionally substituted $C_1\text{-}C_6$ alkyl $C_3\text{-}C_{10}$ carbocyclyl, or optionally substituted $C_1\text{-}C_6$ alkyl $C_6\text{-}C_{10}$ aryl;

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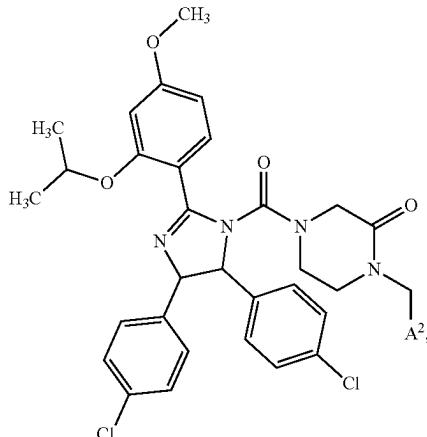
v5 is 0, 1, 2, 3, or 4;

each R^{C12} is, independently, halogen, optionally substituted $C_1\text{-}C_6$ alkyl, optionally substituted $C_1\text{-}C_6$ heteroalkyl, optionally substituted $C_3\text{-}C_{10}$ carbocyclyl, optionally substituted $C_2\text{-}C_9$ heterocyclyl, optionally substituted $C_6\text{-}C_{10}$ aryl, optionally substituted $C_2\text{-}C_9$ heteroaryl, optionally substituted $C_2\text{-}C_6$ alkenyl, optionally substituted $C_2\text{-}C_6$ heteroalkenyl, hydroxy, thiol, or optionally substituted amino;

v6 is 0, 1, 2, 3, or 4; and

each R^{21} is, independently, halogen, optionally substituted $C_1\text{-}C_6$ alkyl, optionally substituted $C_1\text{-}C_6$ heteroalkyl, optionally substituted $C_3\text{-}C_{10}$ carbocyclyl, optionally substituted $C_2\text{-}C_9$ heterocyclyl, optionally substituted $C_6\text{-}C_{10}$ aryl, optionally substituted $C_2\text{-}C_9$ heteroaryl, optionally substituted $C_2\text{-}C_6$ alkenyl, optionally substituted $C_2\text{-}C_6$ heteroalkenyl, hydroxy, thiol, or optionally substituted amino, or a pharmaceutically acceptable salt thereof.

In some embodiments, the structure of Formula E is



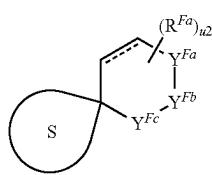
or derivative or analog thereof.

In some embodiments, the degradation moiety includes the structure of Formula FA:

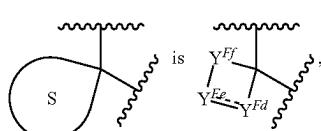
Formula E

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Formula FA

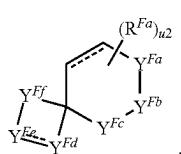


where



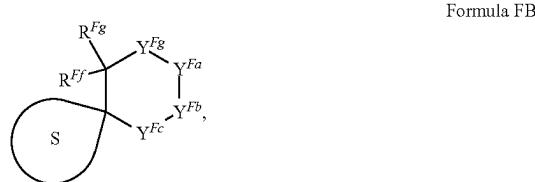
or a bicyclic moiety which is substituted with A^2 and substituted with one or more groups independently selected from H, R^{FF1} , and oxo;

— is a single bond or a double bond;
 u_2 is 0, 1, 2, or 3;
 A^2 is a bond between the degrader and the linker;
 Y^{Fa} is $CR^{Fd}R^{Fc}$, $C=O$, $C=S$, $C=CH_2$, SO_2 , $S(O)$,
 $P(O)Oalkyl$, $P(O)NHalkyl$, $P(O)N(alkyl)_2$, $P(O)alkyl$, 5
 $P(O)OH$, $P(O)NH_2$;
 Y^{Fb} is NH , NR^{FF1} , CH_2 , CHR^{FF1} , $C(R^{FF1})_2$, O , or S ;
 Y^{Fc} is $CR^{Fd}R^{Fe}$, $C=O$, $C=S$, $C=CH_2$, SO_2 , $S(O)$,
 $P(O)Oalkyl$, $P(O)NHalkyl$, $P(O)N(alkyl)_2$, $P(O)alkyl$,
 $P(O)OH$, $P(O)NH_2$;
each of R^{Fd} , R^{Fc} , R^{Fd} , and R^{Fe} is, independently, H , alkyl,
aliphatic, heteroaliphatic, aryl, heteroaryl, carbocyclyl,
hydroxyl, alkoxy, amino, $-NHalkyl$, or $-Nalkyl_2$; 10
or R^{Fd} and R^{Fc} , together with the carbon atom to which
each is attached, combine to form a 3-, 4-, 5-, or
6-membered spirocarbocyclylene, or a 4-, 5-, or
6-membered spiroheterocyclene comprising 1 or 2 15
heteroatoms selected from N and O ;
or R^{Fd} and R^{Fe} , together with the carbon atom to which
each is attached, combine to form a 3-, 4-, 5-, or
6-membered spirocarbocyclylene, or a 4-, 5-, or
6-membered spiroheterocyclene comprising 1 or 2 20
heteroatoms selected from N and O ; and
or R^{Fd} and R^{Fb} , together with the carbon atoms to which
each is attached, combine to form a 1, 2, 3, or 4 carbon
bridged ring;
each of Y^{Fd} and Y^{Ff} is, independently, CH_2 , CHR^{FF2} ,
 $C(R^{FF2})_2$, $C(O)$, N , NH , NR^{FF3} , O , S , or $S(O)$;
 Y^{Fe} is a bond or a divalent moiety attached to Y^{Fd} and Y^{Ff}
that contains 1 to 5 contiguous carbon atoms that form
a 3 to 8-membered ring, 25
wherein 1, 2, or 3 carbon atoms can be replaced with a
nitrogen, oxygen, or sulfur atom;
wherein one of the ring atoms is substituted with A^2 and
the others are substituted with one or more groups
independently selected from H and R^{FF1} ; and
wherein the contiguous atoms of Y^{Fe} can be attached 30
through a single or double bond;
each R^{FF1} is, independently, H , alkyl, alkenyl, alkynyl,
aliphatic, heteroaliphatic, carbocyclyl, halogen,
hydroxyl, amino, cyano, alkoxy, aryl, heteroaryl, het-
erocyclyl, alkylamino, alkylhydroxyl, or haloalkyl;
each R^{FF2} is, independently, alkyl, alkene, alkyne, halo-
gen, hydroxyl, alkoxy, azide, amino, $-C(O)H$, $-C(O)$
 OH , $-C(O)(aliphatic, including alkyl)$, $-C(O)O(aliphatic,$ 40
including alkyl), $-NH(aliphatic, including$
alkyl), $-N(aliphatic including alkyl)(aliphatic includ- 45
ing alkyl)$, $-NHSO_2alkyl$, $-N(alkyl)SO_2alkyl$,
 $-NHSO_2aryl$, $-N(alkyl)SO_2aryl$, $-NHSO_2alkenyl$,
 $-N(alkyl)SO_2alkenyl$, $-NHSO_2alkynyl$, $-N(alkyl)$
 $SO_2alkynyl$, aliphatic, heteroaliphatic, aryl, heteroaryl,
heterocyclic, carbocyclic, cyano, nitro, nitroso, $-SH$,
 $-Salkyl$, or haloalkyl; and 50
 R^{FF3} is alkyl, alkenyl, alkynyl, $-C(O)H$, $-C(O)OH$,
 $-C(O)alkyl$, or $-C(O)Oalkyl$,
wherein if Y^{Fd} or Y^{Ff} is substituted with A^2 , then Y^{Fe} is
a bond, or a pharmaceutically acceptable salt thereof.
In some embodiments, the compound of Formula FA has
the structure of Formula FA1: 55



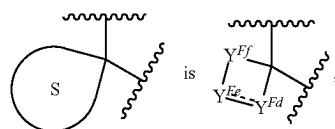
Formula FA1

In some embodiments, the degradation moiety includes
the structure of Formula FB:



Formula FB

where



or a bicyclic moiety which is substituted with A^2 and
substituted with one or more groups independently selected
from H , R^{FF1} , and oxo;

A^2 is a bond between the degrader and the linker;
 Y^{Fa} is $CR^{Fd}R^{Fc}$, $C=O$, $C=S$, $C=CH_2$, SO_2 , $S(O)$,
 $P(O)Oalkyl$, $P(O)NHalkyl$, $P(O)N(alkyl)_2$, $P(O)alkyl$,
 $P(O)OH$, $P(O)NH_2$;

each of Y^{Fb} and Y^{Fg} is, independently, NH , NR^{FF1} , CH_2 ,
 CHR^{FF1} , $C(R^{FF1})_2$, O , or S ;

Y^{Fc} is $CR^{Fd}R^{Fe}$, $C=O$, $C=S$, $C=CH_2$, SO_2 , $S(O)$,
 $P(O)Oalkyl$, $P(O)NHalkyl$, $P(O)N(alkyl)_2$, $P(O)alkyl$,
 $P(O)OH$, $P(O)NH_2$;

each of R^{Fd} , R^{Fc} , R^{Fd} , R^{Fe} , R^{Ff} , and R^{Fg} is, indepen-
dently, H , alkyl, aliphatic, heteroaliphatic, aryl, het-
eroaryl, carbocyclyl, hydroxyl, alkoxy, amino,
 $-NHalkyl$, or $-Nalkyl_2$;

or R^{Fd} and R^{Fc} , together with the carbon atom to which
each is attached, combine to form a 3-, 4-, 5-, or
6-membered spirocarbocyclylene, or a 4-, 5-, or
6-membered spiroheterocyclene comprising 1 or 2
heteroatoms selected from N and O ;

or R^{Fd} and R^{Fe} , together with the carbon atom to which
each is attached, combine to form a 3-, 4-, 5-, or
6-membered spirocarbocyclylene, or a 4-, 5-, or
6-membered spiroheterocyclene comprising 1 or 2
heteroatoms selected from N and O ;

or R^{Fd} and R^{Fg} , together with the carbon atom to which
each is attached, combine to form a 3-, 4-, 5-, or
6-membered spirocarbocyclylene, or a 4-, 5-, or
6-membered spiroheterocyclene comprising 1 or 2
heteroatoms selected from N and O ;

or R^{Fd} and R^{Fb} , together with the carbon atoms to which
each is attached, combine to form a 1, 2, 3, or 4 carbon
bridged ring;

or R^{Fd} and R^{Ff} , together with the carbon atoms to which
each is attached, combine to form a 1, 2, 3, or 4 carbon
bridged ring;

or R^{Fb} and R^{Fg} , together with the carbon atoms to which
each is attached, combine to form a 1, 2, 3, or 4 carbon
bridged ring;

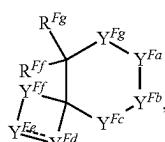
each of Y^{Fd} and Y^{Ff} is, independently, CH_2 , CHR^{FF2} ,
 $C(R^{FF2})_2$, $C(O)$, N , NH , NR^{FF3} , O , S , or $S(O)$;

or a pharmaceutically acceptable salt thereof.

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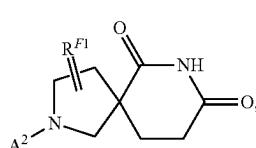
Y^{Fe} is a bond or a divalent moiety attached to Y^{Fd} and Y^{Ff} that contains 1 to 5 contiguous carbon atoms that form a 3 to 3-membered ring,
 wherein 1, 2, or 3 carbon atoms can be replaced with a nitrogen, oxygen, or sulfur atom;
 wherein one of the ring atoms is substituted with A^2 and the others are substituted with one or more groups independently selected from H and R^{FF1} ; and
 wherein the contiguous atoms of Y^{Fe} can be attached through a single or double bond;
 each R^{FF1} is, independently, H, alkyl, alkenyl, alkynyl, aliphatic, heteroaliphatic, carbocyclic, halogen, hydroxyl, amino, cyano, alkoxy, aryl, heteroaryl, heterocyclic, alkylamino, alkylhydroxyl, or haloalkyl;
 each R^{FF2} is, independently, alkyl, alkenyl, alkyne, halogen, hydroxyl, alkoxy, azide, amino, $—C(O)H$, $—C(O)OH$, $—C(O)(\text{aliphatic, including alkyl})$, $—C(O)O(\text{aliphatic, including alkyl})$, $—NH(\text{aliphatic, including alkyl})$, $—N(\text{aliphatic including alkyl})(\text{aliphatic including alkyl})$, $—NHSO_2\text{alkyl}$, $—N(\text{alkyl})SO_2\text{alkyl}$, $—NHSO_2\text{aryl}$, $—N(\text{alkyl})SO_2\text{aryl}$, $—NHSO_2\text{alkenyl}$, $—N(\text{alkyl})SO_2\text{alkenyl}$, $—NHSO_2\text{alkynyl}$, $—N(\text{alkyl})SO_2\text{alkynyl}$, aliphatic, heteroaliphatic, aryl, heteroaryl, heterocyclic, carbocyclic, cyano, nitro, nitroso, $—SH$, $—S\text{alkyl}$, or haloalkyl; and
 R^{FF3} is alkyl, alkenyl, alkynyl, $—C(O)H$, $—C(O)OH$, $—C(O)\text{alkyl}$, or $—C(O)\text{Oalkyl}$, wherein if Y^{Fd} is substituted with A^2 , then Y^{Fe} is a

wherein if Y⁻ or is substituted with A⁺, then Y⁻ is a bond, or a pharmaceutically acceptable salt thereof.



or a pharmaceutically acceptable salt thereof.

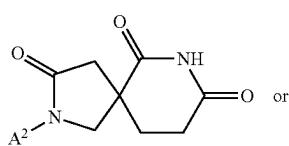
In some embodiments, the degradation moiety includes the structure of Formula F1:



where A² is a bond between the degrader and the linker; and R^{F1} is absent or O, or a pharmaceutically acceptable salt thereof.

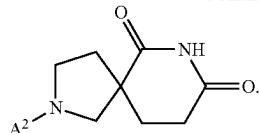
In some embodiments, R^{F1} is absent. In some embodiments, R^{F1} is Q.

In some embodiments, the structure of Formula F1 is

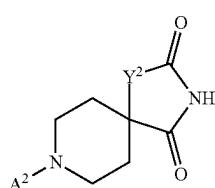


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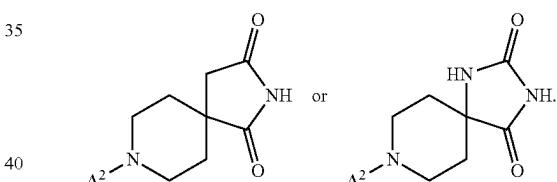
In some embodiments, the degradation moiety includes
 10 the structure Formula F2:



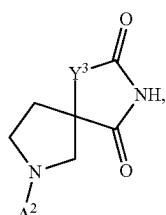
where A² is a bond between the degrader and the linker; and Y² is CH₂ or NH, or a pharmaceutically acceptable salt thereof.

In some embodiments, Y² is NH. In some embodiments, Y² is CH₂.

In some embodiments, structure of Formula F2 is



In some embodiments, the degradation moiety includes the structure Formula G:

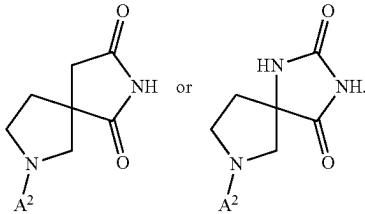


where A² is a bond between the degrader and the linker; and Y³ is CH₂ or NH, or a pharmaceutically acceptable salt thereof.

In some embodiments, Y³ is NH. In some embodiments, Y³ is CH.

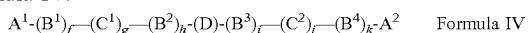
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In some embodiments, structure of Formula G is



The degradation moiety may also include structures found in, e.g., WO2017/197036; WO2019/204354, WO2019/236483, WO2020/010177; and WO2020/010227, the structures of which are herein incorporated by reference.

In some embodiments, the linker has the structure of Formula IV:



where

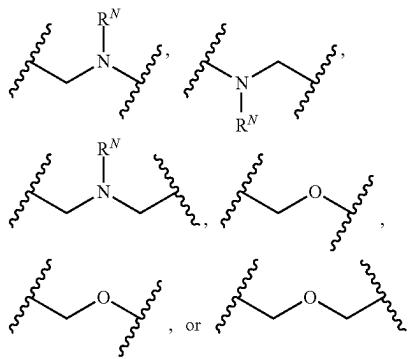
 A^1 is a bond between the linker and A ; A^2 is a bond between B and the linker;each of B^1 , B^2 , B^3 , and B^4 is, independently, optionally substituted C_1 - C_2 alkylene, optionally substituted C_1 - C_3 heteroalkylene, O, S, $S(O)_2$, or NR^N ;each R^N is, independently, H, optionally substituted C_{1-4} alkyl, optionally substituted C_{2-4} alkenyl, optionally substituted C_{2-4} alkynyl, optionally substituted C_{2-6} heterocyclcyl, optionally substituted C_{6-12} aryl, or optionally substituted C_{1-7} heteroalkyl;each of C^1 and C^2 is, independently, carbonyl, thiocarbonyl, sulphonyl, or phosphoryl;each of f , g , h , i , j , and k is, independently, 0 or 1; and D is optionally substituted C_{1-10} alkylene, optionally substituted C_{2-10} alkenylene, optionally substituted C_{2-10} alkynylene, optionally substituted C_{2-6} heterocyclcylene, optionally substituted C_{6-12} arylene, optionally substituted C_2 - C_{10} polyethylene glycol, or optionally substituted C_{1-10} heteroalkylene, or a chemical bond linking $A^1-(B^1)_f-(C^1)_g-(B^2)_h-$ to $-(B^3)_i-(C^2)_j-(B^4)_k-A^2$.

In some embodiments, each of B^1 , B^2 , B^3 , and B^4 is, independently, optionally substituted C_1 - C_4 alkylene, optionally substituted C_1 - C_4 heteroalkylene, or NR^N .

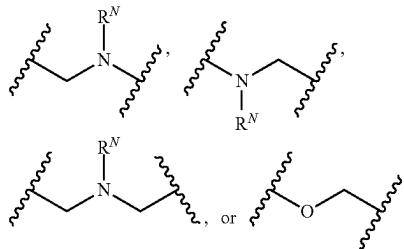
In some embodiments, each R^N is, independently, H or optionally substituted C_1 - C_4 alkylene.

In some embodiments, each R^N is, independently, H or methyl.

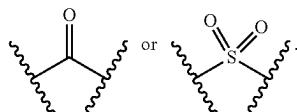
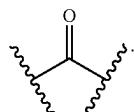
In some embodiments, each of B^1 and B^4 is, independently,



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In some embodiments, B^1 is

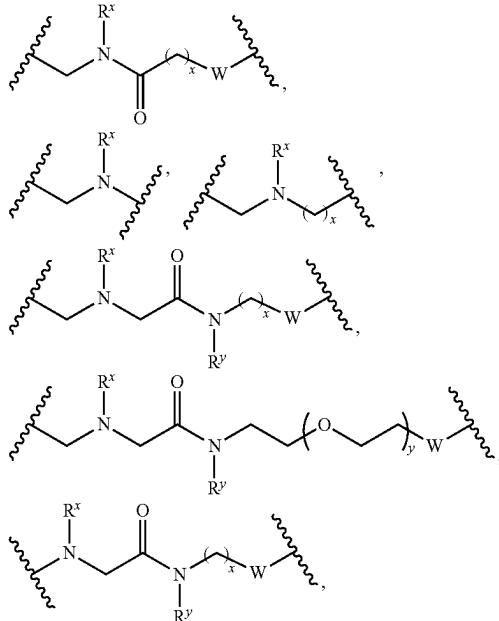
15 In some embodiments, each of C^1 and C^2 is, independently

In some embodiments, C^1 is

In some embodiments, B^2 is NR^N . In some embodiments, B^2 is optionally substituted C_1 - C_4 alkylene.

In some embodiments, f is 0. In some embodiments, f is 1.In some embodiments, g is 1. In some embodiments, h is 0.In some embodiments, h is 1. In some embodiments, i is 0.In some embodiments, i is 1. In some embodiments, j is 0.In some embodiments, j is 1. In some embodiments, k is 0.In some embodiments, k is 1.

In some embodiments, the linker has the structure of



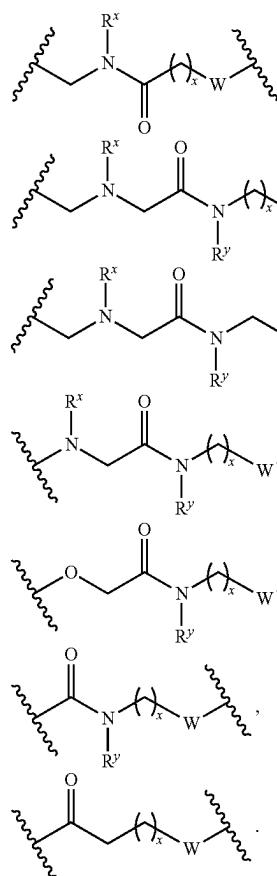
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wherein
x is 1, 2, 3, 4, 5, 6, 7, or 8;
y is 1, 2, 3, or 4;

R^x is H, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, or optionally substituted C_3 - C_6 carbocyclyl;
 R^y is H, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, or optionally substituted C_3 - C_6 carbocyclyl; and
 W is O or NR^w , wherein R^w is H, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, or optionally substituted C_2 - C_6 carbocyclyl.

In some embodiments, the linker has the structure of



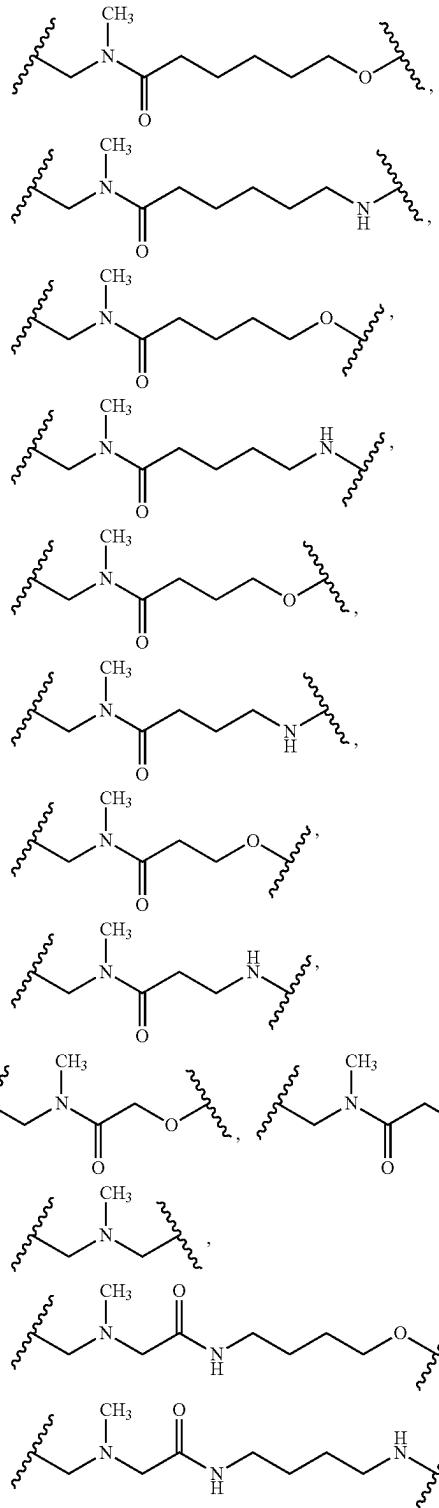
In some embodiments, R^x is H or me optionally substituted C₁-C₆ alkyl. In some embodiments, R^y is H or option-

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ally substituted C₁-C₆ alkyl. In some embodiments, R^w is H or optionally substituted C₁-C₆ alkyl.

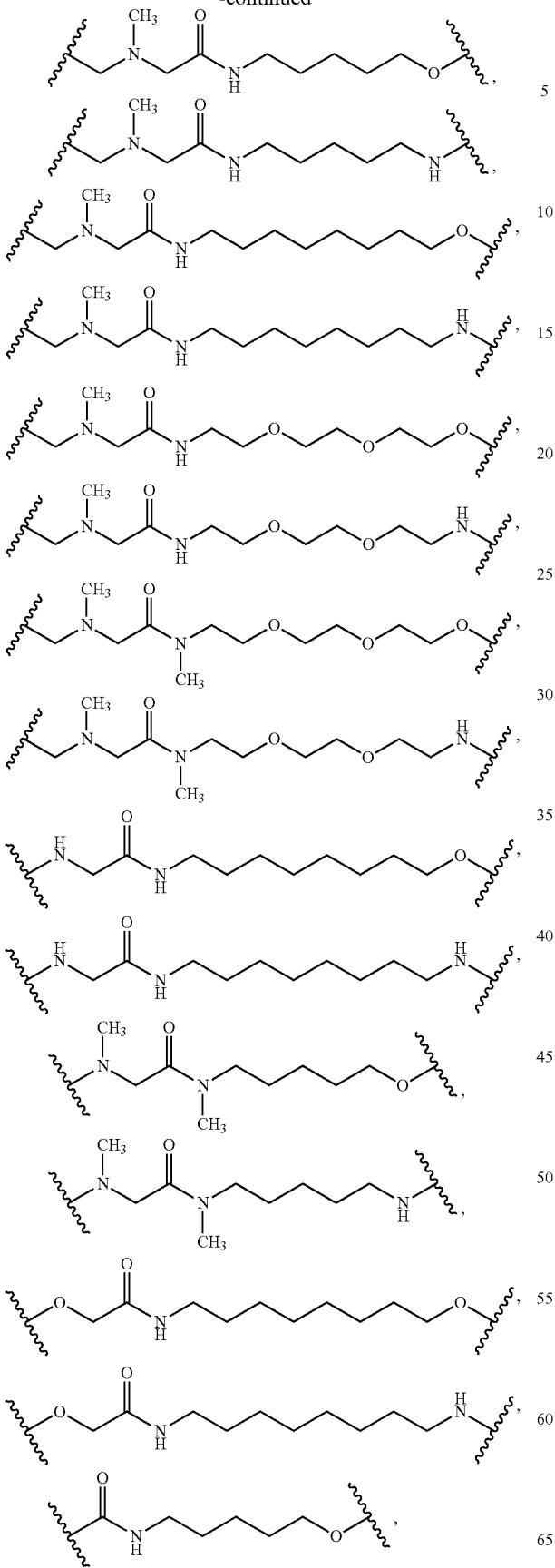
In some embodiments, R^x is H or methyl. In some embodiments, RY is H or methyl. In some embodiments, R^w is H or methyl.

In some embodiments, the linker has the structure of



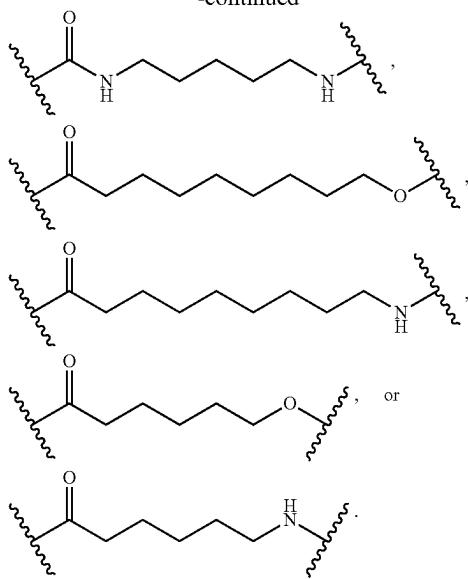
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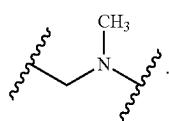


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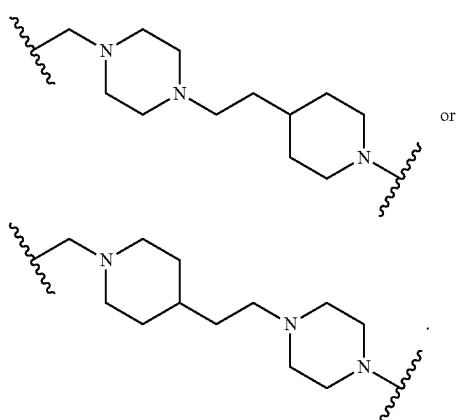
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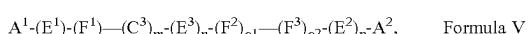
In some embodiments, the linker has the structure of



In some embodiments, the linker has the structure of



In some embodiments, the linker has the structure of Formula V:



where

 A^1 is a bond between the linker and A; A^2 is a bond between B and the linker;

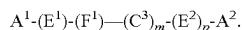
each of m, n, o1, o2, and p is, independently, 0 or 1;

each of E^1 and E^2 is, independently, O, S, NR^N , optionally substituted C_{1-10} alkylene, optionally substituted C_{2-10} alkenylene, optionally substituted C_{2-10} alkynylene, optionally substituted C_2-C_{10} polyethylene glycol, or optionally substituted C_{1-10} heteroalkylene;

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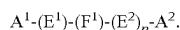
E^3 is optionally substituted C_1 - C_6 alkylene, optionally substituted C_1 - C_6 heteroalkylene, O, S, or NR^N ; each R^N is, independently, H, optionally substituted C_{1-4} alkyl, optionally substituted C_{2-4} alkenyl, optionally substituted C_{2-4} alkynyl, optionally substituted C_{2-6} heterocyclyl, optionally substituted C_{6-12} aryl, or optionally substituted C_{1-7} heteroalkyl; C^3 is carbonyl, thiocarbonyl, sulphonyl, or phosphoryl; and each of F^1 , F^2 , and F^3 is, independently, optionally substituted C_3 - C_{10} carbocyclylene, optionally substituted C_{2-10} heterocyclylene, optionally substituted C_6 - C_{10} arylene, or optionally substituted C_2 - C_9 heteroarylene.

In some embodiments, the linker has the structure of Formula Va:



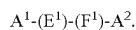
Formula Va

In some embodiments, the linker has the structure of Formula Vb:



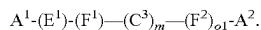
Formula Vb

In some embodiments, the linker has the structure of Formula Vc:



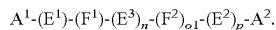
Formula Vc

In some embodiments, the linker has the structure of Formula Vd:



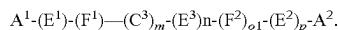
Formula Vd

In some embodiments, the linker has the structure of Formula Ve:



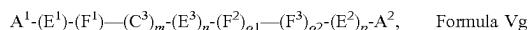
Formula Ve

In some embodiments, the linker has the structure of Formula Vf:



Formula Vf

In some embodiments, the linker has the structure of Formula Vg:



Formula Vg

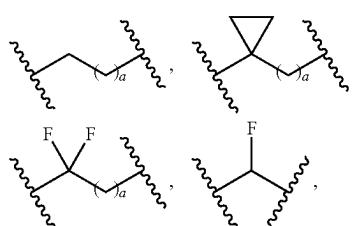
In some embodiments, each of E^1 and E^2 is, independently, NR^N , optionally substituted C_{1-10} alkyl, optionally substituted C_2 - C_{10} polyethylene glycol, or optionally substituted C_{1-10} heteroalkyl.

In some embodiments, E^3 is optionally substituted C_1 - C_6 alkylene, O, S, or NR^N ;

In some embodiments, E^3 is optionally substituted C_1 - C_6 alkylene. In some embodiments, E^3 is optionally substituted C_1 - C_3 alkylene. In some embodiments, E^3 is O, S, or NR^N .

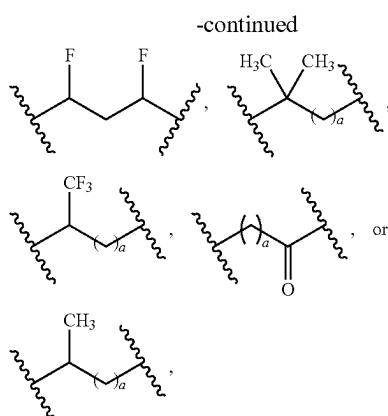
In some embodiments, E^3 is C_1 - C_6 alkylene. In some embodiments, E^3 is C_1 - C_3 alkylene. In some embodiments, E^3 is O.

In some embodiments, E^3 is



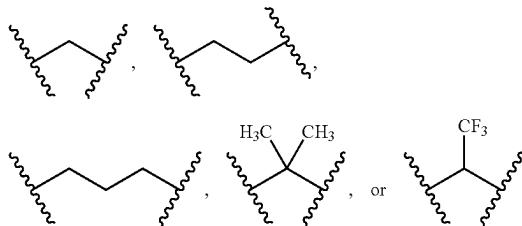
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where a is 0, 1, 2, 3, 4, or 5.

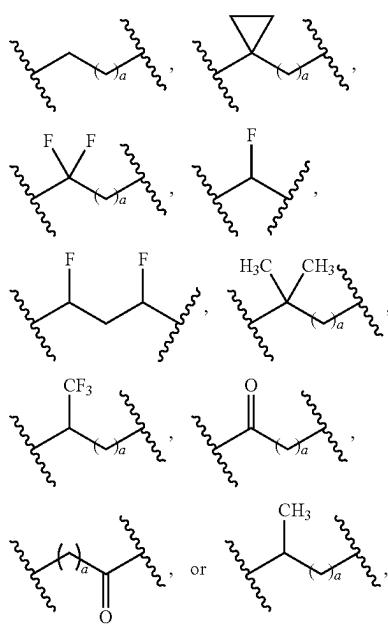
In some embodiments, E^3 is



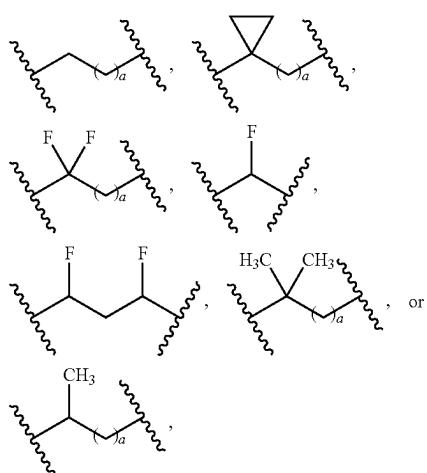
In some embodiments, each R^N is, independently, H or optionally substituted C_{1-4} alkyl.

In some embodiments, each R^N is, independently, H or methyl.

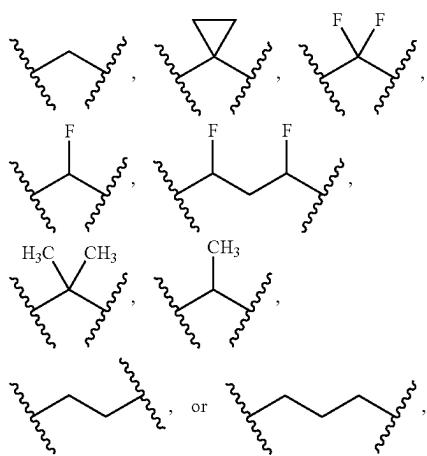
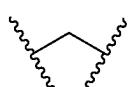
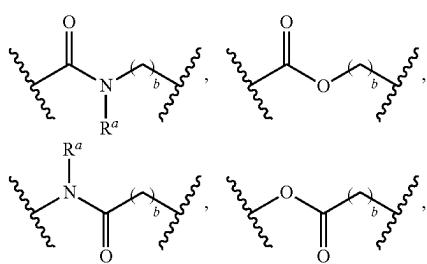
In some embodiments, E^1 is



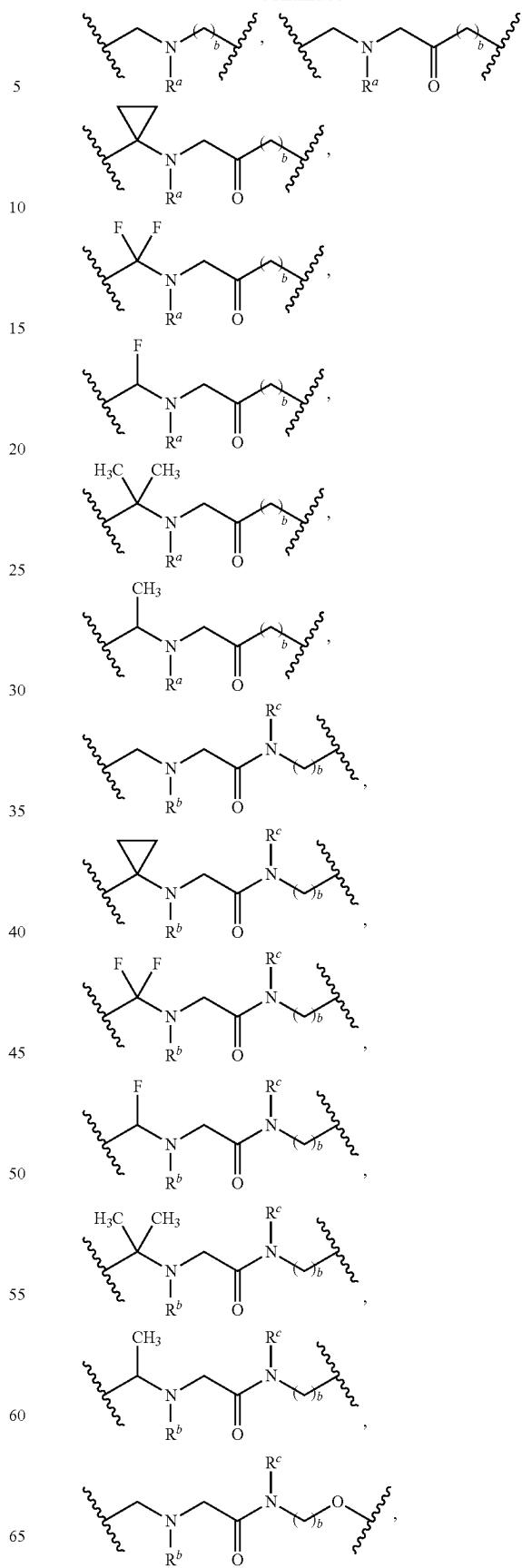
where a is 0, 1, 2, 3, 4, or 5.

125In some embodiments, E¹ is

where a is 0, 1, 2, 3, 4, or 5.

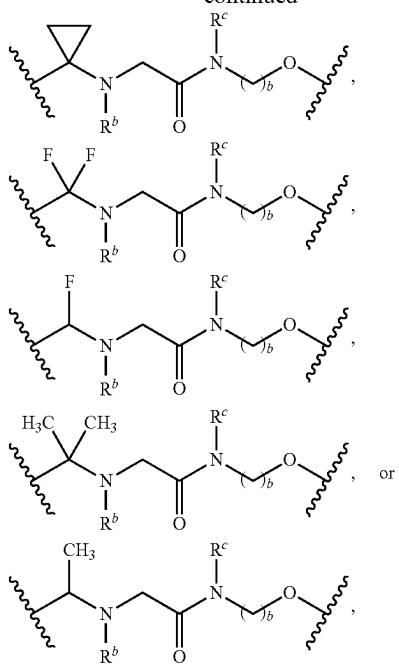
In some embodiments, E¹ isIn some embodiments, E¹ isIn some embodiments, E¹ is**126**

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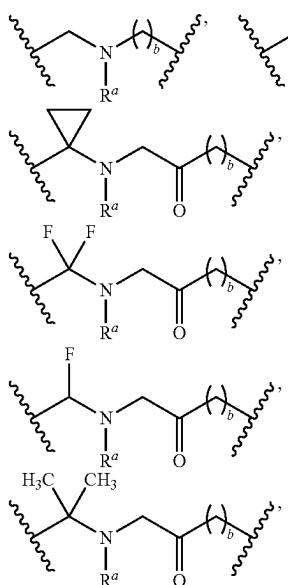


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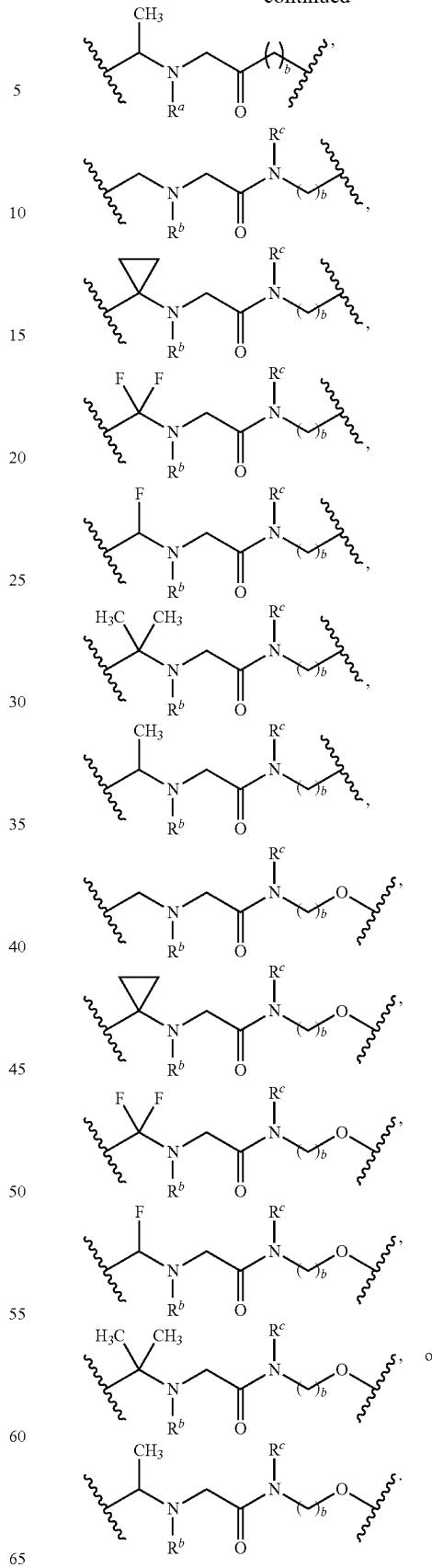
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where

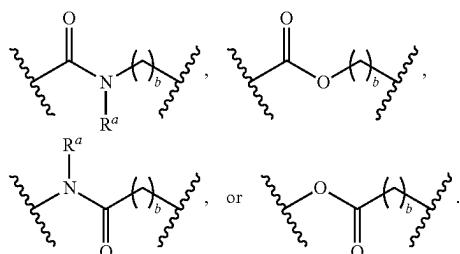
 b is 0, 1, 2, 3, 4, 5, or 6; R^a is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_3-C_6 carbocyclyl; R^b is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_3-C_6 carbocyclyl; and R^c is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_3-C_6 carbocyclyl.In some embodiments, E^1 is**128**

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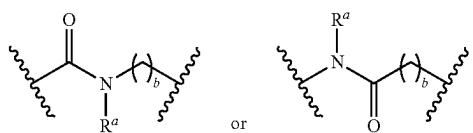


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In some embodiments, E^1 is



In some embodiments, E¹ is

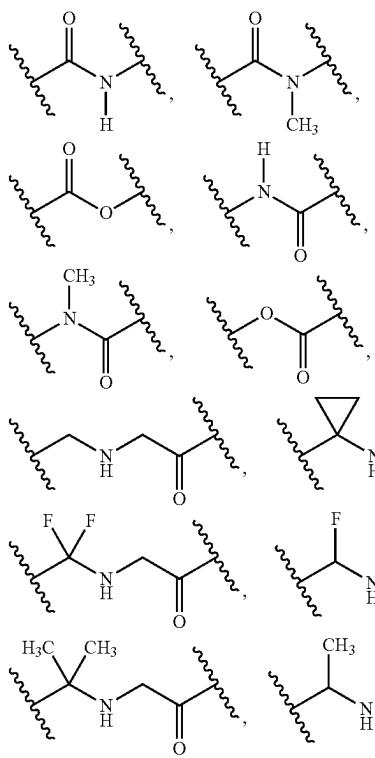


In some embodiments, R^a is H or optionally substituted C₁-C₆ alkyl. In some embodiments, R^b is H or optionally substituted C₁-C₆ alkyl. In some embodiments, R^c is H or optionally substituted C₁-C₆ alkyl.

In some embodiments, R^a is H or methyl. In some embodiments, R^b is H or methyl. In some embodiments, R^c is H or methyl.

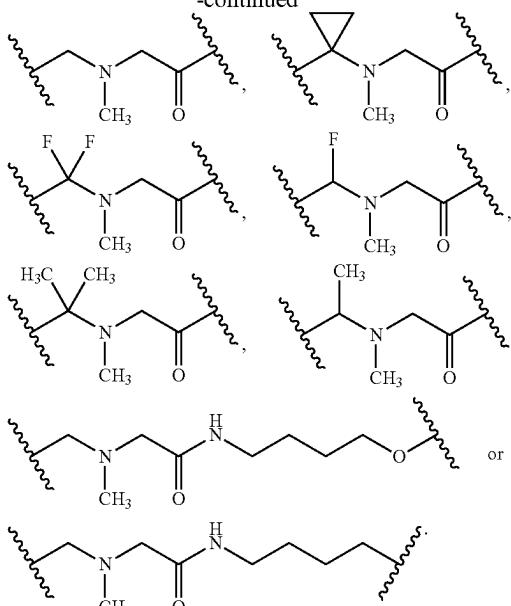
In some embodiments, b is 0, 1, 2, or 3. In some embodiments, b is 0. In some embodiments, b is 1. In some embodiments, b is 2. In some embodiments, b is 3.

In some embodiments, E^1 is

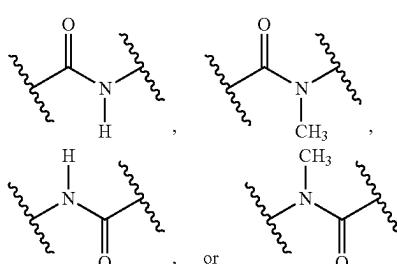


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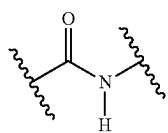
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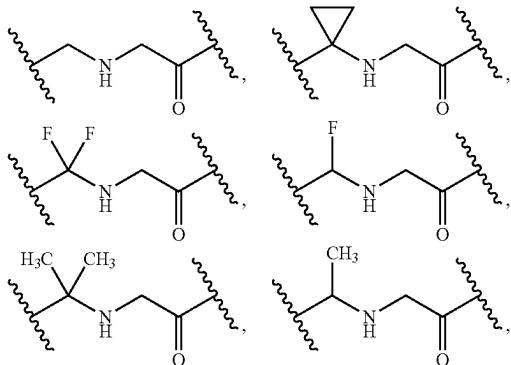
In some embodiments, E^1 is



In some embodiments, E¹ is

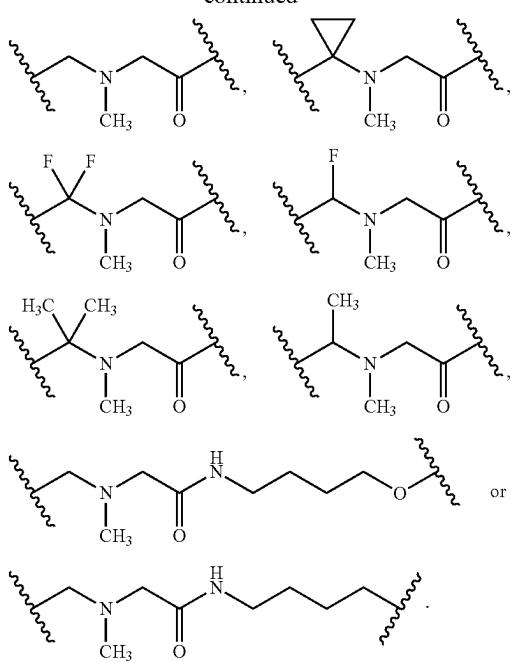
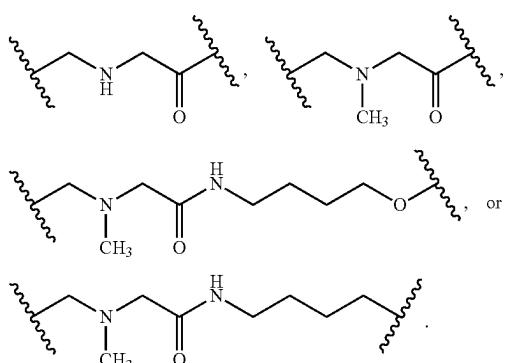
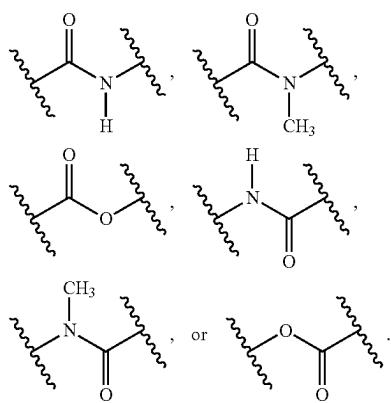
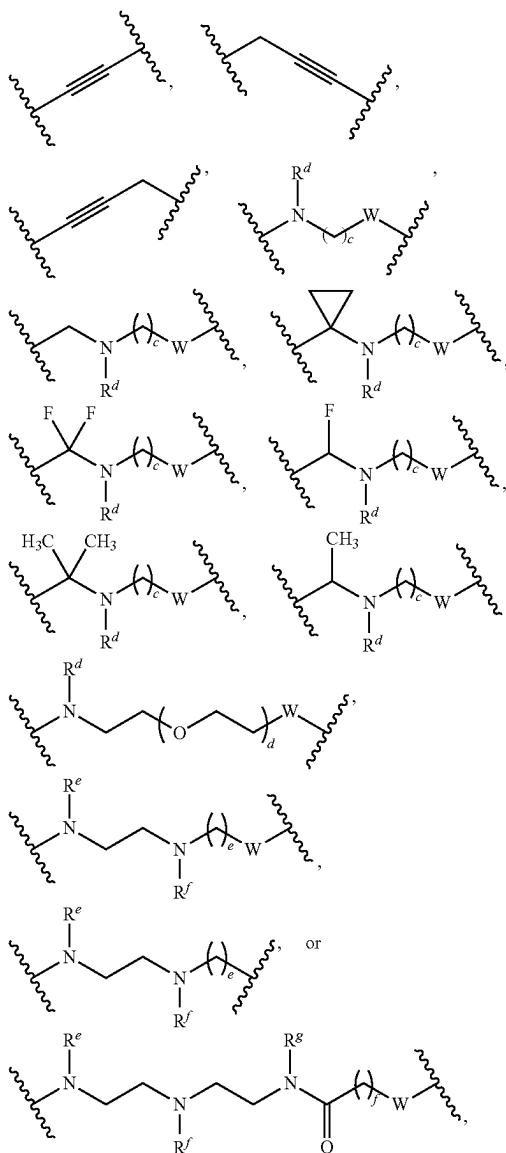


In some embodiments, E¹ is



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In some embodiments, E¹ isIn some embodiments, E¹ is**132**In some embodiments, E² is O, NR^w,

wherein

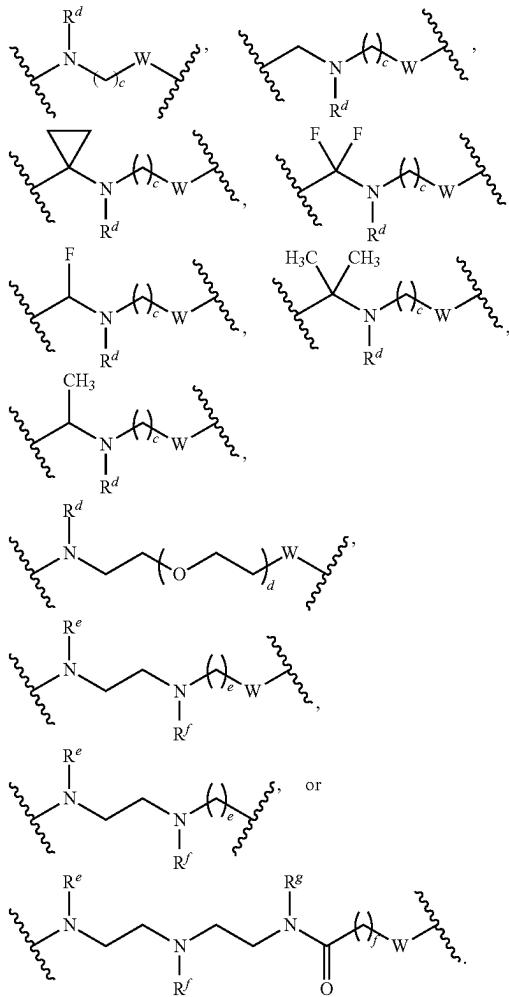
c is 0, 1, 2, 3, 4, 5, 6, 7, or 8;

d is 0, 1, 2, or 3;

e is 0, 1, 2, 3, 4, 5, or 6;

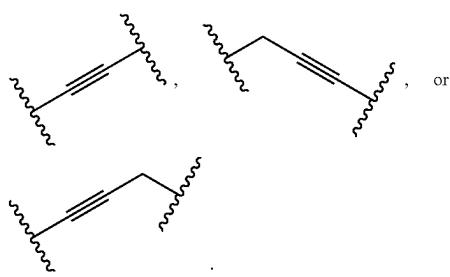
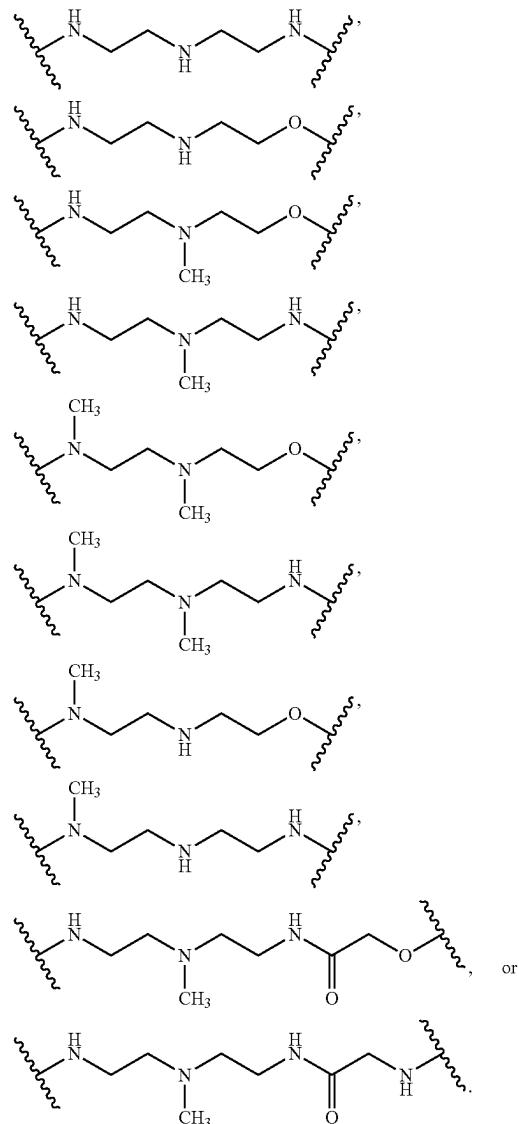
f is 0, 1, 2, 3, or 4;

R^d is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₆ carbocyclyl;R^e is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₆ carbocyclyl;R^f is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₆ carbocyclyl;R^g is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₆ carbocyclyl; andW is O or NR^w, wherein R^w is H or optionally substituted C₁-C₆ alkyl.

133In some embodiments, E^2 is O, NR^w,

In some embodiments, R^d is H or optionally substituted C₁-C₆ alkyl. In some embodiments, R^e is H or optionally substituted C₁-C₆ alkyl. In some embodiments, R^f is H or optionally substituted C₁-C₆ alkyl. In some embodiments, R^g is H or optionally substituted C₁-C₆ alkyl. In some embodiments, R^w is H or optionally substituted C₁-C₆ alkyl.

In some embodiments, R^d is H or methyl. In some embodiments, R^e is H or methyl. In some embodiments, R^f is H or methyl. In some embodiments, R^g is H or methyl. In some embodiments, R^w is H or methyl.

In some embodiments, E² is**134**In some embodiments, E² is O,

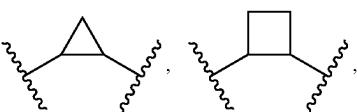
In some embodiments, each of F¹, F², or F³ is, independently, optionally substituted C₃-C₁₀ carbocyclene.

In some embodiments, the C₃-C₁₀ carbocyclene is monocyclic. In some embodiments, the C₃-C₁₀ carbocyclene is polycyclic.

In some embodiments, the C₃-C₁₀ carbocyclene is bicyclic.

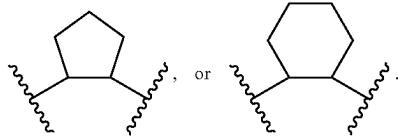
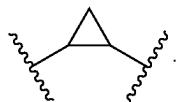
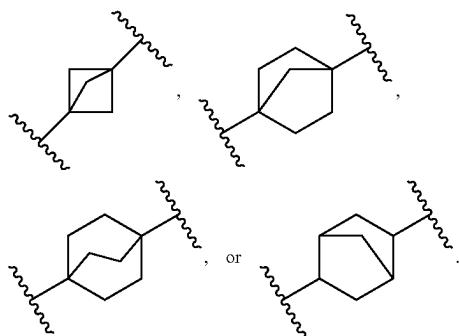
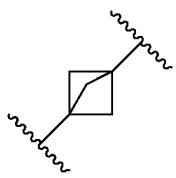
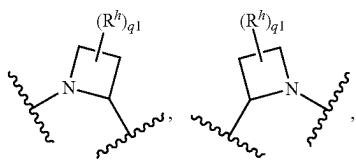
In some embodiments, the C₃-C₁₀ carbocyclene is bridged. In some embodiments, the C₃-C₁₀ carbocyclene is fused. In some embodiments, the C₃-C₁₀ carbocyclene is spirocyclic.

In some embodiments, the C₃-C₁₀ carbocyclene is

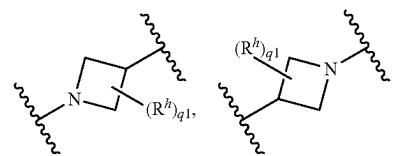


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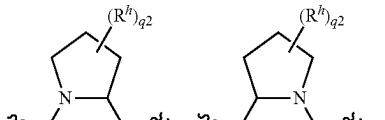
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In some embodiments, F^2 isIn some embodiments, the C_3 - C_{10} carbocyclene isIn some embodiments, F^1 isIn some embodiments, each of F^1 , F^2 , or F^3 is, independently, optionally substituted C_2 - C_9 heterocyclene.In some embodiments, the C_2 - C_9 heterocyclene is monocyclic. In some embodiments, the C_2 - C_9 heterocyclene is polycyclic.In some embodiments, the C_2 - C_9 heterocyclene is bicyclic.In some embodiments, the C_2 - C_9 heterocyclene is bridged. In some embodiments, the C_2 - C_9 heterocyclene is fused. In some embodiments, the C_2 - C_9 heterocyclene is spirocyclic.In some embodiments, the C_2 - C_9 heterocyclene includes a quaternary amine.In some embodiments, the C_2 - C_9 heterocyclene is**136**

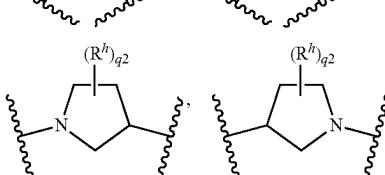
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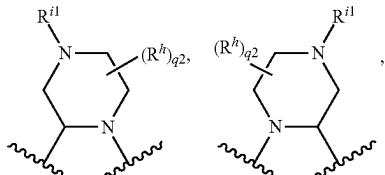
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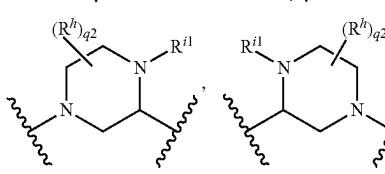
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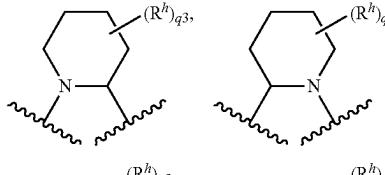
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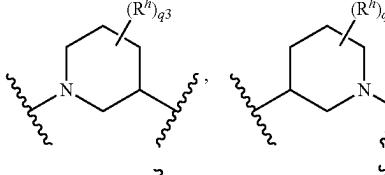
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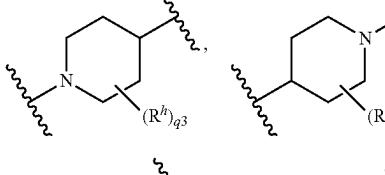
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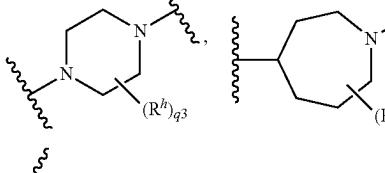
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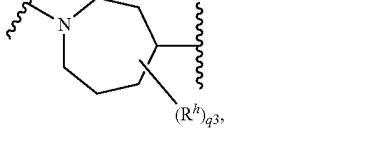
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where

q_1 is 0, 1, 2, 3, or 4;

q_2 is 0, 1, 2, 3, 4, 5, or 6;

q_3 is 0, 1, 2, 3, 4, 5, 6, 7, or 8;

each R^h is, independently, 2H , halogen, optionally substituted C_1 - C_6 alkyl, OR^{i2} , or $NR^{i3}R^{i4}$; or two R^h groups, together with the carbon atom to which each is attached, combine to form optionally substituted C_3 - C_{10} carbocyclyl or optionally substituted C_2 - C_9 heterocyclyl; or two R^h groups, together with the carbon atoms to which each is attached, combine to form optionally substituted C_3 - C_{10} carbocyclyl or optionally substituted C_2 - C_9 heterocyclyl;

R^{i1} is H or optionally substituted C_1 - C_6 alkyl;

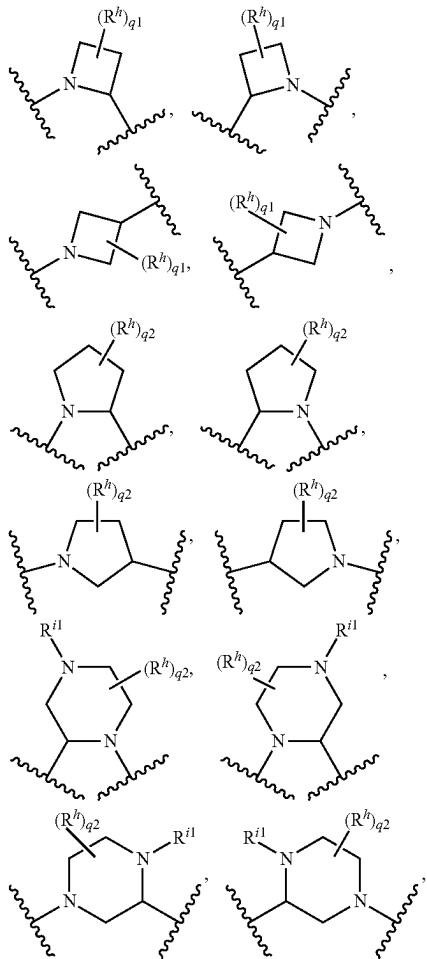
R^{i2} is H, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, or optionally substituted C_3 - C_6 carbocyclyl;

R^{i3} is H or optionally substituted C_1 - C_6 alkyl; and

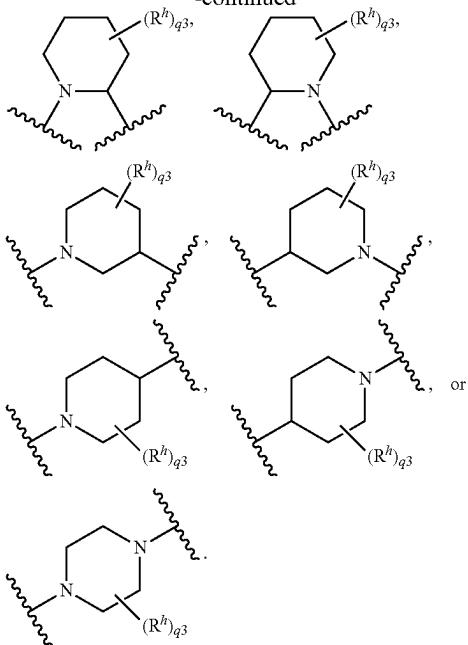
R^{i4} is H or optionally substituted C_1 - C_6 alkyl.

In some embodiments, each R^h is, independently, halogen, optionally substituted C_1 - C_6 alkyl, OR^{i2} , or $NR^{i3}R^{i4}$. In some embodiments, R^{i1} is H or optionally substituted C_1 - C_6 alkyl. In some embodiments, R^{i2} is H or optionally substituted C_1 - C_6 alkyl. In some embodiments, R^{i3} is H or optionally substituted C_1 - C_6 alkyl. In some embodiments, R^{i4} is H or optionally substituted C_1 - C_6 alkyl.

In some embodiments, the C_2 - C_9 heterocyclylene is



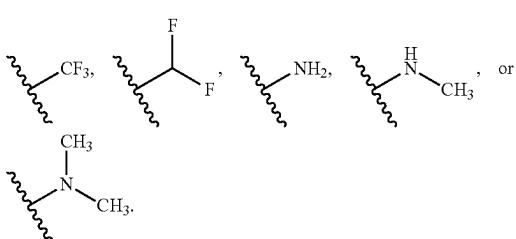
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In some embodiments, each R^h is, independently, halogen, optionally substituted C_1 - C_6 alkyl, OR^{i2} , or $NR^{i3}R^{i4}$. In some embodiments, each R^h is, independently, halogen, optionally substituted C_1 - C_6 alkyl, or $NR^{i3}R^{i4}$.

In some embodiments, each R^h is, independently, 2H , halogen, cyano, optionally substituted C_1 - C_6 alkyl, OR^{i2} , or $NR^{i3}R^{i4}$. In some embodiments, two R^h groups, together with the carbon atom to which each is attached, combine to form optionally substituted C_3 - C_{10} carbocyclyl or optionally substituted C_2 - C_9 heterocyclyl. In some embodiments, two R^h groups, together with the carbon atoms to which each is attached, combine to form optionally substituted C_3 - C_{10} carbocyclyl or optionally substituted C_2 - C_9 heterocyclyl.

In some embodiments, each R^h is, independently, H, 2H , F, methyl,

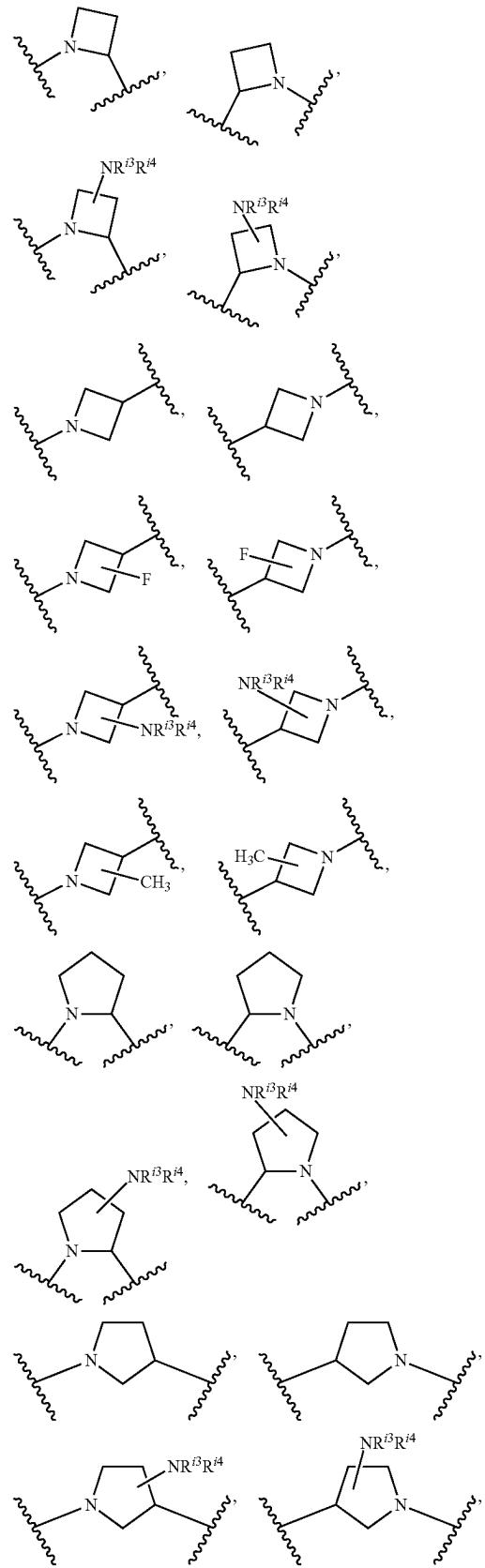


In some embodiments, each R^h is, independently, F, methyl, or $NR^{i3}R^{i4}$.

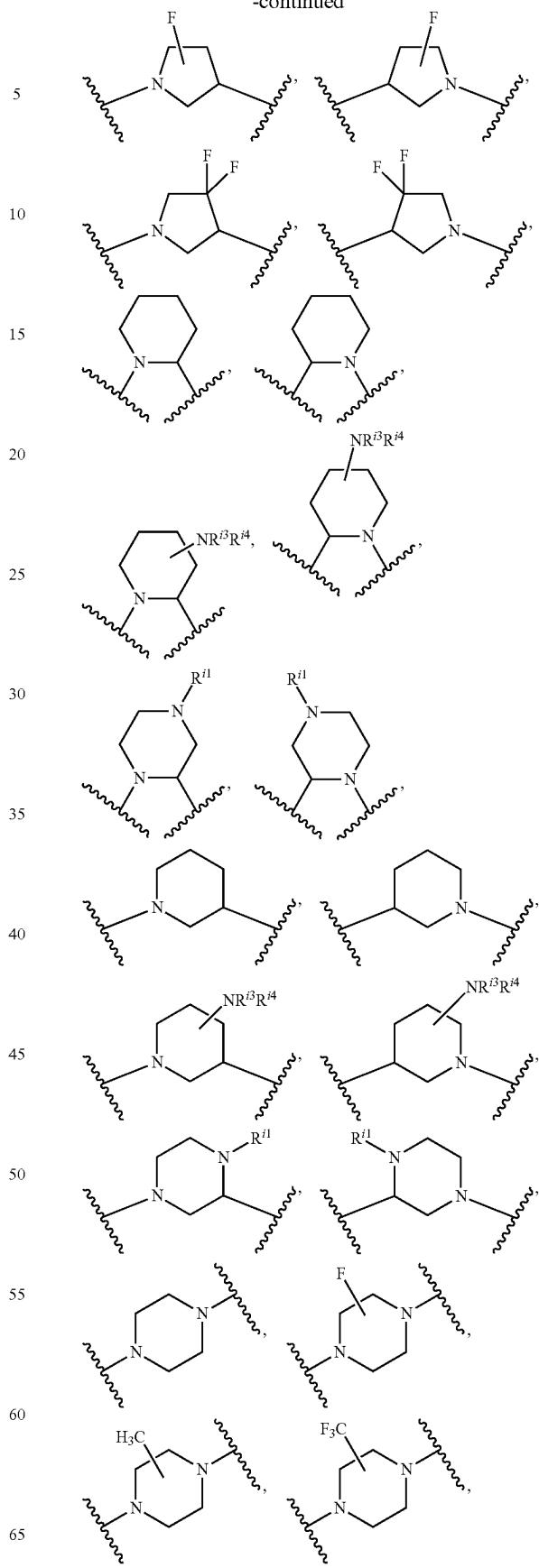
In some embodiments, q_1 is 0, 1, or 2. In some embodiments, q_1 is 0. In some embodiments, q_1 is 1. In some embodiments, q_1 is 2.

In some embodiments, q_2 is 0, 1, or 2. In some embodiments, q_2 is 0. In some embodiments, q_2 is 1. In some embodiments, q_2 is 2.

In some embodiments, q_3 is 0, 1, or 2. In some embodiments, q_3 is 0. In some embodiments, q_3 is 1. In some embodiments, q_3 is 2.

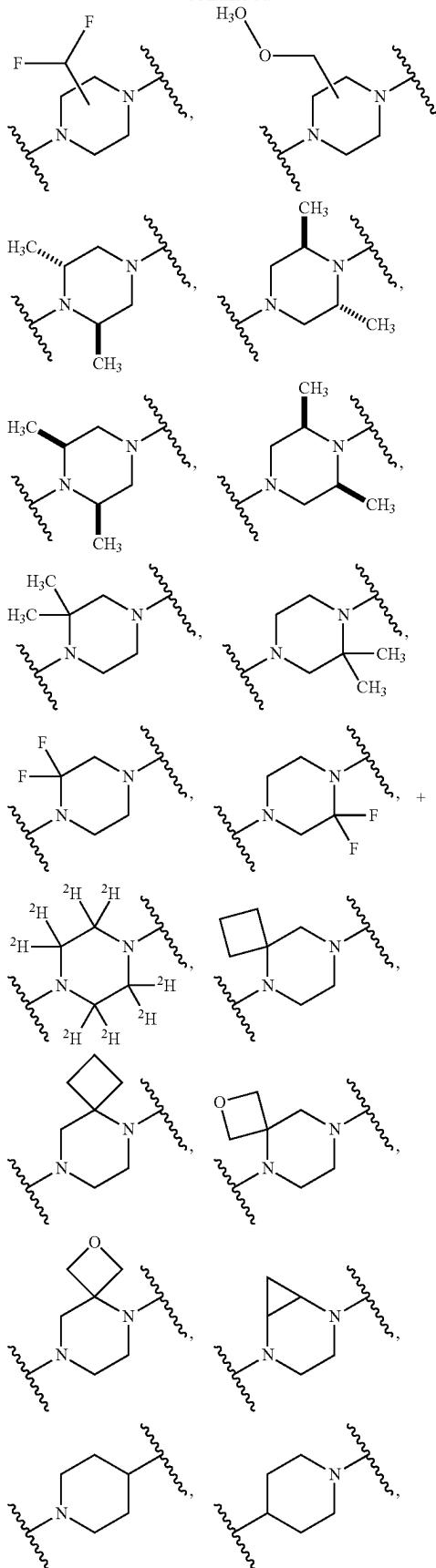
139In some embodiments, the C₂-C₉ heterocyclylene is**140**

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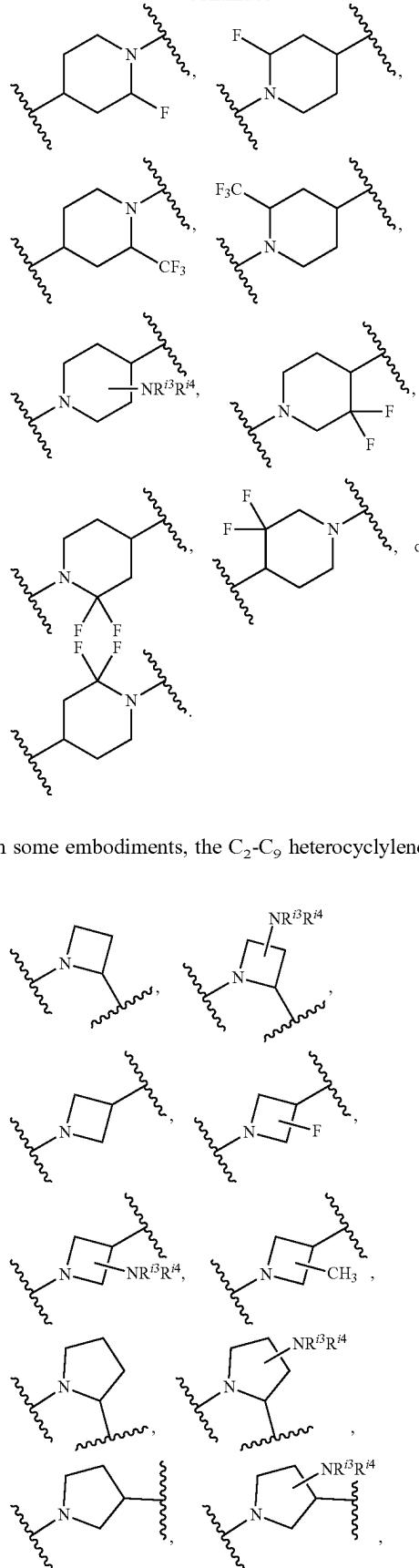
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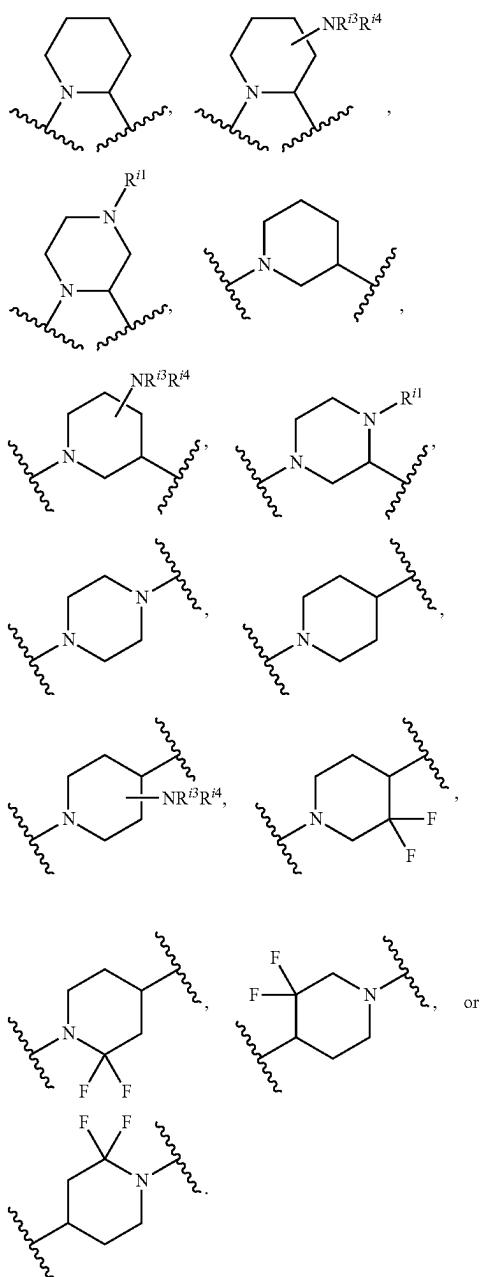
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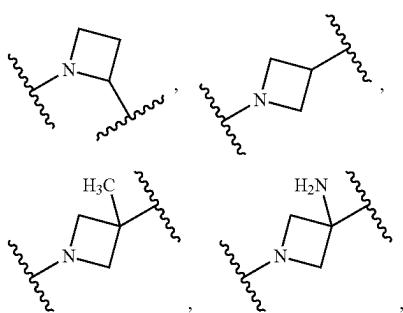
In some embodiments, the C₂-C₉ heterocyclylene is

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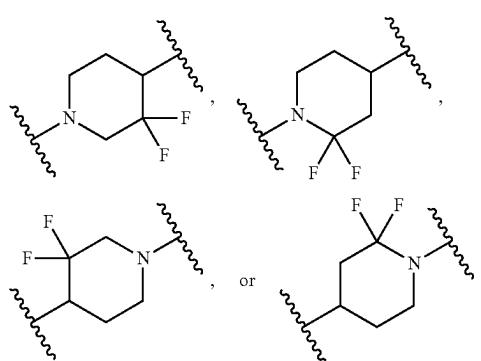


In some embodiments, F^1 is

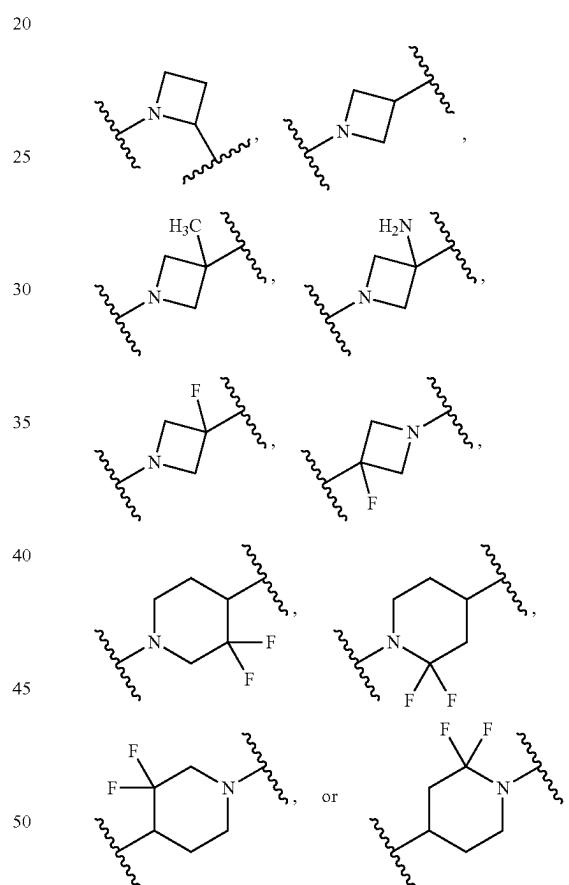


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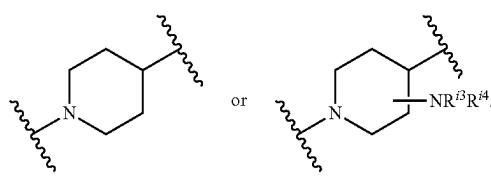
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In some embodiments, F^1 is

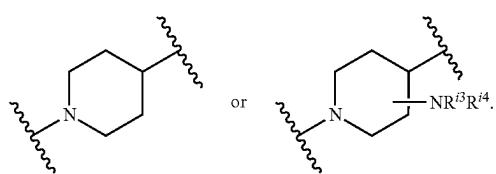


55 In some embodiments, F^2 is



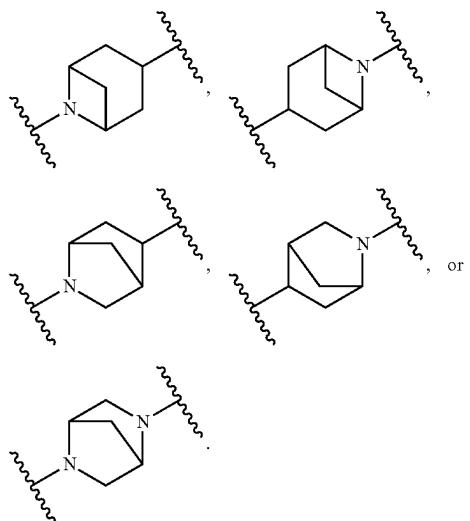
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In some embodiments, F^3 is

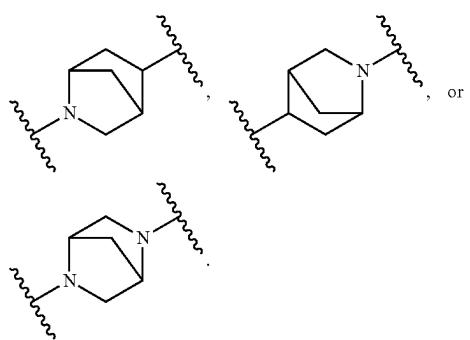


In some embodiments, R^{i1} is H or methyl. In some embodiments, R^{i2} is H or methyl. In some embodiments, R^{i3} is H or methyl. In some embodiments, R^{i4} is H or methyl.

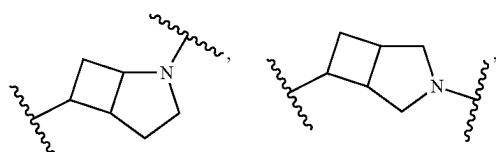
In some embodiments, the C₂-C₉ heterocyclylene is



In some embodiments, the C₂-C₆ heterocyclylene is

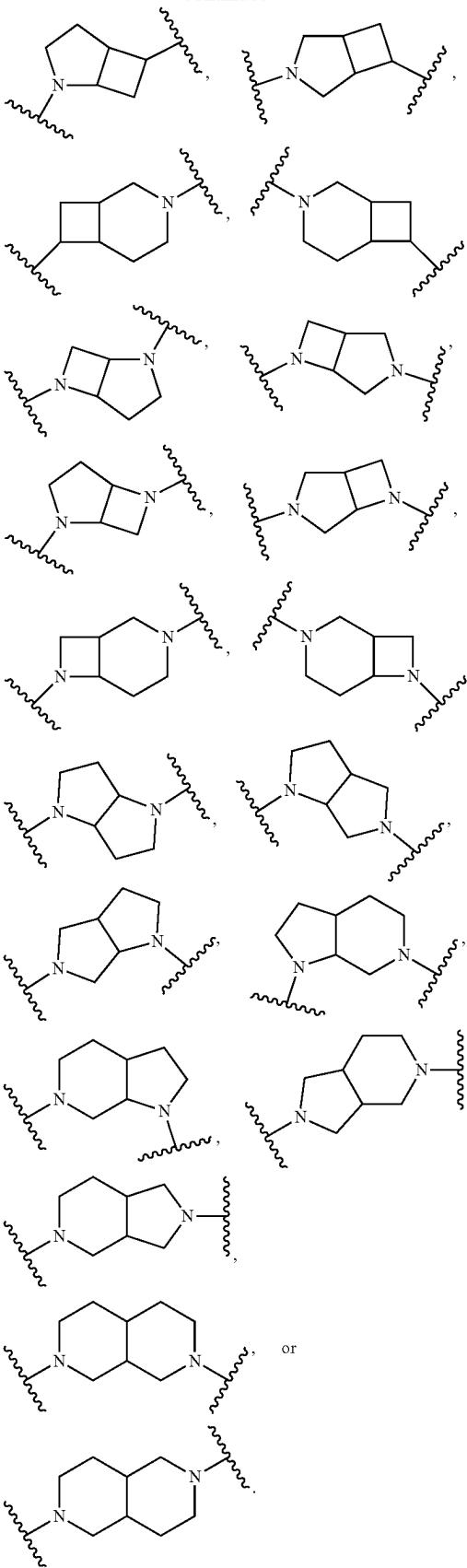


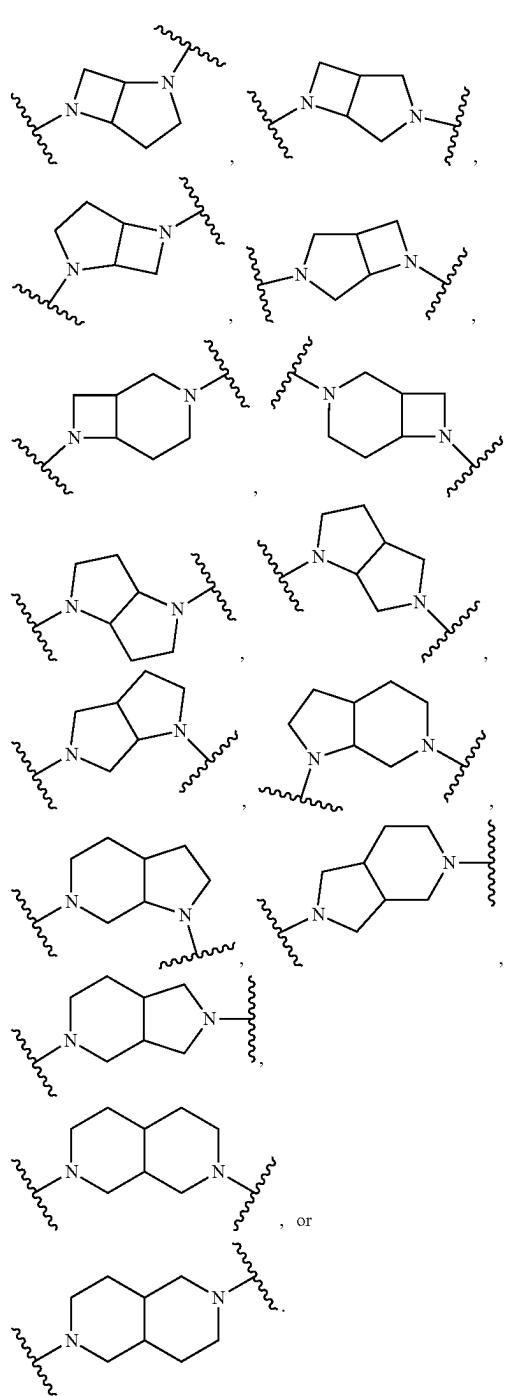
In some embodiments, the C₂-C₉ heterocyclylene is



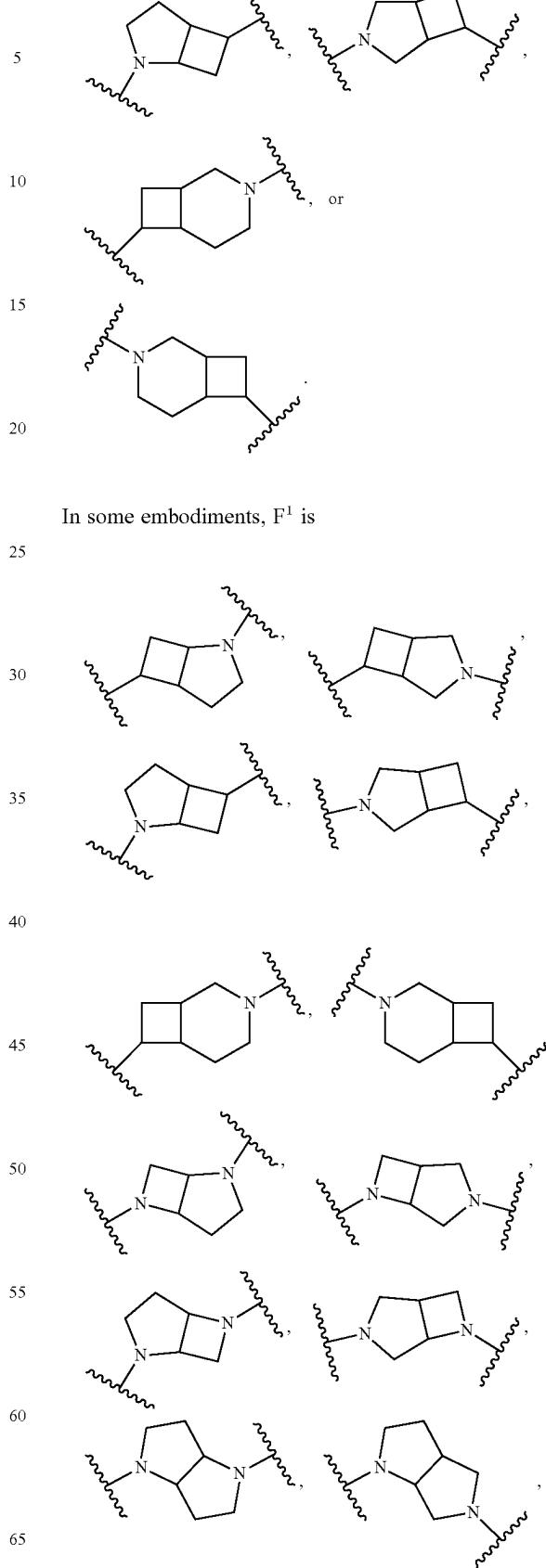
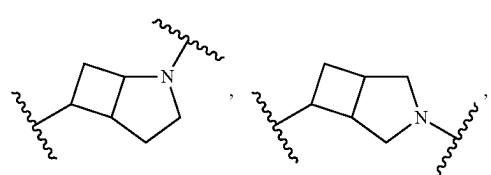
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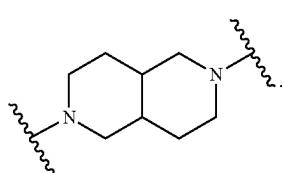
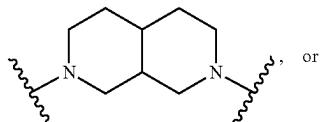
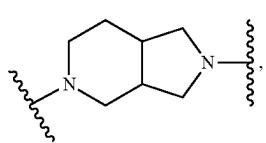
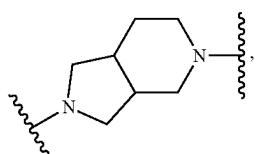
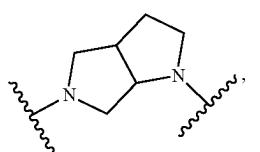
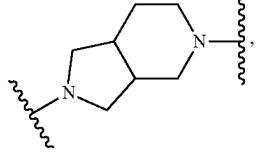
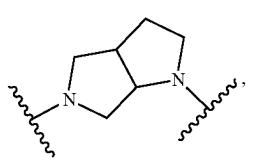
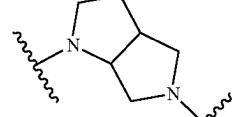
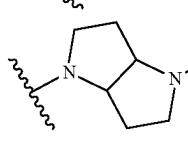
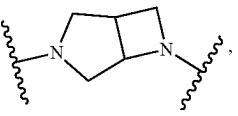
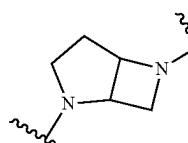
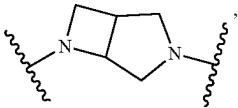
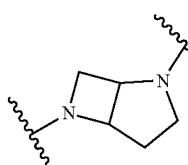
147In some embodiments, the C₂-C₉ heterocyclylene is**148**

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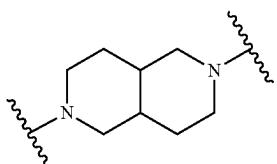
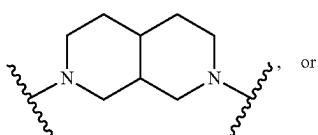
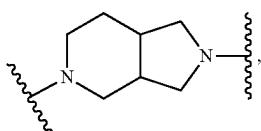
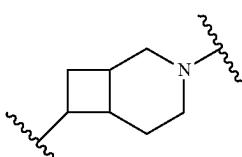
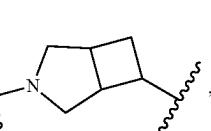
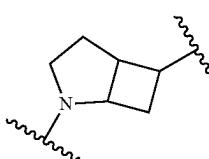
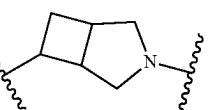
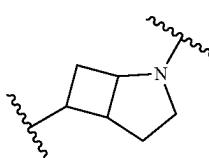
In some embodiments, the C₂-C₉ heterocyclylene is

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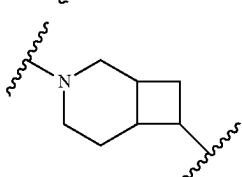
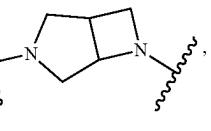
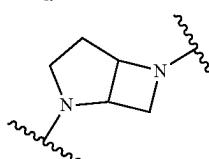
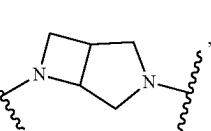
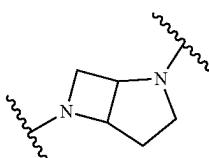
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In some embodiments, F¹ is**150**

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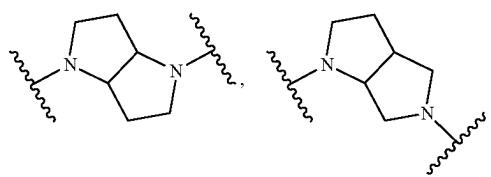
In some embodiments, F¹ is

, or

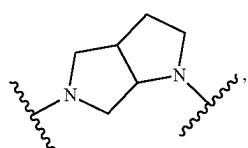
In some embodiments, F² is

151

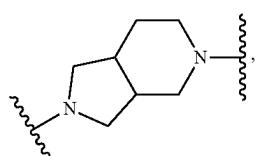
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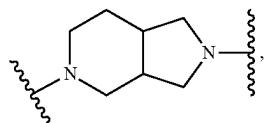
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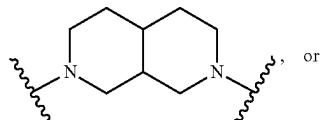
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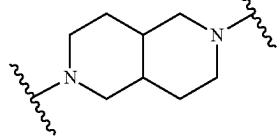
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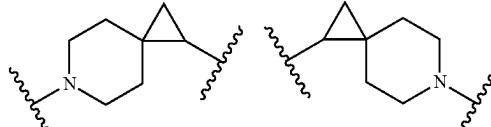
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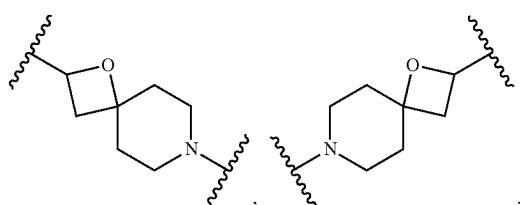
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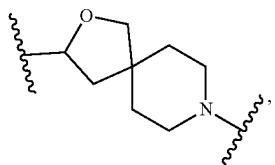
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In some embodiments, the C₂-C₉ heterocyclylene is

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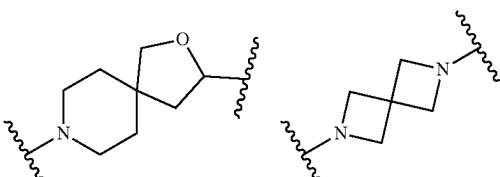
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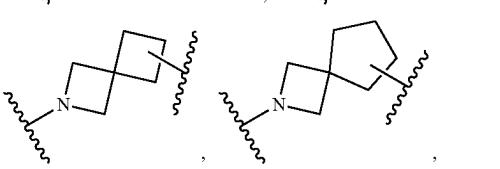
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152

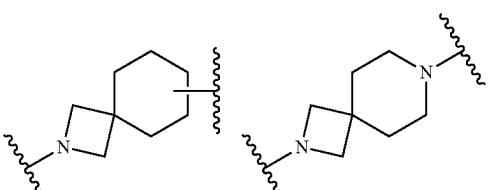
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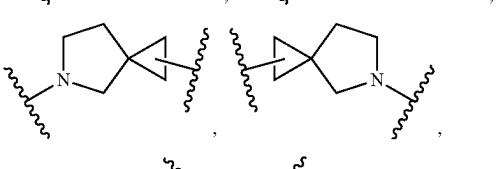
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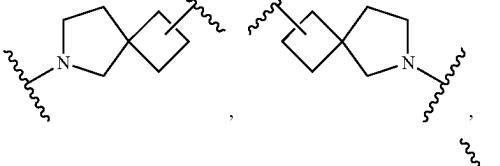
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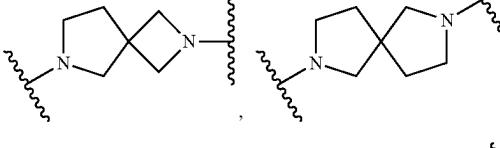
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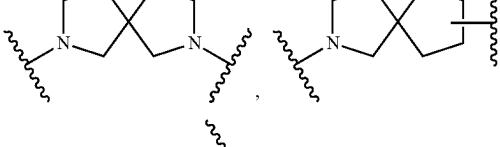
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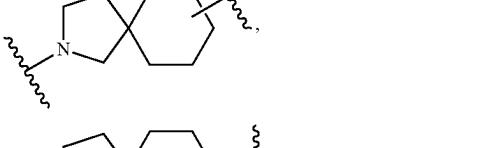
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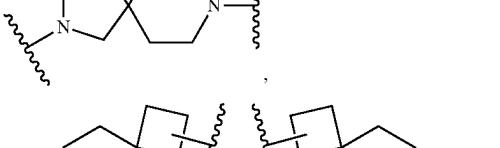
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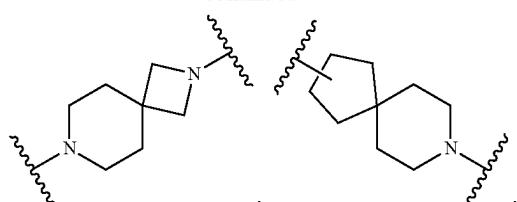
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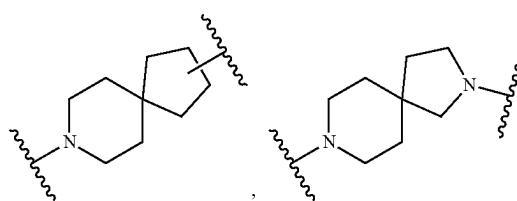
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153

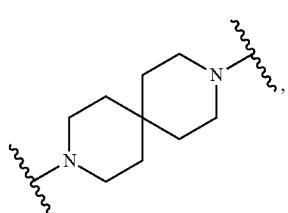
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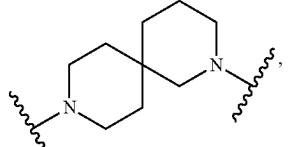
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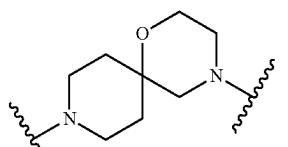
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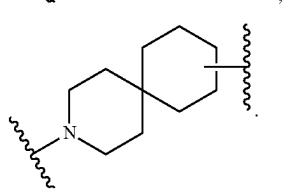
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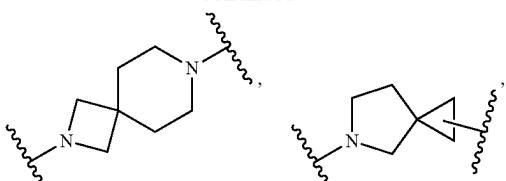
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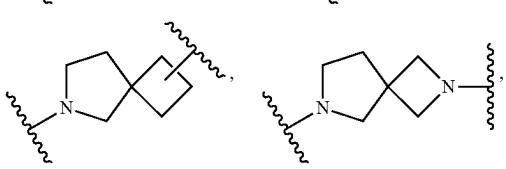
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In some embodiments, the C₂-C₉ heterocyclylene is**154**

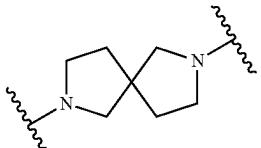
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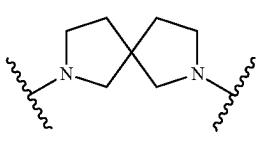
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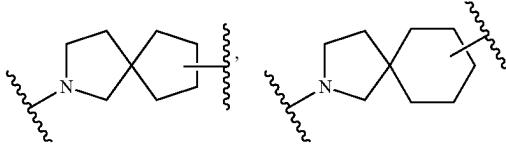
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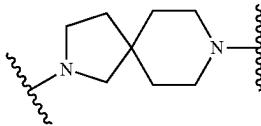
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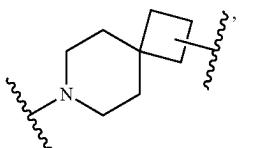
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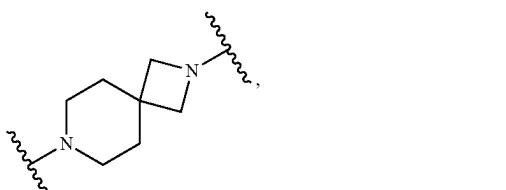
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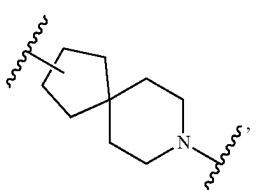
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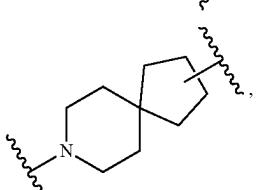
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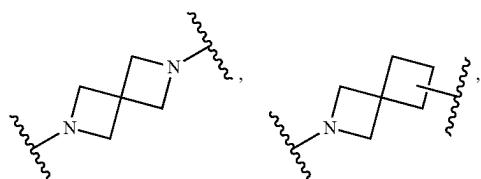
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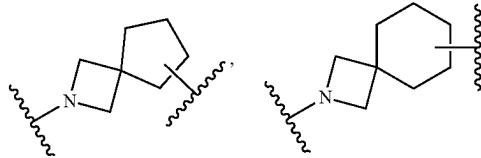
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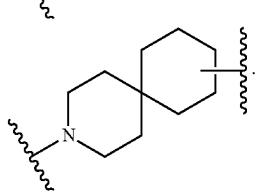
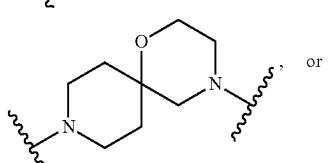
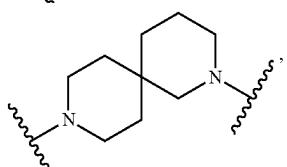
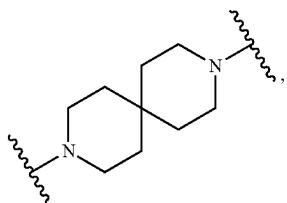
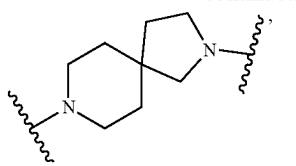
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155

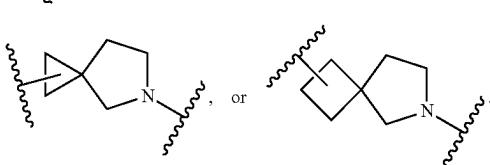
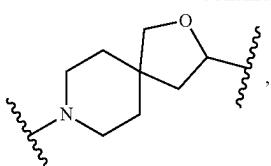
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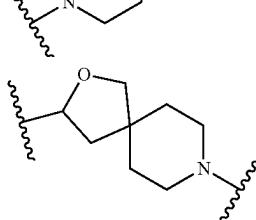
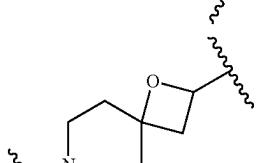
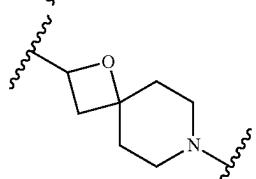
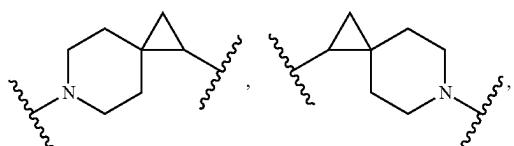
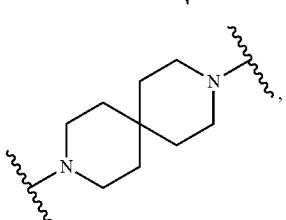
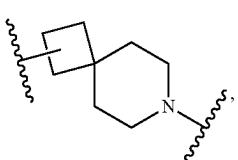
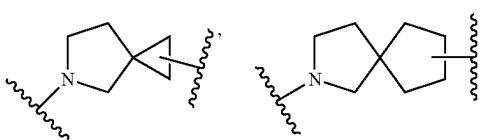
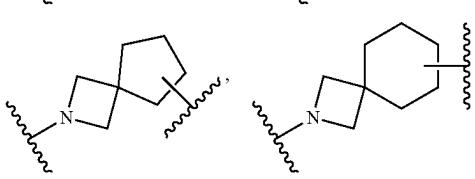
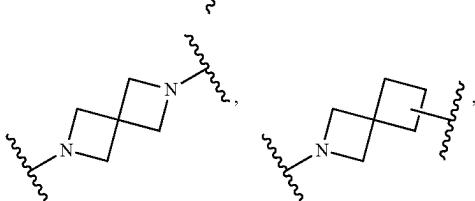
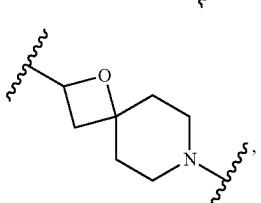
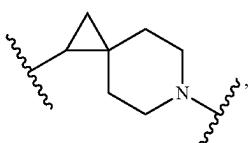
In some embodiments, the C₂-C₉ heterocyclylene is

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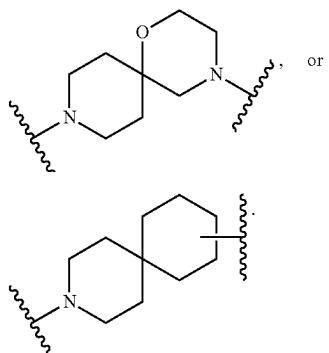
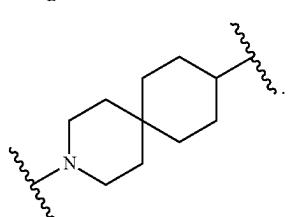
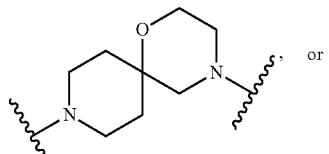
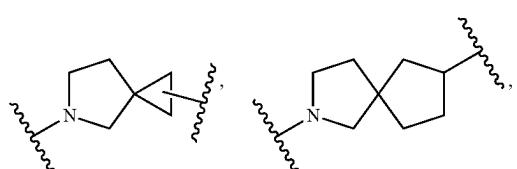
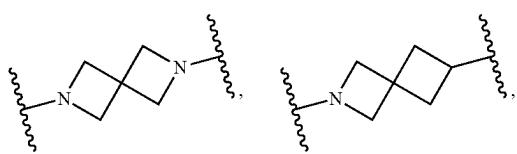
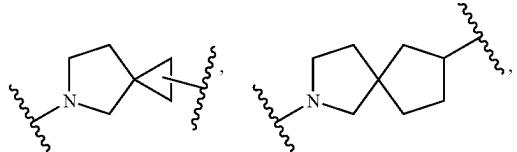
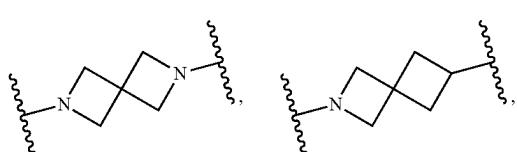


In some embodiments, E^1 is



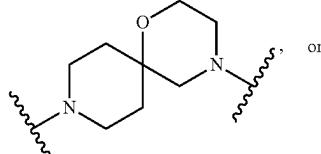
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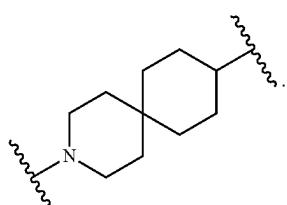
In some embodiments, F¹ isIn some embodiments, F¹ is**158**

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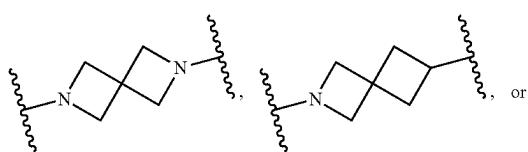
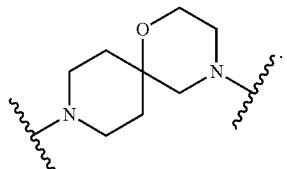
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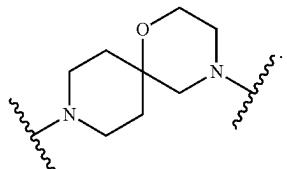
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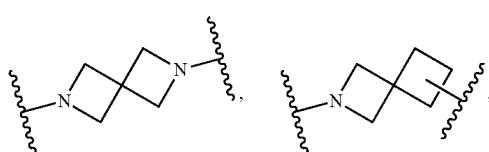
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In some embodiments, F¹ is

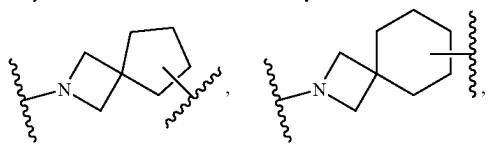
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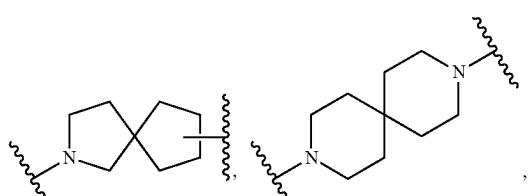
In some embodiments, F² is

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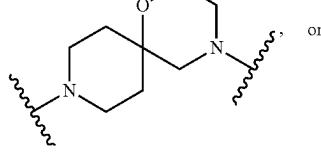


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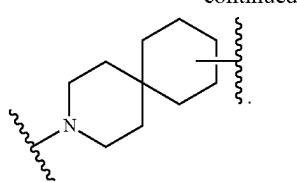


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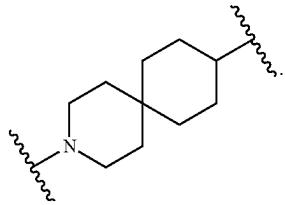
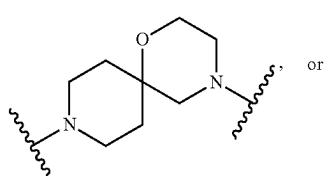
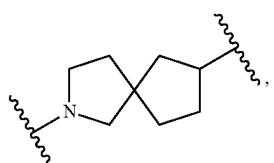
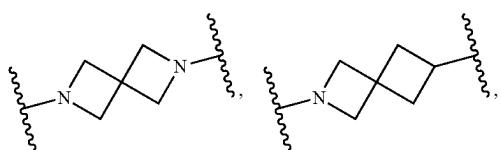
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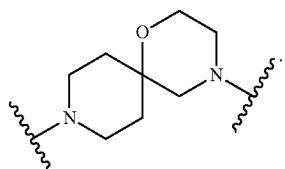
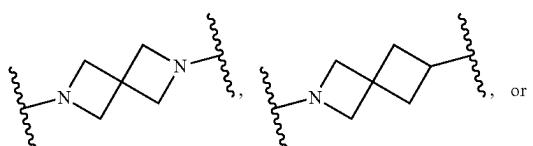
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In some embodiments, F^2 is



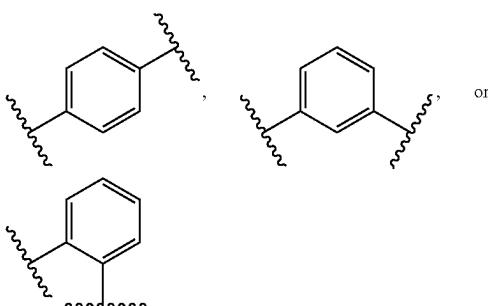
In some embodiments, F^2 is



In some embodiments, each of F¹, F², or F³ is, independently, optionally substituted C₆-C₁₀ arylene.

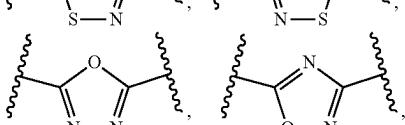
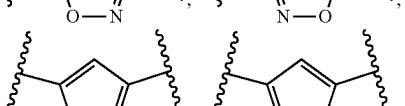
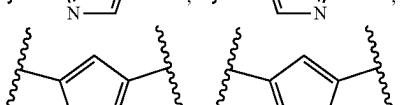
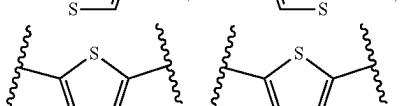
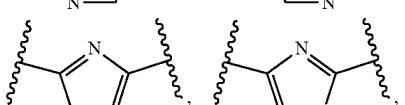
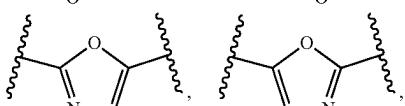
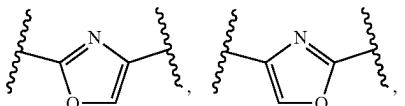
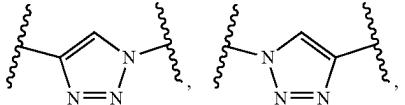
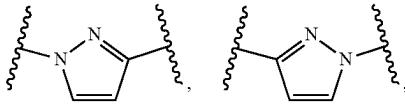
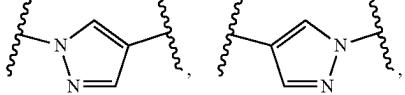
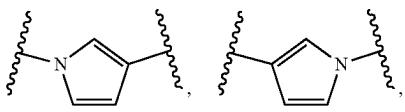
160

In some embodiments, the C₆-C₁₀ arylene is



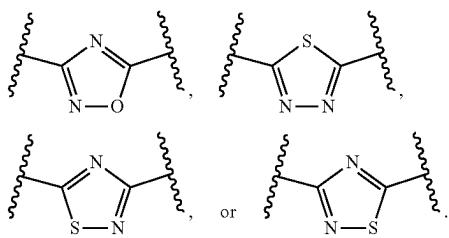
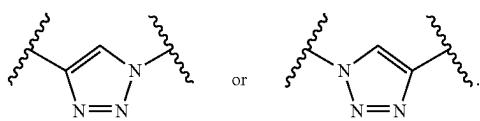
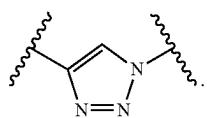
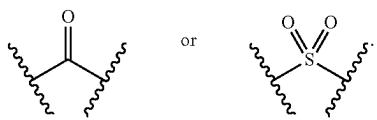
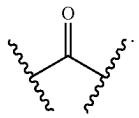
In some embodiments, each of F¹, F², or F³ is, independently, optionally substituted C₂-C₉ heteroarylene.

In some embodiments, the C₂-C₉ heteroarylene is



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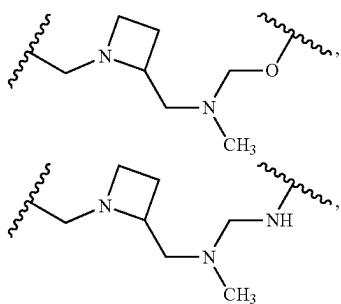
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In some embodiments, F² isIn some embodiments, F² isIn some embodiments, C³ isIn some embodiments, C³ is

In some embodiments, m is 1. In some embodiments, p is

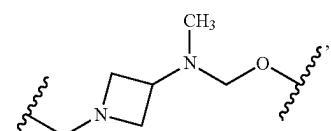
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In some embodiments, the linker has the structure of

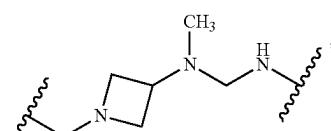
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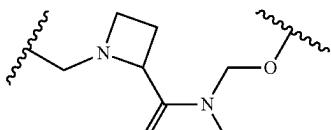
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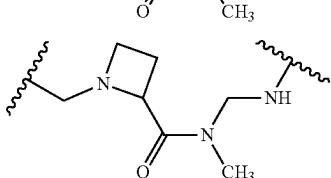
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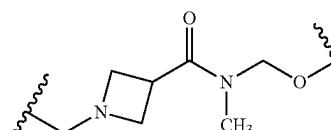
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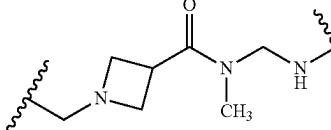
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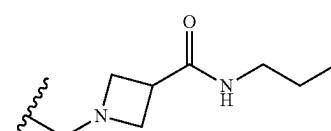
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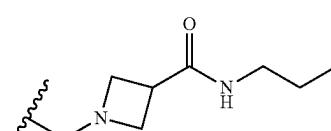
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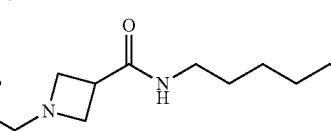
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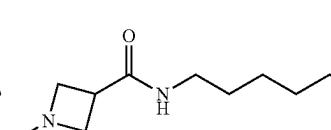
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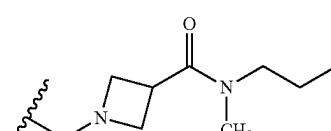
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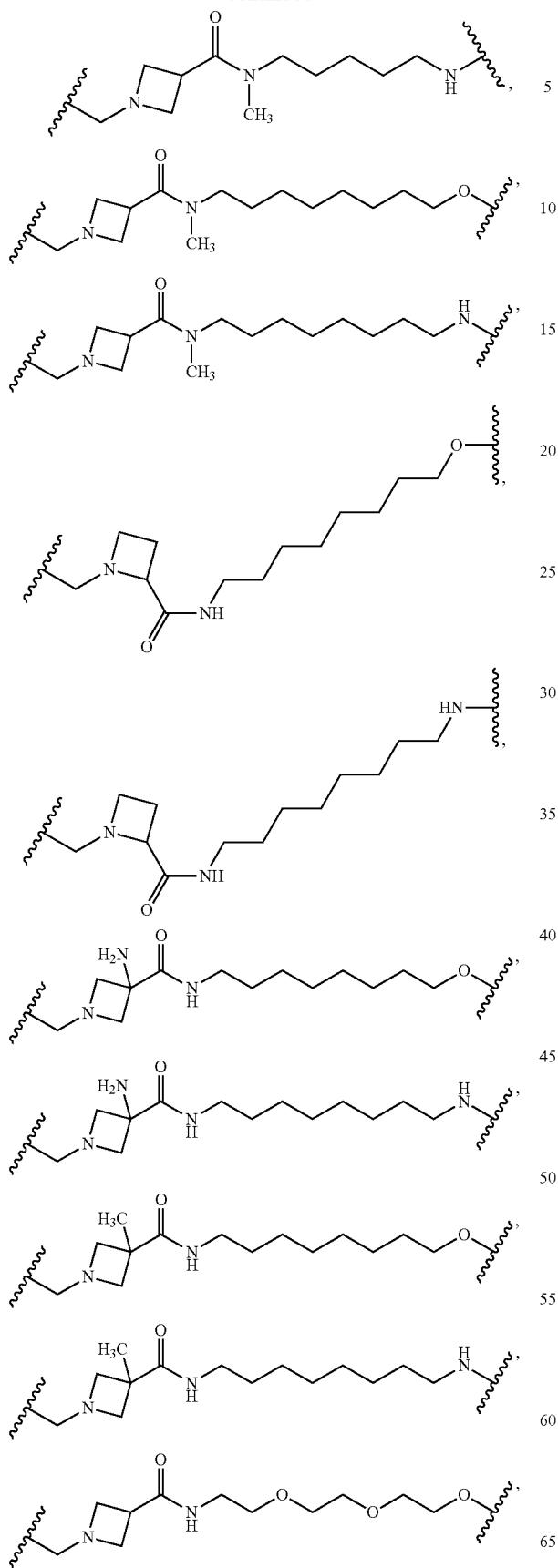


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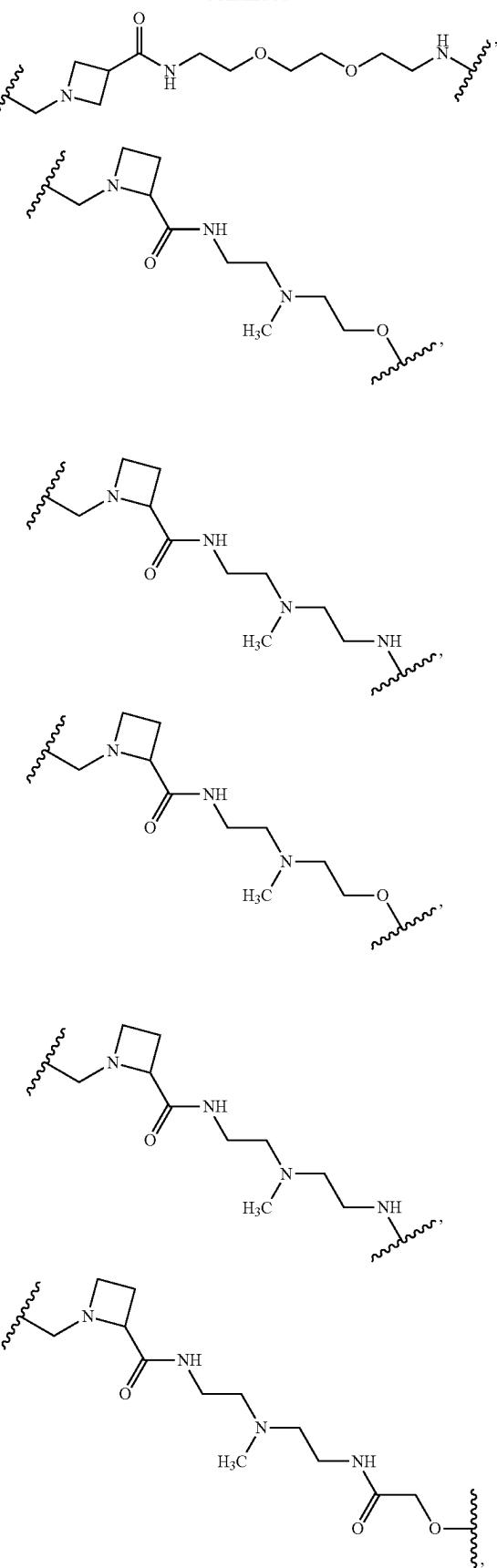


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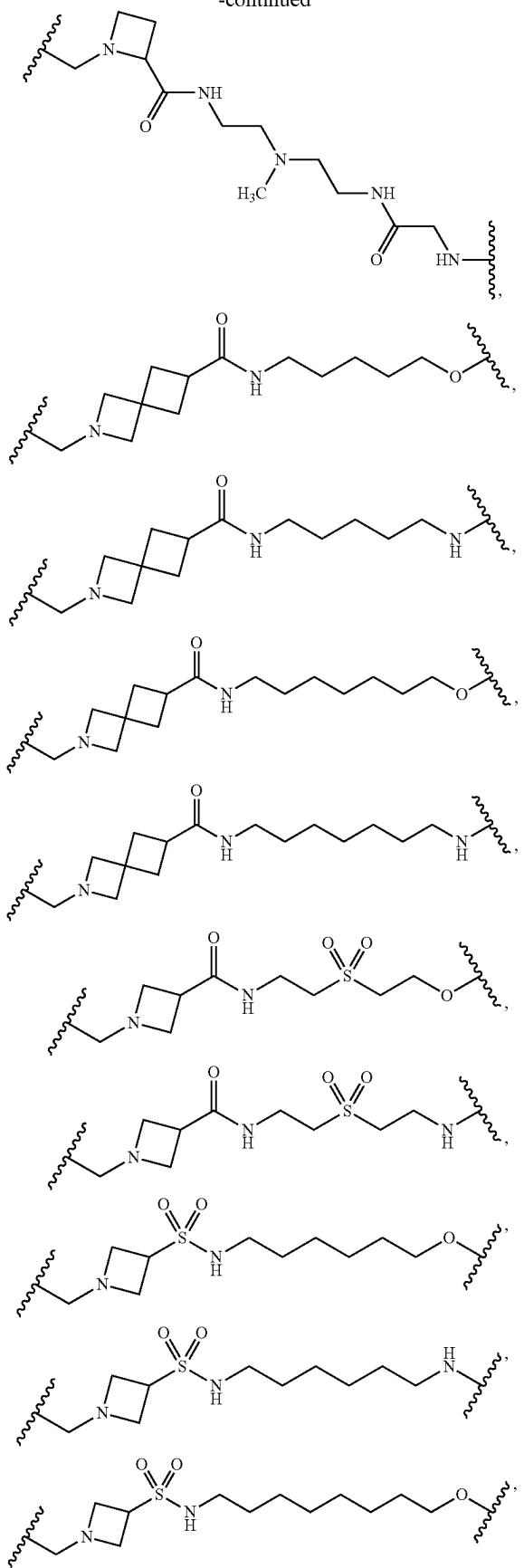
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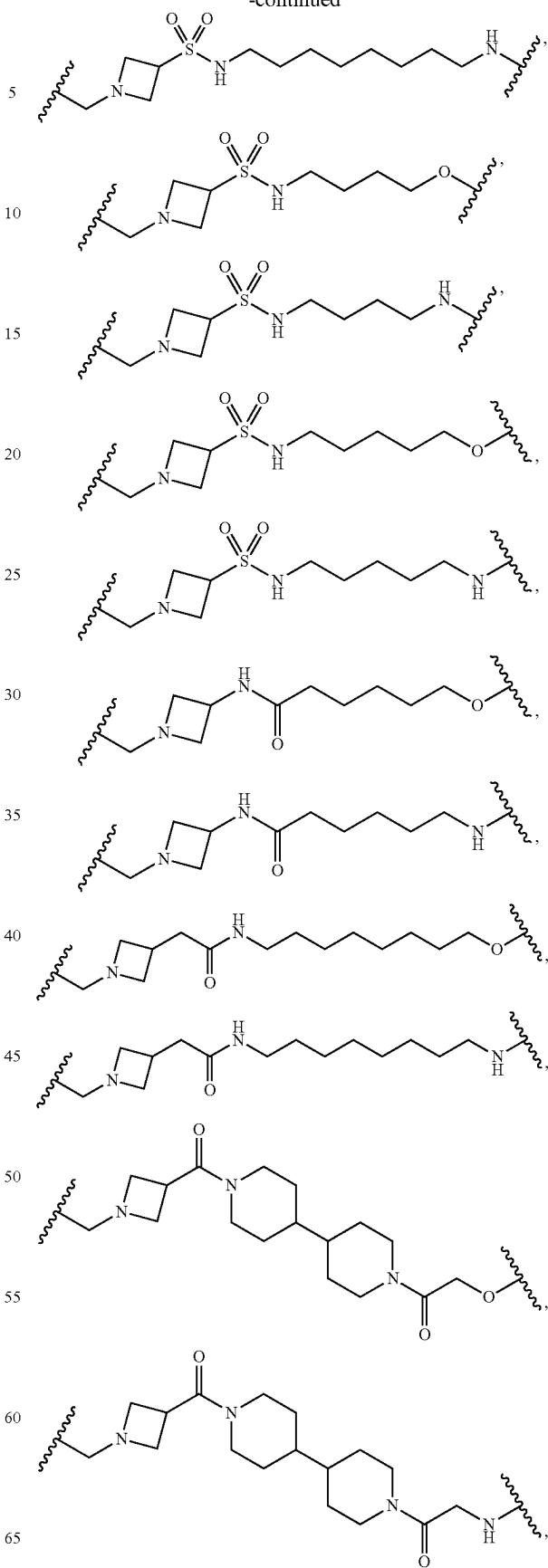


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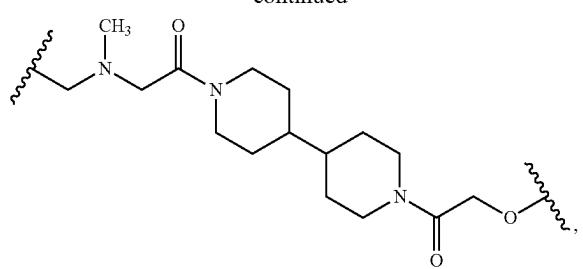
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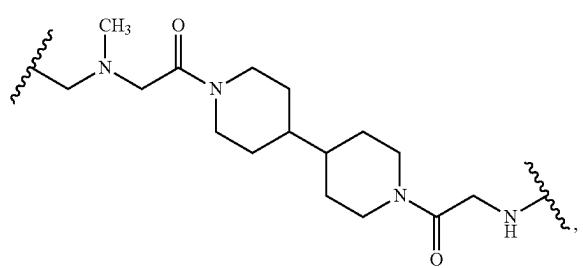


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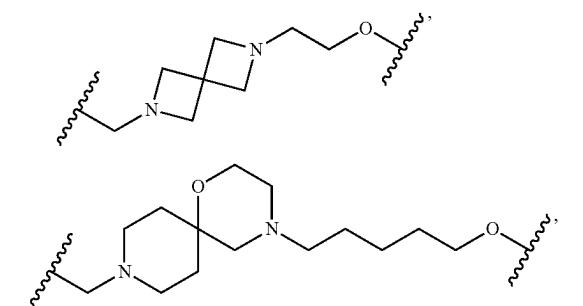
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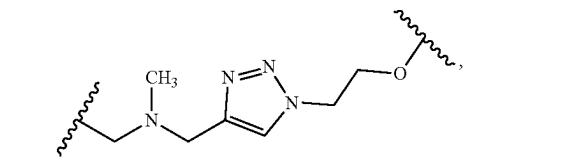
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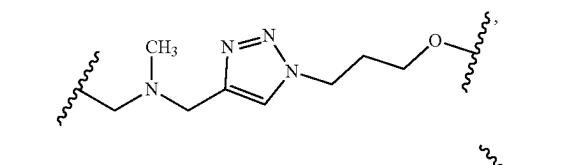
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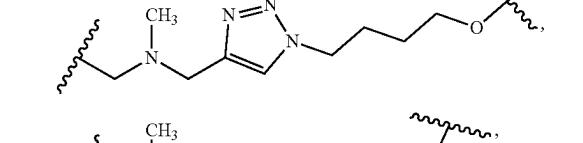
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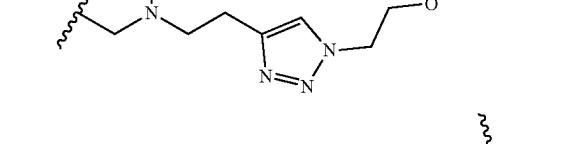
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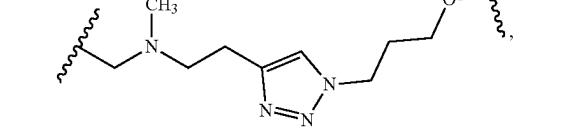
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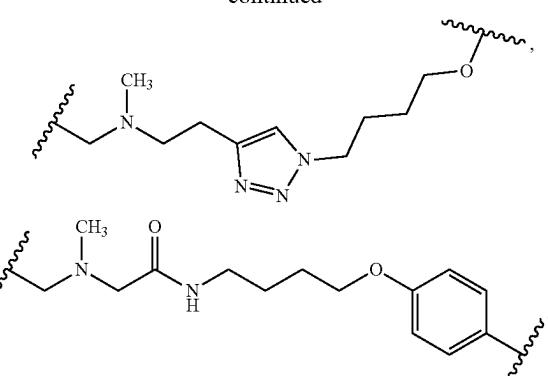
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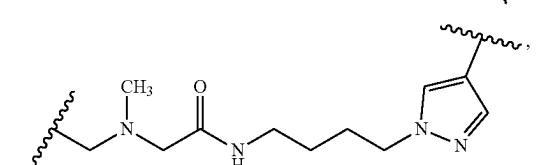
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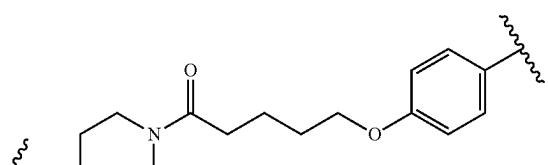
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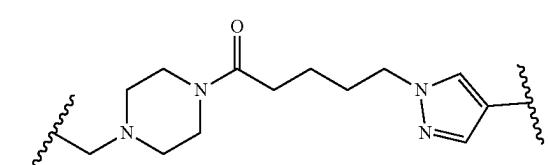
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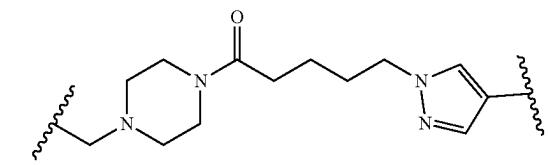
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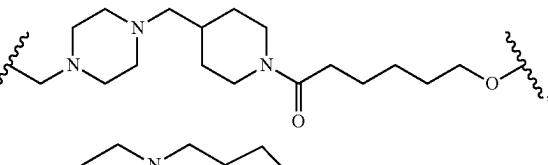
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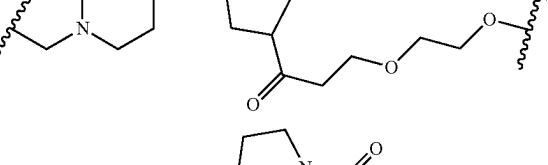
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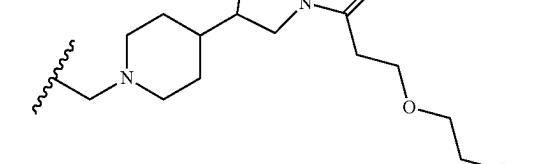
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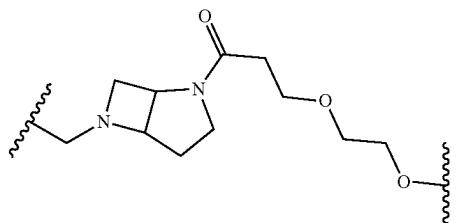
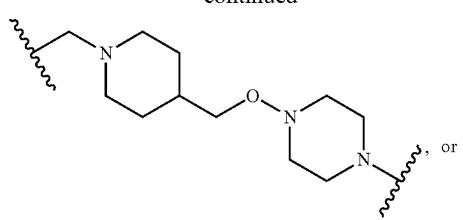
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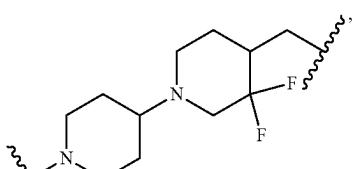
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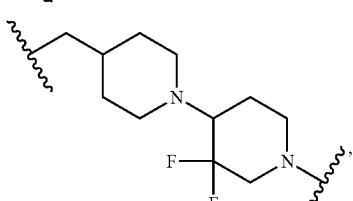
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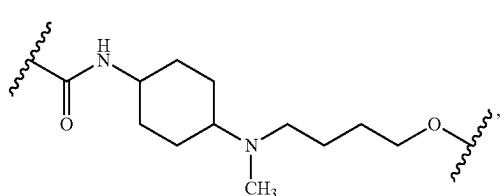
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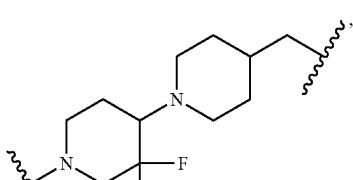
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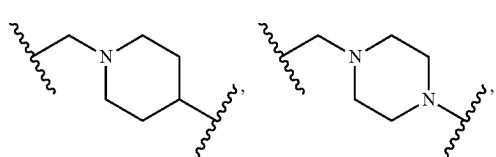
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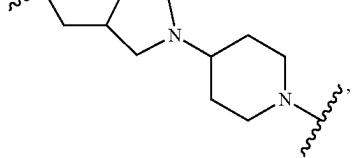
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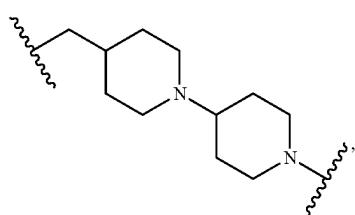
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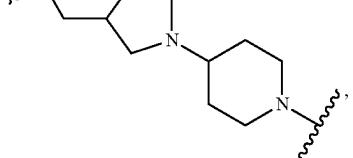
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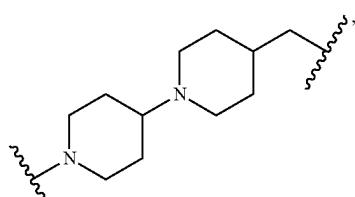
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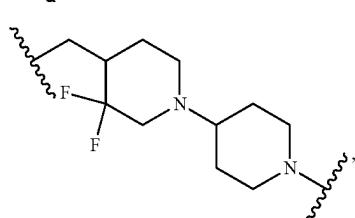
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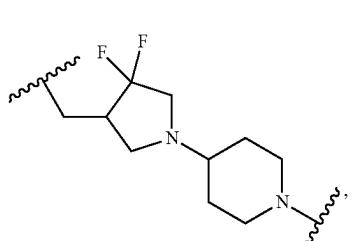
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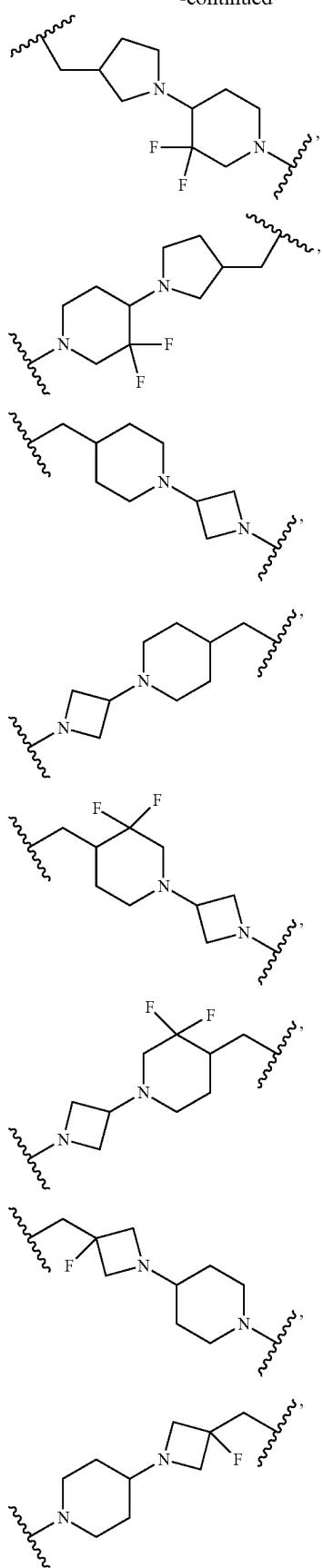
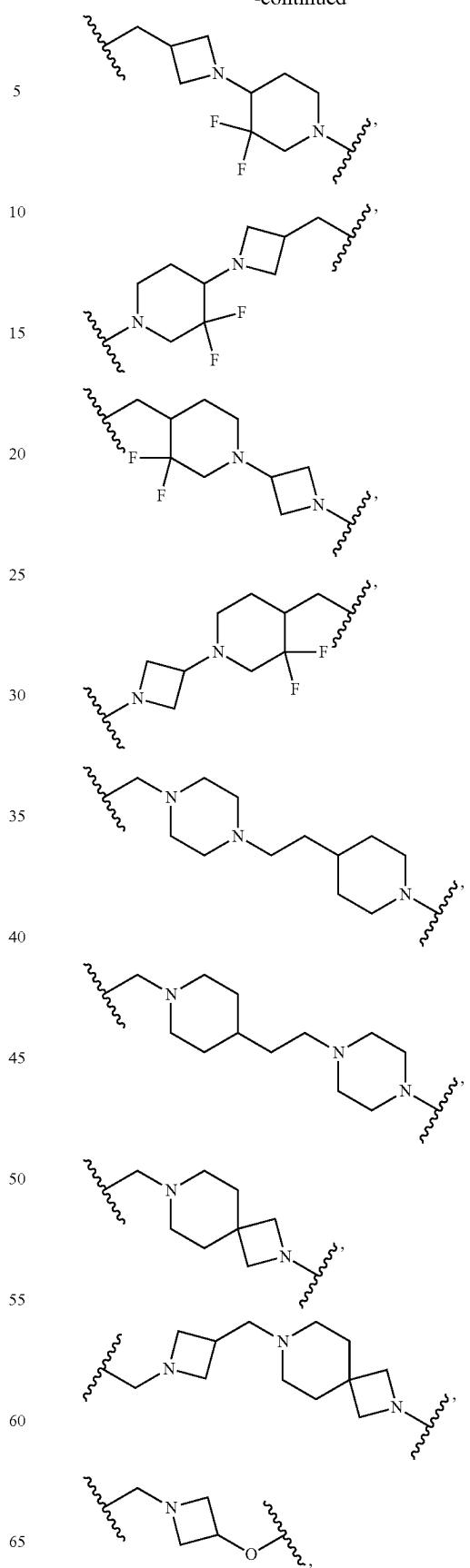
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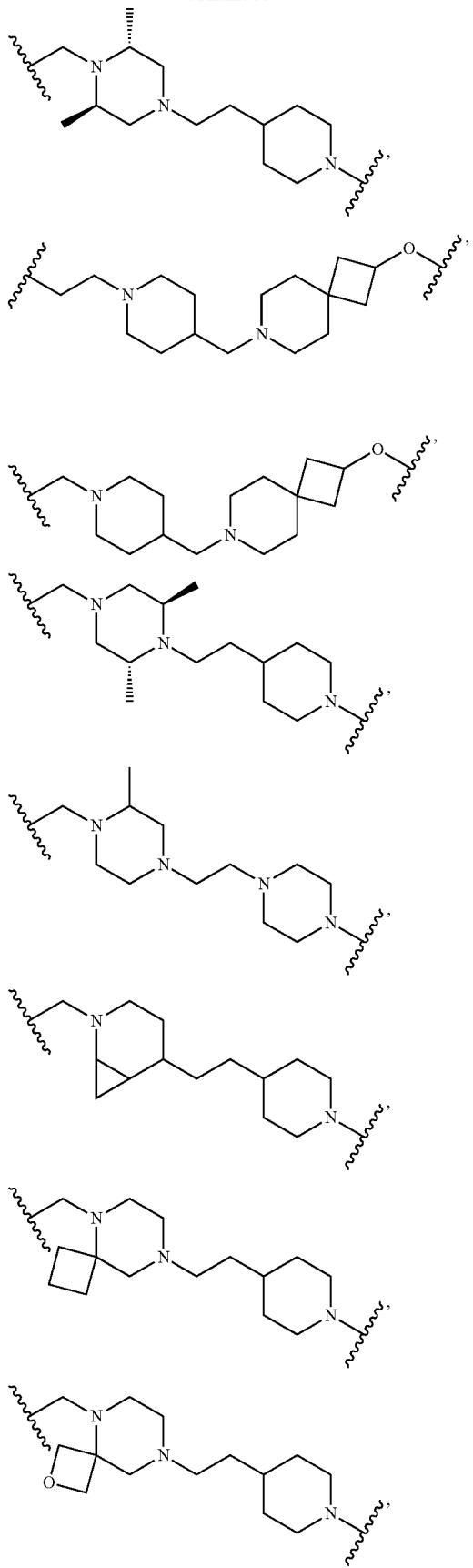


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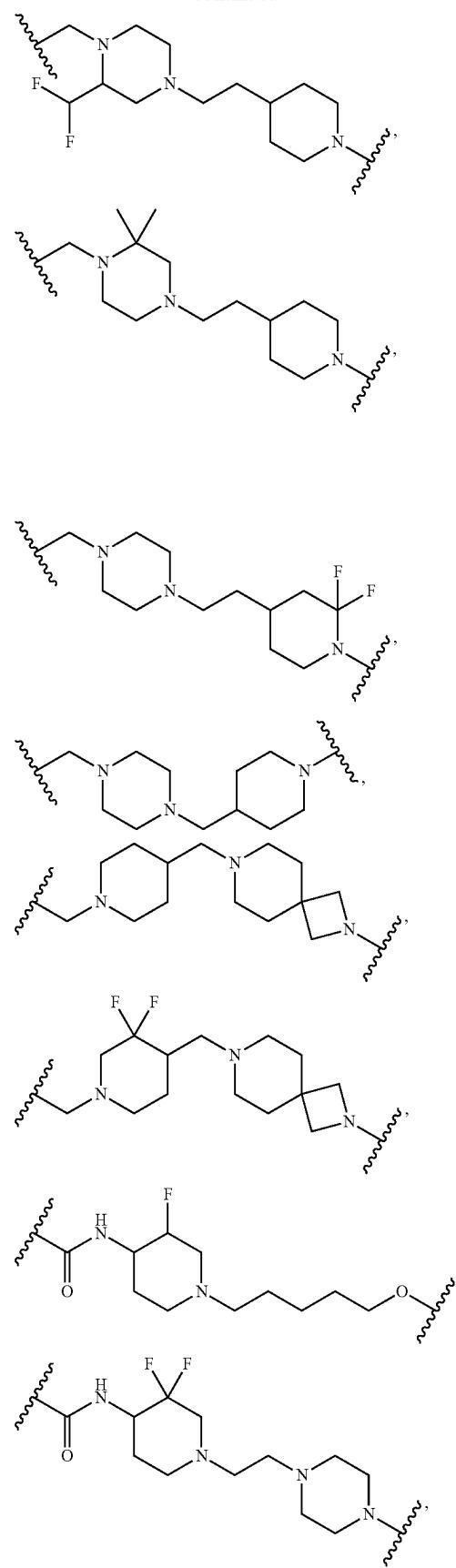
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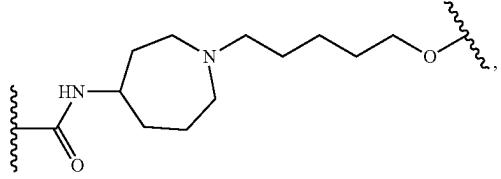
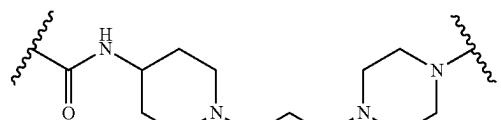
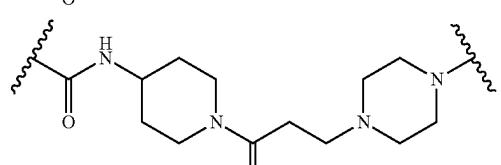
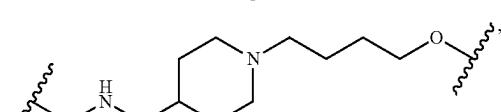
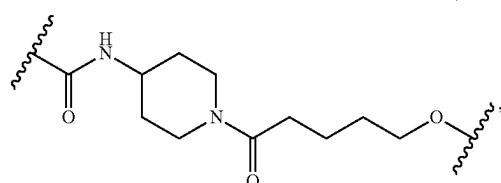
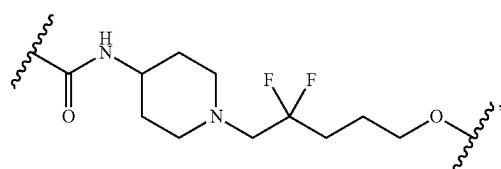
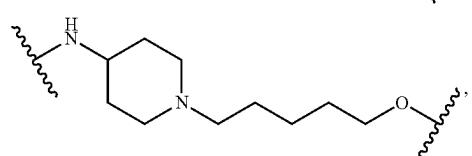
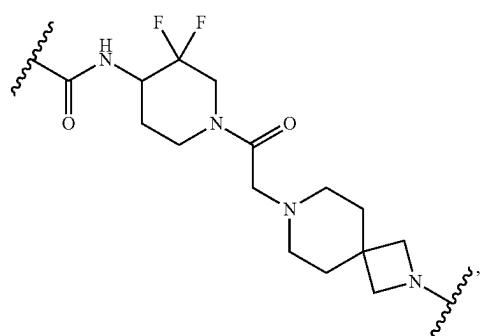
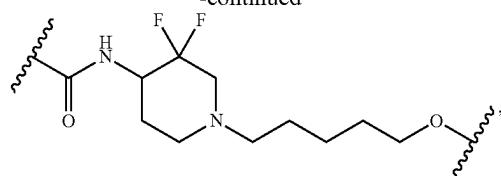
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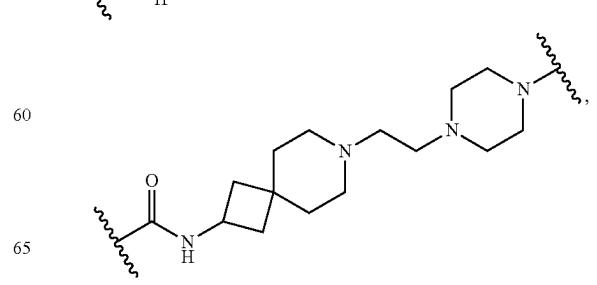
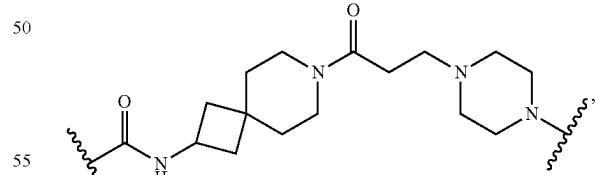
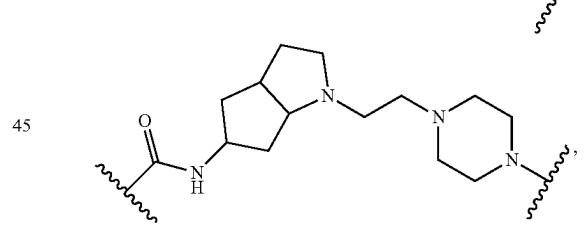
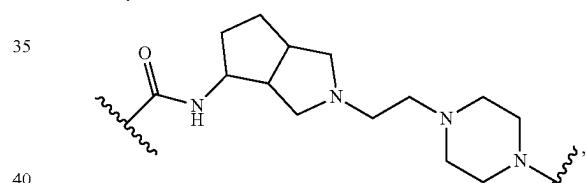
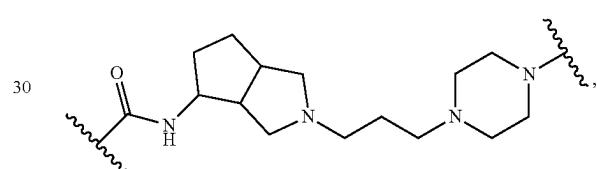
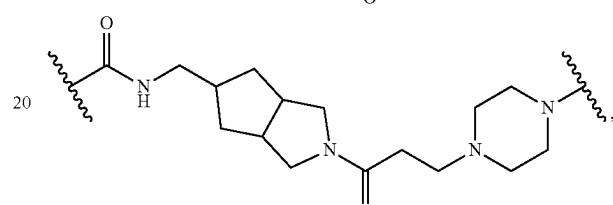
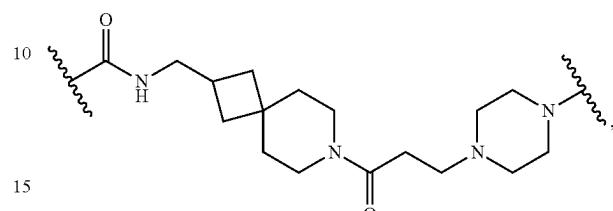
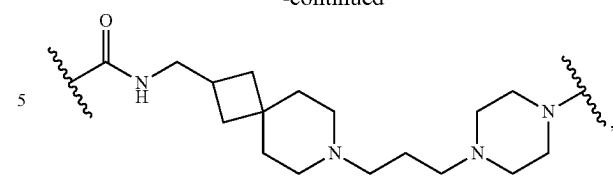
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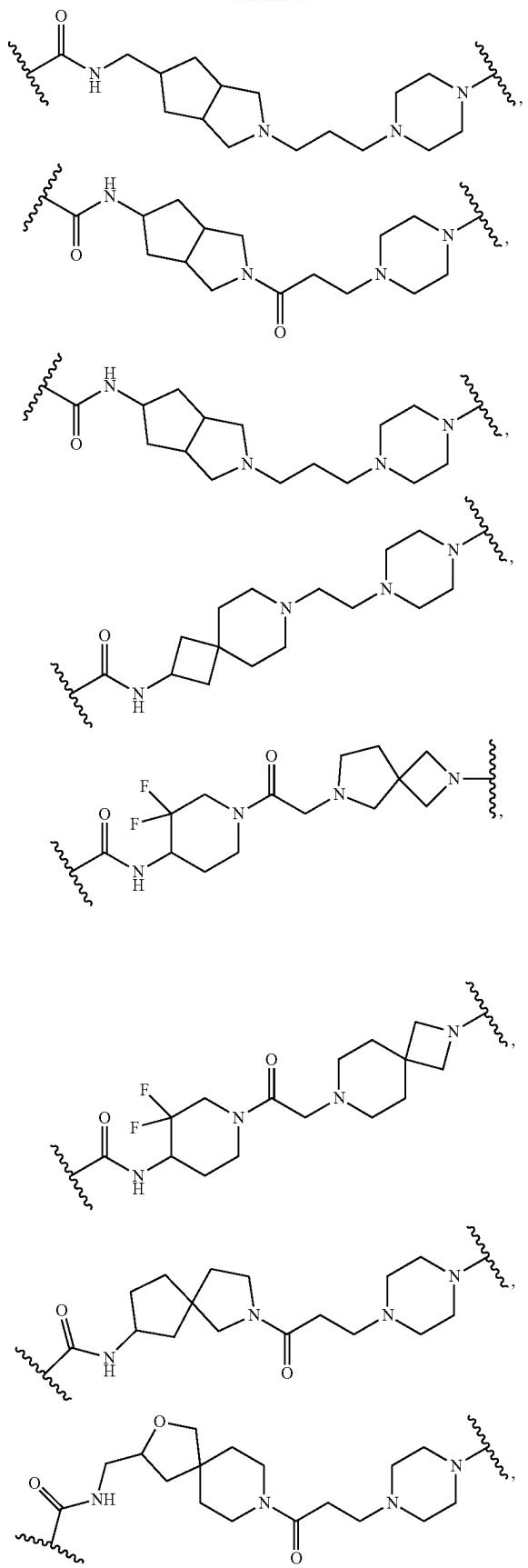
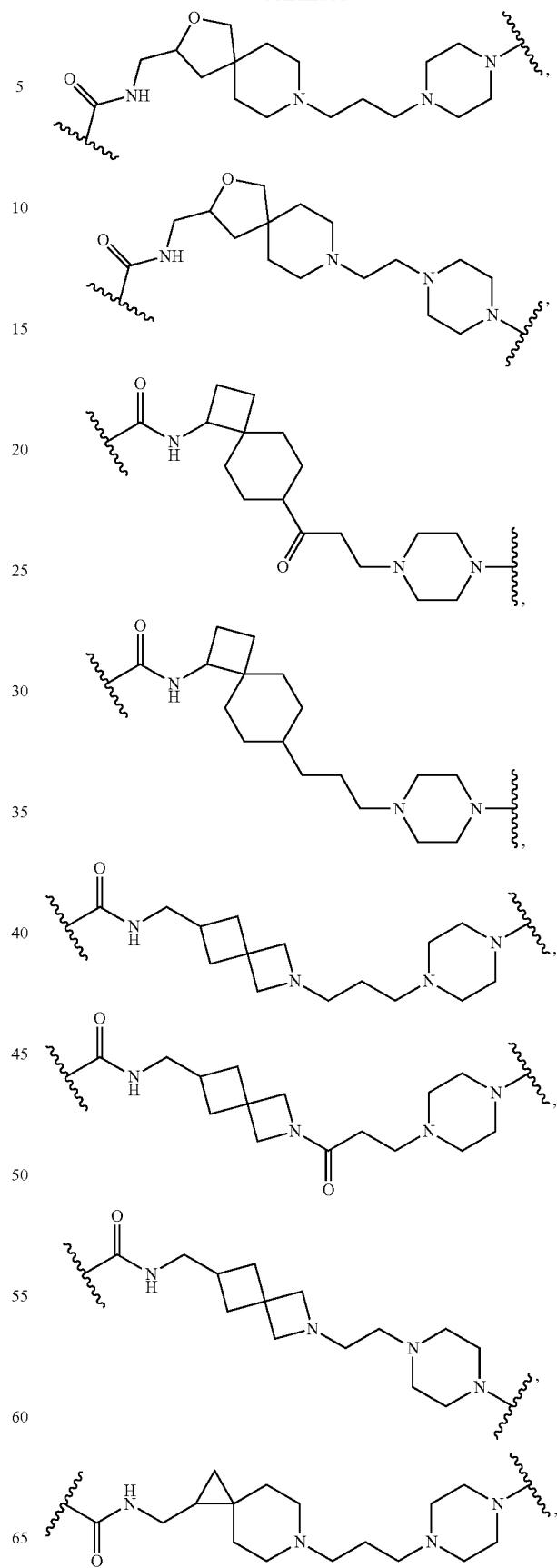
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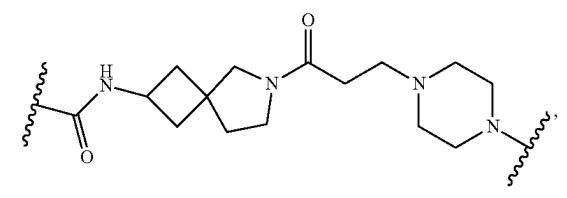
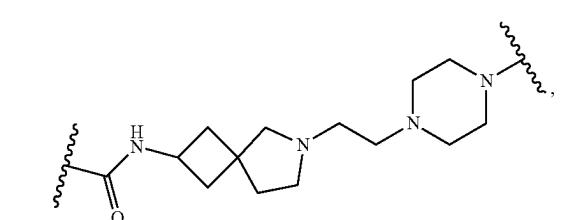
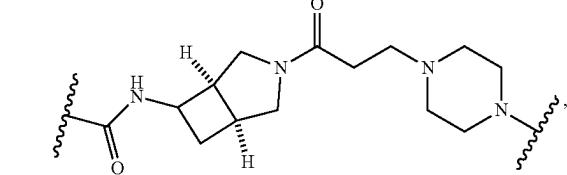
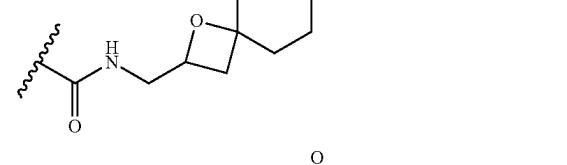
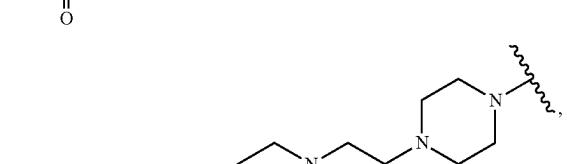
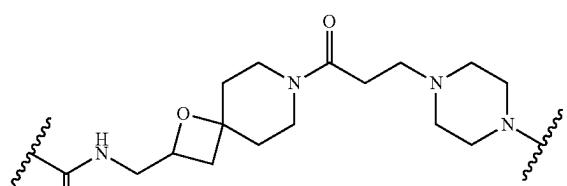
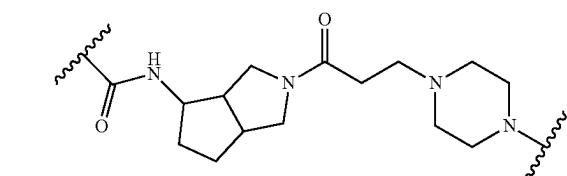
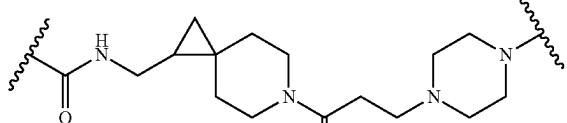
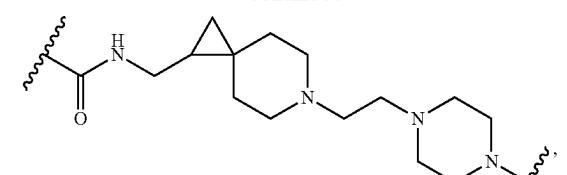
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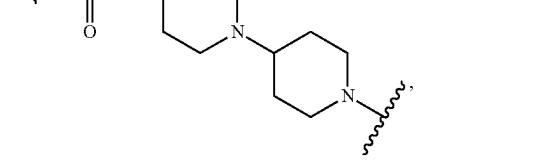
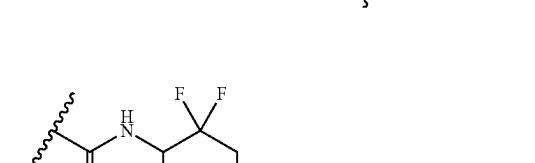
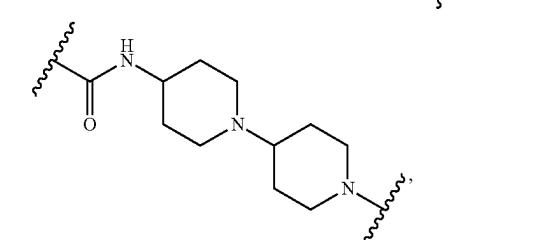
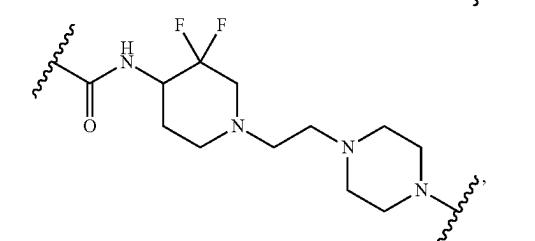
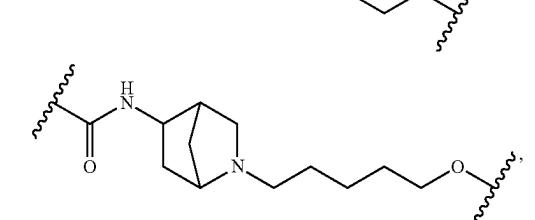
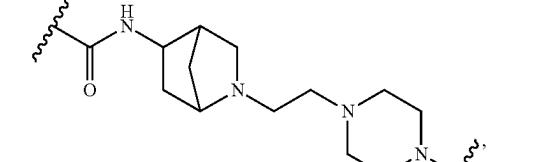
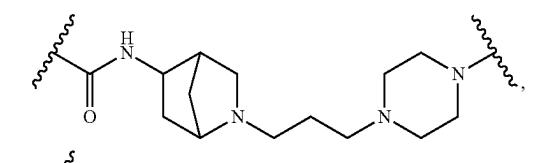
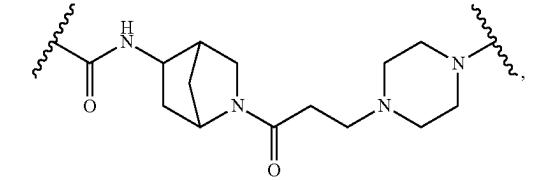
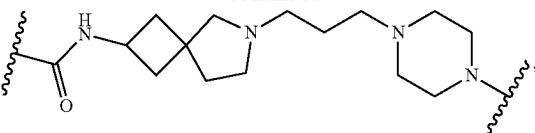
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55

180

-continued



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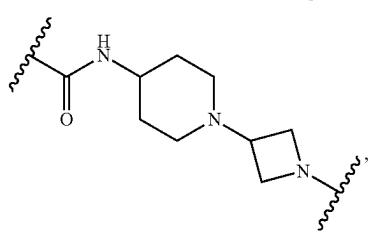
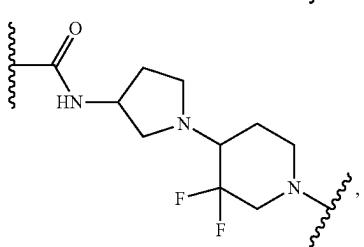
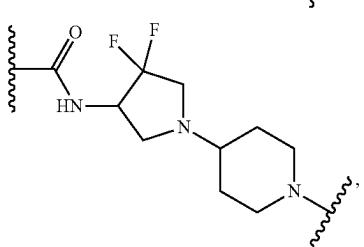
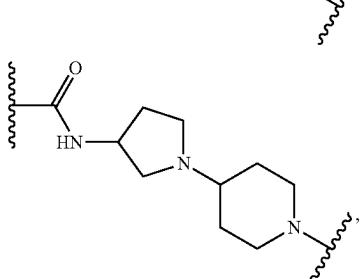
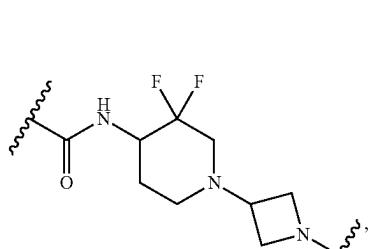
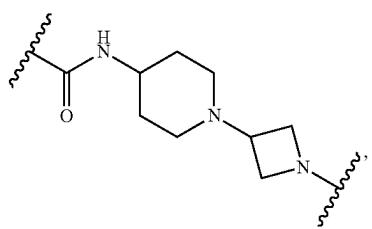
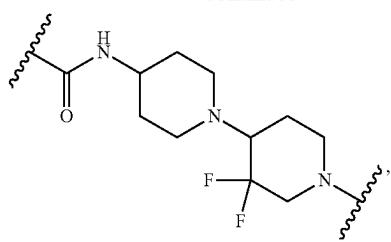
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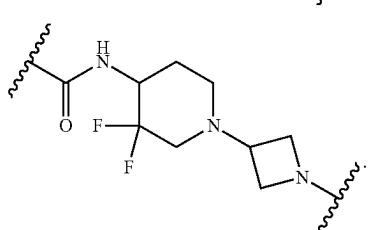
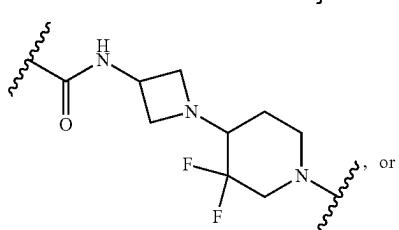
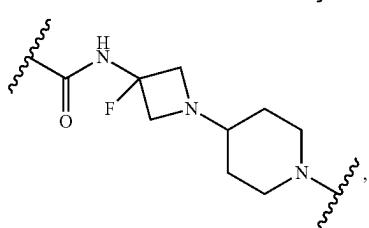
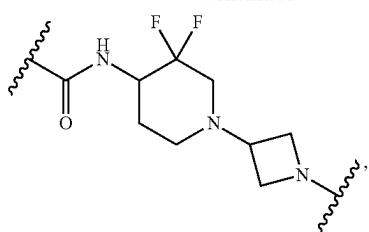
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181

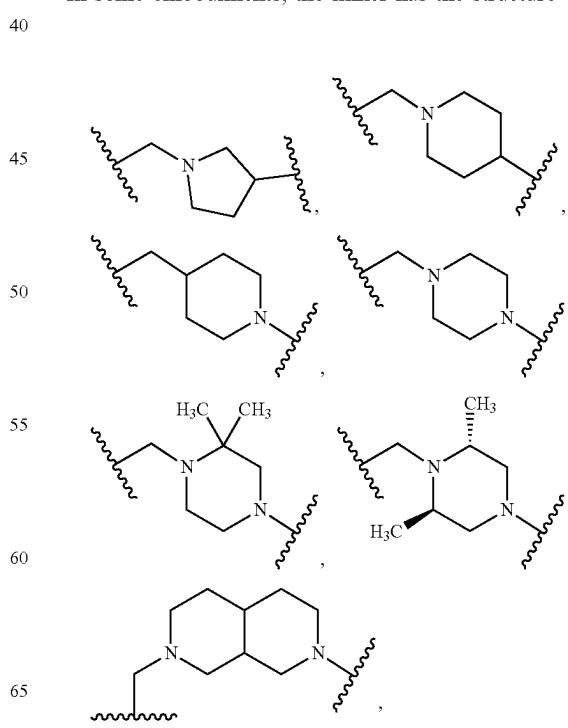
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**182**

-continued

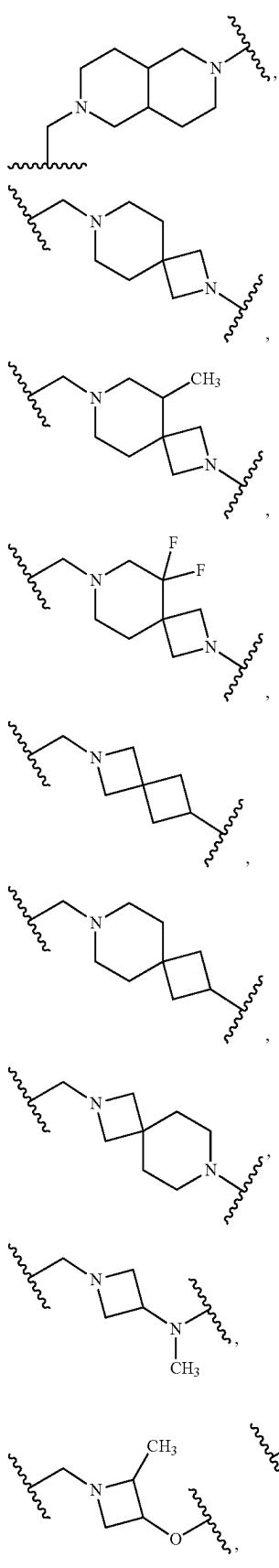


In some embodiments, the linker has the structure of:

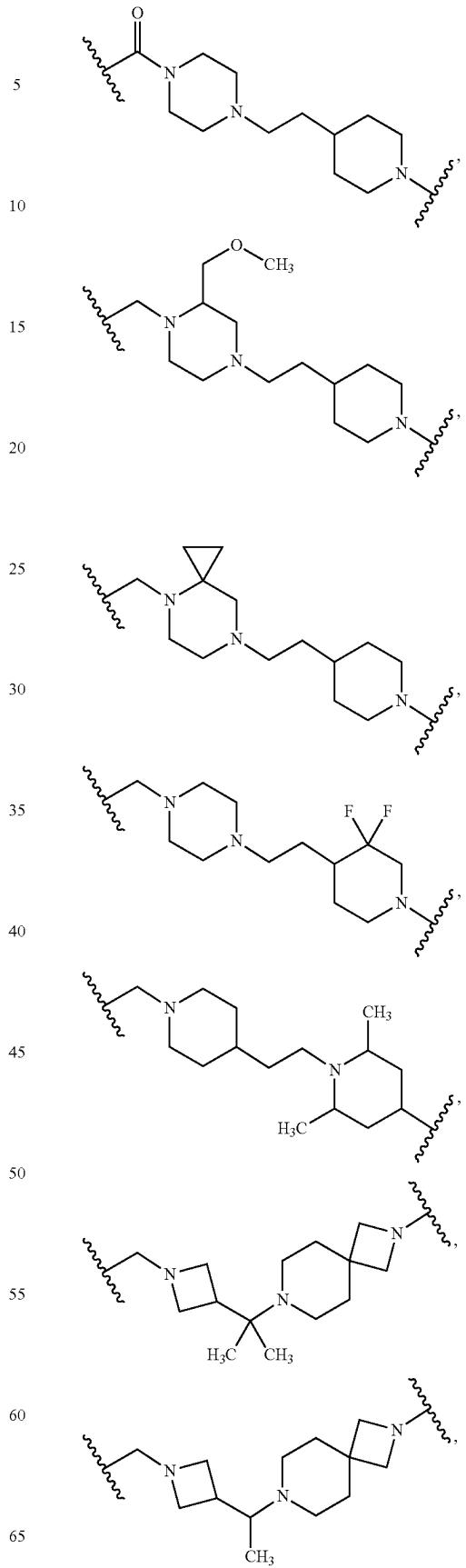


183

-continued

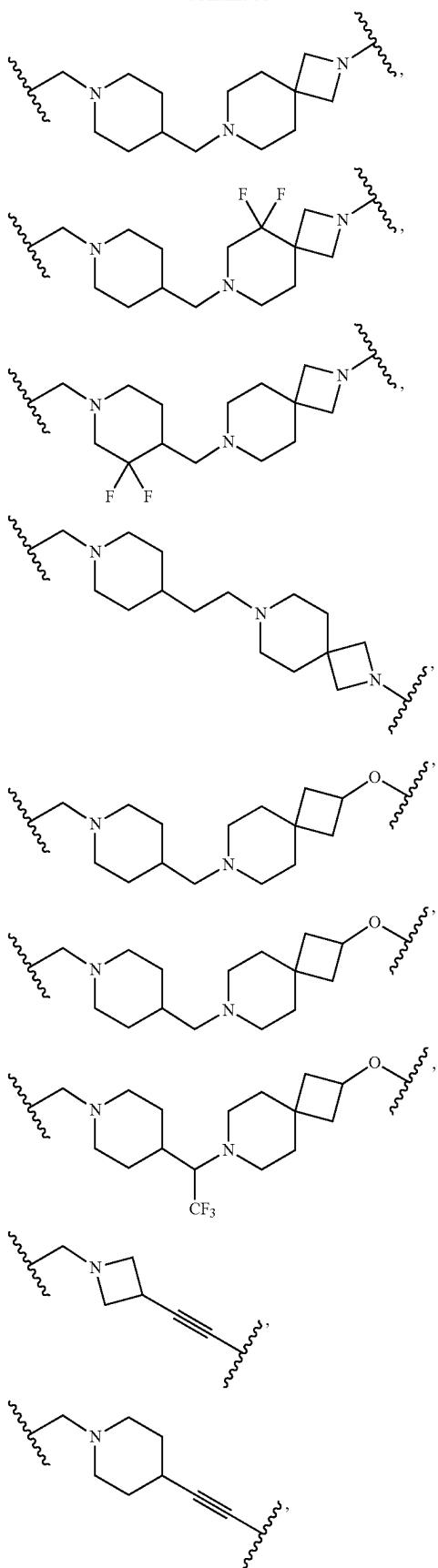
**184**

-continued



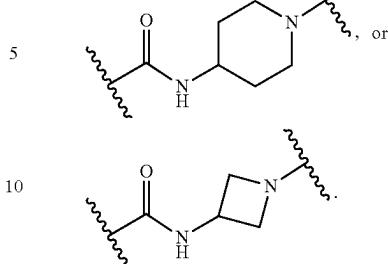
185

-continued



186

-continued



¹⁵ In some embodiments, the linker is a bond.

In some embodiments, the linker is optionally substituted $C_3\text{-}C_{10}$ carbocyclylene, optionally substituted $C_{2\text{-}10}$ heterocyclylene, optionally substituted $C_6\text{-}C_{10}$ arylene, or optionally substituted $C_2\text{-}C_6$ heteroarylene.

In some embodiments, the linker is optionally substituted C₃-C₁₀ carbocyclene or optionally substituted C₂₋₁₀ heterocyclylene. In some embodiments, the linker is optionally substituted C₆-C₁₀ arylene or optionally substituted C₂-C₉ heteroarylene.

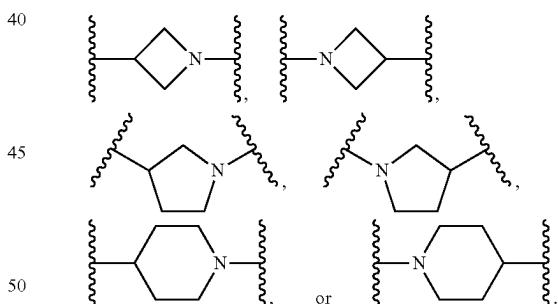
In some embodiments, the linker is optionally substituted C₂₋₁₀ heterocyclene.

In some embodiments, the C₂-C₉ heterocyclylene is monocyclic. In some embodiments, the C₂-C₉ heterocyclylene is polycyclic.

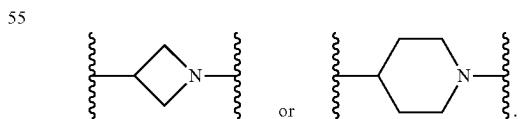
In some embodiments, the C₂-C₉ heterocyclylene is bicyclic.

In some embodiments, the C₂-C₉ heterocyclylene is bridged. In some embodiments, the C₂-C₉ heterocyclylene is fused. In some embodiments, the C₂-C₉ heterocyclylene is spirocyclic.

In some embodiments, the linker has the structure of



In some embodiments, the linker has the structure of



60 In some embodiments, the compound has the structure of
any one of compounds D1-D38 in Table 2A, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound has the structure of any one of compounds
65 D1-D33 in Table 2A, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound has the structure of any one of compounds D34-D38 in Table 2A, or a

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pharmaceutically acceptable salt thereof. In some embodiments, the compound has the structure of any one of compounds D39-D302 in Table 2B, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound has the structure of any one of compounds D303-D375 in Table 2C, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound has the structure of any one of compounds D9, D22, D25, D28, or D29 in Table 2A, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound has the structure of any one of compounds D39-D49, D51, D52, D55, D56, D58, D58, D63, D64, D68, D69, D71-D73, D76, D78, D80-89, D91, D93, D95-107, D109, D110, D112-119, D121, D123-D1256, D127, D128, D130-D136, D138-D143, D145-D147, D149, D151, D152, D154-D166, D169-D174, D178-D183, D195-D201, D222, D224, D227, D231, D246, D251, D253-

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256, D283, or D299-302 in Table 2B, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound has the structure of any one of compounds D303, D304, D306-D312, D314, D315, D317-D327, D329, D330, D332-336, D338-D342, D344-D348, D350, OR D353-D373, or a pharmaceutically acceptable salt thereof.

In an aspect, the disclosure features compounds D1-D38 in Table 2A, or a pharmaceutically acceptable salt thereof.

In another aspect, the disclosure features compounds D1-D33 in Table 2A, or a pharmaceutically acceptable salt thereof.

In another aspect, the disclosure features compounds D39-D302 in Table 2B, or a pharmaceutically acceptable salt thereof.

In yet another aspect, the disclosure features compounds D303-D375 in Table 2C, or a pharmaceutically acceptable salt thereof.

TABLE 2A

Compounds D1-D38 of the Disclosure	
Compound No.	Structure
D1	
D2	

TABLE 2A-continued

Compounds D1-D38 of the Disclosure

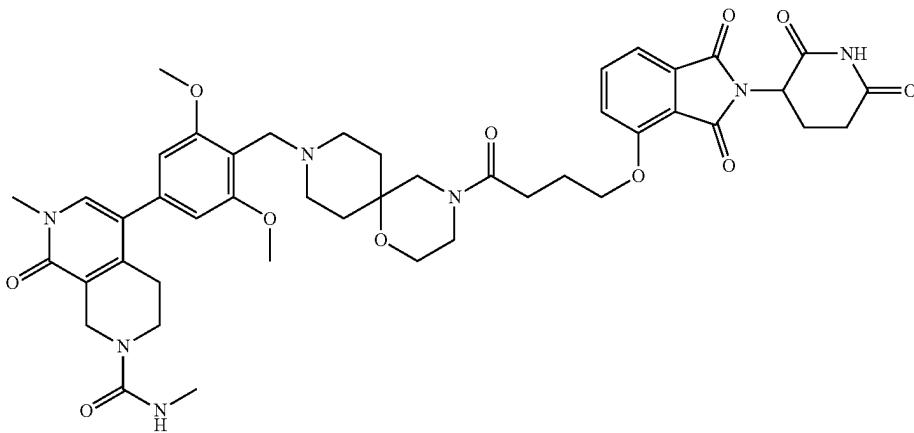
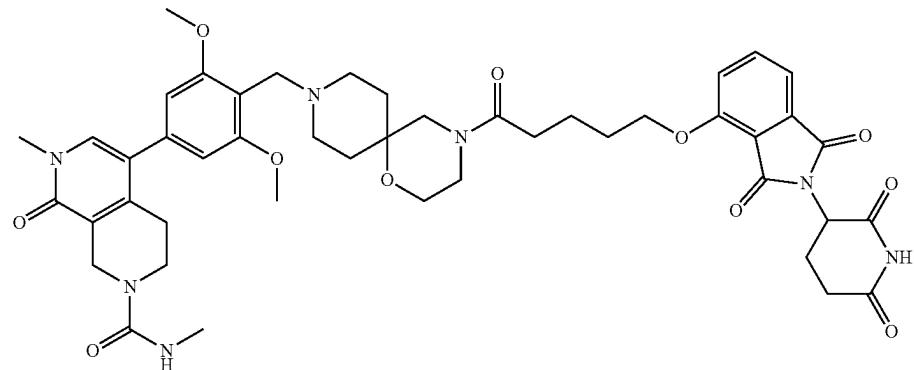
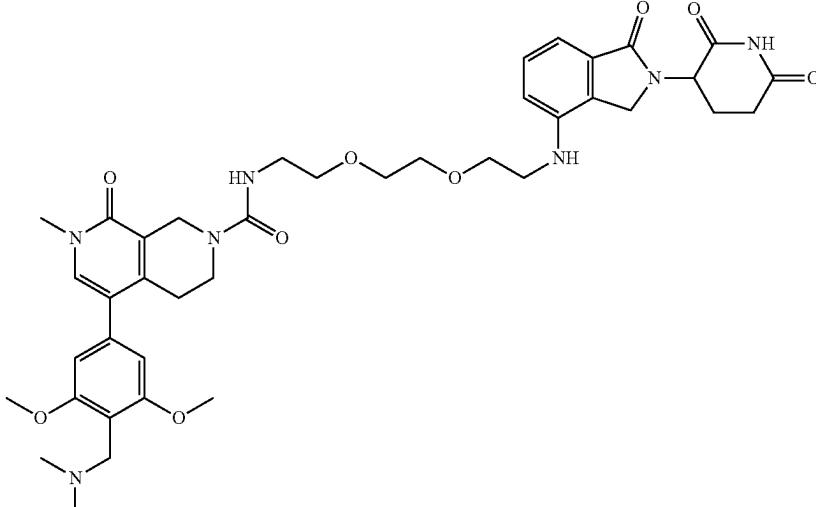
Compound No.	Structure
D3	
D4	
D5	

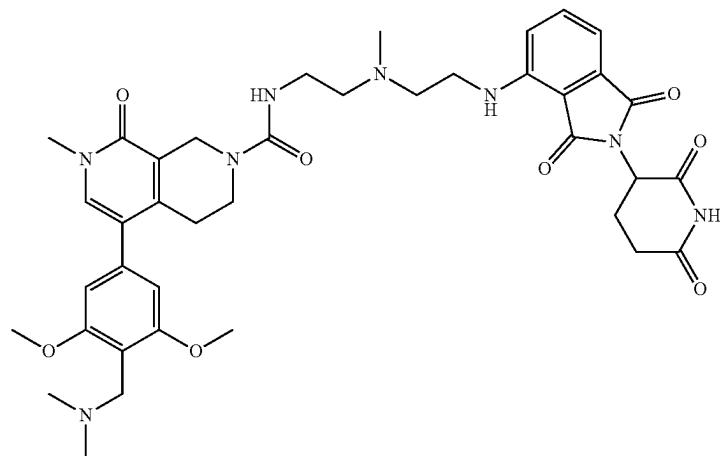
TABLE 2A-continued

Compounds D1-D38 of the Disclosure

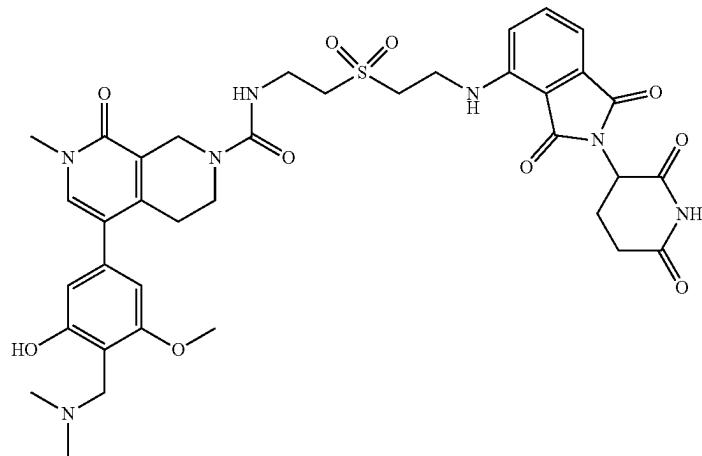
Compound No.

Structure

D6



D7



D8

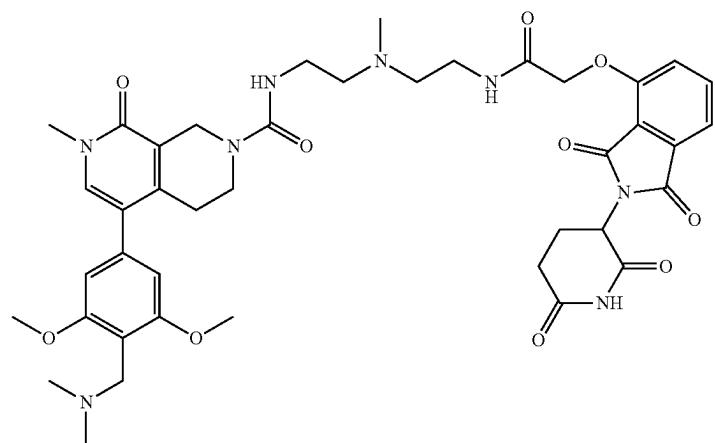


TABLE 2A-continued

Compounds D1-D38 of the Disclosure

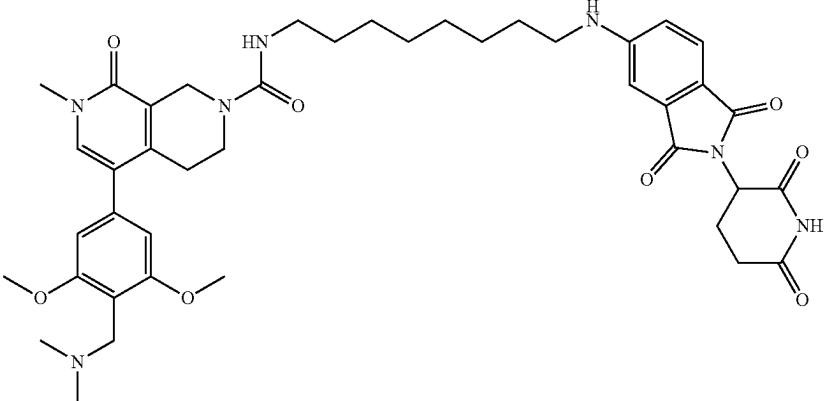
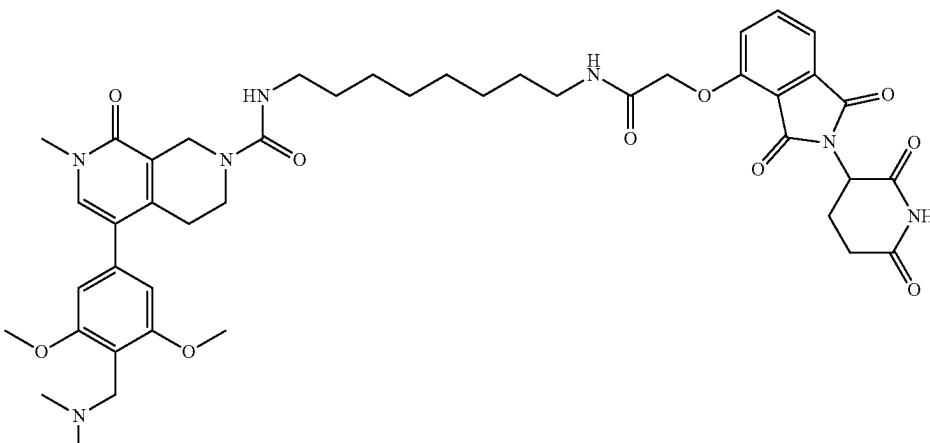
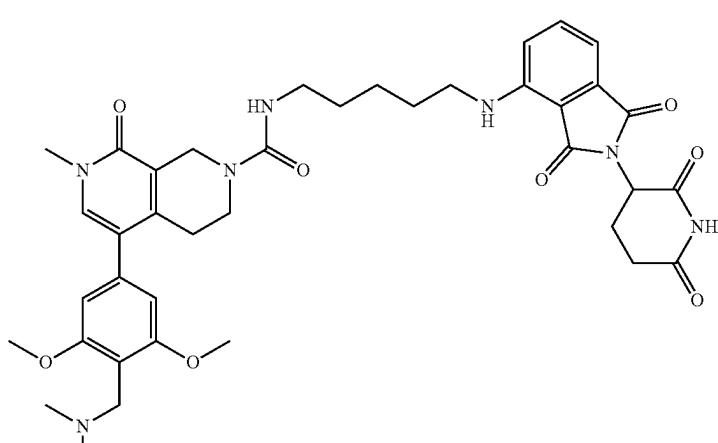
Compound No.	Structure
D9	
D10	
D11	

TABLE 2A-continued

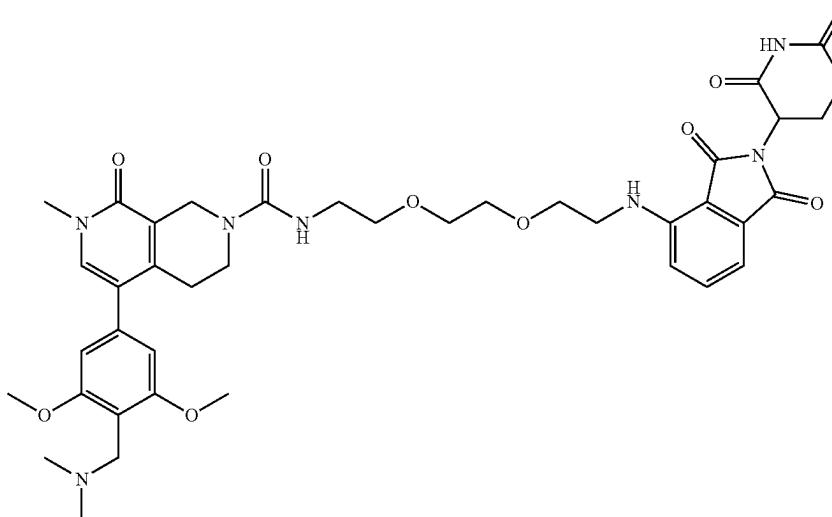
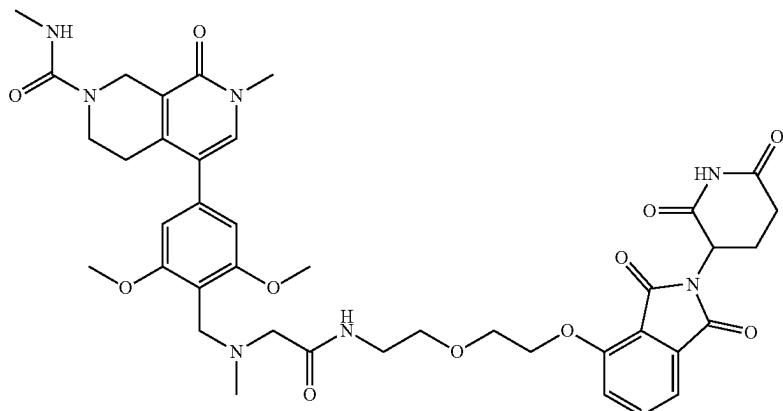
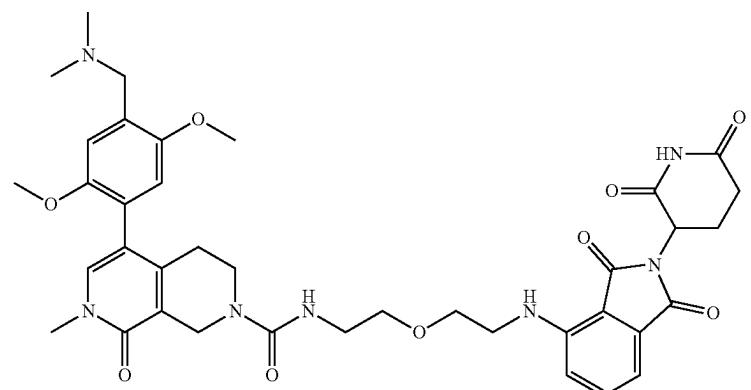
Compounds D1-D38 of the Disclosure	
Compound No.	Structure
D12	
D13	
D14	

TABLE 2A-continued

Compounds D1-D38 of the Disclosure

Compound No.	Structure
D15	
D16	
D17	

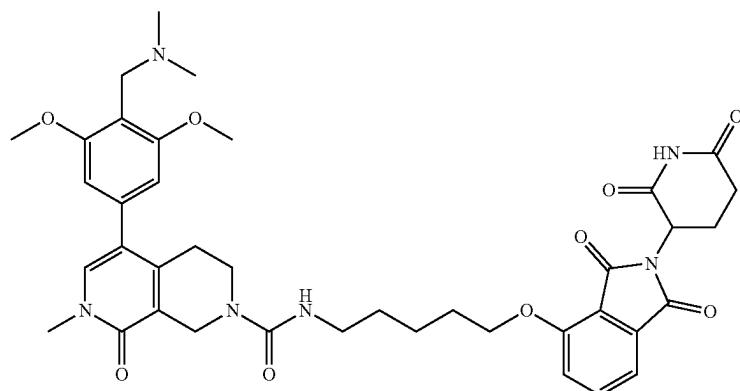
TABLE 2A-continued

Compounds D1-D38 of the Disclosure

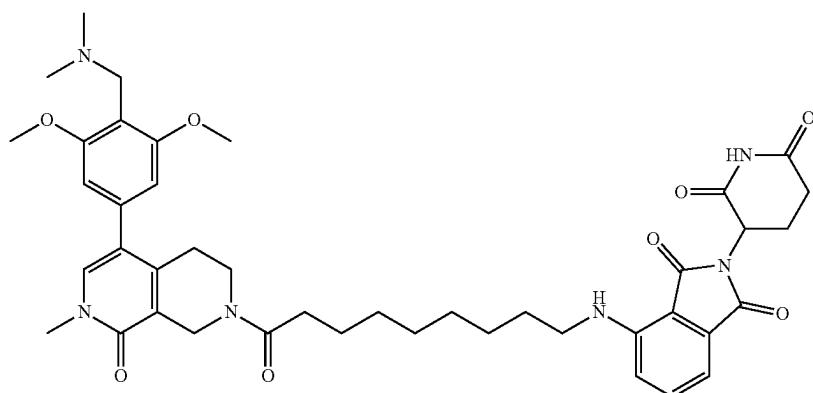
Compound No.

Structure

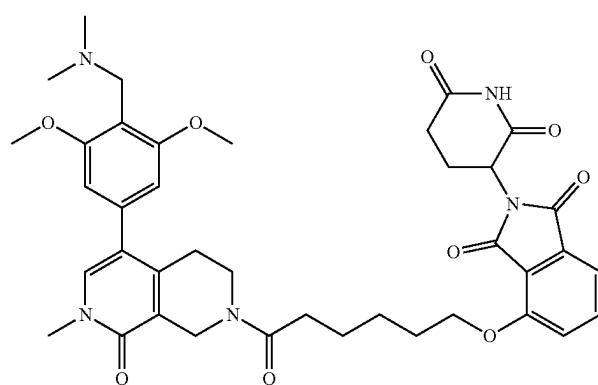
D18



D19



D20



201

202

TABLE 2A-continued

Compounds D1-D38 of the Disclosure

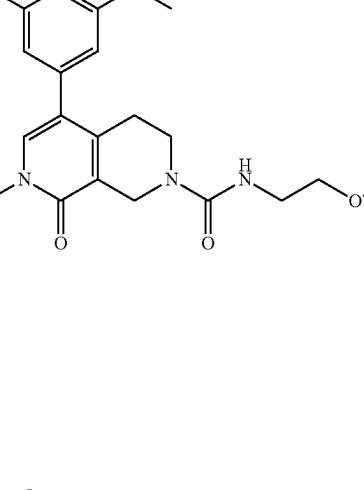
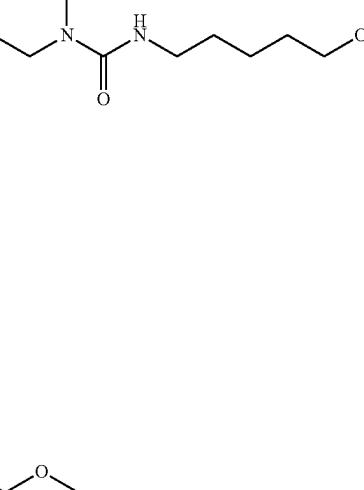
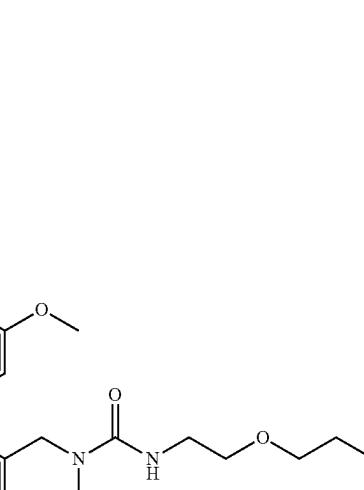
Compound No.	Structure
D21	
D22	
D23	

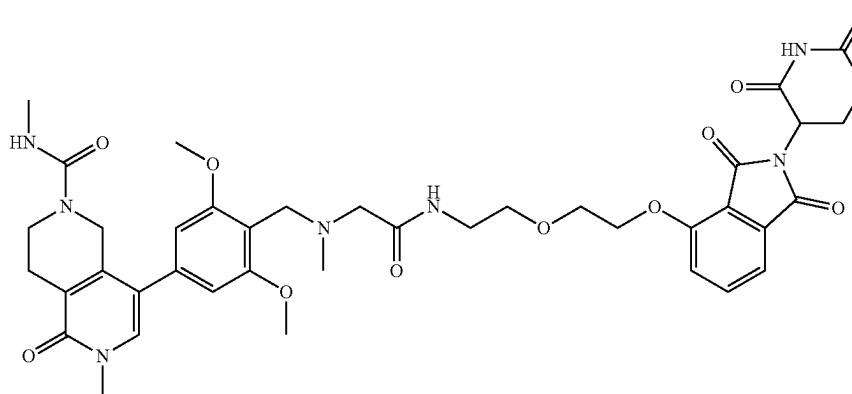
TABLE 2A-continued

Compounds D1-D38 of the Disclosure

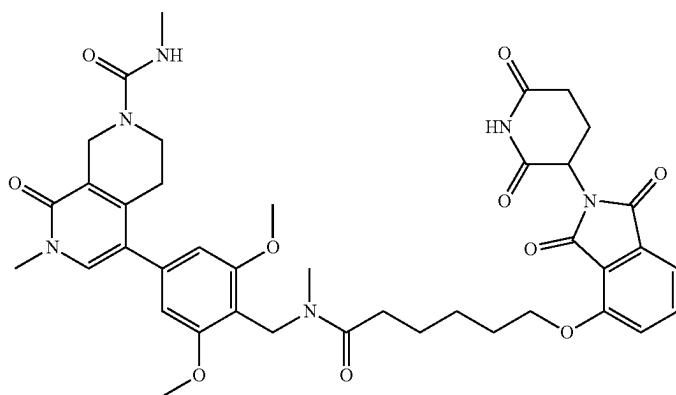
Compound No.

Structure

D24



D25



D26

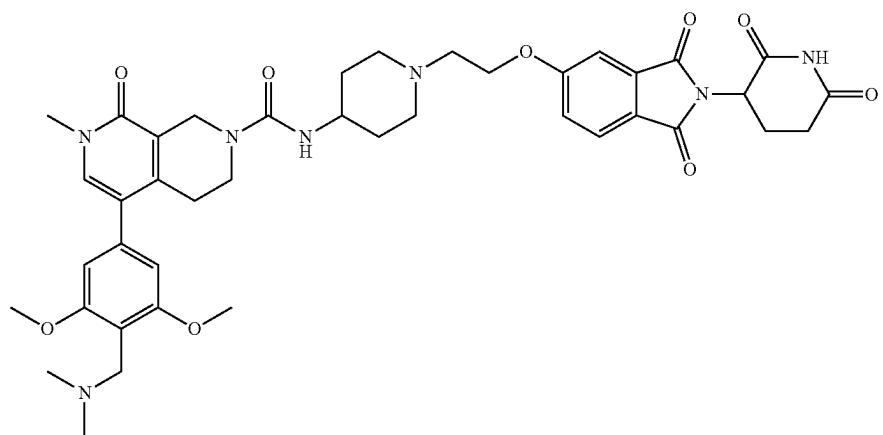


TABLE 2A-continued

Compounds D1-D38 of the Disclosure

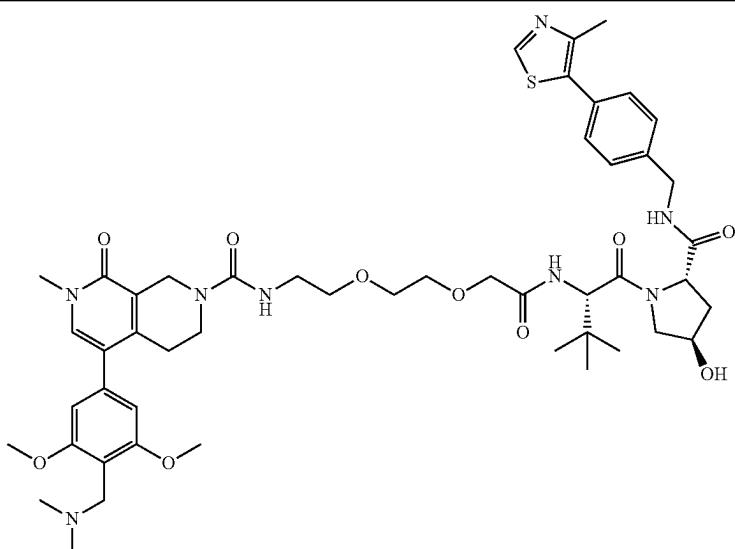
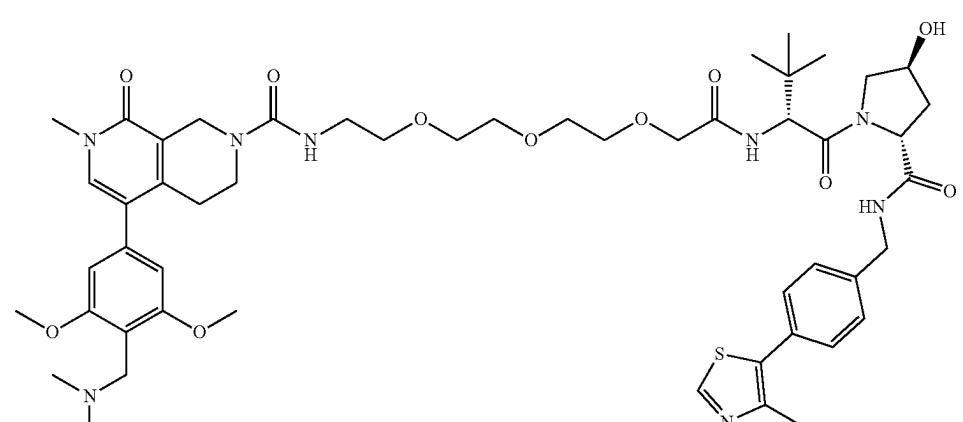
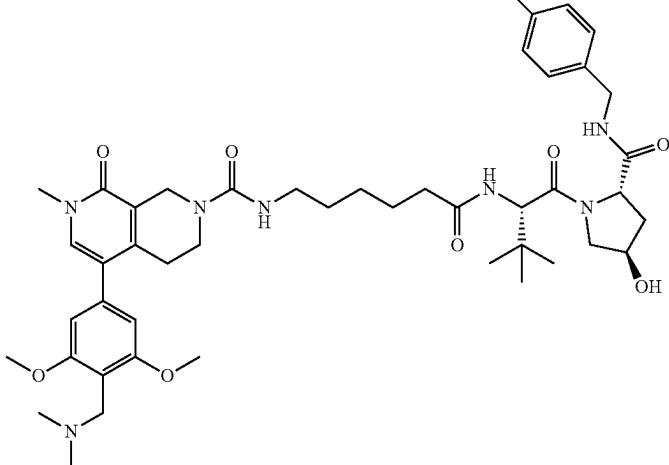
Compound No.	Structure
D27	
D28	
D29	
D30	

TABLE 2A-continued

Compounds D1-D38 of the Disclosure	
Compound No.	Structure
D31	
D32	
D33	

TABLE 2A-continued

Compounds D1-D38 of the Disclosure

Compound No.	Structure
D34	
D35	
D36	

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TABLE 2A-continued

Compounds D1-D38 of the Disclosure

Compound No.	Structure
D37	
D38	

TABLE 2B

Compounds D39-D302 of the Disclosure

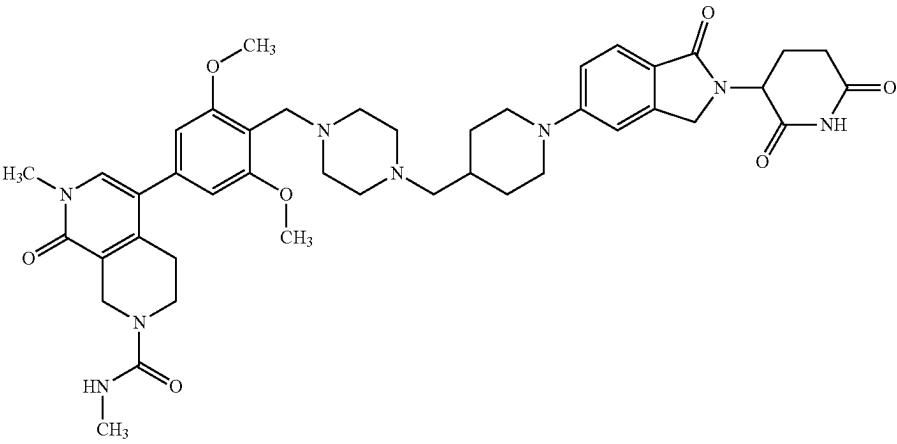
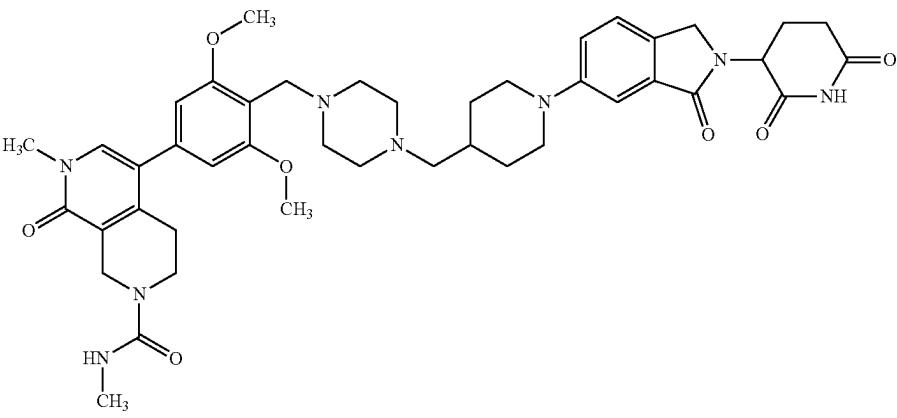
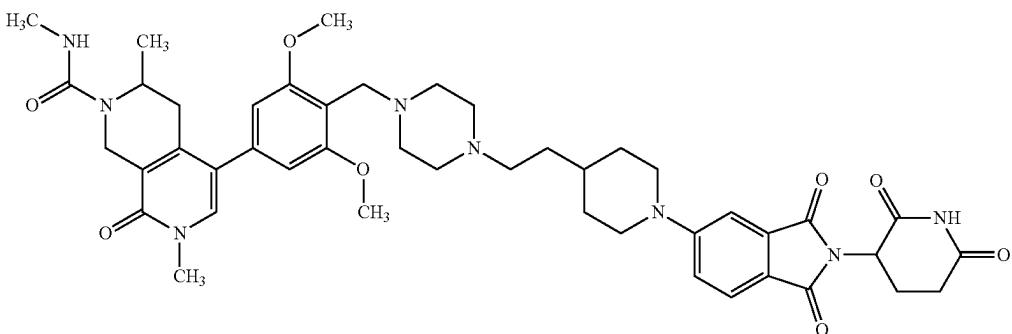
Com- pound No.	Structure
D39	
D40	
D41	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

Compound No.

Structure

D42

Chemical structure of compound D42: A complex molecule featuring a 4-(dimethylamino)phenyl ring substituted with a 2-(dimethylamino)-4-methoxyphenyl group. This is connected via a methylene bridge to a piperazine ring, which is further substituted with a 2-methylpropyl group and a 2-methylbutyl group. The chain continues through a cyclohexyl ring, a 4-(dimethylamino)phenyl ring, and a tricyclic core consisting of a 2,3-dihydroindolinone fused with a 4,5-dihydro-1H-imidazole.

D43

Chemical structure of compound D43: A complex molecule featuring a 4-(dimethylamino)phenyl ring substituted with a 2-(dimethylamino)-4-methoxyphenyl group. This is connected via a methylene bridge to a piperazine ring, which is further substituted with a 2-methylpropyl group and a 2-methylbutyl group. The chain continues through a cyclohexyl ring, a 4-(dimethylamino)phenyl ring, and a tricyclic core consisting of a 2,3-dihydroindolinone fused with a 4,5-dihydro-1H-imidazole.

D44

Chemical structure of compound D44: A complex molecule featuring a 4-(dimethylamino)phenyl ring substituted with a 2-(dimethylamino)-4-methoxyphenyl group. This is connected via a methylene bridge to a piperazine ring, which is further substituted with a 2-methylpropyl group and a 2-methylbutyl group. The chain continues through a cyclohexyl ring, a 4-(dimethylamino)phenyl ring, and a tricyclic core consisting of a 2,3-dihydroindolinone fused with a 4,5-dihydro-1H-imidazole. Two deuterium atoms (²H) are explicitly labeled on the 2-methylpropyl side chain.

D45

Chemical structure of compound D45: A complex molecule featuring a 4-(dimethylamino)phenyl ring substituted with a 2-(dimethylamino)-4-methoxyphenyl group. This is connected via a methylene bridge to a piperazine ring, which is further substituted with a 2-methylpropyl group and a 2-methylbutyl group. The chain continues through a cyclohexyl ring, a 4-(dimethylamino)phenyl ring, and a tricyclic core consisting of a 2,3-dihydroindolinone fused with a 4,5-dihydro-1H-imidazole. Two deuterium atoms (²H) are explicitly labeled on the 2-methylpropyl side chain.

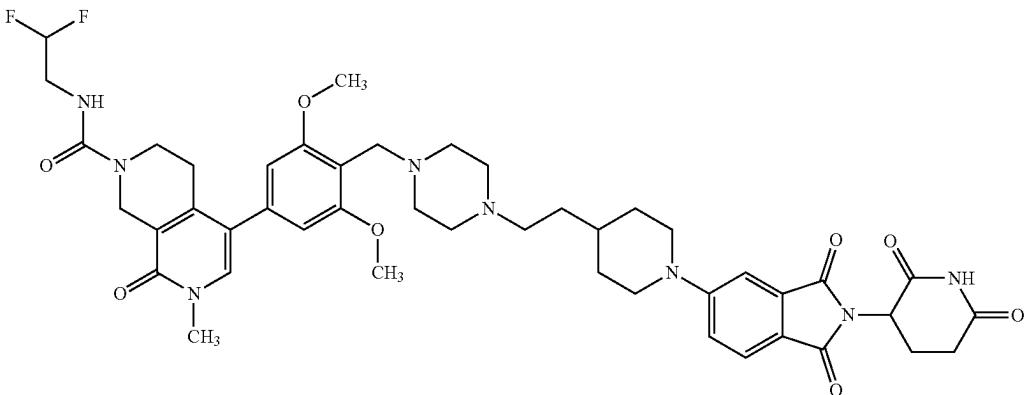
TABLE 2B-continued

Compounds D39-D302 of the Disclosure

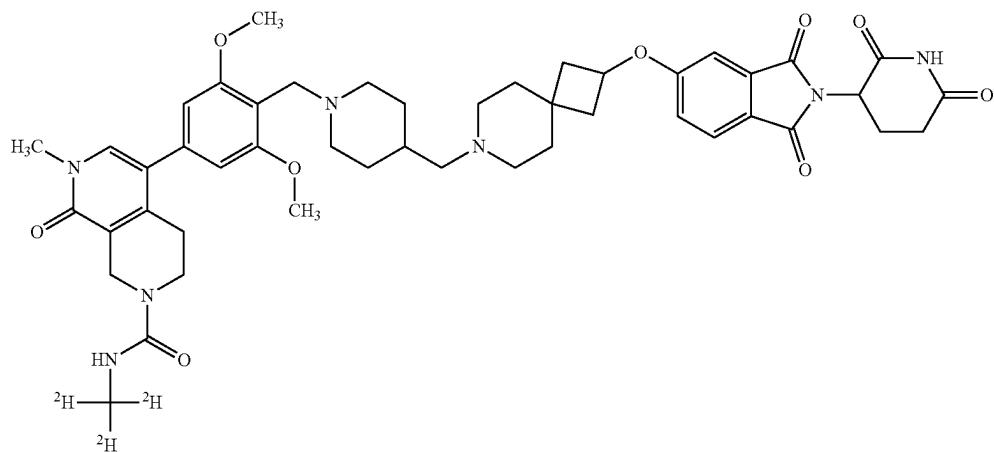
Com-
ound
No.

Structure

D46



D47



D48

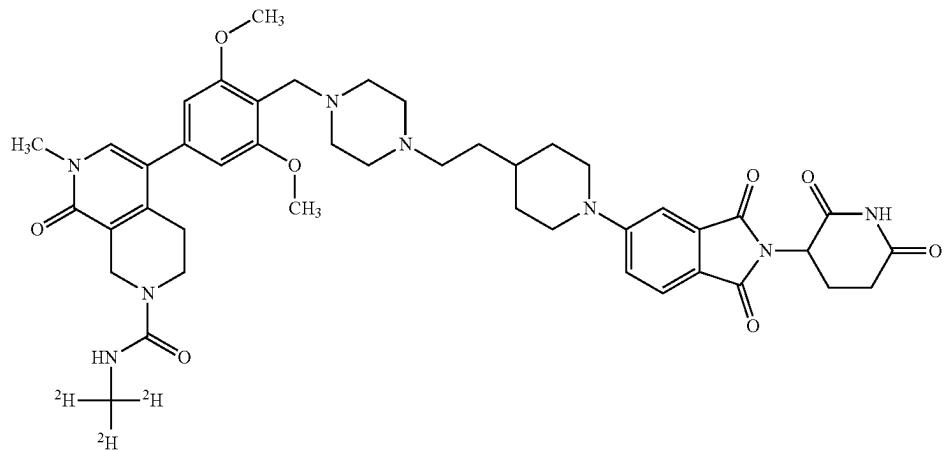


TABLE 2B-continued

Compounds D39-D302 of the Disclosure

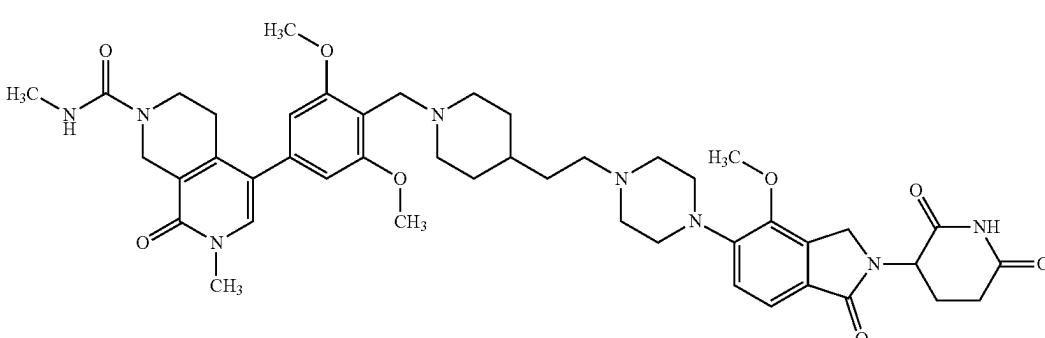
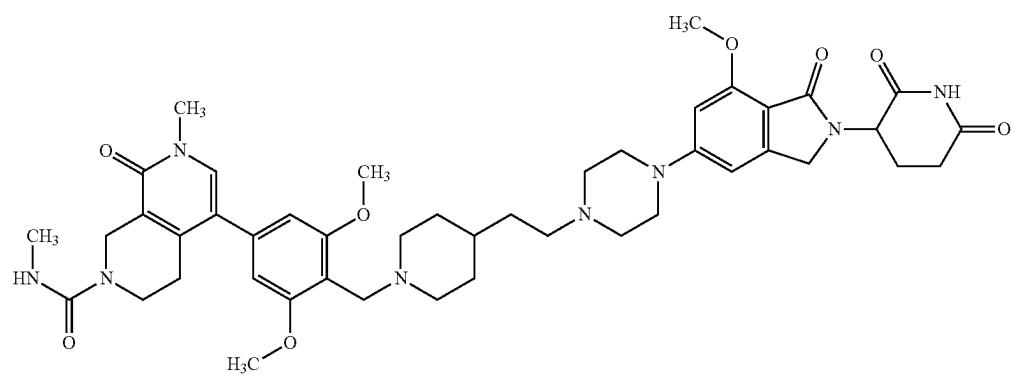
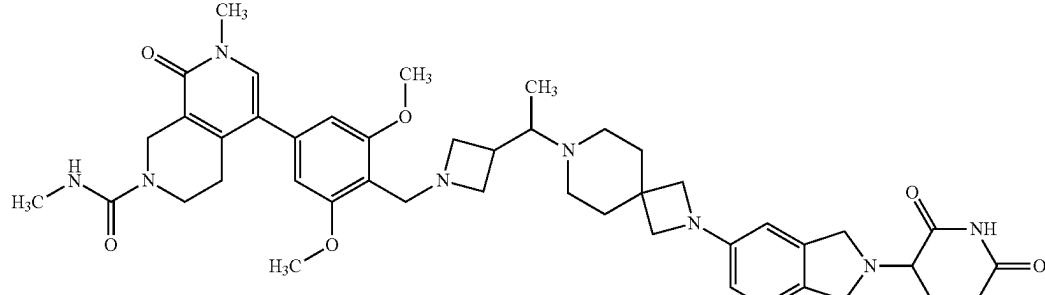
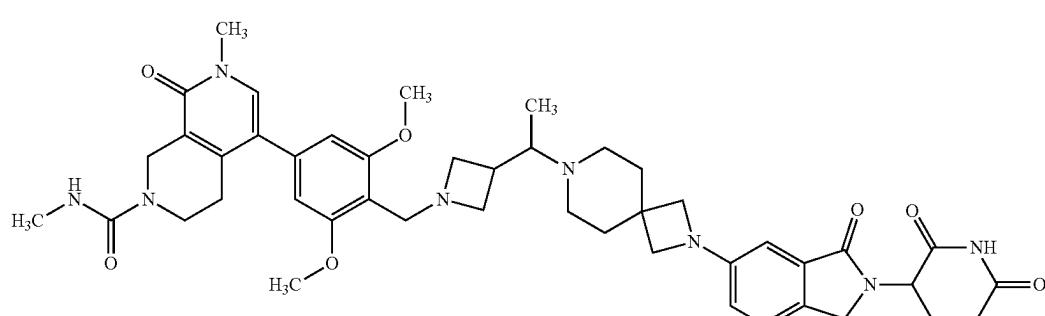
Com- ound No.	Structure
D49	
D50	
D51	
D52	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

Compound No.	Structure
D53	
D54	
D55	
D56	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

Com- ound No.	Structure
D57	
D58	
D59	
D60	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

Compound No.	Structure
D61	
D62	
D63	
D64	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

Com- ound No.	Structure
D65	
D66	
D67	
D68	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

Com- ound No.	Structure
D69	
D70	
D71	
D72	

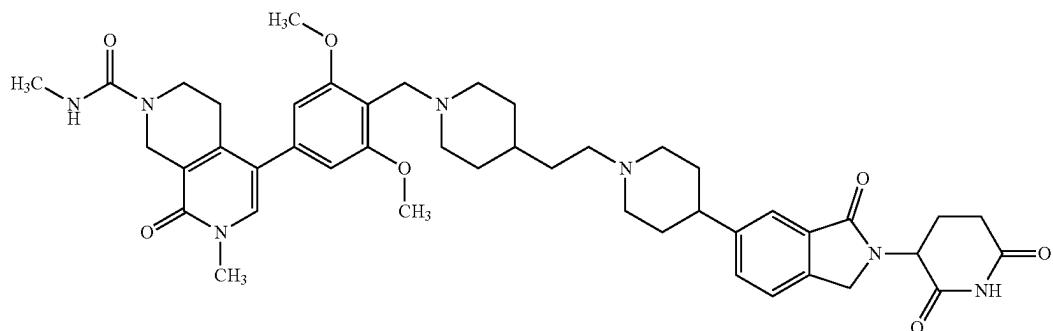
TABLE 2B-continued

Compounds D39-D302 of the Disclosure

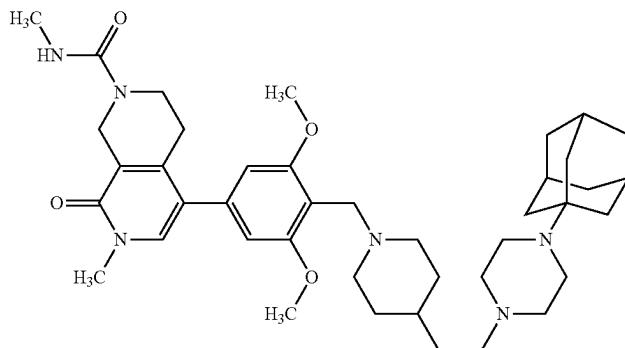
Com-
ound
No.

Structure

D73



D74



D75

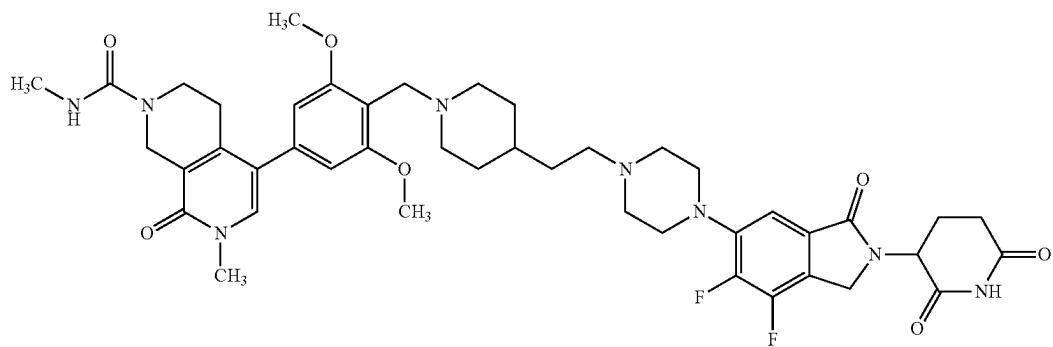


TABLE 2B-continued

Compounds D39-D302 of the Disclosure

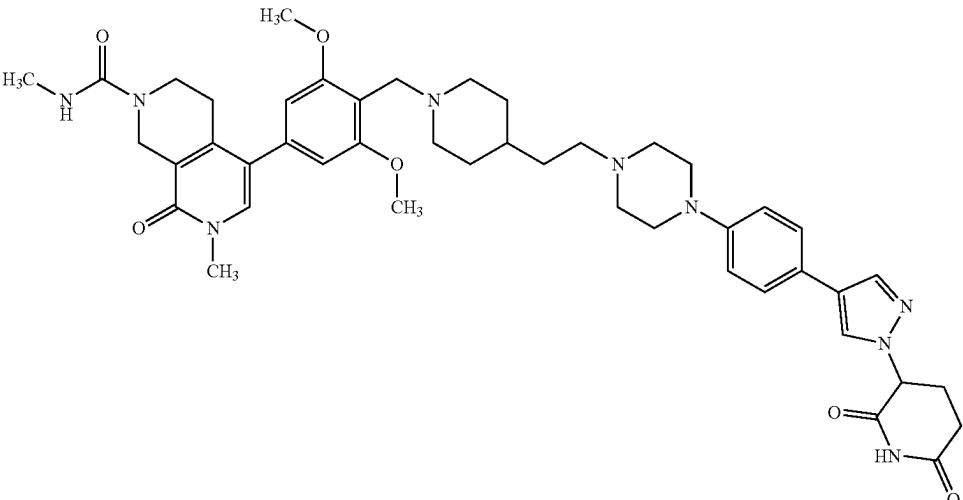
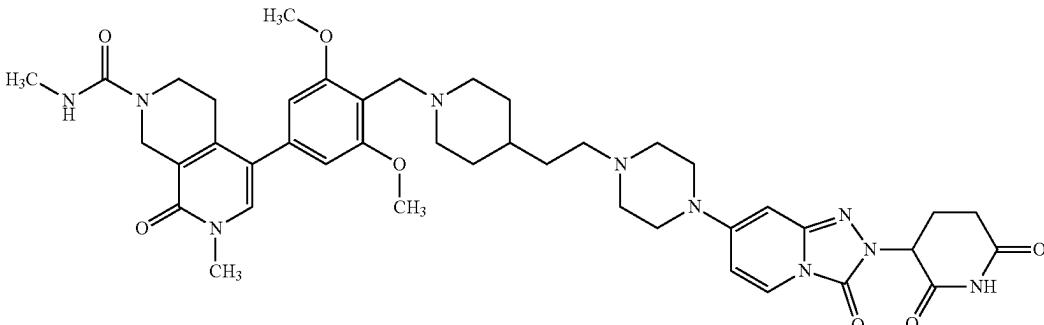
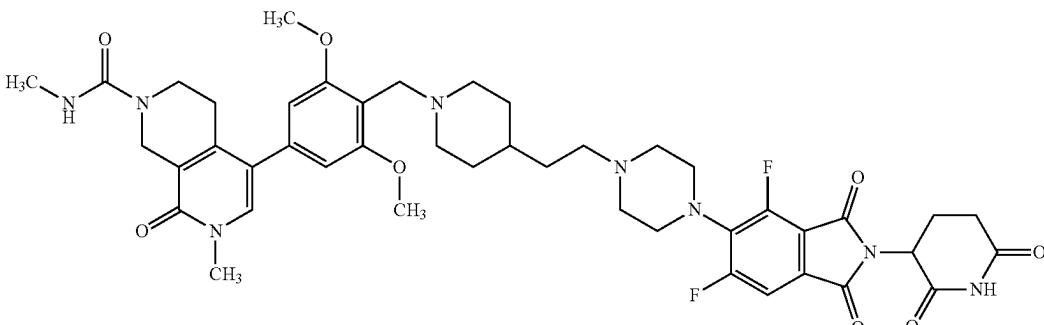
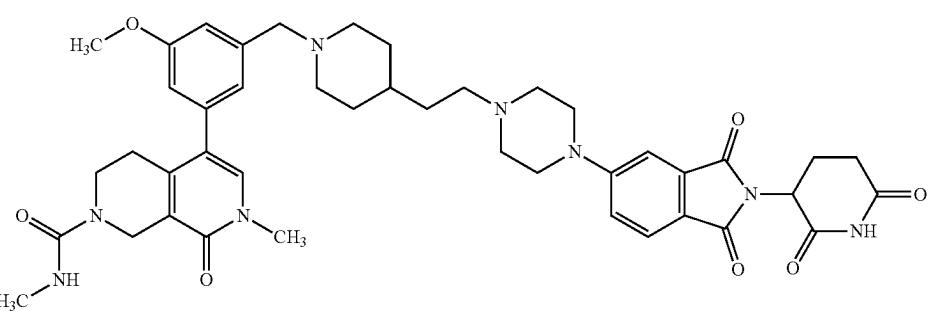
Compound No.	Structure
D76	
D77	
D78	
D79	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

Com- ound No.	Structure
D80	
D81	
D82	
D83	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

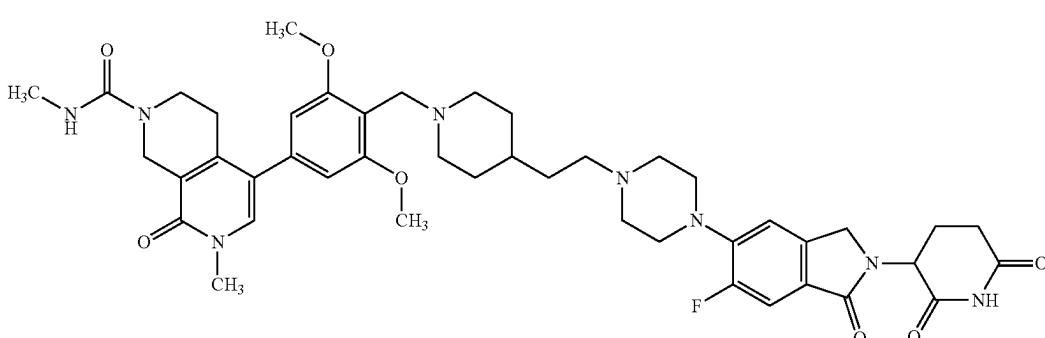
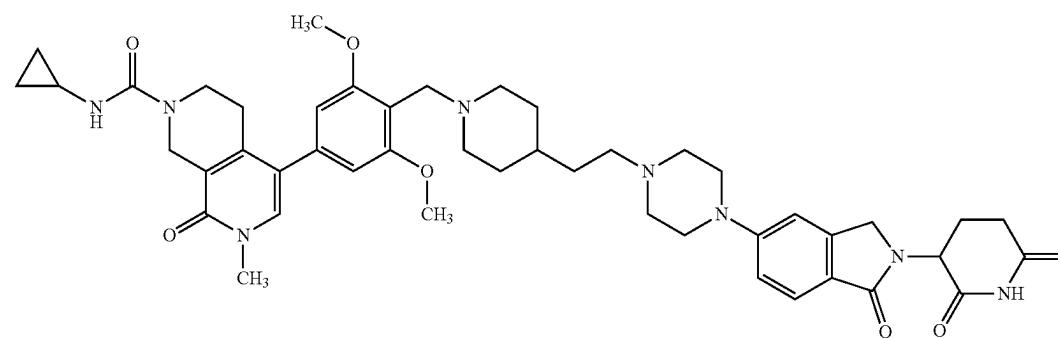
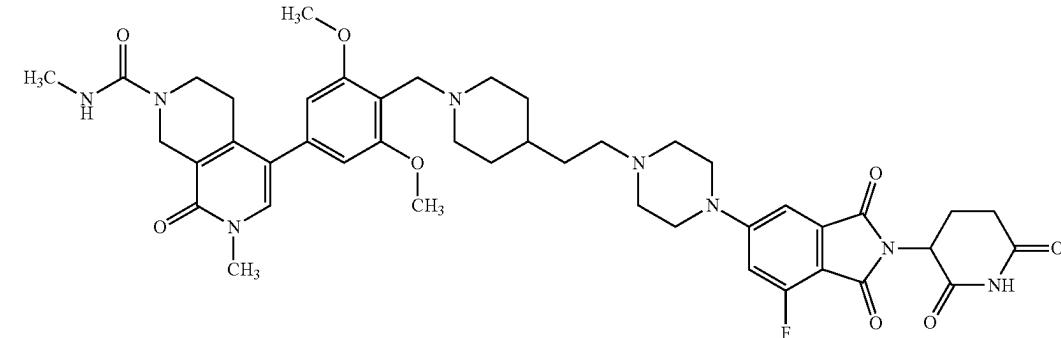
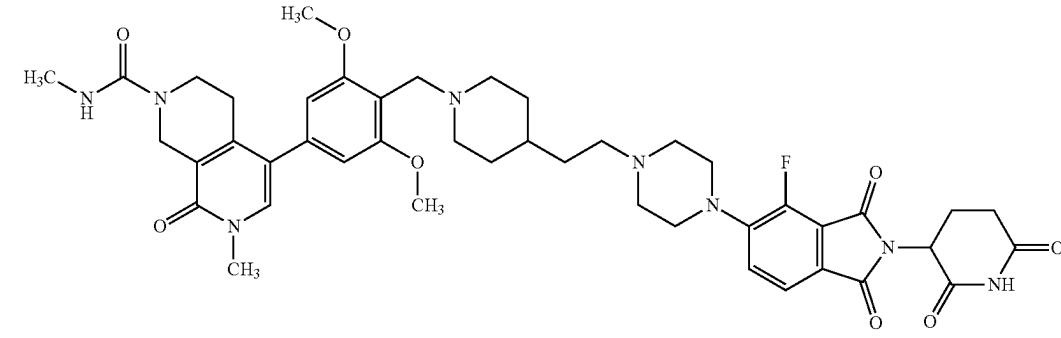
Com- ound No.	Structure
D84	
D85	
D86	
D87	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

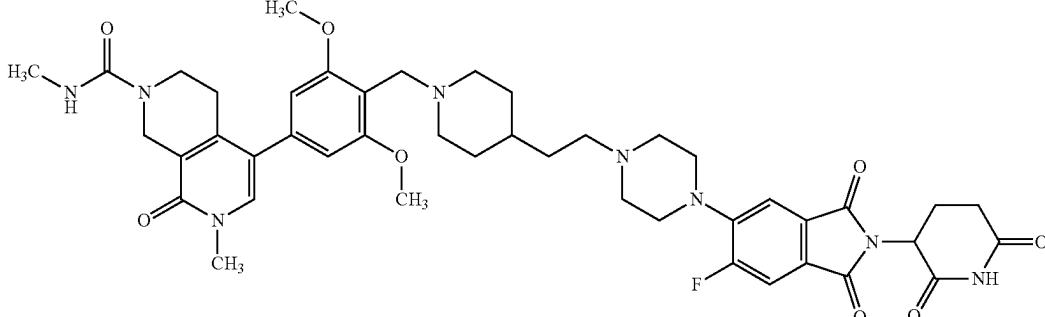
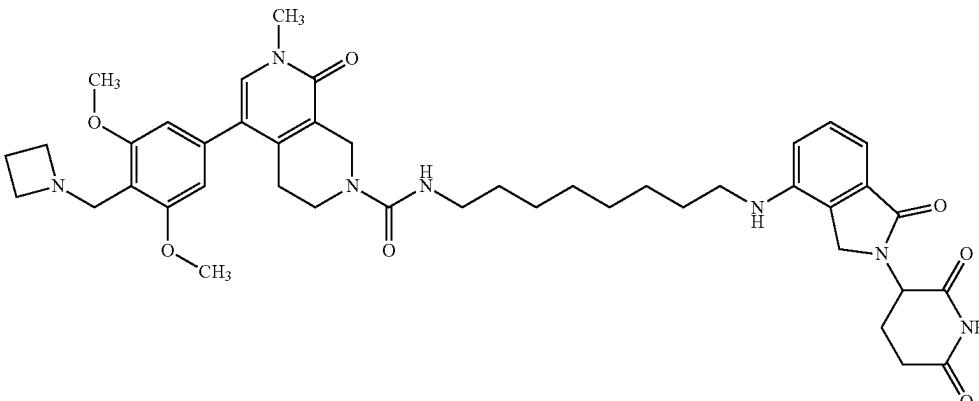
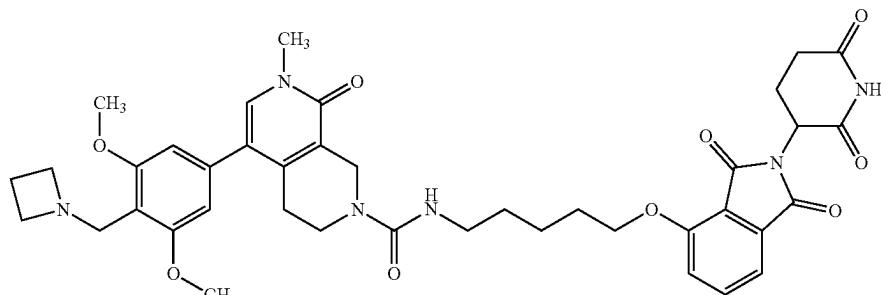
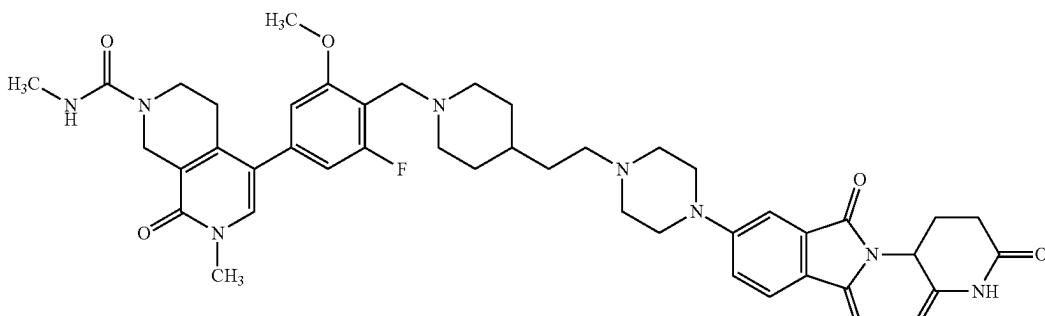
Com- ound No.	Structure
D88	
D89	
D90	
D91	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

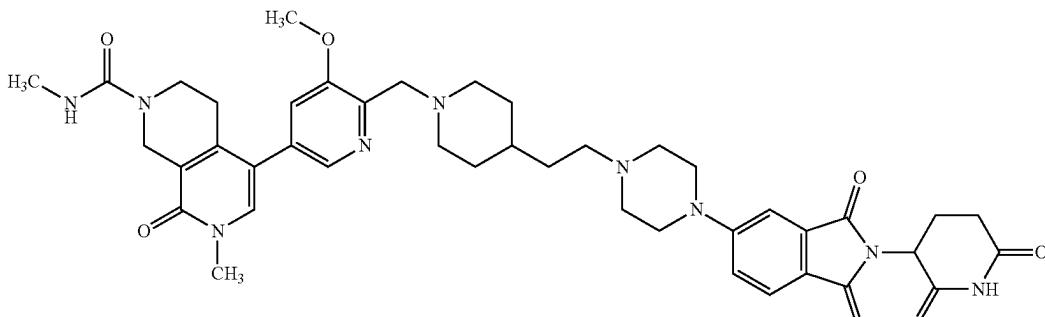
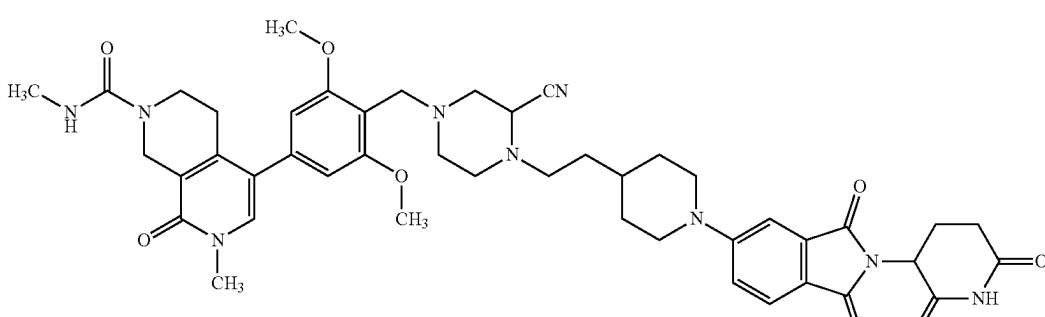
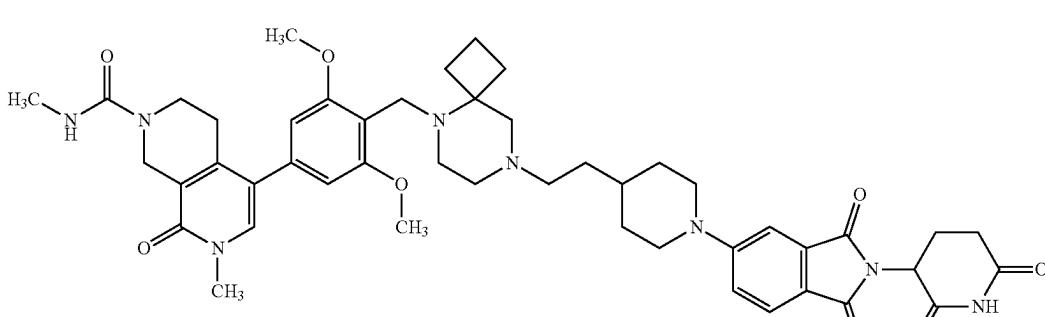
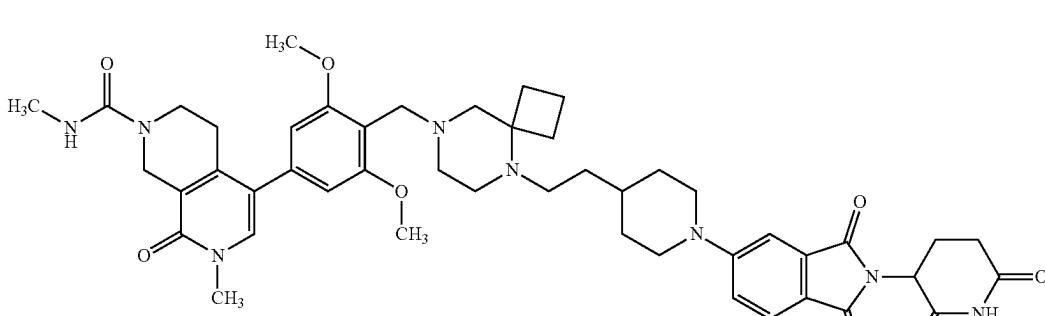
Com- ound No.	Structure
D92	
D93	
D94	
D95	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

Com- ound No.	Structure
D96	
D97	
D98	
D99	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

Com- ound No.	Structure
D100	
D101	
D102	
D103	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

Com- ound No.	Structure
D104	
D105	
D106	
D107	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

Com- ound No.	Structure
D109	
D110	
D111	
D112	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

Com- ound No.	Structure
D113	
D114	
D115	
D116	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

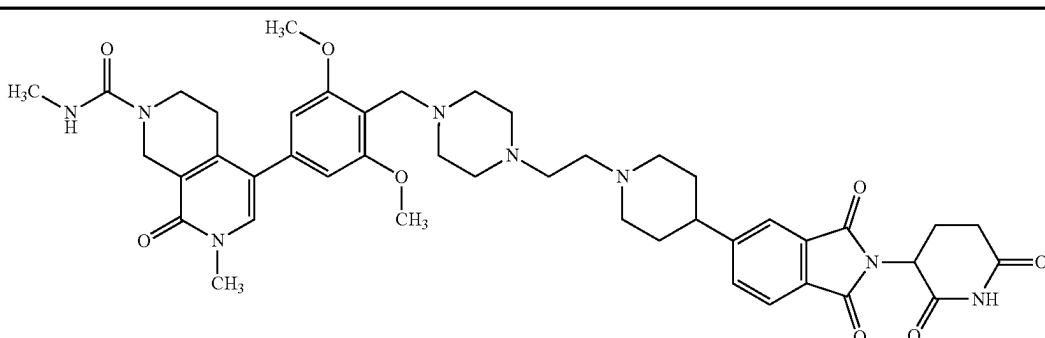
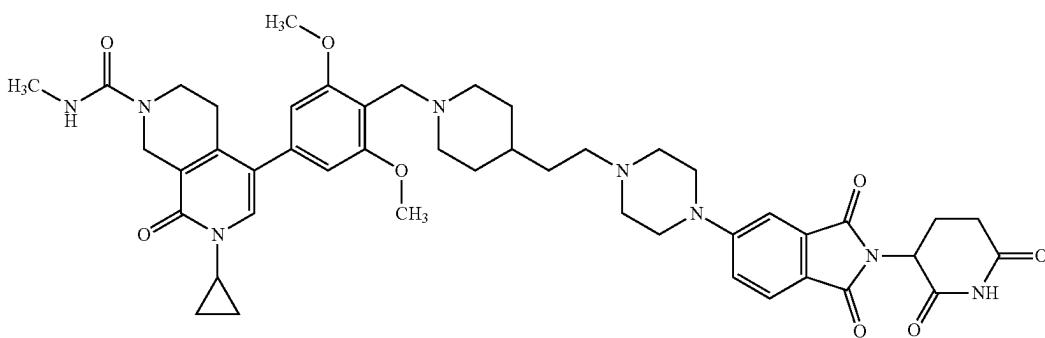
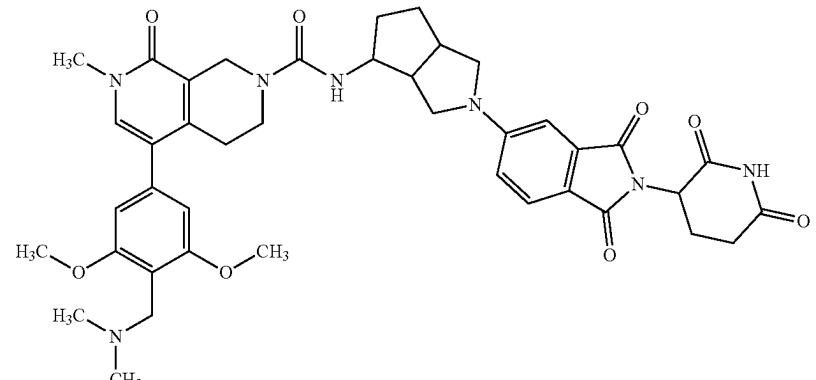
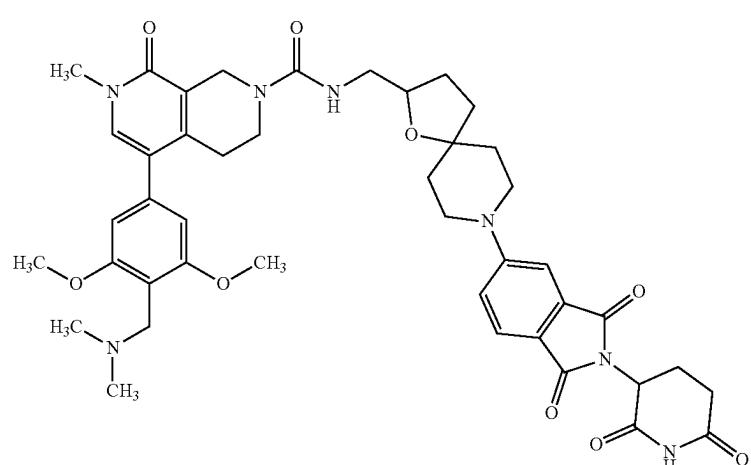
Compound No.	Structure
D117	
D118	
D119	
D120	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

Compound No.	Structure
D121	
D122	
D123	
D124	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

Compound No.	Structure
D125	
D126	
D127	
D128	
D129	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

Com- ound No.	Structure
D130	
D131	
D132	
D133	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

Com- ound No.	Structure
D134	
D135	
D136	
D137	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

Com- ound No.	Structure
D138	
D139	
D140	
D141	

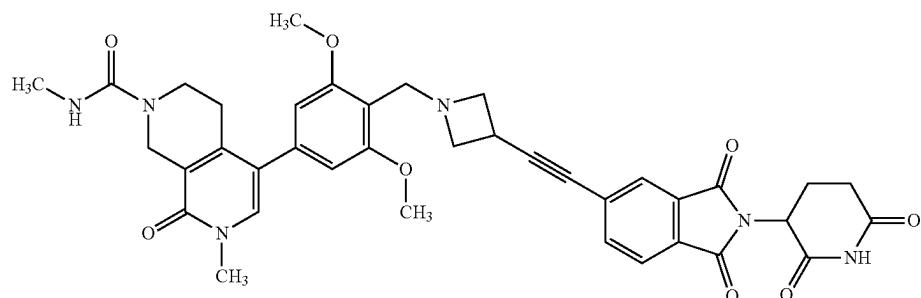
TABLE 2B-continued

Compounds D39-D302 of the Disclosure

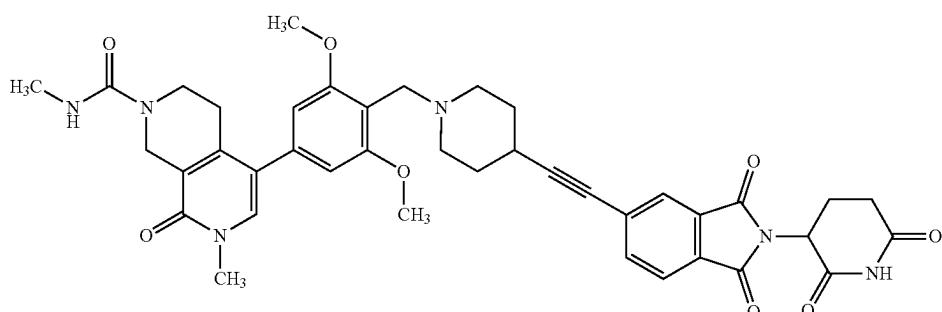
Com-
ound
No.

Structure

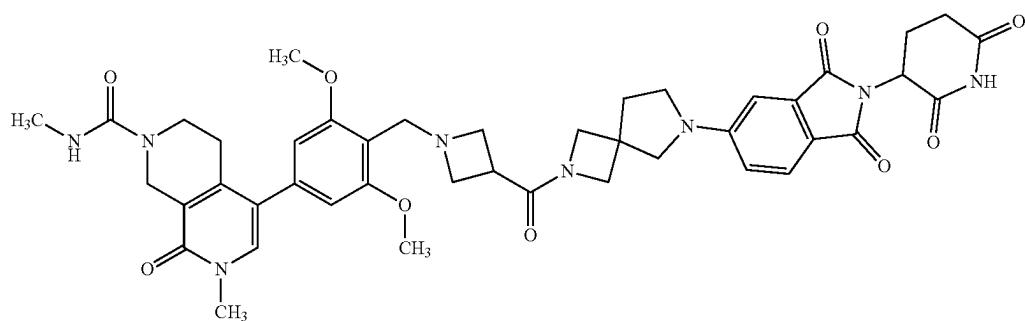
D142



D143



D144



D145

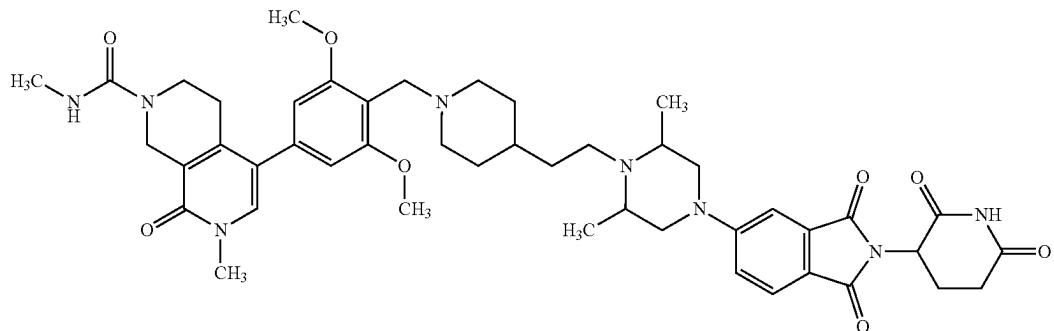


TABLE 2B-continued

Compounds D39-D302 of the Disclosure

Com- ound No.	Structure
D146	
D147	
D148	
D149	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

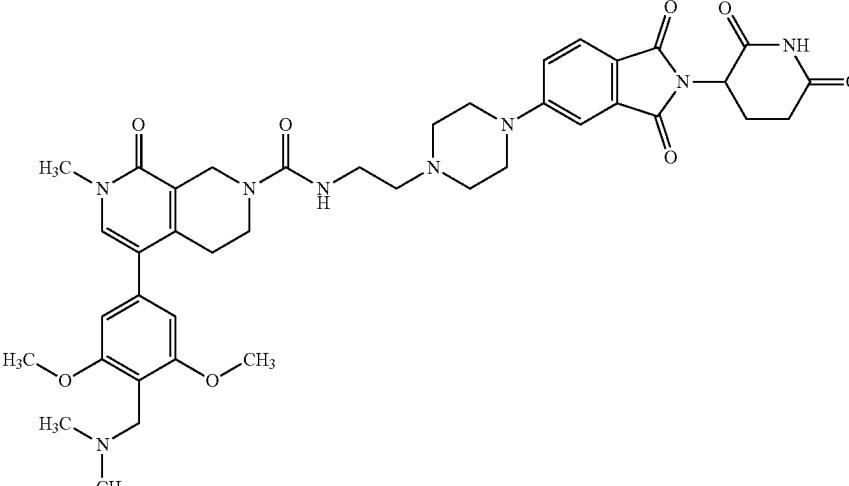
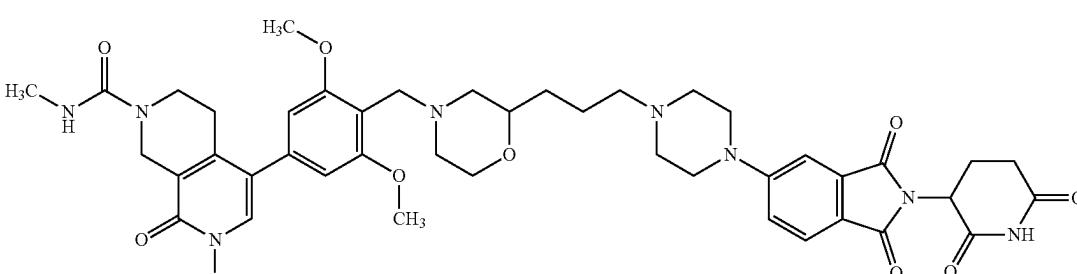
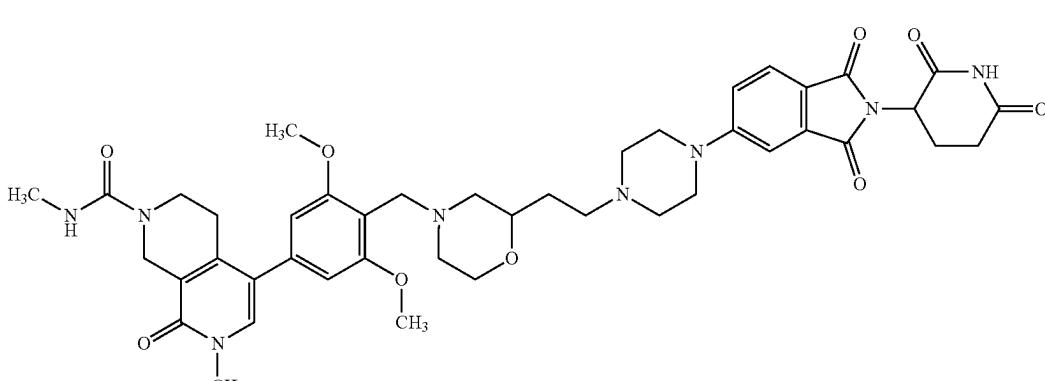
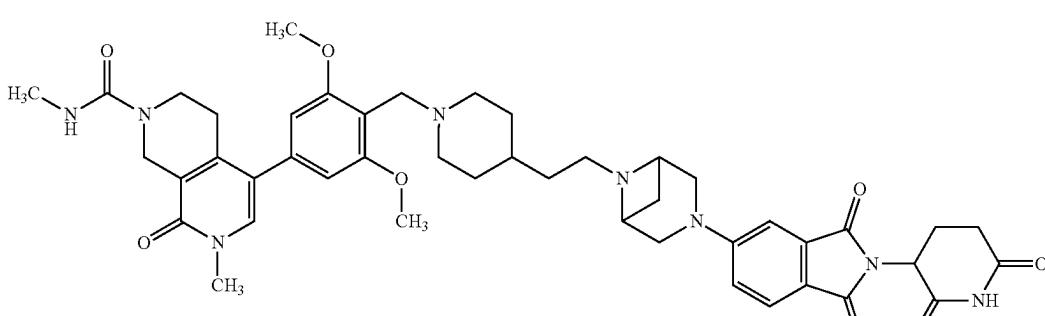
Compound No.	Structure
D150	
D151	
D152	
D153	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

Compound No.	Structure
D154	
D155	
D156	
D157	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

Compound No.	Structure
D158	
D159	
D161	
D162	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

Com- ound No.	Structure
D163	
D164	
D165	
D166	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

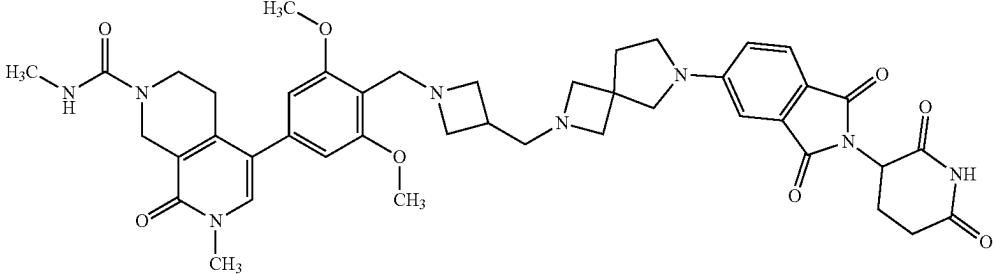
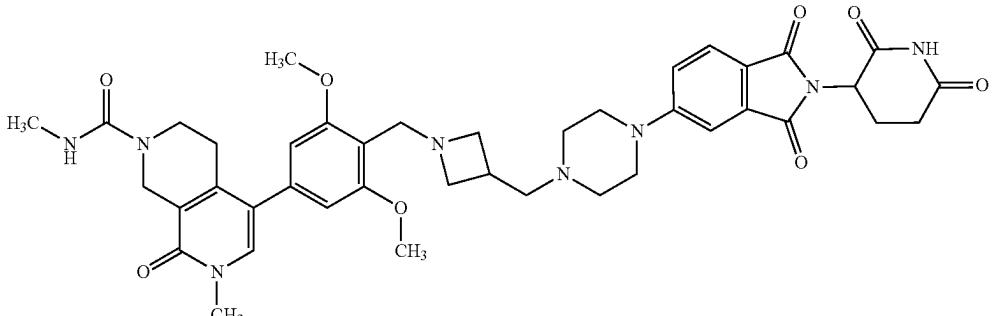
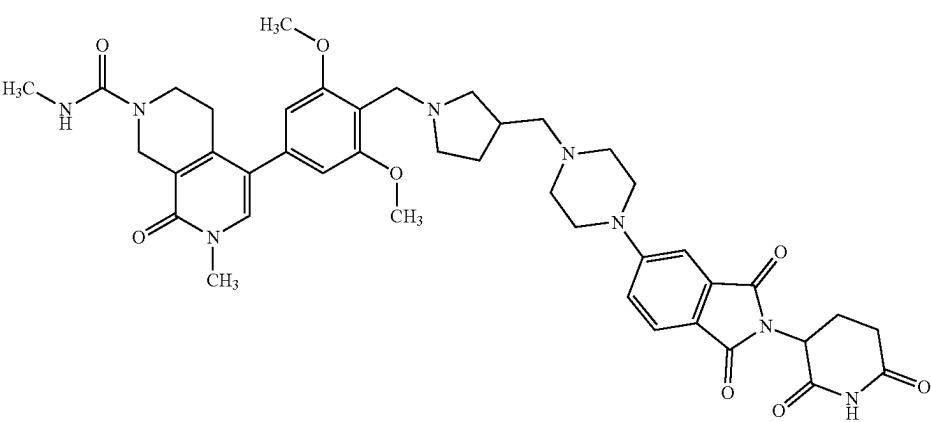
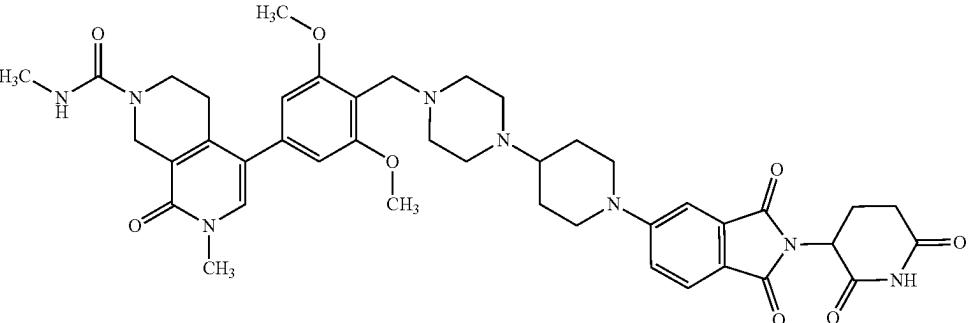
Com- ound No.	Structure
D167	
D168	
D169	
D170	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

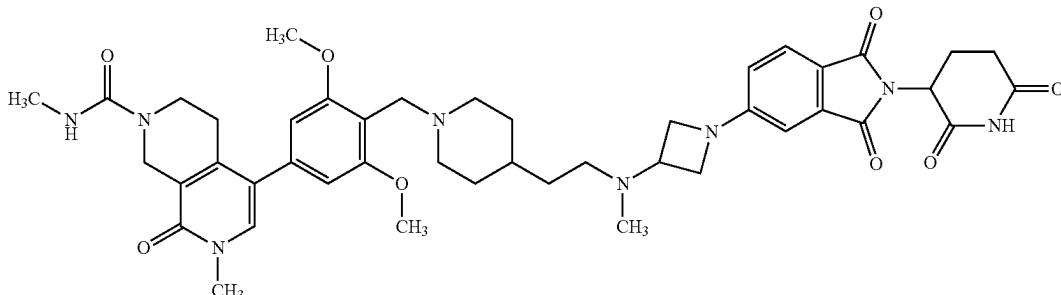
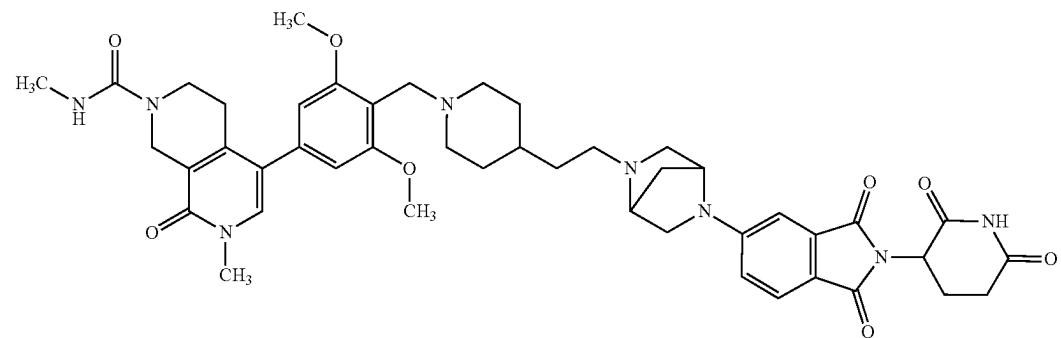
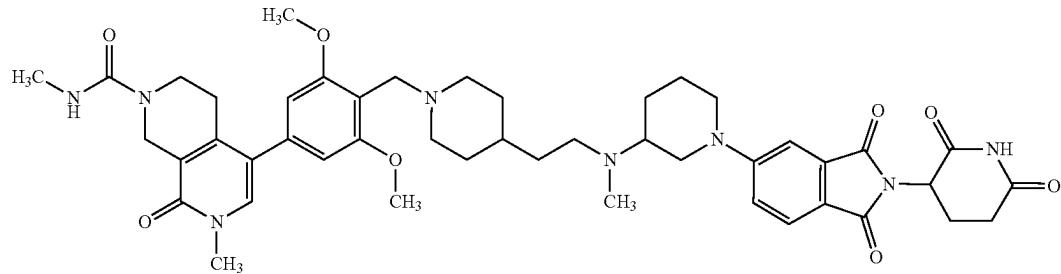
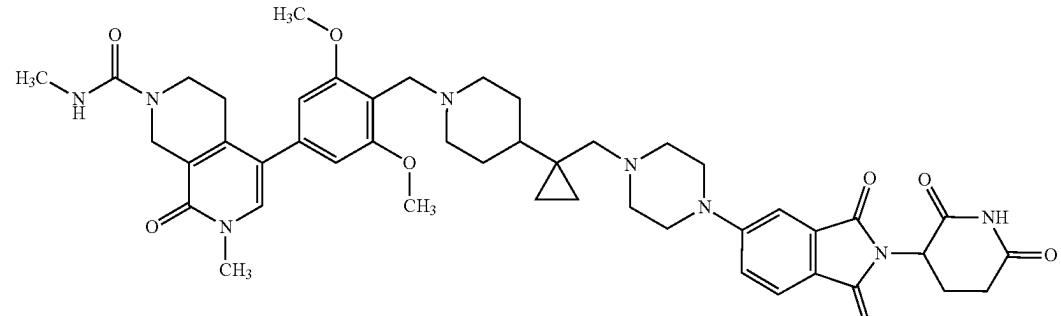
Compound No.	Structure
D171	
D172	
D173	
D174	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

Com- ound No.	Structure
D175	
D176	
D177	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

Compound No.	Structure
D178	
D179	
D180	
D181	

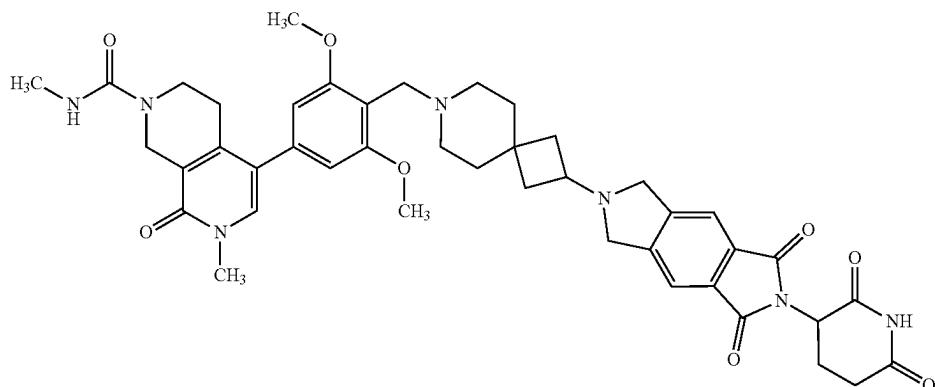
TABLE 2B-continued

Compounds D39-D302 of the Disclosure

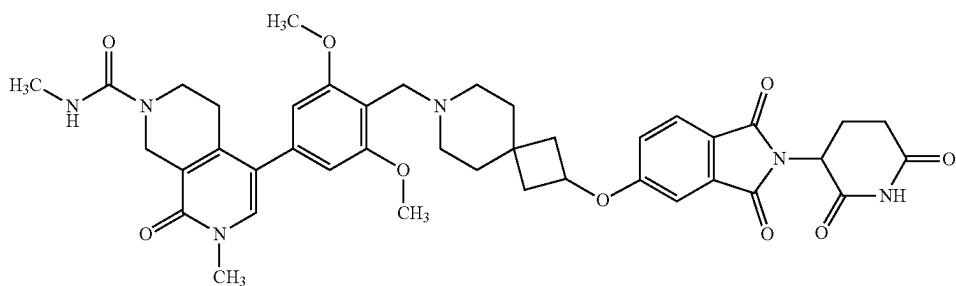
Com-
ound
No.

Structure

D182



D183



D184

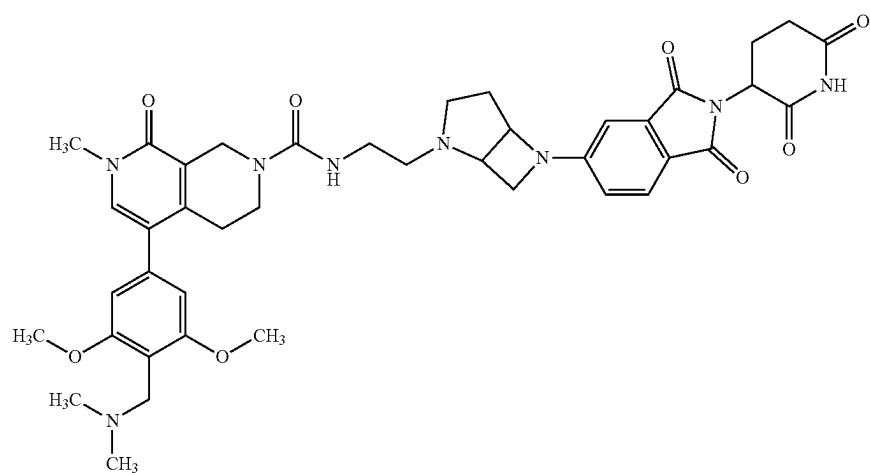


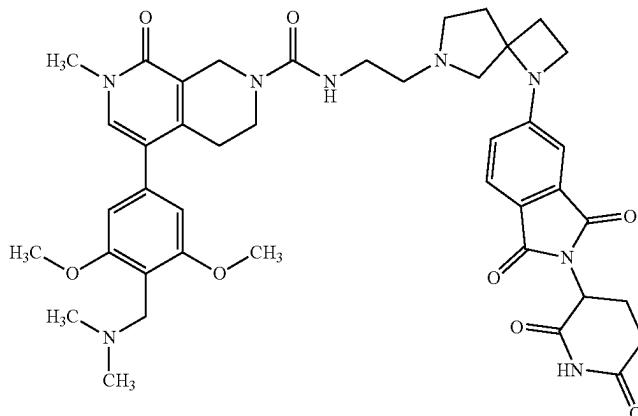
TABLE 2B-continued

Compounds D39-D302 of the Disclosure

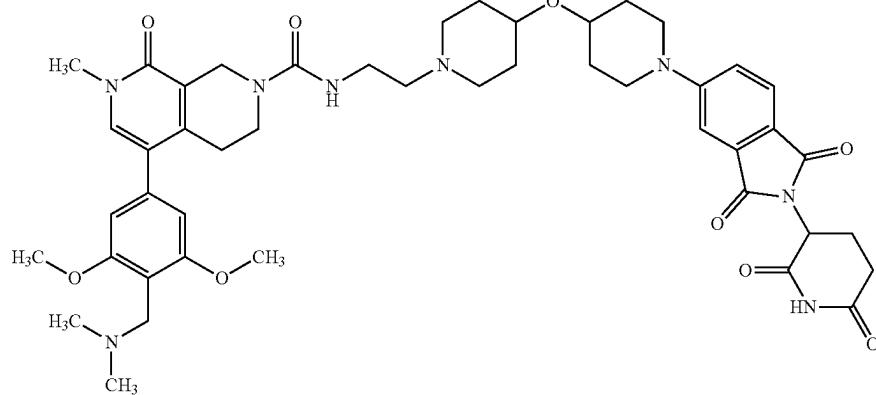
Com-
ound
No.

Structure

D185



D186



D187

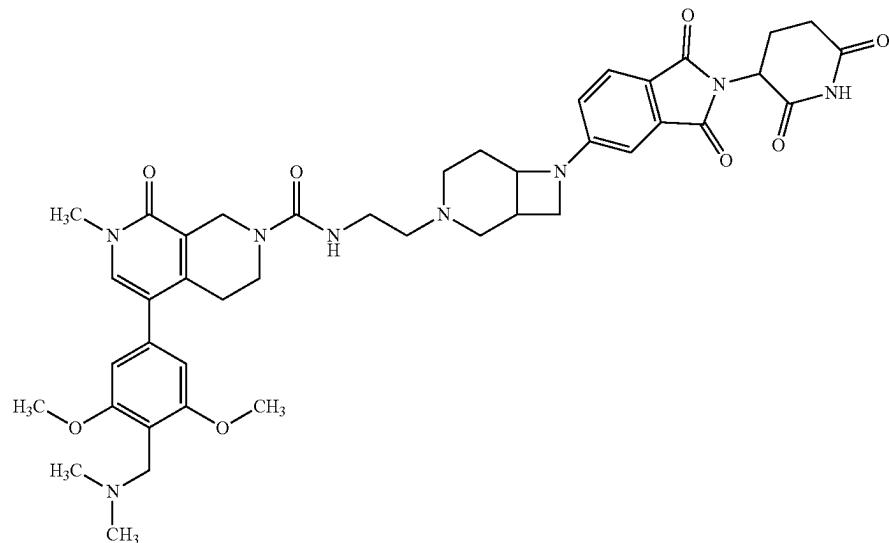


TABLE 2B-continued

Compounds D39-D302 of the Disclosure

Com- ound No.	Structure
D188	
D189	
D190	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

Com- ound No.	Structure
D191	
D192	
D193	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

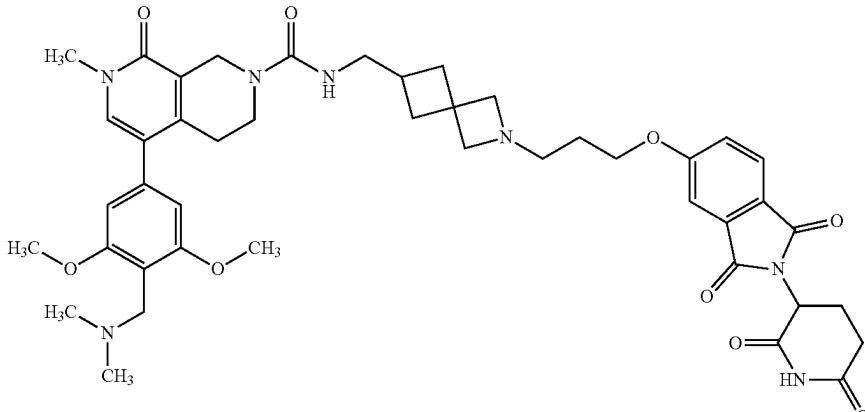
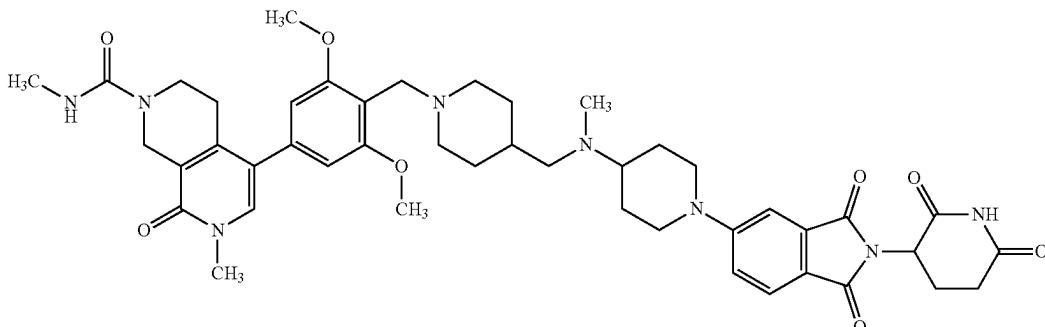
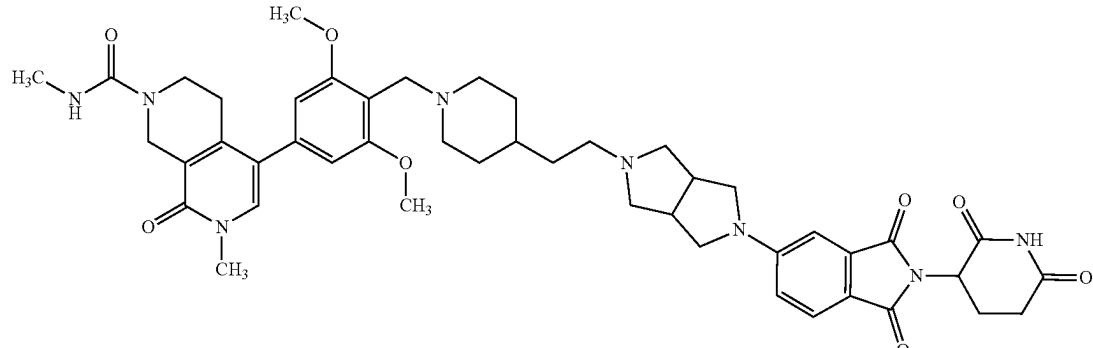
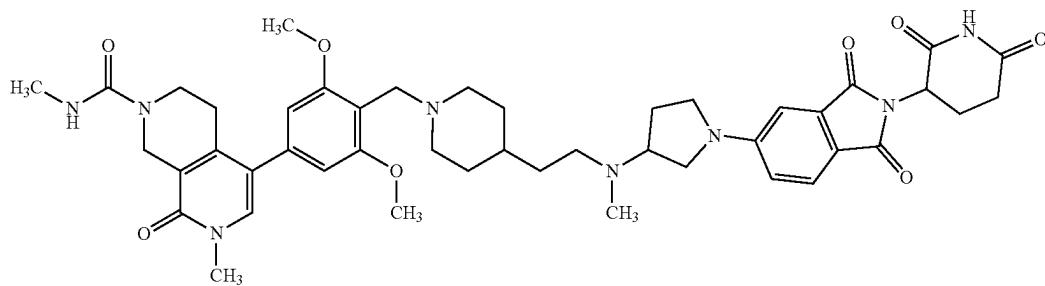
Com- ound No.	Structure
D194	
D195	
D196	
D197	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

Com- ound No.	Structure
D198	
D199	
D200	
D201	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

Compound No.	Structure
D202	
D203	
D204	
D205	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

Com- ound No.	Structure
D206	
D207	
D208	

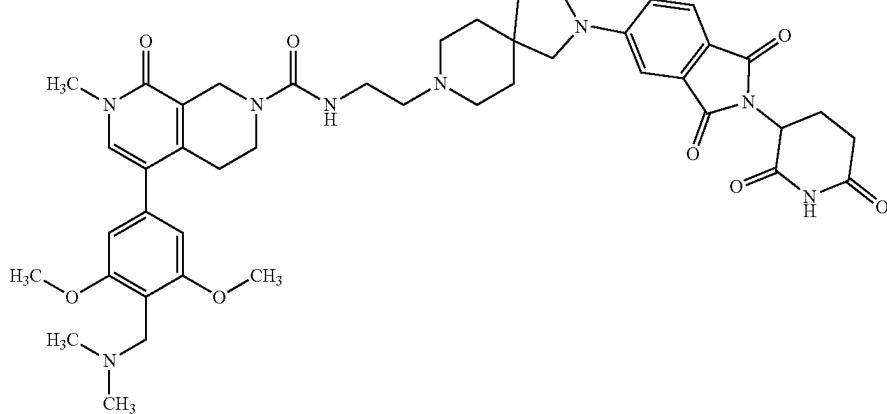
TABLE 2B-continued

Compounds D39-D302 of the Disclosure

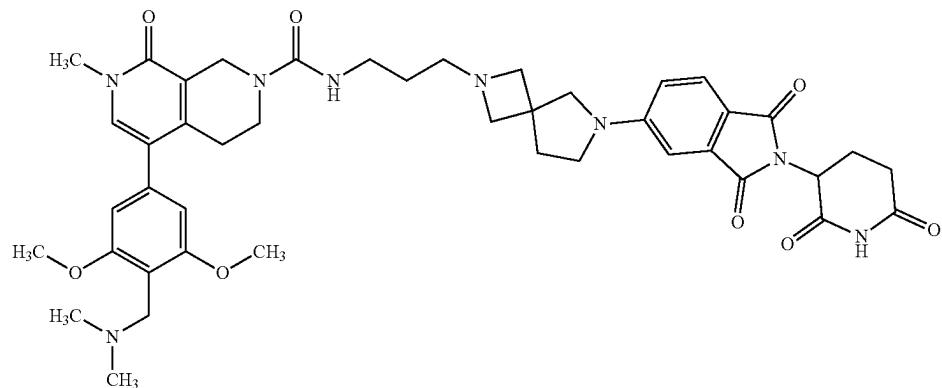
Com-
ound
No.

Structure

D209



D210



D211

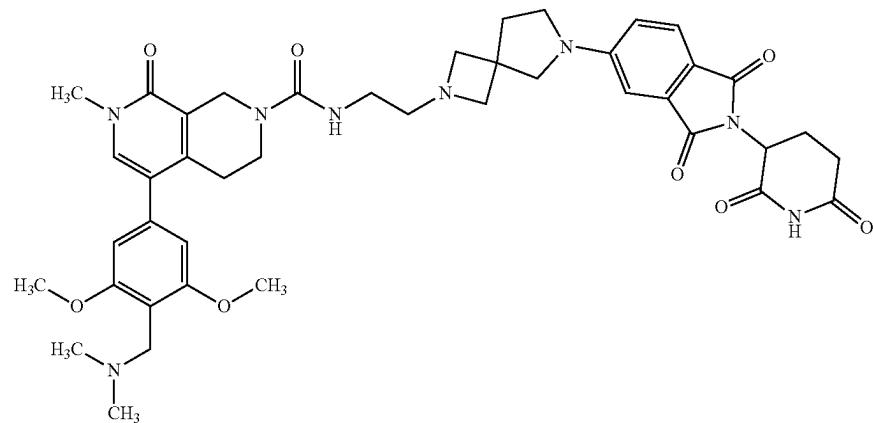


TABLE 2B-continued

Compounds D39-D302 of the Disclosure

Com- ound No.	Structure
D212	
D213	
D214	

305

306

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

Compound No. Structure

D215

D216

D217

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

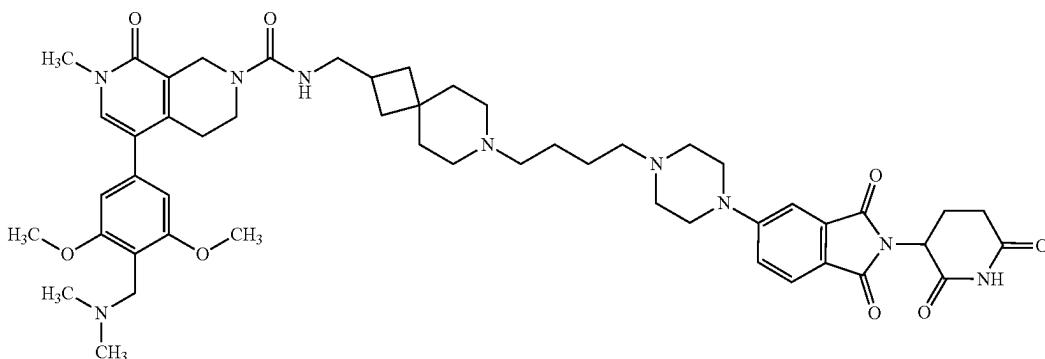
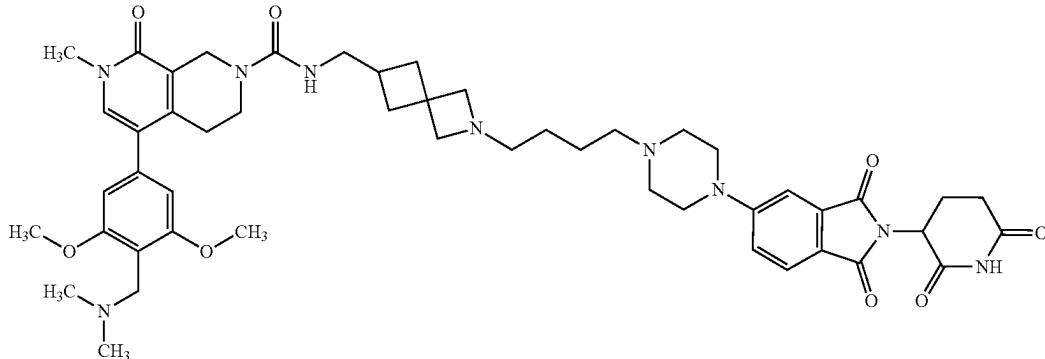
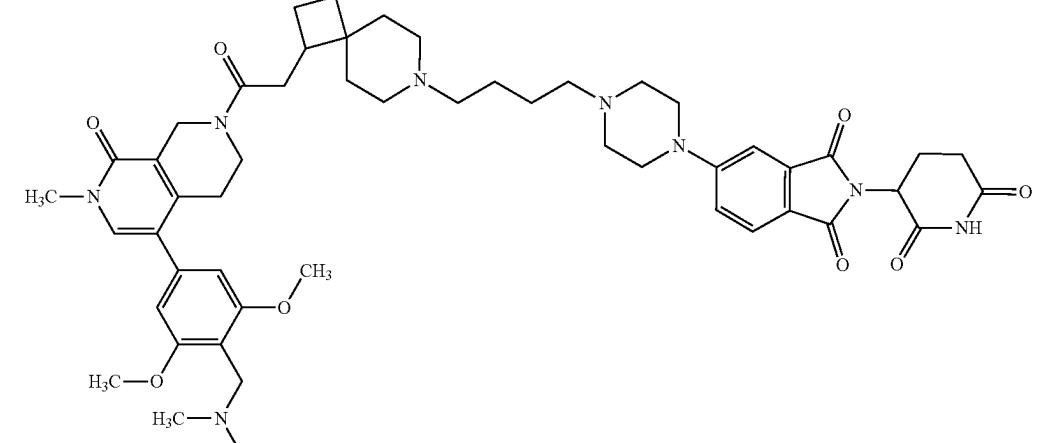
Compound No.	Structure
D218	
D219	
D220	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

Com- ound No.	Structure
D221	
D222	
D223	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

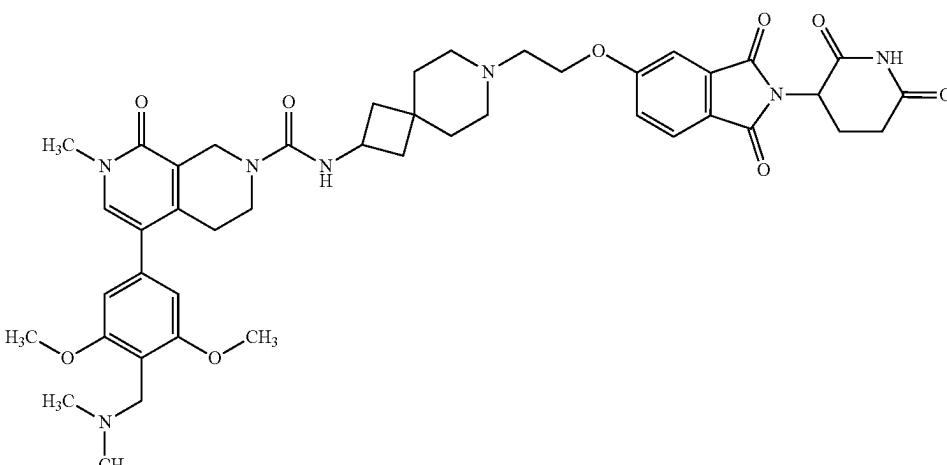
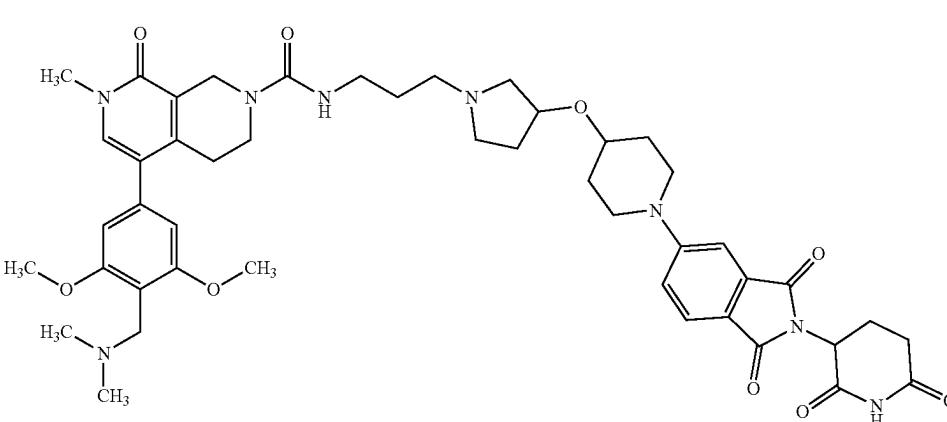
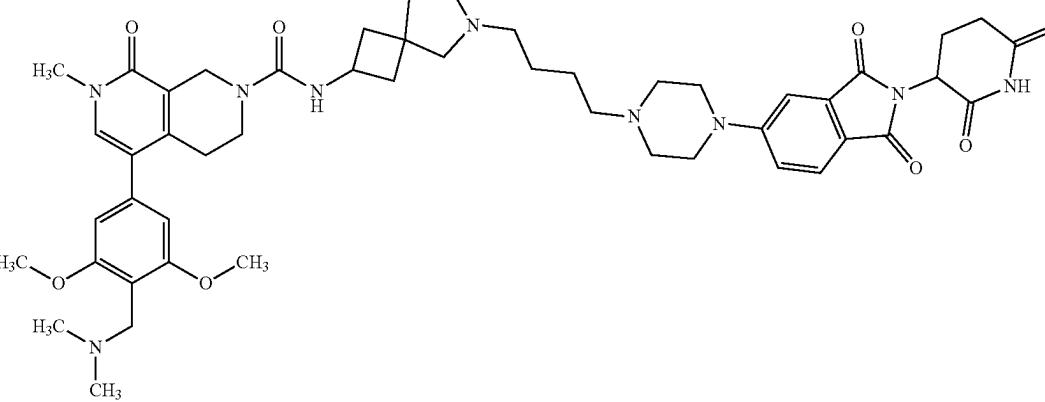
Com- ound No.	Structure
D224	
D225	
D226	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

Com- ound No.	Structure
D227	
D228	
D229	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

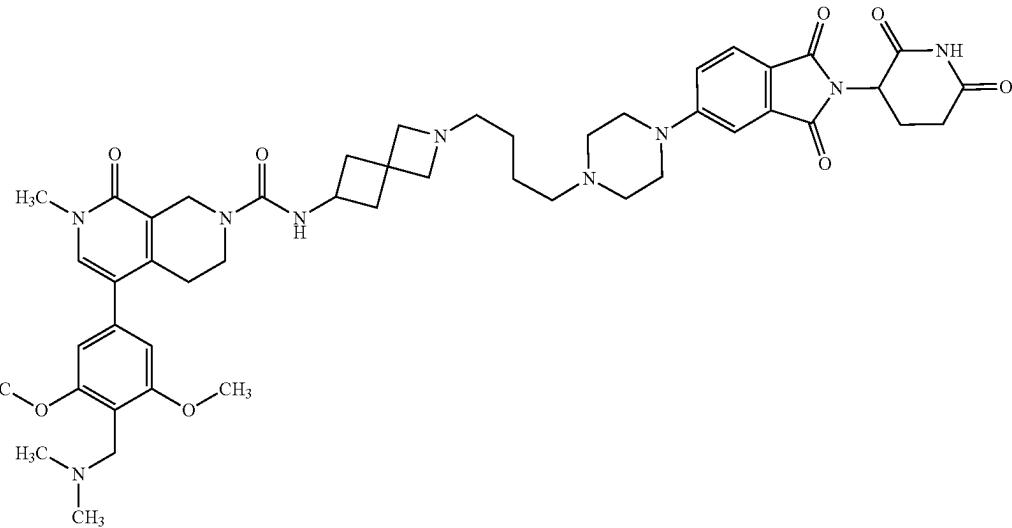
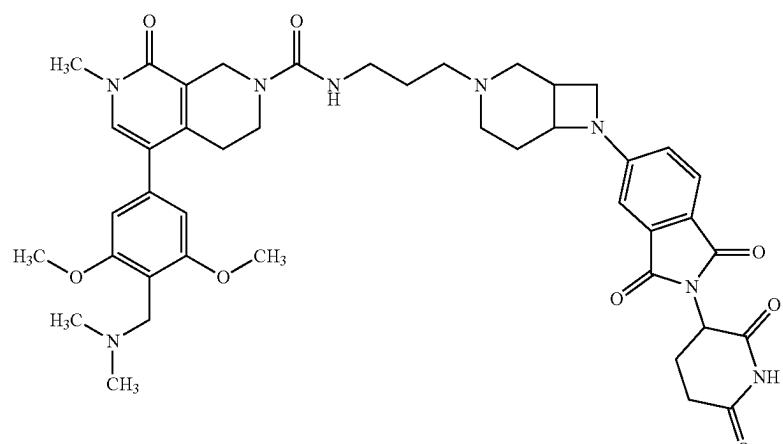
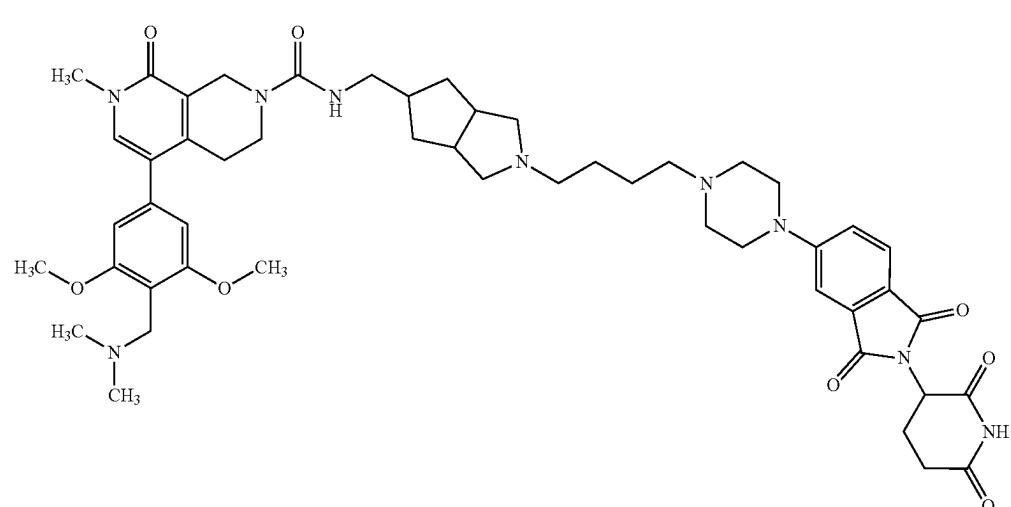
Com- ound No.	Structure
D230	
D231	
D232	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

Com- ound No.	Structure
D233	
D234	
D235	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

Com- ound No.	Structure
D236	
D237	
D238	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

Com- ound No.	Structure
D239	
D240	
D241	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

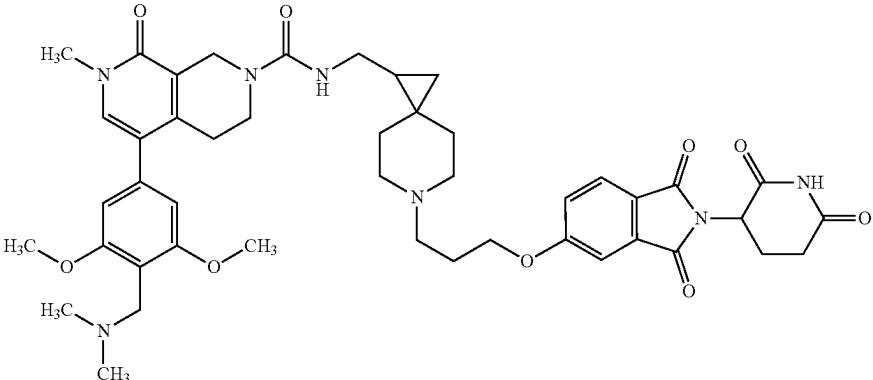
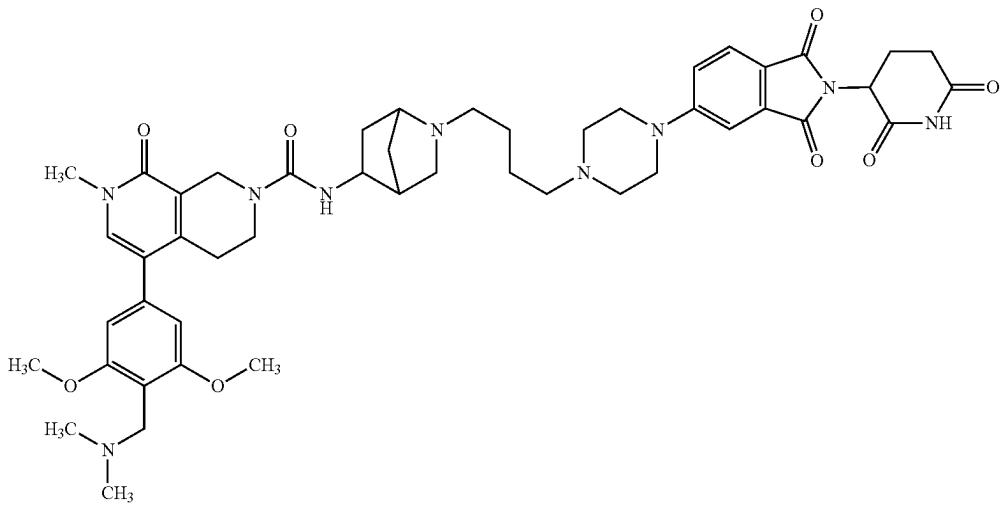
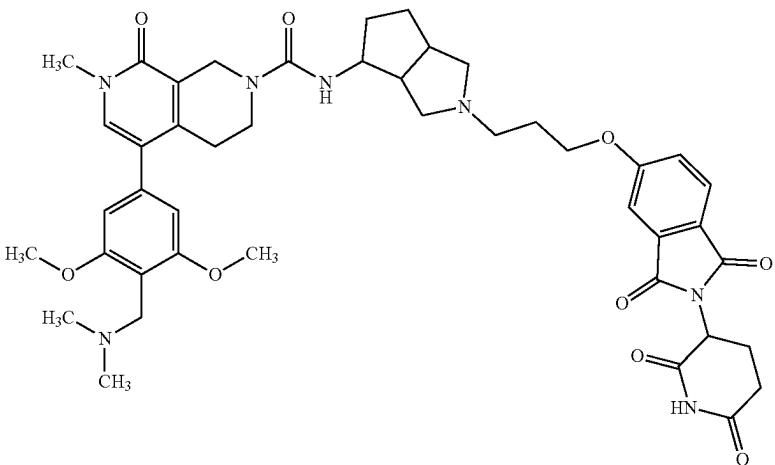
Com- ound No.	Structure
D242	
D243	
D244	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

Com- ound No.	Structure
D245	
D246	
D247	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

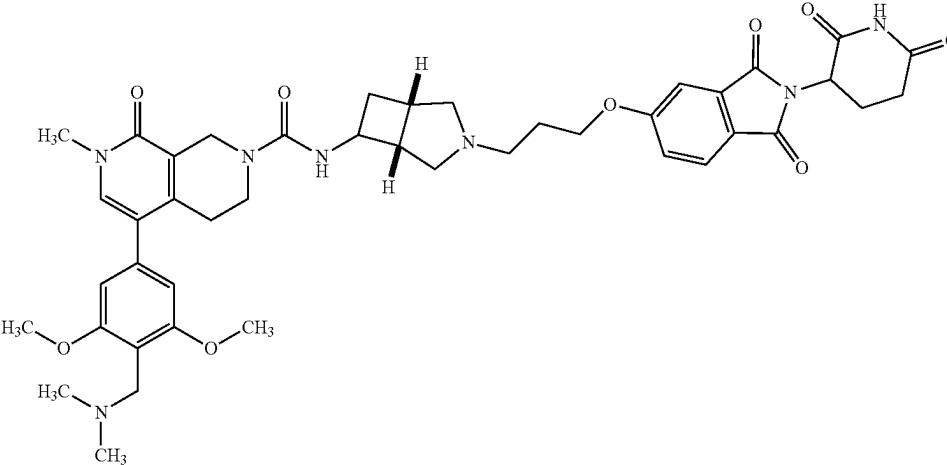
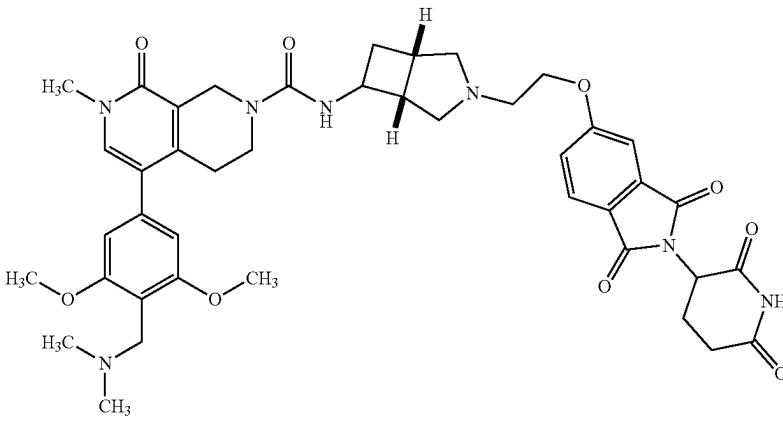
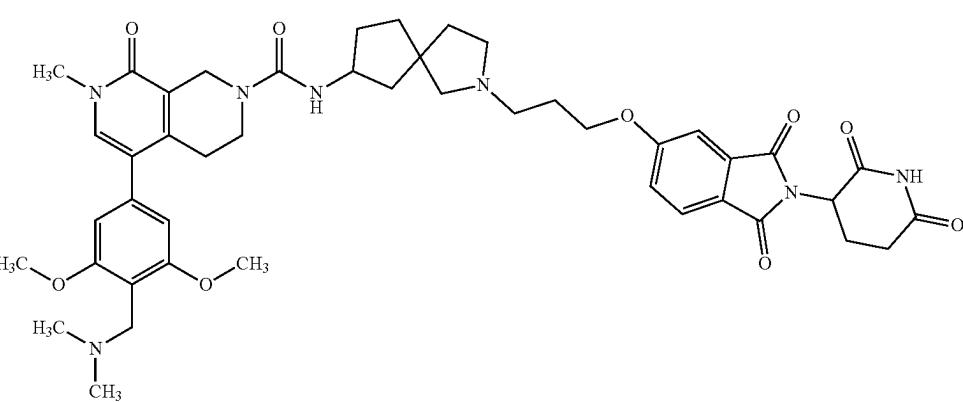
Com- ound No.	Structure
D248	
D249	
D250	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

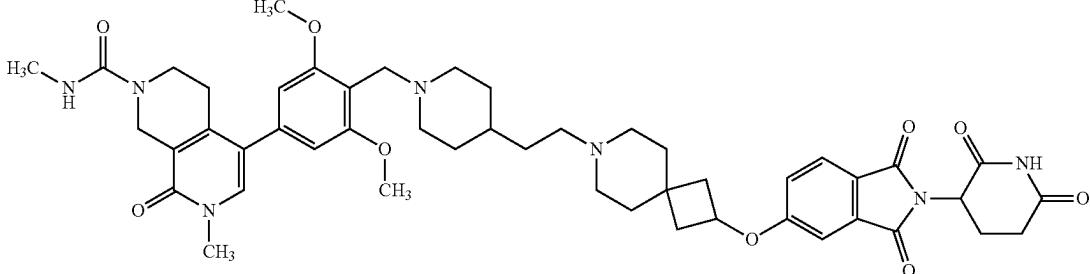
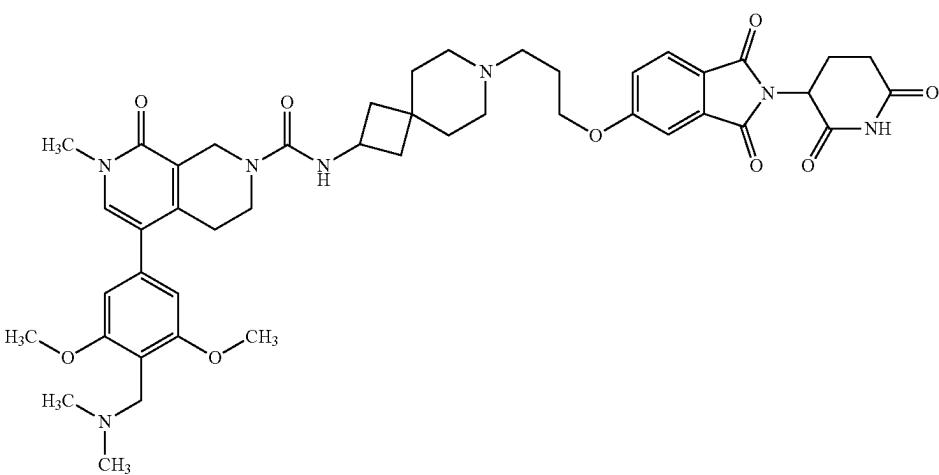
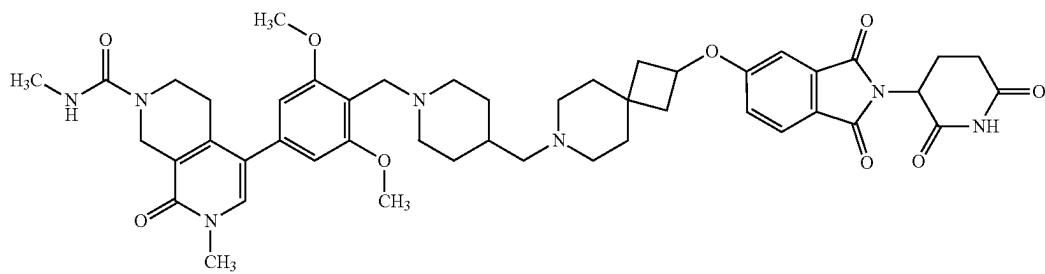
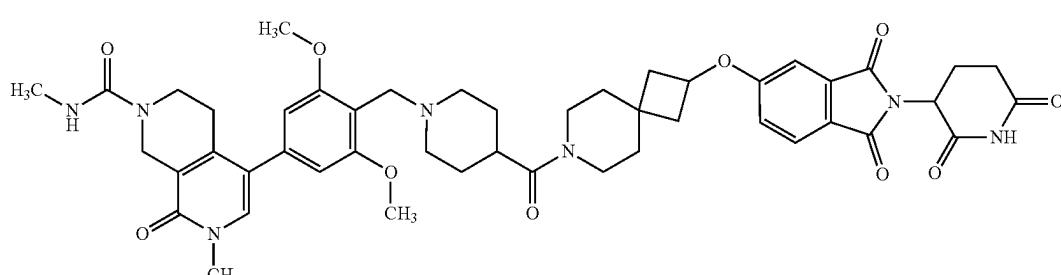
Com- ound No.	Structure
D251	
D252	
D253	
D254	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

Com- ound No.	Structure
D255	
D256	
D257	
D258	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

Com- ound No.	Structure
D259	
D260	
D261	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

Com- ound No.	Structure
D262	
D263	
D264	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

Com- ound No.	Structure
D265	
D266	
D267	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

Com- ound No.	Structure
D268	
D269	
D270	

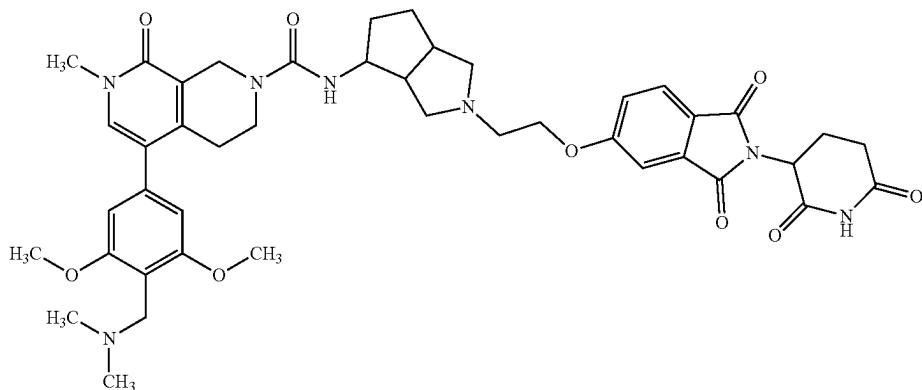
TABLE 2B-continued

Compounds D39-D302 of the Disclosure

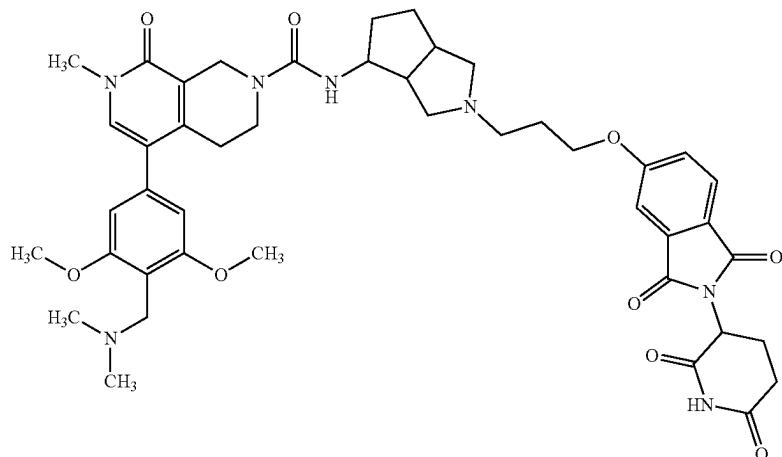
Com-
ound
No.

Structure

D271



D272



D273

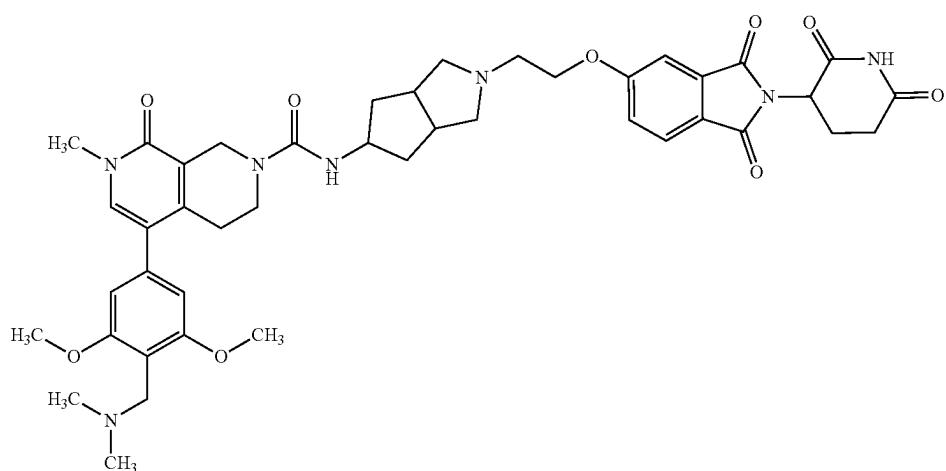


TABLE 2B-continued

Compounds D39-D302 of the Disclosure

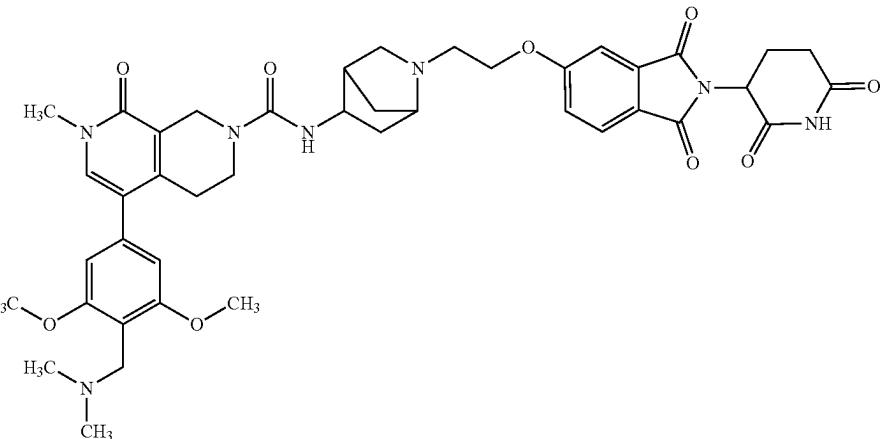
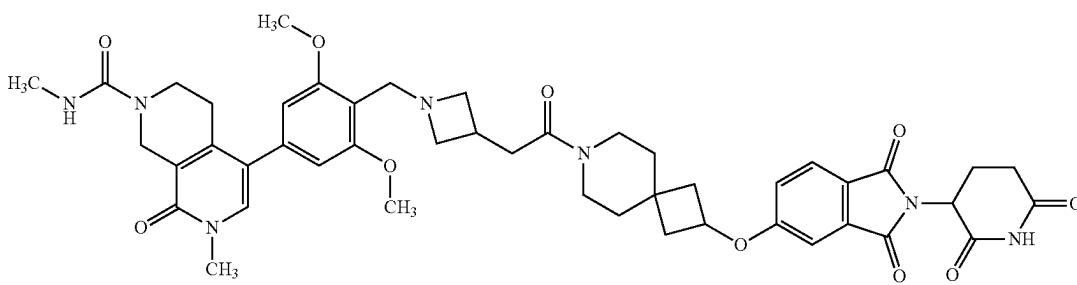
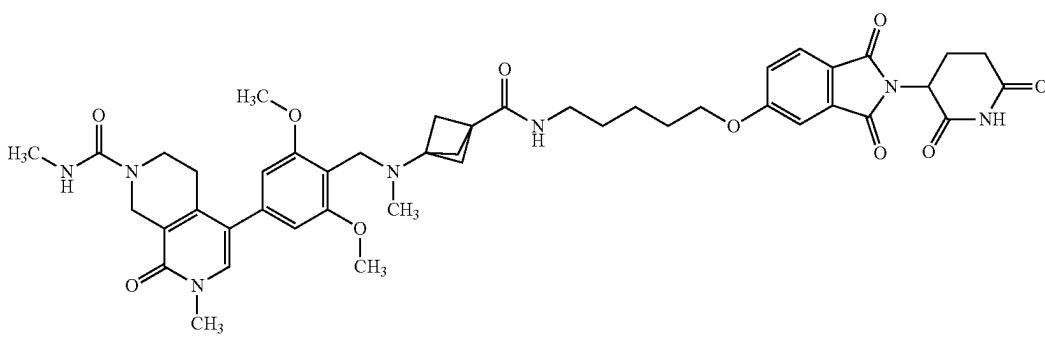
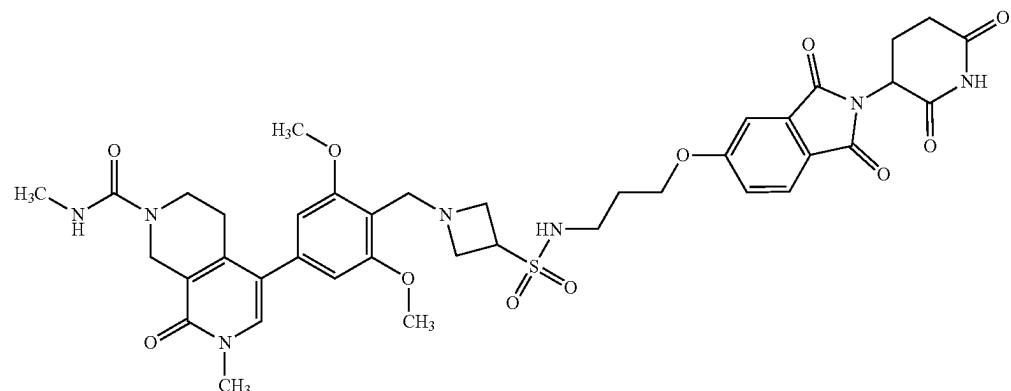
Compound No.	Structure
D274	
D275	
D276	
D277	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

Com- ound No.	Structure
D278	
D279	
D280	
D281	

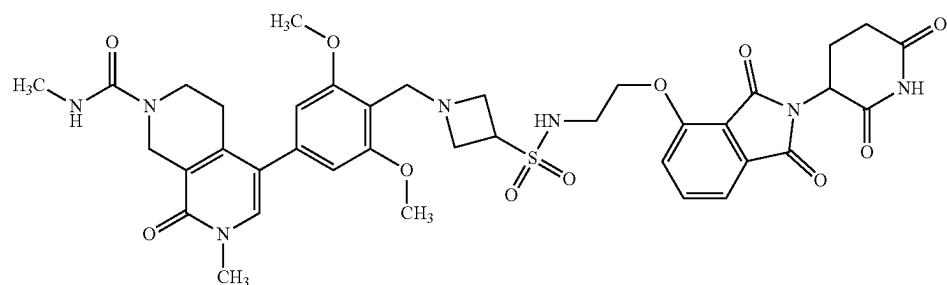
TABLE 2B-continued

Compounds D39-D302 of the Disclosure

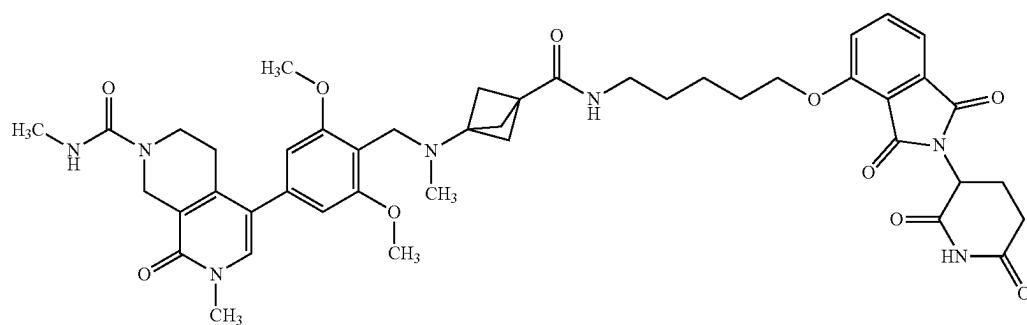
Com-
ound
No.

Structure

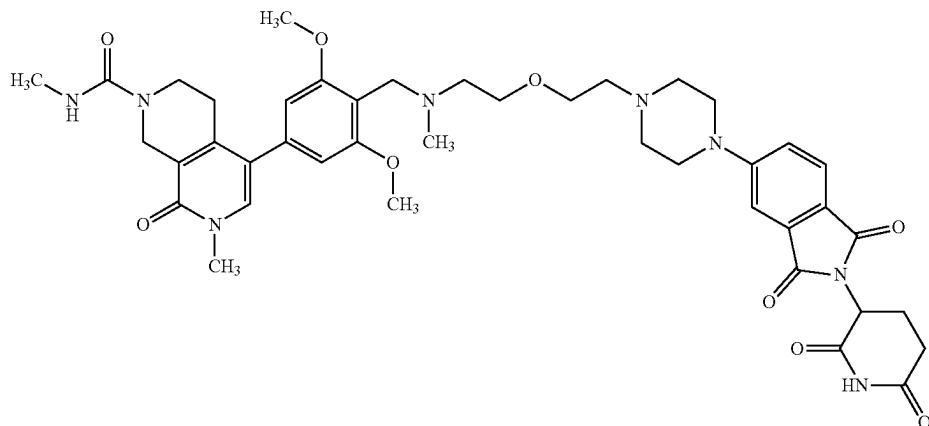
D282



D283



D284



D285

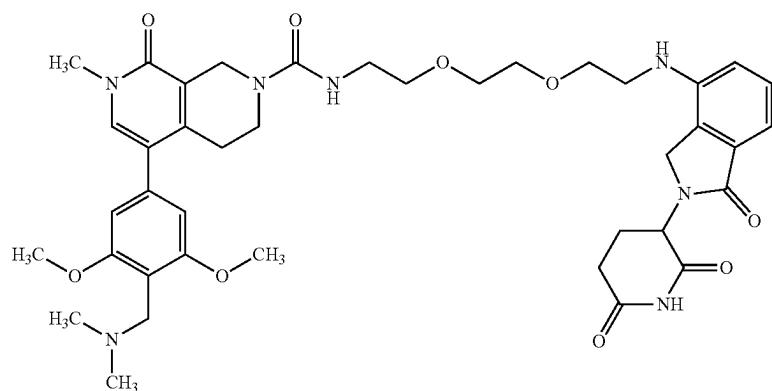


TABLE 2B-continued

Compounds D39-D302 of the Disclosure

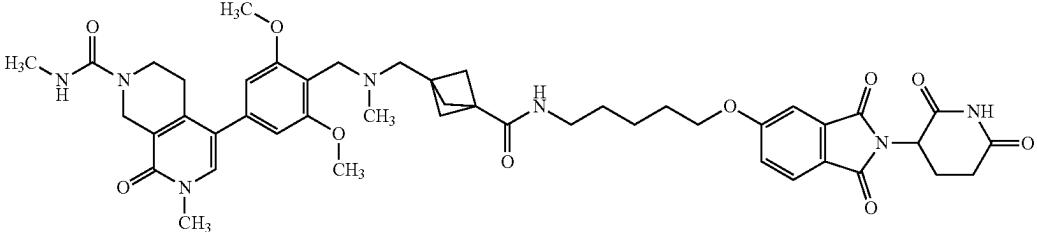
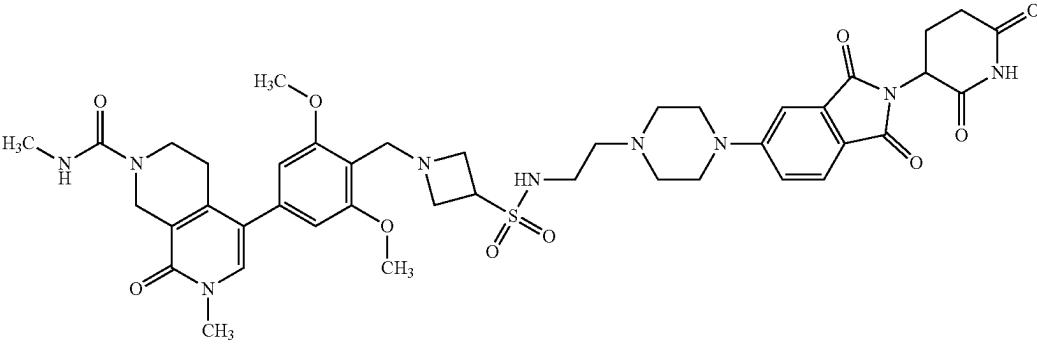
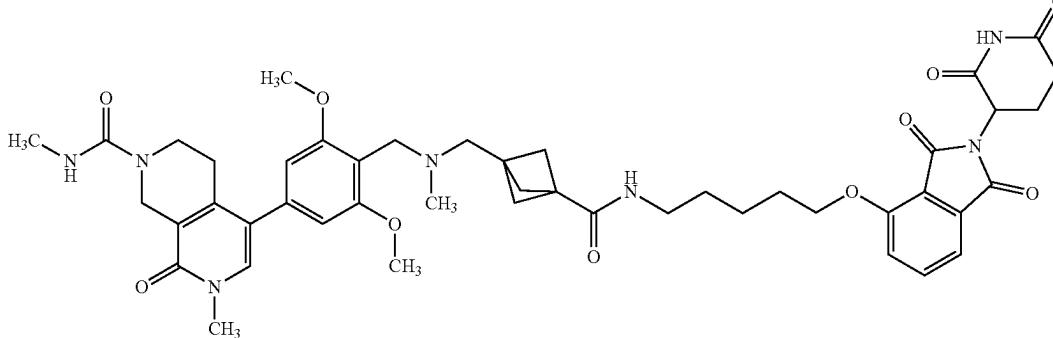
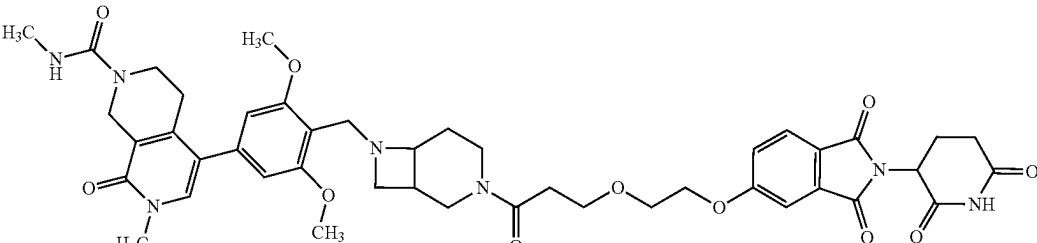
Compound No.	Structure
D286	
D287	
D288	
D289	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

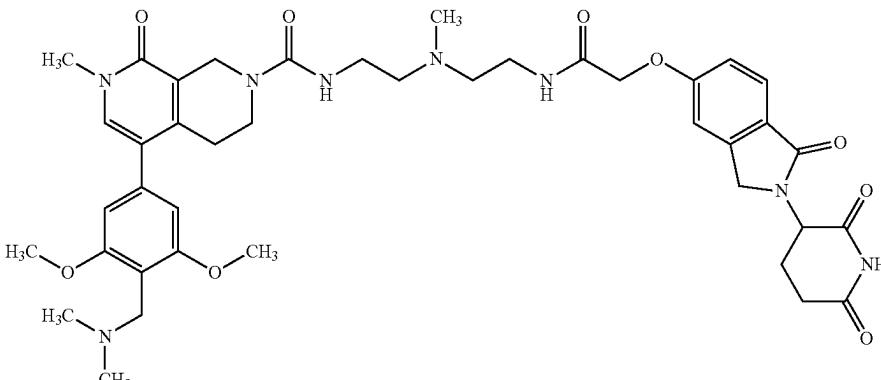
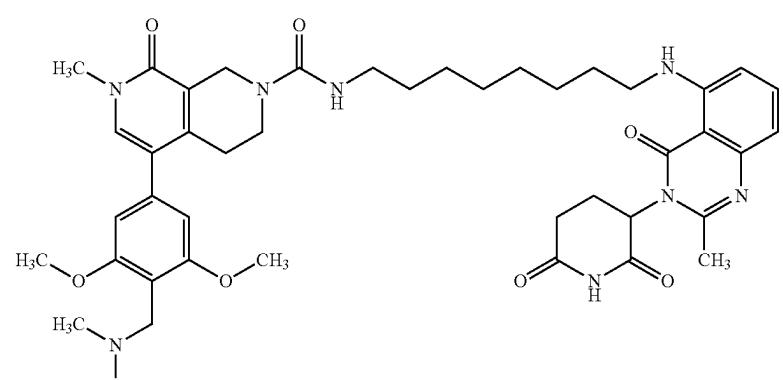
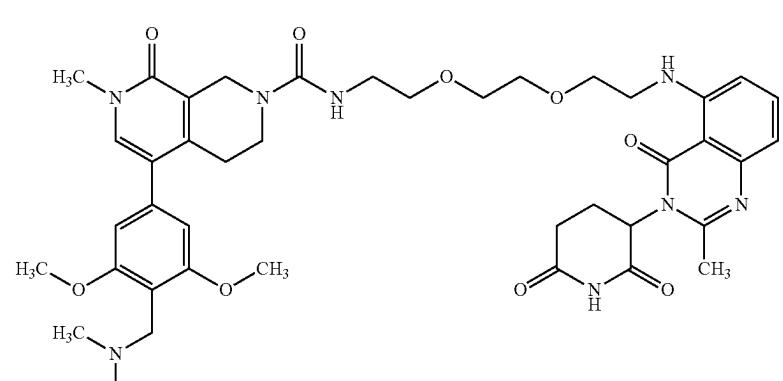
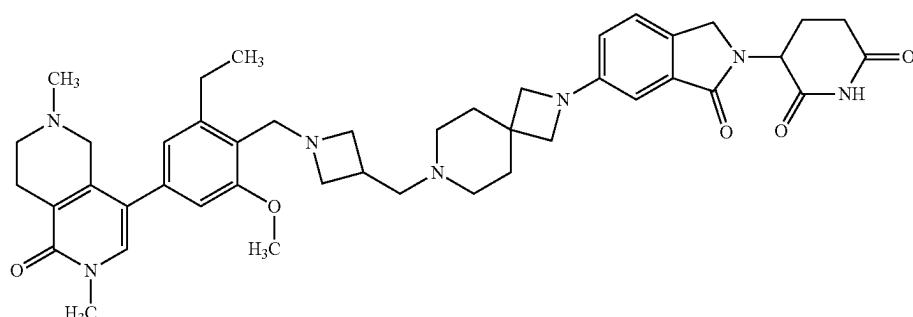
Compound No.	Structure
D290	
D291	
D292	
D293	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

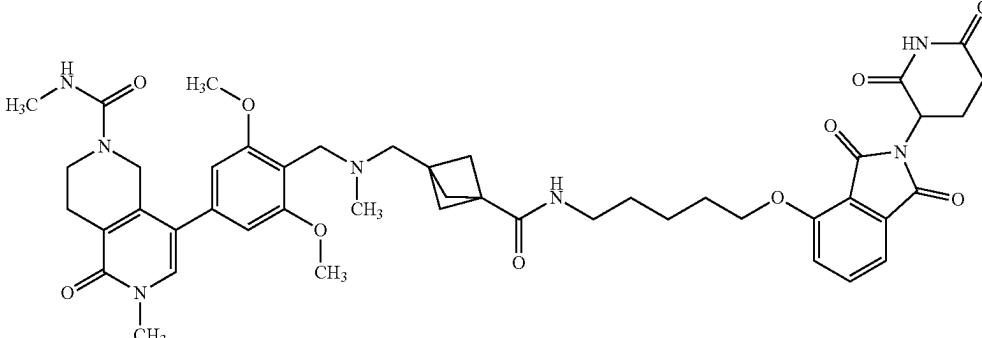
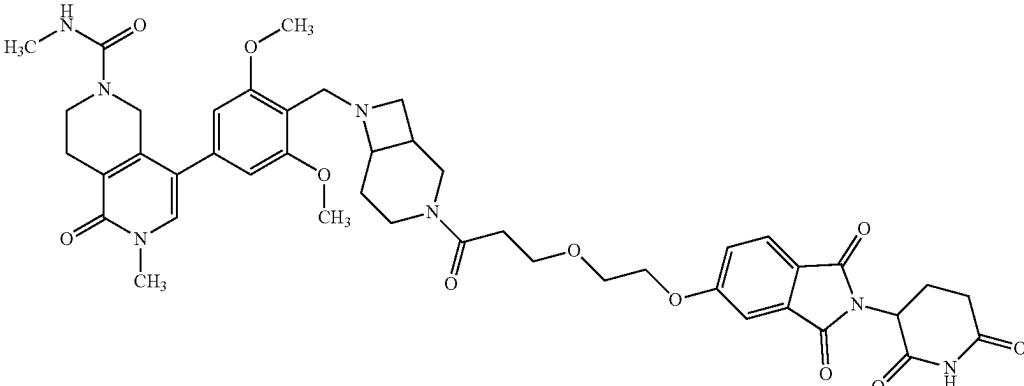
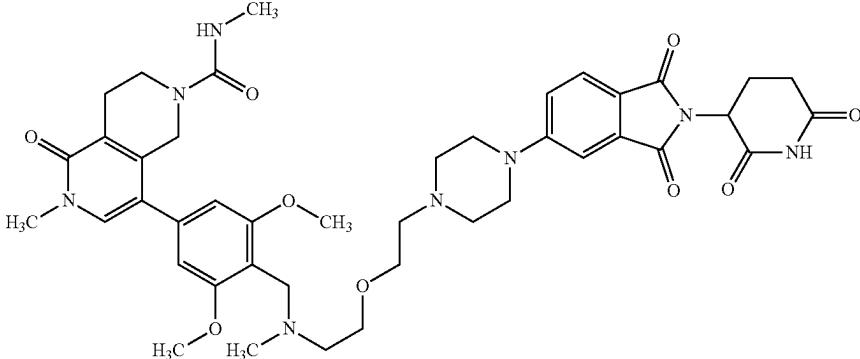
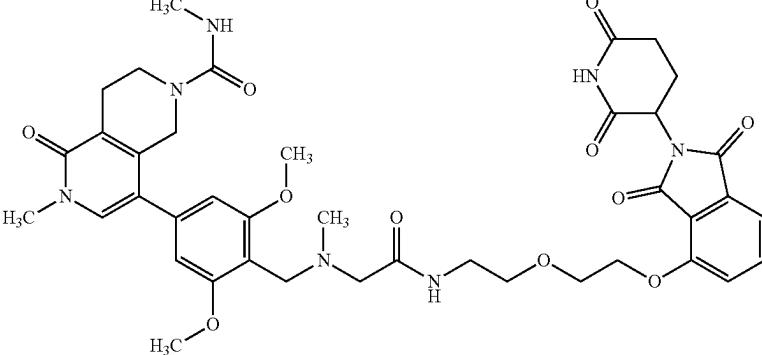
Compound No.	Structure
D294	
D295	
D296	
D297	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

Compound No.	Structure
D298	
D299	
D300	
D301	

TABLE 2B-continued

Compounds D39-D302 of the Disclosure

Compound No.	Structure
D302	

TABLE 2C

Compounds D303-D375 of the Disclosure

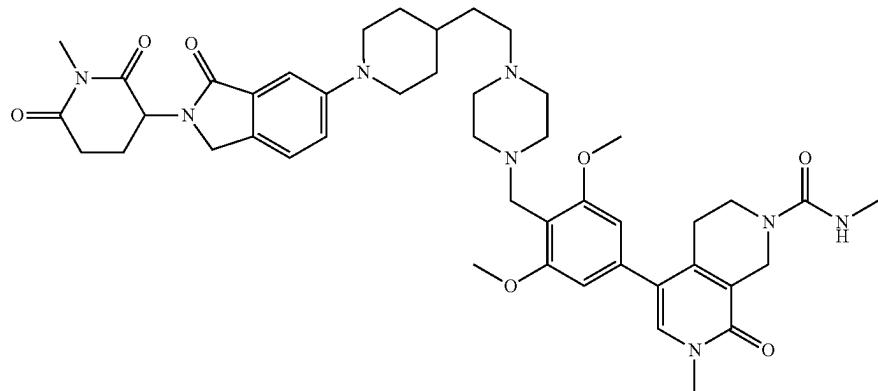
Compound No.	Structure
D303	
D304	

TABLE 2C-continued

Compounds D303-D375 of the Disclosure

Compound No.	Structure
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D305



D306

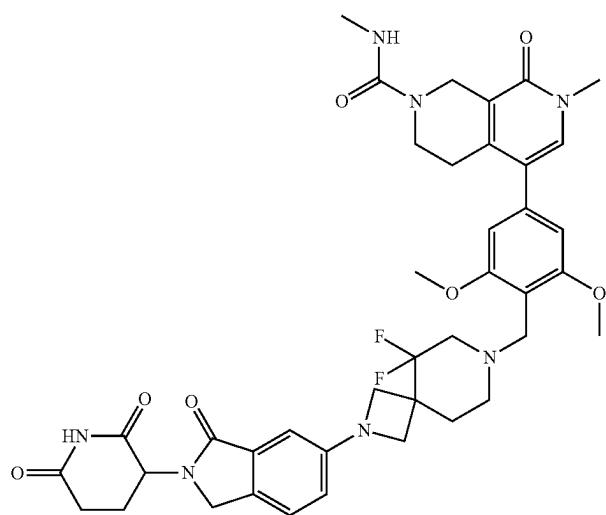
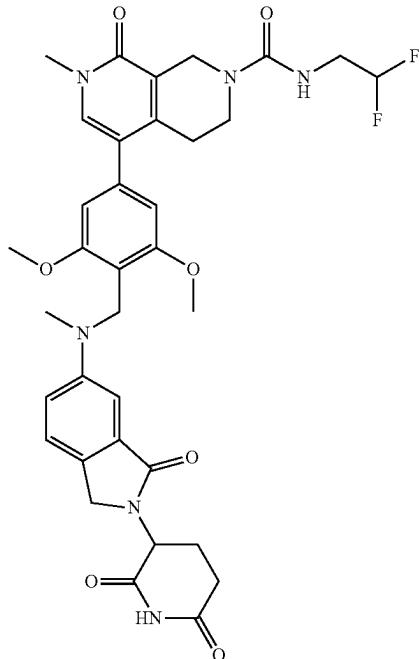


TABLE 2C-continued

Compounds D303-D375 of the Disclosure

Compound No.	Structure
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D307



D308

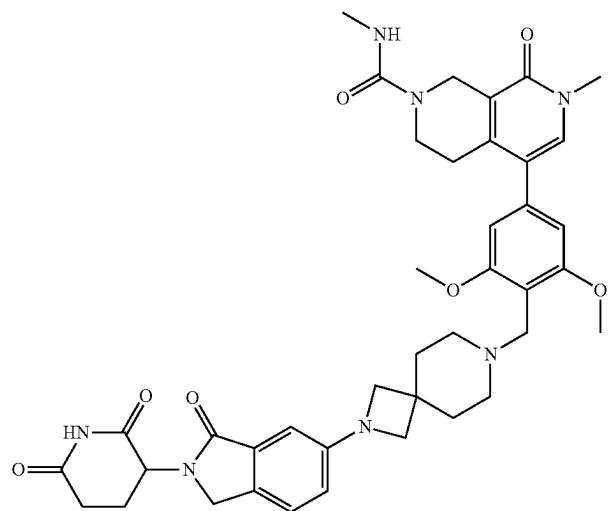


TABLE 2C-continued

Compounds D303-D375 of the Disclosure

Compound No.	Structure
D309	
D310	

TABLE 2C-continued

Compounds D303-D375 of the Disclosure

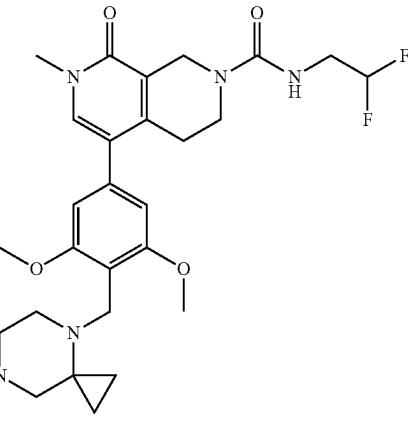
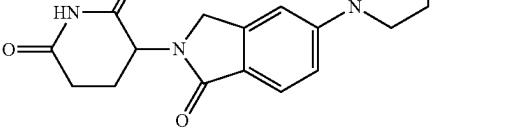
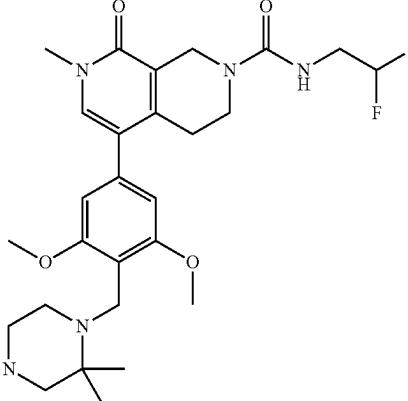
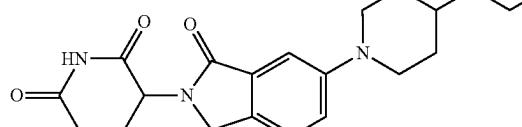
Compound No.	Structure
D311	
D312	

TABLE 2C-continued

Compounds D303-D375 of the Disclosure

Compound No.	Structure
D313	
D314	

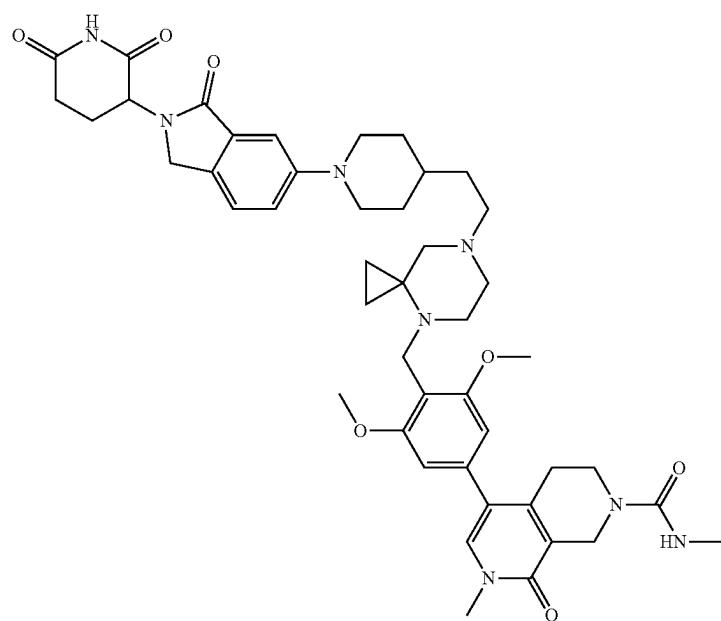


TABLE 2C-continued

Compounds D303-D375 of the Disclosure

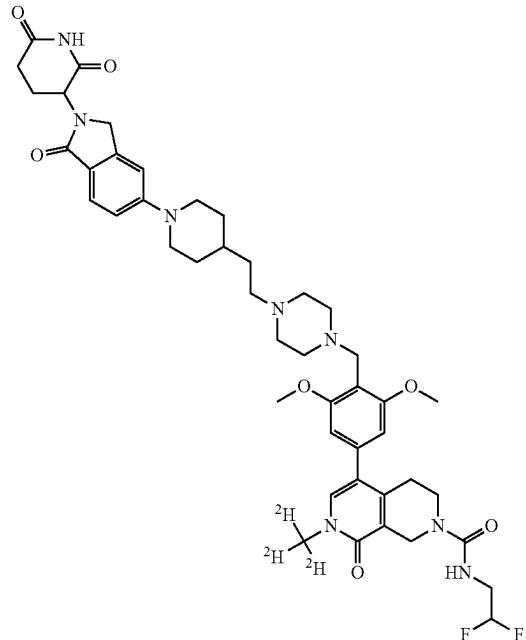
Compound No.	Structure
D315	
D316	

371

372

TABLE 2C-continued

Compounds D303-D375 of the Disclosure	
Compound No.	Structure



D318

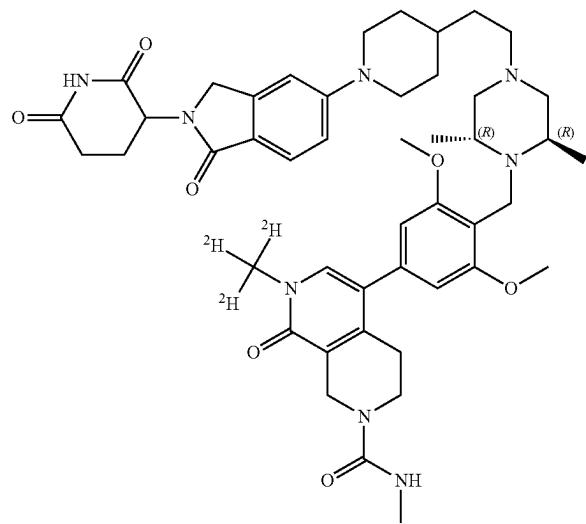


TABLE 2C-continued

Compounds D303-D375 of the Disclosure

Compound No.	Structure
D319	
D320	

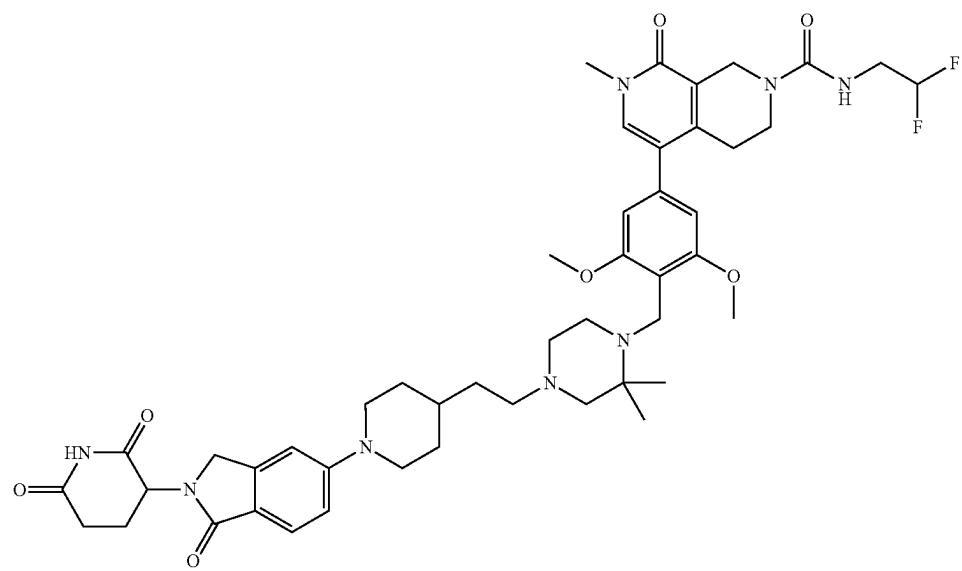


TABLE 2C-continued

Compounds D303-D375 of the Disclosure

Compound No.	Structure
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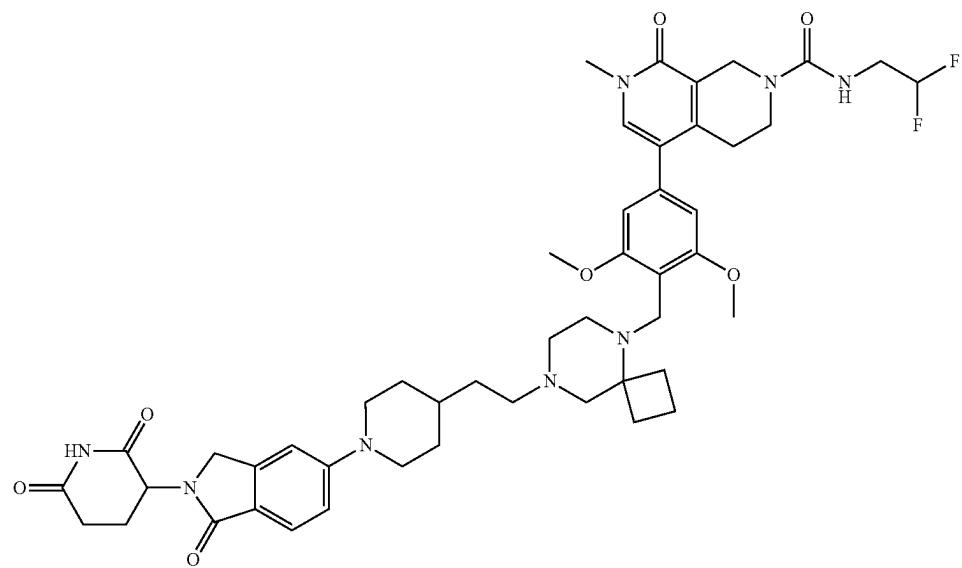
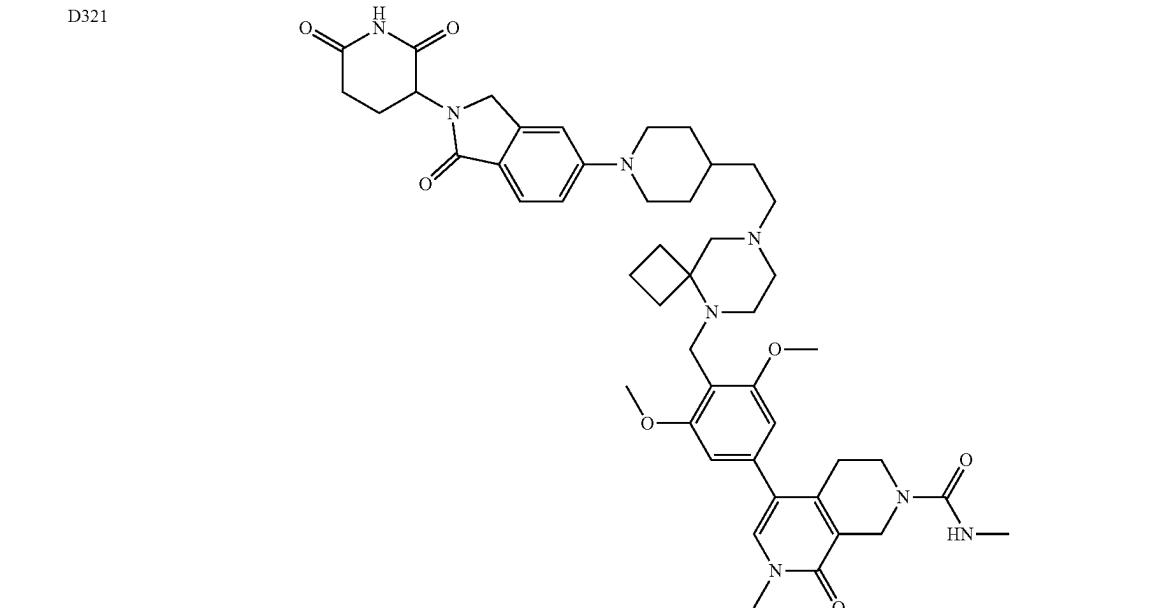


TABLE 2C-continued

Compounds D303-D375 of the Disclosure

Compound No.	Structure
D323	
D324	

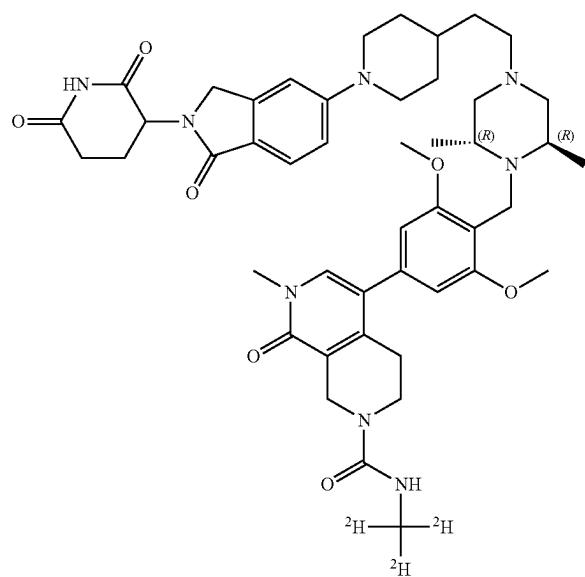
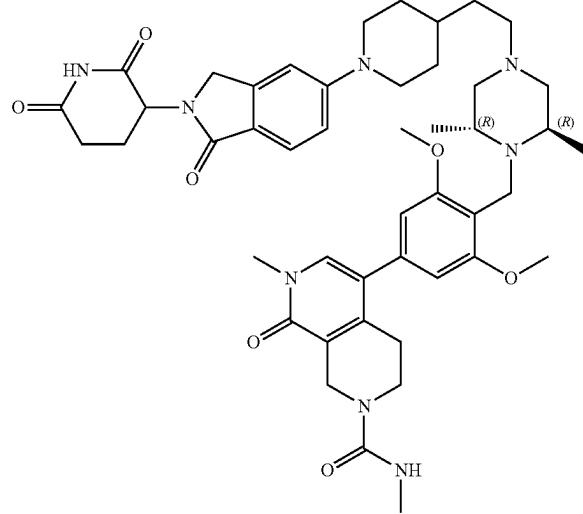


TABLE 2C-continued

Compounds D303-D375 of the Disclosure

Compound No.	Structure
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D325



D326

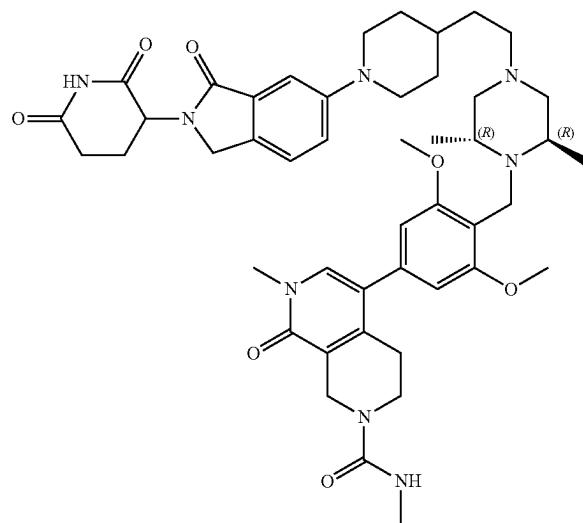


TABLE 2C-continued

Compounds D303-D375 of the Disclosure

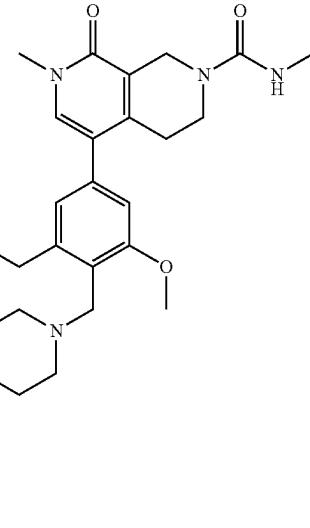
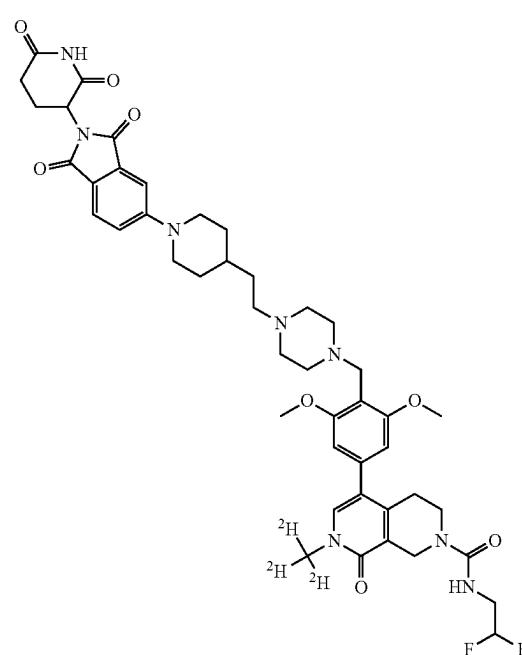
Compound No.	Structure
D327	
D328	

TABLE 2C-continued

Compounds D303-D375 of the Disclosure

Compound No.	Structure
D329	
D330	
D331	

TABLE 2C-continued

Compounds D303-D375 of the Disclosure

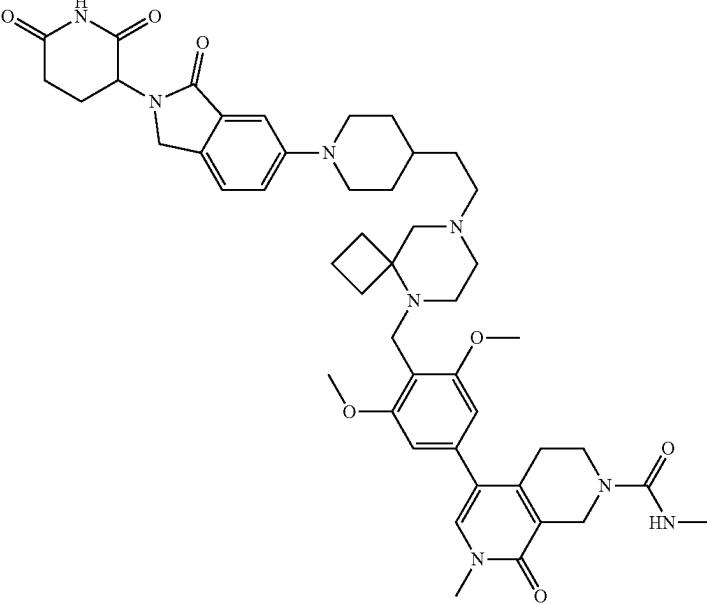
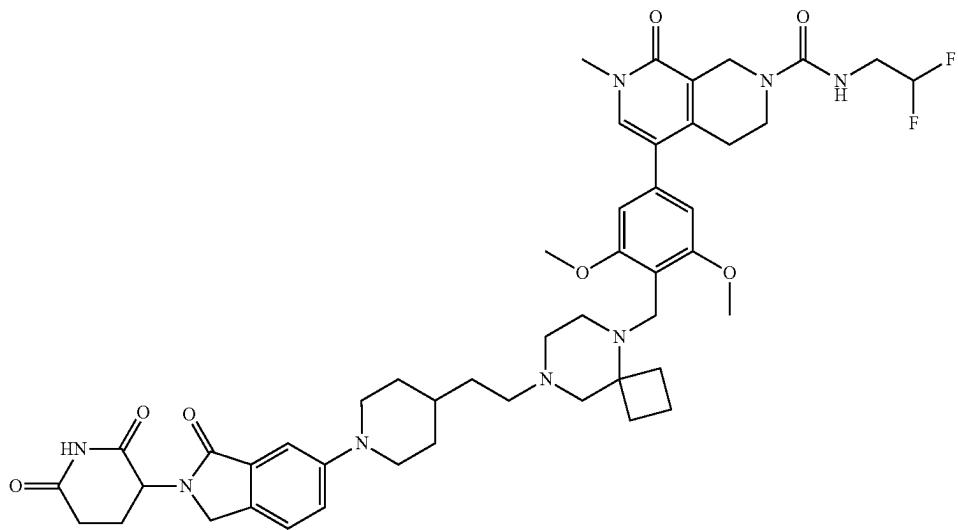
Compound No.	Structure
D332	
D333	

TABLE 2C-continued

Compounds D303-D375 of the Disclosure

Compound No.	Structure
D334	
D335	

TABLE 2C-continued

Compounds D303-D375 of the Disclosure

Compound No.	Structure
D336	
D337	
D338	

TABLE 2C-continued

Compounds D303-D375 of the Disclosure

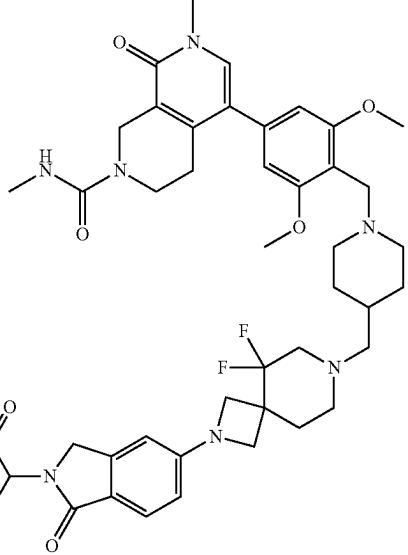
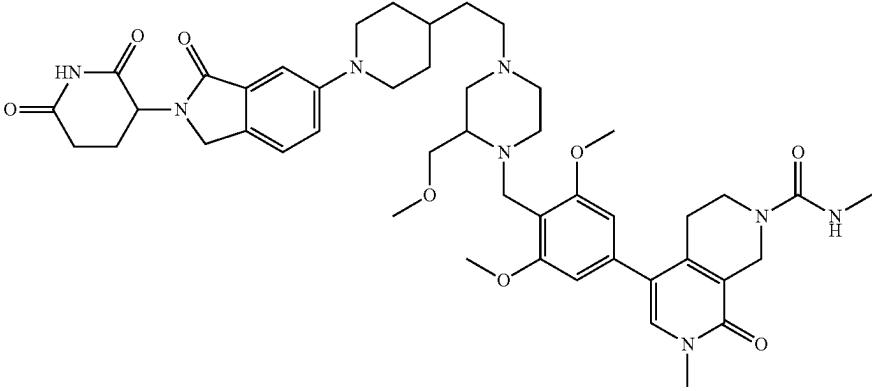
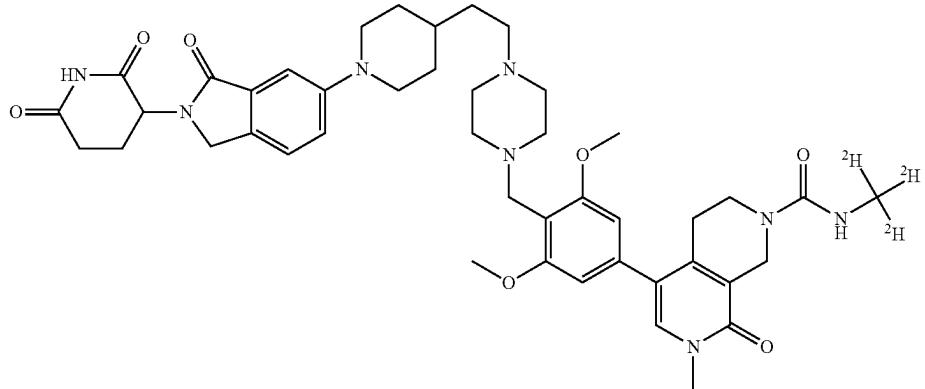
Compound No.	Structure
D339	 <p>Chemical structure of compound D339: A complex multi-ring system. It features a central quinoline ring substituted with a piperazine ring at position 4 and a piperidine ring at position 7. The piperazine ring is further substituted with a 4-methoxyphenyl group. The piperidine ring is substituted with a 4-(dimethylaminophenyl)phenyl group. The phenyl ring of the latter is also substituted with a 4-methoxyphenyl group. The overall structure is highly substituted and contains multiple nitrogen atoms.</p>
D340	 <p>Chemical structure of compound D340: Similar to D339, it features a central quinoline ring substituted with a piperazine ring at position 4 and a piperidine ring at position 7. The piperazine ring is substituted with a 4-methoxyphenyl group. The piperidine ring is substituted with a 4-(dimethylaminophenyl)phenyl group. The phenyl ring of the latter is substituted with a 4-methoxyphenyl group. The structure is complex with multiple nitrogen atoms.</p>
D341	 <p>Chemical structure of compound D341: Similar to D339 and D340, it features a central quinoline ring substituted with a piperazine ring at position 4 and a piperidine ring at position 7. The piperazine ring is substituted with a 4-methoxyphenyl group. The piperidine ring is substituted with a 4-(dimethylaminophenyl)phenyl group. The phenyl ring of the latter is substituted with a 4-methoxyphenyl group. The terminal group is a dimethylaminocarbonyl group ($\text{CH}_3\text{NHC(=O)NCH}_3$) instead of a piperidine ring.</p>

TABLE 2C-continued

Compounds D303-D375 of the Disclosure

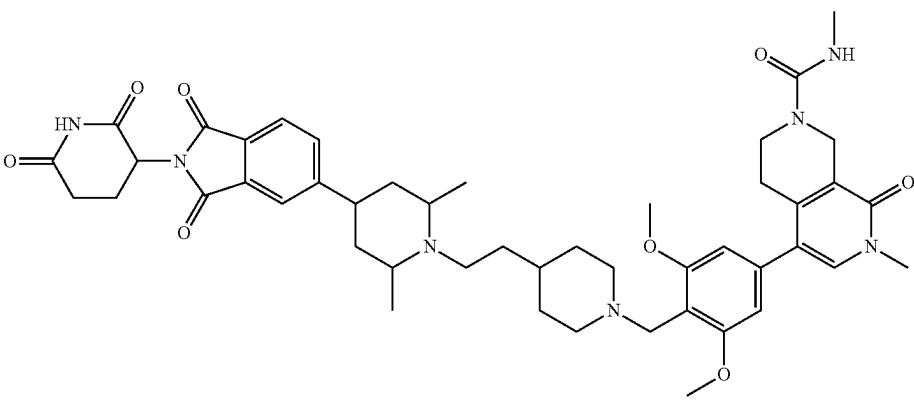
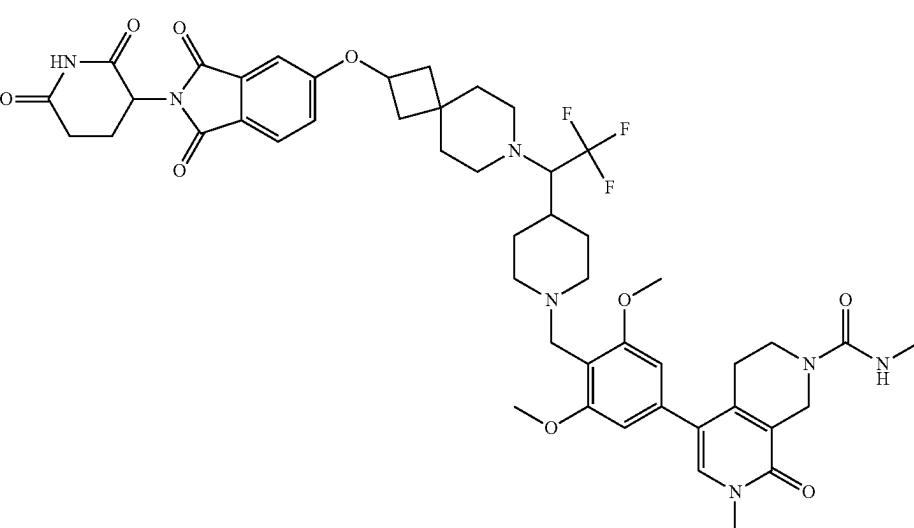
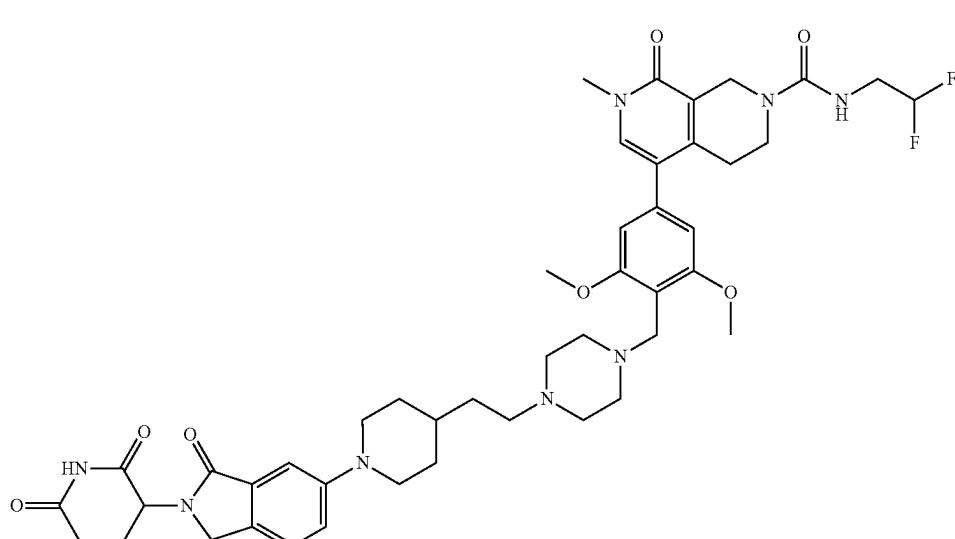
Compound No.	Structure
D342	
D343	
D344	

TABLE 2C-continued

Compounds D303-D375 of the Disclosure

Compound No.	Structure
D345	
D346	
D347	

TABLE 2C-continued

Compounds D303-D375 of the Disclosure

Compound No.	Structure
D348	
D349	
D350	
D351	

TABLE 2C-continued

Compounds D303-D375 of the Disclosure

Compound No.	Structure
D352	
D353	
D354	
D355	
D356	

TABLE 2C-continued

Compounds D303-D375 of the Disclosure

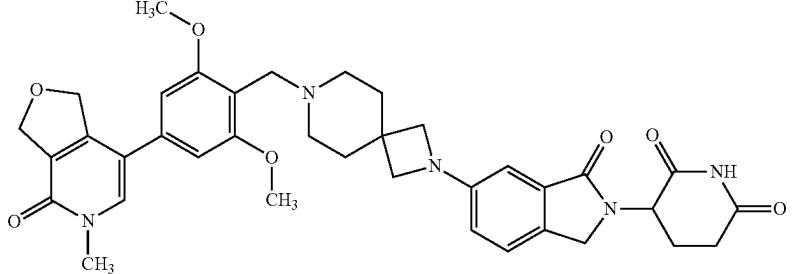
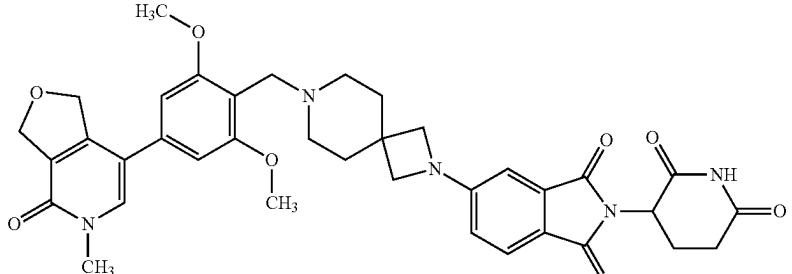
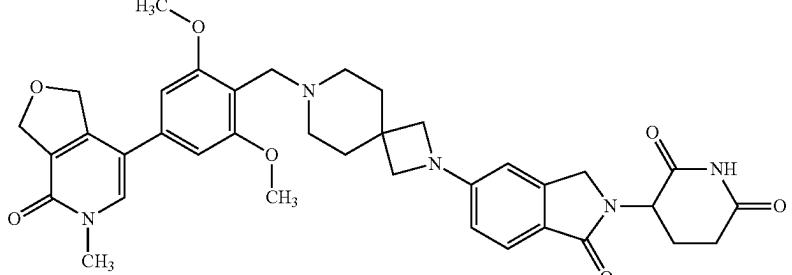
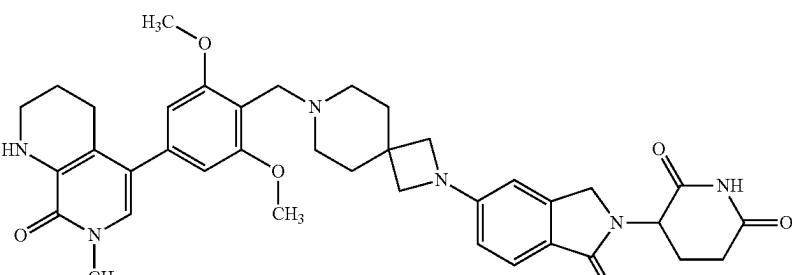
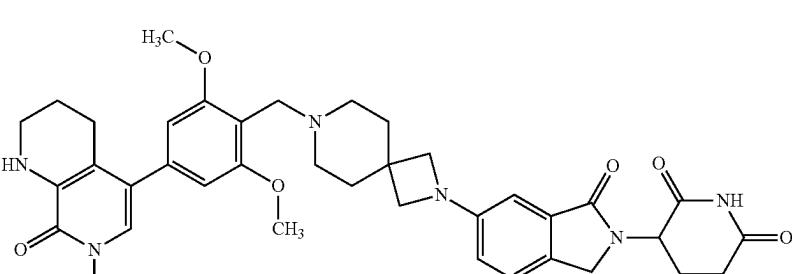
Compound No.	Structure
D357	
D358	
D359	
D360	
D361	

TABLE 2C-continued

Compounds D303-D375 of the Disclosure

Compound No.	Structure
D362	
D363	
D364	
D365	
D366	

TABLE 2C-continued

Compounds D303-D375 of the Disclosure

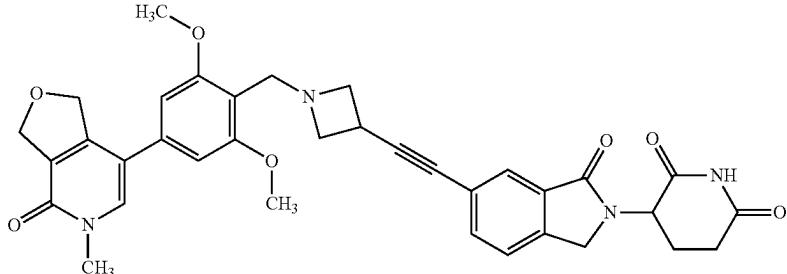
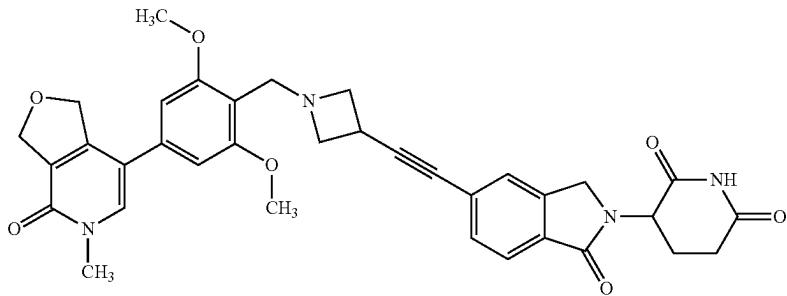
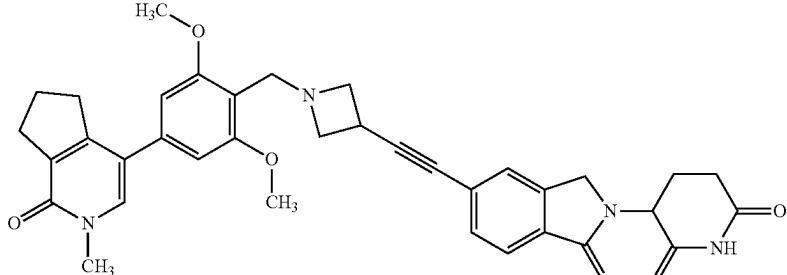
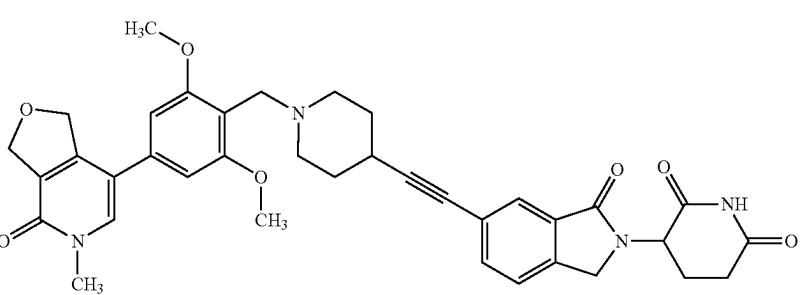
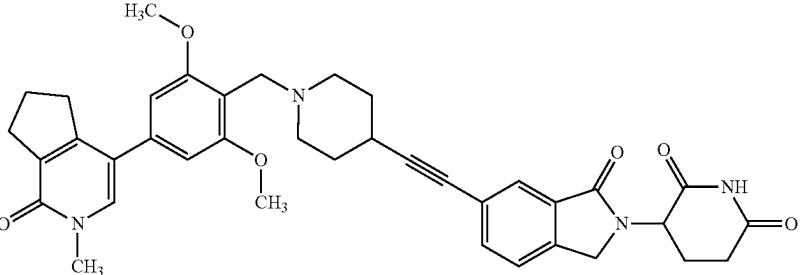
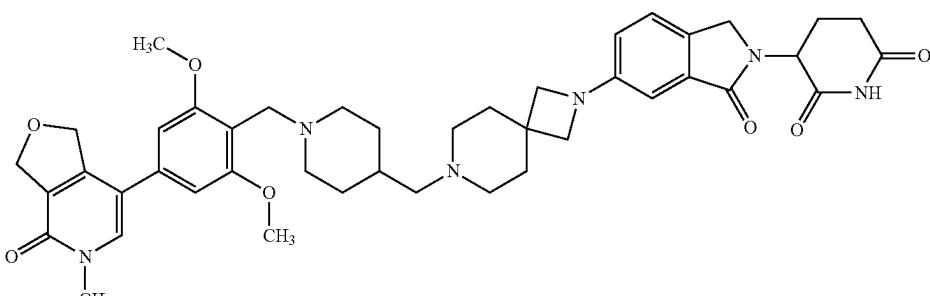
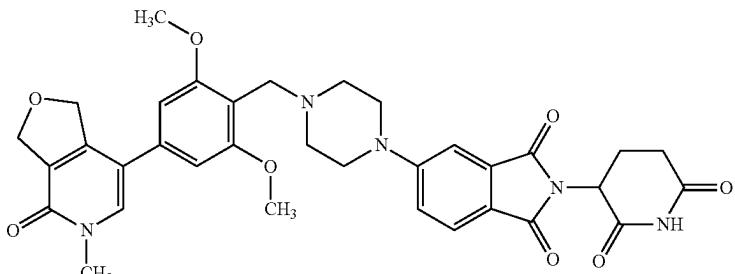
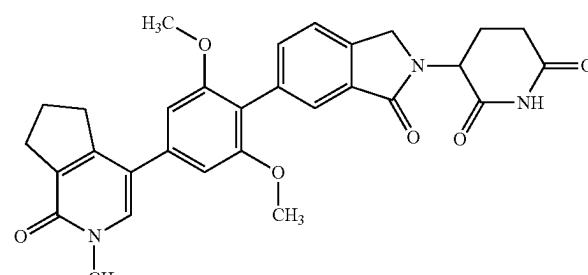
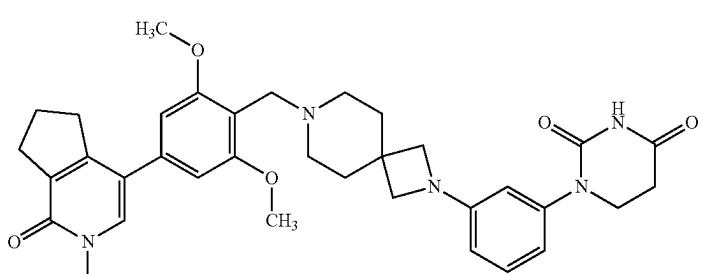
Compound No.	Structure
D367	
D368	
D369	
D370	
D371	

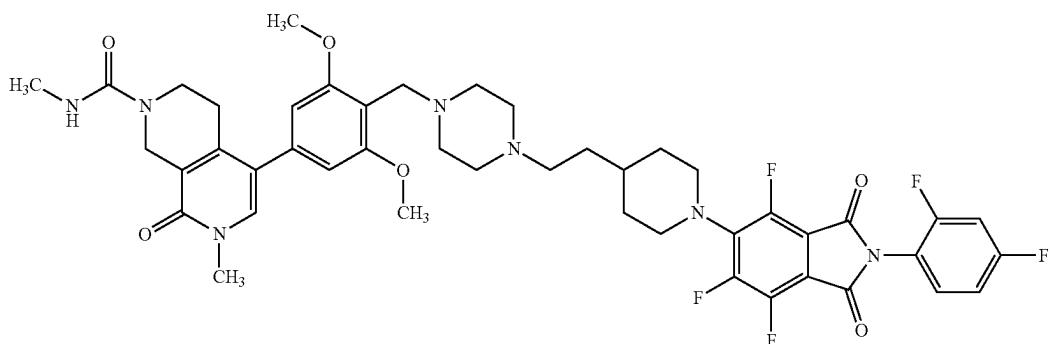
TABLE 2C-continued

Compounds D303-D375 of the Disclosure

Compound No.	Structure
D372	
D373	
D374	
D375	

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In an aspect, the disclosure features a compound having the structure of DD1, or a pharmaceutically acceptable salt thereof.



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In another aspect, the disclosure features a pharmaceutical composition including any of the foregoing compounds, or pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable excipient.

In an aspect, the disclosure features a method of inhibiting the level and/or activity of BRD9 in a cell, the method involving contacting the cell with an effective amount of any of the foregoing compounds, or pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof.

In another aspect, the disclosure features a method of reducing the level and/or activity of BRD9 in a cell, the method involving contacting the cell with an effective amount of any of the foregoing compounds, or pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof.

In some embodiments, the cell is a cancer cell.

In some embodiments, the cancer is a malignant, rhabdoid tumor, a CD8+ T-cell lymphoma, endometrial carcinoma, ovarian carcinoma, bladder cancer, stomach cancer, pancreatic cancer, esophageal cancer, prostate cancer, renal cell carcinoma, melanoma, colorectal cancer, a sarcoma (e.g., a soft tissue sarcoma, synovial sarcoma, Ewing's sarcoma, osteosarcoma, rhabdomyosarcoma, adult fibrosarcoma, alveolar soft-part sarcoma, angiosarcoma, clear cell sarcoma, desmoplastic small round cell tumor, epithelioid sarcoma, fibromyxoid sarcoma, gastrointestinal stromal tumor, Kaposi's sarcoma, liposarcoma, leiomyosarcoma, malignant mesenchymoma, malignant peripheral nerve sheath tumors, myxofibrosarcoma, low-grade rhabdomyosarcoma), non-small cell lung cancer (e.g., squamous or adenocarcinoma), stomach cancer, or breast cancer. In some embodiments, the cancer is a malignant, rhabdoid tumor, a CD8+ T-cell lymphoma, endometrial carcinoma, ovarian carcinoma, bladder cancer, stomach cancer, pancreatic cancer, esophageal cancer, prostate cancer, renal cell carcinoma, melanoma, or colorectal cancer. In some embodiments, the cancer is a sarcoma (e.g., synovial sarcoma or Ewing's sarcoma), non-small cell lung cancer (e.g., squamous or adenocarcinoma), stomach cancer, or breast cancer. In some embodiments, the cancer is sarcoma (e.g., synovial sarcoma or Ewing's sarcoma). In some embodiments, the sarcoma is synovial sarcoma.

In an aspect, the disclosure features a method of treating a BAF complex-related disorder in a subject in need thereof, the method involving administering to the subject an effective amount of any of the foregoing compounds, or phar-

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maceutically acceptable salts thereof, or a pharmaceutical composition thereof. In some embodiments, the BAF complex-related disorder is cancer. In some embodiments, the BAF complex-related disorder is infection.

In another aspect, the disclosure features a method of treating an SS18-SSX fusion protein-related disorder in a subject in need thereof, the method involving administering to the subject an effective amount of any of the foregoing compounds, or pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof. In some embodiments, the SS18-SSX fusion protein-related disorder is cancer. In some embodiments, the SS18-SSX fusion protein-related disorder is infection. In some embodiments of any of the foregoing methods, the SS18-SSX fusion protein is a SS18-SSX1 fusion protein, a SS18-SSX2 fusion protein, or a SS18-SSX4 fusion protein.

In yet another aspect, the disclosure features a method of treating a BRD9-related disorder in a subject in need thereof, the method involving administering to the subject an effective amount of any of the foregoing compounds, or pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof. In some embodiments, the BRD9-related disorder is cancer. In some embodiments, the BRD9-related disorder is infection.

In some embodiments, the cancer is squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, hepatocellular carcinomas, and renal cell carcinomas, cancer of the bladder, bowel, breast, cervix, colon, esophagus, head, kidney, liver, lung, neck, ovary, pancreas, prostate, and stomach; leukemias; benign and malignant lymphomas, particularly Burkitt's lymphoma and Non-Hodgkin's lymphoma; benign and malignant melanomas; myeloproliferative diseases; sarcomas, including Ewing's sarcoma, hemangiosarcoma, Kaposi's sarcoma, liposarcoma, myosarcomas, peripheral neuroepithelioma, synovial sarcoma, gliomas, astrocytomas, oligodendrogiomas, ependymomas, glioblastomas, neuroblastomas, ganglioneuromas, gangliogliomas, medulloblastomas, pineal cell tumors, meningiomas, meningeal sarcomas, neurofibromas, and Schwannomas; bowel cancer, breast cancer, prostate cancer, cervical cancer, uterine cancer, lung cancer, ovarian cancer, testicular cancer, thyroid cancer, astrocytoma, esophageal cancer, pancreatic cancer, stomach cancer, liver cancer, colon cancer, melanoma; carcinosarcoma, Hodgkin's disease, Wilms' tumor and teratocarcinomas. Additional cancers which may be treated using the disclosed compounds according to the

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present invention include, for example, acute granulocytic leukemia, acute lymphocytic leukemia (ALL), acute myelogenous leukemia (AML), adenocarcinoma, adenosarcoma, adrenal cancer, adrenocortical carcinoma, anal cancer, anaplastic astrocytoma, angiosarcoma, appendix cancer, astrocytoma, Basal cell carcinoma, B-Cell lymphoma, bile duct cancer, bladder cancer, bone cancer, bone marrow cancer, bowel cancer, brain cancer, brain stem glioma, breast cancer, triple (estrogen, progesterone and HER-2) negative breast cancer, double negative breast cancer (two of estrogen, progesterone and HER-2 are negative), single negative (one of estrogen, progesterone and HER-2 is negative), estrogen-receptor positive, HER2-negative breast cancer, estrogen receptor-negative breast cancer, estrogen receptor positive breast cancer, metastatic breast cancer, luminal A breast cancer, luminal B breast cancer, Her2-negative breast cancer, HER2-positive or negative breast cancer, progesterone receptor-negative breast cancer, progesterone receptor-positive breast cancer, recurrent breast cancer, carcinoid tumors, cervical cancer, cholangiocarcinoma, chondrosarcoma, chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), colon cancer, colorectal cancer, craniopharyngioma, cutaneous lymphoma, cutaneous melanoma, diffuse astrocytoma, ductal carcinoma in situ (DCIS), endometrial cancer, ependymoma, epithelioid sarcoma, esophageal cancer, ewing sarcoma, extrahepatic bile duct cancer, eye cancer, fallopian tube cancer, fibrosarcoma, gallbladder cancer, gastric cancer, gastrointestinal cancer, gastrointestinal carcinoid cancer, gastrointestinal stromal tumors (GIST), germ cell tumor glioblastoma multiforme (GBM), glioma, hairy cell leukemia, head and neck cancer, hemangioendothelioma, Hodgkin lymphoma, hypopharyngeal cancer, infiltrating ductal carcinoma (IDC), infiltrating lobular carcinoma (ILC), inflammatory breast cancer (IBC), intestinal Cancer, intrahepatic bile duct cancer, invasive/infiltrating breast cancer, Islet cell cancer, jaw cancer, Kaposi sarcoma, kidney cancer, laryngeal cancer, leiomyosarcoma, leptomeningeal metastases, leukemia, lip cancer, liposarcoma, liver cancer, lobular carcinoma in situ, low-grade astrocytoma, lung cancer, lymph node cancer, lymphoma, male breast cancer, medullary carcinoma, medulloblastoma, melanoma, meningioma, Merkel cell carcinoma, mesenchymal chondrosarcoma, mesenchymous, mesothelioma metastatic breast cancer, metastatic melanoma metastatic squamous neck cancer, mixed gliomas, monodermal teratoma, mouth cancer mucinous carcinoma, mucosal melanoma, multiple myeloma, Mycosis Fungoïdes, myelodysplastic syndrome, nasal cavity cancer, nasopharyngeal cancer, neck cancer, neuroblastoma, neuroendocrine tumors (NETs), non-Hodgkin's lymphoma, non-small cell lung cancer (NSCLC), oat cell cancer, ocular cancer, ocular melanoma, oligodendrogloma, oral cancer, oral cavity cancer, oropharyngeal cancer, osteogenic sarcoma, osteosarcoma, ovarian cancer, ovarian epithelial cancer ovarian germ cell tumor, ovarian primary peritoneal carcinoma, ovarian sex cord stromal tumor, Paget's disease, pancreatic cancer, papillary carcinoma, paranasal sinus cancer, parathyroid cancer, pelvic cancer, penile cancer, peripheral nerve cancer, peritoneal cancer, pharyngeal cancer, pheochromocytoma, pilocytic astrocytoma, pineal region tumor, pineoblastoma, pituitary gland cancer, primary central nervous system (CNS) lymphoma, prostate cancer, rectal cancer, renal cell carcinoma, renal pelvis cancer, rhabdomyosarcoma, salivary gland cancer, soft tissue sarcoma, bone sarcoma, sarcoma, sinus cancer, skin cancer, small cell lung cancer (SCLC), small intestine cancer, spinal cancer, spinal column cancer, spinal cord cancer, squamous cell carcinoma, stomach can-

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cer, synovial sarcoma, T-cell lymphoma, testicular cancer, throat cancer, thymoma/thymic carcinoma, thyroid cancer, tongue cancer, tonsil cancer, transitional cell cancer, tubal cancer, tubular carcinoma, undiagnosed cancer, ureteral cancer, urethral cancer, uterine adenocarcinoma, uterine cancer, uterine sarcoma, vaginal cancer, vulvar cancer, T-cell lineage acute lymphoblastic leukemia (T-ALL), T-cell lineage lymphoblastic lymphoma (T-LL), peripheral T-cell lymphoma, Adult T-cell leukemia, Pre-B ALL, Pre-B lymphomas, large B-cell lymphoma, Burkitts lymphoma, B-cell ALL, Philadelphia chromosome positive ALL, Philadelphia chromosome positive CML, juvenile myelomonocytic leukemia (JMML), acute promyelocytic leukemia (a subtype of AML), large granular lymphocytic leukemia, Adult T-cell chronic leukemia, diffuse large B cell lymphoma, follicular lymphoma; Mucosa-Associated Lymphatic Tissue lymphoma (MALT), small cell lymphocytic lymphoma, mediastinal large B cell lymphoma, nodal marginal zone B cell lymphoma (NMZL); splenic marginal zone lymphoma (SMZL); intravascular large B-cell lymphoma; primary effusion lymphoma; or lymphomatoid granulomatosis; B-cell prolymphocytic leukemia; splenic lymphoma/leukemia, unclassifiable, splenic diffuse red pulp small B-cell lymphoma; lymphoplasmacytic lymphoma; heavy chain diseases, for example, Alpha heavy chain disease, Gamma heavy chain disease, Mu heavy chain disease, plasma cell myeloma, solitary plasmacytoma of bone; extraosseous plasmacytoma; primary cutaneous follicle center lymphoma, T cell/histocyte rich large B-cell lymphoma, DLBCL associated with chronic inflammation; Epstein-Barr virus (EBV)+ DLBCL of the elderly; primary mediastinal (thymic) large B-cell lymphoma, primary cutaneous DLBCL, leg type, ALK+ large B-cell lymphoma, plasmablastic lymphoma; large B-cell lymphoma arising in HHV8-associated multicentric, Castleman disease; B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma, or B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma.

In some embodiments, the cancer is a malignant, rhabdoid tumor, a CD8+ T-cell lymphoma, endometrial carcinoma, ovarian carcinoma, bladder cancer, stomach cancer, pancreatic cancer, esophageal cancer, prostate cancer, renal cell carcinoma, melanoma, colorectal cancer, a sarcoma (e.g., a soft tissue sarcoma, synovial sarcoma, Ewing's sarcoma, osteosarcoma, rhabdomyosarcoma, adult fibrosarcoma, alveolar soft-part sarcoma, angiosarcoma, clear cell sarcoma, desmoplastic small round cell tumor, epithelioid sarcoma, fibromyxoid sarcoma, gastrointestinal stromal tumor, Kaposi sarcoma, liposarcoma, leiomyosarcoma, malignant mesenchymoma, malignant peripheral nerve sheath tumors, myxofibrosarcoma, low-grade rhabdomyosarcoma), non-small cell lung cancer (e.g., squamous or adenocarcinoma), stomach cancer, or breast cancer. In some embodiments, the cancer is a malignant, rhabdoid tumor, a CD8+ T-cell lymphoma, endometrial carcinoma, ovarian carcinoma, bladder cancer, stomach cancer, pancreatic cancer, esophageal cancer, prostate cancer, renal cell carcinoma, melanoma, or colorectal cancer. In some embodiments, the cancer is a sarcoma (e.g., synovial sarcoma or Ewing's sarcoma), non-small cell lung cancer (e.g., squamous or adenocarcinoma), stomach cancer, or breast cancer. In some embodiments, the cancer is sarcoma (e.g., synovial sarcoma or Ewing's sarcoma). In some embodiments, the sarcoma is synovial sarcoma.

In some embodiments, the infection is viral infection (e.g., an infection with a virus of the Retroviridae family such as the lentiviruses (e.g. Human immunodeficiency virus (HIV) and deltaretroviruses (e.g., human T cell leukemia virus I (HTLV-I), human T cell leukemia virus II (HTLV-II)); Hepadnaviridae family (e.g. hepatitis B virus (HBV)); Flaviviridae family (e.g. hepatitis C virus (HCV)); Adenoviridae family (e.g. Human Adenovirus); Herpesviridae family (e.g. Human cytomegalovirus (HCMV), Epstein-Barr virus, herpes simplex virus 1 (HSV-1), herpes simplex virus 2 (HSV-2), human herpesvirus 6 (HHV-6), Herpesvitus K*, CMV, varicella-zoster virus); Papillomaviridae family (e.g. Human Papillomavirus (HPV, HPV E1)); Parvoviridae family (e.g. Parvovirus B19); Polyomaviridae family (e.g. JC virus and BK virus); Paramyxoviridae family (e.g. Measles virus); or Togaviridae family (e.g. Rubella virus)). In some embodiments, the disorder is Coffin Siris, Neurofibromatosis (e.g., NF-1, NF-2, or Schwannomatosis), or Multiple Meningioma. In an aspect, the disclosure features a method of treating a cancer in a subject in need thereof, the method including administering to the subject an effective amount of any of the foregoing compounds, or pharmaceutically acceptable salts thereof, or any of the foregoing pharmaceutical compositions.

In some embodiments, the cancer is squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, hepatocellular carcinomas, and renal cell carcinomas, cancer of the bladder, bowel, breast, cervix, colon, esophagus, head, kidney, liver, lung, neck, ovary, pancreas, prostate, and stomach; leukemias; benign and malignant lymphomas, particularly Burkitt's lymphoma and Non-Hodgkin's lymphoma; benign and malignant melanomas; myeloproliferative diseases; sarcomas, including Ewing's sarcoma, hemangiosarcoma, Kaposi's sarcoma, liposarcoma, myosarcomas, peripheral neuroepithelioma, synovial sarcoma, gliomas, astrocytomas, oligodendrogiomas, ependymomas, glioblastomas, neuroblastomas, ganglioneuromas, gangliogliomas, medulloblastomas, pineal cell tumors, meningiomas, meningeal sarcomas, neurofibromas, and Schwannomas; bowel cancer, breast cancer, prostate cancer, cervical cancer, uterine cancer, lung cancer, ovarian cancer, testicular cancer, thyroid cancer, astrocytoma, esophageal cancer, pancreatic cancer, stomach cancer, liver cancer, colon cancer, melanoma; carcinosarcoma, Hodgkin's disease, Wilms' tumor and teratocarcinomas. Additional cancers which may be treated using the disclosed compounds according to the present invention include, for example, acute granulocytic leukemia, acute lymphocytic leukemia (ALL), acute myelogenous leukemia (AML), adenocarcinoma, adenosarcoma, adrenal cancer, adrenocortical carcinoma, anal cancer, anaplastic astrocytoma, angiosarcoma, appendix cancer, astrocytoma, Basal cell carcinoma, B-Cell lymphoma, bile duct cancer, bladder cancer, bone cancer, bone marrow cancer, bowel cancer, brain cancer, brain stem glioma, breast cancer, triple (estrogen, progesterone and HER-2) negative breast cancer, double negative breast cancer (two of estrogen, progesterone and HER-2 are negative), single negative (one of estrogen, progesterone and HER-2 is negative), estrogen-receptor positive, HER2-negative breast cancer, estrogen receptor-negative breast cancer, estrogen receptor positive breast cancer, metastatic breast cancer, luminal A breast cancer, luminal B breast cancer, Her2-negative breast cancer, HER2-positive or negative breast cancer, progesterone receptor-negative breast cancer, progesterone receptor-positive breast cancer, recurrent breast cancer, carcinoid tumors, cervical cancer, cholangiocarcinoma, chondrosarcoma, chronic lymphocytic leukemia (CLL), chronic myel-

ogenous leukemia (CML), colon cancer, colorectal cancer, craniopharyngioma, cutaneous lymphoma, cutaneous melanoma, diffuse astrocytoma, ductal carcinoma in situ (DCIS), endometrial cancer, ependymoma, epithelioid sarcoma, esophageal cancer, ewing sarcoma, extrahepatic bile duct cancer, eye cancer, fallopian tube cancer, fibrosarcoma, gallbladder cancer, gastric cancer, gastrointestinal cancer, gastrointestinal carcinoid cancer, gastrointestinal stromal tumors (GIST), germ cell tumor glioblastoma multiforme (GBM), glioma, hairy cell leukemia, head and neck cancer, hemangioendothelioma, Hodgkin lymphoma, hypopharyngeal cancer, infiltrating ductal carcinoma (IDC), infiltrating lobular carcinoma (ILC), inflammatory breast cancer (IBC), intestinal Cancer, intrahepatic bile duct cancer, invasive/infiltrating breast cancer, Islet cell cancer, jaw cancer, Kaposi sarcoma, kidney cancer, laryngeal cancer, leiomyosarcoma, leptomeningeal metastases, leukemia, lip cancer, liposarcoma, liver cancer, lobular carcinoma in situ, low-grade astrocytoma, lung cancer, lymph node cancer, lymphoma, male breast cancer, medullary carcinoma, medulloblastoma, melanoma, meningioma, Merkel cell carcinoma, mesenchymal chondrosarcoma, mesenchymous, mesothelioma metastatic breast cancer, metastatic melanoma metastatic squamous neck cancer, mixed gliomas, monodermal teratoma, mouth cancer mucinous carcinoma, mucosal melanoma, multiple myeloma, Mycosis Fungoidea, myelodysplastic syndrome, nasal cavity cancer, nasopharyngeal cancer, neck cancer, neuroblastoma, neuroendocrine tumors (NETs), non-Hodgkin's lymphoma, non-small cell lung cancer (NSCLC), oat cell cancer, ocular cancer, ocular melanoma, oligodendrogloma, oral cancer, oral cavity cancer, oropharyngeal cancer, osteogenic sarcoma, osteosarcoma, ovarian cancer, ovarian epithelial cancer ovarian germ cell tumor, ovarian primary peritoneal carcinoma, ovarian sex cord stromal tumor, Paget's disease, pancreatic cancer, papillary carcinoma, paranasal sinus cancer, parathyroid cancer, pelvic cancer, penile cancer, peripheral nerve cancer, peritoneal cancer, pharyngeal cancer, pheochromocytoma, pilocytic astrocytoma, pineal region tumor, pineoblastoma, pituitary gland cancer, primary central nervous system (CNS) lymphoma, prostate cancer, rectal cancer, renal cell carcinoma, renal pelvis cancer, rhabdomyosarcoma, salivary gland cancer, soft tissue sarcoma, bone sarcoma, sarcoma, sinus cancer, skin cancer, small cell lung cancer (SCLC), small intestine cancer, spinal cancer, spinal column cancer, spinal cord cancer, squamous cell carcinoma, stomach cancer, synovial sarcoma, T-cell lymphoma, testicular cancer, throat cancer, tonsil cancer, transitional cell cancer, tubal cancer, tubular carcinoma, undiagnosed cancer, ureteral cancer, urethral cancer, uterine adenocarcinoma, uterine cancer, uterine sarcoma, vaginal cancer, vulvar cancer, T-cell lineage acute lymphoblastic leukemia (T-ALL), T-cell lineage lymphoblastic lymphoma (T-LL), peripheral T-cell lymphoma, Adult T-cell leukemia, Pre-B ALL, Pre-B lymphomas, large B-cell lymphoma, Burkitts lymphoma, B-cell ALL, Philadelphia chromosome positive ALL, Philadelphia chromosome positive CML, juvenile myelomonocytic leukemia (JMML), acute promyelocytic leukemia (a subtype of AML), large granular lymphocytic leukemia, Adult T-cell chronic leukemia, diffuse large B cell lymphoma, follicular lymphoma; Mucosa-Associated Lymphatic Tissue lymphoma (MALT), small cell lymphocytic lymphoma, mediastinal large B cell lymphoma, nodal marginal zone B cell lymphoma (NMZL); splenic marginal zone lymphoma (SMZL); intravascular large B-cell lymphoma; primary effusion lymphoma; or lymphomatoid granulomatosis;

B-cell prolymphocytic leukemia; splenic lymphoma/leukemia, unclassifiable, splenic diffuse red pulp small B-cell lymphoma; lymphoplasmacytic lymphoma; heavy chain diseases, for example, Alpha heavy chain disease, Gamma heavy chain disease, Mu heavy chain disease, plasma cell myeloma, solitary plasmacytoma of bone; extraosseous plasmacytoma; primary cutaneous follicle center lymphoma, T cell/histocyte rich large B-cell lymphoma, DLBCL associated with chronic inflammation; Epstein-Barr virus (EBV)+ DLBCL of the elderly; primary mediastinal (thymic) large B-cell lymphoma, primary cutaneous DLBCL, leg type, ALK+ large B-cell lymphoma, plasmablastic lymphoma; large B-cell lymphoma arising in HHV8-associated multicentric, Castleman disease; B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma, or B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma.

In some embodiments, the cancer is a malignant, rhabdoid tumor, a CD8+ T-cell lymphoma, endometrial carcinoma, ovarian carcinoma, bladder cancer, stomach cancer, pancreatic cancer, esophageal cancer, prostate cancer, renal cell carcinoma, melanoma, colorectal cancer, a sarcoma (e.g., a soft tissue sarcoma, synovial sarcoma, Ewing's sarcoma, osteosarcoma, rhabdomyosarcoma, adult fibrosarcoma, alveolar soft-part sarcoma, angiosarcoma, clear cell sarcoma, desmoplastic small round cell tumor, epithelioid sarcoma, fibromyxoid sarcoma, gastrointestinal stromal tumor, Kaposi sarcoma, liposarcoma, leiomyosarcoma, malignant mesenchymoma malignant peripheral nerve sheath tumors, myxofibrosarcoma, low-grade rhabdomyosarcoma), non-small cell lung cancer (e.g., squamous or adenocarcinoma), stomach cancer, or breast cancer. In some embodiments, the cancer is a malignant, rhabdoid tumor, a CD8+ T-cell lymphoma, endometrial carcinoma, ovarian carcinoma, bladder cancer, stomach cancer, pancreatic cancer, esophageal cancer, prostate cancer, renal cell carcinoma, melanoma, or colorectal cancer. In some embodiments, the cancer is a sarcoma (e.g., synovial sarcoma or Ewing's sarcoma), non-small cell lung cancer (e.g., squamous or adenocarcinoma), stomach cancer, or breast cancer. In some embodiments, the cancer is sarcoma (e.g., synovial sarcoma or Ewing's sarcoma). In some embodiments, the sarcoma is synovial sarcoma.

In another aspect, the disclosure features a method for treating a viral infection in a subject in need thereof. This method includes administering to the subject an effective amount of any of the foregoing compounds, or pharmaceutically acceptable salts thereof, or any of the foregoing pharmaceutical compositions. In some embodiments, the viral infection is an infection with a virus of the Retroviridae family such as the lentiviruses (e.g. Human immunodeficiency virus (HIV) and deltaretroviruses (e.g., human T cell leukemia virus I (HTLV-I), human T cell leukemia virus II (HTLV-II)); Hepadnaviridae family (e.g. hepatitis B virus (HBV)), Flaviviridae family (e.g. hepatitis C virus (HCV)), Adenoviridae family (e.g. Human Adenovirus), Herpesviridae family (e.g. Human cytomegalovirus (HCMV), Epstein-Barr virus, herpes simplex virus 1 (HSV-1), herpes simplex virus 2 (HSV-2), human herpesvirus 6 (HHV-6), Herpesvirus K*, CMV, varicella-zoster virus), Papillomaviridae family (e.g. Human Papillomavirus (HPV, HPV E1)), Parvoviridae family (e.g. Parvovirus B19), Polyomaviridae family (e.g. JC virus and BK virus), Paramyxoviridae family (e.g. Measles virus), Togaviridae family (e.g. Rubella virus).

In another embodiment of any of the foregoing methods, the method further includes administering to the subject an additional anticancer therapy (e.g., chemotherapeutic or cytotoxic agent or radiotherapy).

5 In particular embodiments, the additional anticancer therapy is: a chemotherapeutic or cytotoxic agent (e.g., doxorubicin or ifosfamide), a differentiation-inducing agent (e.g., retinoic acid, vitamin D, cytokines), a hormonal agent, an immunological agent, or an anti-angiogenic agent. Chemotherapeutic and cytotoxic agents include, but are not limited to, alkylating agents, cytotoxic antibiotics, antimetabolites, vinca alkaloids, etoposides, and others (e.g., paclitaxel, taxol, docetaxel, taxotere, cis-platinum). A list of additional compounds having anticancer activity can be found in L. Brunton, B. Chabner and B. Knollman (eds). Goodman and Gilman's The Pharmacological Basis of Therapeutics, Twelfth Edition, 2011, McGraw Hill Companies, New York, NY.

In particular embodiments, the compound of the invention 20 and the additional anticancer therapy and any of the foregoing compounds or pharmaceutical compositions are administered within 28 days of each other (e.g., within 21, 14, 10, 7, 5, 4, 3, 2, or 1 days) or within 24 hours (e.g., 12, 6, 3, 2, or 1 hours; or concomitantly) each in an amount that 25 together are effective to treat the subject.

Chemical Terms

The terminology employed herein is for the purpose of 30 describing particular embodiments and is not intended to be limiting.

For any of the following chemical definitions, a number 35 following an atomic symbol indicates that total number of atoms of that element that are present in a particular chemical moiety. As will be understood, other atoms, such as hydrogen atoms, or substituent groups, as described herein, may be present, as necessary, to satisfy the valences of the atoms. For example, an unsubstituted C₂ alkyl group has the formula —CH₂CH₃. When used with the groups defined 40 herein, a reference to the number of carbon atoms includes the divalent carbon in acetal and ketal groups but does not include the carbonyl carbon in acyl, ester, carbonate, or carbamate groups. A reference to the number of oxygen, nitrogen, or sulfur atoms in a heteroaryl group only includes 45 those atoms that form a part of a heterocyclic ring.

Herein a phrase of the form "optionally substituted X" (e.g., optionally substituted alkyl) is intended to be equivalent to "X, wherein X is optionally substituted" (e.g., "alkyl, wherein said alkyl is optionally substituted"). It is not intended to mean that the feature "X" (e.g., alkyl) per se is optional. As described herein, certain compounds of interest 50 may contain one or more "optionally substituted" moieties. In general, the term "substituted", whether preceded by the term "optionally" or not, means that one or more hydrogens 55 of the designated moiety are replaced with a suitable substituent, e.g., any of the substituents or groups described herein. Unless otherwise indicated, an "optionally substituted" group may have a suitable substituent at each substitutable position of the group, and when more than one 60 position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by the present disclosure are preferably those that result in the formation of stable or chemically feasible compounds. The term "stable", as used herein, refers to compounds that are 65 not substantially altered when subjected to conditions to

allow for their production, detection, and, in certain embodiments, their recovery, purification, and use for one or more of the purposes disclosed herein.

The term "aliphatic," as used herein, refers to a saturated or unsaturated, straight, branched, or cyclic hydrocarbon. "Aliphatic" is intended herein to include, but is not limited to, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, and cycloalkynyl moieties, and thus incorporates each of these definitions. In one embodiment, "aliphatic" is used to indicate those aliphatic groups having 1-20 carbon atoms. The aliphatic chain can be, for example, mono-unsaturated, di-unsaturated, tri-unsaturated, or polyunsaturated, or alkynyl. Unsaturated aliphatic groups can be in a cis or trans configuration. In one embodiment, the aliphatic group contains from 1 to about 12 carbon atoms, more generally from 1 to about 6 carbon atoms or from 1 to about 4 carbon atoms. In one embodiment, the aliphatic group contains from 1 to about 8 carbon atoms. In certain embodiments, the aliphatic group is C₁-C₂, C₁-C₃, C₁-C₄, C₁-C₅, or C₁-C₆. The specified ranges as used herein indicate an aliphatic group having each member of the range described as an independent species. For example, the term C₁-C₆ aliphatic as used herein indicates a straight or branched alkyl, alkenyl, or alkynyl group having from 1, 2, 3, 4, 5, or 6 carbon atoms and is intended to mean that each of these is described as an independent species. For example, the term C₁-C₄ aliphatic as used herein indicates a straight or branched alkyl, alkenyl, or alkynyl group having from 1, 2, 3, or 4 carbon atoms and is intended to mean that each of these is described as an independent species. In one embodiment, the aliphatic group is substituted with one or more functional groups that results in the formation of a stable moiety.

The term "heteroaliphatic," as used herein, refers to an aliphatic moiety that contains at least one heteroatom in the chain, for example, an amine, carbonyl, carboxy, oxo, thio, phosphate, phosphonate, nitrogen, phosphorus, silicon, or boron atoms in place of a carbon atom. In one embodiment, the only heteroatom is nitrogen. In one embodiment, the only heteroatom is oxygen. In one embodiment, the only heteroatom is sulfur. "Heteroaliphatic" is intended herein to include, but is not limited to, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocycloalkyl, heterocycloalkenyl, and heterocycloalkynyl moieties. In one embodiment, "heteroaliphatic" is used to indicate a heteroaliphatic group (cyclic, acyclic, substituted, unsubstituted, branched or unbranched) having 1-20 carbon atoms. In one embodiment, the heteroaliphatic group is optionally substituted in a manner that results in the formation of a stable moiety. Nonlimiting examples of heteroaliphatic moieties are polyethylene glycol, polyalkylene glycol, amide, polyamide, polylactide, polyglycolide, thioether, ether, alkyl-heterocycle-alkyl, —O-alkyl-O-alkyl, and alkyl-O-haloalkyl.

The term "acyl," as used herein, represents a hydrogen or an alkyl group that is attached to a parent molecular group through a carbonyl group, as defined herein, and is exemplified by formyl (i.e., a carboxyaldehyde group), acetyl, trifluoroacetyl, propionyl, and butanoyl. Exemplary unsubstituted acyl groups include from 1 to 6, from 1 to 11, or from 1 to 21 carbons.

The term "alkyl," as used herein, refers to a branched or straight-chain monovalent saturated aliphatic hydrocarbon radical of 1 to 20 carbon atoms (e.g., 1 to 16 carbon atoms, 1 to 10 carbon atoms, 1 to 6 carbon atoms, or 1 to 3 carbon atoms). An "alkylene" is a divalent alkyl group.

The term "alkenyl," as used herein, alone or in combination with other groups, refers to a straight chain or branched hydrocarbon residue having a carbon-carbon double bond

and having 2 to 20 carbon atoms (e.g., 2 to 16 carbon atoms, 2 to 10 carbon atoms, 2 to 6, or 2 carbon atoms). An "alkynylene" is a divalent alkynyl group.

The term "alkynyl," as used herein, alone or in combination with other groups, refers to a straight chain or branched hydrocarbon residue having a carbon-carbon triple bond and having 2 to 20 carbon atoms (e.g., 2 to 16 carbon atoms, 2 to 10 carbon atoms, 2 to 6, or 2 carbon atoms). An "alkynylene" is a divalent alkynyl group.

10 The term "amino," as used herein, represents —N(R^{N1})₂, wherein each R^{N1} is, independently, H, OH, NO₂, N(R^{N2})₂, SO₂OR^{N2}, SO₂R^{N2}, SOR^{N2}, an N-protecting group, alkyl, alkoxy, aryl, arylalkyl, cycloalkyl, acyl (e.g., acetyl, trifluoroacetyl, or others described herein), wherein each of these recited R^{N1} groups can be optionally substituted; or two R^{N1} combine to form an alkylene or heteroalkylene, and wherein each R^{N2} is, independently, H, alkyl, or aryl. The amino groups of the compounds described herein can be an unsubstituted amino (i.e., —NH₂) or a substituted amino (i.e., 20 —N(R^{N1})₂).

15 The term "aryl," as used herein, refers to an aromatic mono- or polycyclic radical of, e.g., 6 to 12, carbon atoms having at least one aromatic ring. Examples of such groups include, but are not limited to, phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, 1,2-dihydronaphthyl, indanyl, and 1H-indenyl.

20 The term "arylalkyl," as used herein, represents an alkyl group substituted with an aryl group. Exemplary unsubstituted arylalkyl groups are from 7 to 30 carbons (e.g., from 7 to 16 or from 7 to 20 carbons, such as C₁-C₆ alkyl C₆-C₁₀ aryl, C₁-C₁₀ alkyl C₆-C₁₀ aryl, or C₁-C₂₀ alkyl C₆-C₁₀ aryl), such as, benzyl and phenethyl. In some embodiments, the alkyl and the aryl each can be further substituted with 1, 2, 3, or 4 substituent groups as defined herein for the respective groups.

25 The term "azido," as used herein, represents a —N₃ group.

The term "bridged cyclyl," as used herein, refers to a bridged polycyclic group of 5 to 20 atoms, containing from 1 to 3 bridges. Bridged cyclyl includes bridged carbocyclyl (e.g., norbornyl) and bridged heterocyclyl (e.g., 1,4-diazabicyclo[2.2.2]octane).

The term "cyano," as used herein, represents a —CN group.

30 The term "carbocyclyl," as used herein, refers to a non-aromatic C₃-C₁₂, monocyclic or polycyclic (e.g., bicyclic or tricyclic) structure in which the rings are formed by carbon atoms. Carbocyclyl structures include cycloalkyl groups (e.g., cyclohexyl) and unsaturated carbocyclyl radicals (e.g., cyclohexenyl). Polycyclic carbocyclyl includes spirocyclic carbocyclyl, bridged carbocyclyl, and fused carbocyclyl. A "carbocyclene" is a divalent carbocyclyl group.

35 The term "cycloalkyl," as used herein, refers to a saturated, non-aromatic, monovalent mono- or polycarbocyclic radical of 3 to 10, preferably 3 to 6 carbon atoms. This term is further exemplified by radicals such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, and adamantyl.

40 The terms "halo" or "halogen," as used herein, mean a fluorine (fluoro), chlorine (chloro), bromine (bromo), or iodine (iodo) radical.

45 The term "heteroalkyl," as used herein, refers to an alkyl group, as defined herein, in which one or more of the constituent carbon atoms have been replaced by nitrogen, oxygen, or sulfur. In some embodiments, the heteroalkyl group can be further substituted with 1, 2, 3, or 4 substituent groups as described herein for alkyl groups. Examples of

heteroalkyl groups are an “alkoxy” which, as used herein, refers to alkyl-O— (e.g., methoxy and ethoxy), and an “alkylamino” which, as used herein, refers to —N(alkyl) R^{N_a}, where R^{N_a} is H or alkyl (e.g., methylamino). A “heteroalkylene” is a divalent heteroalkyl group.

The term “heteroalkenyl,” as used herein, refers to an alkenyl group, as defined herein, in which one or more of the constituent carbon atoms have been replaced by nitrogen, oxygen, or sulfur. In some embodiments, the heteroalkenyl group can be further substituted with 1, 2, 3, or 4 substituent groups as described herein for alkenyl groups. Examples of heteroalkenyl groups are an “alkenoxy” which, as used herein, refers to alkenyl-O—. A “heteroalkenylene” is a divalent heteroalkenyl group.

The term “heteroalkynyl,” as used herein, refers to an alkynyl group, as defined herein, in which one or more of the constituent carbon atoms have been replaced by nitrogen, oxygen, or sulfur. In some embodiments, the heteroalkynyl group can be further substituted with 1, 2, 3, or 4 substituent groups as described herein for alkynyl groups. Examples of heteroalkynyl groups are an “alkynoxy” which, as used herein, refers to alkynyl-O—. A “heteroalkynylene” is a divalent heteroalkynyl group.

The term “heteroaryl,” as used herein, refers to an aromatic monocyclic or polycyclic structure of 5 to 12 atoms having at least one aromatic ring containing 1, 2, or 3 ring atoms selected from nitrogen, oxygen, and sulfur, with the remaining ring atoms being carbon. One or two ring carbon atoms of the heteroaryl group may be replaced with a carbonyl group. Examples of heteroaryl groups are pyridyl, pyrazoyl, benzoxazolyl, benzoimidazolyl, benzothiazolyl, imidazolyl, oxazolyl, and thiazolyl. A “heteroarylene” is a divalent heteroaryl group.

The term “heteroarylalkyl,” as used herein, represents an alkyl group substituted with a heteroaryl group. Exemplary unsubstituted heteroarylalkyl groups are from 7 to 30 carbons (e.g., from 7 to 16 or from 7 to 20 carbons, such as C₁-C₆ alkyl C₂-C₉ heteroaryl, C₁-C₁₀ alkyl C₂-C₉ heteroaryl, or C₁-C₂₀ alkyl C₂-C₉ heteroaryl). In some embodiments, the alkyl and the heteroaryl each can be further substituted with 1, 2, 3, or 4 substituent groups as defined herein for the respective groups.

The term “heterocyclyl,” as used herein, refers a monocyclic or polycyclic radical (e.g., bicyclic or tricyclic) having 3 to 12 atoms having at least one non-aromatic ring containing 1, 2, 3, or 4 ring atoms selected from N, O, or S, and no aromatic ring containing any N, O, or S atoms. Polycyclic heterocyclyl includes spirocyclic heterocyclyl, bridged heterocyclyl, and fused heterocyclyl. Examples of heterocyclyl groups include, but are not limited to, morpholinyl, thiomorpholinyl, furyl, piperazinyl, piperidinyl, pyranyl, pyrrolidinyl, tetrahydropyranyl, tetrahydrofuranyl, and 1,3-dioxanyl. A “heterocyclylene” is a divalent heterocyclyl group.

The term “heterocyclylalkyl,” as used herein, represents an alkyl group substituted with a heterocyclyl group. Exemplary unsubstituted heterocyclylalkyl groups are from 7 to 30 carbons (e.g., from 7 to 16 or from 7 to 20 carbons, such as C₁-C₆ alkyl C₂-C₉ heterocyclyl, C₁-C₁₀ alkyl C₂-C₉ heterocyclyl, or C₁-C₂₀ alkyl C₂-C₉ heterocyclyl). In some embodiments, the alkyl and the heterocyclyl each can be further substituted with 1, 2, 3, or 4 substituent groups as defined herein for the respective groups.

The term “hydroxalkyl,” as used herein, represents alkyl group substituted with an —OH group.

The term “hydroxyl,” as used herein, represents an —OH group.

The term “imine,” as used herein, represents =NR^{N_v} group, where R^{N_v} is, e.g., H or alkyl.

The term “N-protecting group,” as used herein, represents those groups intended to protect an amino group against undesirable reactions during synthetic procedures. Commonly used N-protecting groups are disclosed in Greene, “Protective Groups in Organic Synthesis,” 3rd Edition (John Wiley & Sons, New York, 1999). N-protecting groups include, but are not limited to, acyl, aryloyl, or carbamyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, phthalyl, o-nitrophenoxyacetyl, α -chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and chiral auxiliaries such as protected or unprotected D, L, or D, L-amino acids such as alanine, leucine, and phenylalanine; sulfonyl-containing groups such as benzenesulfonyl, and p-toluenesulfonyl; carbamate forming groups such as benzyloxycarbonyl, p-chlorobenzylloxycarbonyl, p-methoxybenzylloxycarbonyl, p-nitrobenzylloxycarbonyl, 2-nitrobenzylloxycarbonyl, p-bromobenzylloxycarbonyl, 3,4-dimethoxybenzylloxycarbonyl, 3,5-dimethoxybenzylloxycarbonyl, 2,4-20 dimethoxybenzylloxycarbonyl, 4-methoxybenzylloxycarbonyl, 2-nitro-4,5-dimethoxybenzylloxycarbonyl, 3,4,5-trimethoxybenzylloxycarbonyl, 1-(p-biphenyl)-1-methylmethoxycarbonyl, α,α -dimethyl-3,5-dimethoxybenzylloxycarbonyl, benzhydryloxy carbonyl, t-butyloxycarbonyl, diisopropylmethoxycarbonyl, isopropylloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, phenoxy carbonyl, 4-nitrophenoxy carbonyl, fluorenyl-9-methoxycarbonyl, cyclopentyloxycarbonyl, adamantlyloxycarbonyl, cyclohexyloxycarbonyl, and phenylthiocarbonyl, arylalkyl groups such as benzyl, triphenylmethyl, and benzyloxymethyl, and silyl groups, such as trimethylsilyl. Preferred N-protecting groups are alloc, formyl, acetyl, benzoyl, pivaloyl, t-butylacetyl, alanyl, phenylsulfonyl, benzyl, t-butylcarbonyl (Boc), and benzyloxycarbonyl (Cbz).

The term “nitro,” as used herein, represents an —NO₂ group.

The term “oxo,” as used herein, represents an =O group.

The term “thiol,” as used herein, represents an —SH group.

The alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl (e.g., cycloalkyl), aryl, heteroaryl, and heterocyclyl groups may be substituted or unsubstituted. When substituted, there will generally be 1 to 4 substituents present, unless otherwise specified. Substituents include, for example: alkyl (e.g., unsubstituted and substituted, where the substituents include any group described herein, e.g., aryl, halo, hydroxy), aryl (e.g., substituted and unsubstituted phenyl), carbocyclyl (e.g., substituted and unsubstituted cycloalkyl), halogen (e.g., fluoro), hydroxyl, heteroalkyl (e.g., substituted and unsubstituted methoxy, ethoxy, or thioalkoxy), heteroaryl, heterocyclyl, amino (e.g., NH₂ or mono- or dialkyl amino), azido, cyano, nitro, oxo, sulfonyl, or thiol. Aryl, carbocyclyl (e.g., cycloalkyl), heteroaryl, and heterocyclyl groups may also be substituted with alkyl (unsubstituted and substituted such as arylalkyl (e.g., substituted and unsubstituted benzyl)).

Compounds described herein (e.g., compounds of the invention) can have one or more asymmetric carbon atoms and can exist in the form of optically pure enantiomers, mixtures of enantiomers such as, for example, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, or mixtures of diastereoisomeric racemates. The optically active forms can be

obtained for example by resolution of the racemates, by asymmetric synthesis or asymmetric chromatography (chromatography with a chiral adsorbent or eluant). That is, certain of the disclosed compounds may exist in various stereoisomeric forms. Stereoisomers are compounds that differ only in their spatial arrangement. Enantiomers are pairs of stereoisomers whose mirror images are not superimposable, most commonly because they contain an asymmetrically substituted carbon atom that acts as a chiral center. "Enantiomer" means one of a pair of molecules that are mirror images of each other and are not superimposable. Diastereomers are stereoisomers that are not related as mirror images, most commonly because they contain two or more asymmetrically substituted carbon atoms and represent the configuration of substituents around one or more chiral carbon atoms. Enantiomers of a compound can be prepared, for example, by separating an enantiomer from a racemate using one or more well-known techniques and methods, such as, for example, chiral chromatography and separation methods based thereon. The appropriate technique and/or method for separating an enantiomer of a compound described herein from a racemic mixture can be readily determined by those of skill in the art. "Racemate" or "racemic mixture" means a compound containing two enantiomers, wherein such mixtures exhibit no optical activity; i.e., they do not rotate the plane of polarized light. "Geometric isomer" means isomers that differ in the orientation of substituent atoms in relationship to a carbon-carbon double bond, to a cycloalkyl ring, or to a bridged bicyclic system. Atoms (other than H) on each side of a carbon-carbon double bond may be in an E (substituents are on opposite sides of the carbon-carbon double bond) or Z (substituents are oriented on the same side) configuration. "R," "S," "S*," "R*," "E," "Z," "cis," and "trans," indicate configurations relative to the core molecule. Certain of the disclosed compounds may exist in atropisomeric forms. Atropisomers are stereoisomers resulting from hindered rotation about single bonds where the steric strain barrier to rotation is high enough to allow for the isolation of the conformers. The compounds described herein (e.g., the compounds of the invention) may be prepared as individual isomers by either isomer-specific synthesis or resolved from an isomeric mixture. Conventional resolution techniques include forming the salt of a free base of each isomer of an isomeric pair using an optically active acid (followed by fractional crystallization and regeneration of the free base), forming the salt of the acid form of each isomer of an isomeric pair using an optically active amine (followed by fractional crystallization and regeneration of the free acid), forming an ester or amide of each of the isomers of an isomeric pair using an optically pure acid, amine or alcohol (followed by chromatographic separation and removal of the chiral auxiliary), or resolving an isomeric mixture of either a starting material or a final product using various well known chromatographic methods. When the stereochemistry of a disclosed compound is named or depicted by structure, the named or depicted stereoisomer is at least 60%, 70%, 80%, 90%, 99%, or 99.9% by weight relative to the other stereoisomers. When a single enantiomer is named or depicted by structure, the depicted or named enantiomer is at least 60%, 70%, 80%, 90%, 99%, or 99.9% by weight optically pure. When a single diastereomer is named or depicted by structure, the depicted or named diastereomer is at least 60%, 70%, 80%, 90%, 99%, or 99.9% by weight pure. Percent optical purity is the ratio of the weight of the enantiomer or over the weight of the enantiomer plus the weight of its optical isomer. Diastereomeric purity by weight

is the ratio of the weight of one diastereomer or over the weight of all the diastereomers. When the stereochemistry of a disclosed compound is named or depicted by structure, the named or depicted stereoisomer is at least 60%, 70%, 80%, 90%, 99%, or 99.9% by mole fraction pure relative to the other stereoisomers. When a single enantiomer is named or depicted by structure, the depicted or named enantiomer is at least 60%, 70%, 80%, 90%, 99%, or 99.9% by mole fraction pure. When a single diastereomer is named or depicted by structure, the depicted or named diastereomer is at least 60%, 70%, 80%, 90%, 99%, or 99.9% by mole fraction pure. Percent purity by mole fraction is the ratio of the moles of the enantiomer or over the moles of the enantiomer plus the moles of its optical isomer. Similarly, percent purity by moles fraction is the ratio of the moles of the diastereomer or over the moles of the diastereomer plus the moles of its isomer. When a disclosed compound is named or depicted by structure without indicating the stereochemistry, and the compound has at least one chiral center, it is to be understood that the name or structure encompasses either enantiomer of the compound free from the corresponding optical isomer, a racemic mixture of the compound, or mixtures enriched in one enantiomer relative to its corresponding optical isomer. When a disclosed compound is named or depicted by structure without indicating the stereochemistry and has two or more chiral centers, it is to be understood that the name or structure encompasses a diastereomer free of other diastereomers, a number of diastereomers free from other diastereomeric pairs, mixtures of diastereomers, mixtures of diastereomeric pairs, mixtures of diastereomers in which one diastereomer is enriched relative to the other diastereomer(s), or mixtures of diastereomers in which one or more diastereomer is enriched relative to the other diastereomers. The invention embraces all of these forms.

Compounds of the present disclosure also include all of the isotopes of the atoms occurring in the intermediate or final compounds. "Isotopes" refers to atoms having the same atomic number but different mass numbers resulting from a different number of neutrons in the nuclei. For example, isotopes of hydrogen include tritium and deuterium.

Unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. Exemplary isotopes that can be incorporated into compounds of the present invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, chlorine, and iodine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{13}N , ^{15}N , ^{15}O , ^{17}O , ^{18}O , ^{32}P , ^{33}P , ^{35}S , ^{18}F , ^{36}Cl , ^{123}I and ^{125}I . Isotopically-labeled compounds (e.g., those labeled with ^3H and ^{14}C) can be useful in compound or substrate tissue distribution assays. Tritiated (i.e., ^3H) and carbon-14 (i.e., ^{14}C) isotopes can be useful for their ease of preparation and detectability.

Further, substitution with heavier isotopes such as deuterium (i.e., ^2H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements). In some embodiments, one or more hydrogen atoms are replaced by ^2H or ^3H , or one or more carbon atoms are replaced by ^{13}C - or ^{14}C -enriched carbon. Positron emitting isotopes such as ^{15}O , ^{13}N , ^{11}C , and ^{18}F are useful for positron emission tomography (PET) studies to examine substrate receptor occupancy. Preparations of isotopically labelled compounds are known to those of skill in the art. For example, isotopically labeled compounds can generally be prepared by following procedures analogous to those disclosed for compounds of

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the present invention described herein, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

As is known in the art, many chemical entities can adopt a variety of different solid forms such as, for example, amorphous forms or crystalline forms (e.g., polymorphs, hydrates, solvate). In some embodiments, compounds of the present invention may be utilized in any such form, including in any solid form. In some embodiments, compounds described or depicted herein may be provided or utilized in hydrate or solvate form.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Methods and materials are described herein for use in the present disclosure; other, suitable methods and materials known in the art can also be used. The materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control.

Definitions

In this application, unless otherwise clear from context, (i) the term "a" may be understood to mean "at least one"; (ii) the term "or" may be understood to mean "and/or"; and (iii) the terms "including" and "including" may be understood to encompass itemized components or steps whether presented by themselves or together with one or more additional components or steps.

As used herein, the terms "about" and "approximately" refer to a value that is within 10% above or below the value being described. For example, the term "about 5 nM" indicates a range of from 4.5 to 5.5 nM.

As used herein, the term "administration" refers to the administration of a composition (e.g., a compound or a preparation that includes a compound as described herein) to a subject or system. Administration to an animal subject (e.g., to a human) may be by any appropriate route. For example, in some embodiments, administration may be bronchial (including by bronchial instillation), buccal, enteral, interdermal, intra-arterial, intradermal, intragastric, intramedullary, intramuscular, intranasal, intraperitoneal, intrathecal, intratumoral, intravenous, intraventricular, mucosal, nasal, oral, rectal, subcutaneous, sublingual, topical, tracheal (including by intratracheal instillation), transdermal, vaginal, and vitreal.

As used herein, the term "adult soft tissue sarcoma" refers to a sarcoma that develops in the soft tissues of the body, typically in adolescent and adult subjects (e.g., subjects who are at least 10 years old, 11 years old, 12 years old, 13 years old, 14 years old, 15 years old, 16 years old, 17 years old, 18 years old, or 19 years old). Non-limiting examples of adult soft tissue sarcoma include, but are not limited to, synovial sarcoma, fibrosarcoma, malignant fibrous histiocytoma, dermatofibrosarcoma, liposarcoma, leiomyosarcoma, hemangiosarcoma, Kaposi's sarcoma, lymphangiosarcoma, malignant peripheral nerve sheath tumor/neurofibrosarcoma, extraskeletal chondrosarcoma, extraskeletal osteosarcoma, extraskeletal myxoid chondrosarcoma, and extraskeletal mesenchymal.

The term "antisense," as used herein, refers to a nucleic acid comprising a polynucleotide that is sufficiently complementary to all or a portion of a gene, primary transcript, or

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processed mRNA, so as to interfere with expression of the endogenous gene (e.g., BRD9). "Complementary" polynucleotides are those that are capable of base pairing according to the standard Watson-Crick complementarity rules.

Specifically, purines will base pair with pyrimidines to form a combination of guanine paired with cytosine (G:C) and adenine paired with either thymine (A:T) in the case of DNA, or adenine paired with uracil (A:U) in the case of RNA. It is understood that two polynucleotides may hybridize to each other even if they are not completely complementary to each other, provided that each has at least one region that is substantially complementary to the other.

The term "antisense nucleic acid" includes single-stranded RNA as well as double-stranded DNA expression cassettes that can be transcribed to produce an antisense RNA. "Active" antisense nucleic acids are antisense RNA molecules that are capable of selectively hybridizing with a primary transcript or mRNA encoding a polypeptide having at least 80% sequence identity (e.g., 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.9% identity, or more) with the targeted polypeptide sequence (e.g., a BRD9 polypeptide sequence). The antisense nucleic acid can be complementary to an entire coding strand, or to only a portion thereof. In some embodiments, an antisense nucleic acid molecule is antisense to a "coding region" of the coding strand of a nucleotide sequence. The term "coding region" refers to the region of the nucleotide sequence comprising codons that are translated into amino acid residues. In some embodiments, the antisense nucleic acid molecule is antisense to a "noncoding region" of the coding strand of a nucleotide sequence. The term "noncoding region" refers to 5' and 3' sequences that flank the coding region that are not translated into amino acids (i.e., also referred to as 5' and 3' untranslated regions). The antisense nucleic acid molecule can be complementary to the entire coding region of mRNA, or can be antisense to only a portion of the coding or noncoding region of an mRNA. For example, the antisense oligonucleotide can be complementary to the region surrounding the translation start site. An antisense oligonucleotide can be, for example, about 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50 nucleotides in length.

As used herein, the term "BAF complex" refers to the BRG1- or HRBM-associated factors complex in a human cell.

As used herein, the term "BAF complex-related disorder" refers to a disorder that is caused or affected by the level and/or activity of a BAF complex.

As used herein, the terms "GBAF complex" and "GBAF" refer to a SWI/SNF ATPase chromatin remodeling complex in a human cell. GBAF complex subunits may include, but are not limited to, ACTB, ACTL6A, ACTL6B, BICRA, BICRAL, BRD9, SMARCA2, SMARCA4, SMARCC1, SMARCD1, SMARCD2, SMARCD3, and SS18. The term "cancer" refers to a condition caused by the proliferation of malignant neoplastic cells, such as tumors, neoplasms, carcinomas, sarcomas, leukemias, and lymphomas.

As used herein, the term "BRD9" refers to bromodomain-containing protein 9, a component of the BAF (BRG1- or BRM-associated factors) complex, a SWI/SNF ATPase chromatin remodeling complex, and belongs to family IV of the bromodomain-containing proteins. BRD9 is encoded by the BRD9 gene, the nucleic acid sequence of which is set forth in SEQ ID NO: 1. The term "BRD9" also refers to natural variants of the wild-type BRD9 protein, such as proteins having at least 85% identity (e.g., 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%,

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98%, 99%, 99.9% identity, or more) to the amino acid sequence of wild-type BRD9, which is set forth in SEQ ID NO: 2.

As used herein, the term “BRD9-related disorder” refers to a disorder that is caused or affected by the level and/or activity of BRD9. The term “cancer” refers to a condition caused by the proliferation of malignant neoplastic cells, such as tumors, neoplasms, carcinomas, sarcomas, leukemias, and lymphomas.

As used herein, a “combination therapy” or “administered in combination” means that two (or more) different agents or treatments are administered to a subject as part of a defined treatment regimen for a particular disease or condition. The treatment regimen defines the doses and periodicity of administration of each agent such that the effects of the separate agents on the subject overlap. In some embodiments, the delivery of the two or more agents is simultaneous or concurrent and the agents may be co-formulated. In some embodiments, the two or more agents are not co-formulated and are administered in a sequential manner as part of a prescribed regimen. In some embodiments, administration of two or more agents or treatments in combination is such that the reduction in a symptom, or other parameter related to the disorder is greater than what would be observed with one agent or treatment delivered alone or in the absence of the other. The effect of the two treatments can be partially additive, wholly additive, or greater than additive (e.g., synergistic). Sequential or substantially simultaneous administration of each therapeutic agent can be effected by any appropriate route including, but not limited to, oral routes, intravenous routes, intramuscular routes, and direct absorption through mucous membrane tissues. The therapeutic agents can be administered by the same route or by different routes. For example, a first therapeutic agent of the combination may be administered by intravenous injection while a second therapeutic agent of the combination may be administered orally.

A “compound of the present invention” and similar terms as used herein, whether explicitly noted or not, refers to compounds useful for treating BAF-related disorders (e.g., cancer or infection) described herein, including, e.g., compounds of Formula I or Formula II (e.g., compounds of Table 2A, Table 2B, and Table 2C), as well as salts (e.g., pharmaceutically acceptable salts), solvates, hydrates, stereoisomers (including atropisomers), and tautomers thereof. Those skilled in the art will appreciate that certain compounds described herein can exist in one or more different isomeric (e.g., stereoisomers, geometric isomers, atropisomers, and tautomers) or isotopic (e.g., in which one or more atoms has been substituted with a different isotope of the atom, such as hydrogen substituted for deuterium) forms. Unless otherwise indicated or clear from context, a depicted structure can be understood to represent any such isomeric or isotopic form, individually or in combination. Compounds described herein can be asymmetric (e.g., having one or more stereocenters). All stereoisomers, such as enantiomers and diastereomers, are intended unless otherwise indicated. Compounds of the present disclosure that contain asymmetrically substituted carbon atoms can be isolated in optically active or racemic forms. Methods on how to prepare optically active forms from optically active starting materials are known in the art, such as by resolution of racemic mixtures or by stereoselective synthesis. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present disclosure. Cis and trans geometric isomers of the compounds of the present

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disclosure are described and may be isolated as a mixture of isomers or as separated isomeric forms. In some embodiments, one or more compounds depicted herein may exist in different tautomeric forms. As will be clear from context, unless explicitly excluded, references to such compounds encompass all such tautomeric forms. In some embodiments, tautomeric forms result from the swapping of a single bond with an adjacent double bond and the concomitant migration of a proton. In certain embodiments, a tautomeric form may be a prototropic tautomer, which is an isomeric protonation states having the same empirical formula and total charge as a reference form. Examples of moieties with prototropic tautomeric forms are ketone-enol pairs, amide-imidic acid pairs, lactam-lactim pairs, amide-imidic acid pairs, enamine-imine pairs, and annular forms where a proton can occupy two or more positions of a heterocyclic system, such as, 1H- and 3H-imidazole, 1H-, 2H- and 4H-1,2,4-triazole, 1H- and 2H-isoindole, and 1H- and 2H-pyrazole. In some embodiments, tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution. In certain embodiments, tautomeric forms result from acetal interconversion.

As used herein, the term “degrader” refers to a small molecule compound including a degradation moiety, wherein the compound interacts with a protein (e.g., BRD9) in a way which results in degradation of the protein, e.g., binding of the compound results in at least 5% reduction of the level of the protein, e.g., in a cell or subject.

As used herein, the term “degradation moiety” refers to a moiety whose binding results in degradation of a protein, e.g., BRD9. In one example, the moiety binds to a protease or a ubiquitin ligase that metabolizes the protein, e.g., BRD9.

By “determining the level of a protein” is meant the detection of a protein, or an mRNA encoding the protein, by methods known in the art either directly or indirectly. “Directly determining” means performing a process (e.g., performing an assay or test on a sample or “analyzing a sample” as that term is defined herein) to obtain the physical entity or value. “Indirectly determining” refers to receiving the physical entity or value from another party or source (e.g., a third-party laboratory that directly acquired the physical entity or value). Methods to measure protein level generally include, but are not limited to, western blotting, immunoblotting, enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), immunoprecipitation, immunofluorescence, surface plasmon resonance, chemiluminescence, fluorescent polarization, phosphorescence, immunohistochemical analysis, matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry, liquid chromatography (LC)-mass spectrometry, microcytometry, microscopy, fluorescence activated cell sorting (FACS), and flow cytometry, as well as assays based on a property of a protein including, but not limited to, enzymatic activity or interaction with other protein partners. Methods to measure mRNA levels are known in the art.

As used herein, the terms “effective amount,” “therapeutically effective amount,” and “a “sufficient amount” of an agent that reduces the level and/or activity of BRD9 (e.g., in a cell or a subject) described herein refer to a quantity sufficient to, when administered to the subject, including a human, effect beneficial or desired results, including clinical results, and, as such, an “effective amount” or synonym thereto depends on the context in which it is being applied. For example, in the context of treating cancer, it is an amount of the agent that reduces the level and/or activity of BRD9 sufficient to achieve a treatment response as com-

pared to the response obtained without administration of the agent that reduces the level and/or activity of BRD9. The amount of a given agent that reduces the level and/or activity of BRD9 described herein that will correspond to such an amount will vary depending upon various factors, such as the given agent, the pharmaceutical formulation, the route of administration, the type of disease or disorder, the identity of the subject (e.g., age, sex, and/or weight) or host being treated, and the like, but can nevertheless be routinely determined by one of skill in the art. Also, as used herein, a "therapeutically effective amount" of an agent that reduces the level and/or activity of BRD9 of the present disclosure is an amount which results in a beneficial or desired result in a subject as compared to a control. As defined herein, a therapeutically effective amount of an agent that reduces the level and/or activity of BRD9 of the present disclosure may be readily determined by one of ordinary skill by routine methods known in the art. Dosage regimen may be adjusted to provide the optimum therapeutic response.

As used herein, the term "inhibitor" refers to any agent which reduces the level and/or activity of a protein (e.g., BRD9). Non-limiting examples of inhibitors include small molecule inhibitors, degraders, antibodies, enzymes, or polynucleotides (e.g., siRNA).

The term "inhibitory RNA agent" refers to an RNA, or analog thereof, having sufficient sequence complementarity to a target RNA to direct RNA interference. Examples also include a DNA that can be used to make the RNA. RNA interference (RNAi) refers to a sequence-specific or selective process by which a target molecule (e.g., a target gene, protein, or RNA) is down-regulated. Generally, an interfering RNA ("iRNA") is a double-stranded short-interfering RNA (siRNA), short hairpin RNA (shRNA), or single-stranded micro-RNA (miRNA) that results in catalytic degradation of specific mRNAs, and also can be used to lower or inhibit gene expression.

By "level" is meant a level of a protein, or mRNA encoding the protein, as compared to a reference. The reference can be any useful reference, as defined herein. By a "decreased level" or an "increased level" of a protein is meant a decrease or increase in protein level, as compared to a reference (e.g., a decrease or an increase by about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 100%, about 150%, about 200%, about 300%, about 400%, about 500%, or more; a decrease or an increase of more than about 10%, about 15%, about 20%, about 50%, about 75%, about 100%, or about 200%, as compared to a reference; a decrease or an increase by less than about 0.01-fold, about 0.02-fold, about 0.1-fold, about 0.3-fold, about 0.5-fold, about 0.8-fold, or less; or an increase by more than about 1.2-fold, about 1.4-fold, about 1.5-fold, about 1.8-fold, about 2.0-fold, about 3.0-fold, about 3.5-fold, about 4.5-fold, about 5.0-fold, about 10-fold, about 15-fold, about 20-fold, about 30-fold, about 40-fold, about 50-fold, about 100-fold, about 1000-fold, or more). A level of a protein may be expressed in mass/vol (e.g., g/dL, mg/mL, μ g/mL, ng/mL) or percentage relative to total protein or mRNA in a sample.

The terms "miRNA" and "microRNA" refer to an RNA agent, preferably a single-stranded agent, of about 10-50 nucleotides in length, preferably between about 15-25 nucleotides in length, which is capable of directing or mediating RNA interference. Naturally-occurring miRNAs are generated from stem-loop precursor RNAs (i.e., pre-miRNAs) by Dicer. The term "Dicer" as used herein,

includes Dicer as well as any Dicer ortholog or homolog capable of processing dsRNA structures into siRNAs, miRNAs, siRNA-like or miRNA-like molecules. The term microRNA ("miRNA") is used interchangeably with the term "small temporal RNA" ("stRNA") based on the fact that naturally-occurring miRNAs have been found to be expressed in a temporal fashion (e.g., during development).

By "modulating the activity of a BAF complex," is meant altering the level of an activity related to a BAF complex (e.g., GBAF), or a related downstream effect. The activity level of a BAF complex may be measured using any method known in the art, e.g., the methods described in Kadoch et al, Cell 153:71-85 (2013), the methods of which are herein incorporated by reference.

"Percent (%) sequence identity" with respect to a reference polynucleotide or polypeptide sequence is defined as the percentage of nucleic acids or amino acids in a candidate sequence that are identical to the nucleic acids or amino acids in the reference polynucleotide or polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity. Alignment for purposes of determining percent nucleic acid or amino acid sequence identity can be achieved in various ways that are within the capabilities of one of skill in the art, for example, using publicly available computer software such as BLAST, BLAST-2, or Megalign software. Those skilled in the art can determine appropriate parameters for aligning sequences, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared. For example, percent sequence identity values may be generated using the sequence comparison computer program BLAST. As an illustration, the percent sequence identity of a given nucleic acid or amino acid sequence, A, to, with, or against a given nucleic acid or amino acid sequence, B, (which can alternatively be phrased as a given nucleic acid or amino acid sequence, A that has a certain percent sequence identity to, with, or against a given nucleic acid or amino acid sequence, B) is calculated as follows:

$$100 \text{ multiplied by } (\text{the fraction } X/Y)$$

where X is the number of nucleotides or amino acids scored as identical matches by a sequence alignment program (e.g., BLAST) in that program's alignment of A and B, and where Y is the total number of nucleic acids in B. It will be appreciated that where the length of nucleic acid or amino acid sequence A is not equal to the length of nucleic acid or amino acid sequence B, the percent sequence identity of A to B will not equal the percent sequence identity of B to A.

A "pharmaceutically acceptable excipient," as used herein, refers any ingredient other than the compounds described herein (for example, a vehicle capable of suspending or dissolving the active compound) and having the properties of being substantially nontoxic and non-inflammatory in a patient. Excipients may include, for example: antiadherents, antioxidants, binders, coatings, compression aids, disintegrants, dyes (colors), emollients, emulsifiers, fillers (diluents), film formers or coatings, flavors, fragrances, glidants (flow enhancers), lubricants, preservatives, printing inks, sorbents, suspending or dispersing agents, sweeteners, and waters of hydration. Exemplary excipients include, but are not limited to: butylated hydroxytoluene (BHT), calcium carbonate, calcium phosphate (dibasic), calcium stearate, croscarmellose, crosslinked polyvinyl pyrrolidone, citric acid, crospovidone, cysteine, ethylcellulose, gelatin, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, maltitol, mannitol,

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methionine, methylcellulose, methyl paraben, microcrystalline cellulose, polyethylene glycol, polyvinyl pyrrolidone, povidone, pregelatinized starch, propyl paraben, retinyl palmitate, shellac, silicon dioxide, sodium carboxymethyl cellulose, sodium citrate, sodium starch glycolate, sorbitol, starch (corn), stearic acid, sucrose, talc, titanium dioxide, vitamin A, vitamin E, vitamin C, and xylitol.

As used herein, the term “pharmaceutically acceptable salt” means any pharmaceutically acceptable salt of the compound of any of the compounds described herein. For example, pharmaceutically acceptable salts of any of the compounds described herein include those that are within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and animals without undue toxicity, irritation, allergic response and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, pharmaceutically acceptable salts are described in: Berge et al., *J. Pharmaceutical Sciences* 66:1-19, 1977 and in *Pharmaceutical Salts: Properties, Selection, and Use*, (Eds. P. H. Stahl and C. G. Wermuth), Wiley-VCH, 2008. The salts can be prepared in situ during the final isolation and purification of the compounds described herein or separately by reacting a free base group with a suitable organic acid.

The compounds described herein may have ionizable groups so as to be capable of preparation as pharmaceutically acceptable salts. These salts may be acid addition salts involving inorganic or organic acids or the salts may, in the case of acidic forms of the compounds described herein, be prepared from inorganic or organic bases. Frequently, the compounds are prepared or used as pharmaceutically acceptable salts prepared as addition products of pharmaceutically acceptable acids or bases. Suitable pharmaceutically acceptable acids and bases and methods for preparation of the appropriate salts are well-known in the art. Salts may be prepared from pharmaceutically acceptable non-toxic acids and bases including inorganic and organic acids and bases. Representative acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptonate, glycerophosphate, hemisulfate, heptone, hexanoate, hydrobromide, hydrochloride, hydroiodide, 2-hydroxyethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, toluenesulfonate, undecanoate, and valerate salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, and magnesium, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, and ethylamine.

The term “pharmaceutical composition,” as used herein, represents a composition containing a compound described herein formulated with a pharmaceutically acceptable excipient, and manufactured or sold with the approval of a governmental regulatory agency as part of a therapeutic regimen for the treatment of disease in a mammal. Pharmaceutical compositions can be formulated, for example, for oral administration in unit dosage form (e.g., a tablet, capsule, caplet, gelcap, or syrup); for topical administration (e.g., as a cream, gel, lotion, or ointment); for intravenous

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administration (e.g., as a sterile solution free of particulate emboli and in a solvent system suitable for intravenous use); or in any other pharmaceutically acceptable formulation.

By “reducing the activity of BRD9,” is meant decreasing the level of an activity related to an BRD9, or a related downstream effect. A non-limiting example of inhibition of an activity of BRD9 is decreasing the level of a BAF complex (e.g., GBAF) in a cell. The activity level of BRD9 may be measured using any method known in the art. In some embodiments, an agent which reduces the activity of BRD9 is a small molecule BRD9 inhibitor. In some embodiments, an agent which reduces the activity of BRD9 is a small molecule BRD9 degrader.

By “reducing the level of BRD9,” is meant decreasing the level of BRD9 in a cell or subject. The level of BRD9 may be measured using any method known in the art.

By a “reference” is meant any useful reference used to compare protein or mRNA levels. The reference can be any sample, standard, standard curve, or level that is used for comparison purposes. The reference can be a normal reference sample or a reference standard or level. A “reference sample” can be, for example, a control, e.g., a predetermined negative control value such as a “normal control” or a prior sample taken from the same subject; a sample from a normal healthy subject, such as a normal cell or normal tissue; a sample (e.g., a cell or tissue) from a subject not having a disease; a sample from a subject that is diagnosed with a disease, but not yet treated with a compound described herein; a sample from a subject that has been treated by a compound described herein; or a sample of a purified protein (e.g., any described herein) at a known normal concentration. By “reference standard or level” is meant a value or number derived from a reference sample. A “normal control value” is a pre-determined value indicative of non-disease state, e.g., a value expected in a healthy control subject. Typically, a normal control value is expressed as a range (“between X and Y”), a high threshold (“no higher than X”), or a low threshold (“no lower than X”). A subject having a measured value within the normal control value for a particular biomarker is typically referred to as “within normal limits” for that biomarker. A normal reference standard or level can be a value or number derived from a normal subject not having a disease or disorder (e.g., cancer); a subject that has been treated with a compound described herein. In preferred embodiments, the reference sample, standard, or level is matched to the sample subject sample by at least one of the following criteria: age, weight, sex, disease stage, and overall health. A standard curve of levels of a purified protein, e.g., any described herein, within the normal reference range can also be used as a reference.

The terms “short interfering RNA” and “siRNA” (also known as “small interfering RNAs”) refer to an RNA agent, preferably a double-stranded agent, of about 10-50 nucleotides in length, the strands optionally having overhanging ends comprising, for example 1, 2 or 3 overhanging nucleotides (or nucleotide analogs), which is capable of directing or mediating RNA interference. Naturally-occurring siRNAs are generated from longer dsRNA molecules (e.g., >25 nucleotides in length) by a cell’s RNAi machinery (e.g., Dicer or a homolog thereof).

The term “shRNA”, as used herein, refers to an RNA agent having a stem-loop structure, comprising a first and second region of complementary sequence, the degree of complementarity and orientation of the regions being sufficient such that base pairing occurs between the regions, the first and second regions being joined by a loop region, the

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loop resulting from a lack of base pairing between nucleotides (or nucleotide analogs) within the loop region.

As used herein, the term "subject" refers to any organism to which a composition in accordance with the invention may be administered, e.g., for experimental, diagnostic, prophylactic, and/or therapeutic purposes. Typical subjects include any animal (e.g., mammals such as mice, rats, rabbits, non-human primates, and humans). A subject may seek or be in need of treatment, require treatment, be receiving treatment, be receiving treatment in the future, or be a human or animal who is under care by a trained professional for a particular disease or condition.

As used herein, the term "SS18-SSX fusion protein-related disorder" refers to a disorder that is caused or affected by the level and/or activity of SS18-SSX fusion protein.

As used herein, the terms "treat," "treated," or "treating" mean both therapeutic treatment and prophylactic or preventative measures wherein the object is to prevent or slow down (lessen) an undesired physiological condition, disorder, or disease, or obtain beneficial or desired clinical results. Beneficial or desired clinical results include, but are not limited to, alleviation of symptoms; diminishment of the extent of a condition, disorder, or disease; stabilized (i.e., not worsening) state of condition, disorder, or disease; delay in onset or slowing of condition, disorder, or disease progression; amelioration of the condition, disorder, or disease state or remission (whether partial or total), whether detectable or undetectable; an amelioration of at least one measurable physical parameter, not necessarily discernible by the patient; or enhancement or improvement of condition, disorder, or disease. Treatment includes eliciting a clinically significant response without excessive levels of side effects. Treatment also includes prolonging survival as compared to expected survival if not receiving treatment.

As used herein, the terms "variant" and "derivative" are used interchangeably and refer to naturally-occurring, synthetic, and semi-synthetic analogues of a compound, peptide, protein, or other substance described herein. A variant or derivative of a compound, peptide, protein, or other substance described herein may retain or improve upon the biological activity of the original material.

The details of one or more embodiments of the invention are set forth in the description below. Other features, objects, and advantages of the invention will be apparent from the description and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a series of graphs illustrating the effect of specific guide RNA (sgRNA) targeting of the BRD9 BAF complex subunit on synovial sarcoma cell growth. The Y-axis indicated the dropout ratio. The X-axis indicates the nucleotide position of the BRD9 gene. The grey box indicates the range of the negative control sgRNAs in the screen. The SYO1 cell line carries SS18-SSX2 fusion protein. The breakpoint joining the N-terminal region of SS18 to the C-terminal region of SSX2 are indicated by the black lines in their respective panel. The linear protein sequence is shown with BRD9 PFAM domains annotated from the PFAM database.

FIG. 2 is an image illustrating dose dependent depletion of BRD9 levels in a synovial sarcoma cell line (SYO1) in the presence of a BRD9 degrader.

FIG. 3 is an image illustrating sustained suppression of BRD9 levels in a synovial sarcoma cell line (SYO1) in the presence of a BRD9 degrader over 72 hours.

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FIG. 4 is an image illustrating sustained suppression of BRD9 levels in two cell lines (293T and SYO1) in the presence of a BRD9 degrader over 5 days.

FIG. 5 is an image illustrating sustained suppression of BRD9 levels in synovial sarcoma cell lines (SYO1 and Yamato) in the presence of a BRD9 degrader over 7 days compared to the levels in cells treated with CRISPR reagents.

FIG. 6 is an image illustrating the effect on cell growth of six cell lines (SYO1, Yamato, A549, HS-SY-II, ASKA, and 10 293T) in the presence of a BRD9 degrader and a BRD9 inhibitor.

FIG. 7 is an image illustrating the effect on cell growth of two cell lines (SYO1 and G401) in the presence of a BRD9 degrader.

FIG. 8 is an image illustrating the effect on cell growth of three synovial sarcoma cell lines (SYO1, HS-SY-II, and ASKA) in the presence of a BRD9 degrader, BRD9 binder 20 and E3 ligase binder.

FIG. 9 is an image illustrating the effect on cell growth of three non-synovial sarcoma cell lines (RD, HCT116, and Calu6) in the presence of a BRD9 degrader, BRD9 binder and E3 ligase binder.

FIG. 10 is a graph illustrating the percentage of SYO1 in various cell cycle phases following treatment with DMSO, Compound 1 at 200 nM, or Compound 1 at 1 μ M for 8 or 13 days.

FIG. 11 is a series of contour plots illustrating the percentage of SYO1 cells in various cell cycle phases following treatment with DMSO, Compound 1 at 200 nM, Compound 1 at 1 μ M, or lenalidomide at 200 nM for 8 days. Numerical values corresponding to each contour plot are found in the table below.

FIG. 12 is a series of contour plots illustrating the percentage of SYO1 cells in various cell cycle phases following treatment with DMSO, Compound 1 at 200 nM, Compound 1 at 1 μ M, or lenalidomide at 200 nM for 13 days. Numerical values corresponding to each contour plot are found in the table below.

FIG. 13 is a series of contour plots illustrating the percentage of early- and late-apoptotic SYO1 cells following treatment with DMSO, Compound 1 at 200 nM, Compound 1 at 1 μ M, or lenalidomide at 200 nM for 8 days. Numerical values corresponding to each contour plot are found in the table below.

FIG. 14 is a graph illustrating the proteins present in BAF complexes including the SS18-SSX fusion protein.

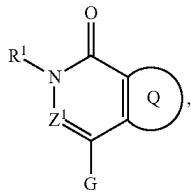
DETAILED DESCRIPTION

The present disclosure features compositions and methods useful for the treatment of BAF-related disorders (e.g., cancer and infection). The disclosure further features compositions and methods useful for inhibition of the level and/or activity of BRD9, e.g., for the treatment of disorders such as cancer (e.g., sarcoma) and infection (e.g., viral infection), e.g., in a subject in need thereof.

Compounds

Compounds described herein reduce the level of an activity related to BRD9, or a related downstream effect, or reduce the level of BRD9 in a cell or subject. Exemplary compounds described herein have the structure according to Formula I or Formula II.

Formula I is:

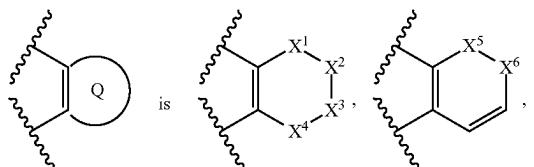


where

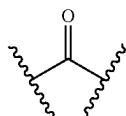
R¹ is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₁₀ carbocycl¹⁵ clyl;

Z¹ is CR² or N;

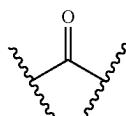
R² is H, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocycl²⁰ clyl, optionally substituted C₂-C₉ heterocycl²⁵ clyl, optionally substituted C₆-C₁₀ aryl, or optionally substituted C₂-C₉ heteroaryl;



X¹ is a bond, O, NR^{3a},

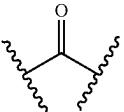


or CR^{4a}R^{5a};
X² is O, NR^{3b},

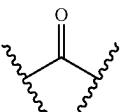


Formula I

or CR^{4b}R^{5b},
X³ is O, NR^{3c},



or CR^{4c}R^{5c};
X⁴ is a bond, O, NR^{3d},



or CR^{4d}R^{5d},
X⁵ is O or NR^{3e} and X⁶ is CR^{4f}R^{5f}, or X⁵ is CR^{4g}R^{5g} and X⁶ is O or NR^{3f},

X⁷ is O, NR^{3g}, or CR^{4h}R^{5g},

X⁸ is O, NR^{3h}, or CR^{4h}R^{5h},

each of R^{3a}, R^{3b}, R^{3c}, and R^{3d} is, independently, H, halogen, hydroxyl, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocycl²⁰ clyl, optionally substituted C₂-C₉ heterocycl²⁵ clyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, optionally substituted C₁-C₆ acyl, thiol, optionally substituted sulfone, optionally substituted sulfonamide, or optionally substituted amino, or R^{3a} and R^{4b}, R^{4a} and R^{3b}, R^{4b} and R^{4a}, R^{3b} and R^{4c}, R^{4b} and R^{4c}, R^{3c} and R^{4d}, R^{4c} and R^{4d}, and/or R^{3d} and R^{4c}, together with the atoms to which each is attached, combine to form optionally substituted C₂-C₉ heterocycl³⁰ clyl;

each of R^{4a}, R^{4b}, R^{4c}, and R^{4d} is, independently, H, halogen, hydroxyl, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocycl³⁵ clyl, optionally substituted C₂-C₉ heterocycl⁴⁰ clyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, optionally substituted C₁-C₆ acyl, thiol, optionally substituted sulfone, or optionally substituted amino, or R^{3a} and R^{4b}, R^{4a} and R^{3b}, R^{4b} and R^{4a}, R^{3b} and R^{4c}, R^{4b} and R^{4c}, R^{3c} and R^{4d}, R^{3c} and R^{4d}, and/or R^{3d} and R^{4c}, together with the atoms to which each is attached, combine to form optionally substituted C₂-C₉ heterocycl⁴⁵ clyl;

each of R^{5a}, R^{5b}, R^{5c}, and R^{5d} is, independently, H, halogen, hydroxyl, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocycl⁵⁰ clyl, optionally substituted C₂-C₉ heterocycl⁵⁵ clyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, hydroxyl, thiol, or optionally substituted amino;

each of R^{3e}, R^{3f}, R^{3g}, and R^{3h} is, independently, H, halogen, hydroxyl, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocycl⁶⁰ clyl, optionally substituted C₂-C₉ heterocycl⁶⁵ clyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, hydroxyl, thiol, or optionally substituted amino;

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heteroalkenyl, optionally substituted C_1-C_6 acyl, thiol, optionally substituted sulfone, optionally substituted sulfonamide, or optionally substituted amino, or R^{3e} and R^{4f} or R^{4e} and R^{3f} , together with the atoms to which each is attached, combine to form optionally substituted heterocyclycl;

each of R^{4e} , R^{4f} , R^{4g} , and R^{4h} is, independently, H, halogen, hydroxyl, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_1-C_6 acyl, thiol, optionally substituted sulfone, optionally substituted sulfonamide, or optionally substituted amino, or R^{3e} and R^{4f} or R^{4e} and R^{3f} , together with the atoms to which each is attached, combine to form optionally substituted heterocyclycl;

each of R^{5e} , R^{5f} , R^{5g} , and R^{5h} is, independently, H, halogen, hydroxyl, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, hydroxyl, thiol, or optionally substituted amino; and

G is optionally substituted C_6-C_{10} aryl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heteroaryl, or C_2-C_9 heterocyclyl, or a pharmaceutically acceptable salt thereof.

Formula II is:

A-L-B

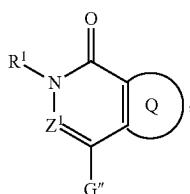
Formula II,

where

B is a degradation moiety,

L is a linker, and

A has the structure of Formula III:



where

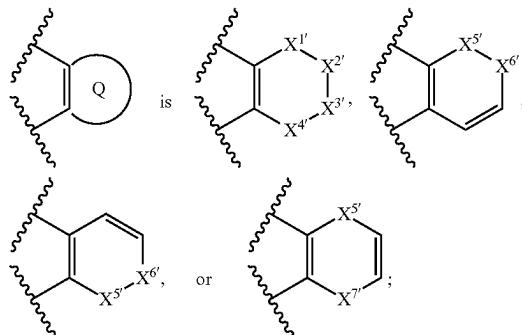
R^1 is H, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_3-C_{10} carbocyclyl;

Z^1 is CR^2 or N;

R^2 is H, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, or optionally substituted C_2-C_9 heteroaryl;

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X^{1t} is a bond, O, NR^{3a1} , or $CR^{4a1}R^{5a1}$;

X^{2t} is O, NR^{3b1} , or $CR^{4b1}R^{5b1}$;

X^{3t} is O, NR^{3c1} , or $CR^{4c1}R^{5c1}$;

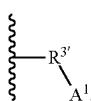
X^{4t} is a bond, O, NR^{3d1} , or $CR^{4d1}R^{5d1}$;

X^{5t} is O, NR^{3e1} , or $CR^{4e1}R^{5e1}$;

X^{6t} is O, NR^{3f1} , or $CR^{4f1}R^{5f1}$;

X^{7t} is O, NR^{3g1} , or $CR^{4g1}R^{5g1}$;

each of R^{3a1} , R^{3b1} , R^{3c1} , and R^{3d1} is, independently, H,



halogen, hydroxyl, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, optionally substituted C_1-C_6 acyl, thiol, optionally substituted sulfone, optionally substituted sulfonamide, or optionally substituted amino, or R^{3a1} and R^{4b1} , R^{4a1} and R^{3b1} , R^{4b1} and R^{4a1} , R^{3b1} and R^{4c1} , R^{4b1} and R^{4c1} , R^{3c1} and R^{4b1} , R^{3c1} and R^{4d1} , R^{4c1} and R^{4d1} , and/or R^{3d1} and R^{4c1} , together with the atoms to which each is attached, combine to form optionally substituted C_2-C_9 heterocyclyl;

R^{3t} is absent, optionally substituted C_1-C_6 alkylene, optionally substituted C_1-C_6 heteroalkylene, optionally substituted C_3-C_{10} carbocyclylene, optionally substituted C_2-C_9 heterocyclylene, optionally substituted C_6-C_{10} arylene, optionally substituted C_2-C_9 heteroarylene, optionally substituted C_2-C_6 alkenylene, optionally substituted C_2-C_6 heteroalkenylene, optionally substituted sulfone, optionally substituted sulfonamide, or optionally substituted amino;

each of R^{4a1} , R^{4b1} , R^{4c1} , and R^{4d1} is, independently, H, halogen, hydroxyl, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} carbocyclyl, optionally substituted C_2-C_9 heterocyclyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 heteroalkenyl, thiol, optionally substituted sulfone, or optionally substituted amino, or R^{3a1} and R^{4b1} , R^{4a1} and R^{3b1} , R^{4b1} and R^{4a1} , R^{3b1} and R^{4c1} , R^{4b1} and R^{4c1} , R^{3c1} and R^{4b1} , R^{3c1} and R^{4d1} , R^{4c1} and R^{4d1} , and/or R^{3d1} and R^{4c1} , together with the atoms to which each is attached, combine to form optionally substituted C_2-C_9 heterocyclyl;

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each of R^{5a}, R^{5b}, R^{5c}, and R^{5d} is, independently, H, halogen, hydroxyl, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, hydroxyl, thiol, or optionally substituted amino;

each of R^{3e}, R^{3f}, and R^{3g} is, independently, H,



halogen, hydroxyl, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, optionally substituted C₁-C₆ acyl, thiol, optionally substituted sulfone, optionally substituted sulfonamide, or optionally substituted amino, or R^{3e} and R^{4f} or R^{4e} and R^{3f}, together with the atoms to which each is attached, combine to form optionally substituted heterocyclyl;

each of R^{4e}, R^{4f}, and R^{4g} is, independently, H, halogen, hydroxyl, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, optionally substituted C₁-C₆ acyl, thiol, optionally substituted sulfone, optionally substituted sulfonamide, or optionally substituted amino, or R^{3e} and R^{4f} or R^{4e} and R^{3f}, together with the atoms to which each is attached, combine to form optionally substituted heterocyclyl;

each of R^{5e}, R^{5f}, and R^{5g} is, independently, H, halogen, hydroxyl, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, hydroxyl, thiol, or optionally substituted amino;

G" is



optionally substituted C₆-C₁₀ aryl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heteroaryl, or C₂-C₉ heterocyclyl;

G' is optionally substituted C₃-C₁₀ carbocyclylene, C₂-C₉ heterocyclylene, optionally substituted C₆-C₁₀ arylene, or optionally substituted C₂-C₉ heteroarylene; and

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A¹ is a bond between A and the linker, where one of R^{3a}, R^{3b}, R^{3c}, R^{3d}, R^{3e}, R^{3f}, and R^{3g} is



or G is



or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound has the structure of any one of compounds D1-D38 in Table 2A, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound has the structure of any one of compounds D39-D302 in Table 2B, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound has the structure of any one of compounds D303-D375 in Table 2C, or a pharmaceutically acceptable salt thereof.

Other embodiments, as well as exemplary methods for the synthesis of production of these compounds, are described herein.

Pharmaceutical Uses

The compounds described herein are useful in the methods of the invention and, while not bound by theory, are believed to exert their desirable effects through their ability to modulate the level, status, and/or activity of a BAF complex, e.g., by inhibiting the activity or level of the BRD9 protein in a cell within the BAF complex in a mammal.

An aspect of the present invention relates to methods of treating disorders related to BRD9 such as cancer in a subject in need thereof. In some embodiments, the compound is administered in an amount and for a time effective to result in one of (or more, e.g., two or more, three or more, four or more of): (a) reduced tumor size, (b) reduced rate of tumor growth, (c) increased tumor cell death (d) reduced tumor progression, (e) reduced number of metastases, (f) reduced rate of metastasis, (g) decreased tumor recurrence (h) increased survival of subject, and (i) increased progression free survival of a subject.

Treating cancer can result in a reduction in size or volume of a tumor. For example, after treatment, tumor size is reduced by 5% or greater (e.g., 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or greater) relative to its size prior to treatment. Size of a tumor may be measured by any reproducible means of measurement. For example, the size of a tumor may be measured as a diameter of the tumor.

Treating cancer may further result in a decrease in number of tumors. For example, after treatment, tumor number is reduced by 5% or greater (e.g., 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or greater) relative to number prior to treatment. Number of tumors may be measured by any reproducible means of measurement, e.g., the number of tumors may be measured by counting tumors visible to the naked eye or at a specified magnification (e.g., 2x, 3x, 4x, 5x, 10x, or 50x).

Treating cancer can result in a decrease in number of metastatic nodules in other tissues or organs distant from the primary tumor site. For example, after treatment, the number of metastatic nodules is reduced by 5% or greater (e.g., 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or greater) relative to number prior to treatment. The number of meta-

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static nodules may be measured by any reproducible means of measurement. For example, the number of metastatic nodules may be measured by counting metastatic nodules visible to the naked eye or at a specified magnification (e.g., 2 \times , 10 \times , or 50 \times).

Treating cancer can result in an increase in average survival time of a population of subjects treated according to the present invention in comparison to a population of untreated subjects. For example, the average survival time is increased by more than 30 days (more than 60 days, 90 days, or 120 days). An increase in average survival time of a population may be measured by any reproducible means. An increase in average survival time of a population may be measured, for example, by calculating for a population the average length of survival following initiation of treatment with the compound described herein. An increase in average survival time of a population may also be measured, for example, by calculating for a population the average length of survival following completion of a first round of treatment with a pharmaceutically acceptable salt of a compound described herein.

Treating cancer can also result in a decrease in the mortality rate of a population of treated subjects in comparison to an untreated population. For example, the mortality rate is decreased by more than 2% (e.g., more than 5%, 10%, or 25%). A decrease in the mortality rate of a population of treated subjects may be measured by any reproducible means, for example, by calculating for a population the average number of disease-related deaths per unit time following initiation of treatment with a pharmaceutically acceptable salt of a compound described herein. A decrease in the mortality rate of a population may also be measured, for example, by calculating for a population the average number of disease-related deaths per unit time following completion of a first round of treatment with a pharmaceutically acceptable salt of a compound described herein.

Combination Therapies

A method of the invention can be used alone or in combination with an additional therapeutic agent, e.g., other agents that treat cancer or symptoms associated therewith, or in combination with other types of therapies to treat cancer. In combination treatments, the dosages of one or more of the therapeutic compounds may be reduced from standard dosages when administered alone. For example, doses may be determined empirically from drug combinations and permutations or may be deduced by isobolographic analysis (e.g., Black et al., *Neurology* 65:S3-S6 (2005)). In this case, dosages of the compounds when combined should provide a therapeutic effect.

In some embodiments, the second therapeutic agent is a chemotherapeutic agent (e.g., a cytotoxic agent or other chemical compound useful in the treatment of cancer). These include alkylating agents, antimetabolites, folic acid analogs, pyrimidine analogs, purine analogs and related inhibitors, vinca alkaloids, epipodophyllotoxins, antibiotics, L-Asparaginase, topoisomerase inhibitors, interferons, platinum coordination complexes, anthracenedione substituted urea, methyl hydrazine derivatives, adrenocortical suppressant, adrenocorticosteroids, progestins, estrogens, antiestrogen, androgens, antiandrogen, and gonadotropin-releasing hormone analog. Also included is 5-fluorouracil (5-FU), leucovorin (LV), irinotecan, oxaliplatin, capecitabine, paclitaxel, and doxetaxel. Non-limiting examples of chemotherapeutic agents include alkylating agents such as thiotepa and cyclophosphamide; alkyl sulfonates such as busulfan, imrosulfan and pipsulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and

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methylamalamines including altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide and trimethylololomelamine; acetogenins (especially bullatacin and bullatacinone); a camptothecin (including the synthetic analogue topotecan); bryostatin; calystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogues); cryptophycins (particularly cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogues, KW-2189 and CB1-TM1); eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlornapthazine, chlophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimustine; antibiotics such as the enediyne antibiotics (e.g., calicheamicin, especially calicheamicin gammall and calicheamicin omegall (see, e.g., Agnew, *Chem. Int. Ed Engl.* 33:183-186 (1994)); dynemicin, including dynemicin A; bisphosphonates, such as clodronate; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromophores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabicin, caminomycin, carzinophilin, chremomycin, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, ADRIAMYCIN® (doxorubicin, including morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodothiocarb, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as folinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demeclocycline; diaziquone; elfomithine; elliptinium acetate; an epothilone; etoglibucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; moidanmol; niraerine; pentostatin; phenacetin; pirarubicin; losoxantrone; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK® polysaccharide complex (JHS Natural Products, Eugene, OR); razoxane; rhizoxin; sizofuran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2"-trichlorotriethylamine; trichothecenes (especially T-2 toxin, verrucarin A, roridin A and anguidine); urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; taxoids, e.g., TAXOL® (paclitaxel; Bristol-Myers Squibb Oncology, Princeton, NJ), ABRAXANE®, cremophor-free, albumin-engineered nanoparticle formulation of paclitaxel (American Pharmaceutical Partners, Schaumberg, IL), and TAXOTERE® doxetaxel (Rhone-Poulenc Rorer, Antony, France); chlorambucil; GEMZAR® gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum coordination complexes such as cisplatin, oxaliplatin and carboplatin; vin-

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blastine; platinum; etoposide (VP-16); ifosfamide; mitoxantrone; vincristine; NAVELBINE® vinorelbine; novantrone; teniposide; edatrexate; daunomycin; aminopterin; xeloda; ibandronate; irinotecan (e.g., CPT-11); topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoids such as retinoic acid; capecitabine; and pharmaceutically acceptable salts, acids or derivatives of any of the above. Two or more chemotherapeutic agents can be used in a cocktail to be administered in combination with the first therapeutic agent described herein. Suitable dosing regimens of combination chemotherapies are known in the art and described in, for example, Saltz et al., *Proc. Am. Soc. Clin. Oncol.* 18:233a (1999), and Douillard et al., *Lancet* 355(9209):1041-1047 (2000).

In some embodiments, the second therapeutic agent is a therapeutic agent which is a biologic such a cytokine (e.g., interferon or an interleukin (e.g., IL-2)) used in cancer treatment. In some embodiments the biologic is an anti-angiogenic agent, such as an anti-VEGF agent, e.g., bevacizumab (AVASTIN®). In some embodiments the biologic is an immunoglobulin-based biologic, e.g., a monoclonal antibody (e.g., a humanized antibody, a fully human antibody, an Fc fusion protein or a functional fragment thereof) that agonizes a target to stimulate an anti-cancer response, or antagonizes an antigen important for cancer. Such agents include RITUXAN® (rituximab); ZENAPAX® (daclizumab); SIMULECT® (basiliximab); SYNAGIS® (palivizumab); REMICADE® (infliximab); HERCEPTIN® (trastuzumab); MYLOTARG® (gemtuzumab ozogamicin); CAMPATH® (alemtuzumab); ZEVALIN® (ibritumomab tiuxetan); HUMIRA® (adalimumab); XOLAIR® (omalizumab); BEXXAR® (tosotumomab-I-131); RAPTIVA® (efalizumab); ERBITUX® (cetuximab); AVASTIN® (bevacizumab); TYSABRI® (natalizumab); ACTEMRA® (tocilizumab); VECTIBIX® (panitumumab); LUCENTIS® (ranibizumab); SOLIRIS® (eculizumab); CIMZIA® (certolizumab pegol); SIMPONI® (golimumab); ILARIS® (canakinumab); STELARA® (ustekinumab); ARZERRA® (ofatumumab); PROLIA® (denosumab); NUMAX® (motavizumab); ABTHRAX® (raxibacumab); BENLYSTA® (belimumab); YERVOY® (ipilimumab); ADCETRIS® (brentuximab vedotin); PERJETA® (pertuzumab); KADCYLA® (ado-trastuzumab emtansine); and GAZYVA® (obinutuzumab). Also included are antibody-drug conjugates.

The second agent may be a therapeutic agent which is a non-drug treatment. For example, the second therapeutic agent is radiation therapy, cryotherapy, hyperthermia, and/or surgical excision of tumor tissue.

The second agent may be a checkpoint inhibitor. In one embodiment, the inhibitor of checkpoint is an inhibitory antibody (e.g., a monospecific antibody such as a monoclonal antibody). The antibody may be, e.g., humanized or fully human. In some embodiments, the inhibitor of checkpoint is a fusion protein, e.g., an Fc-receptor fusion protein. In some embodiments, the inhibitor of checkpoint is an agent, such as an antibody, that interacts with a checkpoint protein. In some embodiments, the inhibitor of checkpoint is an agent, such as an antibody, that interacts with the ligand of a checkpoint protein. In some embodiments, the inhibitor of checkpoint is an inhibitor (e.g., an inhibitory antibody or small molecule inhibitor) of CTLA-4 (e.g., an anti-CTLA4 antibody or fusion a protein such as ipilimumab/YERVOY® or tremelimumab). In some embodiments, the inhibitor of checkpoint is an inhibitor (e.g., an inhibitory antibody or small molecule inhibitor) of PD-1 (e.g., nivolumab/OP-DIVO®; pembrolizumab/KEYTRUDA®; pidilizumab/CT-

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011). In some embodiments, the inhibitor of checkpoint is an inhibitor (e.g., an inhibitory antibody or small molecule inhibitor) of PDL1 (e.g., MPDL3280A/RG7446; MEDI4736; MSB0010718C; BMS 936559). In some 5 embodiments, the inhibitor of checkpoint is an inhibitor (e.g., an inhibitory antibody or Fc fusion or small molecule inhibitor) of PDL2 (e.g., a PDL2/Ig fusion protein such as AMP 224). In some embodiments, the inhibitor of checkpoint is an inhibitor (e.g., an inhibitory antibody or small 10 molecule inhibitor) of B7-H3 (e.g., MGA271), B7-H4, BTLA, HVEM, TIM3, GAL9, LAG3, VISTA, KIR, 2B4, CD160, CGEN-15049, CHK 1, CHK2, A2aR, B-7 family ligands, or a combination thereof.

In some embodiments, the anti-cancer therapy is a T cell 15 adoptive transfer (ACT) therapy. In some embodiments, the T cell is an activated T cell. The T cell may be modified to express a chimeric antigen receptor (CAR). CAR modified T (CAR-T) cells can be generated by any method known in the art. For example, the CAR-T cells can be generated by 20 introducing a suitable expression vector encoding the CAR to a T cell. Prior to expansion and genetic modification of the T cells, a source of T cells is obtained from a subject. T cells can be obtained from a number of sources, including peripheral blood mononuclear cells, bone marrow, lymph node 25 tissue, cord blood, thymus tissue, tissue from a site of infection, ascites, pleural effusion, spleen tissue, and tumors. In certain embodiments of the present invention, any number of T cell lines available in the art, may be used. In some 30 embodiments, the T cell is an autologous T cell. Whether prior to or after genetic modification of the T cells to express a desirable protein (e.g., a CAR), the T cells can be activated and expanded generally using methods as described, for example, in U.S. Pat. Nos. 6,352,694; 6,534,055; 6,905,680; 6,692,964; 5,858,358; 6,887,466; 6,905,681; 7,144,575; 35 7,067,318; 7,172,869; 7,232,566; 7,175,843; 5,883,223; 6,905,874; 6,797,514; 6,867,041; and U.S. Patent Application Publication No. 20060121005.

In any of the combination embodiments described herein, the first and second therapeutic agents are administered 40 simultaneously or sequentially, in either order. The first therapeutic agent may be administered immediately, up to 1 hour, up to 2 hours, up to 3 hours, up to 4 hours, up to 5 hours, up to 6 hours, up to 7 hours, up to, 8 hours, up to 9 hours, up to 10 hours, up to 11 hours, up to 12 hours, up to 13 hours, 14 hours, up to hours 16, up to 17 hours, up to 18 hours, up to 19 hours up to 20 hours, up to 21 hours, up to 22 hours, up to 23 hours up to 24 hours or up to 1-7, 1-14, 1-21 or 1-30 days before or after the second therapeutic agent.

50 Pharmaceutical Compositions

The pharmaceutical compositions described herein are preferably formulated into pharmaceutical compositions for administration to human subjects in a biologically compatible form suitable for administration *in vivo*.

55 The compounds described herein may be used in the form of the free base, in the form of salts, solvates, and as prodrugs. All forms are within the methods described herein. In accordance with the methods of the invention, the described compounds or salts, solvates, or prodrugs thereof 60 may be administered to a patient in a variety of forms depending on the selected route of administration, as will be understood by those skilled in the art. The compounds described herein may be administered, for example, by oral, parenteral, buccal, sublingual, nasal, rectal, patch, pump, intratumoral, or transdermal administration and the pharmaceutical compositions formulated accordingly. Parenteral administration includes intravenous, intraperitoneal, subcu-

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taneous, intramuscular, transepithelial, nasal, intrapulmonary, intrathecal, rectal, and topical modes of administration. Parenteral administration may be by continuous infusion over a selected period of time.

A compound described herein may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or it may be enclosed in hard or soft shell gelatin capsules, or it may be compressed into tablets, or it may be incorporated directly with the food of the diet. For oral therapeutic administration, a compound described herein may be incorporated with an excipient and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, and wafers. A compound described herein may also be administered parenterally. Solutions of a compound described herein can be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, DMSO, and mixtures thereof with or without alcohol, and in oils. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms. Conventional procedures and ingredients for the selection and preparation of suitable formulations are described, for example, in Remington's Pharmaceutical Sciences (2012, 22nd ed.) and in The United States Pharmacopeia: The National Formulary (USP 41 NF36), published in 2018. The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that may be easily administered via syringe. Compositions for nasal administration may conveniently be formulated as aerosols, drops, gels, and powders. Aerosol formulations typically include a solution or fine suspension of the active substance in a physiologically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomizing device. Alternatively, the sealed container may be a unitary dispensing device, such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal after use. Where the dosage form includes an aerosol dispenser, it will contain a propellant, which can be a compressed gas, such as compressed air or an organic propellant, such as fluorochlorohydrocarbon. The aerosol dosage forms can also take the form of a pump-atomizer. Compositions suitable for buccal or sublingual administration include tablets, lozenges, and pastilles, where the active ingredient is formulated with a carrier, such as sugar, acacia, tragacanth, gelatin, and glycerine. Compositions for rectal administration are conveniently in the form of suppositories containing a conventional suppository base, such as cocoa butter. A compound described herein may be administered intratumorally, for example, as an intratumoral injection. Intratumoral injection is injection directly into the tumor vasculature and is specifically contemplated for discrete, solid, accessible tumors. Local, regional, or systemic administration also may be appropriate. A compound described herein may advantageously be contacted by administering an injection or multiple injections to the tumor, spaced for example, at approximately, 1 cm intervals. In the case of surgical intervention, the present invention may be used preoperatively, such as to render an inoperable tumor subject to resection. Continuous administration also may be applied where appropriate, for example, by implanting a catheter into a tumor or into tumor vasculature.

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The compounds described herein may be administered to an animal, e.g., a human, alone or in combination with pharmaceutically acceptable carriers, as noted herein, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of administration, and standard pharmaceutical practice. Dosages

The dosage of the compounds described herein, and/or compositions including a compound described herein, can vary depending on many factors, such as the pharmacodynamic properties of the compound; the mode of administration; the age, health, and weight of the recipient; the nature and extent of the symptoms; the frequency of the treatment, and the type of concurrent treatment, if any; and the clearance rate of the compound in the animal to be treated. One of skill in the art can determine the appropriate dosage based on the above factors. The compounds described herein may be administered initially in a suitable dosage that may be adjusted as required, depending on the clinical response. In general, satisfactory results may be obtained when the compounds described herein are administered to a human at a daily dosage of, for example, between 0.05 mg and 3000 mg (measured as the solid form). Dose ranges include, for example, between 10-1000 mg (e.g., 50-800 mg). In some embodiments, 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, or 1000 mg of the compound is administered.

Alternatively, the dosage amount can be calculated using the body weight of the patient. For example, the dose of a compound, or pharmaceutical composition thereof, administered to a patient may range from 0.1-100 mg/kg (e.g., 0.1-50 mg/kg (e.g., 0.25-25 mg/kg)). In exemplary, non-limiting embodiments, the dose may range from 0.5-5.0 mg/kg (e.g., 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, or 5.0 mg/kg) or from 5.0-20 mg/kg (e.g., 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 mg/kg).

Kits

The invention also features kits including (a) a pharmaceutical composition including an agent that reduces the level and/or activity of BRD9 in a cell or subject described herein, and (b) a package insert with instructions to perform any of the methods described herein. In some embodiments, the kit includes (a) a pharmaceutical composition including an agent that reduces the level and/or activity of BRD9 in a cell or subject described herein, (b) an additional therapeutic agent (e.g., an anti-cancer agent), and (c) a package insert with instructions to perform any of the methods described herein.

EXAMPLES

Example 1—High Density Tiling sgRNA Screen Against Human BAF Complex Subunits in Synovial Sarcoma Cell Line SYO1

The following example shows that BRD9 sgRNA inhibits cell growth in synovial sarcoma cells.

Procedure: To perform high density sgRNA tiling screen, an sgRNA library against BAF complex subunits was custom synthesized at Cellecta (Mountain View, CA). Sequences of DNA encoding the BRD9-targeting sgRNAs used in this screen are listed in Table 3. Negative and positive control sgRNA were included in the library. Negative controls consisted of 200 sgRNAs that do not target human genome. The positive controls are sgRNAs targeting essential genes (CDC16, GTF2B, HSPA5, HSPA9,

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PAFAH1B1, PCNA, POLR2L, RPL9, and SF3A3). DNA sequences encoding all positive and negative control sgRNAs are listed in Table 4. Procedures for virus production, cell infection, and performing the sgRNA screen were previously described (Tsherniak et al, *Cell* 170:564-576 (2017); Munoz et al, *Cancer Discovery* 6:900-913 (2016)). For each sgRNA, 50 counts were added to the sequencing counts and for each time point the resulting counts were normalized to the total number of counts. The log 2 of the ratio between the counts (defined as dropout ratio) at day 24 and day 1 post-infection was calculated. For negative control sgRNAs, the 2.5 and 97.5 percentile of the log 2 dropout ratio of all non-targeting sgRNAs was calculated and considered as background (grey box in the graph). Protein domains were obtained from PFAM regions defined for the UNIPROT identifier: Q9H8M2.

Results: As shown in FIG. 1, targeted inhibition of the GBAF complex component BRD9 by sgRNA resulted in growth inhibition of the SYO1 synovial sarcoma cell line. sgRNAs against other components of the BAF complexes resulted in increased proliferation of cells, inhibition of cell growth, or had no effect on SYO1 cells. These data show that targeting various subunits of the GBAF complex represents a therapeutic strategy for the treatment of synovial sarcoma.

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TABLE 3-continued

BRD9 sgRNA Library	
SEQ ID NO.	Nucleic Acid Sequence
225	ACTCCAGTTACTATGATGAC
226	CTTTGTGCCTCTCTCGCTCA
227	GGTCAGACCATGAGCGAGAG
228	GAAGAAGAAGAAGTCGAGA
229	GTCCAGATGCTTCTCCTTCT
230	GTCCGAGAAGGAGAACATC
231	GGAGAACATCTGGACGATG
232	TGAGGAAAGAAGGAAGCGAA
233	ATCTGGACGATGAGGAAAGA
234	AGAAGAACGAGAACGAGAG
235	GAAGAACGAGAACGAGAGA
236	CCGCCAGGAAGAGAAGAAG
237	AGAGAGGGAGCACTGTGACA
238	AGGGAGCACTGTGACACCGA
239	GAGGGAGCACTGTGACACGG
240	GCACTGTGACACCGAGGGAG
241	GAGGCTGACGACTTTGATCC
242	AGGCTGACGACTTTGATCCT
243	TCCACCTCCACCTTCTCCC
244	CGACTTTGATCCTGGAAAGA
245	CTTGATCCTGGAAAGAAGG
246	TGATCCTGGGAAGAAGGTGG
247	TCCTGGGAAGAAGGTGGAGG
248	CGGACTGGCCGATCTGGGG
249	ACGCTGGACTGGCCGATCT
250	AGGTGGAGCCGCCCCAGAT
251	CGCTCGGACTGGCCGATCTG
252	GCTCGGACTGGCCGATCTGG
253	CACGCTCGGACTGGCCGATC
254	TGTGTCGGCAGCCTGGAC
255	CTGGCTGTGTCGGCACGCT
256	ATCGGCCAGTCCGAGCGTGC
257	CACCCCTGCGCTGGCTGTGTC
258	CGAGCGTGCCGGACACAGCC
259	TGTTCCAGGAGTTGCTGAAT
260	CACACCTATTCAAGCAACTCC
261	GCTGGCGGAGGAAGTGTCC
262	TTTACCTCTGAAGCTGGCGG

TABLE 3

BRD9 sgRNA Library	
SEQ ID NO.	Nucleic Acid Sequence
203	CAAGAACGACAAGAACGACA
204	CTTGTGCTTCTTGCCTATGG
205	CTTCTTGCTCTTGCCTA
206	ACAAGAACGACAAGGCCGAG
207	CTCGTAGGACGAGCGCCACT
208	CGAGTGGCGCTCGTCCTACG
209	GAGTGGCGCTCGTCCTACGA
210	AGGCTTCTCCAGGGCTTGT
211	AGATTATGCCGACAAGCCCC
212	ACCTTCAGGACTAGCTTAG
213	AGCTTTAGAGGCTCTCCAG
214	CTAGCTTAGAGGCTCTCC
215	TAGCTTTAGAGGCTCTCCA
216	CTAAAGCTAGTCCTGAAGGT
217	GCCTCTAAAGCTAGTCCTGA
218	CTTCACTTCCCTCGACCTTC
219	AAGCTAGTCCTGAAGGTGG
220	AGTGAAGTGACTGAACCTC
221	GTGACTGAACCTCAGGATC
222	ATAGTAACGGAGTCGTGGC
223	CATCATAGTAACGGAGTCG
224	TGACCTGTCACTCATAGTAAC

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TABLE 3-continued

BRD9 sqRNA Library	
SEQ ID NO.	Nucleic Acid Sequence
263	CCCCGGTTTACCTCTGAAGC
264	ACTTCCTCCGCCAGCTTCAG
265	CAGGAAAAGCAAAAAATCCA
266	GCTTCAGAAAAGATCCCCA
267	AGGAAAAGCAAAAAATCCAT
268	GGAAAAGCAAAAAATCCATG
269	GGAGCAATTGCATCCGTGAC
270	GTCACGGATGCAATTGCTCC
271	TTTATTATCATGAAATATCC
272	AATGATAATAAACATCCCA
273	ATAAAACATCCCATGGATT
274	TTCATGGTGCCAAAATCCAT
275	TTTCATGGTGCCAAAATCCA
276	TAATGAATACAAGTCAGTTA
277	CAAGTCAGTTACCGGAAATT
278	ATAATGCAATGACATACAAT
279	AACTTGTTAGTACACGGTATC
280	CTTCGCCAACCTTGTTAGTACA
281	AGATACCGTGTACTACAAGT
282	GCGAAGAAAGATCCTTCACGC
283	TCATCTTAAAGCCTGCGTGA
284	TTCTCAGCAGGCAGCTCTT
285	CAATGAAGATAACAGCTGTTG
286	ACTGGTACAACCTCAGGGAC
287	CTTGTACTGGTACAACATTCA
288	ACTTGTACTGGTACAACATT
289	TTGGCAGTTCTACTTGTAC
290	TACCTGATAACCTCTCTACT
291	AGCCGAGTAGAGAAAGTTATC
292	AGCTGCATTTGAGCCTGA
293	GCTGCATTTGAGCCTGA
294	AAGCTGCAGGCATTCCCTTC
295	GGTACTGTCCGTCAAGCTGC
296	AGGGAAATGCCCTGCAGCTTG
297	CTTGACGGACAGTACCGCAG
298	CGCCAGCACGTGCTCCTCTG
299	TACCGCAGAGGAGCACGTGC

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TABLE 3-continued

BRD9 sqRNA Library	
SEQ ID NO.	Nucleic Acid Sequence
5	
300	AGAGGAGCACGTGCTGGCGC
301	GGAGCACGTGCTGGCGCTGG
302	AGCACGCAGCTGACGAAGCT
303	GCACGCAGCTGACGAAGCTC
304	CAGCTGACGAAGCTGGGAC
305	AAGCTCGGGACAGGATCAAC
306	CCTTGCCGCTGGGAGGAAC
307	AGGATCAACCGGTTCTCCC
308	ATCAACCGGTTCTCCCAGG
309	GCACTACCTTGCCGCTGGG
310	AGAGCACTACCTTGCCGCT
311	CCGGTTCCCTCCAGGCGCA
312	TCCTCTTCAGATAGCCCATC
313	ATGGGCTATCTGAAGAGGAA
314	GGGCTATCTGAAGAGGAACG
315	TGGGCTATCTGAAGAGGAAC
316	TATCTGAAGAGGAACGGGGA
317	ATCTGAAGAGGAACGGGAC
318	TGTTGACCACGCTGTAGAGC
319	GCTCTACAGCGTGGTCAACA
320	CGGGAGCCTGCTCTACAGCG
321	CGTGGTCAACACGGCCGAGC
322	CCCACCATCAGCGTCCGGCT
323	ACGGCCGAGCCGGACGCTGA
324	GGGCACCCACCATCAGCGTC
325	GCCGAGCCGGACGCTGATGG
326	CCATGTCCGTGTTGCAGAGG
327	CCGAGCCGGACGCTGATGGT
328	CGAGCTCAAGTCCACCGGGT
329	GCGAGCTCAAGTCCACCGGG
330	AGAGCGAGCTCAAGTCCACC
331	GAGAGCGAGCTCAAGTCCAC
332	GAAGCCTGGGAGTAGCTTAC
333	CTCTCCAGTAAGCTACTCCC
334	AGCCCAGCGTGGTGAAGCCT
335	AAGCCCAGCGTGGTGAAGCC
336	ACTCCCAGGCTTACCCACGC
337	CTCCCAGGCTTCACCAACGCT

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TABLE 3-continued

BRD9 sqRNA Library	
SEQ ID NO.	Nucleic Acid Sequence
338	CTCGTCTTGAAGCCCAGCG
339	CACTGGAGAGAAAGGTGACT
340	GCACTGGAGAGAAAGGTGAC
341	AGTAGTGGCACTGGAGAGAA
342	CGAAAGCAGTAGTGGCAC
343	CTGCATCGAAAGCGCAGTAG
344	ATGCAGAATAATTCACTATT
345	AGTATTTGGCAGTTGAAGT
346	CGACTTGAAAGTCGGACGAGA
347	GAGCTGCTCTACTCAGCCTA
348	CACGCCCTGTCATCTCCGT
349	TCAGCCTACGGAGATGAGAC
350	CAGGCCTGCAGTGTGCGCTG
351	CCGGCGCCCCCTAGCCTGC
352	CATCCTTCACAAAACCTCTGC
353	TAGCCTGCAGGAGTTGTGA
354	CAGGAGTTTGTGAAGGATGC
355	AGGAGTTTGTGAAGGATGCT
356	TGGGAGCTACAGCAAGAAAG
357	GAGCTACAGCAAGAAAGTGG
358	GAAAGTGGTGGACGACCTCC
359	CGCCTGTGATCTGGTCCAGG
360	CTCCGCCTGTGATCTGGTCC
361	GACCTCCTGGACCAGATCAC
362	CTCCTGGACCAGATCACAGG
363	GCTGGAAGAGCGTCTAGAG
364	TGCAGCCCACCTGCTTCAGC
365	GACGCTCTTCAGCTGAAGC
366	CTCTTCCAGCTGAAGCAGGT
367	GCTCTTCCAGCTGAAGCAGG
368	CCTCCAGATGAAGCCAAGGT
369	GCTTCATCTGGAGGCTTCAT
370	GGCTTCATCTGGAGGCTTCA
371	CTTACCTTGGCTTCATCTGG
372	AAACTTACCTTGGCTTCATC
373	GAAGCCTCCAGATGAAGCCA
374	TCCTAGGGTGTCCCCAACCT

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TABLE 3-continued

BRD9 sqRNA Library	
SEQ ID NO.	Nucleic Acid Sequence
5	
375	CCTAGGGTGTCCCCAACCTG
376	GTGTCTGTCTCCACAGGTTG
377	TGTGTCTGTCTCCACAGGTT
378	CCACAGGTTGGGACACCCCT
379	AGAGCTGCTGCTGTCTCCTA
380	CAGAGCTGCTGCTGTCTCCT
381	AGACAGCAGCAGCTCTGTT
382	ATCCACAGAACGTCGGGAT
383	GAGATATCCACAGAACGTC
384	GGAGATATCCACAGAACGT
385	GTCCTATCCGACGTTCTG
386	TCTCCATGCTCAGCTCTG
387	CTCACCCAGAGAGCTGAGCA
388	ATCTCCATGCTCAGCTCT
389	TATCTCCATGCTCAGCTCTC
390	ATGTCCTGTTACACAGGGA
391	TTACACAGGGAAGGTGAAGA
392	AGTTCAAATGGCTGTCGTCA
393	TGACGACAGCCATTGAACT
394	AAGTTCAAATGGCTGTCGT
395	TCGTCATCCAAAGTCAAA
396	TGAGACGACGAAGCTCCTGC
397	GTGCTCGTGCAGGTCCTGC
398	GCAGGACCTGCACGAAGCAC
399	GCTCCGCCTGTGCTTCGTGC
400	GGACCTGCACGAAGCACAGG
401	CACGAAGCACAGGCGGAGCG
402	AGGCAGGCGCGCGCGCTCT
403	AGGGAGCTGAGGTTGGACGA
404	GTTGGACAGGGAGCTGAGGT
405	AGGCAGTGGACAGGGAGCTG
406	CCCTCTCGAGGGCGTGGAC
407	CCTCTCGAGGGCGTGGACA
408	CTGGTCCCTCTCGAGGGCGT
409	CCCTGTCCAACGCCTCCGAG
410	CCTGTCCAACGCCTCCGAGA
411	GTGGTGCCTGGCTGGCCCTCTGG
412	CAGGTGGTGCCTGGTCCCTCT

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TABLE 3-continued

BRD9 sqRNA Library	
SEQ ID NO.	Nucleic Acid Sequence
413	GCATCTCACCCAGGTGGTGC
414	CGAGAGGGACCAAGCACCACC
415	GAGAGGGACCAGCACCACCT
416	GTGGGGGCATCTCACCCAGG
417	CCCCGACACTCAGGCAGAA
418	TCCCCGACACTCAGGCAGA
419	AGCCCTTCTCGCCTGAGTGT
420	CTGGCTGCTCCCCGACACTC
421	CCCTTCTCGCCTGAGTGTG
422	GCCCTTCTCGCCTGAGTGT
423	TAGGGTCGTGGGTGACGTC

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TABLE 3-continued

BRD9 sqRNA Library	
SEQ ID NO.	Nucleic Acid Sequence
5	
424	AAGAAACTCATAGGGTCGT
425	GAAGAAACTCATAGGGTCG
426	GAGACTGAAGAAACTCATAG
427	GGAGACTGAAGAAACTCATA
428	TGGAGACTGAAGAAACTCAT
429	TCTTCAGTCTCCAGAGCCTG
430	TTGGCAGAGGCCAGGCTC
431	TAGGTCTTGGCAGAGGCCGC
432	CTAGAGTTAGGTCTTGGCAG
433	GGTGGTCTAGAGTTAGGTCT

TABLE 4

Control sqRNA Library	
SEQ ID NO. gRNA Label	Gene Nucleic Acid Sequence
4341 sg_Non_Targeting_Human_0001 Non_Targeting_Human	Non_Targeting_Human GTAGCGAACGTGTCCGGCGT
4351 sg_Non_Targeting_Human_0002 Non_Targeting_Human	Non_Targeting_Human GACCGAACGATCTCGCGTA
4361 sg_Non_Targeting_Human_0003 Non_Targeting_Human	Non_Targeting_Human GGCAGTCGTTGGTTGATAT
4371 sg_Non_Targeting_Human_0004 Non_Targeting_Human	Non_Targeting_Human GCTTGAGCACATAACGCGAAT
4381 sg_Non_Targeting_Human_0005 Non_Targeting_Human	Non_Targeting_Human GTGGTAGAATAACGTATTAC
4391 sg_Non_Targeting_Human_0006 Non_Targeting_Human	Non_Targeting_Human GTCATACATGGATAAGGCTA
4401 sg_Non_Targeting_Human_0007 Non_Targeting_Human	Non_Targeting_Human GATACACGAAGCATACTAG
4411 sg_Non_Targeting_Human_0008 Non_Targeting_Human	Non_Targeting_Human GAACGTTGGCACTACTTCAC
4421 sg_Non_Targeting_Human_0009 Non_Targeting_Human	Non_Targeting_Human GATCCATGAAATGCGTCGA
4431 sg_Non_Targeting_Human_0010 Non_Targeting_Human	Non_Targeting_Human GTCGTGAAGTGCATTGATC
4441 sg_Non_Targeting_Human_0011 Non_Targeting_Human	Non_Targeting_Human GTTCGACTCGCGTGACCGTA
4451 sg_Non_Targeting_Human_0012 Non_Targeting_Human	Non_Targeting_Human GAATCTACCGCAGCGGTTCG
4461 sg_Non_Targeting_Human_0013 Non_Targeting_Human	Non_Targeting_Human GAAGTGACGTCGATTGATA
4471 sg_Non_Targeting_Human_0014 Non_Targeting_Human	Non_Targeting_Human GCGGTGTATGACAACCGCCG

TABLE 4 - continued

Control sgRNA Library			
SEQ ID NO. gRNA Label	Gene	Nucleic Acid Sequence	
4481 sg_Non_Targeting_Human_0015 Non_Targeting_Human	Non_Targeting_Human	GTACCGCGCCTGAAGTTTCGC	
4491 sg_Non_Targeting_Human_0016 Non_Targeting_Human	Non_Targeting_Human	GCAGCTCGTGTGTCGTACTC	
4501 sg_Non_Targeting_Human_0017 Non_Targeting_Human	Non_Targeting_Human	GCGCCTTAAGAGTACTCATC	
4511 sg_Non_Targeting_Human_0018 Non_Targeting_Human	Non_Targeting_Human	GAGTGTCTCGTTGCTCCTA	
4521 sg_Non_Targeting_Human_0019 Non_Targeting_Human	Non_Targeting_Human	GCAGCTCGACCTCAAGCCGT	
4531 sg_Non_Targeting_Human_0020 Non_Targeting_Human	Non_Targeting_Human	GTATCCTGACCTACGCGCTG	
4541 sg_Non_Targeting_Human_0021 Non_Targeting_Human	Non_Targeting_Human	GTGTATCTCAGCACGCTAAC	
4551 sg_Non_Targeting_Human_0022 Non_Targeting_Human	Non_Targeting_Human	GTCGTCATACAACGGCAACG	
4561 sg_Non_Targeting_Human_0023 Non_Targeting_Human	Non_Targeting_Human	GTCGTGCGTTCCGGCGGT	
4571 sg_Non_Targeting_Human_0024 Non_Targeting_Human	Non_Targeting_Human	GCGGTCCCTCAGTAAGCGCGT	
4581 sg_Non_Targeting_Human_0025 Non_Targeting_Human	Non_Targeting_Human	GCTCTGCTGCGGAAGGATT	
4591 sg_Non_Targeting_Human_0026 Non_Targeting_Human	Non_Targeting_Human	GCATGGAGGAGCGTCGCAGA	
4601 sg_Non_Targeting_Human_0027 Non_Targeting_Human	Non_Targeting_Human	GTAGCGCGCTAGGAGTGGC	
4611 sg_Non_Targeting_Human_0028 Non_Targeting_Human	Non_Targeting_Human	GATCACCTGCATTGTACAC	
4621 sg_Non_Targeting_Human_0029 Non_Targeting_Human	Non_Targeting_Human	GCACACCTAGATATCGAATG	
4631 sg_Non_Targeting_Human_0030 Non_Targeting_Human	Non_Targeting_Human	GTTGATCAACGCGCTTCGCG	
4641 sg_Non_Targeting_Human_0031 Non_Targeting_Human	Non_Targeting_Human	GCGTCTCACTCACTCCATCG	
4651 sg_Non_Targeting_Human_0032 Non_Targeting_Human	Non_Targeting_Human	GCCGACCAACGTCAGCGGT	
4661 sg_Non_Targeting_Human_0033 Non_Targeting_Human	Non_Targeting_Human	GGATACGGTGCCTCAATCTA	
4671 sg_Non_Targeting_Human_0034 Non_Targeting_Human	Non_Targeting_Human	GAATCCAGTGGCGCGACAA	
4681 sg_Non_Targeting_Human_0035 Non_Targeting_Human	Non_Targeting_Human	GCACTGTCAGTGCAACGATA	
4691 sg_Non_Targeting_Human_0036 Non_Targeting_Human	Non_Targeting_Human	GCGATCCTCAAGTATGCTCA	
4701 sg_Non_Targeting_Human_0037 Non_Targeting_Human	Non_Targeting_Human	GCTAATATCGACACGCCGC	
4711 sg_Non_Targeting_Human_0038 Non_Targeting_Human	Non_Targeting_Human	GGAGATGCATCGAAGTCGAT	
4721 sg_Non_Targeting_Human_0039 Non_Targeting_Human	Non_Targeting_Human	GGATGCACTCCATCTCGTCT	

TABLE 4 - continued

Control sgRNA Library		
SEQ ID NO. gRNA Label	Gene	Nucleic Acid Sequence
4731 sg_Non_Targeting_Human_0040 Non_Targeting_Human	Non_Targeting_Human	GTCGCCAGTAATAACCGGAG
4741 sg_Non_Targeting_Human_0041 Non_Targeting_Human	Non_Targeting_Human	GAGATTCCGATGTAACGTAC
4751 sg_Non_Targeting_Human_0042 Non_Targeting_Human	Non_Targeting_Human	GTCGTCACGAGCAGGATTGC
4761 sg_Non_Targeting_Human_0043 Non_Targeting_Human	Non_Targeting_Human	GCGTTAGTCACTTAGCTCGA
4771 sg_Non_Targeting_Human_0044 Non_Targeting_Human	Non_Targeting_Human	GTTCACACGGTGTGGATAG
4781 sg_Non_Targeting_Human_0045 Non_Targeting_Human	Non_Targeting_Human	GGATAGGTGACCTTAGTACG
4791 sg_Non_Targeting_Human_0046 Non_Targeting_Human	Non_Targeting_Human	GTATGAGTCAAGCTAATGCG
4801 sg_Non_Targeting_Human_0047 Non_Targeting_Human	Non_Targeting_Human	GCAACTATTGGAATACGTGA
4811 sg_Non_Targeting_Human_0048 Non_Targeting_Human	Non_Targeting_Human	GTTACCTTCGCTCGTCTATA
4821 sg_Non_Targeting_Human_0049 Non_Targeting_Human	Non_Targeting_Human	GTACCGAGCACACAGGCCG
4831 sg_Non_Targeting_Human_0050 Non_Targeting_Human	Non_Targeting_Human	GTCAGCCATCGGATAGAGAT
4841 sg_Non_Targeting_Human_0051 Non_Targeting_Human	Non_Targeting_Human	GTACGGCACTCCTAGCCGCT
4851 sg_Non_Targeting_Human_0052 Non_Targeting_Human	Non_Targeting_Human	GGTCCTGTCGTATGCTTGCA
4861 sg_Non_Targeting_Human_0053 Non_Targeting_Human	Non_Targeting_Human	GCCGCAATATATGCGGTAAG
4871 sg_Non_Targeting_Human_0054 Non_Targeting_Human	Non_Targeting_Human	GCGCACGTATAATCCTGCGT
4881 sg_Non_Targeting_Human_0055 Non_Targeting_Human	Non_Targeting_Human	GTGCACAAACACGATCCACGA
4891 sg_Non_Targeting_Human_0056 Non_Targeting_Human	Non_Targeting_Human	GCACAATGTTGACGTAAGTG
4901 sg_Non_Targeting_Human_0057 Non_Targeting_Human	Non_Targeting_Human	GTAAGATGCTGCTCACCGTG
4911 sg_Non_Targeting_Human_0058 Non_Targeting_Human	Non_Targeting_Human	GTCGGTGATCCAACGTATCG
4921 sg_Non_Targeting_Human_0059 Non_Targeting_Human	Non_Targeting_Human	GAGCTAGTAGGACGCAAGAC
4931 sg_Non_Targeting_Human_0060 Non_Targeting_Human	Non_Targeting_Human	GTACGTGGAAGCTTGTGGCC
4941 sg_Non_Targeting_Human_0061 Non_Targeting_Human	Non_Targeting_Human	GAGAACTGCCAGTTCTCGAT
4951 sg_Non_Targeting_Human_0062 Non_Targeting_Human	Non_Targeting_Human	GCCATTGGCGCGGGACTTC
4961 sg_Non_Targeting_Human_0063 Non_Targeting_Human	Non_Targeting_Human	GCACACGACCAATCCGCTTC

TABLE 4 - continued

Control sgRNA Library		
SEQ ID NO. gRNA Label	Gene	Nucleic Acid Sequence
4971 sg_Non_Targeting_Human_0064 Non_Targeting_Human	Non_Targeting_Human	GAGGTGATCGATTAAGTACA
4981 sg_Non_Targeting_Human_0065 Non_Targeting_Human	Non_Targeting_Human	GTCACTCGCAGACGCCTAAC
4991 sg_Non_Targeting_Human_0066 Non_Targeting_Human	Non_Targeting_Human	GCGCTACGGAATCATACGTT
5001 sg_Non_Targeting_Human_0067 Non_Targeting_Human	Non_Targeting_Human	GGTAGGACCTCACGGCGCG
5011 sg_Non_Targeting_Human_0068 Non_Targeting_Human	Non_Targeting_Human	GAAGTCATCTTGTGTTAGT
5021 sg_Non_Targeting_Human_0069 Non_Targeting_Human	Non_Targeting_Human	GATCCTGATCCGGCGCGCG
5031 sg_Non_Targeting_Human_0070 Non_Targeting_Human	Non_Targeting_Human	GGTATGCGCGATCCTGAGTT
5041 sg_Non_Targeting_Human_0071 Non_Targeting_Human	Non_Targeting_Human	GCGGAGCTAGAGAGCGGTCA
5051 sg_Non_Targeting_Human_0072 Non_Targeting_Human	Non_Targeting_Human	GAATGGCAATTACGGCTGAT
5061 sg_Non_Targeting_Human_0073 Non_Targeting_Human	Non_Targeting_Human	GTATGGTGAGTAGTCGCTTG
5071 sg_Non_Targeting_Human_0074 Non_Targeting_Human	Non_Targeting_Human	GTGTAATTGCGCTAGTCGG
5081 sg_Non_Targeting_Human_0075 Non_Targeting_Human	Non_Targeting_Human	GGTCCTGGCGAGGAGCCTTG
5091 sg_Non_Targeting_Human_0076 Non_Targeting_Human	Non_Targeting_Human	GAAGATAAGTCGCTGTCTCG
5101 sg_Non_Targeting_Human_0077 Non_Targeting_Human	Non_Targeting_Human	GTCGGCGTTCTGTTGTGACT
5111 sg_Non_Targeting_Human_0078 Non_Targeting_Human	Non_Targeting_Human	GAGGCAAGCCGTTAGGTGTA
5121 sg_Non_Targeting_Human_0079 Non_Targeting_Human	Non_Targeting_Human	GCGGATCCAGATCTCATTG
5131 sg_Non_Targeting_Human_0080 Non_Targeting_Human	Non_Targeting_Human	GGAACATAGGAGCACGTAGT
5141 sg_Non_Targeting_Human_0081 Non_Targeting_Human	Non_Targeting_Human	GTCATCATTATGGCGTAAGG
5151 sg_Non_Targeting_Human_0082 Non_Targeting_Human	Non_Targeting_Human	GCGACTAGCGCCATGAGCGG
5161 sg_Non_Targeting_Human_0083 Non_Targeting_Human	Non_Targeting_Human	GGCGAAGTTCGACATGACAC
5171 sg_Non_Targeting_Human_0084 Non_Targeting_Human	Non_Targeting_Human	GCTGTCGTGTGGAGGCTATG
5181 sg_Non_Targeting_Human_0085 Non_Targeting_Human	Non_Targeting_Human	GC GGAGAGCATTGACCTCAT
5191 sg_Non_Targeting_Human_0086 Non_Targeting_Human	Non_Targeting_Human	GACTAATGGACCAAGTCAGT
5201 sg_Non_Targeting_Human_0087 Non_Targeting_Human	Non_Targeting_Human	GC GGATTAGAGGTAATGCGG

TABLE 4 -continued

Control sgRNA Library		
SEQ ID NO. gRNA Label	Gene	Nucleic Acid Sequence
5211 sg_Non_Targeting_Human_0088 Non_Targeting_Human	Non_Targeting_Human	GCCGACGGCAATCAGTACGC
5221 sg_Non_Targeting_Human_0089 Non_Targeting_Human	Non_Targeting_Human	GTAACCTCTCGAGCGATAGA
5231 sg_Non_Targeting_Human_0090 Non_Targeting_Human	Non_Targeting_Human	GACTTGTATGTGGCTTACGG
5241 sg_Non_Targeting_Human_0091 Non_Targeting_Human	Non_Targeting_Human	GTCACTGTGGTCGAACATGT
5251 sg_Non_Targeting_Human_0092 Non_Targeting_Human	Non_Targeting_Human	GTACTCCAATCCGCGATGAC
5261 sg_Non_Targeting_Human_0093 Non_Targeting_Human	Non_Targeting_Human	GCGTTGGCACGATGTTACGG
5271 sg_Non_Targeting_Human_0094 Non_Targeting_Human	Non_Targeting_Human	GAACCAGCCGGCTAGTATGA
5281 sg_Non_Targeting_Human_0095 Non_Targeting_Human	Non_Targeting_Human	GTATACTAGCTAACACACG
5291 sg_Non_Targeting_Human_0096 Non_Targeting_Human	Non_Targeting_Human	GAATCGGAATAGTTGATTG
5301 sg_Non_Targeting_Human_0097 Non_Targeting_Human	Non_Targeting_Human	GAGCACTTGCATGAGGCGGT
5311 sg_Non_Targeting_Human_0098 Non_Targeting_Human	Non_Targeting_Human	GAACGGCGATGAAGCCAGCC
5321 sg_Non_Targeting_Human_0099 Non_Targeting_Human	Non_Targeting_Human	GCAACCGAGATGAGAGGTTTC
5331 sg_Non_Targeting_Human_0100 Non_Targeting_Human	Non_Targeting_Human	GCAAGATCAATATGCGTGAT
5341 sg_Non_Targeting_Human_GA_0101 Non_Targeting_Human	Non_Targeting_Human	ACGGAGGCTAACGTCGCAA
5351 sg_Non_Targeting_Human_GA_0102 Non_Targeting_Human	Non_Targeting_Human	CGCTTCCGGGCCCGTCAA
5361 sg_Non_Targeting_Human_GA_0103 Non_Targeting_Human	Non_Targeting_Human	ATCGTTCCGCTTAACGGCG
5371 sg_Non_Targeting_Human_GA_0104 Non_Targeting_Human	Non_Targeting_Human	GTAGGGCGGCCGCTCTCTAC
5381 sg_Non_Targeting_Human_GA_0105 Non_Targeting_Human	Non_Targeting_Human	CCATATGGGGCGAGACATG
5391 sg_Non_Targeting_Human_GA_0106 Non_Targeting_Human	Non_Targeting_Human	TACTAACGCCGCTCCTACAG
5401 sg_Non_Targeting_Human_GA_0107 Non_Targeting_Human	Non_Targeting_Human	TGAGGGATCATGTCGAGCGCC
5411 sg_Non_Targeting_Human_GA_0108 Non_Targeting_Human	Non_Targeting_Human	GGGCCCGCATAGGATATCGC
5421 sg_Non_Targeting_Human_GA_0109 Non_Targeting_Human	Non_Targeting_Human	TAGACAACCGCGGAGAAATGC
5431 sg_Non_Targeting_Human_GA_0110 Non_Targeting_Human	Non_Targeting_Human	ACGGGCGGCTATCGCTGACT
5441 sg_Non_Targeting_Human_GA_0111 Non_Targeting_Human	Non_Targeting_Human	CGCGGAAATTTACCGACGA

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TABLE 4 -continued

Control sgRNA Library			
SEQ ID NO. gRNA Label	Gene	Nucleic Acid Sequence	
5451 sg_Non_Targeting_Human_GA_0112 Non_Targeting_Human	Non_Targeting_Human	CTTACAATCGTCGGTCCAAT	
5461 sg_Non_Targeting_Human_GA_0113 Non_Targeting_Human	Non_Targeting_Human	GCGTGCGTCCGGGTTACCC	
5471 sg_Non_Targeting_Human_GA_0114 Non_Targeting_Human	Non_Targeting_Human	CGGAGTAACAAGCGGACGGA	
5481 sg_Non_Targeting_Human_GA_0115 Non_Targeting_Human	Non_Targeting_Human	CGAGTGTATACGCACCGTT	
5491 sg_Non_Targeting_Human_GA_0116 Non_Targeting_Human	Non_Targeting_Human	CGACTAACCGGAAACTTTT	
5501 sg_Non_Targeting_Human_GA_0117 Non_Targeting_Human	Non_Targeting_Human	CAACGGGTTCTCCGGCTAC	
5511 sg_Non_Targeting_Human_GA_0118 Non_Targeting_Human	Non_Targeting_Human	CAGGAGTCGCCGATACCGT	
5521 sg_Non_Targeting_Human_GA_0119 Non_Targeting_Human	Non_Targeting_Human	TTCACGTCGTCGCGACCA	
5531 sg_Non_Targeting_Human_GA_0120 Non_Targeting_Human	Non_Targeting_Human	GTGTCGGATTCCGCCGCTTA	
5541 sg_Non_Targeting_Human_GA_0121 Non_Targeting_Human	Non_Targeting_Human	CACGAACTCACACCGCGCGA	
5551 sg_Non_Targeting_Human_GA_0122 Non_Targeting_Human	Non_Targeting_Human	CGCTAGTACGCTCCTCTATA	
5561 sg_Non_Targeting_Human_GA_0123 Non_Targeting_Human	Non_Targeting_Human	TCGCCTGGTTATACGCT	
5571 sg_Non_Targeting_Human_GA_0124 Non_Targeting_Human	Non_Targeting_Human	CTATCTGAGTGGTAATGCG	
5581 sg_Non_Targeting_Human_GA_0125 Non_Targeting_Human	Non_Targeting_Human	AATCGACTCGAACCTCGTGT	
5591 sg_Non_Targeting_Human_GA_0126 Non_Targeting_Human	Non_Targeting_Human	CCCGATGGACTATACCGAAC	
5601 sg_Non_Targeting_Human_GA_0127 Non_Targeting_Human	Non_Targeting_Human	ACGTTCGAGTACGACCAGCT	
5611 sg_Non_Targeting_Human_GA_0128 Non_Targeting_Human	Non_Targeting_Human	CGCGACGACTAACCTAGTC	
5621 sg_Non_Targeting_Human_GA_0129 Non_Targeting_Human	Non_Targeting_Human	GGTCACCGATCGAGAGCTAG	
5631 sg_Non_Targeting_Human_GA_0130 Non_Targeting_Human	Non_Targeting_Human	CTCAACCGACCGTATGGTCA	
5641 sg_Non_Targeting_Human_GA_0131 Non_Targeting_Human	Non_Targeting_Human	CGTATTGACTCTAACGCG	
5651 sg_Non_Targeting_Human_GA_0132 Non_Targeting_Human	Non_Targeting_Human	CTAGCCGCCAGATCGAGCC	
5661 sg_Non_Targeting_Human_GA_0133 Non_Targeting_Human	Non_Targeting_Human	GAATCGACCGACACTAATGT	
5671 sg_Non_Targeting_Human_GA_0134 Non_Targeting_Human	Non_Targeting_Human	ACTTCAGTCGGCGTAGTCA	
5681 sg_Non_Targeting_Human_GA_0135 Non_Targeting_Human	Non_Targeting_Human	GTGCGATGTCGCTAACGT	

TABLE 4 -continued

Control sgRNA Library			
SEQ ID NO. gRNA Label	Gene	Nucleic Acid Sequence	
5691 sg_Non_Targeting_Human_GA_0136 Non_Targeting_Human	CGCTTAATTCCGGATCAAT Non_Targeting_Human		
5701 sg_Non_Targeting_Human_GA_0137 Non_Targeting_Human	CGTGGCCGGAACCGTCATAG Non_Targeting_Human		
5711 sg_Non_Targeting_Human_GA_0138 Non_Targeting_Human	ACCCTCCGAATCGTAACGGA Non_Targeting_Human		
5721 sg_Non_Targeting_Human_GA_0139 Non_Targeting_Human	AAACGGTACGACAGCGTGTG Non_Targeting_Human		
5731 sg_Non_Targeting_Human_GA_0140 Non_Targeting_Human	ACATAGTCGACGGCTCGATT Non_Targeting_Human		
5741 sg_Non_Targeting_Human_GA_0141 Non_Targeting_Human	GATGGCGCTTCAGTCGTCGG Non_Targeting_Human		
5751 sg_Non_Targeting_Human_GA_0142 Non_Targeting_Human	ATAATCCGGAAACGCTCGAC Non_Targeting_Human		
5761 sg_Non_Targeting_Human_GA_0143 Non_Targeting_Human	CGCCGGGCTGACAATTAACG Non_Targeting_Human		
5771 sg_Non_Targeting_Human_GA_0144 Non_Targeting_Human	CGTCGCCATATGCCGGTGGC Non_Targeting_Human		
5781 sg_Non_Targeting_Human_GA_0145 Non_Targeting_Human	CGGGCCTATAAACACCATCGA Non_Targeting_Human		
5791 sg_Non_Targeting_Human_GA_0146 Non_Targeting_Human	CGCCGTTCCGAGATACTTGA Non_Targeting_Human		
5801 sg_Non_Targeting_Human_GA_0147 Non_Targeting_Human	CGGGACGTCGCGAAAATGTA Non_Targeting_Human		
5811 sg_Non_Targeting_Human_GA_0148 Non_Targeting_Human	TCGGCATA CGGGACACACGC Non_Targeting_Human		
5821 sg_Non_Targeting_Human_GA_0149 Non_Targeting_Human	AGCTCCATCGCCCGATAAT Non_Targeting_Human		
5831 sg_Non_Targeting_Human_GA_0150 Non_Targeting_Human	ATCGTATCATCAGCTAGCGC Non_Targeting_Human		
5841 sg_Non_Targeting_Human_GA_0151 Non_Targeting_Human	TCGATCGAGGTTGCATT CGG Non_Targeting_Human		
5851 sg_Non_Targeting_Human_GA_0152 Non_Targeting_Human	CTCGACAGTTCGTCCCAGC Non_Targeting_Human		
5861 sg_Non_Targeting_Human_GA_0153 Non_Targeting_Human	CGGTAGTATTAATCGCTGAC Non_Targeting_Human		
5871 sg_Non_Targeting_Human_GA_0154 Non_Targeting_Human	TGAACCGGTGTTCTTGCA Non_Targeting_Human		
5881 sg_Non_Targeting_Human_GA_0155 Non_Targeting_Human	CGACGCTAGGT AACGTAGAG Non_Targeting_Human		
5891 sg_Non_Targeting_Human_GA_0156 Non_Targeting_Human	CATTGTTGAGCGGGCGCGCT Non_Targeting_Human		
5901 sg_Non_Targeting_Human_GA_0157 Non_Targeting_Human	CCGCTATTGAAACGCCAC Non_Targeting_Human		
5911 sg_Non_Targeting_Human_GA_0158 Non_Targeting_Human	AGACACGTACCGGTAAAAA Non_Targeting_Human		
5921 sg_Non_Targeting_Human_GA_0159 Non_Targeting_Human	TTTACGATCTAGCGCGTAG Non_Targeting_Human		

TABLE 4 -continued

Control sgRNA Library			
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5941 sg_Non_Targeting_Human_GA_0161 Non_Targeting_Human	Non_Targeting_Human	GGTTAGAGACTAGGCACGCG	
5951 sg_Non_Targeting_Human_GA_0162 Non_Targeting_Human	Non_Targeting_Human	CCTCCGTGCTAACGCCGACG	
5961 sg_Non_Targeting_Human_GA_0163 Non_Targeting_Human	Non_Targeting_Human	TTATCCGCTAGTGCTGACGT	
5971 sg_Non_Targeting_Human_GA_0164 Non_Targeting_Human	Non_Targeting_Human	TACGCTTGCCTTAGCGTCC	
5981 sg_Non_Targeting_Human_GA_0165 Non_Targeting_Human	Non_Targeting_Human	CGCGGCCACGCGTCATCGC	
5991 sg_Non_Targeting_Human_GA_0166 Non_Targeting_Human	Non_Targeting_Human	AGCTCGCCATGTCGGTTCTC	
6001 sg_Non_Targeting_Human_GA_0167 Non_Targeting_Human	Non_Targeting_Human	AACTAGCCCAGCAGCTTCG	
6011 sg_Non_Targeting_Human_GA_0168 Non_Targeting_Human	Non_Targeting_Human	CGCAAGGTGTCGGTAACCCT	
6021 sg_Non_Targeting_Human_GA_0169 Non_Targeting_Human	Non_Targeting_Human	CTTCGACGCCATCGTGCTCA	
6031 sg_Non_Targeting_Human_GA_0170 Non_Targeting_Human	Non_Targeting_Human	TCCTGGATAACCGCGTGGTTA	
6041 sg_Non_Targeting_Human_GA_0171 Non_Targeting_Human	Non_Targeting_Human	ATAGCCGCCGCTCATTACTT	
6051 sg_Non_Targeting_Human_GA_0172 Non_Targeting_Human	Non_Targeting_Human	GTCGTCCGGATTACAAAAT	
6061 sg_Non_Targeting_Human_GA_0173 Non_Targeting_Human	Non_Targeting_Human	TAATGCTGCACACGCCGAAT	
6071 sg_Non_Targeting_Human_GA_0174 Non_Targeting_Human	Non_Targeting_Human	TATCGCTTCCGATTAGTCAG	
6081 sg_Non_Targeting_Human_GA_0175 Non_Targeting_Human	Non_Targeting_Human	GTACCATAACCGCGTACCCCT	
6091 sg_Non_Targeting_Human_GA_0176 Non_Targeting_Human	Non_Targeting_Human	TAAGATCCGCGGGTGGCAAC	
6101 sg_Non_Targeting_Human_GA_0177 Non_Targeting_Human	Non_Targeting_Human	GTAGACGTCGTGAGCTTCAC	
6111 sg_Non_Targeting_Human_GA_0178 Non_Targeting_Human	Non_Targeting_Human	TCGCGGACATAGGGCTCTAA	
6121 sg_Non_Targeting_Human_GA_0179 Non_Targeting_Human	Non_Targeting_Human	AGCGCAGATAGCGCGTATCA	
6131 sg_Non_Targeting_Human_GA_0180 Non_Targeting_Human	Non_Targeting_Human	GTTCGCTTCGTAACGAGGAA	
6141 sg_Non_Targeting_Human_GA_0181 Non_Targeting_Human	Non_Targeting_Human	GACCCCCGATAACTTTGAC	
6151 sg_Non_Targeting_Human_GA_0182 Non_Targeting_Human	Non_Targeting_Human	ACGTCCATACTGTCGGCTAC	
6161 sg_Non_Targeting_Human_GA_0183 Non_Targeting_Human	Non_Targeting_Human	GTACCATTGCCGGCTCCCTA	

TABLE 4 -continued

Control sgRNA Library			
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6181 sg_Non_Targeting_Human_GA_0185 Non_Targeting_Human	Non_Targeting_Human	TCTGGCTTGACACGACCGTT	Non_Targeting_Human
6191 sg_Non_Targeting_Human_GA_0186 Non_Targeting_Human	Non_Targeting_Human	CGCTAGGTCCGGTAAGTGCG	Non_Targeting_Human
6201 sg_Non_Targeting_Human_GA_0187 Non_Targeting_Human	Non_Targeting_Human	AGCACGTAATGTCGTGGAT	Non_Targeting_Human
6211 sg_Non_Targeting_Human_GA_0188 Non_Targeting_Human	Non_Targeting_Human	AAGGCCGCGCAATGTGGCAG	Non_Targeting_Human
6221 sg_Non_Targeting_Human_GA_0189 Non_Targeting_Human	Non_Targeting_Human	ACTGCGGAGCGCCCAATATC	Non_Targeting_Human
6231 sg_Non_Targeting_Human_GA_0190 Non_Targeting_Human	Non_Targeting_Human	CGTCGAGTGCTCGAACTCCA	Non_Targeting_Human
6241 sg_Non_Targeting_Human_GA_0191 Non_Targeting_Human	Non_Targeting_Human	TCGCAGCGCGTGGATCGG	Non_Targeting_Human
6251 sg_Non_Targeting_Human_GA_0192 Non_Targeting_Human	Non_Targeting_Human	ATCTGTCTTAATTGGATCG	Non_Targeting_Human
6261 sg_Non_Targeting_Human_GA_0193 Non_Targeting_Human	Non_Targeting_Human	TGCGGCGTAATGCTTGAAAG	Non_Targeting_Human
6271 sg_Non_Targeting_Human_GA_0194 Non_Targeting_Human	Non_Targeting_Human	CGAACTTAATCCGTGGCAA	Non_Targeting_Human
6281 sg_Non_Targeting_Human_GA_0195 Non_Targeting_Human	Non_Targeting_Human	GCCGTGTTGCTGGATACGCC	Non_Targeting_Human
6291 sg_Non_Targeting_Human_GA_0196 Non_Targeting_Human	Non_Targeting_Human	TACCCTCCGGATACGGACTG	Non_Targeting_Human
6301 sg_Non_Targeting_Human_GA_0197 Non_Targeting_Human	Non_Targeting_Human	CCGTTGGACTATGGCGGGTC	Non_Targeting_Human
6311 sg_Non_Targeting_Human_GA_0198 Non_Targeting_Human	Non_Targeting_Human	GTACGGGGCATCATCCACA	Non_Targeting_Human
6321 sg_Non_Targeting_Human_GA_0199 Non_Targeting_Human	Non_Targeting_Human	AAGAGTAGTAGACGCCGGG	Non_Targeting_Human
6331 sg_Non_Targeting_Human_GA_0200 Non_Targeting_Human	Non_Targeting_Human	AAGAGCGAATCGATTCGTG	Non_Targeting_Human
6343 sg_hCDC16_CC_1 CDC16	CDC16	TCAACACCAAGTGCCTGACGG	
6353 sg_hCDC16_CC_2 CDC16	CDC16	AAAGTAGCTTCACTCTCTCG	
6363 sg_hCDC16_CC_3 CDC16	CDC16	GAGCCAACCAATAGATGTCC	
6373 sg_hCDC16_CC_4 CDC16	CDC16	GCGCCGCCATGAACCTAGAG	
6383 sg_hGTF2B_CC_1 GTF2B	GTF2B	ACAAAAGTTGGAACAGAAC	
6393 sg_hGTF2B_CC_2 GTF2B	GTF2B	GGTGACCGGGTTATTGATGT	
6403 sg_hGTF2B_CC_3 GTF2B	GTF2B	TTAGTGGAGGACTACAGAGC	
6413 sg_hGTF2B_CC_4 GTF2B	GTF2B	ACATATAGCCCCGATAAGCTG	
6423 sg_hHSPA5_CC_1 HSPA5	HSPA5	CGTTGGCGATGATCTCCACG	
6433 sg_hHSPA5_CC_2 HSPA5	HSPA5	TGGCCTTTCTACCTCGCGC	
6443 sg_hHSPA5_CC_3 HSPA5	HSPA5	AATGGAGATACTCATCTGGG	

TABLE 4 -continued

Control sgRNA Library		
SEQ ID NO. gRNA Label	Gene	Nucleic Acid Sequence
6453 sg_hHSPA5_CC_4 HSPA5	HSPA5	GAAGCCCGTCCAGAAAGTGT
6463 sg_hHSPA9_CC_1 HSPA9	HSPA9	CAATCTGAGGAACTCCACGA
6473 sg_hHSPA9_CC_2 HSPA9	HSPA9	AGGCTCGGGCGCCCACGAGA
6483 sg_hHSPA9_CC_3 HSPA9	HSPA9	ACTTTGACCAGGCCTTGCTA
6493 sg_hHSPA9_CC_4 HSPA9	HSPA9	ACCTTCATAACTGCCACGC
6503 sg_hPAFAH1B1_CC_1 PAFAH1B1	PAFAH1B1	CGAGGCGTACATACCCAAGG
6513 sg_hPAFAH1B1_CC_2 PAFAH1B1	PAFAH1B1	ATGGTACGGCAAATCAAGA
6523 sg_hPAFAH1B1_CC_3 PAFAH1B1	PAFAH1B1	TCTTGTAAATCCCATACGCGT
6533 sg_hPAFAH1B1_CC_4 PAFAH1B1	PAFAH1B1	ATTACAGGACACAGAGAAT
6543 sg_hPCNA_CC_1 PCNA	PCNA	CCAGGGCTCCATCCTCAAGA
6553 sg_hPCNA_CC_2 PCNA	PCNA	TGAGCTGCACCAAAGAGACG
6563 sg_hPCNA_CC_3 PCNA	PCNA	ATGTCAGCAGATGTACCCCT
6573 sg_hPCNA_CC_4 PCNA	PCNA	CGAAGATAACGCGGATAACCT
6583 sg_hPOLR2L_CC_1 POLR2L	POLR2L	GCTGCAGGCCGAGTACACCG
6593 sg_hPOLR2L_CC_2 POLR2L	POLR2L	ACAAGTGGGAGGCTTACCTG
6603 sg_hPOLR2L_CC_3 POLR2L	POLR2L	GCAGCGTACAGGGATGATCA
6613 sg_hPOLR2L_CC_4 POLR2L	POLR2L	GCAGTAGCGCTTCAGGCCA
6623 sg_hRPL9_CC_1 RPL9	RPL9	CAAATGGTGGGTAACAGAA
6633 sg_hRPL9_CC_2 RPL9	RPL9	GAAAGGAAGTGGCTACCGTT
6643 sg_hRPL9_CC_3 RPL9	RPL9	AGGGCTTCCGTTACAAGATG
6653 sg_hRPL9_CC_4 RPL9	RPL9	GAACAAAGCAACACCTAAAAG
6663 sg_hSF3A3_CC_1 SF3A3	SF3A3	TGAGGAGAAGGAACGGCTCA
6673 sg_hSF3A3_CC_2 SF3A3	SF3A3	GGAAGAAATGCAGAGTATAAG
6683 sg_hSF3A3_CC_3 SF3A3	SF3A3	GGAATTGAGGAACCTCTGA
6693 sg_hSF3A3_CC_4 SF3A3	SF3A3	GCTCACCGGCCATCCAGGAA
6703 sg_hSF3B3_CC_1 SF3B3	SF3B3	ACTGGCCAGGAACGATGCGA
6713 sg_hSF3B3_CC_2 SF3B3	SF3B3	GCAGCTCCAAGATCTTCCCA
6723 sg_hSF3B3_CC_3 SF3B3	SF3B3	GAATGAGTACACAGAACGGA
6733 sg_hSF3B3_CC_4 SF3B3	SF3B3	GGAGCAGGACAAGGTCGGGG

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Example 2—BRD9 Degrader Depletes BRD9 Protein

The following example demonstrates the depletion of the BRD9 protein in synovial sarcoma cells treated with a 5 BRD9 degrader.

Procedure: Cells were treated with DMSO or the BRD9 degrader, Compound 1 (also known as dBRD9, see Remillard et al, *Angew. Chem. Int. Ed. Engl.* 56(21):5738-5743 (2017); see structure of compound 1 below), for indicated doses and timepoints.

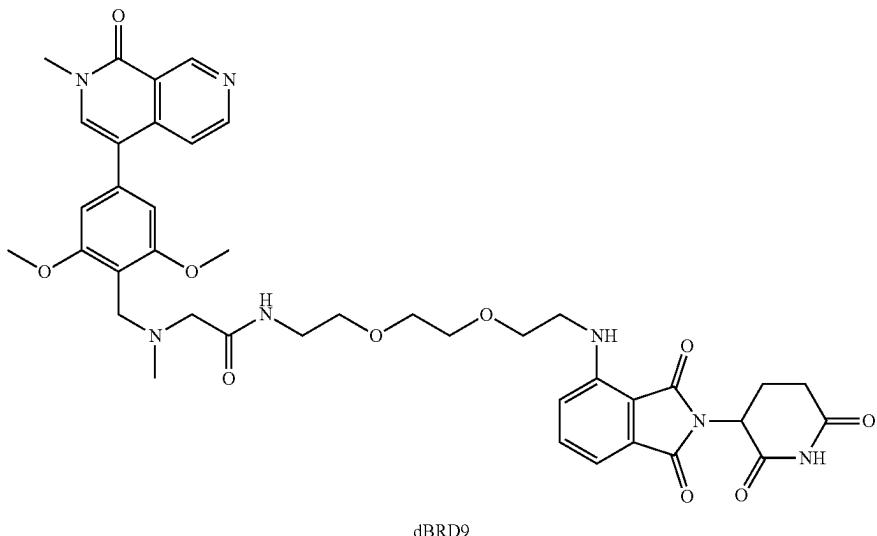
472

Procedures:

Cells were treated with DMSO or the BRD9 degrader, Compound 1, at indicated concentrations, and proliferation was monitored from day 7 to day 14 by measuring confluence over time using an IncuCyte live cell analysis system (FIG. 5). Growth medium and compounds were refreshed every 3-4 days.

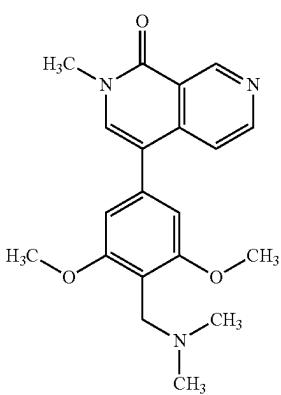
Cells were seeded into 12-well plates and treated with DMSO, 1 µM BRD9 inhibitor, Compound 2 (also known as BI-7273, see Martin et al, *J Med Chem.* 59(10):4462-4475 (2016); see structure of compound 2 below), or 1 µM BRD9 degrader, Compound 1.

(Compound 1)



dBRD9

(Compound 2)



BI-7273

Whole cell extracts were fractionated by SDS-PAGE and transferred to a polyvinylidene difluoride membrane using a transfer apparatus according to the manufacturer's protocols (Bio-Rad). After incubation with 5% nonfat milk in TBST (10 mM Tris, pH 8.0, 150 mM NaCl, 0.5% Tween 20) for 60 min, the membrane was incubated with antibodies against BRD9 (1:1,000, Bethyl laboratory A303-781A), GAPDH (1:5,000, Cell Signaling Technology), and/or MBP (1:1,000, BioRad) overnight at 4° C. Membranes were washed three times for 10 min and incubated with anti-mouse or anti-rabbit antibodies conjugated with either horseradish peroxidase (HRP, FIGS. 2-3) or IRDye (FIG. 4, 1:20,000, LI-COR) for at least 1 h. Blots were washed with TBST three times and developed with either the ECL system according to the manufacturer's protocols (FIGS. 2-3) or scanned on an Odyssey CLx Imaging system (FIG. 4).

Results: Treatment of SYO1 synovial sarcoma cells with the BRD9 degrader Compound 1 results in dose dependent (FIG. 2) and time dependent (FIG. 3) depletion of BRD9 in the cells. Further, as shown in FIG. 4, the depletion of BRD9 by Compound 1 is replicated in a non-synovial sarcoma cell line (293T) and may be sustained for at least 5 days.

Example 3—Inhibition of Growth of Synovial Cell Lines by BRD9 Inhibitors and BRD9 Degraders

The following example demonstrates that BRD9 degraders and inhibitors selectively inhibit growth of synovial sarcoma cells.

The number of cells was optimized for each cell line. Growth medium and compounds were refreshed every 3-5 days. SYO1, Yamato, A549, 293T and HS-SY-II cells were fixed and stained at day 11. ASKA cells were fixed and stained at day 23. Staining was done by incubation with crystal violet solution (0.5 g Crystal Violet, 27 ml 37% Formaldehyde, 100 mL 10×PBS, 10 mL Methanol, 863 dH₂O to 1 L) for 30 min followed by 3× washes with water and drying the plates for at least 24 h at room temperature. Subsequently plates were scanned on an Odyssey CLx Imaging system (FIG. 6).

Cells were seeded into 96-well ultra low cluster plate (Costar, #7007) in 200 μ L complete media and treated at day 2 with DMSO, Staurosporin, or BRD9 degrader, Compound 1, at indicated doses (FIG. 3C). Media and compounds were changed every 5 d and cell colonies were imaged at day 14.

Results: As shown in FIGS. 5, 6, and 7, treatment of synovial sarcoma cell lines (SYO1, Yamato, HS-SY-II, and ASKA) with a BRD9 inhibitor, Compound 2, or a BRD9 degrader, Compound 1, results in inhibition of the growth of the cells, but does not result in inhibition of the growth of non-synovial control cancer cell lines (293T, A549, G401).

Example 4—Selective Inhibition of Growth of Synovial Cell Lines by BRD9 Degraders and BRD9 Binders

The following example demonstrates that BRD9 degraders and binders selectively inhibit growth of synovial sarcoma cells.

Procedure: Cells were seeded into 6-well or 12-well plates and were treated daily with a BRD9 degrader (Compound 1), a bromo-domain BRD9 binder (Compound 2), E3 ligase binder (lenalidomide), DMSO, or staurosporin (positive control for cell killing), at indicated concentrations. The number of cells was optimized for each cell line. Growth media was refreshed every 5 days. By day 14, medium was removed, cells were washed with PBS, and stained using 500 μ L of 0.005% (w/v) crystal violet solution in 25% (v/v) methanol for at least 1 hour at room temperature. Subsequently plates were scanned on an Odyssey CLx Imaging system.

Results: As shown in FIGS. 8 and 9, treatment of synovial sarcoma cell lines (SYO1, HS-SY-II, and ASKA) with Compound 1 or Compound 2 resulted in inhibition of the growth of the cells, but did not result in inhibition of the growth of non-synovial control cancer cell lines (RD, HCT116, and Calu6). Overall, Compound 1 showed most significant growth inhibition in all synovial cell lines.

Example 5—Inhibition of Cell Growth in Synovial Sarcoma Cells

The following example shows that BRD9 degraders inhibit cell growth and induce apoptosis in synovial sarcoma cells.

Procedure: SYO1 cells were treated for 8 or 13 days with DMSO, a BRD9 degrader (Compound 1) at 200 nM or 1 μ M, or an E3 ligase binder (lenalidomide) at 200 nM. Compounds were refreshed every 5 days. Cell cycle analysis was performed using the Click-iT™ Plus EdU Flow Cytometry Assay (Invitrogen). The apoptosis assay was performed using the Annexin V-FITC Apoptosis Detection Kit (Sigma A9210). Assays were performed according to the manufacturer's protocol.

Results: As shown in FIGS. 10-13, treatment with Compound 1 for 8 or 13 days resulted in reduced numbers of cells in the S-phase of the cell cycle as compared to DMSO and lenalidomide. Treatment with Compound 1 for 8 days also resulted in increased numbers of early- and late-apoptotic cells as compared to DMSO controls.

Example 6—Composition for SS18-SSX1-BAF

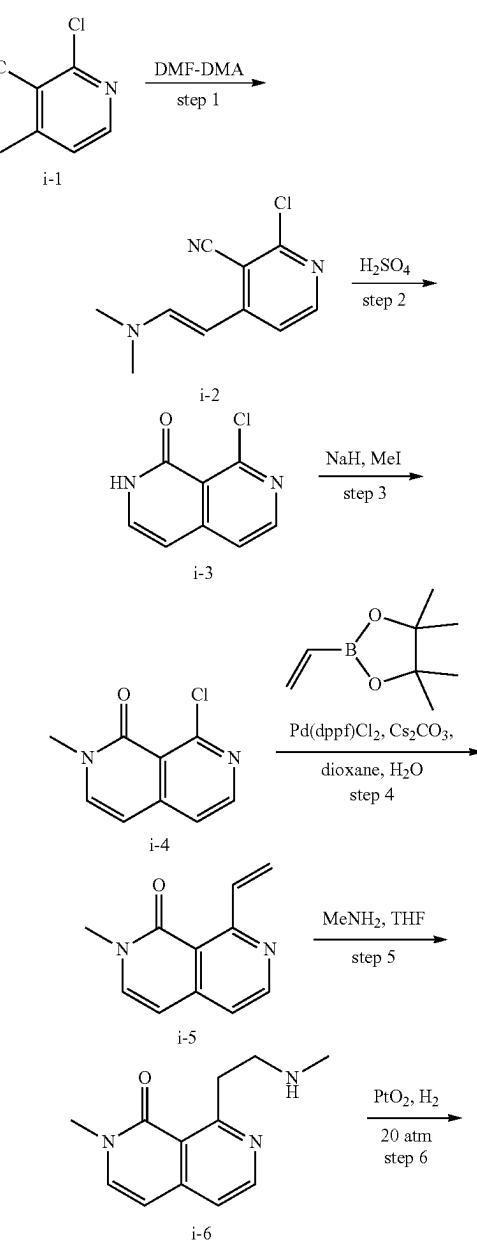
The following example shows the identification of BRD9 as a component of SS18-SSX containing BAF complexes.

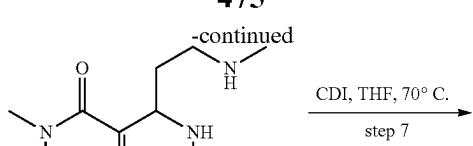
Procedure: A stable 293T cell line expressing HA-SS18SSX1 was generated using lentiviral integration.

SS18-SSX1 containing BAF complexes were subject to affinity purification and subsequent mass spectrometry analysis revealed SS18-SSX1 interacting proteins.

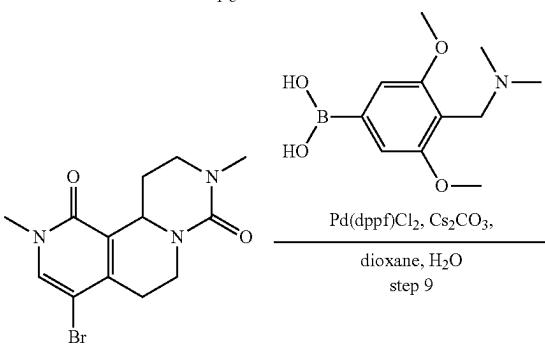
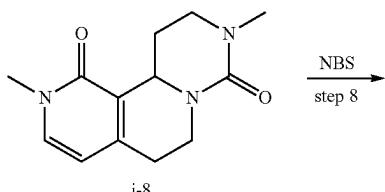
Results: As shown in FIG. 14, BAF complexes including the SS18-SSX fusion protein also included BRD9. More than 5 unique peptides were identified for ARID1A (95 peptides), ARID1B (77 peptides), SMARCC1 (69 peptides), SMARCD1 (41 peptides), SMARCD2 (37 peptides), DPF2 (32 peptides), SMARCD3 (26 peptides), ACTL6A (25 peptides), BRD9 (22 peptides), DPF1 Isoform 2 (18 peptides), DPF3 (13 peptides), and ACTL6B (6 peptides).

Example 7—Preparation of 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2,9-dimethyl-5H,6H,10H,11H,11aH-pyrimido[4,3-a] 2,7-naphthyridine-1,8-dione (Compound B1)

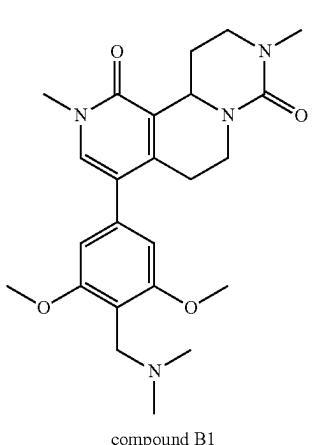


475CDI, THF, 70° C.
step 7

i-7



i-9

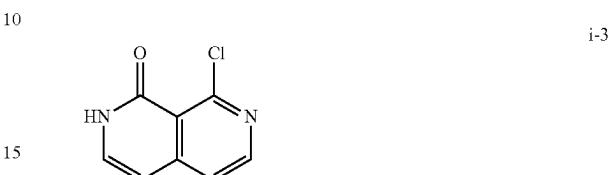


Step 1: Preparation of 6-bromo-3-methyl-[1,2,4]triazolo[4,3-a]pyridin-8-amine (i-2)

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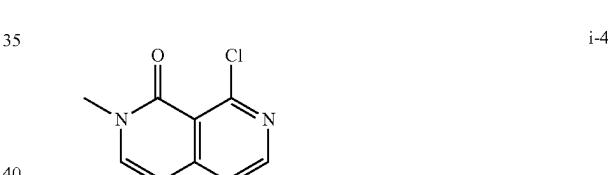
petroleum ether (1:1). This resulted in 3.4 g (83.27%) of 2-chloro-4-[*(E*)-2-(dimethylamino)ethenyl]pyridine-3-carbonitrile as a light yellow solid. LCMS (ESI) m/z: [M+H]⁺= 208.

Step 2: Preparation of 8-chloro-1,2-dihydro-2,7-naphthyridin-1-one (i-3)



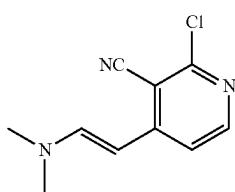
Into a 250-mL round-bottom flask, was placed 2-chloro-4-[*(E*)-2-(dimethylamino)ethenyl]pyridine-3-carbonitrile (3.40 g, 16.373 mmol, 1.00 equiv), H₂SO₄ (100.00 mL). The resulting solution was stirred for 2 hours at 110° C. The reaction was then quenched by the addition of 100 mL of water/ice. The pH of the solution was adjusted to pH>7 by addition of aqueous (aq.) K₂CO₃. The resulting solution was extracted with ethyl acetate (3×300 mL) and the organic layers combined and concentrated. This resulted in 2.7 g (91.32%) of 8-chloro-1,2-dihydro-2,7-naphthyridin-1-one as a light yellow solid. LCMS (ESI) m/z: [M+H]⁺=181.

Step 3: Preparation of 8-chloro-1,2-dihydro-2,7-naphthyridin-1-one (i-4)

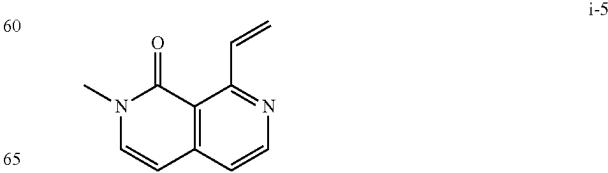


To a solution of 8-chloro-1,2-dihydro-2,7-naphthyridin-1-one (2.20 g, 12.182 mmol, 1.00 equiv) in THE (120.00 mL) was added NaH (321.00 mg, 13.376 mmol, 1.10 equiv) and Mel (3.45 g, 24.306 mmol, 2.00 equiv). The resulting solution was stirred for 2 hours at room temperature. The reaction was then quenched by the addition of 100 mL of water and extracted with ethyl acetate (3×250 mL), and the organic layers were combined and concentrated. This resulted in 2 g (84.36%) of 8-chloro-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one as a light yellow solid. LCMS (ESI) m/z: [M+H]⁺=195.

Step 4: Preparation of 8-ethenyl-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (i-5)



i-2

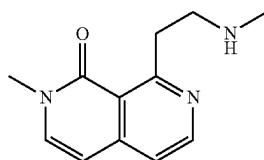


A solution of 2-chloro-4-methylpyridine-3-carbonitrile (3.00 g, 19.662 mmol, 1.00 equiv) in DMF-DMA (120.00 mL, 896.257 mmol, 45.58 equiv) was stirred for 6 hours at 110° C. The resulting mixture was concentrated. The residue was applied onto a silica gel column with ethyl acetate/

477

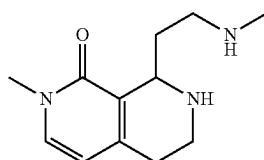
To a solution of 8-chloro-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (2.0 g, 10.276 mmol, 1.00 equiv) in 1,4-dioxane (72.00 mL) and H₂O (24.00 mL), was added Cs₂CO₃ (10.0 g, 30.727 mmol, 2.99 equiv) and 2-ethenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.2 g, 20.758 mmol, 2.02 equiv), Pd(dppf)Cl₂·CH₂Cl₂ (1.68 g, 2.055 mmol, 0.20 equiv) at 25° C. The resulting solution was stirred for 2 hours at 80° C. The resulting mixture was concentrated. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:1). This resulted in 980 mg (51.21%) of 8-ethenyl-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one as a light yellow solid. LCMS (ESI) m/z: [M+H]⁺=187.

Step 5: Preparation of 2-methyl-8-[2-(methylamino)ethyl]-1,2-dihydro-2,7-naphthyridin-1-one (i-6)



To a solution of 8-ethenyl-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (580 mg, 2.67 mmol, 1.00 equiv) in THE (2.00 mL) was added 4 M MeNH₂ THF solution (20 mL) dropwise at 25° C. The resulting solution was stirred for 5 hours at 90° C. The reaction was cooled and concentrated, the crude product was purified by Flash-Prep-HPLC (Conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, acetonitrile (MeCN or ACN) in water, 10% to 50% gradient in 10 minutes; detector, UV 254 nm). This resulted in 480 mg (71.0%) of 2-methyl-8-[2-(methylamino)ethyl]-1,2-dihydro-2,7-naphthyridin-1-one as light yellow oil. LCMS (ESI) m/z: [M+H]⁺=218.

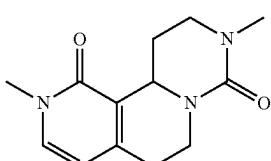
Step 6: Preparation of 2-methyl-8-[2-(methylamino)ethyl]-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (i-7)



To a solution of 2-methyl-8-[2-(methylamino)ethyl]-1,2-dihydro-2,7-naphthyridin-1-one (480.00 mg, 2.201 mmol, 1.00 equiv) in MeOH (10.00 mL) was added PtO₂ (386.71 mg, 1.703 mmol, 0.74 equiv) under high pressure of H₂ (22.0 atm) atmosphere at 25° C. The resulting solution was stirred for 12 hours at room temperature. The solids were filtered out. The filtrate was concentrated. This resulted in 350 mg crude of 2-methyl-8-[2-(methylamino)ethyl]-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one as light yellow oil, that was used directly without further purification. LCMS (ESI) m/z: [M+H]⁺=222.

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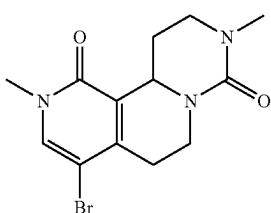
Step 7: Preparation of 2,9-dimethyl-1H,2H,5H,6H,8H,9H,10H,11H,11aH-pyrimido[4,3-a]2,7-naphthyridine-1,8-dione (i-8)



i-8

To a solution of 2-methyl-8-[2-(methylamino)ethyl]-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (350.00 mg, 1.576 mmol, 1.00 equiv) in THE (3.00 mL) was added CDI (1,1'-carbonyldiimidazole) (511.0 mg, 3.153 mmol, 2.00 equiv) at room temperature. The resulting solution was stirred for 6 hours at 70° C. The mixture was concentrated. This resulted in 340 mg crude of 2,9-dimethyl-1H,2H,5H,6H,8H,9H,10H,11H,11aH-pyrimido[4,3-a]2,7-naphthyridine-1,8-dione as light yellow oil, that was used directly without further purification. LCMS (ESI) m/z: [M+H]⁺=248.

Step 8: Preparation of 4-bromo-2,9-dimethyl-1H,2H,5H,6H,8H,9H,10H,11H,11aH-pyrimido[4,3-a]2,7-naphthyridine-1,8-dione (i-9)

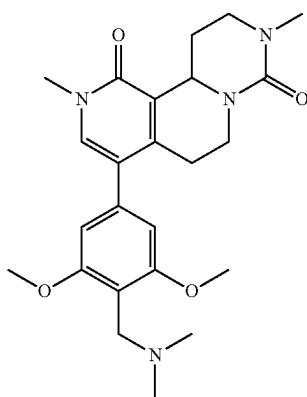


i-9

To a solution of 2,9-dimethyl-1H,2H,5H,6H,8H,9H,10H,11H,11aH-pyrimido[4,3-a]2,7-naphthyridine-1,8-dione (340.00 mg, 1.371 mmol, 1.00 equiv) in HOAc (20.00 mL) was added NBS (732.1 mg, 4.113 mmol, 2.99 equiv) at room temperature. The resulting solution was stirred for 12 hours at room temperature. The mixture was concentrated. The crude product was purified by Flash-Prep-HPLC (Conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, MeCN/H₂O=0 increasing to MeCN/H₂O=100 within 30 minutes; Detector, 254 nm). This resulted in 385 mg of 4-bromo-2,9-dimethyl-1H,2H,5H,6H,8H,9H,10H,11H,11aH-pyrimido[4,3-a]2,7-naphthyridine-1,8-dione as a light yellow solid. LCMS (ESI) m/z: [M+H]⁺=326.

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Step 9: Preparation of 4-((dimethylamino)methyl)-3,5-dimethoxyphenyl)-2,9-dimethyl-5,6,9,10,11,11a-hexahydro-1H-pyrimido[6,1-a][2,7]naphthyridine-1,8 (2H)-dione (Compound B1)



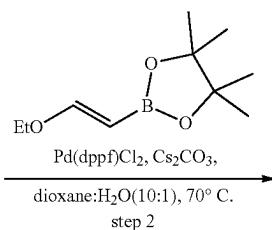
compound B1

To a solution of 4-bromo-2,9-dimethyl-5H,6H,10H,11H,11aH-pyrimido[4,3-a]2,7-naphthyridine-1,8-dione (110.00 mg, 0.337 mmol, 1.00 equiv) in Dioxane (4.00 mL) and H₂O (1.00 mL) was added 4-[(dimethylamino)methyl]-3,5-dimethoxyphenylboronic acid (161.25 mg, 0.674 mmol, 2.00 equiv), Cs₂CO₃ (329.62 mg, 1.012 mmol, 3.00 equiv) and Pd(dppf)Cl₂ (49.35 mg, 0.067 mmol, 0.20 equiv) at 25° C. The resulting solution was stirred for 12 hours at 80° C. The solids were filtered out. The filtrate was concentrated. The crude product was purified by Prep-HPLC with the following conditions: Column, SunFire Prep C18 OBD Column, 19, 150 mm 5 μm 10 nm; mobile phase, Water (0.1% FA) and ACN (3% Phase B up to 10% in 35 minutes); Detector, UV. This resulted in 12 mg (7.31%) of 4-((dimethylamino)methyl)-3,5-dimethoxyphenyl)-2,9-dimethyl-5,6,9,10,11,11a-hexahydro-1H-pyrimido[6,1-a][2,7]naphthyridine-1,8 (2H)-dione formate as a light yellow semi-solid. ¹H NMR (300 MHz, Methanol-d4) δ 8.51 (s, 1.35H, FA), 7.66 (s, 1H), 6.74 (s, 2H), 4.75-4.46 (m, 2H), 4.38 (s, 2H), 3.96 (s, 6H), 3.64 (s, 3H), 3.61-3.50 (m, 1H), 3.29 (dd, J=5.3, 1.8 Hz, 1H), 2.99 (s, 4H), 2.89 (s, 6H), 2.85-2.73 (m, 1H), 2.70-2.54 (m, 1H), 2.39 (d, J=16.7 Hz, 1H), 1.73-1.49 (m, 1H). LCMS (ESI) m/z: [M+H]⁺=441.30.

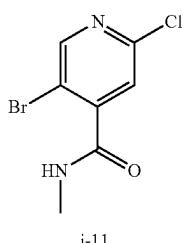
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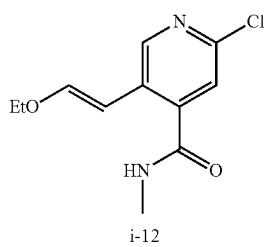
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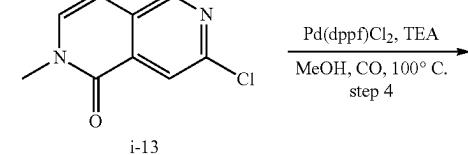
step 2



i-11

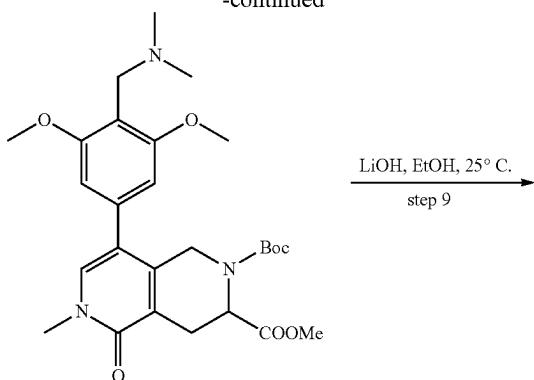


i-12

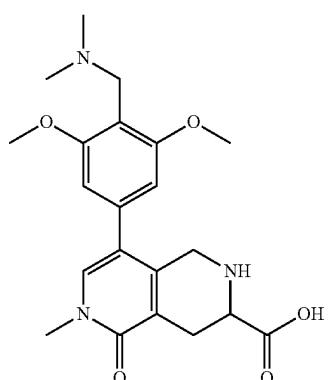
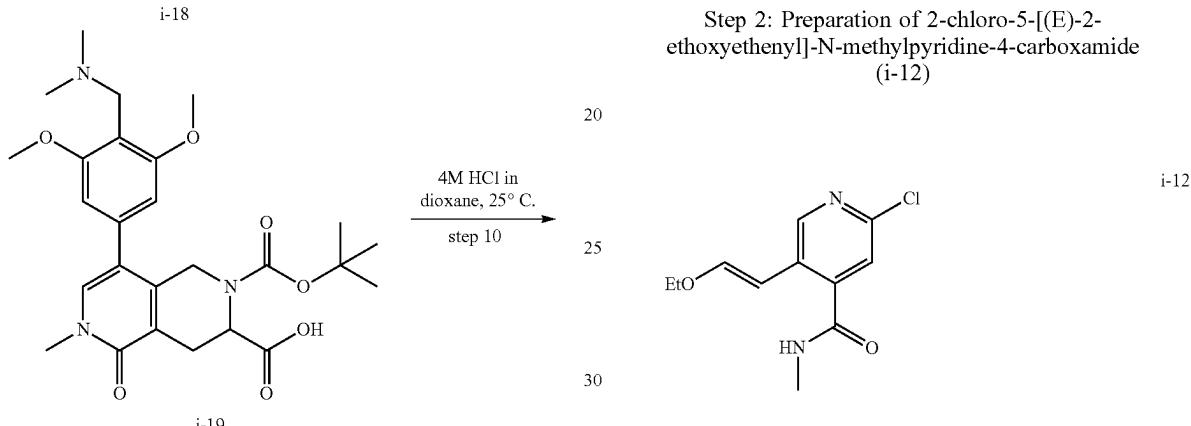


481

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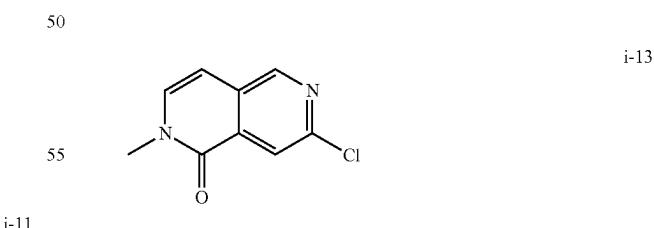
**482**

To a solution of 5-bromo-2-chloropyridine-4-carboxylic acid (10 g, 42.292 mmol, 1 equiv) and methanamine (1.58 g, 50.751 mmol, 1.2 equiv) in solvent DCM (100 mL) was added HATU (24.12 g, 63.438 mmol, 1.5 equiv) and DIEA (27.33 g, 211.461 mmol, 5 equiv). The resulting solution was stirred at 25°C . for 2 hours. The resulting mixture was diluted with H_2O (50 mL) and extracted with DCM (3×50 mL). The organic layers were dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (5:1) to afford 5-bromo-2-chloro-N-methylpyridine-4-carboxamide (8.3 g, 78.66%) as a white solid. LCMS (ESI) m/z: $[\text{M}+\text{H}]^+=248.9, 250.9$.

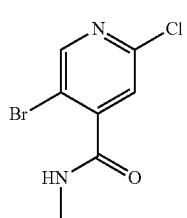


To a solution of 5-bromo-2-chloro-N-methylpyridine-4-carboxamide (8.00 g, 32.065 mmol, 1.00 equiv) and 2-[*(E*)-2-ethoxyethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6.35 g, 32.065 mmol, 1.0 equiv) in dioxane (50.00 mL) and H_2O (5.00 mL) was added Pd(dppf) Cl_2 (2.35 g, 3.207 mmol, 0.1 equiv) and Cs_2CO_3 (20.90 g, 64.131 mmol, 2.0 equiv). The resulting solution was stirred at 90°C . for 2 hours under N_2 atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (4:1) to afford 2-chloro-5-[*(E*)-2-ethoxyethyl]-N-methylpyridine-4-carboxamide (5.4 g, 69.97%) as a yellow solid. LCMS (ESI) m/z: $[\text{M}+\text{H}]^+=241.1$.

Step 3: Preparation of 7-chloro-2-methyl-1,2-dihydro-2,6-naphthyridin-1-one (i-13)



Step 1: Preparation of
5-bromo-2-chloro-N-methylpyridine-4-carboxamide
(i-11)

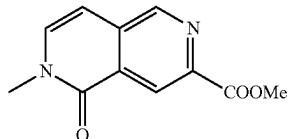


To a solution of 2-chloro-5-[*(E*)-2-ethoxyethyl]-N-methylpyridine-4-carboxamide (5.40 g, 22.435 mmol, 1.00 equiv) in solvent TFA (20.00 mL) was refluxed at 100°C . for 3 hours. The mixture was basified with sodium bicarbonate saturated solution to pH 9. The resulting mixture was extracted with DCM (3×30 mL). The combined organic layers were washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (5:1) to afford 7-chloro-2-methyl-1,2-dihydro-2,6-naphthyridin-1-one (i-13).

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due was purified by silica gel column chromatography, eluted with PE/EA (5:1) to afford 7-chloro-2-methyl-1,2-dihydro-2,6-naphthyridin-1-one (3.2 g, 73.29%) as a yellow solid. LCMS (ESI) m/z: [M+H]⁺=195.0.

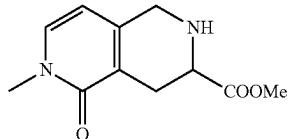
Step 4: Preparation of methyl 6-methyl-5-oxo-5,6-dihydro-2,6-naphthyridine-3-carboxylate (i-14)



i-14

To a solution of 7-chloro-2-methyl-1,2-dihydro-2,6-naphthyridin-1-one (3.20 g, 16.442 mmol, 1.00 equiv) and Pd(dppf)Cl₂ (2.41 g, 3.288 mmol, 0.2 equiv) in MeOH (30.00 mL) and TEA (5 mL) was refluxed at 100° C. for 15 hours under 20 atm CO atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (4:1) to afford methyl 6-methyl-5-oxo-5,6-dihydro-2,6-naphthyridine-3-carboxylate (1.8 g, 50.17%) as a yellow solid. LCMS (ESI) m/z: [M+H]⁺=219.1.

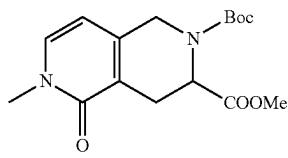
Step 5: Preparation of methyl 6-methyl-5-oxo-1,2,3,4,5,6-hexahydro-2,6-naphthyridine-3-carboxylate (i-15)



i-15

A solution of methyl 6-methyl-5-oxo-5,6-dihydro-2,6-naphthyridine-3-carboxylate (1.80 g, 8.249 mmol, 1.00 equiv) and PtO₂ (0.94 g, 0.004 mmol, 0.5 equiv) in EtOH (20 mL) was stirred at 25° C. for 15 hours under 20 atm H₂ atmosphere. The resulting mixture was concentrated under reduced pressure then purified by silica gel column chromatography, eluted with DCM/MeOH (10/1) to afford methyl 6-methyl-5-oxo-1,2,3,4,5,6-hexahydro-2,6-naphthyridine-3-carboxylate (960 mg, 52.37%) as a yellow solid. LCMS (ESI) m/z: [M+H]⁺=223.1.

Step 6: Preparation of 2-tert-butyl 3-methyl 6-methyl-5-oxo-1,2,3,4,5,6-hexahydro-2,6-naphthyridine-2,3-dicarboxylate (i-16)



i-16

60

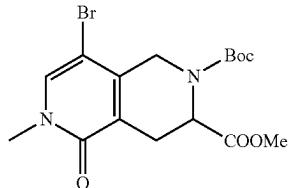
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A solution of methyl 6-methyl-5-oxo-1,2,3,4,5,6-hexahydro-2,6-naphthyridine-3-carboxylate (900.00 mg, 4.050 mmol, 1.00 equiv) and (Boc)₂O (2.65 g, 12.149 mmol, 3.0 equiv) in DCM (30.00 mL) was stirred at 25° C. for 1 hour.

The resulting mixture was concentrated under reduced pressure then purified by silica gel column chromatography, eluted with PE/EA (5/1) to afford 2-tert-butyl 3-methyl 6-methyl-5-oxo-1,2,3,4,5,6-hexahydro-2,6-naphthyridine-2,3-dicarboxylate (760 mg, 58.22%) as a yellow solid. LCMS (ESI) m/z: [M+H]⁺=323.2.

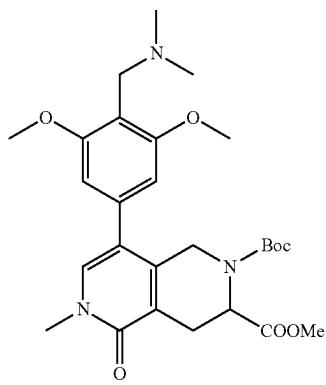
Step 7: Preparation of 2-tert-butyl 3-methyl 8-bromo-6-methyl-5-oxo-1,2,3,4,5,6-hexahydro-2,6-naphthyridine-2,3-dicarboxylate (i-17)



i-17

A solution of 2-tert-butyl 3-methyl 6-methyl-5-oxo-1,2,3,4,5,6-hexahydro-2,6-naphthyridine-2,3-dicarboxylate (760.00 mg, 2.358 mmol, 1.00 equiv) and NBS (503.54 mg, 2.829 mmol, 1.20 equiv) in DCM (10.00 mL) was stirred at 25° C. for 2 hours. The resulting mixture was extracted with DCM (20 mL×3). The combined organic layers were washed with H₂O and then dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure and purified by silica gel column chromatography, eluted with PE/EA (4/1) to afford 2-tert-butyl 3-methyl 8-bromo-6-methyl-5-oxo-1,2,3,4,5,6-hexahydro-2,6-naphthyridine-2,3-dicarboxylate (680 mg, 71.88%) as a yellow solid. LCMS (ESI) m/z: [M+H]⁺=401.1, 403.1.

Step 8: Preparation of 2-tert-butyl 3-methyl 8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-1,2,3,4,5,6-hexahydro-2,6-naphthyridine-2,3-dicarboxylate (i-18)

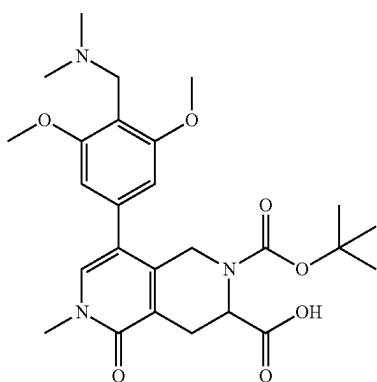


i-18

485

To a solution of 2-tert-butyl 3-methyl 8-bromo-6-methyl-5-oxo-1,2,3,4,5,6-hexahydro-2,6-naphthyridine-2,3-dicarboxylate (680.00 mg, 1.695 mmol, 1.00 equiv) and [4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl] boronic acid (607.74 mg, 2.542 mmol, 1.50 equiv) in dioxane (10.00 mL) and H₂O (2.00 mL) was added Pd(dppf)Cl₂ (248.00 mg, 0.339 mmol, 0.20 equiv) and Cs₂CO₃ (1656.48 mg, 5.084 mmol, 3.00 equiv). The resulting solution was stirred at 90° C. for 2 hours. The resulting mixture was concentrated under reduced pressure then purified by silica gel column chromatography, eluted with DCM/MeOH (10/1) to afford 2-tert-butyl 3-methyl 8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-1,2,3,4,5,6-hexahydro-2,6-naphthyridine-2,3-dicarboxylate (480 mg, 54.93%) as a yellow solid. LCMS (ESI) m/z: [M+H]⁺=516.3.

Step 9: Preparation of 2-[(tert-butoxy)carbonyl]-8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-1,2,3,4,5,6-hexahydro-2,6-naphthyridine-3-carboxylic acid (i-19)

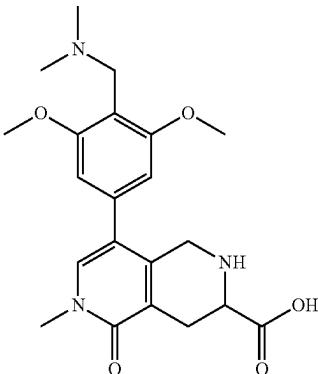


A solution of 2-tert-butyl 3-methyl 8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-1,2,3,4,5,6-hexahydro-2,6-naphthyridine-2,3-dicarboxylate (480.00 mg, 0.931 mmol, 1.00 equiv) and LiOH (44.59 mg, 1.862 mmol, 2.00 equiv) in solvent EtOH (20.00 mL) was stirred at 25° C. for 2 hours. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water, 10% to 20% gradient in 8 minutes; detector, UV 254 nm to afford 2-[(tert-butoxy)carbonyl]-8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-1,2,3,4,5,6-hexahydro-2,6-naphthyridine-3-carboxylic acid (210 mg, 44.97%) as a yellow solid. LCMS (ESI) m/z: [M+H]⁺=502.2.

486

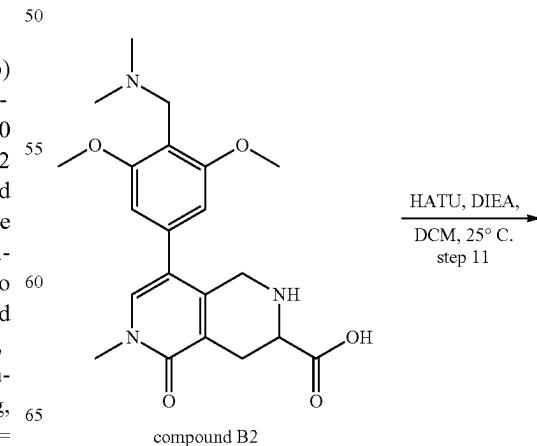
Step 10: Preparation of 8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-1,2,3,4,5,6-hexahydro-2,6-naphthyridine-3-carboxylic acid (Compound B2)

compound B2



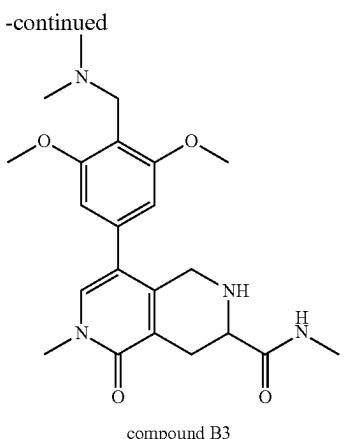
25 2-[(tert-butoxy)carbonyl]-8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-1,2,3,4,5,6-hexahydro-2,6-naphthyridine-3-carboxylic acid (30.00 mg, 0.060 mmol, 1.00 equiv) was added to 4 M HCl 1,4-dioxane solution (5.00 mL), and the resulting solution was stirred at 25° C. for 1 hour. The residue was purified by reverse flash chromatography with the following conditions: column, C18 30 silica gel; mobile phase, MeCN in water, 10% to 50% gradient in 30 minutes; detector, UV 254 nm to afford 8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-1,2,3,4,5,6-hexahydro-2,6-naphthyridine-3-carboxylic acid (18 mg, 74.96%) as a yellow solid. ¹H NMR (400 MHz, Methanol-d₄) δ 7.71 (s, 1H), 6.74 (s, 2H), 4.55-4.26 (m, 4H), 4.07 (d, J=16.9 Hz, 1H), 3.96 (s, 6H), 3.66 (s, 3H), 3.47-3.34 (m, 1H), 2.90 (m, 7H). LCMS (ESI) m/z: [M+H]⁺=402.25.

Example 9—Preparation of and 8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-N,N-dimethyl-5-oxo-1,2,3,4,5,6-hexahydro-2,6-naphthyridine-3-carboxamide and 8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-1,2,3,4,5,6-hexahydro-2,6-naphthyridine-3-carboxamide (Compounds B3 and B4)



487

-continued

**488**

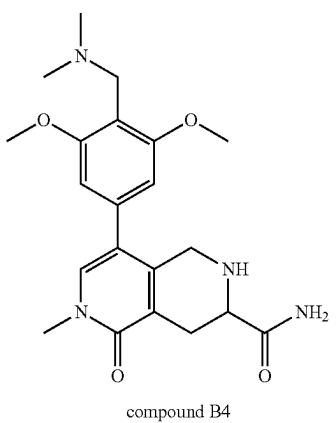
8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-1,2,3,4,5,6-hexahydro-2,6-naphthyridine-3-carboxylic acid (30.00 mg, 0.075 mmol, 1.00 equiv), HATU (42.62 mg, 0.112 mmol, 1.50 equiv), and methyl amine (4.64 mg, 0.149 mmol, 2.00 equiv), and diisopropylethylamine (57.9 mg, 0.448 mmol, 6.00 equiv) were dissolved in DCM (5.0 mL). The resulting solution was stirred at 25° C. for 3 hours. The crude product was purified by Prep-HPLC (conditions: C18 silica gel; mobile phase, MeCN in water, 10% to 50% gradient in 30 minutes; detector, UV 254 nm) to afford 8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-N,N-dimethyl-5-oxo-1,2,3,4,5,6-hexahydro-2,6-naphthyridine-3-carboxamide (6.8 mg, 22%) as a yellow solid.

¹H NMR (400 MHz, Methanol-d₄) δ 7.50 (s, 1H), 6.62 (s, 2H), 3.88 (s, 6H), 3.85-3.69 (m, 4H), 3.63 (s, 3H), 3.52 (dd, J=10.4, 4.8 Hz, 1H), 2.96 (dd, J=17.5, 4.7 Hz, 1H), 2.81 (s, 3H), 2.55 (dd, J=17.7, 10.4 Hz, 1H), 2.42 (s, 6H). LCMS (ESI) m/z: [M+H]⁺=415.30.

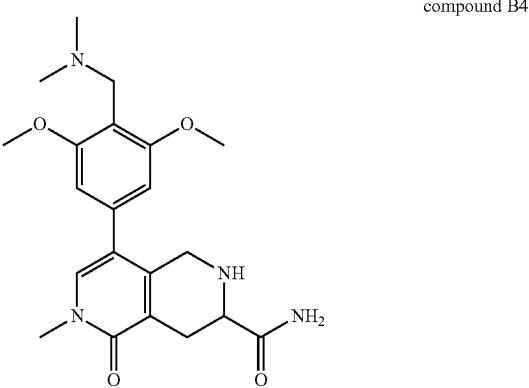
20

Preparation of 8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-1,2,3,4,5,6-hexahydro-2,6-naphthyridine-3-carboxamide (Compound B4)

25



30



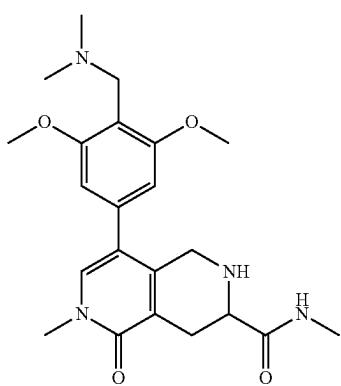
35

Preparation of 8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-N,N-dimethyl-5-oxo-1,2,3,4,5,6-hexahydro-2,6-naphthyridine-3-carboxamide (Compound B3)

40

compound B3

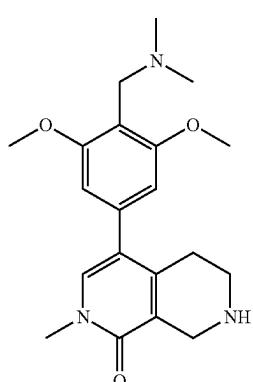
8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-1,2,3,4,5,6-hexahydro-2,6-naphthyridine-3-carboxylic acid (30.00 mg, 0.075 mmol, 1.00 equiv), HATU (42.62 mg, 0.112 mmol and 1.50 equiv), DIEA (57.95 mg, 0.448 mmol, 6.00 equiv) were dissolved in DCM (5.00 mL). Then NH₃ (2.55 mg, 0.149 mmol, 2.00 equiv) in DCM was added to the reaction, and the resulting solution was stirred at 25° C. for 3 hours. The crude product (30 mg) was purified by Prep-HPLC (conditions: C18 silica gel; mobile phase, MeCN in water, 10% to 50% gradient in 30 minutes; detector, UV 254 nm) to afford 8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-1,2,3,4,5,6-hexahydro-2,6-naphthyridine-3-carboxamide (4.7 mg, 15.71%) as a yellow solid. ¹H NMR (400 MHz, Methanol-d₄) δ 7.50 (s, 1H), 6.59 (s, 2H), 3.86 (s, 6H), 3.83-3.66 (m, 4H), 3.63 (s, 3H), 3.57 (dd, J=10.4, 4.8 Hz, 1H), 3.05-2.94 (m, 1H), 2.58 (dd, J=17.8, 10.3 Hz, 1H), 2.32 (s, 6H). LCMS (ESI) m/z: [M+H]⁺=401.30.



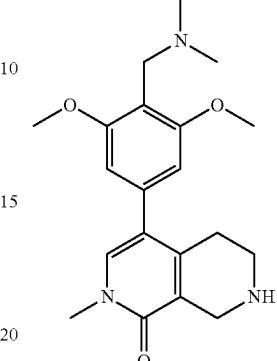
489

Example 10—Preparation of 5-((dimethylamino)methyl)-3,5-dimethoxyphenyl)-N-ethyl-7-methyl-8-oxo-3,4,7,8-tetrahydro-2,7-naphthyridine-2 (1H)-carboxamide (Compound B5)

5

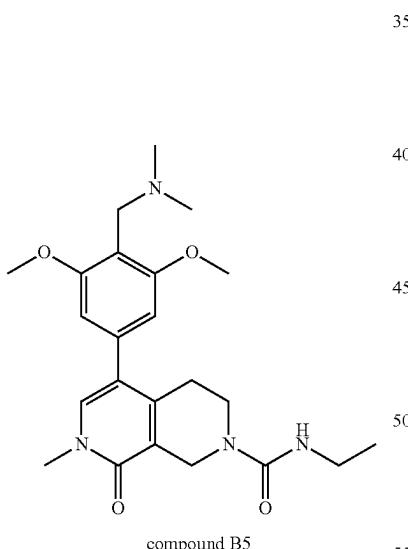


compound B17

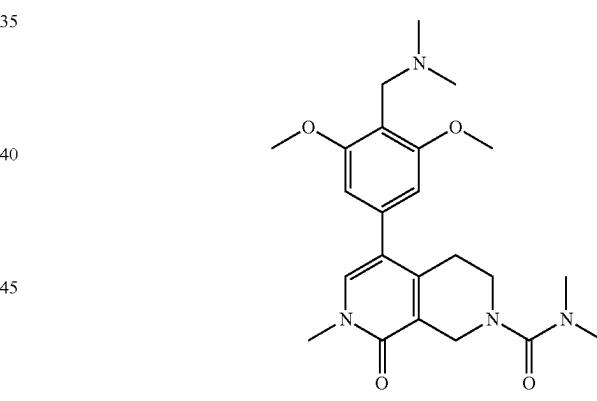


compound B17

25



compound B5



compound B6

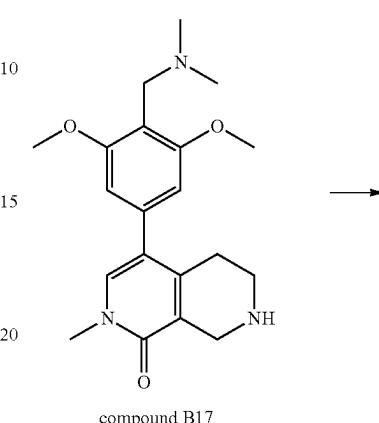
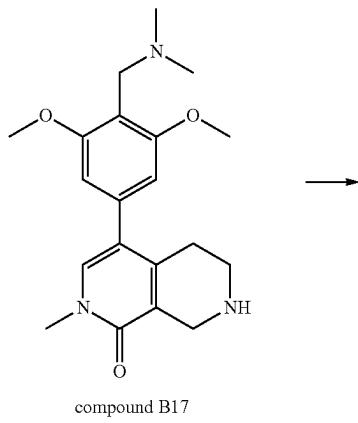
To a solution of 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (30 mg, 83.9 μ mol, 1 equiv) in DCM (1 mL) was added triethylamine (15.1 μ L, 109 μ mol, 1.3 equiv) and N,N-dimethylcarbamoyl chloride (8.48 μ L, 92.2 μ mol, 1.1 equiv) at RT. The reaction was stirred at RT for 2 hours. The reaction mixture was concentrated in vacuo. The crude was purified by flash chromatography eluting with 0-15% MeOH with 0.1% NH₄OH in DCM to afford 5-((dimethylamino)methyl)-3,5-dimethoxyphenyl)-N,N,7-trimethyl-8-oxo-3,4,7,8-tetrahydro-2,7-naphthyridine-2 (1H)-carboxamide (5.2 mg, 14.5 yield) as a white solid. ¹H NMR (400 MHz, Chloroform-d) δ 7.14 (s, 1H), 6.40 (s, 2H), 4.33 (s, 2H), 3.83 (s, 6H), 3.58 (s, 3H), 3.58 (m, 2H), 3.37 (t, J=5.6 Hz, 2H), 2.89 (s, 5H), 2.63-2.52 (m, 2H), 1.25 (s, 6H). LCMS (ESI) m/z: [M+H]⁺= 429.2.

Using the same procedure as for the synthesis of Compound B9 and substituting with ethyl isocyanate afforded 5-((dimethylamino)methyl)-3,5-dimethoxyphenyl)-N-ethyl-7-methyl-8-oxo-3,4,7,8-tetrahydro-2,7-naphthyridine-2 (1H)-carboxamide (18.8 mg, 521% yield) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 7.61 (s, 1H), 6.61 (t, J=5.4 Hz, 1H), 6.55 (s, 2H), 4.19 (s, 2H), 3.75 (s, 5H), 3.47 (s, 3H), 3.43-3.34 (m, 4H), 3.11-2.97 (m, 2H), 2.09 (s, 6H), 1.00 (t, J=7.1 Hz, 3H). LCMS (ESI) m/z: [M+H]⁺= 429.2.

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Example 12—Preparation of N-butyl-5-(4-((dimethylamino)methyl)-3,5-dimethoxyphenyl)-7-methyl-8-oxo-3,4,7,8-tetrahydro-2,7-naphthyridine-2 (1H)-carboxamide (Compound B7)

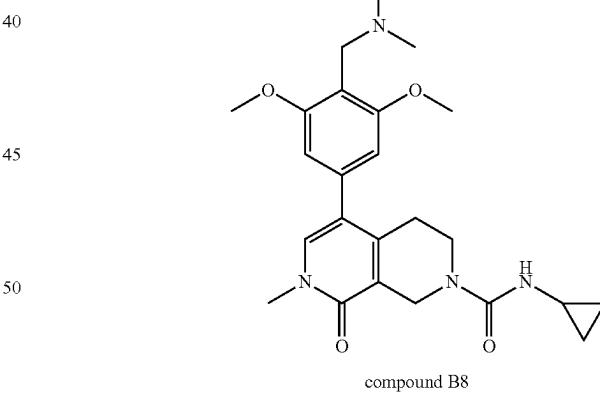
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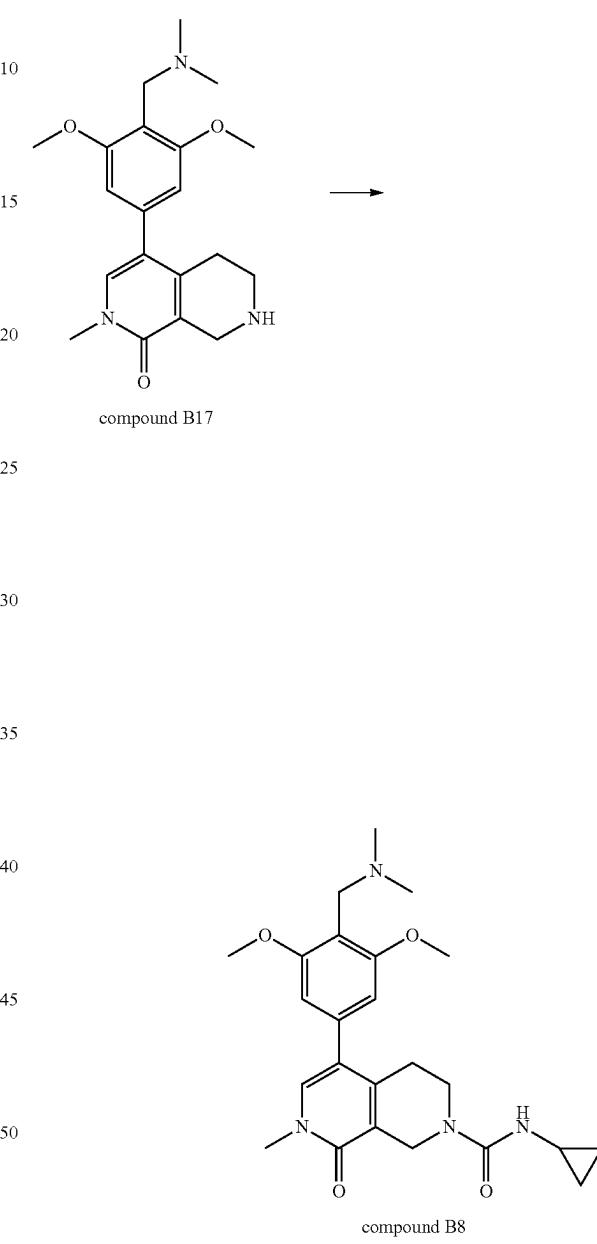
55

Using the same procedure as for the synthesis of Compound B9 and substituting with 1-isocyanatobutane afforded N-butyl-5-(4-((dimethylamino)methyl)-3,5-dimethoxyphenyl)-7-methyl-8-oxo-3,4,7,8-tetrahydro-2,7-naphthyridine-2 (1H)-carboxamide (18.8 mg, 49% yield) as a white solid. ¹H NMR (400 MHz, Chloroform-d) δ 7.18 (s, 1H), 6.37 (s, 2H), 4.68 (t, J=5.5 Hz, 1H), 4.28 (s, 2H), 3.82 (s, 6H), 3.61 (s, 3H), 3.61 (m, 2H), 3.53 (s, 1H), 3.28 (td, J=7.1, 5.3 Hz, 2H), 2.57 (t, J=5.6 Hz, 2H), 2.30 (s, 6H), 1.59-1.45 (m, 9H), 1.43-1.30 (m, 2H), 0.93 (t, J=7.3 Hz, 3H). LCMS (ESI) m/z: [M+H]⁺=457.2.

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Example 13—Preparation of N-cyclopropyl-5-(4-((dimethylamino)methyl)-3,5-dimethoxyphenyl)-7-methyl-8-oxo-3,4,7,8-tetrahydro-2,7-naphthyridine-2 (1H)-carboxamide (Compound B8)

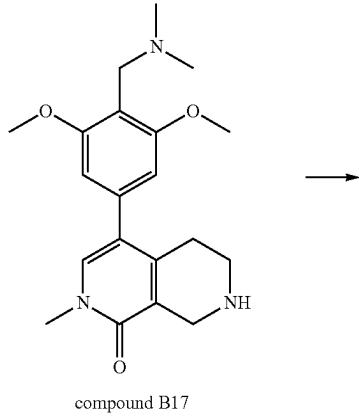
60



Using the same procedure as for the synthesis of Compound B9 and substituting with cyclopropyl isocyanate afforded N-cyclopropyl-5-(4-((dimethylamino)methyl)-3,5-dimethoxyphenyl)-7-methyl-8-oxo-3,4,7,8-tetrahydro-2,7-naphthyridine-2 (1H)-carboxamide (7.8 mg, 21% yield) as a white solid. ¹H NMR (400 MHz, Chloroform-d) δ 7.18 (s, 1H), 6.37 (s, 2H), 4.93 (d, J=1.9 Hz, 1H), 4.23 (s, 2H), 3.82 (s, 6H), 3.60 (d, J=2.2 Hz, 5H), 3.54 (s, 2H), 2.70 (ddd, J=6.9, 4.6, 2.7 Hz, 1H), 2.56 (t, J=5.7 Hz, 2H), 2.31 (s, 6H), 1.25 (s, 6H), 0.79-0.69 (m, 2H), 0.56-0.38 (m, 2H). LCMS (ESI) m/z: [M+H]⁺=441.2.

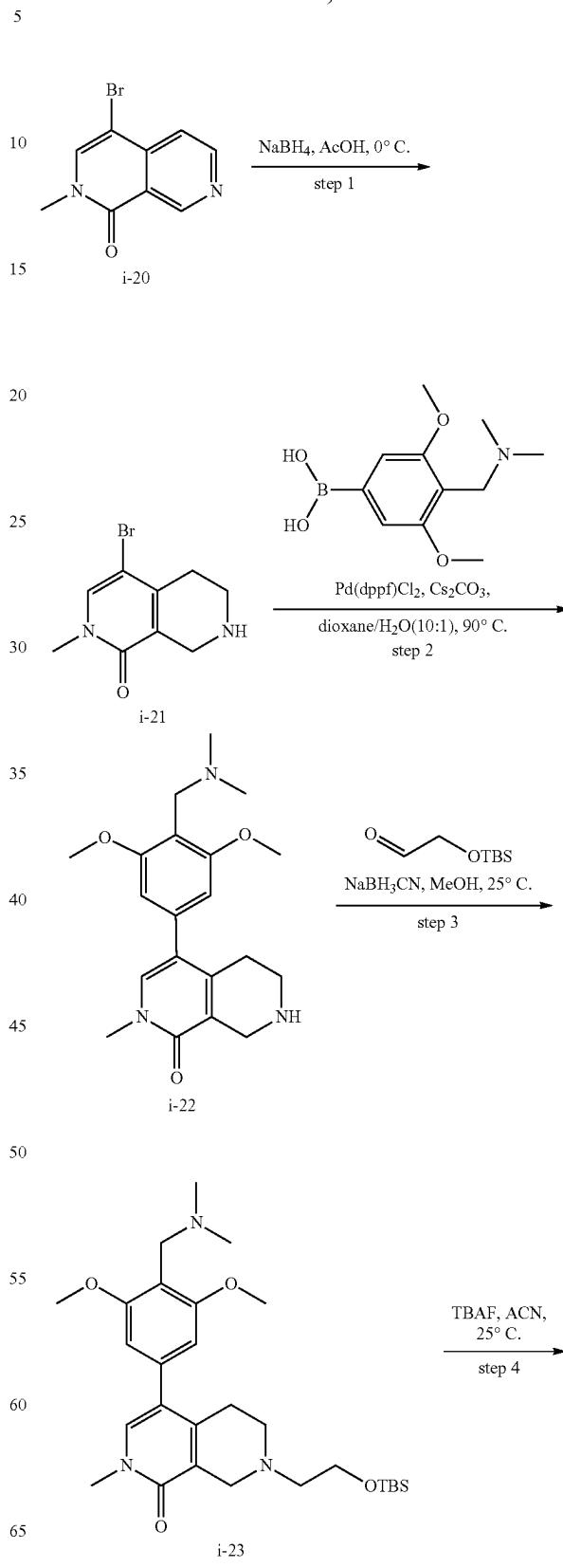
493

Example 14—Preparation of 5-(4-((dimethylamino)methyl)-3,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4,7,8-tetrahydro-2,7-naphthyridine-2 (1H)-carboxamide (Compound B9)



494

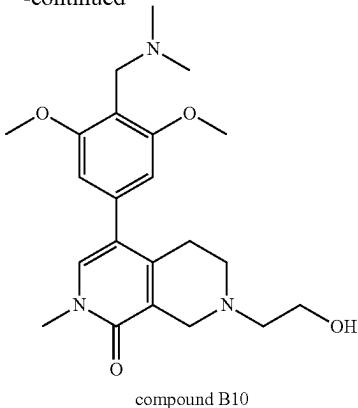
Example 15—Preparation of N-(6-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-3-methyl-1-[1,2,4]triazolo[4,3-a]pyridin-8-yl)acetamide (Compound B10)



To a solution of 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (20 mg, 55.9 μ mol, 1 equiv) in anhydrous DCM (1 mL) was added N-methyl-1H-imidazole-1-carboxamide (7.7 mg, 61.4 μ mol, 1.1 equiv) and triethylamine (10 μ L, 72.6 μ mol, 1.3 equiv). The reaction mixture was stirred at room temperature for 3 hours and concentrated in vacuo. The crude was purified by flash chromatography eluting with 0-15% MeOH w 0.1% NH₄OH in DCM to afford 5-(4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4,7,8-tetrahydro-2,7-naphthyridine-2-(1H)-carboxamide (4.0 mg, 18% yield) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 7.60 (s, 1H), 6.55 (s, 2H), 6.54 (bs, 1H), 4.19 (s, 2H), 3.75 (s, 6H), 3.47 (s, 3H), 3.39 (dd, J=12.4, 7.0 Hz, 4H), 2.57 (d, J=4.3 Hz, 3H), 2.48 (m, 2H), 2.10 (s, 6H). LCMS (ESI) m/z: [M+H]⁺=415.3.

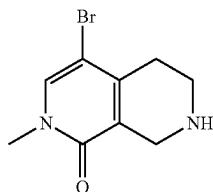
495

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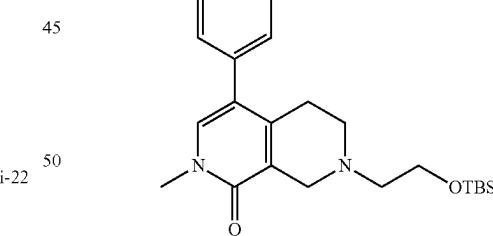
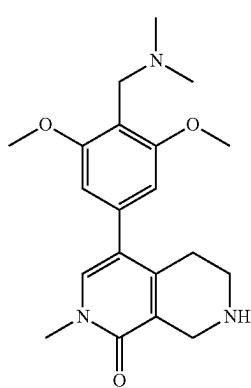
Step 1: Preparation of 4-bromo-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (i-21)

Step 3: Preparation of 7-[2-[(tert-butyldimethylsilyl)oxy]ethyl]-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (i-23)



To a solution of 4-bromo-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (238 mg, 0.996 mmol, 1 equiv) in AcOH (2.0 mL) was added NaBH₄ (263.64 mg, 6.969 mmol, 7 equiv). The mixture was stirred at 0° C. for 1 hour. Ammonium hydroxide was added to the resulting mixture until pH above 7, and then the resulting mixture was extracted with DCM (30 mL×3). The combined organic layers were dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH (10:1) to afford 4-bromo-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (180 mg, 74.38%) as a white solid. LCMS (ESI) m/z: [M+H]⁺=243.

Step 2: Preparation of 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (i-22)



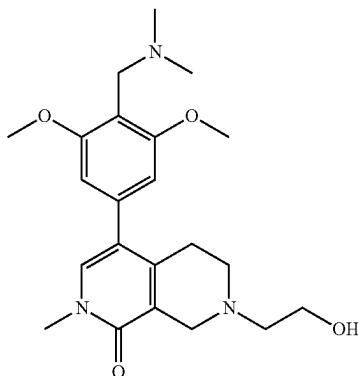
To a solution of 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (200 mg, 0.560 mmol, 1 equiv) and 2-[(tert-butyldimethylsilyl)oxy]acetaldehyde (146.30 mg, 0.839 mmol, 1.5 equiv) in MeOH (5 mL) was added NaBH₃CN (105.48 mg, 1.679 mmol, 3.0 equiv). The mixture was stirred at 25° C. for 1 hour. Then the mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1:1) to afford 7-[2-[(tert-butyldimethylsilyl)oxy]ethyl]-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (224 mg, 77.5%) as a brown oil. LCMS (ESI) m/z: [M+H]⁺=516.

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To a solution of 4-bromo-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (242 mg, 0.995 mmol, 1 equiv) and [4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]boronic acid (237.99 mg, 0.995 mmol, 1 equiv) in dioxane (5 mL) and H₂O (0.5 mL) was added Pd(dppf)Cl₂ (72.84 mg, 0.100 mmol, 0.1 equiv) and Cs₂CO₃ (973.02 mg, 2.986 mmol, 3.0 equiv). The resulting solution was stirred at 90° C. for 2 hours under N₂. The mixture was diluted with 50 mL of H₂O, and the resulting mixture was extracted with DCM (30 mL×3). The combined organic layers were dried over sodium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH (10:1) to afford 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (200 mg, 56.21%) as a yellow solid. LCMS (ESI) m/z: [M+H]⁺=358.

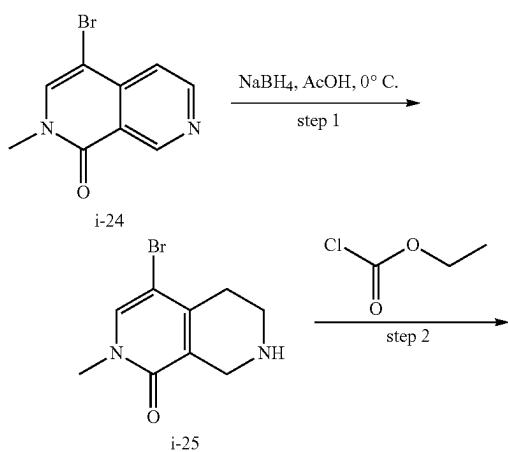
497

Step 4: Preparation of 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-(2-hydroxyethyl)-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (Compound B10)

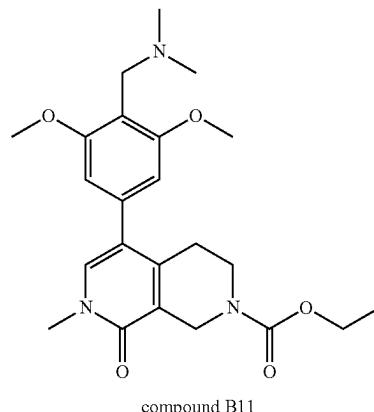
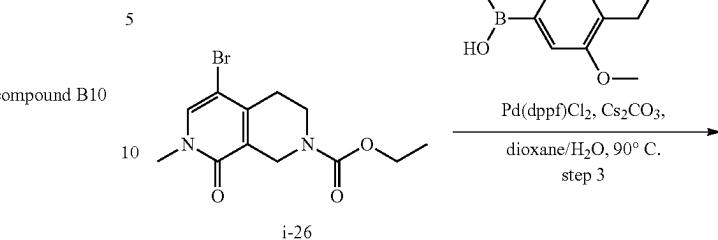


To a solution of 7-[2-[(tert-butyldimethylsilyl)oxy]ethyl]-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (90 mg, 0.174 mmol, 1 equiv) was dissolved in ACN (2.0 mL) was added TBAF (91.25 mg, 0.349 mmol, 2.0 equiv). The resulting solution was stirred at 25° C. for 1 hour. The mixture was concentrated under reduced pressure. The residue was purified by Prep-(conditions: column, Xselect Peptide CSH 19*150 mm 5 μm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: MeOH-HPLC; Flow rate: 25 mL/minute; Gradient: 15% B to 15% B in 12 minutes; 220 nm; R_f: 9.51 minutes; detector, UV 254 nm) to afford gave 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-(2-hydroxyethyl)-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (10 mg, 14.27%) as a yellow solid. ¹H NMR (300 MHz, Methanol-d4) δ 7.51 (s, 1H), 6.61 (s, 2H), 3.87 (s, 6H), 3.83-3.72 (m, 4H), 3.60 (d, J=14.7 Hz, 5H), 2.79-2.68 (m, 6H), 2.37 (s, 6H). LCMS (ESI) m/z: [M+H]⁺=402.40.

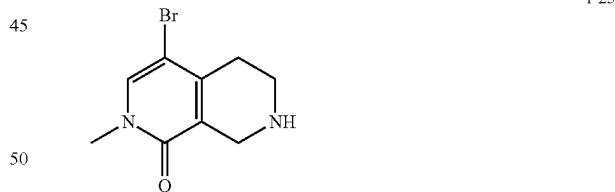
Example 16—Preparation of Ethyl 5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-1,2,3,4,7,8-hexahydro-2,7-naphthyridine-2-carboxylate (Compound B11)

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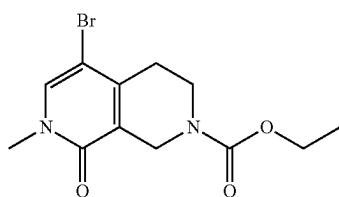
Step 1: Preparation of 4-Bromo-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (i-25)



To a solution of 4-bromo-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (500 mg, 2.091 mmol, 1 equiv) in AcOH (4.20 mL) was added NaBH₄ (553.87 mg, 14.640 mmol, 7 equiv) at 0° C. The resulting solution was stirred at 0° C. for 1 hour. Ammonia was added to the resulting mixture until pH above 7. Then the mixture was diluted with water (10 mL) and extracted with DCM (30 mL×3). The combined organic layers were dried over saturated sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH (10:1) to afford 4-bromo-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (520 mg, 74.38%) as a white solid. LCMS (ESI) m/z: [M+H]⁺=243.

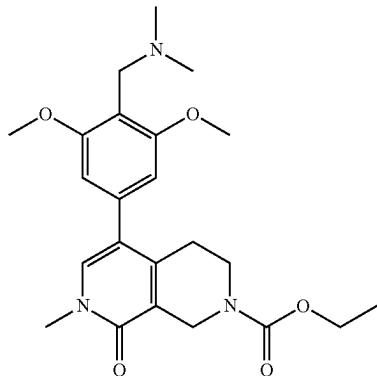
499

Step 2: Preparation of ethyl 5-bromo-7-methyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxylate (i-26)



To a solution of 4-bromo-2-methyl-5,6,7,8-tetrahydro-2,7-naphthyridin-1-one (100.00 mg, 0.411 mmol, 1.00 equiv) in (5.00 mL) was added NaH (19.74 mg, 0.494 mmol, 1.20 equiv, 60%). Then ethyl chloroformate (66.96 mg, 0.617 mmol, 1.50 equiv) was added at 0° C. The resulting mixture was stirred for 2 hours at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE/EtOAc 5:1) to afford ethyl 5-bromo-7-methyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxylate (120 mg, 92.56%) as a yellow solid. LCMS (ESI) m/z: [M+H]⁺=315.

Step 3: Preparation of ethyl 5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-1,2,3,4,7,8-hexahydro-2,7-naphthyridine-2-carboxylate (Compound B11)

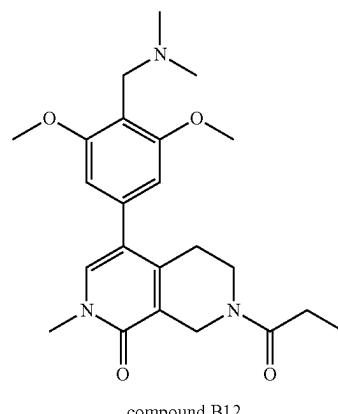
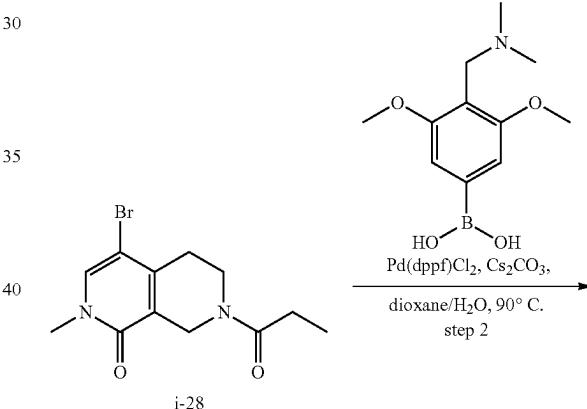
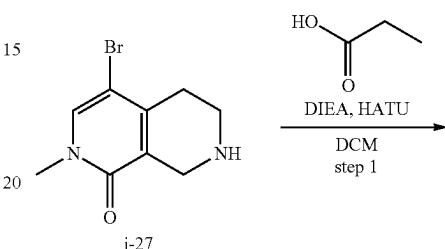


To a solution of ethyl 5-bromo-7-methyl-8-oxo-1,2,3,4,7,8-hexahydro-2,7-naphthyridine-2-carboxylate (96 mg, 0.305 mmol, 1 equiv) and [4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]boronic acid (72.82 mg, 0.305 mmol, 1 equiv) in dioxane (2 mL) and H₂O (0.5 mL) was added Cs₂CO₃ (297.73 mg, 0.914 mmol, 3 equiv) and Pd(dppf)Cl₂ (33.43 mg, 0.046 mmol, 0.15 equiv). The resulting solution was stirred at 90° C. for 2 hours (under N₂ atmosphere). The resulting mixture was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (conditions: XBridge Shield RP18 OBD Column, 5 μm, 19*150 mm; Mobile Phase A: Water (0.05% NH₃/H₂O), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 24% B to 37% B in 8 minutes; 220 nm; Rt: 7.9 minutes) to afford ethyl 5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-1,2,3,4,7,8-hexahydro-2,7-naphthyridine-2-

500

carboxylate (8.2 mg, 6.09%) as a light brown solid. ¹H NMR (300 MHz, Methanol-d4) δ 7.56 (s, 1H), 6.61 (s, 2H), 4.47 (s, 2H), 4.20 (q, J=7.1 Hz, 2H), 3.87 (s, 6H), 3.71 (s, 2H), 3.62 (d, J=8.9 Hz, 5H), 2.65 (t, J=5.8 Hz, 2H), 2.34 (s, 6H), 1.31 (t, J=7.1 Hz, 3H). LCMS (ESI) m/z: [M+H]⁺=430.20.

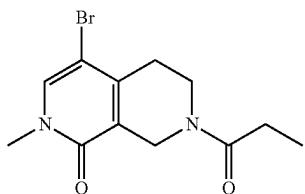
Example 17—Preparation of 4-(3,5-dimethoxy-4-methylphenyl)-2-methyl-7-propanoyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (Compound B12)



compound B12

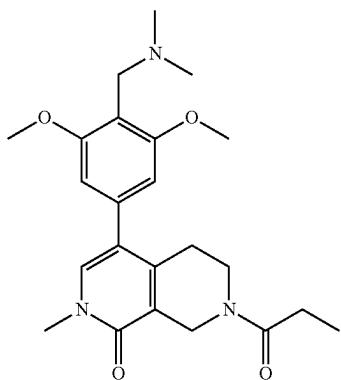
501

Step 1: Preparation of 4-bromo-2-methyl-7-propanoyl-6,8-dihydro-5H-2,7-naphthyridin-1-one (i-28)



To a stirred mixture of 4-bromo-2-methyl-5,6,7,8-tetrahydro-2,7-naphthyridin-1-one (500.00 mg, 2.057 mmol, 1.00 equiv) and propanoic acid (182.83 mg, 2.468 mmol, 1.20 equiv) in DCM (25.00 mL) was added DIEA (79.75 mg, 0.617 mmol, 3.00 equiv). The mixture was stirred at room temperature for 5 minutes, then HATU (938.44 mg, 2.468 mmol, 1.20 equiv) was added. The mixture was stirred for 2 hours at room temperature, and the resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH₂Cl₂/MeOH (20:1) to afford 4-bromo-2-methyl-7-propanoyl-6,8-dihydro-5H-2,7-naphthyridin-1-one (502 mg, 78.88%) as a white solid.

Step 2: Preparation of 4-(3,5-dimethoxy-4-methylphenyl)-2-methyl-7-propanoyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (Compound B12)



To a solution of 4-bromo-2-methyl-7-propanoyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (200 mg, 0.669 mmol, 1 equiv) and [4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]boronic acid (191.80 mg, 0.802 mmol, 1.20 equiv) in dioxane (10 mL) and H₂O (1 mL) was added Cs₂CO₃ (653.45 mg, 2.006 mmol, 3.00 equiv) and Pd(dppf) Cl₂·CH₂Cl₂ (49.13 mg, 0.060 mmol, 0.09 equiv). After stirring for 2 hours at 90° C. under a nitrogen atmosphere, the resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH (10/1) to afford 4-(3,5-dimethoxy-4-methylphenyl)-2-methyl-7-propanoyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (130 mg, 51.44%). ¹H NMR (400 MHz, Methanol-d4) δ 7.61 (d, J=10.5 Hz, 1H), 6.75 (d, J=6.3 Hz, 2H), 4.56 (d, J=14.2 Hz, 1H), 4.39

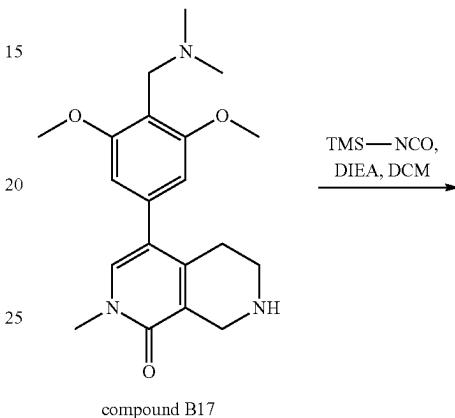
502

(s, 2H), 3.96 (d, J=2.6 Hz, 6H), 3.76-3.57 (m, 5H), 2.90 (s, 6H), 2.72 (d, J=6.1 Hz, 1H), 2.64 (s, 1H), 2.53 (dq, J=15.0, 7.5 Hz, 1H), 1.31 (s, 1H), 1.17 (td, J=7.5, 3.8 Hz, 3H). LCMS (ESI) m/z: [M+H]⁺=414.30.

5

i-28

Example 18—Preparation of 7-acetyl-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (Compound B13)



compound B17

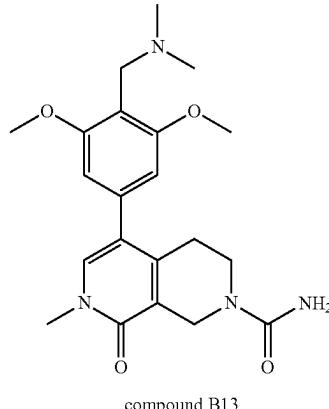
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compound B12

35

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45



compound B13

To a stirred solution of 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (45.4 mg, 0.127 mmol, 1 equiv) in DCM (3 mL) was added isocyanatotrimethylsilane (29.26 mg, 0.254 mmol, 2 equiv) and TEA (38.56 mg, 0.381 mmol, 3 equiv). The resulting mixture was stirred for 2 hours at room temperature. The crude product was purified by Prep-HPLC (conditions: XBridge Prep Phenyl OBD Column 5 μm, 19*250 mm; Mobile Phase A: Water (10 mmol/L NH₄HCO₃), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 14% B to 20% B in 8 minutes; 254 nm; R_f: 7.18 minutes) to afford 5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-1,2,3,4,7,8-hexahydro-2,7-naphthyridine-2-carboxamide (6.6 mg, 12.35%) as a white solid. ¹H NMR (400 MHz, MeOD) δ 7.57 (s, 1H), 6.61 (s, 2H), 4.41 (s, 2H), 3.87 (s, 6H), 3.68 (s, 2H), 3.64 (s, 3H), 3.55 (t, 2H), 2.68-2.65 (m, 2H), 2.31 (s, 6H). LCMS (ESI) m/z: [M+H]⁺=401.4.

55

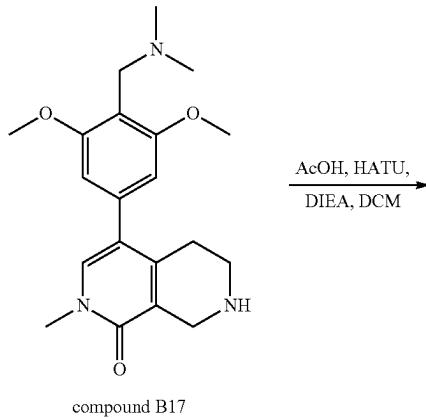
60

65

503

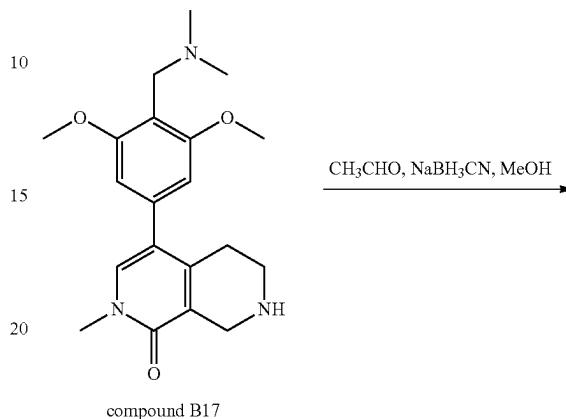
Example 19—Preparation of 7-acetyl-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (Compound B14)

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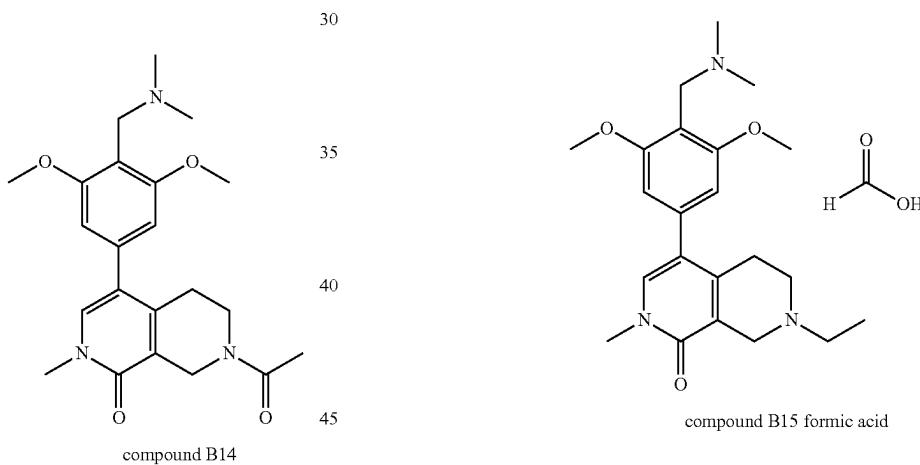
**504**

Example 20—Preparation of 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-ethyl-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one formic acid (Compound B15 formic acid)

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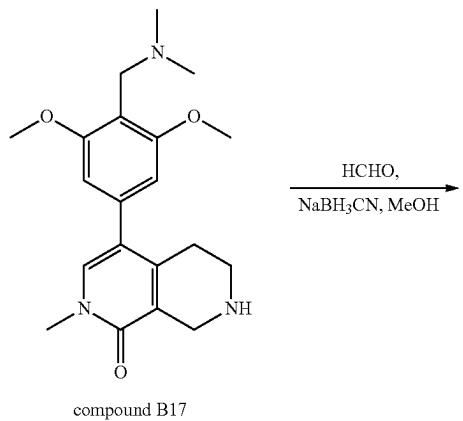


To the solution of 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (35.7 mg, 0.100 mmol, 1 equiv) in DCM (3 mL) was added acetic acid (7.20 mg, 0.120 mmol, 1.2 equiv), HATU (56.96 mg, 0.150 mmol, 1.5 equiv), and DIEA (38.72 mg, 0.300 mmol, 3 equiv). The resulting solution was stirred at room temperature for 1 hour. The resulting solution was concentrated. The crude product was purified by Prep-HPLC (conditions: XBridge Shield RP18 OBD Column, 5 μ m, 19*150 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 0% B to 15% B in 8 minutes; 254/220 nm; R_f: 7.03 minutes) to afford 7-acetyl-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (7.3 mg, 17.64%) as a white solid. ¹H NMR (400 MHz, MeOD) δ 7.58 (d, 1H), 6.61 (d, 2H), 4.55 (d, 2H), 3.87 (d, 6H), 3.75-3.67 (m, 3H), 3.64 (d, 4H), 2.74 (t, 1H), 2.64 (t, 1H), 2.33 (d, 6H), 2.22 (d, 3H). LCMS (ESI) m/z: [M+H]⁺= 400.25.

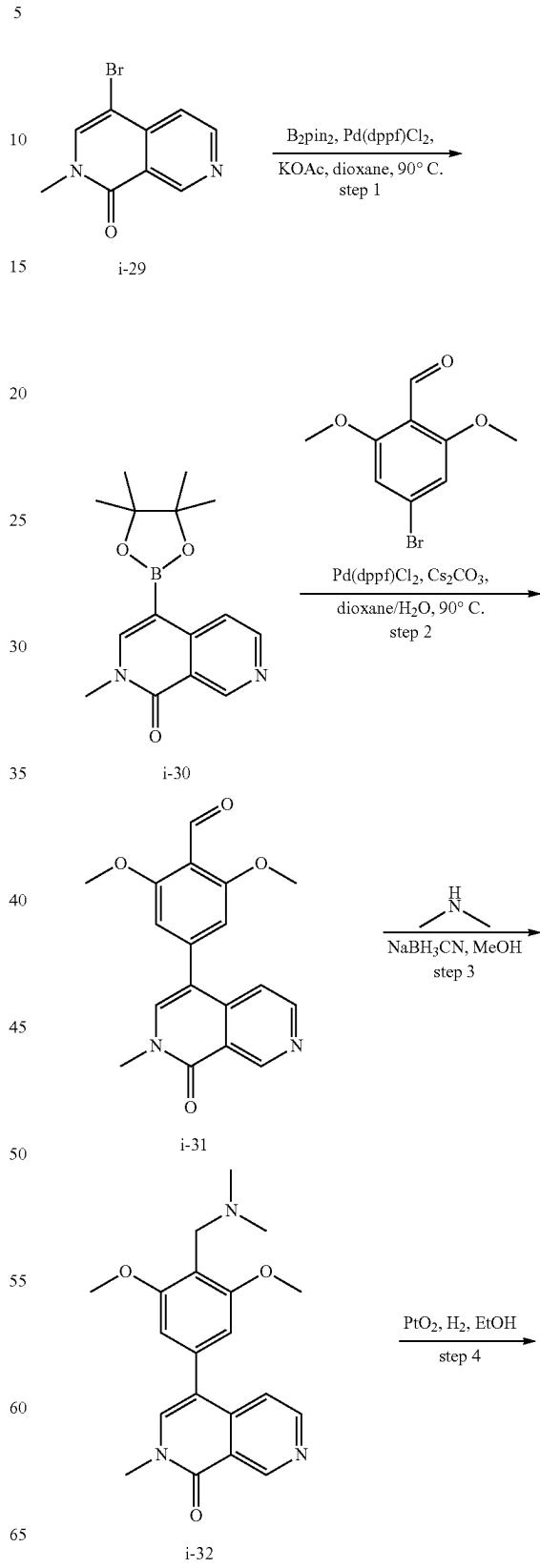
To the solution of 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (20 mg, 0.056 mmol, 1 equiv) in MeOH (2 mL) was added acetaldehyde (24.65 mg, 0.560 mmol, 10 equiv) and NaBH₃CN (10.55 mg, 0.168 mmol, 3 equiv). The resulting solution was stirred at room temperature for 1 hour. The resulting solution was concentrated. The crude product was purified by Prep-HPLC (conditions: XBridge Shield RP18 OBD Column, 5 μ m, 19*150 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 0% B to 15% B in 8 minutes; 254/220 nm; R_f: 7.03 minutes) to afford 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-ethyl-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one formic acid (10.1 mg) as a white oil. ¹H NMR (400 MHz, Methanol-d4) δ 8.47 (s, 1H), 7.59 (s, 1H), 6.73 (s, 2H), 4.38 (s, 2H), 3.96 (s, 6H), 3.74 (s, 2H), 3.64 (s, 3H), 2.89 (s, 1 OH), 2.76 (t, J=5.8 Hz, 2H), 1.31 (t, J=7.2 Hz, 3H). LCMS (ESI) m/z: [M+H]⁺= 386.30.

505

Example 21—Preparation of 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2,7-dimethyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one formic acid (Compound B16 formic acid)

**506**

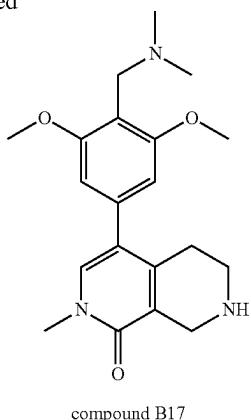
Example 22—Preparation of 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (Compound B17)



To the solution of 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (20 mg, 0.056 mmol, 1 equiv) in MeOH (2 mL) was added formaldehyde (16.80 mg, 0.560 mmol, 10 equiv), NaBH₃CN (10.55 mg, 0.168 mmol, 3 equiv). The resulting solution was stirred at room temperature for 1 hour. The resulting solution was concentrated. The crude product was purified by Prep-HPLC (conditions: XBridge Shield RP18 OBD Column, 5 μm, 19*150 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 0% B to 15% B in 8 minutes; 254/220 nm; R_f: 7.12 minutes) to afford 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2,7-dimethyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one formic acid (10.8 mg) as a white oil. ¹H NMR (400 MHz, Methanol-d4) δ 8.48 (s, 1H), 7.58 (s, 1H), 6.73 (s, 2H), 4.38 (s, 2H), 3.96 (s, 6H), 3.67 (s, 2H), 3.63 (s, 3H), 2.89 (s, 6H), 2.84 (t, J=5.7 Hz, 2H), 2.75 (d, J=5.8 Hz, 2H), 2.66 (s, 3H). LCMS (ESI) m/z: [M+H]⁺=372.25.

507

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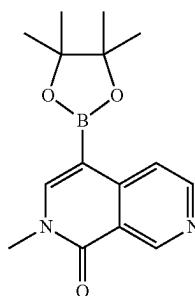
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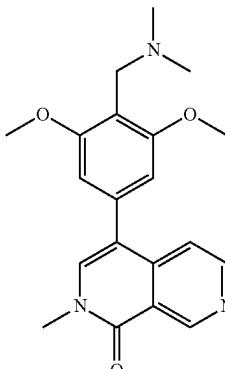
Step 1: Preparation of 2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydro-2,7-naphthyridin-1-one (i-30)



i-30

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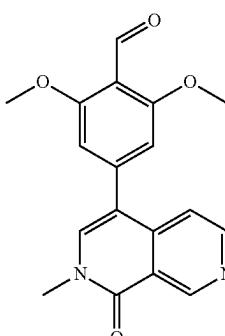
i-32



To the solution of 4-bromo-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (2.7 g, 11.294 mmol, 1 equiv) in dioxane (15 mL) was added 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (3.44 g, 13.552 mmol, 1.2 equiv), Pd(dppf)Cl₂ (0.83 g, 1.129 mmol, 0.1 equiv), and AcOK (3.33 g, 33.881 mmol, 3 equiv). The resulting solution was stirred at 90° C. for 2 hours under nitrogen atmosphere. The resulting solution was concentrated. The residue was purified by Flash column chromatography with EtOAc/PE (0-100%) to afford 2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydro-2,7-naphthyridin-1-one (1.62 g, 50.13%) as light yellow solid. LCMS (ESI) m/z: [M+H]⁺=287.

508

Step 2: Preparation of 2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzaldehyde (i-31)



i-31

To the solution of 2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydro-2,7-naphthyridin-1-one (1.62 g, 5.662 mmol, 1 equiv) in dioxane (30 mL) was added 4-bromo-2,6-dimethoxybenzaldehyde (1.39 g, 5.662 mmol, 1 equiv), Pd(dppf)Cl₂ (414.26 mg, 0.566 mmol, 0.1 equiv), Cs₂CO₃ (5.53 g, 16.985 mmol, 3 equiv), H₂O (3 mL). The resulting solution was stirred at 90° C. for 2 hours under nitrogen atmosphere. The solution was concentrated. The residue was purified by Flash column chromatography with EtOAc/PE (0-100%) to give compound 2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzaldehyde (1.02 g, 55.55%) as yellow solid. LCMS (ESI) m/z: [M+H]⁺=325.

Step 3: Preparation of 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (i-32)

i-30

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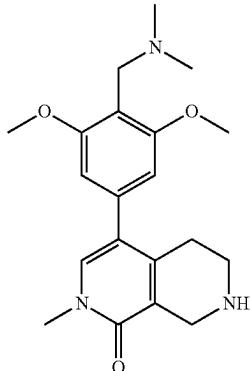
To the solution of 2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzaldehyde (1.20 g, 3.700 mmol, 1.00 equiv) in MeOH (10.00 mL) was added dimethylamine (362.02 mg, 4.440 mmol, 1.20 equiv) and NaBH₃CN (697.52 mg, 11.100 mmol, 3.00 equiv). The resulting solution was stirred at room temperature for 2 hours. The residue was purified by silica gel column chromatography, eluted with CH₂Cl₂/MeOH (20:1) to afford 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-

US 12,384,776 B2

509

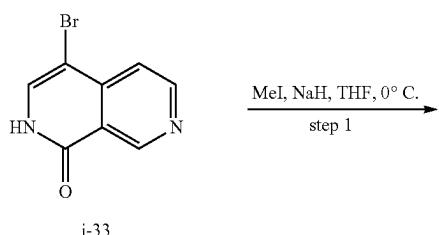
methyl-1,2-dihydro-2,7-naphthyridin-1-one (1 g, 76.48%)
as a yellow solid. LCMS (ESI) m/z: [M+H]⁺=354.

Step 4: Preparation of 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (Compound B17)



To a stirred solution of 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (1 g, 2.829 mmol, 1 equiv) in MeOH (15 mL) was added PtO₂ (1 g, 4.404 mmol, 1.56 equiv). The resulting mixture was stirred for 6 hours at room temperature under hydrogen atmosphere. The resulting mixture was filtered, the filter cake was washed with methanol (3×100 mL). The filtrate was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (conditions: XBridge Prep C18 OBD Column, 5 μm, 19*150 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 15% B to 35% B in 8 minutes; 254/220 nm; R_f: 5.35 minutes) to afford 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (27.2 mg, 2.59%) as a light yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ 7.54 (s, 1H), 6.55 (s, 2H), 3.77 (s, 6H), 3.60 (s, 2H), 3.46 (s, 3H), 3.36 (s, 3H), 2.80 (s, 2H), 2.40 (s, 2H), 2.11 (s, 6H). LCMS (ESI) m/z: [M+H]⁺=358.30.

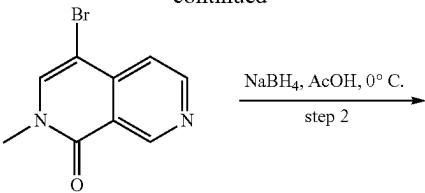
Example 23—Preparation of 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (Compound B17)



510

-continued

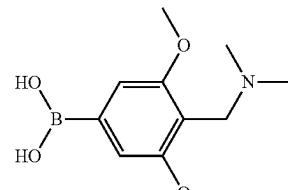
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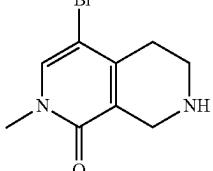
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compound B17

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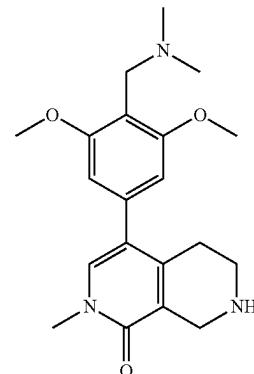


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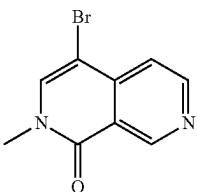
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i-35



Step 1: Preparation of 4-bromo-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (i-34)

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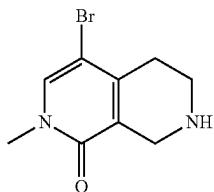


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To a solution of 4-bromo-1,2-dihydro-2,7-naphthyridin-1-one (4.96 g, 22.040 mmol, 1 equiv) and NaH (0.74 g, 30.856 mmol, 1.40 equiv) in DMF (30 mL, 387.653 mmol, 17.59 equiv) was added iodomethane (8.95 g, 63.035 mmol, 2.86 equiv). The resulting solution was stirred at 0° C. for 2 hours under N₂ atmosphere. The resulting mixture was filtered, and the filter cake was washed with ice water to afford 4-bromo-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (4.5 g, 76.86%), which was used directly without further purification. LCMS (ESI) m/z: [M+H]⁺=239.0, 241.0.

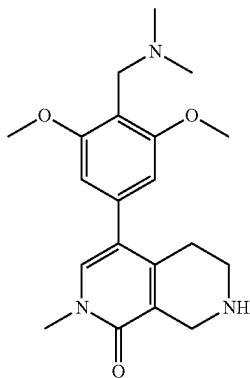
511

Step 2: Preparation of 4-bromo-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (i-35)



⁵ NaBH₄ (4.43 g, 117.120 mmol, 7 equiv) was slowly added to a solution of 4-bromo-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (4.00 g, 16.731 mmol, 1.00 equiv) in AcOH (20.00 mL). The resulting solution was stirred at 0° C. for 1 hour. Ammonia was added to the resulting mixture until pH above 7. Then the resulting mixture was extracted with DCM (3x30 mL). The combined organic layers were dried over by saturated sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH (10:1) to afford 4-bromo-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (2.2 g, 52.64%) as a yellow solid. LCMS (ESI) m/z: [M+H]⁺=243.0, 245.0.

¹⁰ Step 3: Preparation of 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (Compound B17)

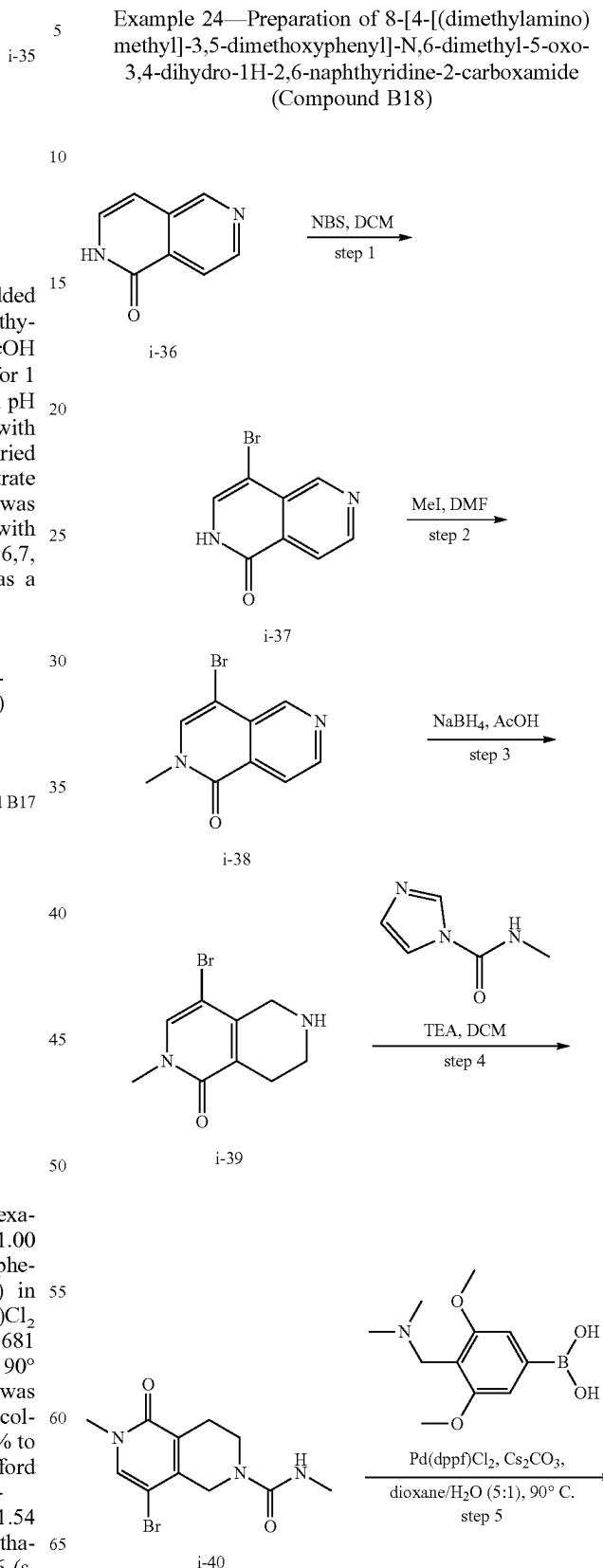


To a solution of 4-bromo-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (2.00 g, 8.227 mmol, 1.00 equiv) and [4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]boronic acid (1.97 g, 8.227 mmol, 1.00 equiv) in dioxane (30 mL) and H₂O (6 mL) was added Pd(dppf)Cl₂ (0.60 g, 0.823 mmol, 0.1 equiv) and Cs₂CO₃ (8.04 g, 24.681 mmol, 3.0 equiv). The resulting solution was stirred at 90° C. for 2 hours under N₂ atmosphere. The residue was purified by reverse flash chromatography (conditions: column, C18 silica gel; mobile phase, MeOH in water, 10% to 50% gradient in 30 minutes; detector, UV 254 nm) to afford 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (1.54 g, 52.21%) as a yellow solid. ¹H NMR (300 MHz, Methanol-d₄) δ 7.50 (s, 1H), 6.59 (s, 2H), 3.88 (s, 1H), 3.86 (s, 6H), 3.81 (s, 2H), 3.64 (d, J=14.9 Hz, 5H), 3.63 (s, 1H), 3.55

512

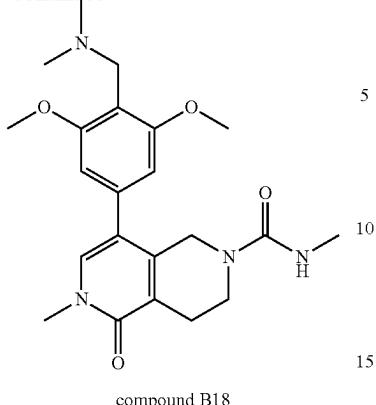
(s, 1H), 2.99 (dt, J=25.5, 5.8 Hz, 2H), 2.60 (dt, J=27.3, 5.7 Hz, 2H), 2.30 (s, 6H). LCMS (ESI) m/z: [M+H]⁺=358.25.

¹⁵ Example 24—Preparation of 8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-N,6-dimethyl-5-oxo-3,4-dihydro-1H-2,6-naphthyridine-2-carboxamide (Compound B18)

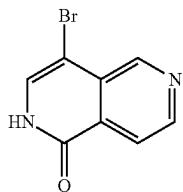


513

-continued

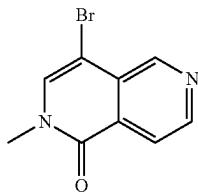


**Step 1: Preparation of
4-bromo-2H-2,6-naphthyridin-1-one (i-37)**



To a stirred solution of 2H-2,6-naphthyridin-1-one (584.00 mg, 3.996 mmol, 1.00 equiv) in DCM (10.00 mL) was added NBS (640.09 mg, 3.596 mmol, 0.9 equiv) in portions at room temperature under air atmosphere. The mixture was stirred for another 1 hour. The reaction mixture was concentrated and purified by silica gel column chromatography, eluted with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (10:1) to afford 4-bromo-2H-2,6-naphthyridin-1-one (1.2 g, 86.74%) as a light yellow solid. LCMS (ESI) m/z: [M+H]⁺=225, 227.

**Step 2: Preparation of
4-bromo-2-methyl-2,6-naphthyridin-1-one (i-38)**

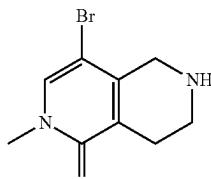


To a stirred solution of 4-bromo-2H-2,6-naphthyridin-1-one (600.00 mg, 2.666 mmol, 1.00 equiv) in DMF (15.00 mL) was added NaH (127.96 mg, 5.332 mmol, 2 equiv) in portions at 0° C. under nitrogen atmosphere. Then Mel (1513.71 mg, 10.665 mmol, 4 equiv) was added drop-wise. The mixture was stirred for another 1 hour at room temperature and quenched with water at 0° C. The product was precipitated by the addition of water. The precipitated solids were collected by filtration and washed with water (2×20

514

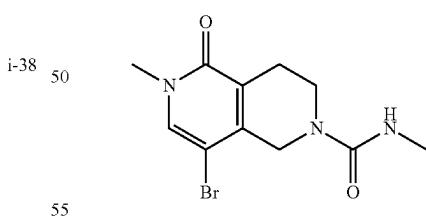
mL). The crude product 4-bromo-2-methyl-2,6-naphthyridin-1-one (369 mg, 57.89%) was used in the next step directly without further purification. LCMS (ESI) m/z: [M+H]⁺=239, 241.

Step 3: Preparation of 4-bromo-2-methyl-5,6,7,8-tetrahydro-2,6-naphthyridin-1-one (i-39)



To a stirred solution of 4-bromo-2-methyl-2,6-naphthyridin-1-one (119.50 mg, 0.500 mmol, 1.00 equiv) in AcOH (5.00 mL) was added NaBH₄ (132.38 mg, 3.499 mmol, 7.00 equiv) in portions at 0° C. under nitrogen atmosphere. The resulting mixture was stirred for 5 minutes at room temperature. Then, the mixture was poured into ice water, basified with ammonium hydroxide, and extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were concentrated under reduced pressure and the resulting crude product 4-bromo-2-methyl-5, 6, 7, 8-tetrahydro-2,6-naphthyridin-1-one (128 mg, 87.43%) was used directly in the next step. LCMS (ESI) m/z: [M+H]⁺=243, 245.

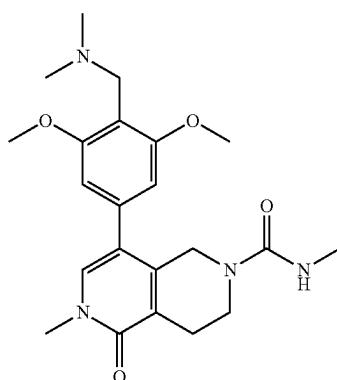
Step 4: Preparation of 8-bromo-N,6-dimethyl-5-oxo-3,4-dihydro-1H-2,6-naphthyridine-2-carboxamide (i-40)



To a stirred solution of 4-bromo-2-methyl-5,6,7,8-tetrahydro-2,6-naphthyridin-1-one (128.00 mg, 0.527 mmol, 1.00 equiv) and N-methylimidazole-1-carboxamide (79.06 mg, 0.632 mmol, 1.20 equiv) in DCM (2.00 mL) was added Et₃N (532.79 mg, 5.265 mmol, 10 equiv). The resulting mixture was stirred for 2 hours at room temperature under air atmosphere. The mixture was concentrated and purified by silica gel column chromatography, eluted with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (12:1) to afford 8-bromo-N,6-dimethyl-5-oxo-3,4-dihydro-1H-2,6-naphthyridine-2-carboxamide (153 mg, 80.35%). LCMS (ESI) m/z: [M+H]⁺=300, 302.

515

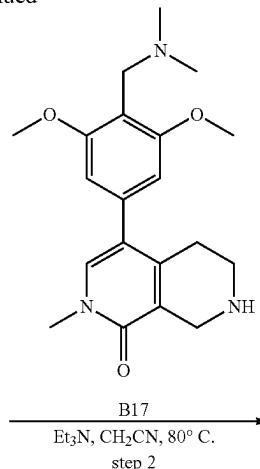
Step 5: Preparation of 8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-N,6-dimethyl-5-oxo-3,4-dihydro-1H-2,6-naphthyridine-2-carboxamide (Compound B18)



compound B18

516

-continued



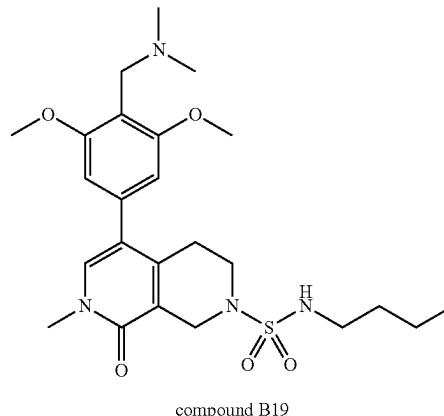
5

10

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i-41

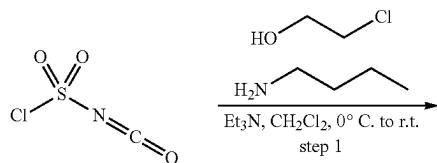
B17
Et₃N, CH₂CN, 80° C.
step 2



compound B19

To a solution of 8-bromo-N,6-dimethyl-5-oxo-3,4-dihydro-1H-2,6-naphthyridine-2-carboxamide (153.00 mg, 0.510 mmol, 1.00 equiv) and [[2,6-dimethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methyl]dimethylamine (163.74 mg, 0.510 mmol, 1 equiv) in dioxane (5.00 mL) and H₂O (1.00 mL) was added Cs₂CO₃ (498.25 mg, 1.529 mmol, 3 equiv) and Pd(dppf)Cl₂·CH₂Cl₂ (41.63 mg, 0.051 mmol, 0.1 equiv). After stirring for 1.5 hours at 100° C. under a nitrogen atmosphere, the resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH₂Cl₂/MeOH (12:1) to afford a crude product, and the crude was further purified by Prep-HPLC (conditions: Xselect CSH F-Phenyl OBD column, 19*250, 5 μm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 4 B to 22 B in 8 minutes; 254/220 nm; R_{T1}:6.32 minutes) to afford 8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-N,6-dimethyl-5-oxo-3,4-dihydro-1H-2,6-naphthyridine-2-carboxamide (49 mg, 23.19%) as a white solid. ¹H NMR (300 MHz, Methanol-d₄) δ 8.56 (brs, 0.5H, FA), 7.52 (s, 1H), 6.74 (s, 2H), 4.39 (s, 2H), 4.28 (s, 2H), 3.96 (s, 6H), 3.67-3.59 (m, 5H), 2.81 (s, 6H), 2.75-2.67 (m, 5H). LCMS (ESI) m/z: [M+H]⁺=415.35.

Example 25—Preparation of N-butyl-5-{4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl}-7-methyl-8-oxo-1,2,3,4,7,8-hexahydro-2,7-naphthyridine-2-sulfonamide (compound B19)



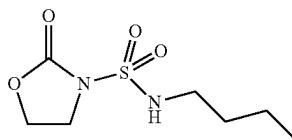
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i-41

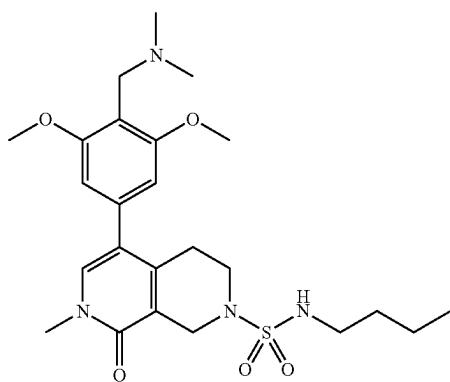


To a solution of chlorosulfonyl isocyanate (539 μL, 6.21 mmol, 1.00 equiv) in dry dichloromethane (8.8 mL) at 0° C. under nitrogen atmosphere was added a solution of 2-chloroethanol (416 μL, 6.21 mmol, 1.00 equiv) in dry dichloromethane (2.6 mL) dropwise over 30 minutes. The reaction mixture was then stirred at 0° C. for an additional 30 minutes. A solution of butylamine (674 μL, 6.83 mmol, 1.10 equiv) and triethylamine (1.88 mL, 13.6 mmol, 2.20 equiv) in dry dichloromethane (5.2 mL) was then added dropwise and the reaction mixture was warmed to room temperature and stirred for 2 hours. Then 1 N aqueous hydrochloric acid was added to adjust the pH to 2. The organic layer was separated and washed with 1 N aqueous hydrochloric acid (1×7 mL) then water (1×7 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford N-butyl-2-oxo-1,3-oxazolidine-3-sulfonamide (1.49 g,

517

100%) as a white solid. The crude product was used in the next step without further purification.

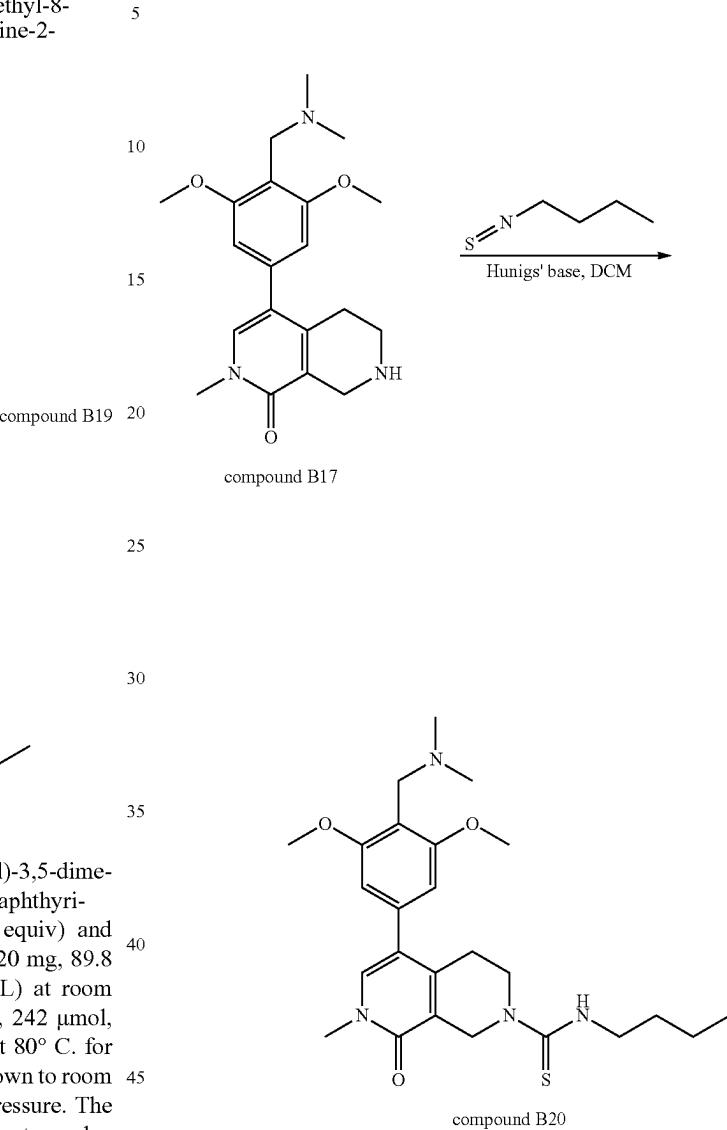
Step 2: Preparation of N-butyl-5-{4-[{dimethylamino)methyl]-3,5-dimethoxyphenyl}-7-methyl-8-oxo-1,2,3,4,7,8-hexahydro-2,7-naphthyridine-2-sulfonamide (compound B19)



To a mixture of 4-(4-((dimethylamino)methyl)-3,5-dimethoxyphenyl)-2-methyl-5,6,7,8-tetrahydro-2,7-naphthyridin-1 (2H)-one (48.0 mg, 134.6 μ mol, 1.50 equiv) and N-butyl-2-oxo-1,3-oxazolidine-3-sulfonamide (20 mg, 89.8 μ mol, 1.00 equiv) in dry acetonitrile (0.44 mL) at room temperature was added triethylamine (33.6 μ L, 242 μ mol, 2.70 equiv). The reaction mixture was stirred at 80° C. for 6 hours. The reaction mixture was then cooled down to room temperature and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography, elution gradient 0 to 100% dichloromethane/methanol/ammonium hydroxide (90:10:1) in dichloromethane. Fractions containing the expected product were evaporated to dryness to afford 15.9 mg of impure product. Purification by Prep-HPLC (conditions: waters Xterra C18 Column, 19*100 mm, 10 μ m particles; mobile phase A=0.1% ammonium hydroxide in water, mobile phase B=acetonitrile; flow Rate=40 mL/minute; gradient: 40-82% B in 6 minutes, then a 2 minutes hold at 98% B; wavelength=215 and 254 nm) afforded N-butyl-5-{4-[{dimethylamino)methyl]-3,5-dimethoxyphenyl}-7-methyl-8-oxo-1,2,3,4,7,8-hexahydro-2,7-naphthyridine-2-sulfonamide (3.5 mg, 7.9%) as a white solid. 1 H NMR (400 MHz, DMSO-d₆) δ 7.64 (s, 1H), 7.36 (s, 1H), 6.57 (s, 2H), 4.00 (s, 2H), 3.77 (s, 6H), 3.49 (s, 3H), 3.40 (s, 2H), 3.23 (t, J=5.6 Hz, 2H), 2.89 (t, J=7.0 Hz, 2H), 2.63 (t, J=5.4 Hz, 2H), 2.10 (s, 6H), 1.46-1.37 (m, 2H), 1.34-1.25 (m, 2H), 0.85 (t, J=7.3 Hz, 3H). LCMS (ESI) m/z: [M+H]⁺=493.6.

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Example 26—Preparation of N-butyl-5-{4-((dimethylamino)methyl)-3,5-dimethoxyphenyl}-7-methyl-8-oxo-3,4,7,8-tetrahydro-2,7-naphthyridine-2 (1H)-carbothioamide (compound B20)

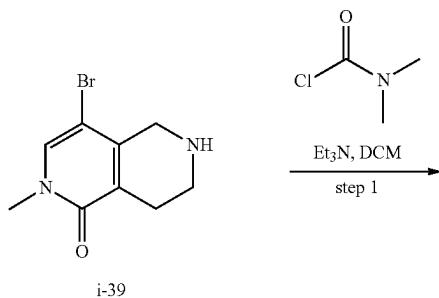


4-(4-((dimethylamino)methyl)-3,5-dimethoxyphenyl)-2-methyl-5,6,7,8-tetrahydro-2,7-naphthyridin-1 (2H)-one (25 mg, 0.069 mmol, 1.00 equiv) was dissolved in dichloromethane. Diisopropylethylamine (0.0126 mL, 0.104 mmol, 1.50 equiv) was then added followed by 1-isothiocyanatobutane (0.0133 mL, 0.0768 mmol, 1.10 equiv). The reaction was allowed to stir at room temperature for 1 hour. The solvent was removed under reduced pressure and the resulting oil was purified by prep-HPLC to obtain N-butyl-5-{4-((dimethylamino)methyl)-3,5-dimethoxyphenyl}-7-methyl-8-oxo-3,4,7,8-tetrahydro-2,7-naphthyridine-2 (1H)-carbothioamide (30 mg, 47%). 1 H NMR (400 MHz, DMSO-d₆) δ 8.16 (s, 1H), 7.80 (t, J=5.3 Hz, 1H), 7.65 (s, 1H), 6.59 (s, 2H), 4.59 (s, 2H), 3.87 (q, J=5.1, 4.7 Hz, 2H), 3.77 (s, 6H), 3.51 (d, J=15.7 Hz, 7H), 3.15 (s, 1H), 2.57 (t, J=5.6 Hz, 2H), 2.19 (s, 6H), 1.52 (tt, J=8.0, 6.6 Hz, 2H), 1.27 (h, J=7.3 Hz, 2H), 0.87 (t, J=7.3 Hz, 3H). LCMS (ESI) m/z: [M+H]⁺=473.4.

519

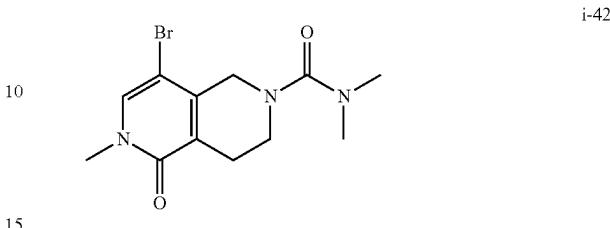
Example 27—Preparation of 8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-N,N,6-trimethyl-5-oxo-3,4-dihydro-1H-2,6-naphthyridine-2-carboxamide (compound B21)

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**520**

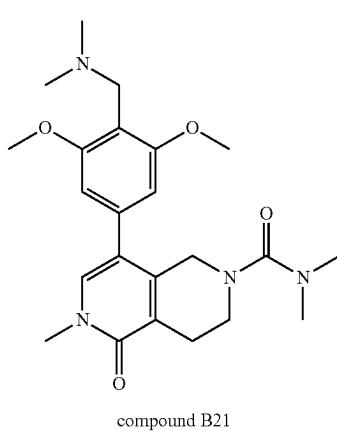
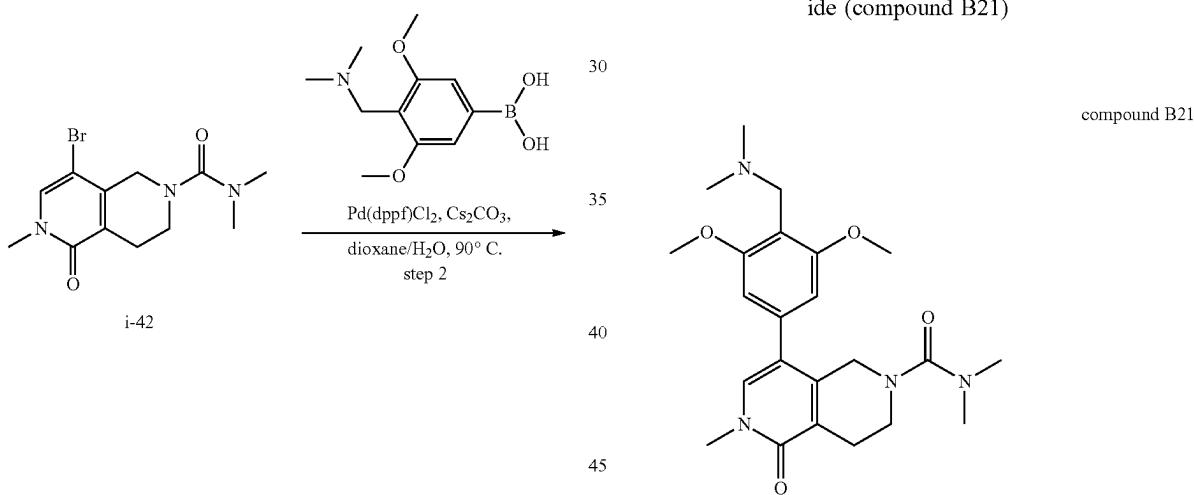
Step 1: preparation of 8-bromo-N,N,6-trimethyl-5-oxo-3,4-dihydro-1H-2,6-naphthyridine-2-carboxamide (i-42)

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Using the same procedure as described in Example 24, step 4 and substituting with dimethylcarbamyl chloride (25.8 mg, 0.240 mmol, 1.20 equiv) afforded 8-bromo-N,N,6-trimethyl-5-oxo-3,4-dihydro-1H-2,6-naphthyridine-2-carboxamide (73 mg, 94%) as an off-white solid. LCMS (ESI) m/z: [M+H]⁺=314.

25 Step 2: Preparation of 8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-N,N,6-trimethyl-5-oxo-3,4-dihydro-1H-2,6-naphthyridine-2-carboxamide (compound B21)



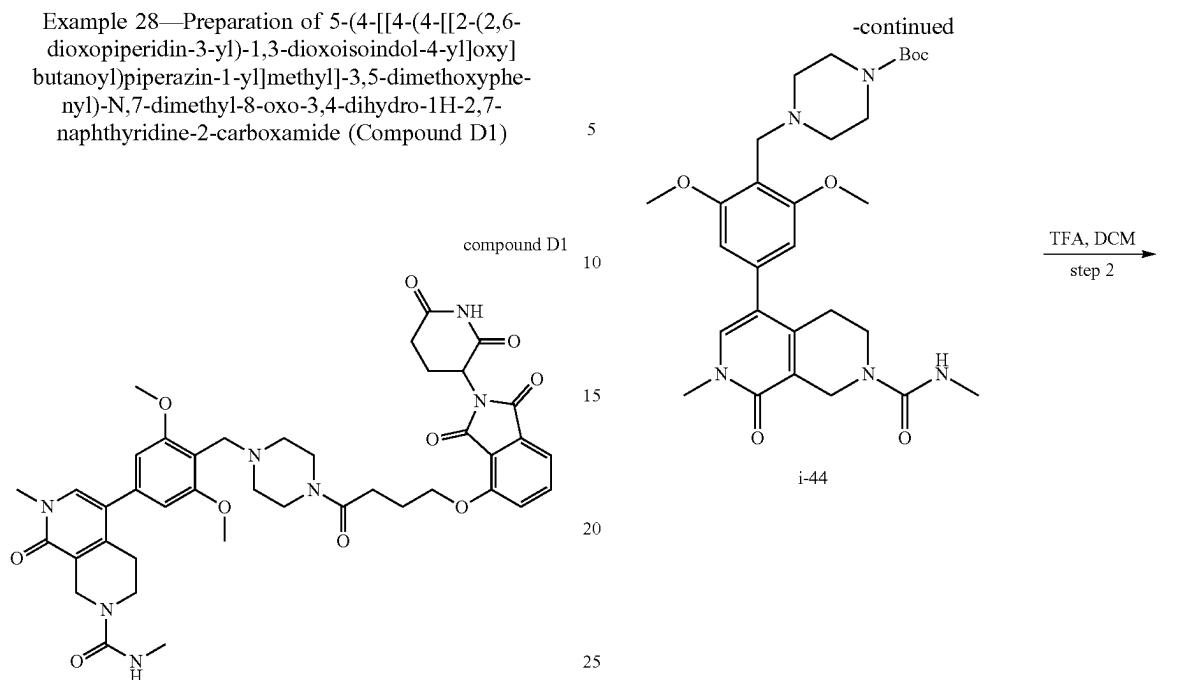
50 Using the same procedure as described in Example 23, step 2 and substituting with 8-bromo-N,N,6-trimethyl-5-oxo-3,4-dihydro-1H-2,6-naphthyridine-2-carboxamide (64.2 mg, 0.204 mmol, 1.00 equiv) afforded 8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-N,N,6-trimethyl-5-oxo-3,4-dihydro-1H-2,6-naphthyridine-2-carboxamide (26.1 mg, 29%) as an off-white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 7.57 (s, 1H), 6.60 (s, 2H), 4.00 (s, 2H), 3.78 (s, 6H), 3.48 (s, 3H), 3.46 (s, 2H), 3.37 (t, J=5.9 Hz, 2H), 2.70 (s, 6H), 2.57 (t, J=6.0 Hz, 2H), 2.14 (s, 6H). LCMS (ESI) m/z: [M+H]⁺=429.35

55 Compound B22: LCMS 482.2.

60 Compound B23: LCMS 511.2; ¹H NMR (400 MHz, DMSO-d₆) δ 7.60 (s, 1H), 6.55 (s, 3H), 4.19 (s, 2H), 4.06 (d, J=5.3 Hz, 1H), 3.75 (s, 7H), 3.48 (d, J=8.1 Hz, 6H), 3.38 (t, J=5.5 Hz, 2H), 3.24 (s, 1H), 3.15 (d, J=4.6 Hz, 2H), 2.96 (s, 6H), 2.57 (d, J=4.2 Hz, 3H), 2.37 (s, 4H), 2.13 (s, 4H).

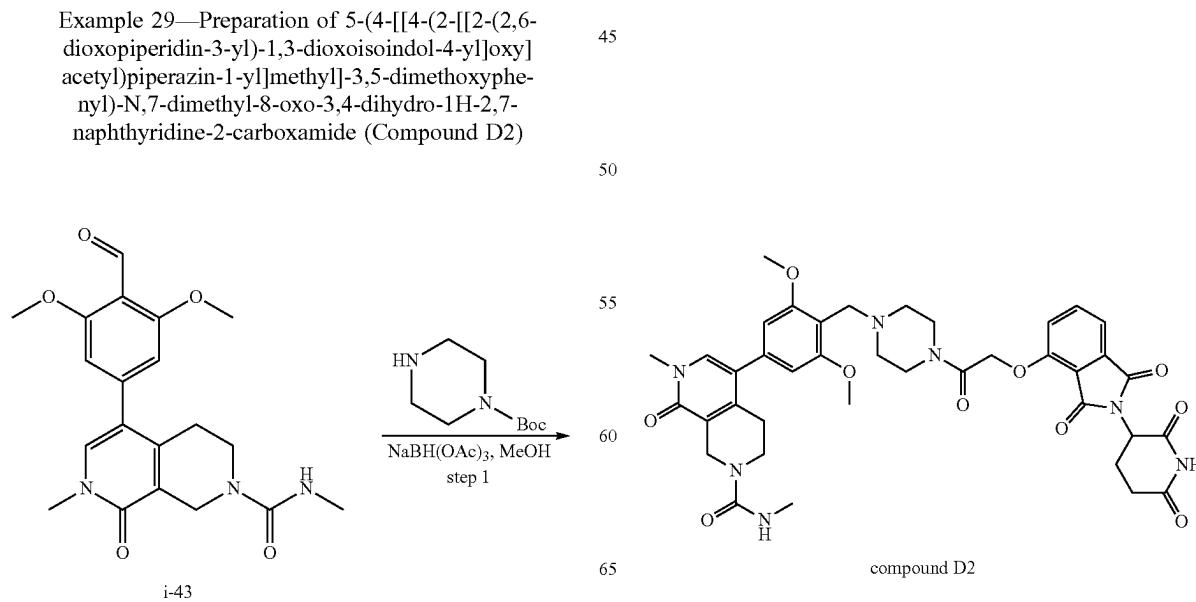
521

Example 28—Preparation of 5-(4-[[4-(4-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoxindol-4-yl]oxy]butanoyl)piperazin-1-yl)methyl]-3,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (Compound D1)



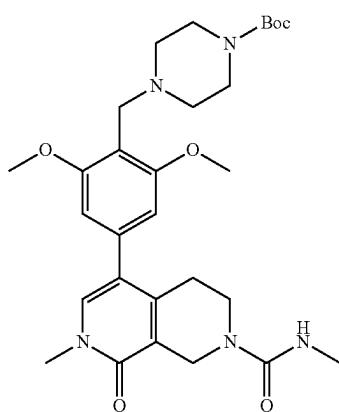
Compound D1 was prepared in a similar manner to the preparation of compound D2. PyBOP in step 3 was substituted with HATU. 5-(4-[[4-(4-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]oxy]butanoyl)piperazin-1-yl]methyl]-3,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (21.2 mg) was obtained as a white solid. ^1H NMR (300 MHz, Methanol-d₄) δ 7.80 (t, $J=7.9$ Hz, 1H), 7.57 (s, 1H), 7.48 (d, $J=7.8$ Hz, 2H), 6.64 (s, 2H), 5.11 (dd, $J=12.1, 5.4$ Hz, 1H), 4.36 (s, 2H), 4.30 (t, $J=5.7$ Hz, 2H), 4.00 (s, 2H), 3.88 (s, 6H), 3.80-3.69 (m, 4H), 3.64 (s, 3H), 3.53 (d, $J=5.7$ Hz, 2H), 2.94-2.81 (m, 5H), 2.78 (s, 4H), 2.72 (t, $J=7.1$ Hz, 3H), 2.67-2.59 (m, 2H), 2.22-2.09 (m, 3H). LCMS (ESI) m/z: [M+H]⁺=798.40.

Example 29—Preparation of 5-(4-[[4-(2-((2,6-dioxopiperidin-3-yl)-1,3-dioxoisooindol-4-yl)oxy]acetyl)piperazin-1-yl)methyl]-3,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (Compound D2)



523

Step 1: Preparation of tert-butyl4-((2,6-dimethoxy-4-[2-methyl-7-(methylcarbamoyl)-1-oxo-6,8-dihydro-5H-2,7-naphthyridin-4-yl]phenyl)methyl)piperazine-1-carboxylate (i-44)



i-44

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A solution of TFA (1.00 mL) and tert-butyl 4-((2,6-dimethoxy-4-[2-methyl-7-(methylcarbamoyl)-1-oxo-6,8-dihydro-5H-2,7-naphthyridin-4-yl]phenyl)methyl)piperazine-1-carboxylate (10.00 mg, 0.018 mmol, 1.00 equiv) in DCM (2.00 mL) was stirred for 1 hour at room temperature under air atmosphere. The reaction mixture was concentrated under vacuum. The crude product mixture was used in the next step directly without further purification. LCMS (ESI) m/z: [M+H]⁺=456.

Step 3: 5-(4-[[4-(2-[(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]oxy]acetyl)piperazin-1-yl]methyl)-3,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (Compound D2)

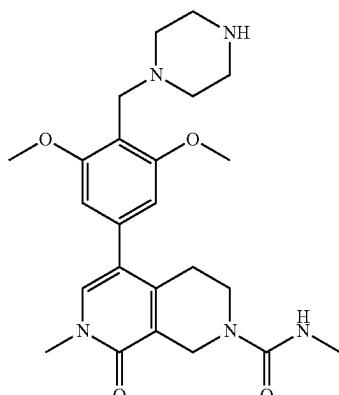
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A mixture of 5-(4-formyl-3,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (400.00 mg, 1.038 mmol, 1.00 equiv) and tert-butyl piperazine-1-carboxylate (193.30 mg, 1.038 mmol, 1.00 equiv) in MeOH (2 mL) was stirred for 30 minutes at room temperature under air atmosphere. To the above mixture was added NaBH(AcO)₃ (439.92 mg, 2.076 mmol, 2.00 equiv) in portions for 2 hours at room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by reverse flash chromatography (conditions: column, C18 silica gel; mobile phase, MeOH in water, 10% to 50% gradient in 50 minutes; detector, UV 254 nm). This resulted in tert-butyl4-((2,6-dimethoxy-4-[2-methyl-7-(methylcarbamoyl)-1-oxo-6,8-dihydro-5H-2,7-naphthyridin-4-yl]phenyl)methyl)piperazine-1-carboxylate (300 mg, 52.02%) as a yellow oil. LCMS (ESI) m/z: [M+H]⁺=556.

Step 2: Preparation of 5-[3,5-dimethoxy-4-(piperazin-1-ylmethyl)phenyl]-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (i-45)



i-45

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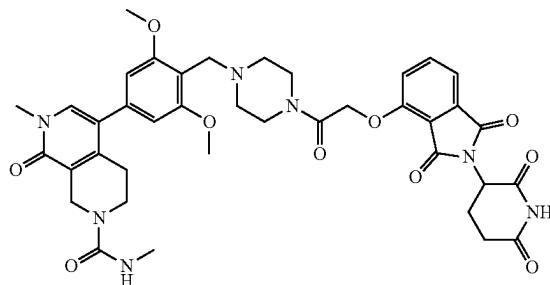
A mixture of [[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]oxy]acetic acid (36.47 mg, 0.110 mmol, 1.00 equiv), DIEA (70.93 mg, 0.549 mmol, 5.00 equiv), PyBOP (114.23 mg, 0.220 mmol, 2.00 equiv), and [[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]oxy]acetic acid (36.47 mg, 0.110 mmol, 1.00 equiv) in DMF (2 mL) was stirred for 2 hours at room temperature under air atmosphere. The crude product was purified by Prep-HPLC (conditions: SunFire C18 OBD Prep Column, 100 Å, 5 µm, 19 mm×250 mm; Mobile Phase A: water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 7 B to 20 B in 12 minutes; 254 nm; R_f: 10.95 minutes) to afford 5-(4-[[4-(2-[(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]oxy]acetyl)piperazin-1-yl]methyl)-3,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (21.2 mg) as a white solid. ¹H NMR (300 MHz, Methanol-d₄) δ 7.85-7.72 (m, 1H), 7.61-7.49 (m, 2H), 7.48-7.35 (m, 1H), 6.74 (s, 2H), 5.13 (dd, J=12.2, 5.4 Hz, 3H), 5.04 (d, J=4.2 Hz, 1H), 4.66-4.42 (m, 3H), 4.40-4.18 (m, 3H), 3.96 (s, 6H), 3.72-3.62 (m, 4H), 3.61-3.45 (m, 5H), 2.96-2.70 (m, 7H), 2.69-2.57 (m, 2H), 2.22-2.09 (m, 1H). LCMS (ESI) m/z: [M+H]⁺=770.55.

524

A solution of TFA (1.00 mL) and tert-butyl 4-((2,6-dimethoxy-4-[2-methyl-7-(methylcarbamoyl)-1-oxo-6,8-dihydro-5H-2,7-naphthyridin-4-yl]phenyl)methyl)piperazine-1-carboxylate (10.00 mg, 0.018 mmol, 1.00 equiv) in DCM (2.00 mL) was stirred for 1 hour at room temperature under air atmosphere. The reaction mixture was concentrated under vacuum. The crude product mixture was used in the next step directly without further purification. LCMS (ESI) m/z: [M+H]⁺=456.

Step 3: 5-(4-[[4-(2-[(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]oxy]acetyl)piperazin-1-yl]methyl)-3,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (Compound D2)

compound D2



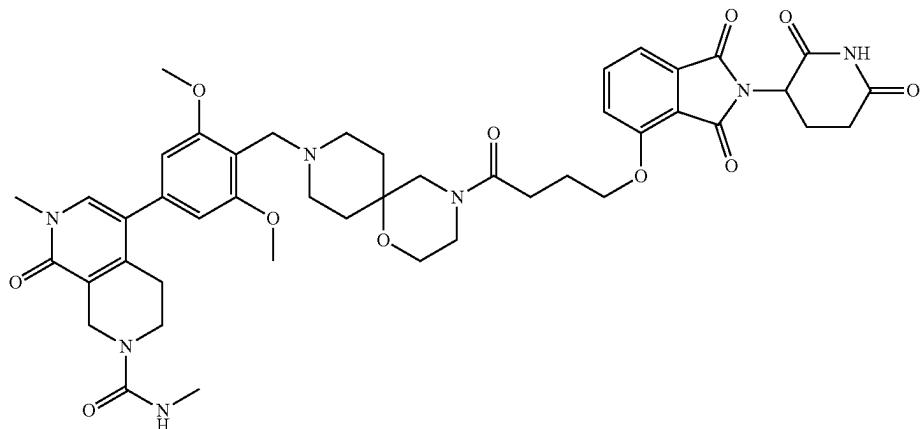
525

Example 30—Preparation of 5-(4-[[4-([2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]oxy]butanoyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl]methyl]-3,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-
3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide
(Compound D3)

526

5

compound D3

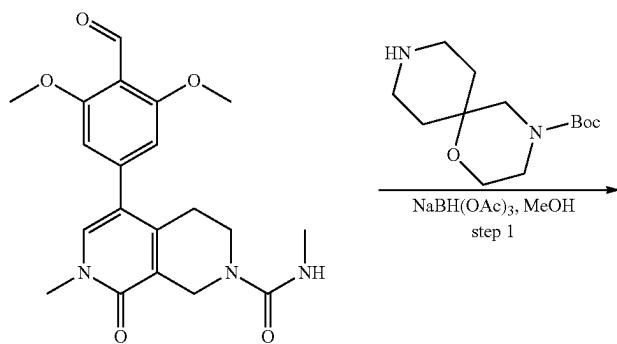


Compound D3 was prepared in a similar manner to the preparation of compound D4. Compound D3 (19 mg, 19.2%) was obtained as an off-white solid. ¹H NMR (300 MHz, Methanol-d4) δ 7.84-7.76 (m, 1H), 7.60 (d, J=7.8 Hz, 1H), 7.51-7.43 (m, 2H), 6.71 (d, J=5.0 Hz, 2H), 5.17-5.06 (m, 1H), 4.41-4.20 (m, 6H), 3.99-3.86 (m, 6H), 3.83-3.67 (m, 4H), 3.66-3.62 (m, 3H), 3.59-3.46 (m, 4H), 2.96-2.69 (m, 8H), 2.69-2.51 (m, 3H), 2.43-1.91 (m, 6H), 1.88-1.61 (m, 2H). LCMS (ESI) m/z: [M+H]⁺=868.80.

40

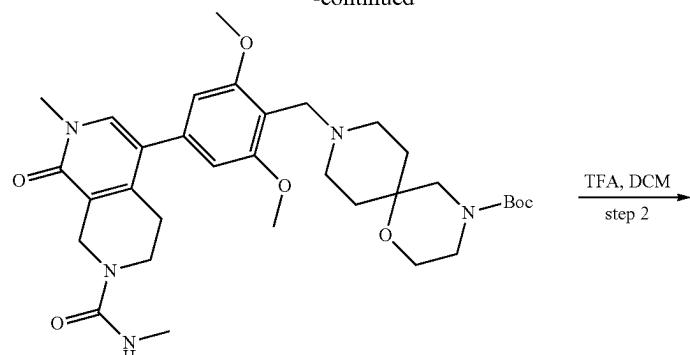
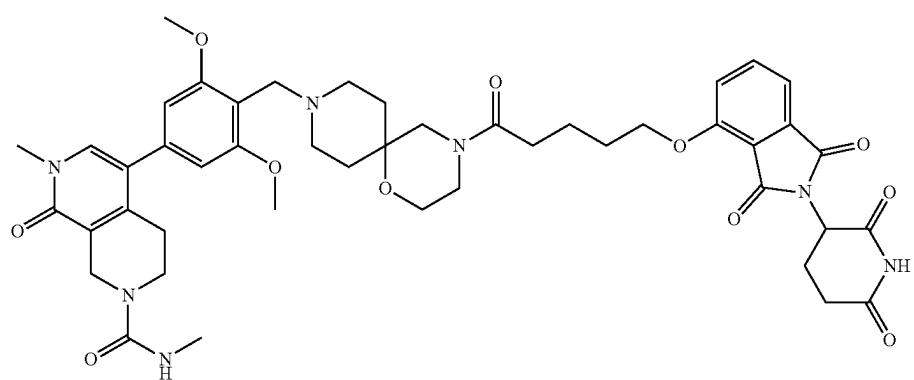
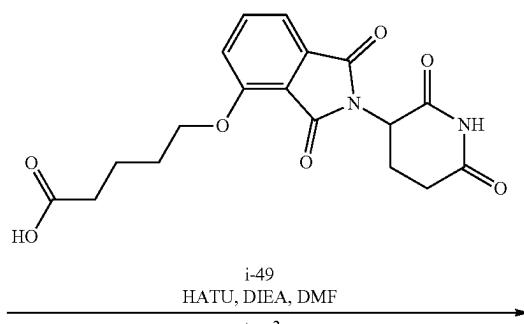
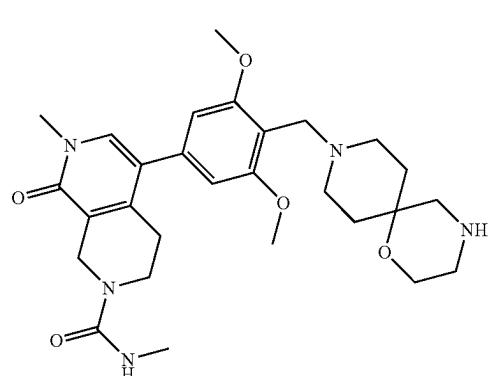
Example 31—Preparation of 5-(4-[[4-([2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]oxy]pentanoyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl]methyl]-3,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-
3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide
formic acid (Compound D4)

45



527**528**

-continued

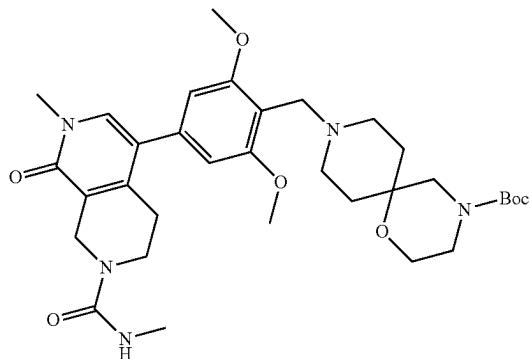
TFA, DCM
step 2

compound D4

529

Step 1: Preparation of tert-butyl 9-([2,6-dimethoxy-4-[2-methyl-7-(methylcarbamoyl)-1-oxo-6,8-dihydro-5H-2,7-naphthyridin-4-yl]phenyl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecane-4-carboxylate
(i-47)

5

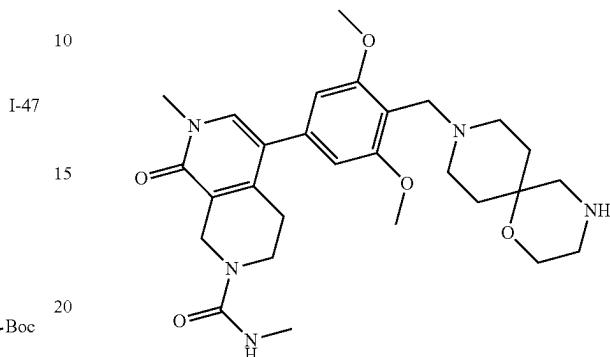


Using a similar procedure as described in Example 29, step 1 and substituting with tert-butyl 1-oxa-4,9-diazaspiro[5.5]undecane-4-carboxylate (93.1 mg, 0.363 mmol, 1 equiv) afforded tert-butyl 9-([2,6-dimethoxy-4-[2-methyl-7-(methylcarbamoyl)-1-oxo-6,8-dihydro-5H-2,7-naphthyridin-4-yl]phenyl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecane-4-carboxylate (290 mg, 93.1%) as a light brown oil. LCMS (ESI) m/z: [M+H]+= 356.

530

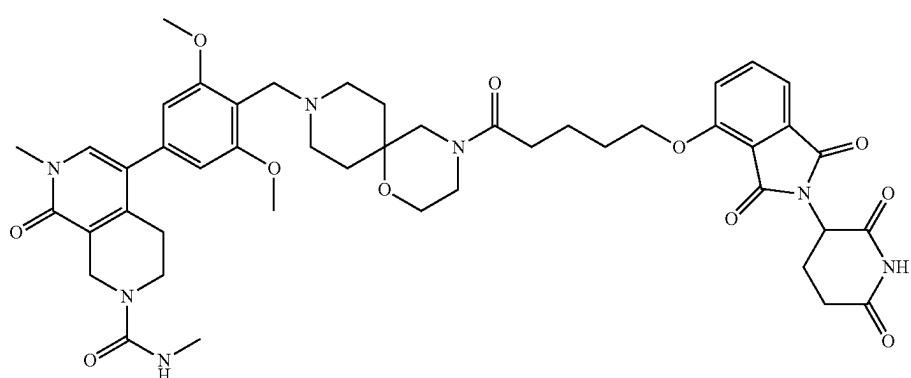
Step 2: Preparation of 5-(3,5-dimethoxy-4-[1-oxa-4,9-diazaspiro[5.5]undecan-9-ylmethyl]phenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (i-48)

i-48



Using a similar procedure as described in Example 29, step 2 afforded 5-(3,5-dimethoxy-4-[1-oxa-4,9-diazaspiro[5.5]undecan-9-ylmethyl]phenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (114 mg, 46.8%) as a light brown solid. LCMS (ESI) m/z: [M+H]+= 526.

Step 3: Preparation of 5-(4-[[4-(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisooindol-4-yl]oxy]pentanoyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl]methyl]-3,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide formic acid (Compound D4)



compound D4

531

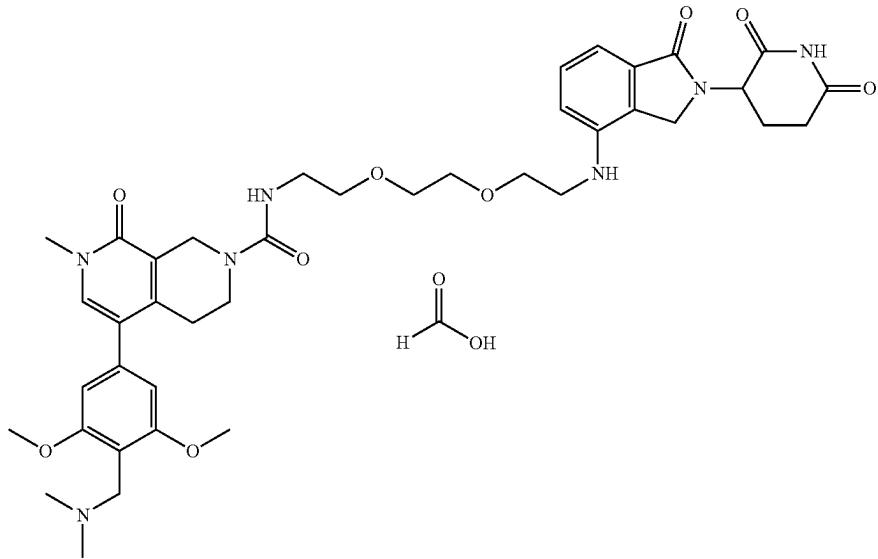
Using a similar procedure as described in Example 29, step 3 and substituting with 5-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]oxy]pentanoic acid (28.5 mg, 0.076 mmol, 1.00 equiv) and 5-(3,5-dimethoxy-4-[1-oxa-4,9-diazaspiro[5.5]undecan-9-ylmethyl]phenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (40 mg, 0.076 mmol, 1.00 equiv) afforded 5-(4-[[4-(5-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]oxy]pentanoic acid)-1-oxa-4,9-diazaspiro[5.5]undecan-9-ylmethyl]-3,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide formic acid (23 mg, 32.6%) as an off-white solid. ¹H NMR (300 MHz, Methanol-d₄) δ 8.55 (brs, 0.6H, formic acid), 7.79 (t, J=7.9 Hz, 1H), 7.58 (s, 1H), 7.46 (d, J=8.7 Hz, 2H), 6.70 (d, J=5.7 Hz, 2H), 5.15-5.07 (m, 1H), 4.39-4.25 (m, 6H), 3.93 (d, J=5.5 Hz, 6H), 3.82-3.72 (m, 2H), 3.64 (s, 5H), 3.59-3.50 (m, 4H), 3.31-3.05 (m, 4H), 2.93-2.83 (m, 1H), 2.78 (s, 3H), 2.77-2.56 (m, 6H), 2.21-2.03 (m, 3H), 2.01-1.68 (m, 6H). LCMS (ESI) m/z: [M+H]⁺=882.60.

Example 32—Preparation of 5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-N-[2-[2-(2-[2-(2,6-dioxopiperidin-3-yl)-1-oxo-3H-isooindol-4-yl]amino)ethoxy]ethoxy]ethyl]-7-methyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide formic acid
(Compound D5 formic acid)

532

20

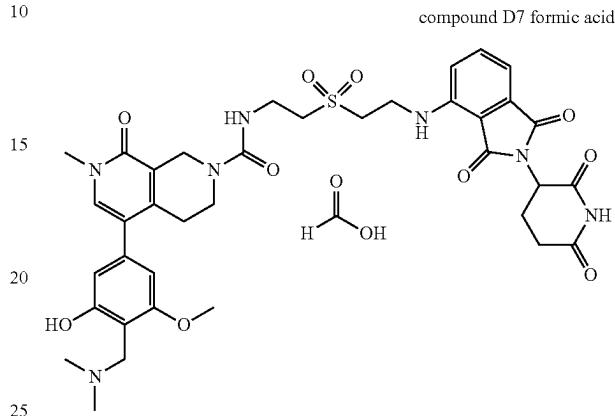
compound D5 formic acid



533

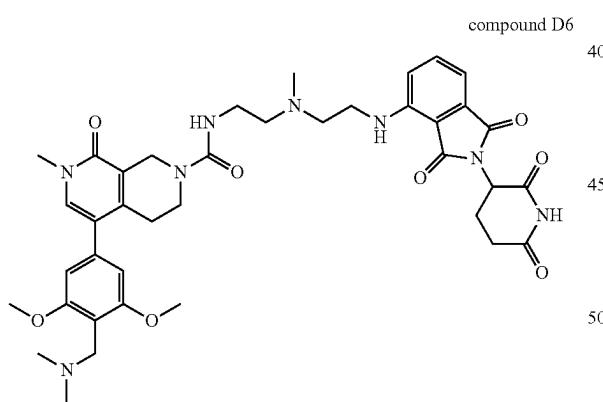
Compound D5 was prepared in a similar manner to the preparation of compound D21. Compound D5 formic acid (12.8 mg, 21.5%) was obtained as a green solid. ¹H NMR (300 MHz, Methanol-d4) δ 8.56 (brs, 1.7H, FA), 7.55 (s, 1H), 7.24 (t, J=7.7 Hz, 1H), 7.09 (d, J=7.6 Hz, 1H), 6.91 (d, J=7.9 Hz, 1H), 6.71 (s, 2H), 5.19 (dd, J=13.4, 5.1 Hz, 1H), 4.39-4.27 (m, 5H), 4.09-3.98 (m, 2H), 3.94 (s, 6H), 3.67-3.50 (m, 14H), 3.40 (t, J=5.4 Hz, 2H), 3.04-2.91 (m, 2H), 2.85 (s, 6H), 2.61 (s, 2H), 2.53-2.39 (m, 1H), 2.24-2.12 (m, 1H). LCMS (ESI) m/z: [M-H]⁺=774.37.

Example 33—Preparation of 5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-N-[2-[(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl)amino]ethyl](methyl)amino]ethyl]-7-methyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (Compound D6)



Compound D7 was prepared in a similar manner to the preparation of compound D21. Compound D7 formic acid (13.1 mg, 22.5%) was obtained as a green solid. ¹H NMR (300 MHz, Methanol-d4) δ 8.56 (brs, 1H, FA), 7.66-7.54 (m, 2H), 7.12 (dd, J=17.2, 7.8 Hz, 2H), 6.69 (s, 2H), 5.05 (dd, J=12.6, 5.4 Hz, 1H), 4.35 (s, 2H), 4.24 (s, 2H), 3.94 (s, 6H), 3.89 (t, J=6.4 Hz, 2H), 3.70 (t, J=6.3 Hz, 2H), 3.63 (s, 3H), 3.49 (t, J=6.3 Hz, 4H), 3.42-3.37 (m, 2H), 2.86-2.68 (m, 9H), 2.67-2.60 (m, 3H), 2.13-2.01 (m, 1H). LCMS (ESI) m/z: [M+H]⁺=792.45.

Example 35—Preparation of N-(2-[[2-(5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carbonylamino)ethyl](methyl)amino]ethyl)-2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]oxy]acetamide formic acid (Compound D8 formic acid)

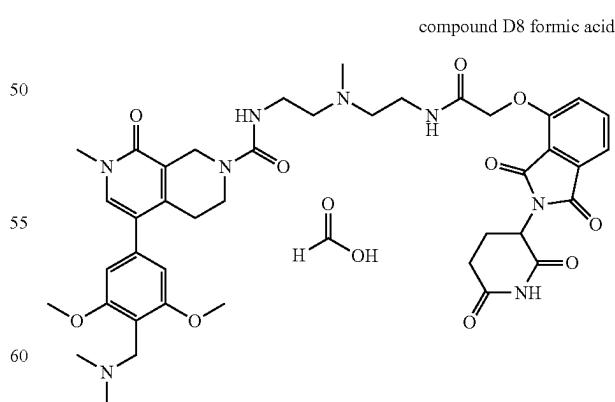
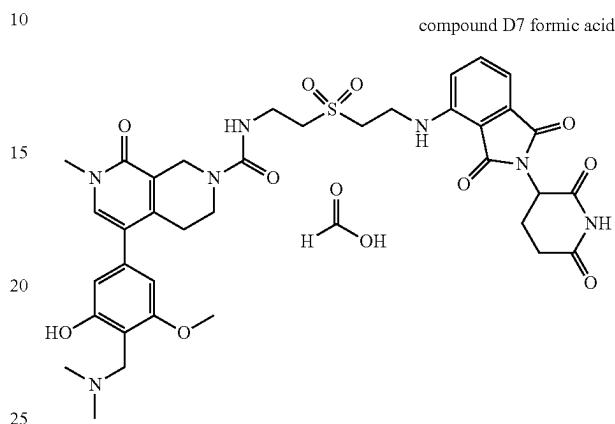


Compound D6 was prepared in a similar manner to the preparation of compound D21. Compound D6 (2.1 mg, 3.45%) was obtained as a green solid. ¹H NMR (300 MHz, Acetonitrile-d3) δ 9.17 (s, 1H), 7.58 (t, J=7.7 Hz, 1H), 7.43 (s, 1H), 7.15 (d, J=8.4 Hz, 1H), 7.06 (d, J=7.0 Hz, 1H), 6.67-6.47 (m, 4H), 4.95 (dd, J=12.2, 5.2 Hz, 1H), 4.35-4.17 (m, 4H), 3.87 (s, 6H), 3.77 (d, J=5.8 Hz, 2H), 3.55 (s, 4H), 3.44-3.24 (m, 5H), 2.92 (s, 3H), 2.77 (s, 6H), 2.73-2.60 (m, 3H), 2.54 (s, 2H), 2.30-2.22 (m, 1H), 2.14-2.02 (m, 1H). LCMS (ESI) m/z: [M-H]⁺=757.36.

Compound D7 was prepared in a similar manner to the preparation of compound D21. Compound D8 formic acid (10.9 mg, 19.24%) was obtained as a white solid. ¹H NMR (300 MHz, Methanol-d4) δ 8.42 (brs, 2H, FA), 7.72-7.63 (m,

534

Example 34—Preparation of 5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-N-[2-[(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl)amino]ethanesulfonyl]ethyl]-7-methyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide formic acid (Compound D7 formic acid)



535

1H), 7.51 (s, 1H), 7.43-7.37 (m, 2H), 6.67 (s, 2H), 5.12 (dd, J=12.7, 5.4 Hz, 1H), 4.81 (s, 2H), 4.39 (s, 2H), 4.15 (s, 2H), 3.98 (s, 6H), 3.63-3.55 (m, 5H), 3.42 (s, 3H), 2.97-2.85 (m, 11H), 2.82-2.63 (m, 3H), 2.59 (s, 3H), 2.54-2.39 (m, 2H), 2.21-2.09 (m, 1H). LCMS (ESI) m/z: [M+H]⁺=815.36.

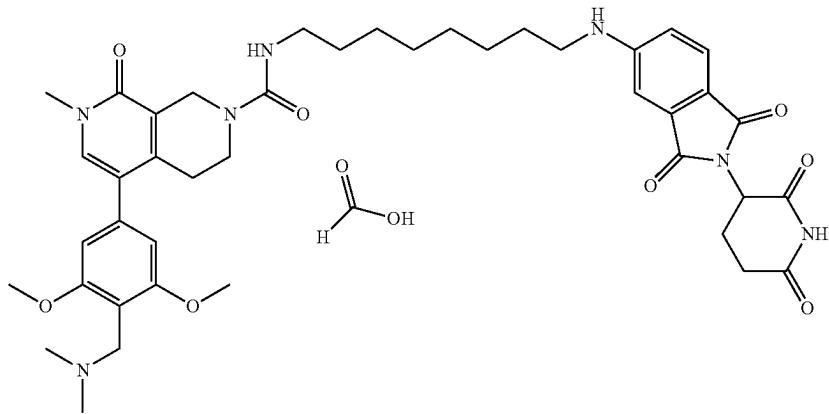
5

Example 36—Preparation of 5-(4-((dimethylamino)methyl)-3,5-dimethoxyphenyl)-N-(8-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)amino)octyl)-7-methyl-8-oxo-3,4,7,8-tetrahydro-2,7-naphthyridine-2 (1H)-carboxamide formic acid
(Compound D9 formic acid)

536

10

compound D9 formic acid



Compound D9 was prepared in a similar manner to the preparation of compound D21. Compound D9 formic acid (9.7 mg, 23.93%) was obtained as a light yellow solid. LCMS (ESI) m/z: [M+H]⁺=784.60. ¹H NMR (300 MHz, Methanol-d4) δ 8.56 (br s, 1H, FA), 7.61-7.50 (m, 2H), 6.96 (d, J=2.1 Hz, 1H), 6.82 (dd, J=8.4, 2.1 Hz, 1H), 6.69 (s, 2H), 5.05 (dd, J=12.4, 5.5 Hz, 1H), 4.36 (s, 2H), 4.21 (s, 2H), 3.93 (s, 6H), 3.63 (s, 3H), 3.54 (t, J=5.6 Hz, 2H), 3.25-3.15 (m, 4H), 2.96-2.81 (m, 1H), 2.75 (s, 8H), 2.63 (t, J=5.2 Hz, 2H),

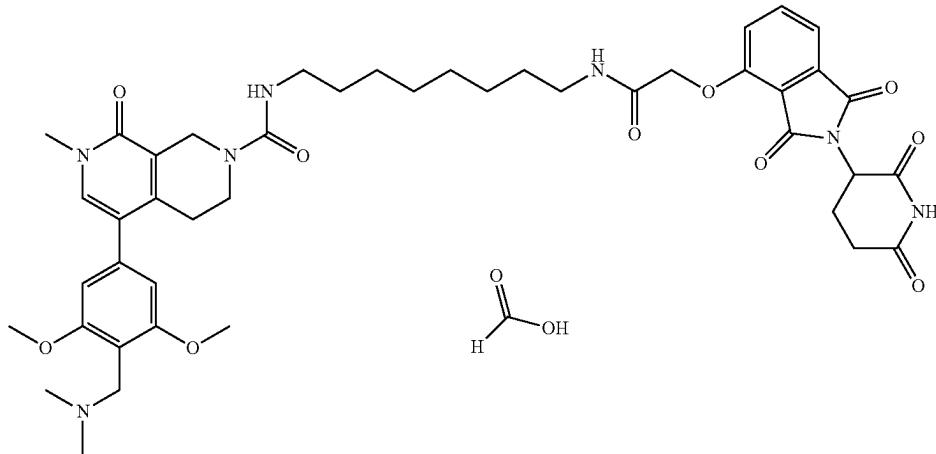
35

2.15-2.03 (m, 1H), 1.73-1.61 (m, 2H), 1.60-1.49 (m, 2H), 1.48-1.33 (m, 8H).

40

Example 37—Preparation of 5-(4-((dimethylamino)methyl)-3,5-dimethoxyphenyl)-N-(8-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)oxy)acetamido)octyl)-7-methyl-8-oxo-3,4,7,8-tetrahydro-2,7-naphthyridine-2 (1H)-carboxamide formic acid
(Compound D10 formic acid)

compound D10 formic acid



537

Compound D10 was prepared in a similar manner to the preparation of compound D21. Compound D10 formic acid (8.5 mg, 21.8%) was obtained as a white solid. LCMS (ESI) m/z: [M+H]⁺=842.65. ¹H NMR (300 MHz, Methanol-d4) δ 8.56 (br s, 0.6H, FA), 7.82 (dd, J=8.4, 7.4 Hz, 1H), 7.61-7.52 (m, 2H), 7.44 (d, J=8.4 Hz, 1H), 6.71 (s, 2H), 5.15 (dd, J=12.4, 5.5 Hz, 1H), 4.77 (s, 2H), 4.36 (s, 2H), 4.27 (s, 2H), 3.94 (s, 6H), 3.64 (s, 3H), 3.54 (t, J=5.6 Hz, 2H), 3.30 (s, 2H), 3.19 (t, J=7.0 Hz, 2H), 2.98-2.83 (m, 1H), 2.83-2.70 (m, 8H), 2.64 (t, J=5.4 Hz, 2H), 2.22-2.10 (m, 1H), 1.65-1.47 (m, 4H), 1.36 (s, 8H).

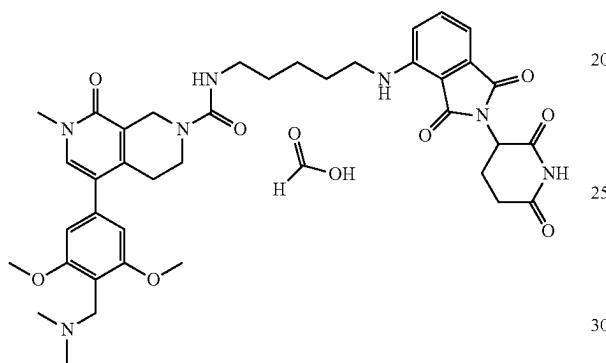
Example 38—Preparation of 5-(4-((dimethylamino)methyl)-3,5-dimethoxyphenyl)-N-(5-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)pentyl)-7-methyl-8-oxo-3,4,7,8-tetrahydro-2,7-naphthyridine-2 (1H)-carboxamide formic acid
(Compound D11 formic acid)

538

Compound D11 was prepared in a similar manner to the preparation of compound D21. Compound D11 formic acid (8.7 mg, 20.7%) was obtained as a light yellow solid. ¹H NMR (300 MHz, Methanol-d4) δ 8.56 (br s, 1H, FA), 7.60-7.52 (m, 2H), 7.04 (dd, J=9.4, 7.8 Hz, 2H), 6.71 (s, 2H), 5.04 (dd, J=12.2, 5.4 Hz, 1H), 4.36 (s, 2H), 4.26 (s, 2H), 3.94 (s, 6H), 3.64 (s, 3H), 3.53 (t, J=5.6 Hz, 2H), 3.36 (t, J=6.8 Hz, 2H), 3.25 (t, J=6.8 Hz, 2H), 2.87-2.72 (m, 8H), 2.70-2.59 (m, 3H), 2.15-2.03 (m, 1H), 1.78-1.66 (m, 2H), 1.66-1.56 (m, 2H), 1.56-1.45 (m, 2H). LCMS (ESI) m/z: [M+H]⁺= 742.55.

15

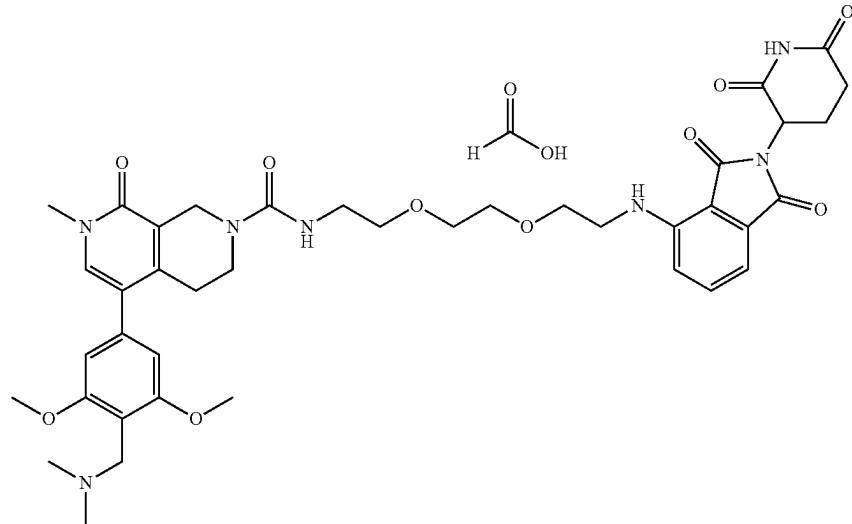
compound D11 formic acid



Example 39—Preparation of 5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-N-[2-[2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]ethoxy]ethoxyethyl]-7-methyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide formic acid
(Compound D12 formic acid)

30

compound D12 formic acid



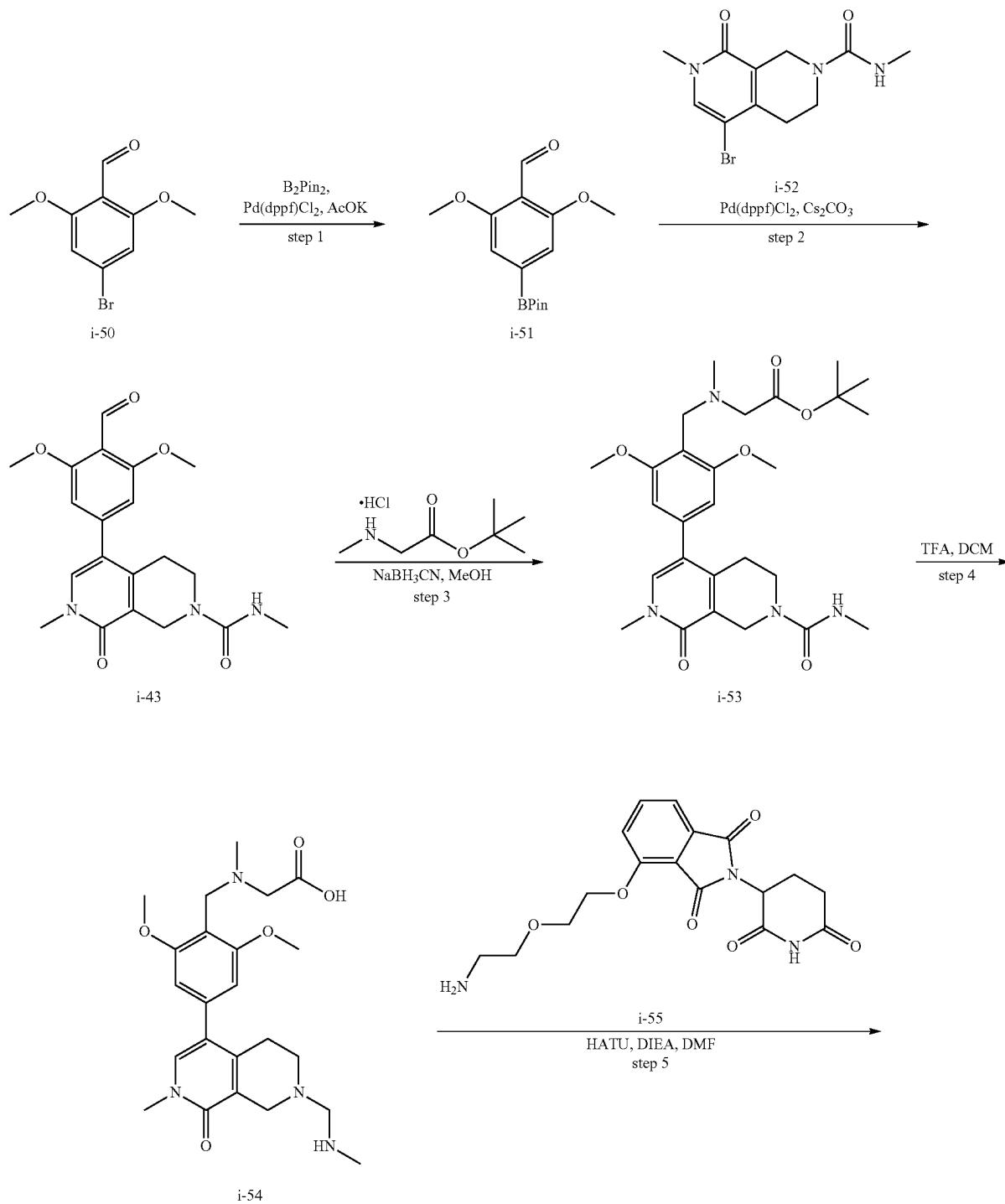
539

Compound D12 was prepared in a similar manner to the preparation of compound D21. Compound D12 formic acid (100 mg, 17.1%) was obtained as a yellow solid. ^1H NMR (300 MHz, Methanol-d4) δ 8.56 (br s, 0.9H, FA), 7.54 (s, 1H), 7.48 (dd, $J=8.6, 7.1$ Hz, 1H), 7.06 (d, $J=8.5$ Hz, 1H), 6.99 (d, $J=7.1$ Hz, 1H), 6.69 (s, 2H), 5.03 (dd, $J=12.5, 5.4$ Hz, 1H), 4.34 (s, 2H), 4.30 (s, 2H), 3.95 (s, 6H), 3.79 (t, $J=5.2$ Hz, 2H), 3.72-3.65 (m, 4H), 3.64-3.58 (m, 5H), 3.56-3.46 (m, 4H), 3.41 (t, $J=5.4$ Hz, 2H), 2.89-2.79 (m,

540

7H), 2.77-2.64 (m, 2H), 2.63-2.52 (m, 2H), 2.16-2.05 (m, 1H). LCMS (ESI) m/z: [M+H]⁺=812.45.

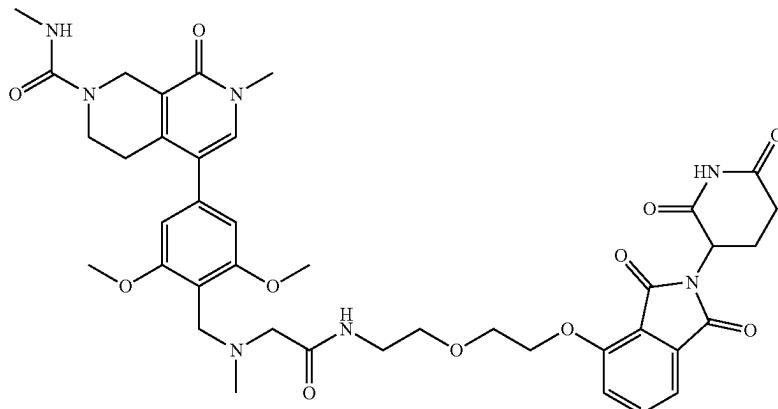
Example 40—Preparation of 5-(4-[[[1,3-dioxoisindol-4-yl]oxy]ethoxy]ethyl carbamoyl)methyl)(methyl)amino)methyl]-3,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (Compound D13)



541

542

-continued



Step 1: Preparation of 2,6-dimethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde
(i-51)

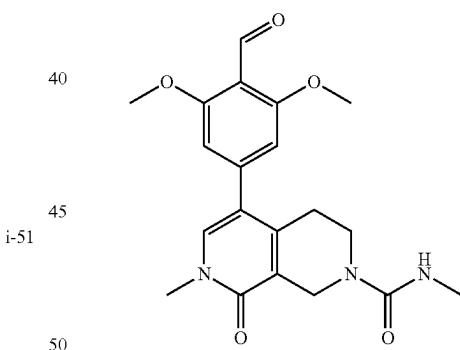
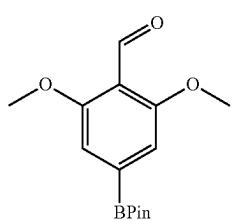
25

Step 2: Preparation of 5-(4-formyl-3,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (i-43)

30

35

i-43

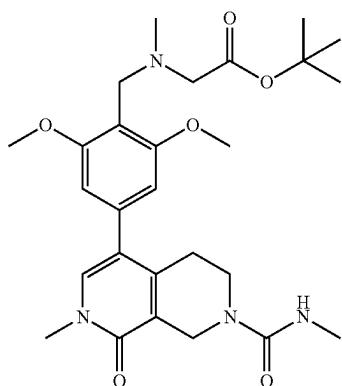


To a stirred solution of bis(pinacolato)diboron (7.62 g, 29.991 mmol, 1.50 equiv) and bis(pinacolato)diboron (7.62 g, 29.991 mmol, 1.50 equiv) in dioxane (70.00 mL) was added Pd(dppf)Cl₂·CH₂Cl₂ (1.63 g, 1.999 mmol, 0.10 equiv) and AcOK (5.89 g, 59.982 mmol, 3.00 equiv). The resulting mixture was stirred for 1 hour at 90° C. under nitrogen atmosphere. Then the reaction was concentrated and purified by silica gel column chromatography, eluted with PE/EtOAc (10:1) to afford 2,6-dimethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (6.3 g, 92.76%) as an orange solid. LCMS (ESI) m/z: [M+H]⁺=293.

To a stirred solution of 2,6-dimethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (291.99 mg, 0.999 mmol, 1.00 equiv) and 5-bromo-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (300.00 mg, 0.999 mmol, 1.00 equiv) in dioxane (5.00 mL) and H₂O (0.60 mL) was added Cs₂CO₃ (976.95 mg, 2.998 mmol, 3.00 equiv) and Pd(dppf)Cl₂·CH₂Cl₂ (81.62 mg, 0.100 mmol, 0.1 equiv). After stirring for 3 hours at 100° C. under a nitrogen atmosphere, the resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH₂Cl₂/MeOH (19:1) to afford 5-(4-formyl-3,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (257 mg, 66.72%) as a brown semi-solid. LCMS (ESI) m/z: [M+H]⁺=386.

543

Step 3: Preparation of tert-butyl 2-[(2,6-dimethoxy-4-[2-methyl-7-(methylcarbamoyl)-1-oxo-6,8-dihydro-5H-2,7-naphthyridin-4-yl]phenyl)methyl](methyl)amino]acetate (i-53)

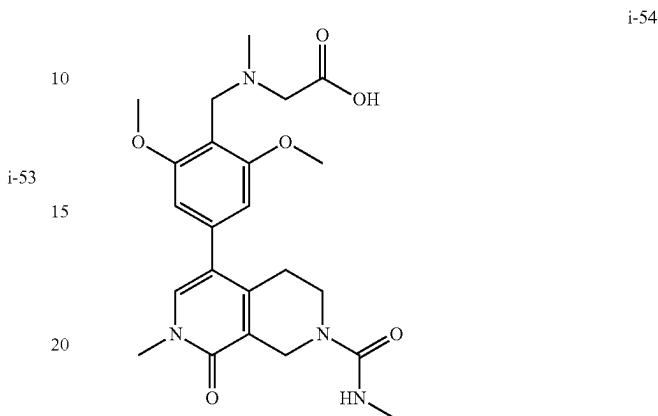


To a stirred solution of 5-(4-formyl-3,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (222.00 mg, 0.576 mmol, 1.00 equiv) and tert-butyl 2-(methylamino)acetate hydrochloride (104.64 mg, 0.576 mmol, 1 equiv) in MeOH (5.00 mL) was added NaBH₃CN (72.39 mg, 1.152 mmol, 2 equiv) in portions. The resulting mixture was stirred for 1 hour at room temperature under air atmosphere. Then the reaction mixture was concentrated, and the resulting residue was purified by silica gel column chromatography, eluted with CH₂Cl₂/MeOH (19:1) to afford tert-butyl 2-[(2,6-dimethoxy-4-[2-methyl-7-(methylcarbamoyl)-1-oxo-6,8-dihydro-5H-2,7-naphthyridin-4-yl]phenyl)methyl](methyl)amino] acetate (268 mg, 90.41%) as a light yellow solid. LCMS (ESI) m/z: [M+H]⁺=515.

544

Step 4: Preparation of [(2,6-dimethoxy-4-[2-methyl-7-(methylcarbamoyl)-1-oxo-6,8-dihydro-5H-2,7-naphthyridin-4-yl]phenyl)methyl](methyl)amino]acetic acid (i-54)

5



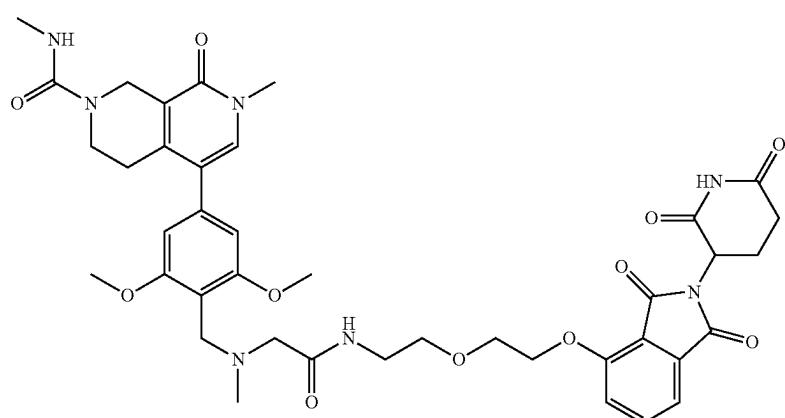
25 A solution of tert-butyl 2-[(2,6-dimethoxy-4-[2-methyl-7-(methylcarbamoyl)-1-oxo-6,8-dihydro-5H-2,7-naphthyridin-4-yl]phenyl)methyl](methyl)amino]acetate (268.00 mg, 0.521 mmol, 1.00 equiv) and TFA (2.00 mL, 26.926 mmol, 51.70 equiv) in DCM (3 mL) was stirred for 1 hour at room temperature under air atmosphere. The reaction mixture was concentrated, and the resulting residue was purified by reverse flash chromatography (conditions: C18 silica gel column; mobile phase, MeCN in water, 10% to 50% gradient in 10 minutes; detector, UV 254 nm) to afford [(2,6-dimethoxy-4-[2-methyl-7-(methylcarbamoyl)-1-oxo-6,8-dihydro-5H-2,7-naphthyridin-4-yl]phenyl)methyl](methyl)amino]acetic acid (135 mg, 56.54%) as a light yellow oil. LCMS (ESI) m/z: [M+H]⁺=459.

30 Step 5: Preparation of 5-(4-[[2-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl)oxy]ethoxyethyl]carbamoyl)methyl(methyl)amino]methyl]-3,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (Compound D13)

35

40

compound D13



545

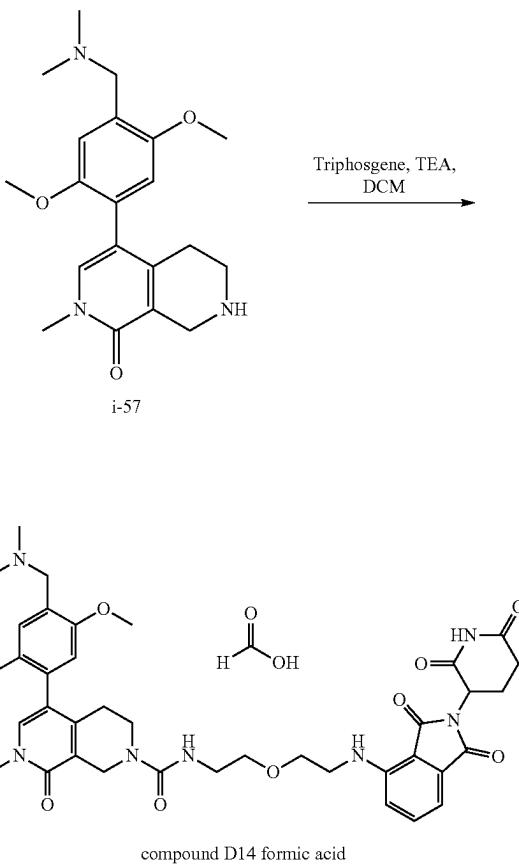
To a stirred solution of [(2,6-dimethoxy-4-[2-methyl-7-(methylcarbamoyl)-1-oxo-6,8-dihydro-5H-2,7-naphthyridin-4-yl]phenyl)methyl](methyl)amino]acetic acid (70.00 mg, 0.153 mmol, 1.00 equiv) and 4-[2-(2-aminoethoxy)ethoxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (55.17 mg, 0.153 mmol, 1.00 equiv) in DMF (1.00 mL) was added DIEA (98.66 mg, 0.763 mmol, 5.00 equiv) and HATU (116.10 mg, 0.305 mmol, 2.00 equiv). The resulting mixture was stirred for 1 hour at room temperature. Then the solution was directly purified by Prep-HPLC (conditions: SunFire C18 OBD Prep Column, 100 Å, 5 µm, 19 mm×250 mm; Mobile Phase A: water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 9% B to 25% B in 12 minutes; 254 nm; R_f: 10.82 minutes) to afford 5-(4-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]oxy]ethoxyethyl)carbamoylmethyl)(methyl)amino]methyl]-3,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (23 mg, 18.79%) as a yellow solid. ¹H NMR (300 MHz, Methanol-d4) δ 8.52 (br s, 0.4H, FA), 7.66-7.57 (m, 1H), 7.54 (s, 1H), 7.30 (d, J=7.2 Hz, 1H), 7.16 (d, J=8.4 Hz, 1H), 6.63 (s, 2H), 5.11 (dd, J=12.8, 5.4 Hz, 1H), 4.32 (s, 2H), 4.10-3.93 (m, 4H), 3.90 (s, 6H), 3.65-3.48 (m, 1 OH), 3.42-3.37 (m, 3H), 2.88 (dd, J=12.6, 4.6 Hz, 2H), 2.77 (s, 3H), 2.65 (d, J=18.1 Hz, 3H), 2.55-2.48 (m, 3H), 2.07-2.12 (s, 1H). LCMS (ESI) m/z: [M+H]⁺=802.55.

Example 41—Preparation of 5-[4-[(dimethylamino)methyl]-2,5-dimethoxyphenyl]-N-[2-(2-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]amino)ethoxyethyl]-7-methyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide formic acid
(Compound D14 formic acid)

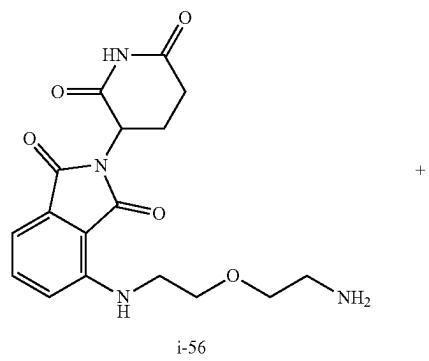
i-56

546

-continued



To a stirred solution of triphosgene (13.2 mg, 0.044 mmol, 0.40 equiv) in DCM (1 mL) was added a solution of 4-[2-(2-aminoethoxy)ethyl]amino]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (40.0 mg, 0.111 mmol, 1.00 equiv) and TEA (50 µL) in DCM (0.6 mL) dropwise at 0° C. After 2 minutes, additional TEA (30 µL) was added dropwise. The resulting mixture was stirred for additional 10 minutes at 0° C. 4-[4-[(dimethylamino)methyl]-2,5-dimethoxyphenyl]-2-methyl-5,6,7,8-tetrahydro-2,7-naphthyridin-1-one (39.7 mg, 0.111 mmol, 1.00 equiv) was then added in one portion. The reaction was stirred for additional 5 minutes at 0° C. and then warmed to room temperature for 25 minutes. The reaction solution was concentrated under vacuum. The crude product was purified by Prep-HPLC (conditions: SunFire C18 OBD Prep Column, 100 Å, 5 µm, 19 mm×250 mm; Mobile Phase A: water (0.1% FA), Mobile Phase B:ACN; Flow rate: 25 mL/minute; Gradient: 9 B to 19 B in 14 minutes; 254 nm; RT: 15.53 minutes) to afford 5-[4-[(dimethylamino)methyl]-2,5-dimethoxyphenyl]-N-[2-(2-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]amino)ethoxyethyl]-7-methyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide formic acid (5.9 mg, 6%) as a yellow solid. ¹H NMR (400 MHz, Methanol-d4) δ 8.56 (s, 0.4H, FA), 7.56 (dd, J=8.6, 7.1 Hz, 1H), 7.44 (s, 1H), 7.11 (d, J=9.3 Hz, 2H), 7.03 (d, J=7.0 Hz, 1H), 6.95 (s, 1H), 5.04 (dd, J=12.4, 5.4 Hz, 1H), 4.36 (br s, 2H), 4.09 (s, 2H), 3.89 (s, 3H), 3.81-3.70 (m, 6H), 3.66-3.56 (m, 6H), 3.51 (t, J=5.2 Hz, 2H), 3.43 (t, J=5.3 Hz, 2H), 2.89-2.62 (m, 9H), 2.53 (br s, 1H), 2.32 (br s, 1H), 2.11-2.02 (m, 1H). LCMS (ESI) m/z: [M+H]⁺=744.50.

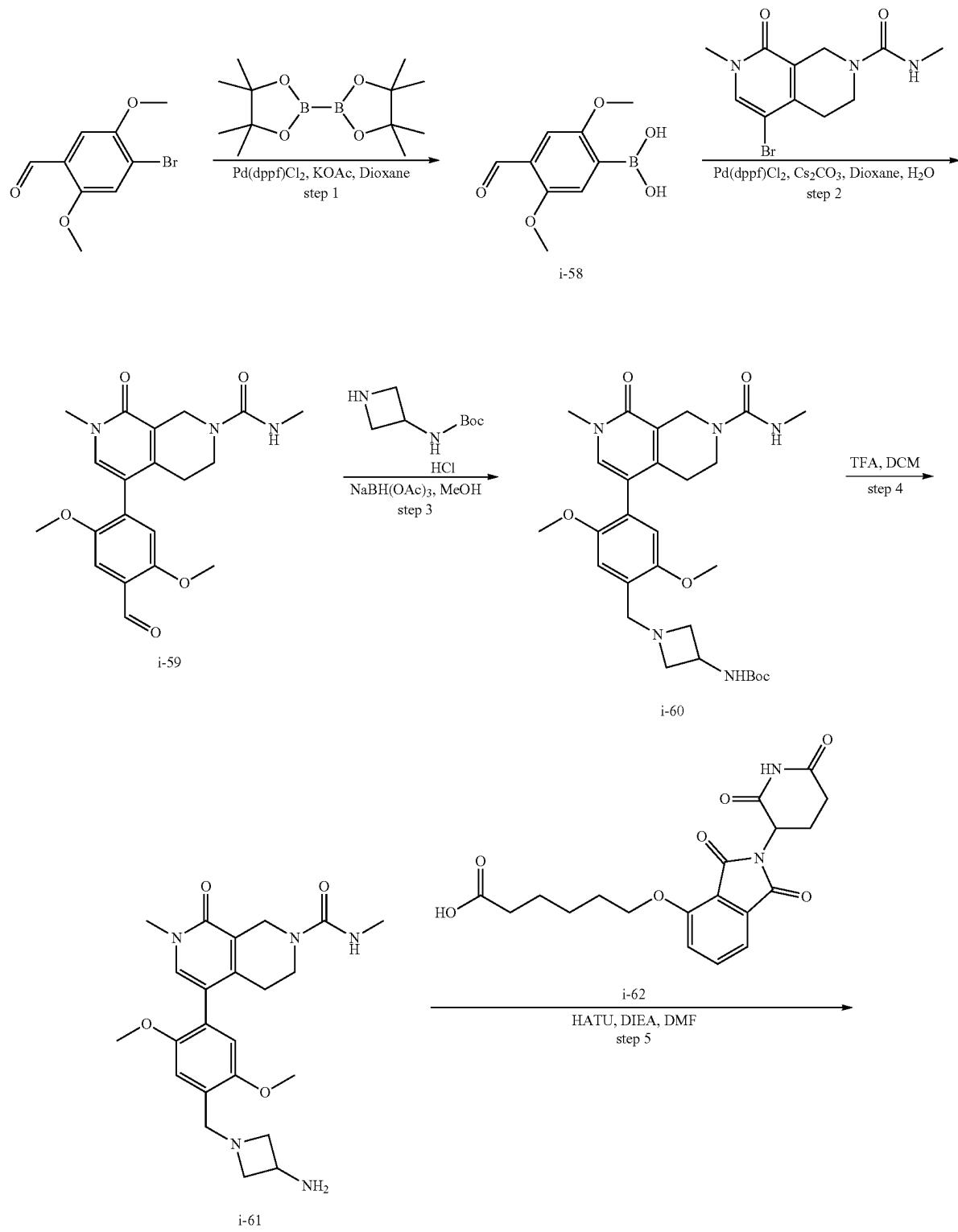


547

Example 42—Preparation of 5-[[3-([2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]oxy)hexanamido]azetidin-1-yl]methyl]-2,5-dimethoxyphenyl)-N,N-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide formic acid
 (Compound D15 formic acid)

548

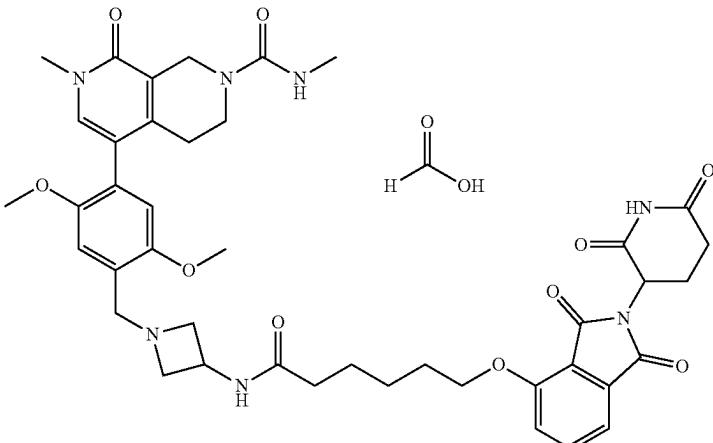
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549

550

-continued



compound D15 formic acid

Step 1: Preparation of
4-Formyl-2,5-dimethoxyphenylboronic acid (i-58)

Step 2: Preparation of 5-(4-Formyl-2,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (i-59)

30

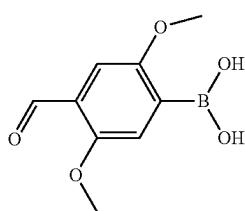
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i-58 45

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i-59

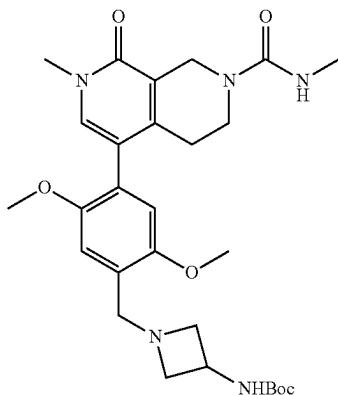


To a stirred solution of 4-bromo-2,5-dimethoxybenzaldehyde (200.00 mg, 0.816 mmol, 1.00 equiv) and bis(pinacolato)diboron (248.68 mg, 0.979 mmol, 1.2 equiv) in dioxane (2 mL) was added KOAc (160.19 mg, 1.632 mmol, 2 equiv) and Pd(dppf)Cl₂ (59.71 mg, 0.082 mmol, 0.1 equiv). The mixture was stirred at 90° C. for 1 hour (under N₂ atmosphere). The resulting mixture was concentrated under reduced pressure to afford 4-formyl-2,5-dimethoxyphenylboronic acid (400 mg, crude) as a brown solid. The crude product was used in the next step directly without further purification. LCMS (ESI) m/z: [M+H]⁺=211.3.

To a stirred solution of 4-formyl-2,5-dimethoxyphenylboronic acid (107.00 mg, 0.510 mmol, 1.00 equiv) and 5-bromo-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (152.94 mg, 0.510 mmol, 1.00 equiv) in dioxane (1.00 mL) and H₂O (5.00 mL) was added CS₂CO₃ (332.04 mg, 1.019 mmol, 2 equiv) and Pd(dppf)Cl₂ (37.28 mg, 0.051 mmol, 0.1 equiv). The mixture was stirred at 90° C. for 1 hour (under N₂ atmosphere). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH₂Cl₂/MeOH (10:1) to afford 5-(4-formyl-2,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (247 mg, crude) as a brown solid. LCMS (ESI) m/z: [M+H]⁺=386.2.

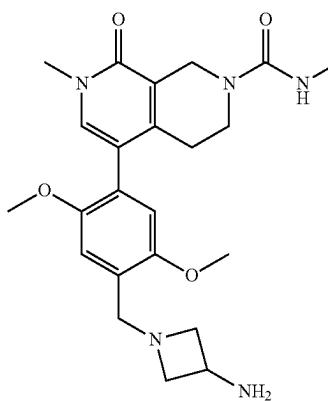
551

Step 3: Preparation of tert-Butyl N-[1-[(2,5-dimethoxy-4-[2-methyl-7-(methylcarbamoyl)-1-oxo-6,8-dihydro-5H-2,7-naphthyridin-4-yl]phenyl]methyl]azetidin-3-yl]carbamate (i-60)



To a stirred solution of 5-(4-formyl-2,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (100.00 mg, 0.259 mmol, 1.00 equiv) and tert-butyl N-(azetidin-3-yl)carbamate (44.69 mg, 0.259 mmol, 1 equiv) in MeOH (2.00 mL) was added NaBH (OAc)₃ (109.98 mg, 0.519 mmol, 2 equiv). The mixture was stirred at room temperature for 1 h. The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (CH₂Cl₂/MeOH 10:1) to afford tert-butyl N-[1-[(2,5-dimethoxy-4-[2-methyl-7-(methylcarbamoyl)-1-oxo-6,8-dihydro-5H-2,7-naphthyridin-4-yl]phenyl]methyl]azetidin-3-yl]carbamate (100 mg, 71.16%) as a brown solid. LCMS (ESI) m/z: [M+H]⁺=542.2

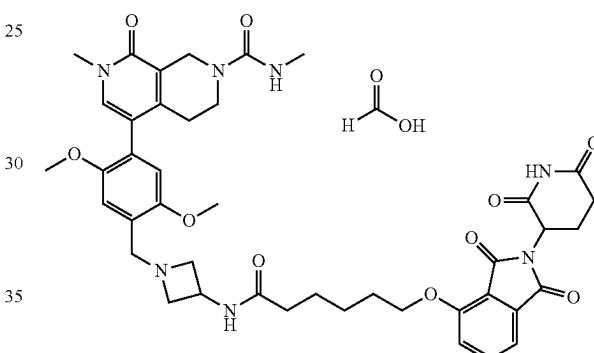
Step 4: Preparation of afford 5-[4-[(3-Aminoazetidin-1-yl)methyl]-2,5-dimethoxyphenyl]-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (i-61)

**552**

To a stirred solution of tert-butyl N-[1-[(2,5-dimethoxy-4-[2-methyl-7-(methylcarbamoyl)-1-oxo-6,8-dihydro-5H-2,7-naphthyridin-4-yl]phenyl]methyl]azetidin-3-yl]carbamate (100.00 mg, 0.185 mmol, 1.00 equiv) in DCM (2.00 mL) was added TFA (0.40 mL). The resulting mixture was concentrated under reduced pressure to afford 5-[4-[(3-aminoazetidin-1-yl)methyl]-2,5-dimethoxyphenyl]-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (80 mg, 98.14%) as a yellow solid. The crude product was used in the next step directly without further purification. LCMS (ESI) m/z: [M+H]⁺=442.2.

Step 5: Preparation of afford 5-(4-[[3-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl)oxy)hexanamido]azetidin-1-yl)methyl]-2,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide formic acid
(Compound D15 formic acid)

compound D15 formic acid

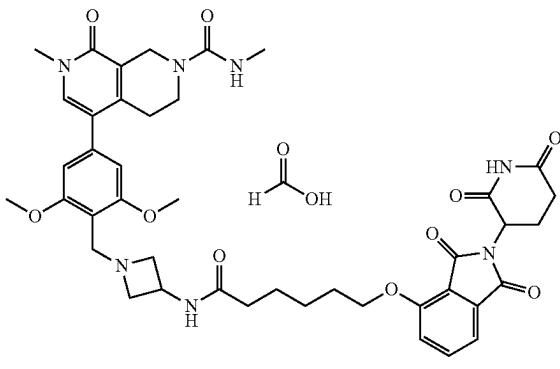


40 To a solution of 5-[4-[(3-aminoazetidin-1-yl)methyl]-2,5-dimethoxyphenyl]-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (70.00 mg, 0.159 mmol, 1.00 equiv) and 6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]oxy]hexanoic acid (61.57 mg, 0.159 mmol, 1.00 equiv) in DMF (1 mL) was added DIEA (102.45 mg, 0.793 mmol, 5.00 equiv) and HATU (90.42 mg, 0.238 mmol, 1.50 equiv). The resulting solution was stirred at room temperature for 1 hour. Without any additional work-up, the mixture was purified by prep-HPLC (conditions: SunFire C18 OBD Prep Column, 100 Å, 5 μm, 19 mm×250 mm; Mobile Phase A: water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 9 B to 23 B in 14 minutes; 254 nm; R_f: 14.33 minutes) to give 5-(4-[[3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl)oxy)hexanamido]azetidin-1-yl)methyl]-2,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide formic acid (9.7 mg, 6.84%) as a white solid.
1^H NMR (400 MHz, Methanol-d4) δ 8.49 (br s, 1H, FA), 7.78 (dd, J=8.4, 7.4 Hz, 1H), 7.49-7.41 (m, 3H), 7.06 (s, 1H), 6.88 (s, 1H), 5.10 (dd, J=12.5, 5.5 Hz, 1H), 4.55-4.44 (m, 1H), 4.34 (s, 2H), 4.25 (t, J=6.1 Hz, 2H), 4.11 (s, 2H), 4.06 (t, J=8.5 Hz, 2H), 3.86 (s, 3H), 3.76 (s, 3H), 3.74-3.64 (m, 3H), 3.61 (s, 3H), 2.95-2.65 (m, 6H), 2.52 (s, 2H), 2.29 (t, J=7.3 Hz, 2H), 2.18-2.07 (m, 1H), 1.96-1.85 (m, 2H), 1.81-1.69 (m, 2H), 1.66-1.54 (m, 2H). LCMS (ESI) m/z: [M+H]⁺=812.45.

553

Example 43—Preparation of 5-(4-[[3-(6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]oxy]hexanamido)azetidin-1-yl]methyl]-3,5-dimethoxyphenyl)-N,N-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide formic acid
(Compound D16 formic acid)

compound D16 formic acid

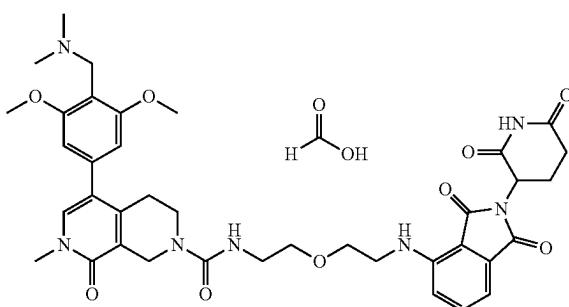


25

Compound D16 was prepared in a similar manner to the preparation of compound D21. 15 Compound D16 formic acid (15 mg, 40.8%) was obtained as a white solid. ¹H NMR (400 MHz, Methanol-d4) δ 8.52 (br s, 1H, FA), 7.78 (dd, J=8.4, 7.3 Hz, 1H), 7.56 (s, 1H), 7.45 (dd, J=7.8, 2.7 Hz, 2H), 6.68 (s, 2H), 5.10 (dd, J=12.4, 5.5 Hz, 1H), 4.55-4.46 (m, 1H), 4.41-4.32 (m, 4H), 4.25 (t, J=6.1 Hz, 2H), 4.19 (s, 2H), 3.92 (s, 7H), 3.64 (s, 3H), 3.54 (t, J=5.6 Hz, 2H), 2.89-2.66 (m, 6H), 2.62 (t, J=5.6 Hz, 2H), 2.29 (t, J=7.3 Hz, 2H), 2.17-2.08 (m, 1H), 1.94-1.85 (m, 2H), 1.79-1.71 (m, 2H), 1.66-1.55 (m, 2H). LCMS (ESI) m/z: [M+H]⁺=812.45.

Example 44—Preparation of 5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-N-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]amino]ethoxy)ethyl]-7-methyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide formic acid
(Compound D17 Formic Acid)

compound D17 formic acid



55

Compound D17 formic acid was prepared in a similar manner to the preparation of compound D21. Compound D17 formic acid (75.8 mg, 22%) was obtained as a yellow solid. ¹H NMR (300 MHz, Methanol-d4) δ 8.57 (s, 0.1H, FA), 7.62-7.50 (m, 2H), 7.11 (d, J=8.5 Hz, 1H), 7.03 (d, J=7.1 Hz, 1H), 6.72 (s, 2H), 5.03 (dd, J=12.3, 5.3 Hz, 1H), 4.38 (s, 2H), 4.27 (s, 2H), 3.94 (s, 6H), 3.74 (t, J=5.0 Hz, 2H), 3.67-3.61 (m, 5H), 3.51 (q, J=4.9 Hz, 4H), 3.44 (t, J=5.3 Hz, 2H), 2.80 (s, 7H), 2.78-2.56 (m, 4H), 2.13-2.00 (m, 1H). LCMS (ESI) m/z: [M+H]⁺=744.45.

554

Compound D17 formic acid was prepared in a similar manner to the preparation of compound D21. Compound D17 formic acid (75.8 mg, 22%) was obtained as a yellow solid. ¹H NMR (300 MHz, Methanol-d4) δ 8.57 (s, 0.1H, FA), 7.62-7.50 (m, 2H), 7.11 (d, J=8.5 Hz, 1H), 7.03 (d, J=7.1 Hz, 1H), 6.72 (s, 2H), 5.03 (dd, J=12.3, 5.3 Hz, 1H), 4.38 (s, 2H), 4.27 (s, 2H), 3.94 (s, 6H), 3.74 (t, J=5.0 Hz, 2H), 3.67-3.61 (m, 5H), 3.51 (q, J=4.9 Hz, 4H), 3.44 (t, J=5.3 Hz, 2H), 2.80 (s, 7H), 2.78-2.56 (m, 4H), 2.13-2.00 (m, 1H). LCMS (ESI) m/z: [M+H]⁺=744.45.

Example 45—Preparation of 5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-N-(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]oxy]pentyl)-7-methyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (Compound D18)

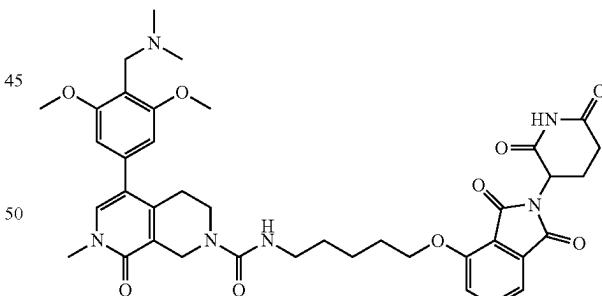
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compound D18



50

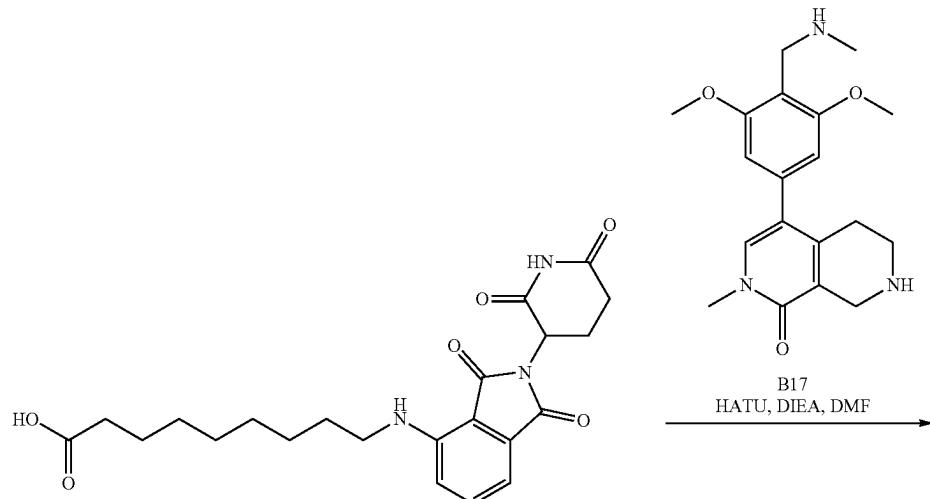
55

Compound D18 was prepared in a similar manner to the preparation of compound D21. Compound D18 (5 mg, 12.10%) was obtained as a yellow solid. ¹H NMR (300 MHz, Methanol-d4) δ 7.78 (dd, J=8.5, 7.2 Hz, 1H), 7.59 (s, 1H), 7.46 (d, J=1.7 Hz, 1H), 7.43 (s, 1H), 6.74 (s, 2H), 5.12 (dd, J=12.3, 5.4 Hz, 1H), 4.38 (s, 4H), 4.26 (t, J=6.1 Hz, 2H), 3.96 (s, 6H), 3.63 (s, 3H), 3.54 (d, J=5.6 Hz, 2H), 3.27 (t, J=6.6 Hz, 1H), 2.89 (s, 7H), 2.90-2.79 (m, 1H), 2.79-2.59 (m, 3H), 2.18-2.05 (m, 1H), 1.97-1.86 (m, 2H), 1.65 (s, 5H). LCMS (ESI) m/z: [M+H]⁺=743.65.

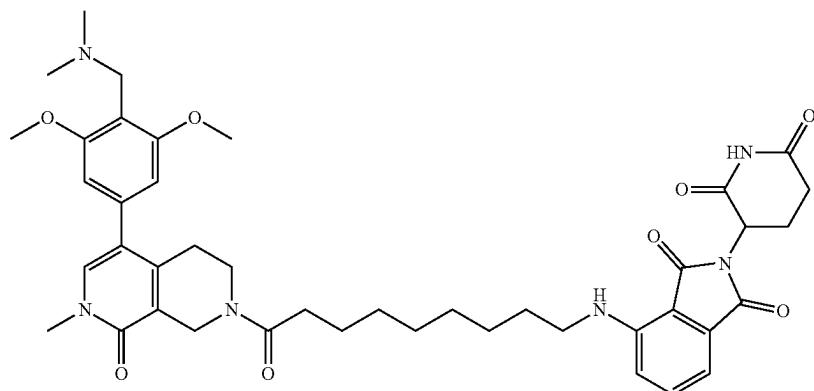
555

Example 46—Preparation of 4-[[9-(5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-1,2,3,4,7,8-hexahydro-2,7-naphthyridin-2-yl)-9-oxononyl]amino]-2-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione (Compound D19)

556



j-63



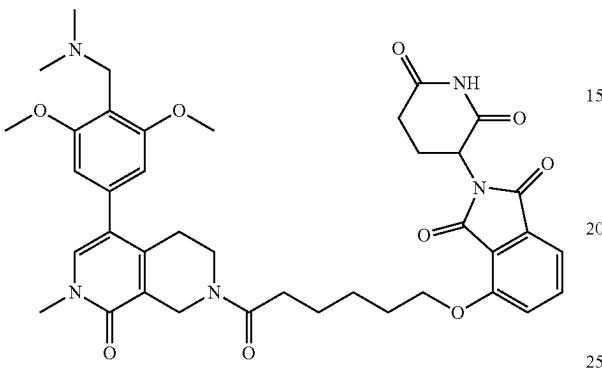
compound D19

To a stirred solution of 9-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amino]nonanoic acid (100 mg, 0.233 mmol, 1 equiv) in DMF (2 mL) was added HATU (115.02 mg, 0.303 mmol, 1.3 equiv) and DIEA (150.46 mg, 1.164 mmol, 5.0 equiv). The mixture was stirred at 25° C. for 30 minutes, and then 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-1-one (83.23 mg, 0.233 mmol, 1 equiv) was added. The mixture was stirred at 25° C. for 2 hours. Then the mixture was diluted with water (20 mL) and extracted with DCM (20 mL×3). The organic layers were combined and washed with saturated sodium chloride (20 mL), then dried over anhydrous sodium sulfate, filtered, and concentrated to give a crude product. The residue was purified by Prep-HPLC (condition: XSelect CSH Prep C18

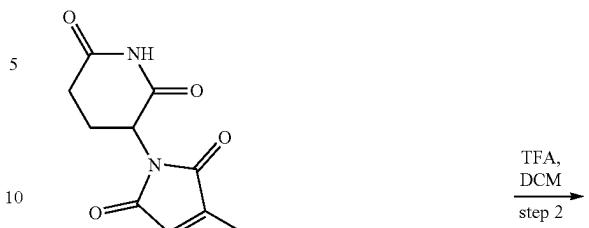
OBD Column, 5 μ m, 19*150 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 20% B to 40% B in 8 minutes; 254/220 nm; R_f: 7.08 minutes; Detector, 254 nm) to give 4-[[9-(5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-1,2,3, 4,7,8-hexahydro-2,7-naphthyridin-2-yl)-9-oxononyl]amino]-2-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione (25 mg, 32.5 μ mol, 13.96%) as a yellow solid. ¹H NMR (400 MHz, Methanol-d4) δ 7.64-7.51 (m, 2H), 7.04 (dd, J=7.9, 6.2 Hz, 2H), 6.72 (d, J=5.9 Hz, 2H), 5.12-5.01 (m, 1H), 4.62 (s, 2H), 4.55 (d, J=5.5 Hz, 2H), 4.33 (d, J=11.1 Hz, 2H), 3.95 (d, J=1.9 Hz, 6H), 3.75-3.63 (m, 5H), 2.86 (d, J=2.3 Hz, 7H), 2.80-2.68 (m, 3H), 2.67-2.59 (m, 1H), 2.50 (dt, J=17.8, 7.6 Hz, 2H), 2.17-2.08 (m, 1H), 1.67 (dd, J=13.6, 6.8 Hz, 4H), 1.45-1.31 (m, 8H). LCMS (ESI) m/z: [M+H]⁺=769.70.

557

Example 47—Preparation of [(4-[7-(6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isooindol-4-yl]oxy]hexanoyl)-2-methyl-1-oxo-1,2,5,6,7,8-hexahydro-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl)methyl](methyl)aminyl
(Compound D20)

**558**

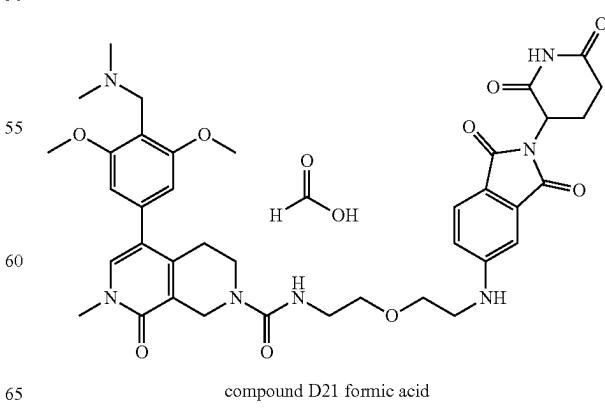
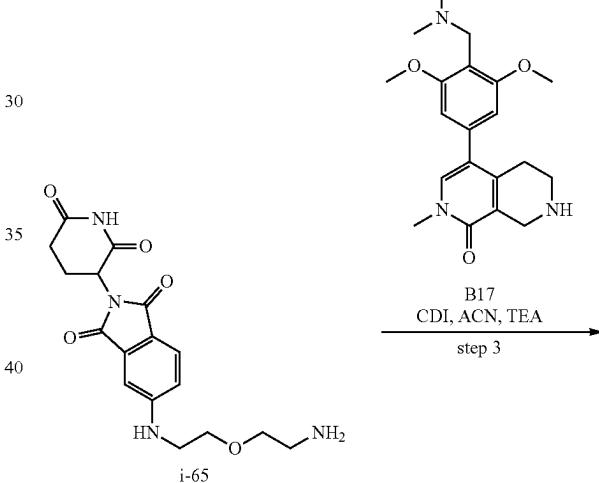
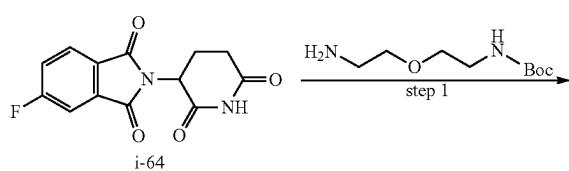
-continued



i-65

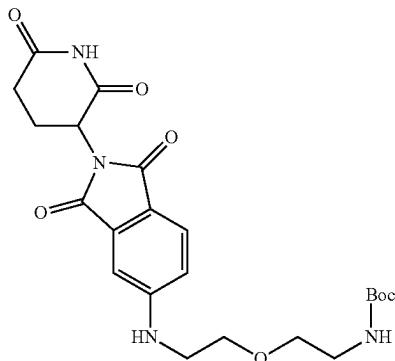
Compound D20 was prepared in a similar manner to the preparation of compound D19 and by substituting the carboxylic acid i-36 with 6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isooindol-4-yl]oxy]hexanoic acid (130 mg, 0.336 mmol, 1.20 equiv) in dimethylformamide (3.0 mL). Compound D20 (7.8 mg, 3.74%) was obtained as a white solid. ¹H NMR (400 MHz, Methanol-d₄) δ 8.56 (s, 1H), 7.76 (td, J=7.9, 3.5 Hz, 1H), 7.59 (d, J=12.7 Hz, 1H), 7.43 (q, J=5.8 Hz, 2H), 6.71 (s, 2H), 5.08 (dd, J=12.6, 5.5 Hz, 1H), 4.55 (s, 2H), 4.25 (dt, J=6.5, 3.2 Hz, 4H), 3.93 (d, J=4.5 Hz, 6H), 3.70 (dt, J=10.4, 5.6 Hz, 2H), 3.63 (d, J=2.9 Hz, 3H), 2.78 (d, J=6.0 Hz, 7H), 2.66 (s, 2H), 2.77-2.51 (m, 4H), 2.11 (tdd, J=10.7, 5.9, 3.1 Hz, 1H), 1.91 (h, J=6.4 Hz, 2H), 1.76 (p, J=7.5 Hz, 2H), 1.70-1.57 (m, 2H). LCMS (ESI) m/z: [M+H]⁺=728.50.

Example 48—Preparation of 5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-N-[2-(2-[(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl)amino]ethoxy)ethyl]-7-methyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide formic acid
(Compound D21 formic acid)



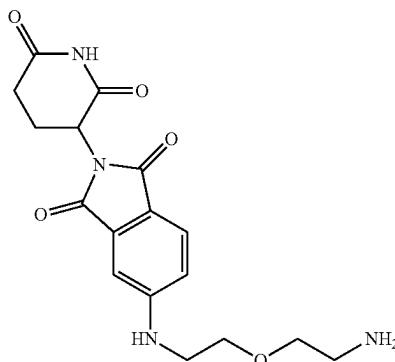
559

Step 1: Preparation of tert-butyl N-[2-[(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl)amino]ethoxy]ethyl]carbamate (i-65)



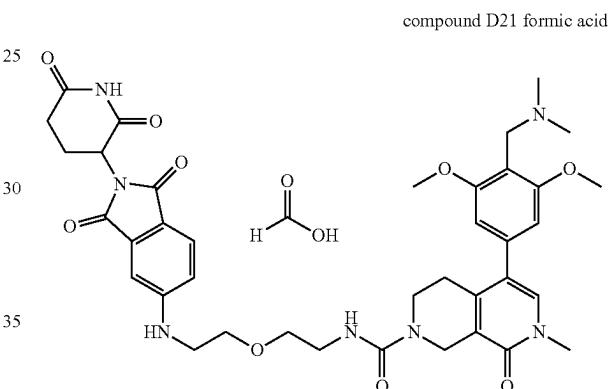
To a stirred solution of 2-(2,6-dioxopiperidin-3-yl)-5-fluoroisoindole-1,3-dione (1.00 g, 3.620 mmol, 1.00 equiv) and tert-butyl N-[2-(2-aminoethoxy)ethyl]carbamate (1.48 g, 7.241 mmol, 2.00 equiv) in NMP (10 mL) was added DIEA (935.79 mg, 7.241 mmol, 2.00 equiv) at room temperature. The resulting mixture was stirred for 4 hours at 90° C. under nitrogen atmosphere. The residue was purified by reverse flash chromatography (conditions: column, C18 silica gel; mobile phase, ACN in water, 0% to 50% gradient in 20 minutes; detector, UV 254 nm). This resulted in tert-butyl N-[2-[(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl)amino]ethoxy]ethyl]carbamate (430 mg, 25.79%) as a yellow oil. LCMS (ESI) m/z: [M+H]⁺=461.20.

Step 2: Preparation of 5-[[2-(2-aminoethoxy)ethyl]amino]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (i-66)

**560**

A solution of tert-butyl N-[2-[(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl)amino]ethoxy]ethyl] carbamate (400.00 mg, 0.869 mmol, 1.00 equiv) and TFA (1.00 mL) in DCM was stirred for 2 hours at room temperature. The resulting mixture was concentrated under vacuum. This resulted in 5-[[2-(2-aminoethoxy)ethyl]amino]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (220 mg, 70.28%) as a brown solid. LCMS (ESI) m/z: [M+H]⁺=361.14.

Step 3: Preparation of 5-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-N-[2-[(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl)amino]ethoxy]ethyl]-7-methyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide formic acid (Compound D21 formic acid)



A solution of 5-[[2-(2-aminoethoxy)ethyl]amino]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (60.00 mg, 0.166 mmol, 1.00 equiv) and CDI (29.70 mg, 0.183 mmol, 1.10 equiv) in acetonitrile (1.5 mL) and DMF (0.3 mL) was stirred for 2 hours at room temperature. Then 4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-5,6,7,8-tetrahydro-2,7-naphthyridin-1-one (119.03 mg, 0.333 mmol, 2.00 equiv) and TEA (33.70 mg, 0.333 mmol, 2.00 equiv) was added to the reaction mixture. The resulting mixture was stirred for overnight at room temperature. The crude product was purified by Prep-HPLC (conditions: SunFire C18 OBD Prep Column, 100 Å, 5 µm, 19 mm×250 mm; mobile phase, Water (0.05% TFA) and ACN (12% Phase B up to 26% in 15 minutes); Detector, UV). This resulted in 5-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-N-[2-[(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl)amino]ethoxy]ethyl]-7-methyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (4 mg, 3.23%) as a green semi-solid. ¹H NMR (400 MHz, Acetonitrile-d3) δ 9.31 (s, 1H), 9.03 (brs, 1.0H, FA), 7.51 (d, J=8.3 Hz, 1H), 7.40 (s, 1H), 7.00 (d, J=2.1 Hz, 1H), 6.91 (dd, J=8.3, 2.2 Hz, 1H), 6.60 (s, 2H), 6.18 (s, 1H), 5.67 (t, J=5.7 Hz, 1H), 4.92 (dd, J=12.5, 5.4 Hz, 1H), 4.28 (d, J=4.8 Hz, 4H), 3.85 (s, 6H), 3.71 (t, J=5.0 Hz, 2H), 3.58-3.49 (m, 7H), 3.39 (q, J=5.3 Hz, 2H), 3.34 (t, J=5.0 Hz, 2H), 2.77 (s, 6H), 2.75-2.65 (m, 2H), 2.57 (t, J=5.6 Hz, 2H), 1.35-1.24 (m, 1H). LCMS (ESI) m/z: [M+H]⁺=744.50.

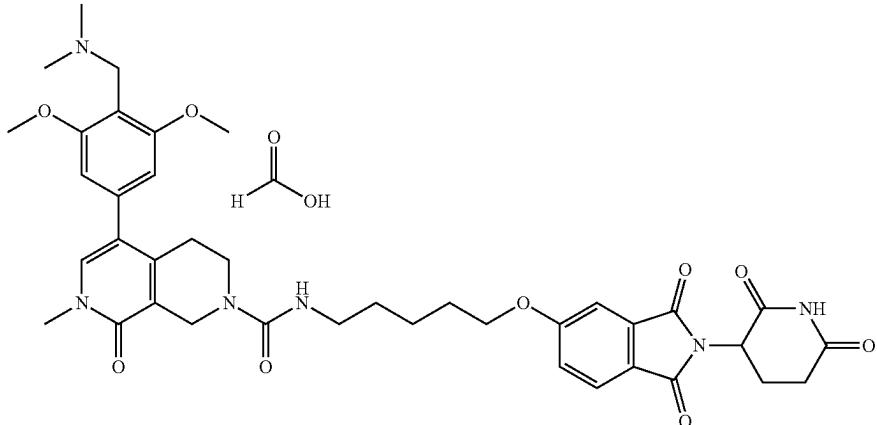
561

Example 49—Preparation of 5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-N-(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]amino]pentyl)-7-methyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide formic acid
(Compound D22 formic acid)

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562

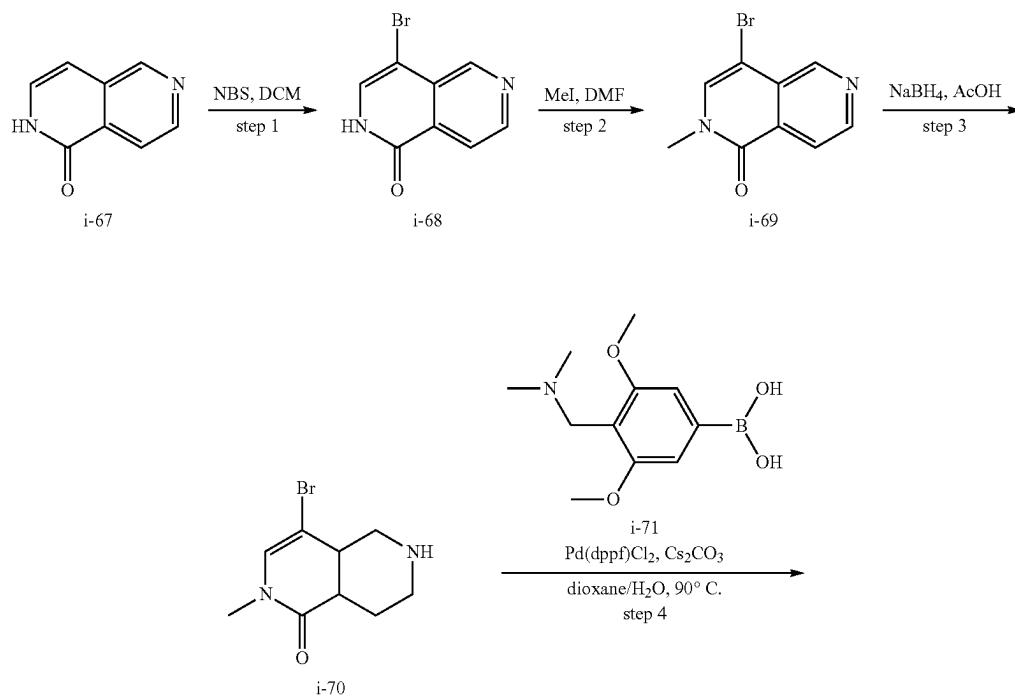
compound D22 formic acid

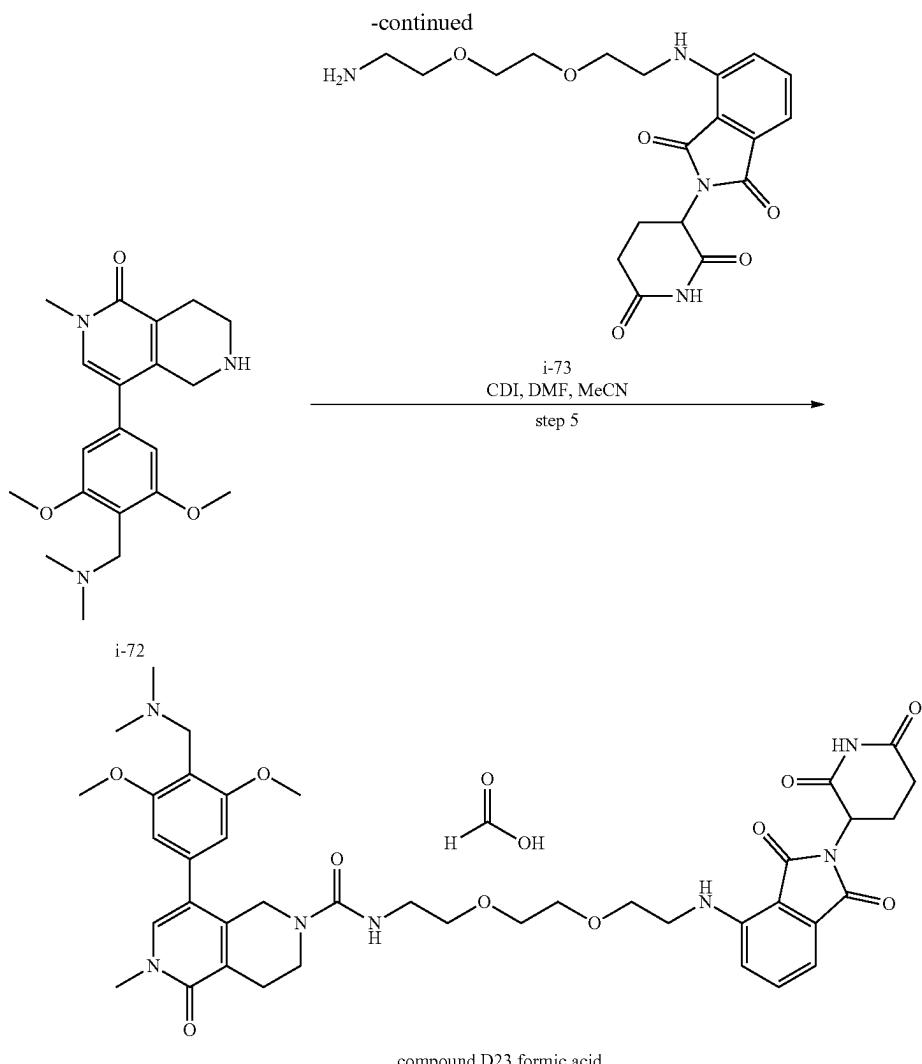


Compound D22 formic acid was prepared in a similar manner to the preparation of compound D21. Compound D22 formic acid (8.7 mg, 20.8%) was obtained as a light yellow solid.¹H NMR (400 MHz, Methanol-d4) δ 8.57 (brs, 0.7H, FA), 7.79 (d, J=8.3 Hz, 1H), 7.58 (s, 1H), 7.37 (d, J=2.2 Hz, 1H), 7.31 (dd, J=8.3, 2.3 Hz, 1H), 6.66 (s, 2H), 5.10 (dd, J=12.6, 5.4 Hz, 1H), 4.36 (s, 2H), 4.17 (t, J=6.3 Hz, 2H), 4.10 (s, 2H), 3.91 (s, 6H), 3.64 (s, 3H), 3.54 (t, J=5.6 Hz, 2H), 3.27 (t, J=6.6 Hz, 2H), 2.93-2.70 (m, 3H), 2.70-

³⁰ 2.58 (m, 8H), 2.17-2.07 (m, 1H), 1.89 (p, J=6.5 Hz, 2H), 1.70-1.52 (m, 4H). LCMS (ESI) m/z: [M+H]⁺=743.35.

Example 50—Preparation of 8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-N-[2-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]amino)ethoxy]ethoxy]ethyl]-6-methyl-8-oxo-3,4-dihydro-1H-2,6-naphthyridine-2-carboxamide formic acid
(Compound D23 formic acid)

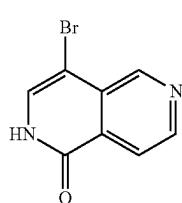
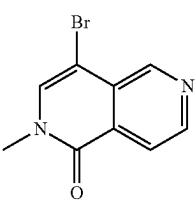


563**564**Step 1: Preparation of
4-bromo-2H-2,6-naphthyridin-1-one (i-68)

45

Step 2: Preparation of
4-bromo-2-methyl-2,6-naphthyridin-1-one (i-69)

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i-68
50

i-69

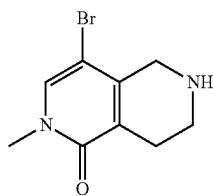
To a stirred solution of 2H-2,6-naphthyridin-1-one (584.00 mg, 3.996 mmol, 1.00 equiv) in DCM (10.00 mL) was added NBS (640.09 mg, 3.596 mmol, 0.9 equiv) in portions at room temperature under air atmosphere. The mixture was stirred for another 1 hour. The reaction mixture was concentrated and purified by silica gel column chromatography, eluted with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (12:1) to afford 4-bromo-2H-2,6-naphthyridin-1-one (1.18 g, 85.29%) as a light yellow solid. LCMS (ESI) m/z: [M+H] $^{+}$ =225, 227.

60 To a stirred solution of 4-bromo-2H-2,6-naphthyridin-1-one (1.18 g, 5.243 mmol, 1.00 equiv) in Mel (2.98 g, 20.974 mmol, 4.00 equiv) was added NaH (0.25 g, 10.487 mmol, 2.00 equiv) in portions at 0° C. under nitrogen atmosphere. Then Mel (1513.71 mg, 10.665 mmol, 4 equiv) was added drop-wise. The mixture was stirred for another 1 hour at room temperature and quenched with water at 0° C. The product was precipitated by the addition of water. The precipitated solids were collected by filtration and washed with water (2 \times 20 mL). The crude product 4-bromo-2-

565

methyl-2, 6-naphthyridin-1-one (568 mg, 45.31%) was used in the next step directly without further purification. LCMS (ESI) m/z: [M+H]⁺=239, 241.

Step 3: Preparation of 4-bromo-2-methyl-5,6,7,8-tetrahydro-2,6-naphthyridin-1-one (i-70)

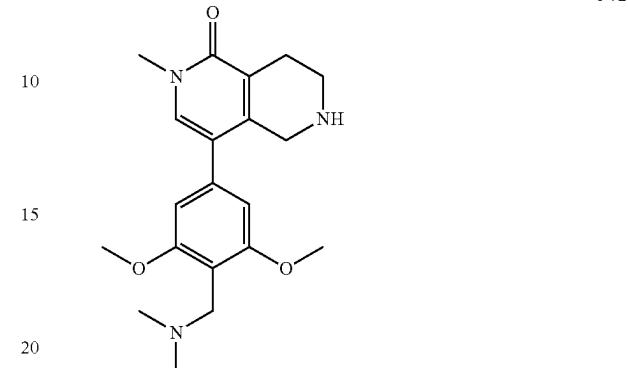


To a stirred solution of 4-bromo-2-methyl-2, 6-naphthyridin-1-one (239.10 mg, 1.000 mmol, 1.00 equiv) in AcOH (5.00 mL) was added NaBH₄ (264.86 mg, 7.001 mmol, 7.00 equiv) in portions at 0° C. under nitrogen atmosphere. The resulting mixture was stirred for 5 minutes at room temperature. Then, the mixture was poured into ice water, basified with ammonium hydroxide, and extracted with CH₂Cl₂ (3×50 mL). The combined organic layers were concentrated under reduced pressure and the resulting crude product 4-bromo-2-methyl-5,6,7,8-tetrahydro-2,6-naphthyridin-1-one (237 mg, 80.91%) was used directly in the next step. LCMS (ESI) m/z: [M+H]⁺=243, 245.

566

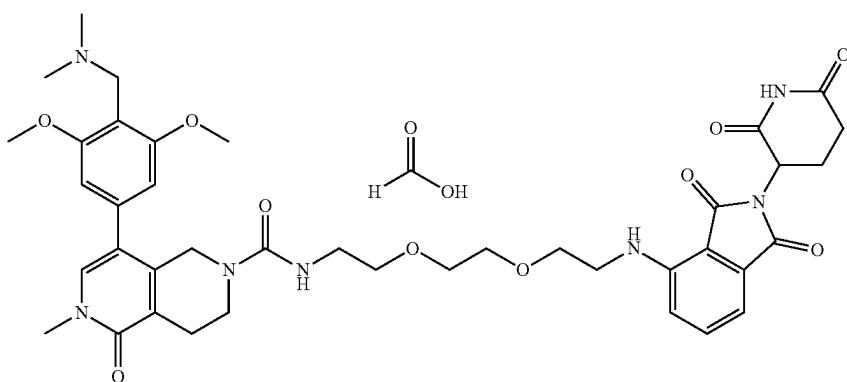
Step 4: Preparation of 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-5,6,7,8-tetrahydro-2,6-naphthyridin-1-one (i-72)

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Step 3: Preparation of 4-bromo-2-methyl-5,6,7,8-tetrahydro-2,6-naphthyridin-1-one (i-70)
i-72



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25
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35
40
i-70 To a solution of 4-bromo-2-methyl-5,6,7,8-tetrahydro-2, 6-naphthyridin-1-one (237.00 mg, 0.975 mmol, 1.00 equiv) and [(2,6-dimethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methyl]dimethyl ethylamine (313.15 mg, 0.975 mmol, 1 equiv) in dioxane (5.00 mL) and H₂O (1.00 mL) was added Cs₂CO₃ (952.92 mg, 2.925 mmol, 3 equiv) and Pd(dppf)Cl₂CH₂Cl₂ (79.61 mg, 0.097 mmol, 0.1 equiv). After stirring for 1.5 h at 100° C. under a nitrogen atmosphere, the resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH₂Cl₂/MeOH (12:1) to afford the crude product, 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-5,6,7,8-tetrahydro-2,6-naphthyridin-1-one (524 mg, 79.69%) as a dark brown solid. LCMS (ESI) m/z: [M+H]⁺=358.

Step 5: Preparation of 8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-N-[2-[2-(2-[2-(2-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]amino)ethoxy]ethoxy]ethyl]-6-methyl-5-oxo-3,4-dihydro-1H-2,6-naphthyridine-2-carboxamide formic acid
(Compound D23 formic acid)



compound D23 formic acid

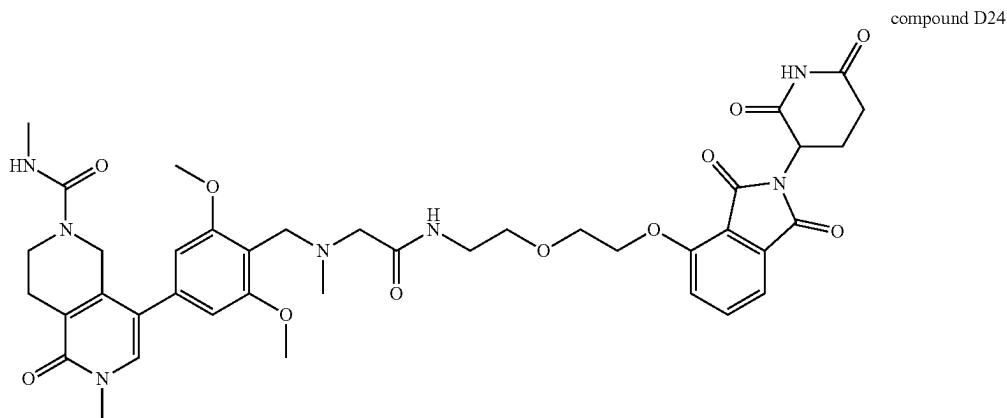
567

To a stirred solution of 4-([2-[2-(2-aminoethoxy)ethoxy]ethyl]amino)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione trifluoroacetic acid salt (40.40 mg, 0.078 mmol, 1.00 equiv) in DMF (0.30 mL) and MeCN (0.90 mL) was added CDI (13.90 mg, 0.086 mmol, 1.10 equiv). The mixture was stirred for 2 hours at room temperature under air atmosphere. Then 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-5,6,7,8-tetrahydro-2,6-naphthyridin-1-one (41.78 mg, 0.117 mmol, 1.50 equiv) and Et₃N (23.66 mg, 0.234 mmol, 3.00 equiv) was added, and the final reaction mixture was stirred for overnight at room temperature under air atmosphere. Without any additional work-up, the resulting mixture was purified by Prep-HPLC (conditions: Xselect CSH F-Phenyl OBD Column 19*150 mm 5 ¹⁵ μm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 9 B to 20 B in 10 minutes; 254 nm; R_{t1}: 9.75 minutes) to afford 8-[4-[(dimeth-

568

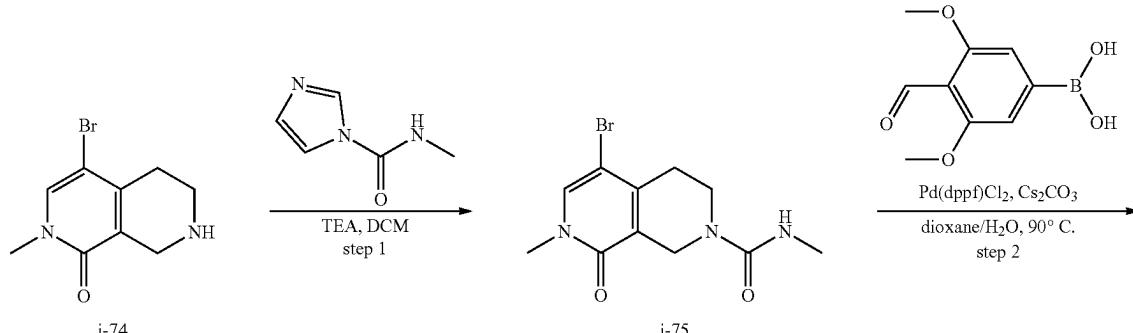
ylamino)methyl]-3,5-dimethoxyphenyl]-N-[2-[2-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]amino]ethoxy]ethoxyethyl]-6-methyl-5-oxo-3,4-dihydro-1H-2,6-naphthyridine-2-carboxamide (21 mg, 33.49%) as a yellow solid. ¹H NMR (300 MHz, Methanol-d₄) δ 8.57 (brs, 0.7H, FA), 7.58-7.48 (m, 2H), 7.07 (dd, J=14.0, 7.8 Hz, 2H), 6.71 (s, 2H), 5.03 (dd, J=12.4, 5.4 Hz, 1H), 4.36 (s, 2H), 4.19 (s, 2H), 3.94 (s, 6H), 3.73 (t, J=5.2 Hz, 2H), 3.68-3.57 (m, 9H), 3.57-3.47 (m, 4H), 3.35 (s, 1H), 2.92-2.75 (m, 2H), 2.74 (s, 6H), 2.71-2.58 (m, 4H), 2.14-2.04 (m, 1H). LCMS (ESI) m/z: [M+H]⁺=788.50.

Example 51—Preparation of 8-(4-((2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)oxy)ethoxy)ethyl)amino)-2-oxoethyl)(methyl)amino)methyl)-3,5-dimethoxyphenyl)-N,6-dimethyl-5-oxo-3,4,5,6-tetrahydro-2,6-naphthyridine-2 (1H)-carboxamide (Compound D24)



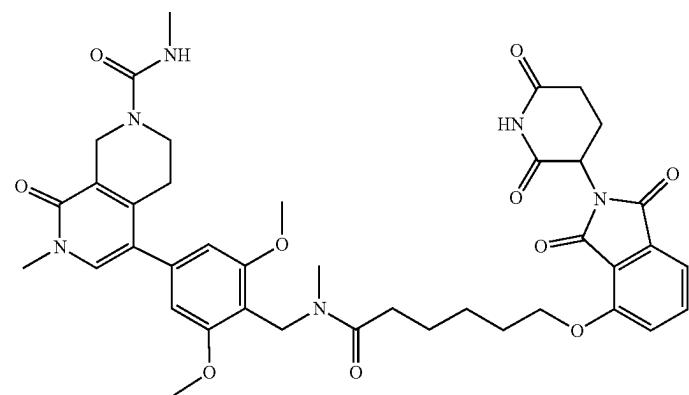
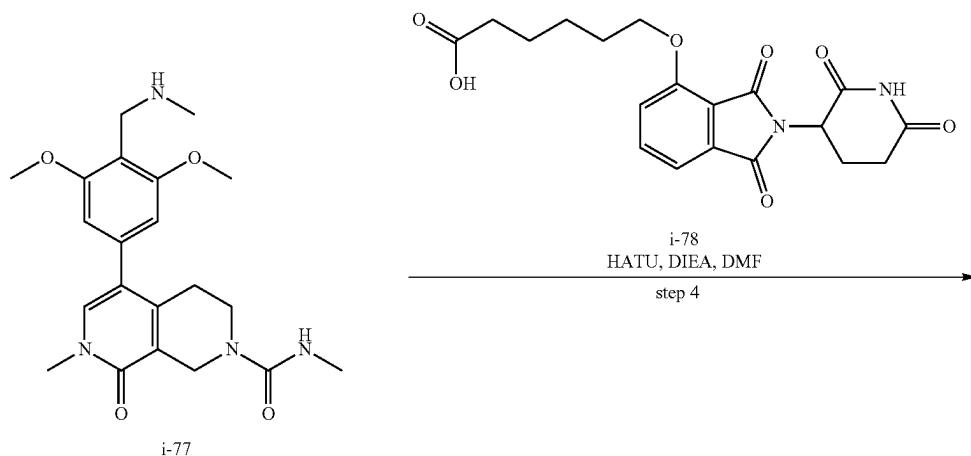
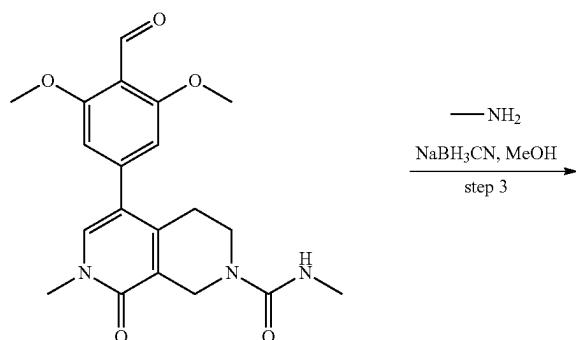
⁴⁰ Compound D24 was prepared in a similar manner to the preparation of compound D13 and compound D23.

Example 52—Preparation of 5-[4-[(6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]oxy]-N-methylhexanamido)methyl]-3,5-dimethoxyphenyl]-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (Compound D25)



569**570**

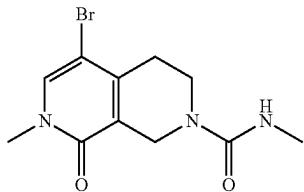
-continued



compound D25

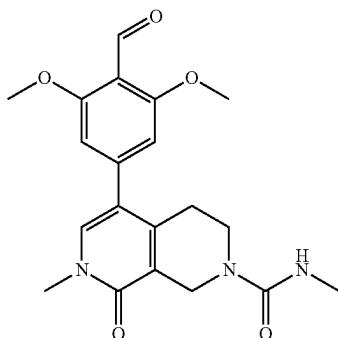
571

Step 1: Preparation of 5-bromo-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (i-75)



Using a similar procedure as described in Example 24, step 4 and substituting with 4-bromo-2-methyl-5,6,7,8-tetrahydro-2,7-naphthyridin-1-one (243 mg, 1.000 mmol) afforded 5-bromo-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (348 mg, 98.6%) as a light yellow solid. LCMS (ESI) m/z: [M+H]⁺=300, 302.

Step 2: Preparation of 5-(4-formyl-3,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (i-76)

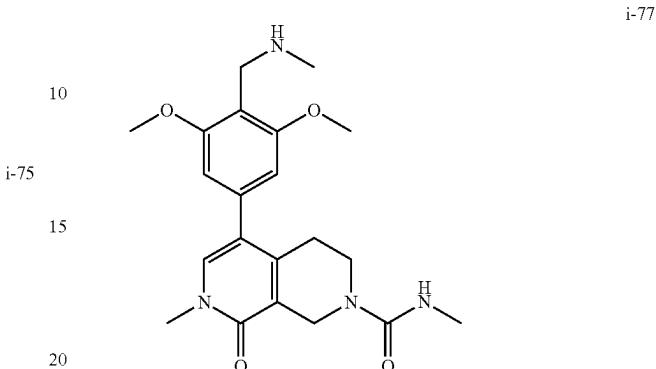


Using a similar procedure as described in Example 23, step 3 and substituting with 5-bromo-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (100 mg, 0.333 mmol, 1.00 equiv) and 2,6-dimethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (97.3 mg, 0.333 mmol, 1.00 equiv) afforded 5-(4-formyl-3,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (132 mg, 91.5%) as a light yellow solid. LCMS (ESI) m/z: [M+H]⁺=386.

572

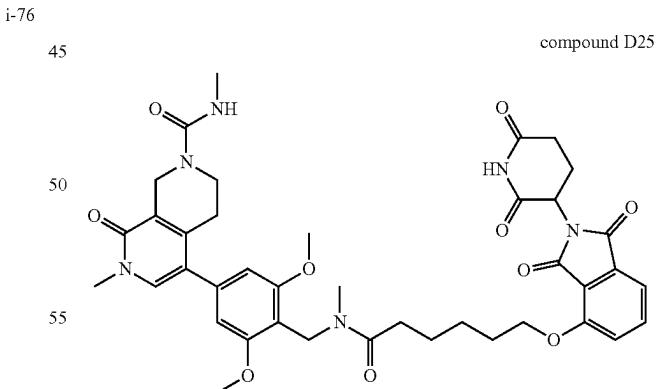
Step 3: Preparation of 5-[3,5-dimethoxy-4-[(methylamino)methyl]phenyl]-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (i-77)

5



To a stirred solution of 5-(4-formyl-3,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (100 mg, 0.259 mmol, 1.00 equiv) and triethylamine (78.76 mg, 0.778 mmol, 3.00 equiv) in methanol (1.00 mL) was added sodium cyanoborohydride (32.6 mg, 0.519 mmol, 2.00 equiv) in portions at room temperature. Solvent was then evaporated under reduced pressure and the residue was purified by silica gel column chromatography, eluted with dichloromethane/methanol (12:1) to afford 5-[3,5-dimethoxy-4-[(methylamino)methyl]phenyl]-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (71 mg, 68.3%) as a yellow solid. LCMS (ESI) m/z: [M+H]⁺=400.

Step 4: Preparation of 5-[4-[[6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisooindol-4-yl]oxy]-N-methylhexanamido)methyl]-3,5-dimethoxyphenyl]-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (Compound D25)



Using a similar procedure as described in Example 46 and substituting with 5-[3,5-dimethoxy-4-[(methylamino)methyl]phenyl]-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (60 mg, 0.150 mmol, 1.00 equiv) and 6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisooindol-4-yl]oxy]hexanoic acid (58.2 mg, 0.150 mmol, 1.00 equiv) afforded 5-[4-[[6-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisooindol-4-yl]oxy]-N-methylhexanamido)methyl]-3,

573

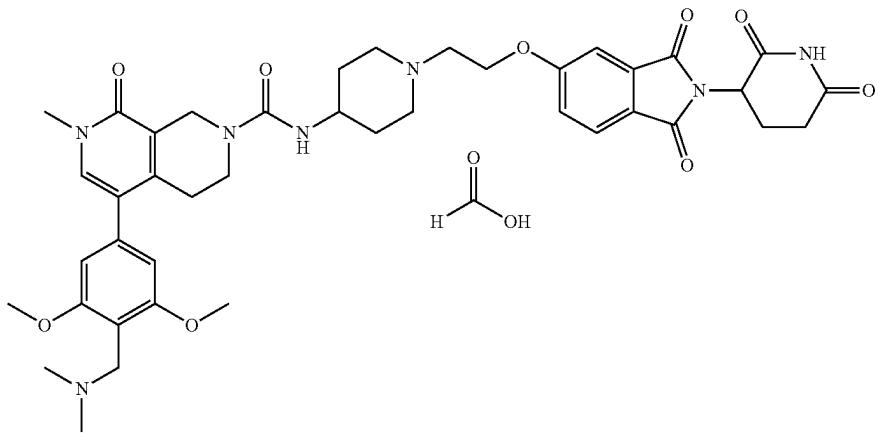
5-dimethoxyphenyl]-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (30 mg, 25.5%) as an off-white solid. ¹H NMR (300 MHz, Methanol-d₄) δ 7.76 (dd, J=8.6, 7.2 Hz, 1H), 7.55 (d, J=2.8 Hz, 1H), 7.49-7.37 (m, 2H), 6.60 (d, J=14.9 Hz, 2H), 5.08 (dd, J=12.3, 5.5 Hz, 1H), 4.76-4.57 (m, 2H), 4.35 (s, 2H), 4.25 (t, J=6.1 Hz, 2H), 3.85 (d, J=11.5 Hz, 6H), 3.63 (d, J=3.6 Hz, 3H), 3.52 (q, J=5.2 Hz, 2H), 2.83 (d, J=2.0 Hz, 4H), 2.77 (d, J=6.8 Hz, 4H), 2.72-2.55 (m, 4H), 2.51-2.39 (m, 1H), 2.20-2.00 (m, 1H), 1.87 (d, J=7.8 Hz, 2H), 1.66 (dd, J=21.4, 2.6 Hz, 4H). LCMS (ESI) m/z: [M+H]⁺=771.40.

574

Example 53—Preparation of 5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-N-[1-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl]oxy]ethyl)piperidin-4-yl]-7-methyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide formic acid (Compound D26 formic acid)

15

compound D26 formic acid



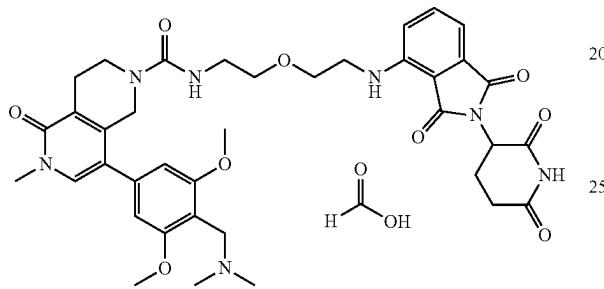
575

Compound D26 was prepared in a similar manner to the preparation of compound D21. Compound D26 formic acid (4.5 mg, 4.68%) was obtained as a white solid. ¹H NMR (300 MHz, Methanol-d4) δ 8.48 (brs, 1.6H, FA), 7.85 (d, J=8.3 Hz, 1H), 7.60 (s, 1H), 7.49 (d, J=2.2 Hz, 1H), 7.39 (dd, J=8.3, 2.3 Hz, 1H), 6.74 (s, 2H), 5.13 (dd, J=12.3, 5.4 Hz, 1H), 4.39 (d, J=3.8 Hz, 6H), 3.95 (s, 6H), 3.78-3.68 (m, 1H), 3.64 (s, 3H), 3.56 (t, J=5.5 Hz, 2H), 3.29-3.22 (m, 2H), 3.13 (s, 2H), 2.89 (s, 6H), 2.86-2.71 (m, 3H), 2.69-2.54 (m, 4H), 2.22-2.09 (m, 1H), 2.01 (d, J=13.0 Hz, 2H), 1.81-1.64 (m, 2H). LCMS (ESI) m/z: [M+H]⁺=784.45.

Example 54—Preparation of 8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-N-[2-(2-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]amino)ethoxyethyl]-6-methyl-5-oxo-3,4-dihydro-1H-2,6-naphthyridine-2-carboxamide formic acid
(Compound D27 formic acid)

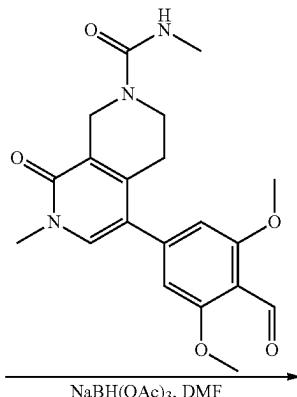
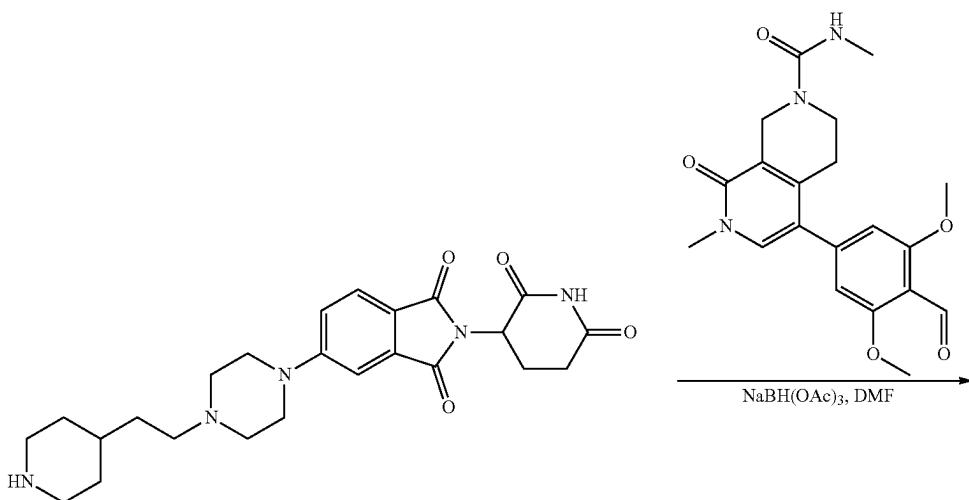
15

compound D27 formic acid



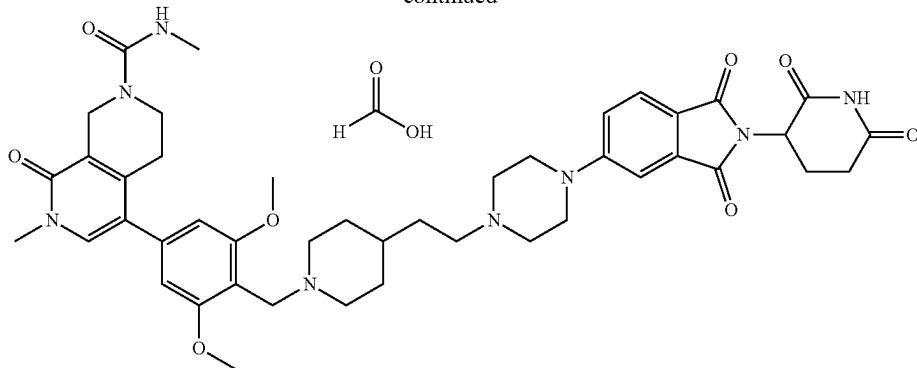
20

Example 55—Preparation of 5-(4-[[4-(2-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl]piperazin-1-yl]ethyl]piperidin-1-yl)methyl]-3,5-dimethoxyphenyl-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide formic acid
(Compound D28 formic acid)

NaBH(OAc)₃, DMF

577

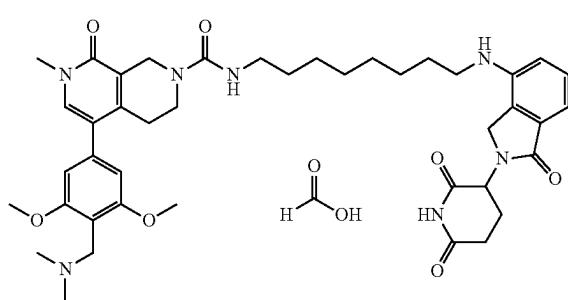
-continued



compound D28 formic acid

Using a similar procedure as described in Example 29, step 1 and substituting with 2-(2,6-dioxopiperidin-3-yl)-5-[4-[2-(piperidin-4-yl)ethyl]piperazin-1-yl]isoindole-1,3-dione (40 mg, 0.088 mmol, 1.00 equiv) in DMF (2 ml) and 5-(4-formyl-3,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide (34 mg, 0.088 mmol, 1.00 equiv) afforded 5-(4-[4-(2-[4-(2,6-dioxo-piperidin-3-yl)-1,3-dioxoisindol-5-yl]piperazin-1-yl]ethyl)piperidin-1-yl)methyl]-3,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide formic acid (11.1 mg, 15.3%) as a yellow solid. ¹H NMR (400 MHz, Methanol-d4) δ 8.34 (brs, 2.4H, FA), 7.72 (d, J=8.5 Hz, 1H), 7.58 (s, 1H), 7.40 (d, J=1.9 Hz, 1H), 7.27 (d, J=10.4 Hz, 1H), 6.73 (s, 2H), 5.09 (dd, J=12.5, 5.4 Hz, 1H), 4.36 (s, 4H), 3.96 (s, 7H), 3.64 (s, 3H), 3.57-3.49 (m, 8H), 3.20-3.04 (m, 2H), 2.96-2.82 (m, 2H), 2.78 (s, 4H), 2.76-2.67 (m, 6H), 2.67-2.60 (m, 2H), 2.59-2.52 (m, 2H), 2.14 (s, 1H), 2.01 (s, 2H), 1.77-1.48 (m, 5H). LCMS (ESI) m/z: [M+H]⁺=823.45.

Example 56—Preparation of 5-(4-((dimethylamino)methyl)-3,5-dimethoxyphenyl)-N-(8-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)amino)octyl)-7-methyl-8-oxo-3,4,7,8-tetrahydro-2,7-naphthyridine-2 (1H)-carboxamide formic acid (Compound D29 formic acid)



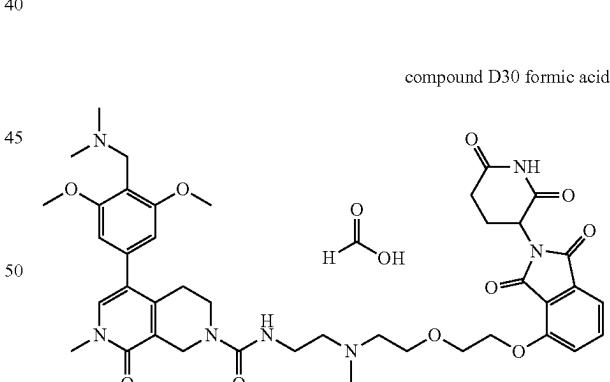
compound D29 formic acid

578

-continued

Compound D29 was prepared in a similar manner to the preparation of compound D21. Compound D29 formic acid (2.4 mg, 4.9%) was obtained as a white solid. ¹H NMR (300 MHz, Methanol-d4) δ 8.57 (brs, 0.8H, FA), 7.57 (s, 1H), 7.32 (t, J=7.8 Hz, 1H), 7.07 (d, J=7.4 Hz, 1H), 6.82 (d, J=7.9 Hz, 1H), 6.69 (s, 2H), 5.17 (dd, J=13.3, 5.2 Hz, 1H), 4.36 (s, 2H), 4.29 (d, J=3.2 Hz, 2H), 4.18 (s, 2H), 3.92 (s, 6H), 3.64 (s, 3H), 3.53 (t, J=5.8 Hz, 2H), 3.21 (q, J=7.3 Hz, 4H), 2.97-2.80 (m, 2H), 2.73 (s, 6H), 2.67-2.60 (m, 2H), 2.49 (dd, J=13.1, 4.8 Hz, 1H), 2.26-2.15 (m, 1H), 1.74-1.62 (m, 2H), 1.60-1.50 (m, 2H), 1.49-1.35 (m, 8H). LCMS (ESI) m/z: [M+H]⁺=770.25.

Example 57—Preparation of 5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-N-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-4-yl]oxy]ethoxyethyl)(methyl)aminoethyl)-7-methyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide formic acid (Compound D30 formic acid)



compound D30 formic acid

Compound D30 was prepared in a similar manner to the preparation of compound D21. Compound D30 formic acid (3 mg, 3.1%) was obtained as an off-white solid. ¹H NMR (400 MHz, Methanol-d4) δ 8.55 (brs, 2.6H, FA), 7.70 (dd, J=8.5, 7.2 Hz, 1H), 7.57 (s, 1H), 7.44 (d, J=8.5 Hz, 1H), 7.36 (d, J=7.3 Hz, 1H), 5.10 (dd, J=12.7, 5.5 Hz, 1H), 4.42 (t, J=4.1 Hz, 2H), 4.37 (s, 2H), 4.21 (s, 2H), 4.04-3.98 (m, 4H), 3.97 (s, 6H), 3.63 (s, 3H), 3.55-3.45 (m, 3H), 3.44-3.35 (m, 3H), 3.26 (s, 2H), 2.93-2.82 (m, 1 OH), 2.79-2.65 (m, 2H), 2.63-2.48 (m, 2H), 2.19-2.10 (m, 1H). LCMS (ESI) m/z: [M+H]⁺=802.30.

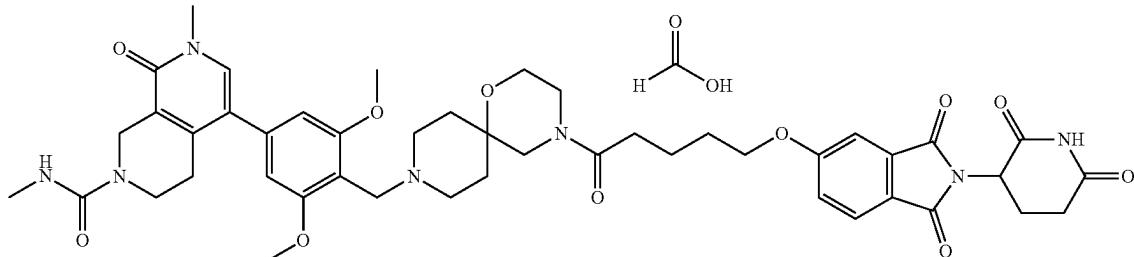
579

Example 58—Preparation of 5-(4-((4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)oxy)pentanoyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)methyl)-3,5-dimethoxyphenyl)-N,7-dimethyl-8-oxo-
3,4,7,8-tetrahydro-2,7-naphthyridine-2 (1H)-
carboxamide formic acid (Compound D31 Formic
Acid)

5

580

compound D31 formic acid



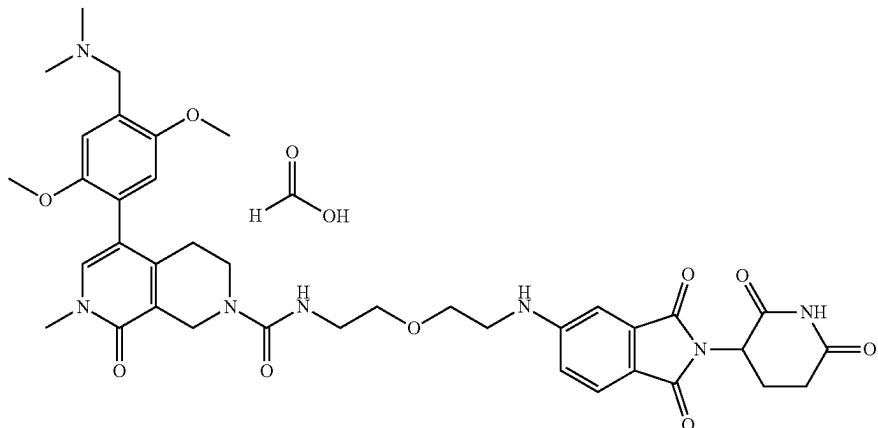
25

Compound D31 was prepared in a similar manner to the preparation of compound D4. Compound D31 formic acid (3.6 mg, 9.4%) was obtained as a white solid. ¹H NMR (400 MHz, Methanol-d4) δ 8.55 (brs, 0.8H, FA), 7.81 (dd, J=8.3, 5.2 Hz, 1H), 7.59 (s, 1H), 7.41 (d, J=2.3 Hz, 1H), 7.33 (dd, J=8.4, 2.2 Hz, 1H), 6.70 (d, J=4.2 Hz, 2H), 5.12 (dd, J=12.6, 5.4 Hz, 1H), 4.36 (s, 2H), 4.34-4.26 (m, 2H), 4.24-4.18 (m, 2H), 3.93 (d, J=3.0 Hz, 6H), 3.81-3.71 (m, 2H), 3.67-3.59 (m, 5H), 3.57-3.47 (m, 4H), 3.30-3.12 (m, 4H), 2.96-2.82 (m, 2H), 2.78 (s, 3H), 2.76-2.72 (m, 1H), 2.66-2.47 (m, 4H), 2.19-2.02 (m, 3H), 1.97-1.74 (m, 6H). LCMS (ESI) m/z: [M+H]⁺=882.25.

Example 59—Preparation of 5-[4-[(dimethylamino)methyl]-2,5-dimethoxyphenyl]-N-[2-(2-[(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)amino]ethoxy)ethyl]-7-methyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carboxamide formic acid (Compound D32 Formic Acid)

40

compound D32 formic acid

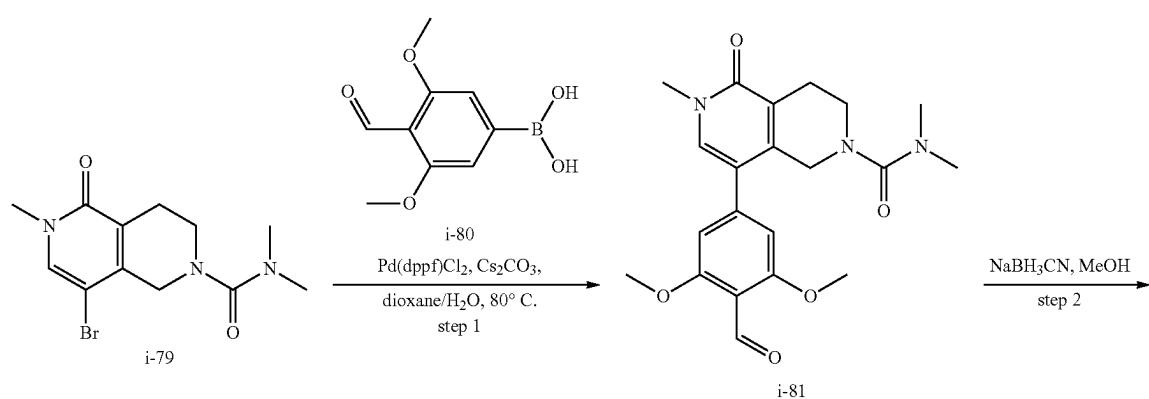


581

Compound D32 was prepared in a similar manner to the preparation of compound D21. Compound D32 formic acid (24.2 mg, 19.5%) was obtained as a green solid. ¹H NMR (400 MHz, Methanol-d4) δ 8.55 (brs, 0.7H, FA), 7.51 (d, J=8.3 Hz, 1H), 7.43 (s, 1H), 7.07 (s, 1H), 7.03 (d, J=2.2 Hz, 1H), 6.91-6.87 (m, 2H), 5.03 (dd, J=12.6, 5.4 Hz, 1H), 4.33 (s, 2H), 4.06-3.93 (m, 2H), 3.86 (s, 3H), 3.73 (s, 6H), 3.61 (s, 6H), 3.45-3.38 (m, 4H), 2.90-2.84 (m, 1H), 2.78-2.69 (m, 2H), 2.69-2.47 (m, 8H), 2.11-2.04 (m, 1H). LCMS (ESI) m/z: [M+H]⁺=744.33.

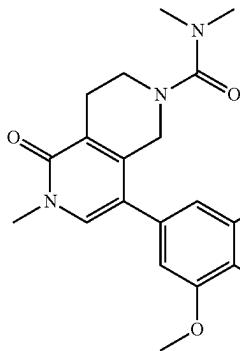
Example 60—Preparation of 8-(4-(((2-(2-(4-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)piperazin-1-yl)ethoxy)ethyl)(methyl)amino)methyl)-3,5-dimethoxyphenyl)-N,N,6-trimethyl-5-oxo-3,4,5,6-tetrahydro-2,6-naphthyridine-2 (1H)-carboxamide formic acid (Compound D33 formic acid)

582



583

-continued



compound D33

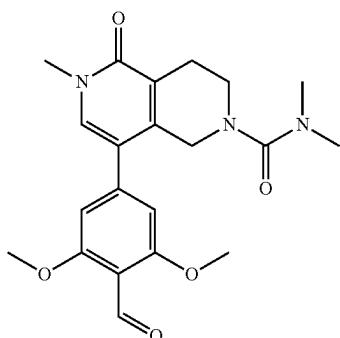
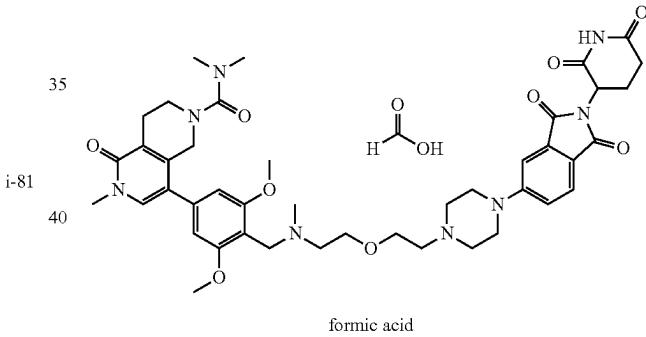
Step 1: Preparation of 8-(4-formyl-3,5-dimethoxyphenyl)-N,N,6-trimethyl-5-oxo-3,4,5,6-tetrahydro-2,6-naphthyridine-2 (1H)-carboxamide (i-81)

25

Step 2: Preparation of 8-(((2-(2-(4-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)piperazin-1-yl)ethoxy)ethyl)(methyl)amino)methyl)-3,5-dimethoxyphenyl)-N,N,6-trimethyl-5-oxo-3,4,5,6-tetrahydro-2,6-naphthyridine-2 (1H)-carboxamide formic acid (Compound D33 formic acid)

30

compound D33



Using a similar procedure as described in Example 23, step 3 and substituting with 8-bromo-N,N,6-trimethyl-5-oxo-3,4-dihydro-1H-2,6-naphthyridine-2-carboxamide (200 mg, 0.637 mmol, 1.00 equiv) and 4-formyl-3,5-dimethoxyphenylboronic acid (200.5 mg, 0.955 mmol, 1.50 equiv) afforded 8-(4-formyl-3,5-dimethoxyphenyl)-N,N,6-trimethyl-5-oxo-3,4,5,6-tetrahydro-2,6-naphthyridine-2 (1H)-carboxamide (200.0 mg, 78.7%) as a yellow oil. LCMS (ESI) m/z: [M+H]⁺=400.

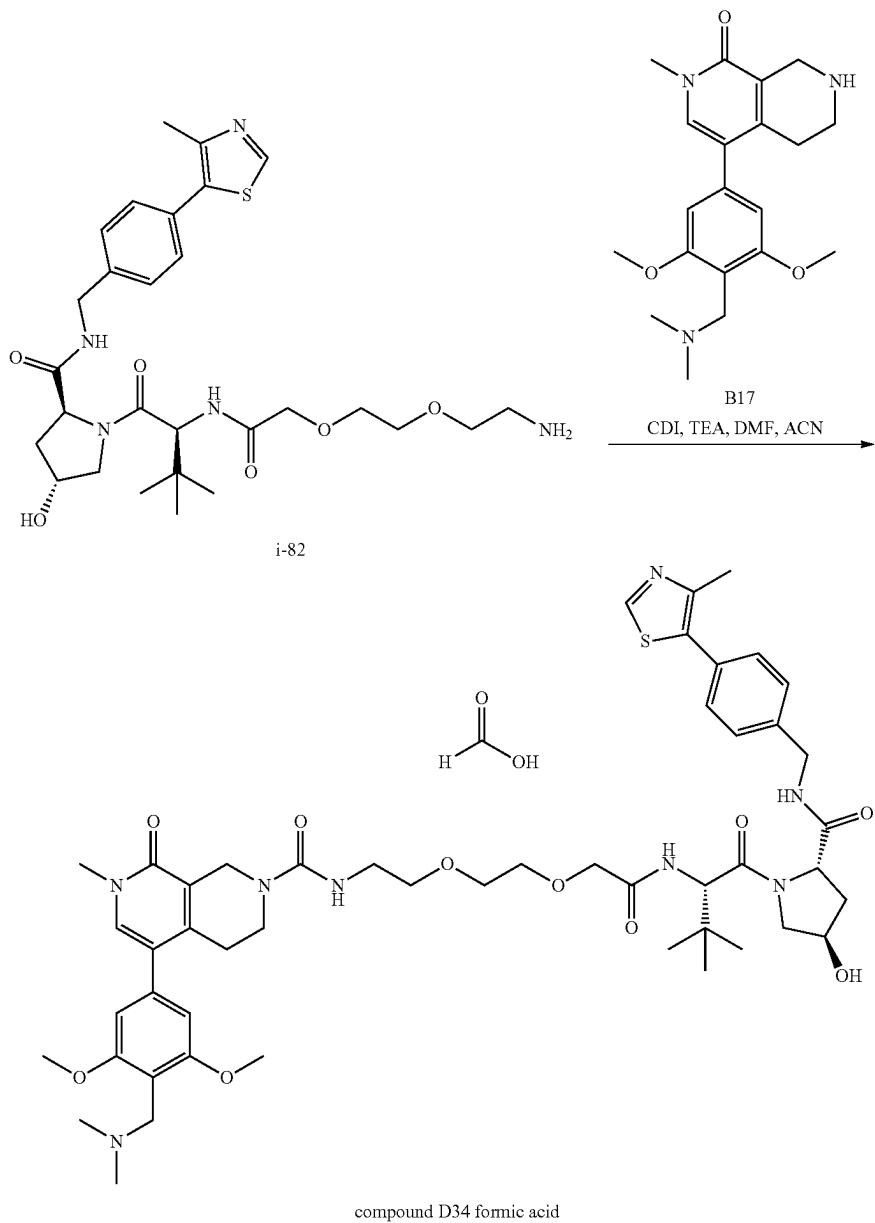
Using a similar procedure as described in Example 52, step 3 and substituting with 8-(4-formyl-3,5-dimethoxyphenyl)-N,N,6-trimethyl-5-oxo-3,4-dihydro-1H-2,6-naphthyridine-2-carboxamide (30.0 mg, 0.075 mmol, 1.00 equiv) and 2-(2,6-dioxopiperidin-3-yl)-5-(4-[2-[2-(methylamino)ethoxy]ethyl)piperazin-1-yl)isoindole-1,3-dione (33.3 mg, 0.075 mmol, 1.00 equiv) afforded 8-[[2-(2-[4-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)piperazin-1-yl)ethoxy]ethyl](methyl)amino)methyl]-3,5-dimethoxyphenyl]-N,N,6-trimethyl-5-oxo-3,4-dihydro-1H-2,6-naphthyridine-2-carboxamide formic acid (7.6 mg, 11.2%) as a yellow green solid. ¹H-NMR (400 MHz, Methanol-d4) δ 8.47 (brs, 1.4H, FA), 7.69 (d, J=8.5 Hz, 1H), 7.50 (s, 1H), 7.34 (d, J=2.3 Hz, 1H), 7.24 (dd, J=8.6, 2.3 Hz, 1H), 6.77 (s, 2H), 5.08 (dd, J=12.4, 5.5 Hz, 1H), 4.50 (s, 2H), 4.09 (s, 2H), 3.97 (s, 6H), 3.92-3.87 (m, 2H), 3.76 (t, J=5.2 Hz, 2H), 3.61 (s, 3H), 3.51-3.45 (m, 8H), 2.90-2.86 (m, 4H), 2.83 (s, 6H), 2.79-2.71 (m, 1 OH), 2.17-2.07 (m, 1H). LCMS (ESI) m/z: [M+H]⁺=827.50.

585

Example 61—Preparation of (2S,4R)-1-[(2S)-2-(2-[2-[2-(5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carbonylamino)ethoxy]ethoxy]acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-[(4-(4-methyl-1,3-thiazol-5-yl)phenyl)methyl]pyrrolidine-2-carboxamide formic acid (Compound D34 formic acid)

5

586



To a stirred mixture of CDI (9.29 mg, 0.057 mmol, 1.10 equiv) in ACN (0.50 mL) and DMF (0.10 mL) was added (2S,4R)-1-[(2S)-2-[2-[2-(2-aminoethoxy)ethoxy]acetamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl]pyrrolidine-2-carboxamide (30 mg, 0.052 mmol, 1.00 equiv) and ACN (0.30 mL) dropwise at room temperature under nitrogen atmosphere. After 3 hours, 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-5,6,7,8-tetrahydro-2,7-naphthyri-

din-1-one (22.35 mg, 0.063 mmol, 1.20 equiv) and TEA (15.82 mg, 0.156 mmol, 3.00 equiv) were added. The resulting mixture was stirred at room temperature for 12 hours under nitrogen atmosphere. Without any additional work-up, the mixture was purified by Prep-HPLC (conditions: Gemini-NX C18 AXAI Packed, 21.2*150 mm, 5 μ m; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 10% B to 25% B in 12 minutes; 254/220 nm; RT: 12.30 minutes). This resulted in

587

(2S,4R)-1-[(2S)-2-(2-[2-(5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carbonylamino)ethoxy]ethoxy]acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-[[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl]pyrrolidine-2-carboxamide formic acid (13.9 mg, 26.23%) as a white solid. ¹H NMR (400 MHz, Methanol-d4) δ 8.88 (s, 1H), 8.56 (brs, 1.0H, FA), 7.56 (s, 1H), 7.49-7.38 (m, 4H), 6.67 (s, 2H), 4.84-4.75 (m, 2H), 4.67-4.59 (m, 1H), 4.52 (s, 1H), 4.48-4.26 (m, 5H), 4.03-3.83 (m, 1 OH), 3.77-3.61 (m, 7H), 3.59 (s, 3H), 3.55-3.48 (m, 1H), 3.43-3.34 (m, 2H), 2.84 (s, 6H), 2.69-2.52 (m, 2H), 2.48 (s, 3H), 2.31 (dd, J=13.1, 7.7 Hz, 1H), 2.18-2.07 (m, 1H), 1.08 (s, 9H). LCMS (ESI) m/z: [M+H]⁺= 959.55.

Example 62—Preparation of (2R,4S)-1-[(2R)-2-[2-(2-[2-(5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carbonylamino)ethoxy]ethoxy]acetamido)-3,3-dimethylbutanoyl]-4-hydroxy-N-[[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl]pyrrolidine-2-carboxamide (Compound D35)

588

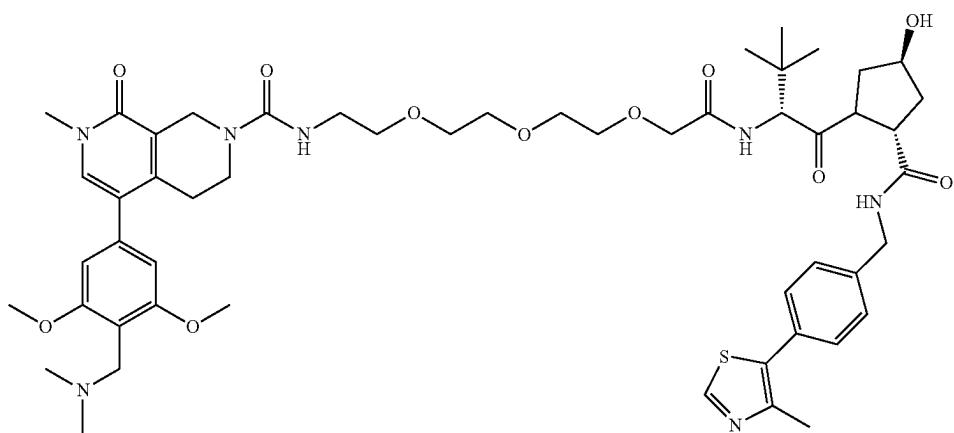
5

10

15

20

compound D35



589

Compound D35 was prepared in a similar manner to the preparation of compound D34. Compound D35 (24.3 mg, 29.8%) was obtained as an off-white solid. ¹H NMR (300 MHz, DMSO-d₆) δ 8.98 (s, 1H), 8.59 (s, 1H), 8.17 (brs, 0.4H, FA), 7.64 (s, 1H), 7.40 (s, 5H), 6.66 (d, J=18.5 Hz, 3H), 5.15 (s, 1H), 4.63-4.53 (m, 1H), 4.51-4.32 (m, 3H), 4.31-4.17 (m, 3H), 3.97 (s, 2H), 3.81 (s, 7H), 3.72 (s, 2H), 3.63-3.47 (m, 12H), 3.40 (s, 4H), 3.20 (s, 2H), 2.44 (s, 6H), 2.35 (s, 5H), 2.13-2.00 (m, 1H), 1.98-1.82 (m, 1H), 0.95 (s, 9H). LCMS (ESI) m/z: [M+H]⁺=1003.60.

Example 63—Preparation of (2S,4R)-1-[(2S)-2-[6-(5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carbonylamino)hexanamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-[[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl]pyrrolidine-2-carboxamide (Compound D36)

5

15

20

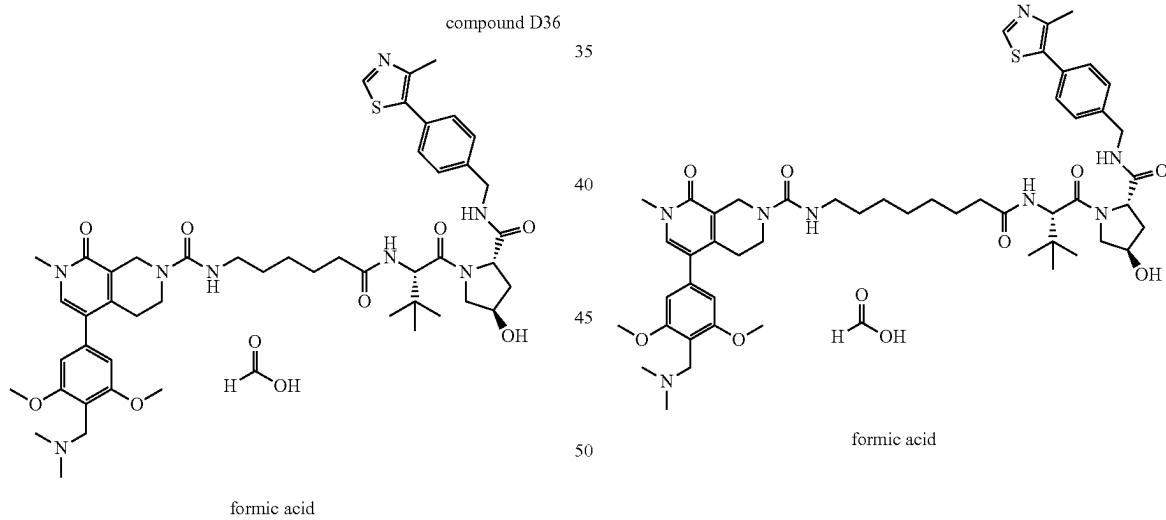
590

Example 64—Preparation of (2S,4R)-1-[(2S)-2-[8-(5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carbonylamino)octanamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-[[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl]pyrrolidine-2-carboxamide formic acid (Compound D37)

25

30

compound D37

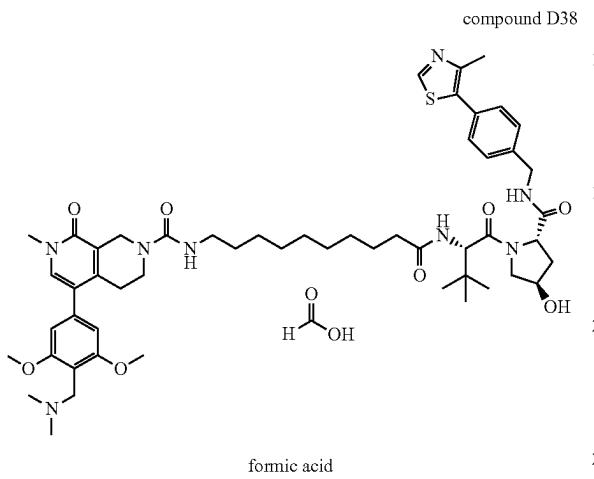


Compound D36 was prepared in a similar manner to the preparation of compound D34. Compound D36 formic acid (13.3 mg, 24.6%) was obtained as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 9.05 (brs, 0.7H, FA), 8.99 (s, 1H), 8.56 (t, J=6.0 Hz, 1H), 7.83 (d, J=9.3 Hz, 1H), 7.66 (s, 1H), 7.41 (q, J=8.2 Hz, 4H), 6.73 (s, 2H), 6.65 (t, J=5.4 Hz, 1H), 6.51 (s, 0.3H, FA), 5.12 (d, J=3.6 Hz, 1H), 4.55 (d, J=9.4 Hz, 1H), 4.47-4.39 (m, 2H), 4.35 (s, 1H), 4.23 (s, 5H), 3.87 (s, 6H), 3.71-3.62 (m, 2H), 3.51 (s, 3H), 3.41 (t, J=5.5 Hz, 2H), 3.30-3.26 (m, 2H), 3.08-2.98 (m, 2H), 2.74 (s, 6H), 2.45 (s, 3H), 2.31-2.22 (m, 1H), 2.17-2.00 (m, 2H), 1.95-1.87 (m, 1H), 1.55-1.38 (m, 4H), 1.29-1.20 (m, 2H), 0.93 (s, 9H). LCMS (ESI) m/z: [M+H]⁺=927.55.

Compound D37 was prepared in a similar manner to the preparation of compound D34. Compound D37 formic acid (19.9 mg, 37.9%) was obtained as a white solid. ¹H NMR (400 MHz, Methanol-d₄) δ 8.89 (s, 1H), 8.57 (brs, 0.6H, FA), 7.58 (s, 1H), 7.51-7.40 (m, 4H), 6.69 (s, 2H), 4.66 (s, 1H), 4.62-4.49 (m, 3H), 4.38 (d, J=12.6 Hz, 3H), 4.16 (s, 2H), 3.92 (s, 6H), 3.90 (s, 1H), 3.82 (dd, J=11.0, 3.9 Hz, 1H), 3.64 (s, 3H), 3.53 (t, J=5.5 Hz, 2H), 3.20 (t, J=7.1 Hz, 2H), 2.71 (s, 6H), 2.63 (t, J=5.2 Hz, 2H), 2.49 (s, 3H), 2.36-2.19 (m, 3H), 2.15-2.05 (m, 1H), 1.63 (t, J=6.8 Hz, 2H), 1.54 (t, J=7.0 Hz, 2H), 1.36 (s, 6H), 1.05 (s, 9H). LCMS (ESI) m/z: [M+H]⁺=955.55.

591

Example 65—Preparation of (2S,4R)-1-[(2S)-2-[10-(5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-3,4-dihydro-1H-2,7-naphthyridine-2-carbonylamino)decanamido]-3,3-dimethylbutanoyl]-4-hydroxy-N-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl]pyrrolidine-2-carboxamide (Compound D38)

**592**

Compound D35 was prepared in a similar manner to the preparation of compound D34. Compound D35 formic acid (15.3 mg, 29.6%) was obtained as a white solid. ¹H NMR (400 MHz, Methanol-d4) δ 8.90 (s, 1H), 8.57 (brs, 0.5H, FA), 7.59 (s, 1H), 7.52-7.41 (m, 4H), 6.69 (s, 2H), 4.65 (s, 1H), 4.62-4.49 (m, 3H), 4.40-4.34 (m, 3H), 4.14 (s, 2H), 3.92 (s, 7H), 3.82 (dd, J=10.9, 3.9 Hz, 1H), 3.64 (s, 3H), 3.54 (t, J=5.6 Hz, 2H), 3.20 (t, J=7.2 Hz, 2H), 2.69 (s, 6H), 2.63 (t, J=5.1 Hz, 2H), 2.49 (s, 3H), 2.37-2.19 (m, 3H), 2.14-2.05 (m, 1H), 1.68-1.48 (m, 4H), 1.34 (s, 1 OH), 1.05 (s, 9H). LCMS (ESI) m/z: [M+H]⁺=983.65.

Example 66—Preparation of Compounds D39-D302 and DD1

In analogy to the procedures described in the examples above, compounds D39-D302 and DD1 were prepared using the appropriate starting materials

Compound No.	LCMS	¹ H NMR
D39	LCMS (ESI) m/z: [M + H] ⁺ = 795.6	¹ H NMR (400 MHz, Methanol-d4) δ 8.39 (s, 2H, FA), 7.66-7.61 (m, 1H), 7.59 (s, 1H), 7.09 (d, J = 7.9 Hz, 2H), 6.72 (s, 2H), 5.11 (dd, J = 13.3, 5.2 Hz, 1H), 4.40 (d, J = 6.8 Hz, 2H), 4.35 (d, J = 7.5 Hz, 4H), 3.95 (s, 8H), 3.64 (s, 3H), 3.55 (t, J = 5.6 Hz, 2H), 3.32-3.17 (m, 4H), 2.99-2.69 (m, 11H), 2.69-2.60 (m, 2H), 2.49 (td, J = 13.1, 4.8 Hz, 1H), 2.41 (d, J = 7.0 Hz, 2H), 2.16 (tdt, J = 12.8, 5.3, 2.4 Hz, 1H), 1.91 (d, J = 13.4 Hz, 2H), 1.84 (d, J = 3.6 Hz, 1H), 1.40-1.26 (m, 2H).
D40	LCMS (ESI) m/z: [M + H] ⁺ = 795.6	¹ H NMR (400 MHz, Methanol-d4) δ 8.52 (s, 1H, FA), 7.58 (s, 1H), 7.45 (d, J = 8.4 Hz, 1H), 7.38-7.29 (m, 2H), 6.70 (s, 2H), 5.15 (dd, J = 13.3, 5.1 Hz, 1H), 4.48-4.39 (m, 2H), 4.36 (s, 2H), 4.23 (s, 2H), 3.93 (s, 6H), 3.82-3.74 (m, 2H), 3.64 (s, 3H), 3.55 (t, J = 5.6 Hz, 2H), 3.18 (s, 4H), 2.92 (ddd, J = 18.3, 13.5, 5.4 Hz, 2H), 2.86-2.59 (m, 11H), 2.49 (td, J = 13.2, 4.7 Hz, 1H), 2.40 (d, J = 7.1 Hz, 2H), 2.19 (ddd, J = 10.0, 5.2, 2.6 Hz, 1H), 1.93 (d, J = 13.0 Hz, 2H), 1.77 (s, 1H), 1.45-1.33 (m, 2H).
D41	LCMS (ESI) m/z: [M + H] ⁺ = 837.5	¹ H NMR (400 MHz, DMSO-d6) δ 11.09 (s, 1H), 7.70-7.64 (m, 2H), 7.33 (d, J = 2.3 Hz, 1H), 7.29-7.22 (m, 1H), 6.69 (s, 2H), 6.58 (d, J = 5.0 Hz, 1H), 5.07 (dd, J = 12.9, 5.4 Hz, 1H), 4.62-4.46 (m, 2H), 4.07 (d, J = 13.0 Hz, 3H), 3.89-3.80 (m, 1H), 3.85 (s, 6H), 3.60-3.30 (m, 9H), 3.14-2.82 (m, 8H), 2.78 (d, J = 4.8 Hz, 1H), 2.63-2.52 (m, 5H), 2.17 (d, J = 17.0 Hz, 1H), 2.06-1.98 (m, 1H), 1.76 (d, J = 12.7 Hz, 2H), 1.60-1.52 (m, 3H), 1.27-1.13 (m, 2H), 0.86 (d, J = 6.7 Hz, 3H).
D42	LCMS (ESI) m/z: [M + H] ⁺ = 851.75	¹ H NMR (400 MHz, DMSO-d6) δ 11.09 (s, 1H), 8.14 (s, 0H), 7.64 (d, J = 9.1 Hz, 2H), 7.31 (d, J = 2.2 Hz, 1H), 7.27-7.18 (m, 1H), 6.60 (d, J = 5.7 Hz, 3H), 5.07 (dd, J = 12.9, 5.4 Hz, 1H), 4.21 (s, 2H), 4.05 (d, J = 12.6 Hz, 2H), 3.79 (s, 6H), 3.66-3.46 (m, 5H), 3.41 (dd, J = 8.1, 2.8 Hz, 2H), 3.31 (s, 4H), 3.00-2.90 (m, 4H), 2.92-2.81 (m, 3H), 2.63-2.55 (m, 4H), 2.09-1.94 (m, 3H), 1.76 (d, J = 12.5 Hz, 2H), 1.63-1.33 (m, 3H), 1.30-1.13 (m, 3H), 1.10-0.95 (m, 6H).
D43	LCMS (ESI) m/z: [M + H] ⁺ = 867.35	¹ H NMR (400 MHz, DMSO-d6) δ 11.09 (s, 1H), 8.16 (s, FA, 1H), 7.67-7.62 (m, 2H), 7.30 (d, J = 2.3 Hz, 1H), 7.23 (dd, J = 8.8, 2.3 Hz, 1H), 6.71 (t, J = 5.5 Hz, 1H), 6.59 (s, 2H), 5.07 (dd, J = 12.9, 5.4 Hz, 1H), 4.22 (s, 2H), 4.03 (d, J = 13.0 Hz, 2H), 3.78 (s, 6H), 3.53 (s, 2H), 3.50 (s, 3H), 3.45-3.31 (m, 8H), 3.24 (s, 3H), 3.24-3.16 (m, 2H), 2.98-2.82 (m, 3H), 2.63-2.53 (m, 2H), 2.43 (s, 5H), 2.35-2.30 (m, 3H), 2.04-1.97 (m, 1H), 1.74 (d, J = 12.7 Hz, 2H), 1.57 (s, 1H), 1.40-1.37 (m, 2H), 1.23-1.10 (m, 2H).
D44	LCMS (ESI) m/z: [M + H] ⁺ = 867.75	¹ H NMR (400 MHz, MeOD) δ 8.49 (s, 2FA, 2H), 7.82 (d, J = 8.3 Hz, 1H), 7.58 (s, 1H), 7.29 (d, J = 2.2 Hz, 1H), 7.25 (dd, J = 8.3, 2.3 Hz, 1H), 6.72 (s, 2H), 5.13 (dd, J = 12.6, 5.5 Hz, 1H), 4.38-4.30 (m, 3H), 3.95 (s, 5H), 3.90-3.81 (m, 1H), 3.80-3.62 (m, 1H), 3.58-3.50 (m,

Compound No.	LCMS	¹ H NMR
D45	LCMS (ESI) m/z: [M + H] ⁺ = 826.35	¹ H NMR (400 MHz, MeOD) δ 8.49 (s, 2H), 7.82 (d, J = 8.3 Hz, 1H), 7.58 (s, 1H), 7.29 (d, J = 2.2 Hz, 1H), 7.25 (dd, J = 8.3, 2.3 Hz, 1H), 6.72 (s, 2H), 5.13 (dd, J = 12.6, 5.5 Hz, 1H), 4.38-4.30 (m, 3H), 3.95 (s, 5H), 3.90-3.81 (m, 1H), 3.80-3.62 (m, 1H), 3.58-3.50 (m, 3H), 3.52-3.45 (m, 1H), 3.15-3.04 (m, 2H), 2.78 (s, 4H), 2.77-2.74 (m, 1H), 2.73-2.68 (m, 1H), 2.67-2.57 (m, 3H), 2.56-2.50 (m, 4H), 2.25-2.09 (m, 1H), 2.09-1.97 (m, 6H), 1.88-1.79 (m, 4H), 1.58-1.53 (m, 2H), 1.38-1.29 (m, 3H).
D46	LCMS (ESI) m/z: [M + H] ⁺ = 873.75	¹ H NMR (400 MHz DMSO) δ 11.09 (s, 1H), 8.20 (s, FA, 1H), 7.68-7.61 (m, 2H), 7.30 (d, J = 2.2 Hz, 1H), 7.22 (dd, J = 8.7, 2.3 Hz, 1H), 7.13 (t, J = 5.7, 5.7 Hz, 1H), 6.59 (s, 2H), 6.15-5.81 (m, 1H), 5.07 (dd, J = 12.9, 5.4 Hz, 1H), 4.26 (s, 2H), 4.03 (d, J = 12.9 Hz, 2H), 3.78 (s, 6H), 3.55-3.48 (m, 5H), 3.47-3.36 (m, 5H), 2.99-2.83 (m, 3H), 2.63-2.52 (m, 4H), 2.44-2.38 (m, 5H), 2.35-2.26 (m, 4H), 2.04-1.97 (m, 1H), 1.78-1.70 (m, 2H), 1.65-1.47 (m, 1H), 1.40-1.32 (m, 2H), 1.26-1.11 (m, 2H).
D47	LCMS (ESI) m/z: [M + H] ⁺ = 867.55	¹ H NMR (400 MHz, MeOD) δ 8.51 (s, 1H), 7.81 (d, J = 8.2 Hz, 1H), 7.58 (s, 1H), 7.32-7.20 (m, 2H), 6.72 (s, 2H), 5.12 (dd, J = 12.6, 5.4 Hz, 1H), 4.41-4.31 (m, 4H), 3.95 (s, 6H), 3.64 (s, 3H), 3.59-3.45 (m, 5H), 3.11-3.07 (m, 2H), 2.92-2.82 (m, 1H), 2.81-2.69 (m, 5H), 2.67-2.59 (m, 3H), 2.53-2.57 (m, 4H), 2.20-2.09 (m, 1H), 2.08-1.96 (m, 5H), 1.87-1.78 (m, 4H), 1.68-1.43 (m, 2H).
D48	LCMS (ESI) m/z: [M + H] ⁺ = 826.55	¹ H NMR (400 MHz, MeOD) δ 7.68 (d, J = 8.5 Hz, 1H), 7.57 (s, 1H), 7.36 (d, J = 2.3 Hz, 1H), 7.23 (dd, J = 8.6, 2.3 Hz, 1H), 6.73 (s, 2H), 5.08 (dd, J = 12.5, 5.5 Hz, 1H), 4.48-4.43 (m, 2H), 4.36 (s, 2H), 4.07 (d, J = 13.1 Hz, 2H), 3.94 (s, 6H), 3.64 (s, 4H), 3.58-3.50 (m, 9H), 3.22-3.17 (m, 2H), 3.01 (t, J = 12.4, 12.4 Hz, 2H), 2.93-2.83 (m, 1H), 2.80-2.70 (m, 2H), 2.69-2.59 (m, 2H), 2.18-2.06 (m, 1), 1.88 (d, J = 12.9 Hz, 2H), 1.74-1.68 (m, 3H), 1.44-1.34 (m, 2H).
D49	LCMS (ESI) m/z: [M + H] ⁺ = 839.31	¹ H NMR (400 MHz, Methanol-d4) δ 7.61-7.50 (m, 2H), 7.18 (d, J = 8.3 Hz, 1H), 6.73 (s, 2H), 5.13 (dd, J = 13.3, 5.2 Hz, 1H), 4.54-4.45 (m, 2H), 4.38-4.34 (m, 4H), 3.95 (s, 9H), 3.65-3.61 (m, 4H), 3.59-3.51 (m, 4H), 3.37-3.32 (m, 2H), 3.18-3.08 (m, 2H), 3.04-2.98 (m, 4H), 2.96-2.86 (m, 1H), 2.86-2.80 (m, 2H), 2.79-2.74 (m, 5H), 2.64 (t, J = 5.7 Hz, 2H), 2.59-2.44 (m, 1H), 2.25-2.11 (m, 1H), 2.07-1.95 (m, 2H), 1.80-1.47 (m, 5H).
D50	LCMS (ESI) m/z: [M + H] ⁺ = 839.35	¹ H NMR (400 MHz, Methanol-d4) δ 7.56 (s, 1H), 6.77-6.64 (m, 3H), 6.57 (s, 1H), 5.04 (dd, J = 13.2, 5.4 Hz, 1H), 4.48-4.28 (m, 6H), 4.17-3.98 (m, 2H), 3.98-3.86 (m, 10H), 3.76-3.45 (m, 10H), 3.28-3.20 (m, 3H), 3.16-3.01 (m, 2H), 2.94-2.81 (m, 1H), 2.81-2.71 (m, 4H), 2.66-2.56 (m, 2H), 2.43 (qd, J = 13.0, 4.7 Hz, 1H), 2.19-2.07 (m, 1H), 2.06-1.87 (m, 3H), 1.86-1.69 (m, 3H), 1.67-1.48 (m, 2H).
D51	LCMS (ESI) m/z: [M + H] ⁺ = 821.40	¹ H NMR (400 MHz, Methanol-d4) δ 7.66-7.52 (m, 2H), 6.72 (s, 2H), 6.57 (d, J = 8.1 Hz, 2H), 5.11 (dd, J = 13.3, 5.1 Hz, 1H), 4.70-4.09 (m, 10H), 3.96 (s, 6H), 3.91-3.73 (m, 4H), 3.64 (s, 3H), 3.55 (t, J = 5.6 Hz, 2H), 3.34 (s, 4H), 3.25-3.10 (m, 1H), 3.08-3.00 (m, 1H), 2.98-2.84 (m, 1H), 2.84-2.72 (m, 4H), 2.62 (t, J = 5.3 Hz, 2H), 2.58-2.40 (m, 1H), 2.35-2.06 (m, 5H), 1.38 (d, J = 6.4 Hz, 3H).
D52	LCMS (ESI) m/z: [M + H] ⁺ = 821.55	¹ H NMR (400 MHz, Methanol-d4) δ 7.57 (s, 1H), 7.42 (d, J = 8.2 Hz, 1H), 6.88 (d, J = 2.3 Hz, 1H), 6.80 (dd, J = 8.2, 2.3 Hz, 1H), 6.73 (s, 2H), 5.14 (dd, J = 13.3, 5.2 Hz, 1H), 4.60-4.45 (m, 2H), 4.43-4.31 (m, 5H), 4.31-4.10 (m, 3H), 3.97 (s, 6H), 3.89-3.70 (m, 5H), 3.64 (s, 3H), 3.55 (t, J = 5.6 Hz, 2H), 3.32 (s, 4H), 3.17-3.00 (m, 1H), 2.99-2.85 (m, 1H), 2.85-2.80 (m, 1H), 2.78 (s, 3H), 2.62 (t, J = 5.5 Hz, 2H), 2.57-2.42 (m, 1H), 2.39-2.05 (m, 5H), 1.39 (d, J = 6.6 Hz, 3H).
D53	LCMS (ESI) m/z: [M + H] ⁺ = 698.50	¹ H NMR (400 MHz, Methanol-d4) δ 7.58 (s, 1H), 7.53 (dd, J = 8.4, 2.0 Hz, 1H), 7.24 (dd, J = 8.4, 2.4 Hz, 1H), 7.13 (dd, J = 8.1, 2.3 Hz, 1H), 6.73 (d, J = 6.8 Hz, 2H), 5.15 (dd, J = 13.3, 5.1 Hz, 1H), 4.61 (s, 1H), 4.57-4.46 (m, 3H), 4.46-4.33 (m, 5H), 4.33-4.26 (m, 1H), 4.23-4.14 (m, 1H), 3.97 (s, 2H), 3.91 (s, 4H), 3.64 (s, 3H), 3.54 (t, J = 5.5 Hz, 2H), 2.98 (d, J = 2.8 Hz, 3H), 2.98-2.86 (m, 1H), 2.82 (dd, J = 4.8, 2.5 Hz, 1H), 2.78 (s, 3H), 2.62 (s, 2H), 2.51 (qd, J = 13.2, 4.7 Hz, 1H), 2.19 (ddd, J = 10.6, 5.3, 2.9 Hz, 1H).
D54	LCMS (ESI) m/z: [M + H] ⁺ = 835.25	¹ H NMR (300 MHz, Methanol-d4) δ 8.46 (s, 2H, FA), 7.68-7.56 (m, 2H), 7.07 (d, J = 9.3 Hz, 1H), 6.75-6.65 (m, 3H), 4.37 (s, 4H), 3.96 (s, 7H), 3.65 (s, 3H), 3.60-3.50 (m, 4H), 3.50-3.40 (m, 4H), 3.20-3.10 (m, 2H), 2.80-2.50 (m, 13H), 2.10-1.90 (m, 3H), 1.80-1.40 (m, 10H).
D55	LCMS (ESI) m/z: [M + H] ⁺ = 813.35	¹ H NMR (300 MHz, DMSO-d6) δ 10.96 (s, 1H), 7.66 (s, 1H), 7.52 (d, J = 8.7 Hz, 1H), 7.15-6.99 (m, 4H), 6.62 (s, 1H), 5.15-4.98 (m, 1H), 4.40-4.13 (m, 4H), 3.99-3.72 (m, 7H), 3.61-3.31 (m, 7H), 3.23-

Compound No.	LCMS	¹ H NMR
D56	LCMS (ESI) m/z: [M + H] ⁺ = 835.85	¹ H NMR (300 MHz, MeOD) δ 8.45 (s, 2H), 7.60 (d, J = 9.4 Hz, 2H), 6.73 (s, 2H), 6.55 (d, J = 7.4 Hz, 2H), 5.10 (dd, J = 13.2, 5.1 Hz, 1H), 4.37 (d, J = 4.4 Hz, 6H), 3.95 (s, 6H), 3.74 (s, 4H), 3.64 (s, 3H), 3.55 (t, J = 5.2, 5.2 Hz, 4H), 3.20-3.06 (m, 2H), 2.97-2.77 (m, 1H), 2.81-2.75 (m, 5H), 2.73-2.59 (m, 5H), 2.51-2.45 (m, 3H), 2.23-1.88 (m, 8H), 1.56 (s, 2H).
D57	LCMS (ESI) m/z: [M + H] ⁺ = 811.30	¹ H NMR (400 MHz, Methanol-d4) δ 7.58 (s, 1H), 7.35 (dd, J = 10.1, 2.2 Hz, 1H), 7.30 (d, J = 7.6 Hz, 1H), 7.22 (dd, J = 10.1, 4.0 Hz, 1H), 6.77-6.71 (m, 2H), 5.36 (dd, J = 12.6, 5.3 Hz, 1H), 4.37 (d, J = 6.9 Hz, 4H), 4.04-3.87 (m, 6H), 3.65 (d, J = 6.4 Hz, 5H), 3.60-3.52 (m, 4H), 3.36-3.43 (m, 2H), 3.28 (d, J = 10.1 Hz, 3H), 3.18-3.05 (m, 2H), 2.93 (d, J = 5.0 Hz, 1H), 2.90 (d, J = 5.2 Hz, 1H), 2.86 (d, J = 4.0 Hz, 1H), 2.80-2.84 (m, 1H), 2.79 (s, 3H), 2.70 (dd, J = 13.0, 4.7 Hz, 1H), 2.63 (s, 3H), 2.33 (t, J = 5.0 Hz, 1H), 2.02 (t, J = 15.9 Hz, 3H), 1.80 (t, J = 8.2 Hz, 2H), 1.65-1.48 (m, 2H).
D58	825.5	¹ H NMR (400 MHz, DMSO-d6) δ 10.96 (s, 1H), 8.14 (s, 1H, FA), 7.89 (q, J = 4.2 Hz, 1H), 7.69 (s, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.13-7.03 (m, 2H), 6.73 (s, 2H), 5.06 (dd, J = 13.2, 5.1 Hz, 1H), 4.59 (s, 2H), 4.34 (d, J = 17.0 Hz, 1H), 4.21 (d, J = 17.0 Hz, 1H), 4.16 (s, 2H), 3.93 (t, J = 5.5 Hz, 2H), 3.87 (s, 6H), 3.53 (s, 3H), 3.48-3.40 (m, 6H), 3.01-2.84 (m, 6H), 2.69-2.55 (m, 7H), 2.47-2.30 (m, 3H), 2.01-1.92 (m, 1H), 1.84 (d, J = 13.0 Hz, 2H), 1.68-1.29 (m, 5H).
D59	LCMS (ESI) m/z: [M + H] ⁺ = 821.55	¹ H NMR (300 MHz, Methanol-d4) δ 8.44 (s, 3H, FA), 7.59 (s, 1H), 7.40 (d, J = 8.2 Hz, 1H), 6.88-6.69 (m, 4H), 5.21-5.04 (m, 2H), 4.43-4.34 (m, 4H), 4.10-3.87 (m, 9H), 3.76-3.61 (m, 8H), 3.56 (s, 2H), 3.19-3.05 (m, 1H), 2.96-2.83 (m, 1H), 2.79 (s, 3H), 2.77-2.71 (m, 3H), 2.68-2.46 (m, 7H), 2.20 (s, 1H), 1.91 (s, 4H), 1.55 (d, J = 6.6 Hz, 3H).
D60	LCMS (ESI) m/z: [M + H] ⁺ = 633.30	¹ H NMR (300 MHz, DMSO-d6) δ 11.01 (s, 1H), 8.14 (s, 1H, FA), 7.65 (s, 1H), 7.30 (s, 1H), 7.22 (s, 1H), 6.65-6.57 (m, 3H), 5.19 (dd, J = 11.6, 4.5 Hz, 1H), 4.22 (s, 2H), 3.81 (s, 6H), 3.67 (s, 2H), 3.50 (s, 3H), 3.43-3.31 (m, 6H), 2.96-2.70 (m, 6H), 2.67-2.56 (m, 6H), 2.19-2.11 (m, 1H).
D61	LCMS (ESI) m/z: [M + H] ⁺ = 700.25	¹ H NMR (400 MHz, DMSO-d6) δ 7.79 (d, J = 7.6 Hz, 1H), 7.62 (s, 1H), 6.75-6.63 (m, 3H), 6.28 (d, J = 1.6 Hz, 1H), 5.23 (dd, J = 12.5, 5.3 Hz, 1H), 4.31 (s, 2H), 4.22 (s, 2H), 3.94-3.87 (m, 2H), 3.87 (s, 6H), 3.50 (s, 3H), 3.4-3.36 (m, 4H), 3.32-3.10 (m, 4H), 2.94-2.81 (m, 1H), 2.70-2.60 (m, 1H), 2.59 (s, 3H), 2.58-2.50 (m, 2H), 2.49-2.42 (m, 1H), 2.22-2.08 (m, 1H).
D62	LCMS (ESI) m/z: [M + H] ⁺ = 664.40	¹ H NMR (400 MHz, Methanol-d4) δ 8.54 (s, 0.3H, FA), 7.56 (s, 1H), 6.62 (s, 2H), 5.05 (dd, J = 12.6, 5.3 Hz, 1H), 4.37 (s, 2H), 3.88 (s, 6H), 3.84 (s, 2H), 3.64 (s, 3H), 3.54 (t, J = 5.6 Hz, 2H), 3.23 (s, 3H), 3.18 (d, J = 5.3 Hz, 4H), 2.93-2.72 (m, 9H), 2.65 (t, J = 5.6 Hz, 2H), 2.62-2.49 (m, 1H), 2.25-2.12 (m, 1H).
D63	839.7	¹ H NMR (300 MHz, DMSO-d6) δ 11.09 (s, 1H), 8.21 (s, 1H, FA), 7.86 (d, J = 4.4 Hz, 1H), 7.68 (t, J = 4.3 Hz, 2H), 7.33 (d, J = 2.2 Hz, 1H), 7.25 (dd, J = 8.7, 2.3 Hz, 1H), 6.61 (s, 2H), 5.07 (dd, J = 12.7, 5.4 Hz, 1H), 4.60 (s, 2H), 3.98-3.85 (m, 2H), 3.79 (s, 6H), 3.78 (s, 1H), 3.58 (s, 3H), 3.51 (s, 3H), 3.47-3.38 (m, 4H), 2.98-2.82 (m, 6H), 2.65-2.54 (m, 3H), 2.49-2.44 (m, 3H), 2.33 (t, J = 7.3 Hz, 2H), 2.19-1.95 (m, 3H), 1.63 (d, J = 12.0 Hz, 2H), 1.48-1.02 (m, 5H).
D64	824.7	¹ H NMR (300 MHz, DMSO-d6) δ 11.09 (s, 1H), 8.15 (s, 0.4H, FA), 7.74-7.63 (m, 2H), 7.36 (d, J = 2.2 Hz, 1H), 7.28 (dd, J = 8.6, 2.2 Hz, 1H), 6.73 (s, 2H), 5.08 (dd, J = 12.7, 5.4 Hz, 1H), 4.29 (s, 2H), 4.17 (s, 2H), 3.87 (s, 6H), 3.66 (s, 3H), 3.54-3.44 (m, 11H), 3.07-2.79 (m, 4H), 2.64-2.53 (m, 7H), 2.49-2.40 (m, 2H), 2.09-1.97 (m, 1H), 1.85 (d, J = 13.0 Hz, 2H), 1.66-1.53 (m, 1H), 1.45 (s, 4H).
D65	LCMS (ESI) m/z: [M + H] ⁺ = 836.65	¹ H NMR (300 MHz, DMSO-d6) δ 7.73-7.52 (m, 3H), 7.40 (d, J = 2.6 Hz, 1H), 6.71 (d, J = 2.0 Hz, 2H), 5.23 (dd, J = 11.4, 5.7 Hz, 1H), 4.20 (d, J = 8.2 Hz, 4H), 3.94 (s, 2H), 3.86 (s, 6H), 3.67-3.62 (m, 1H), 3.51 (s, 4H), 3.45-3.30 (m, 4H), 3.28-3.08 (m, 6H), 3.07-2.92 (m, 3H), 2.93-2.75 (m, 1H), 2.68-2.55 (m, 9H), 2.23-2.08 (m, 1H), 1.92-1.70 (m, 3H), 1.68-1.52 (m, 2H), 1.52-1.28 (m, 2H).
D66	752.3	¹ H NMR (300 MHz, Methanol-d4) δ 7.41 (d, J = 8.2 Hz, 1H), 7.23 (s, 1H), 6.88 (d, J = 2.2 Hz, 1H), 6.86 (s, 2H), 6.80 (dd, J = 8.2, 2.3 Hz, 1H), 5.14 (dd, J = 13.3, 5.1 Hz, 1H), 4.48 (s, 2H), 4.35 (dd, J = 27.7, 5.0 Hz, 6H), 4.13 (d, J = 10.3 Hz, 2H), 3.96 (s, 6H), 3.77 (d, J = 17.5 Hz, 4H), 3.63 (s, 3H), 3.49 (dd, J = 10.8, 6.4 Hz, 7H), 3.10 (d, J = 1.7 Hz, 2H), 2.99-2.84 (m, 1H), 2.79 (dd, J = 13.0, 2.7 Hz, 1H), 2.60-2.41 (m, 1H), 2.32-2.02 (m, 4H).
D67	706.52	¹ H NMR (400 MHz, DMSO-d6) δ 10.81 (s, 1H), 8.17 (s, 2H), 7.60 (s, 1H), 6.56 (s, 3H), 5.73 (s, 1H), 4.19 (s, 2H), 3.76 (s, 6H), 3.51 (s, 2H), 3.47 (s, 3H), 3.38 (t, J = 5.5 Hz, 2H), 3.26-3.08 (m, 1H), 3.07-2.92

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Compound No.	LCMS	¹ H NMR
D68	LCMS (ESI) m/z: [M + H] ⁺ = 808.43	(m, 2H), 2.81 (d, J = 11.5 Hz, 2H), 2.57 (d, J = 4.2 Hz, 3H), 2.28 (t, J = 7.4 Hz, 3H), 2.04 (s, 1H), 1.57 (d, J = 12.0 Hz, 2H), 1.15 (s, 3H), 1.05 (d, J = 11.4 Hz, 2H).
D69	LCMS (ESI) m/z: [M + H] ⁺ = 809.40	¹ H NMR (300 MHz, DMSO-d6) δ 11.00 (s, 1H), 8.23 (s, 2H, FA), 7.69-7.62 (m, 2H), 7.49 (s, 1H), 7.40 (d, J = 7.9 Hz, 1H), 6.61 (s, 3H), 5.11 (dd, J = 13.2, 5.1 Hz, 1H), 4.46-4.26 (m, 3H), 4.22 (s, 2H), 3.80 (s, 6H), 3.64 (s, 2H), 3.50 (s, 3H), 3.44-3.36 (m, 2H), 3.05 (d, J = 10.6 Hz, 2H), 2.92 (d, J = 10.4 Hz, 3H), 2.67-2.57 (m, 5H), 2.49-2.30 (m, 3H), 2.29-2.06 (m, 4H), 2.04-1.94 (m, 1H), 1.87-1.57 (m, 6H), 1.40 (s, 2H), 1.34-1.07 (m, 3H).
D70	LCMS (ESI) m/z: [M + H] ⁺ = 824.35	¹ H NMR (400 MHz, Methanol-d4) δ 7.67-7.48 (m, 2H), 7.45-7.32 (m, 2H), 6.73 (d, J = 6.3 Hz, 2H), 5.25-5.09 (m, 1H), 4.52-4.42 (m, 2H), 4.37 (d, J = 3.6 Hz, 3H), 3.96 (s, 2H), 3.95 (s, 6H), 3.75 (d, J = 13.9 Hz, 2H), 3.64 (s, 3H), 3.60 (d, J = 12.7 Hz, 2H), 3.54 (d, J = 5.6 Hz, 2H), 3.32-3.25 (m, 3H), 3.19 (s, 1H), 3.18-3.05 (m, 2H), 2.98-2.86 (m, 1H), 2.82 (dd, J = 4.8, 2.5 Hz, 1H), 2.78 (s, 3H), 2.64 (t, J = 5.6 Hz, 2H), 2.51 (qd, J = 13.2, 4.7 Hz, 1H), 2.24-2.14 (m, 1H), 2.04 (d, J = 13.9 Hz, 2H), 2.00-1.86 (m, 1H), 1.86-1.70 (m, 3H), 1.68-1.51 (m, 2H).
D71	LCMS (ESI) m/z: [M + H] ⁺ = 809.43	¹ H NMR (300 MHz, DMSO-d6) δ 8.15 (s, 1H, FA), 7.73 (d, J = 8.5 Hz, 1H), 7.66-7.49 (m, 3H), 7.38 (d, J = 2.2 Hz, 1H), 7.33-7.23 (m, 2H), 6.62-6.54 (m, 3H), 4.22 (s, 2H), 4.07 (d, J = 13.1 Hz, 2H), 3.78 (s, 6H), 3.55-3.49 (m, 5H), 3.44-3.39 (m, 4H), 2.97 (t, J = 12.5 Hz, 3H), 2.60 (d, J = 4.2 Hz, 4H), 2.44-2.31 (m, 8H), 1.76 (d, J = 12.9 Hz, 2H), 1.65-1.52 (m, 1H), 1.42-1.30 (m, 2H), 1.25-1.13 (m, 2H).
D72	LCMS (ESI) m/z: [M + H] ⁺ = 809.43	¹ H NMR (300 MHz, DMSO-d6) δ 7.73 (d, J = 7.9 Hz, 1H), 7.62 (s, 1H), 7.53-7.41 (m, 2H), 6.73 (s, 2H), 5.10 (dd, J = 13.2, 5.1 Hz, 1H), 4.50-4.29 (m, 2H), 4.24 (d, J = 10.0 Hz, 4H), 3.87 (s, 6H), 3.67-3.54 (m, 5H), 3.44-3.28 (m, 6H), 3.19-2.86 (m, 8H), 2.79-2.72 (m, 2H), 2.67-2.52 (m, 8H), 2.47-2.31 (m, 2H), 2.06-1.95 (m, 4H).
D73	LCMS (ESI) m/z: [M + H] ⁺ = 808.43	¹ H NMR (300 MHz, DMSO-d6) δ 11.1 (br s, 1H), 8.26 (s, 2H, FA), 7.64 (s, 1H), 7.55 (d, J = 8.9 Hz, 3H), 6.61 (s, 3H), 5.11 (dd, J = 13.2, 5.1 Hz, 1H), 4.42 (d, J = 17.1 Hz, 1H), 4.28 (d, J = 17.2 Hz, 1H), 4.22 (s, 2H), 3.80 (s, 6H), 3.62 (s, 2H), 3.50 (s, 3H), 3.40 (t, J = 5.9 Hz, 2H), 3.05 (d, J = 10.7 Hz, 2H), 2.90 (d, J = 12.0 Hz, 3H), 2.71-2.54 (m, 5H), 2.42 (s, 4H), 2.46-2.35 (m, 3H), 2.16 (q, J = 12.1 Hz, 4H), 2.05-1.93 (m, 1H), 1.82-1.58 (m, 6H), 1.41 (s, 2H), 1.32-1.12 (m, 3H).
D74	LCMS (ESI) m/z: [M + H] ⁺ = 701.50	¹ H NMR (300 MHz, DMSO-d6) δ 8.15 (s, 1H, FA), 7.64 (s, 1H), 6.68 (s, 2H), 6.64-6.57 (m, 1H), 4.22 (s, 2H), 3.95 (s, 2H), 3.84 (s, 6H), 3.51 (s, 4H), 3.44-3.39 (m, 5H), 3.19-3.08 (m, 3H), 2.86 (s, 4H), 2.70-2.57 (m, 7H), 2.46-2.41 (m, 2H), 2.10 (s, 3H), 1.74 (s, 7H), 1.67-1.55 (m, 6H), 1.45-1.26 (m, 5H).
D75	LCMS (ESI) m/z: [M + H] ⁺ = 859.50	¹ H NMR (400 MHz, Methanol-d4) δ 8.22 (s, 1H, FA), 7.58 (s, 1H), 7.38 (d, J = 6.1 Hz, 1H), 6.73 (s, 2H), 5.12 (dd, J = 12.7, 5.4 Hz, 1H), 4.36 (s, 4H), 3.95 (s, 6H), 3.64 (s, 3H), 3.55 (t, J = 5.6 Hz, 4H), 3.50 (t, J = 4.7 Hz, 4H), 3.18-3.06 (m, 2H), 2.98 (s, 4H), 2.90-2.69 (m, 8H), 2.64 (t, J = 5.7 Hz, 2H), 2.19-2.11 (m, 1H), 2.02 (d, J = 13.8 Hz, 2H), 1.80-1.46 (m, 5H).
D76	LCMS (ESI) m/z: [M + H] ⁺ = 820.55	¹ H NMR (400 MHz, DMSO-d6) δ 11.07 (s, 1H), 8.19 (s, 2H, FA), 8.09 (s, 1H), 7.82 (s, 1H), 7.63 (s, 1H), 7.42 (d, J = 8.7 Hz, 2H), 6.93 (d, J = 8.7 Hz, 2H), 6.58 (s, 3H), 5.36 (dd, J = 11.9, 5.1 Hz, 1H), 4.21 (s, 2H), 3.78 (s, 6H), 3.52 (s, 2H), 3.50 (s, 3H), 3.42-3.39 (m, 6H), 3.14-3.11 (m, 4H), 2.86-2.79 (m, 3H), 2.60 (d, J = 4.3 Hz, 4H), 2.49-2.44 (m, 5H), 2.29-2.22 (m, 1H), 2.08-2.00 (m, 2H), 1.65-1.58 (m, 2H), 1.40-1.34 (m, 2H), 1.29-1.22 (m, 1H), 1.18-1.08 (m, 2H).
D77	LCMS (ESI) m/z: [M + H] ⁺ = 811.55	¹ H NMR (300 MHz, Methanol-d4) δ 8.41 (s, 1H, FA), 7.72 (d, J = 7.8 Hz, 1H), 7.58 (s, 1H), 6.73 (s, 3H), 6.17 (s, 1H), 5.27 (dd, J = 12.3, 5.3 Hz, 1H), 4.36 (s, 4H), 3.95 (s, 6H), 3.64 (s, 3H), 3.60-3.49 (m, 4H), 3.43 (s, 4H), 3.13-3.04 (m, 1H), 2.92-2.76 (m, 9H), 2.72-2.54 (m, 6H), 2.36-2.24 (m, 1H), 2.08-1.95 (m, 2H), 1.78-1.44 (m, 5H).
D78	LCMS (ESI) m/z: [M + H] ⁺ = 858.50	¹ H NMR (400 MHz, Methanol-d4) δ 8.50 (s, 2H, FA), 7.58 (s, 1H), 7.51 (d, J = 9.6 Hz, 1H), 6.73 (s, 2H), 5.12 (dd, J = 12.8, 5.4 Hz, 1H), 4.36 (s, 4H), 3.96 (s, 6H), 3.64 (s, 4H), 3.55 (t, J = 5.6 Hz, 3H), 3.44 (s, 4H), 3.14-3.07 (m, 1H), 2.97-2.83 (m, 2H), 2.78 (s, 4H), 2.76-2.69 (m, 5H), 2.66-2.57 (m, 4H), 2.17-2.11 (m, 1H), 2.06-1.98 (m, 2H), 1.75-1.49 (m, 5H).

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Compound No.	LCMS	¹ H NMR
D79	793.47	¹ H NMR (400 MHz, DMSO-d6) δ 11.05 (s, 1H), 8.13 (s, 1H), 7.66 (d, J = 8.5 Hz, 1H), 7.61 (s, 1H), 7.31 (d, J = 2.2 Hz, 1H), 7.23 (dd, J = 8.7, 2.3 Hz, 1H), 6.61 (s, 1H), 4.19 (s, 2H), 3.79 (s, 6H), 3.76 (s, 2H), 3.48 (s, 3H), 3.30 (s, 6H), 2.99 (t, J = 10.0 Hz, 2H), 2.57 (d, J = 4.1 Hz, 2H), 2.36-2.28 (m, 2H), 1.98 (d, J = 12.8 Hz, 1H), 1.37 (s, 3H), 1.80-1.61 (m, 2H), 1.32-1.18 (m, 2H).
D80	826.37	¹ H NMR (400 MHz, DMSO-d6) δ 11.05 (s, 1H), 8.13 (s, 1H), 7.66 (d, J = 8.5 Hz, 1H), 7.61 (s, 1H), 7.31 (d, J = 2.2 Hz, 1H), 7.23 (dd, J = 8.7, 2.3 Hz, 1H), 6.61 (s, 1H), 4.19 (s, 2H), 3.79 (s, 6H), 3.76 (s, 2H), 3.48 (s, 3H), 3.30 (s, 6H), 2.99 (t, J = 10.0 Hz, 2H), 2.57 (d, J = 4.1 Hz, 2H), 2.36-2.28 (m, 2H), 1.98 (d, J = 12.8 Hz, 1H), 1.37 (s, 3H), 1.80-1.61 (m, 2H), 1.32-1.18 (m, 2H).
D81	LCMS (ESI) m/z: [M + H] ⁺ = 849.25.	¹ H NMR (300 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.15 (s, 2H, FA), 7.69 (d, J = 8.5 Hz, 1H), 7.63 (s, 1H), 7.34 (s, 1H), 7.26 (d, J = 8.8 Hz, 1H), 6.75 (s, 1H), 6.64 (s, 2H), 5.07 (dd, J = 12.9, 5.3 Hz, 1H), 4.20 (s, 2H), 3.82 (s, 10H), 3.50 (s, 5H), 3.45-3.41 (m, 8H), 3.05-2.87 (m, 4H), 2.63-2.58 (m, 3H), 2.41-2.26 (m, 3H), 2.06-1.95 (m, 1H), 1.79-1.66 (m, 2H), 1.45-1.36 (m, 3H), 1.33-1.21 (m, 2H), 0.57-0.51 (m, 2H), 0.45-0.39 (m, 2H).
D82	LCMS (ESI) m/z: [M + H] ⁺ = 939.	¹ H NMR (300 MHz, DMSO-d6) δ 7.70 (d, J = 8.5 Hz, 1H), 7.64 (s, 1H), 7.35 (d, J = 2.2 Hz, 1H), 7.27 (d, J = 8.9 Hz, 1H), 6.68-6.56 (m, 3H), 5.72-5.59 (m, 2H), 5.27 (dd, J = 13.0, 5.3 Hz, 1H), 4.77 (p, J = 6.2 Hz, 1H), 4.22 (s, 2H), 3.82 (s, 8H), 3.50 (s, 3H), 3.47-3.38 (m, 8H), 3.16-2.96 (m, 4H), 2.90-2.66 (m, 2H), 2.65-2.53 (m, 7H), 2.40-2.26 (m, 3H), 2.14-2.03 (m, 1H), 1.72 (d, J = 12.3 Hz, 2H), 1.47-1.35 (m, 3H), 1.31-1.19 (m, 8H).
D83	LCMS (ESI) m/z: [M + H] ⁺ = 827.45.	¹ H NMR (300 MHz, DMSO-d6) δ 10.98 (s, 1H), 8.16 (s, 2H, FA), 7.64 (s, 1H), 7.44 (d, J = 11.8 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 6.65-6.52 (m, 3H), 5.09 (dd, J = 13.4, 5.0 Hz, 1H), 4.41-4.19 (m, 5H), 3.80 (s, 7H), 3.65 (s, 4H), 3.50 (s, 5H), 3.41 (s, 2H), 3.04 (s, 4H), 2.98-2.87 (m, 3H), 2.61-2.58 (m, 4H), 2.44-2.30 (m, 4H), 2.07-1.93 (m, 1H), 1.72-1.59 (m, 2H), 1.47-1.10 (m, 6H).
D84	LCMS (ESI) m/z: [M + H] ⁺ = 827.35.	¹ H NMR (300 MHz, DMSO-d6) δ 10.98 (s, 1H), 8.16 (s, 2H, FA), 7.64 (s, 1H), 7.43 (d, J = 11.6 Hz, 1H), 7.23 (d, J = 7.5 Hz, 1H), 6.66-6.56 (m, 3H), 5.08 (dd, J = 13.2, 5.1 Hz, 1H), 4.40-4.25 (m, 2H), 4.22 (s, 2H), 3.88-3.74 (m, 9H), 3.50 (s, 4H), 3.45-3.38 (m, 5H), 3.11 (s, 4H), 3.06-2.85 (m, 4H), 2.65-2.57 (m, 5H), 2.41-2.32 (m, 4H), 2.04-1.93 (m, 1H), 1.71 (d, J = 12.4 Hz, 2H), 1.44-1.24 (m, 5H).
D85	LCMS (ESI) m/z: [M + H] ⁺ = 809.80.	¹ H NMR (400 MHz, DMSO-d6) δ 10.95 (s, 1H), 8.18 (s, 2H, FA), 7.64 (s, 1H), 7.55-7.48 (m, 1H), 7.06 (d, J = 7.9 Hz, 2H), 6.65-6.56 (m, 3H), 5.05 (dd, J = 13.3, 5.1 Hz, 1H), 4.33 (d, J = 16.9 Hz, 1H), 4.26-4.17 (m, 3H), 3.81 (s, 6H), 3.71 (s, 2H), 3.50 (s, 3H), 3.41 (t, J = 5.6 Hz, 3H), 3.30-3.24 (m, 5H), 3.02-2.85 (m, 4H), 2.63-2.52 (m, 6H), 2.43-2.23 (m, 6H), 2.00-1.92 (m, 1H), 1.68 (d, J = 12.5 Hz, 2H), 1.44-1.30 (m, 3H), 1.29-1.16 (m, 2H).
D86	LCMS (ESI) m/z: [M + H] ⁺ = 840.40.	¹ H NMR (400 MHz, DMSO-d6) δ 11.10 (s, 1H), 8.16 (s, 1H, FA), 7.64 (s, 1H), 7.24 (s, 1H), 7.05 (d, J = 13.2 Hz, 1H), 6.66 (s, 2H), 6.60 (d, J = 4.6 Hz, 1H), 5.07 (dd, J = 12.8, 5.4 Hz, 1H), 4.22 (s, 2H), 3.87 (s, 2H), 3.83 (s, 6H), 3.53-3.44 (m, 8H), 3.43-3.38 (m, 3H), 3.09 (d, J = 11.4 Hz, 2H), 2.94-2.83 (m, 1H), 2.63-2.54 (m, 6H), 2.49-2.41 (m, 5H), 2.37-2.30 (m, 2H), 2.06-1.97 (m, 1H), 1.73 (d, J = 12.6 Hz, 2H), 1.47-1.36 (m, 3H), 1.35-1.22 (m, 2H).
D87	LCMS (ESI) m/z: [M + H] ⁺ = 840.95.	¹ H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 8.16 (s, 1H, FA), 7.67-7.61 (m, 2H), 7.37 (t, J = 7.7 Hz, 1H), 6.66-6.55 (m, 3H), 5.10 (dd, J = 12.8, 5.4 Hz, 1H), 4.22 (s, 2H), 3.81 (s, 6H), 3.74 (s, 2H), 3.50 (s, 4H), 3.41 (t, J = 5.5 Hz, 5H), 3.22 (t, J = 4.8 Hz, 5H), 2.99 (d, J = 11.2 Hz, 2H), 2.94-2.78 (m, 2H), 2.64-2.56 (m, 5H), 2.40-2.31 (m, 4H), 2.07-1.97 (m, 1H), 1.69 (d, J = 12.5 Hz, 2H), 1.38 (s, 3H), 1.29-1.16 (m, 2H).
D88	LCMS (ESI) m/z: [M + H] ⁺ = 841.55.	¹ H NMR (300 MHz, DMSO-d6, D20) δ 7.80 (d, J = 11.1 Hz, 1H), 8.14 (s, 0H, FA), 7.64 (s, 1H), 7.56 (s, 1H), 6.73 (s, 2H), 5.12 (dd, J = 12.8, 5.4 Hz, 1H), 4.31-4.14 (m, 4H), 3.87 (s, 6H), 3.51 (s, 3H), 3.48-3.39 (m, 6H), 3.31-3.06 (m, 4H), 3.06-2.80 (m, 4H), 2.66-2.56 (m, 5H), 2.56-2.53 (m, 4H), 2.10-1.99 (m, 1H), 1.91-1.82 (m, 2H), 1.81-1.15 (m, 6H).
D89	LCMS (ESI) m/z: [M + H] ⁺ = 782.65.	¹ H NMR (300 MHz, DMSO-d6) δ 11.02 (s, 1H), 8.27 (s, 1H, FA), 7.67-7.55 (m, 1H), 7.28 (t, J = 7.7 Hz, 1H), 6.92 (d, J = 7.4 Hz, 1H), 6.73 (d, J = 8.1 Hz, 1H), 6.67-6.62 (m, 1H), 6.59 (s, 2H), 5.56 (t, J = 5.0 Hz, 1H), 5.11 (dd, J = 13.2, 5.1 Hz, 1H), 4.27-4.06 (m, 5H), 3.83-3.73 (m, 7H), 3.65 (s, 2H), 3.50 (s, 3H), 3.40 (t, J = 5.4 Hz, 2H), 3.28 (t, J = 7.1 Hz, 3H), 3.14-3.00 (m, 4H), 2.97-2.86 (m, 1H), 2.67-2.53 (m, 2H), 2.34-2.25 (m, 1H), 2.09-1.98 (m, 1H), 1.98-1.84 (m, 2H), 1.63-1.50 (m, 2H), 1.43-1.21 (m, 10H).
D90	LCMS (ESI) m/z: [M + H] ⁺ = 755.65.	¹ H NMR (300 MHz, DMSO-d6) δ 11.12 (s, 1H), 8.18 (s, 0H, FA), 7.83 (d, J = 8.3 Hz, 1H), 7.64 (s, 1H), 7.43 (d, J = 2.2 Hz, 1H), 7.35 (dd, J = 12.9, 5.3 Hz, 1H), 4.19 (dd, J = 13.5, 7.1 Hz, 4H), 3.91 (s, 2H), 3.82 (s, 6H), 3.65-3.55 (m, 4H), 3.50 (s, 3H), 3.41 (t, J = 5.3 Hz, 4H), 3.13-3.04 (m, 2H), 2.96-2.83 (m, 1H), 2.66-2.55 (m, 2H), 2.15-2.00 (m, 3H), 1.85-1.68 (m, 2H), 1.57-1.37 (m, 4H).

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Compound No.	LCMS	¹ H NMR
D91	LCMS (ESI) m/z: [M + H] ⁺ = 811.70	¹ H NMR (300 MHz, Methanol-d4) δ 8.54 (br s, 1H, FA), 7.72 (d, J = 1H), 7.61 (s, 1H), 7.41 (d, J = 2.1 Hz, 1H), 7.28 (d, J = 8.7 Hz, 1H), 6.98-6.87 (m, 2H), 5.10 (dd, J = 12.3, 5.3 Hz, 1H), 4.39-4.33 (m, 4H), 3.99 (s, 3H), 3.64 (s, 4H), 3.55 (s, 8H), 3.09 (t, J = 12.1 Hz, 2H), 2.92-2.80 (m, 5H), 2.80-2.71 (m, 5H), 2.64 (d, J = 5.9 Hz, 4H), 2.14 (s, 1H), 2.00 (s, 1H), 1.78-1.45 (m, 5H).
D92	LCMS (ESI) m/z: [M + H] ⁺ = 794.80.	¹ H NMR (300 MHz, DMSO-d6) δ 11.09 (s, 1H), 8.16 (s, 2H, FA), 8.08 (d, J = 1.7 Hz, 1H), 7.73-7.64 (m, 2H), 7.42 (d, J = 1.8 Hz, 1H), 7.34 (d, J = 2.2 Hz, 1H), 7.26 (dd, J = 8.7, 2.3 Hz, 1H), 6.61 (q, J = 4.4 Hz, 1H), 5.08 (dd, J = 12.8, 5.4 Hz, 1H), 4.22 (s, 2H), 3.85 (s, 3H), 3.69 (s, 2H), 3.50 (s, 3H), 3.46-3.40 (m, 8H), 2.98-2.83 (m, 3H), 2.64-2.55 (m, 5H), 2.45-2.25 (m, 5H), 2.17 (t, J = 11.4 Hz, 2H), 2.06-1.98 (m, 1H), 1.65 (d, J = 11.8 Hz, 2H), 1.44-1.09 (m, 6H)
D93	848.51	
D94	863.63	
D95	863.56	¹ H NMR (400 MHz, DMSO-d6) δ 11.03 (s, 1H), 8.14 (s, 1H), 7.62 (d, J = 8.6 Hz, 2H), 7.27 (d, J = 2.3 Hz, 1H), 7.20 (dd, J = 8.6, 2.4 Hz, 1H), 6.56 (s, 3H), 5.03 (dd, J = 13.0, 5.4 Hz, 1H), 4.19 (s, 2H), 4.10-3.91 (m, 3H), 3.76 (s, 6H), 3.51 (s, 2H), 3.47 (s, 3H), 3.37 (d, J = 5.8 Hz, 1H), 3.15 (d, J = 2.4 Hz, 2H), 2.92 (t, J = 12.1 Hz, 2H), 2.89-2.80 (m, 1H), 2.65 (q, J = 1.9 Hz, 1H), 2.57 (d, J = 4.3 Hz, 3H), 2.34-2.23 (m, 4H), 1.99 (d, J = 14.8 Hz, 3H), 1.77-1.67 (m, 2H), 1.59 (s, 5H), 1.28 (d, J = 7.0 Hz, 1H), 1.24-1.08 (m, 1H).
D96	835.56	¹ H NMR (400 MHz, DMSO-d6) δ 11.03 (s, 1H), 8.16 (s, 1H), 7.70-7.49 (m, 2H), 7.28 (d, J = 2.3 Hz, 1H), 7.20 (dd, J = 8.7, 2.4 Hz, 1H), 6.55 (s, 2H), 5.04 (dd, J = 12.8, 5.4 Hz, 1H), 4.19 (s, 2H), 4.01 (d, J = 13.0 Hz, 2H), 3.75 (s, 5H), 3.73-3.59 (m, 2H), 3.47 (s, 3H), 3.38 (t, J = 5.5 Hz, 2H), 3.15 (s, 2H), 2.99-2.88 (m, 2H), 2.88-2.79 (m, 1H), 2.57 (d, J = 4.3 Hz, 3H), 2.43-2.12 (m, 3H), 2.03-1.93 (m, 1H), 1.74 (d, J = 12.8 Hz, 2H), 1.62 (s, 1H), 1.43 (t, J = 7.1 Hz, 1H), 1.24-1.12 (m, 2H), 0.43 (q, J = 4.8 Hz, 1H), 0.22-0.03 (m, 1H).
D97	890.39	
D98	865.52	
D99	837.59	
D100	837.59	
D101	850.44	
D102	851.59	
D103	867.5	
D104	873.43	
D105	831.57	
D106	LCMS (ESI) m/z: [M + H] ⁺ = 878.55	¹ H NMR (400 MHz, Methanol-d4) δ 7.56 (s, 1H), 6.77-6.64 (m, 3H), 6.57 (s, 1H), 5.04 (dd, J = 13.2, 5.4 Hz, 1H), 4.48-4.28 (m, 6H), 4.17-3.98 (m, 2H), 3.98-3.86 (m, 10H), 3.76-3.45 (m, 10H), 3.28-3.20 (m, 3H), 3.16-3.01 (m, 2H), 2.94-2.81 (m, 1H), 2.81-2.71 (m, 4H), 2.66-2.56 (m, 2H), 2.43 (qd, J = 13.0, 4.7 Hz, 1H), 2.19-2.07 (m, 1H), 2.06-1.87 (m, 3H), 1.86-1.69 (m, 3H), 1.67-1.48 (m, 2H).
D107	LCMS (ESI) m/z: [M + H] ⁺ = 835.45.	¹ H NMR (300 MHz, Methanol-d4) δ 8.45 (br s, 1H, FA), 7.64 (d, J = 8.3 Hz, 1H), 7.58 (s, 1H), 6.82 (d, J = 2.0 Hz, 1H), 6.73 (s, 2H), 6.66 (d, J = 8.3, 2.1 Hz, 1H), 5.07 (dd, J = 12.3, 5.4 Hz, 1H), 4.46 (s, 2H), 4.36 (s, 2H), 4.21-4.08 (m, 3H), 3.99-3.85 (m, 7H), 3.78 (s, 4H), 3.64 (s, 3H), 3.55 (t, J = 5.4 Hz, 2H), 2.97 (s, 2H), 2.91-2.68 (m, 6H), 2.66-2.58 (m, 4H), 2.51-2.41 (m, 2H), 2.19-2.01 (m, 1H), 1.97-1.75 (m, 4H), 0.98 (d, J = 5.0 Hz, 3H).
D109	LCMS (ESI) m/z: [M + H] ⁺ = 821.50.	¹ H NMR (400 MHz, DMSO-d6) δ 11.07 (s, 1H), 8.19 (s, 1H, FA), 7.64 (d, J = 8.3 Hz, 2H), 6.77 (d, J = 2.1 Hz, 1H), 6.65 (dd, J = 8.4, 2.1 Hz, 1H), 6.62-6.57 (m, 3H), 5.05 (dd, J = 12.9, 5.4 Hz, 1H), 4.22 (s, 2H), 3.80 (s, 6H), 3.73 (s, 4H), 3.70 (s, 2H), 3.50 (s, 4H), 3.48-3.45 (m, 6H), 3.09-3.01 (m, 3H), 2.92-2.87 (m, 1H), 2.60 (d, J = 4.3 Hz, 4H), 2.45-2.40 (m, 2H), 2.28 (s, 4H), 2.05-1.97 (m, 1H), 1.78-1.69 (m, 4H).
D110	LCMS (ESI) m/z: [M + H] ⁺ = 794.30	
D111	LCMS (ESI) m/z: [M + H] ⁺ = 643.25	¹ H NMR (400 MHz, DMSO-d6) δ 11.06 (s, 1H), 7.60 (s, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.22-7.14 (m, 2H), 6.98 (dd, J = 8.5, 2.1 Hz, 1H), 6.64 (s, 2H), 6.58 (d, J = 4.6 Hz, 1H), 5.02 (dd, J = 13.0, 5.3 Hz, 1H), 4.32 (d, J = 5.3 Hz, 2H), 4.21 (s, 2H), 3.86 (s, 6H), 3.49 (s, 3H), 3.41 (d, J = 5.5 Hz, 3H), 2.95-2.81 (m, 1H), 2.59 (d, J = 4.3 Hz, 3H), 2.54 (s, 3H), 1.99 (d, J = 12.5 Hz, 1H).
D112	LCMS (ESI) m/z: [M + H] ⁺ = 657.10.	¹ H NMR (400 MHz, DMSO-d6) δ 11.06 (s, 1H), 7.63 (t, J = 4.3 Hz, 2H), 7.31 (d, J = 2.4 Hz, 1H), 7.11-7.01 (m, 1H), 6.64 (s, 2H), 6.58 (s, 2H), 3.85 (s, 6H), 3.48 (s, 3H), 3.09 (s, 3H), 2.86 (d, J = 12.5 Hz, 1H), 2.68 (p, J = 1.8 Hz, 3H), 2.59 (s, 3H), 2.58 (s, 6H), 2.00 (d, J = 12.5 Hz, 1H).

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Compound No.	LCMS	¹ H NMR
D113	LCMS (ESI) m/z: [M + H] ⁺ = 822.70	¹ H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 8.18 (s, 1H), 7.86 (d, J = 7.7 Hz, 1H), 7.81-7.74 (m, 2H), 7.64 (s, 1H), 6.62 (s, 2H), 6.60-6.57 (m, 1H), 5.14 (dd, J = 12.9, 5.4 Hz, 1H), 4.22 (s, 2H), 3.80 (s, 6H), 3.67 (s, 2H), 3.50 (s, 4H), 3.41 (t, J = 5.6 Hz, 4H), 3.03 (d, J = 10.9 Hz, 2H), 2.97-2.88 (m, 3H), 2.77 (t, J = 12.2 Hz, 1H), 2.63-2.58 (m, 4H), 2.43-2.36 (m, 2H), 2.30-2.21 (m, 2H), 2.12-2.02 (m, 3H), 1.86-1.79 (m, 2H), 1.78-1.63 (m, 4H), 1.43-1.28 (m, 3H), 1.25-1.14 (m, 2H).
D114	LCMS (ESI) m/z: [M + H] ⁺ = 892.45	¹ H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.24 (s, 1H, TFA), 8.32 (s, 1H, TFA), 7.86 (d, J = 8.2 Hz, 1H), 7.64 (s, 1H), 7.35-7.26 (m, 2H), 6.75 (s, 2H), 6.62 (d, J = 4.6 Hz, 1H), 5.13 (dd, J = 12.8, 5.4 Hz, 1H), 5.09-5.00 (m, 1H), 4.27-4.10 (m, 4H), 3.89 (d, J = 2.4 Hz, 6H), 3.52 (s, 3H), 3.43-3.41 (m, 4H), 3.24-3.16 (m, 1H), 3.08-2.81 (m, 5H), 2.75-2.69 (m, 1H), 2.66-2.52 (m, 8H), 2.43-2.39 (m, 1H), 2.17-1.96 (m, 6H), 1.94-1.81 (m, 4H), 1.73-1.61 (m, 2H), 1.24 (s, 6H).
D115	LCMS (ESI) m/z: [M + H] ⁺ = 809.35	¹ H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.18 (s, 1H, FA), 7.68 (d, J = 8.5 Hz, 1H), 7.63 (s, 1H), 7.34 (d, J = 2.2 Hz, 1H), 7.26 (dd, J = 8.8, 2.3 Hz, 1H), 6.64 (s, 2H), 6.59 (q, J = 4.4 Hz, 1H), 5.07 (dd, J = 12.9, 5.4 Hz, 1H), 4.21 (s, 2H), 3.90 (s, 2H), 3.82 (s, 6H), 3.50 (s, 3H), 3.44-3.39 (m, 8H), 3.37-3.28 (m, 5H), 3.08 (t, J = 8.9 Hz, 2H), 2.94-2.80 (m, 3H), 2.62-2.56 (m, 4H), 2.30 (t, J = 7.2 Hz, 2H), 2.21-2.13 (m, 1H), 2.06-1.94 (m, 2H), 1.61-1.49 (m, 2H), 1.48-1.39 (m, 1H).
D116	LCMS (ESI) m/z: [M + H] ⁺ = 699.40	¹ H NMR (300 MHz, DMSO-d6) δ 11.12 (s, 1H), 8.19 (s, 2H, FA), 7.86-7.80 (m, 1H), 7.64 (s, 1H), 7.30-7.23 (m, 2H), 6.60 (s, 3H), 5.12 (dd, J = 12.8, 5.4 Hz, 1H), 4.94 (t, J = 5.5 Hz, 1H), 4.21 (s, 2H), 3.78 (s, 6H), 3.72-3.65 (m, 5H), 3.50 (s, 3H), 3.40 (s, 3H), 3.13-3.08 (m, 2H), 2.91-2.86 (m, 1H), 2.63-2.57 (m, 5H), 2.09-2.00 (m, 1H).
D117	LCMS (ESI) m/z: [M + H] ⁺ = 823.55	¹ H NMR (300 MHz, DMSO-d6) δ 11.15 (s, 1H), 9.47 (s, 1H, TFA), 7.93 (d, J = 7.7 Hz, 1H), 7.87 (s, 1H), 7.83-7.77 (m, 1H), 7.64 (s, 1H), 6.74 (s, 2H), 6.63 (s, 1H), 5.16 (dd, J = 12.8, 5.4 Hz, 1H), 4.24 (d, J = 7.7 Hz, 4H), 3.88 (s, 6H), 3.62 (d, J = 10.7 Hz, 2H), 3.52 (s, 3H), 3.44-3.31 (m, 6H), 3.21-3.00 (m, 7H), 2.98-2.72 (m, 4H), 2.66-2.58 (m, 4H), 2.50-2.42 (m, 4H), 2.15-1.93 (m, 5H).
D118	LCMS (ESI) m/z: [M + H] ⁺ = 849.50	¹ H NMR (300 MHz, DMSO-d6) δ 11.09 (s, 1H), 8.18 (s, 2H, FA), 7.69 (d, J = 8.5 Hz, 1H), 7.34 (d, J = 2.8 Hz, 2H), 7.26 (dd, J = 8.7, 2.2 Hz, 1H), 6.68-6.56 (m, 3H), 5.08 (dd, J = 12.8, 5.3 Hz, 1H), 4.23 (s, 2H), 3.82 (s, 9H), 3.49-3.30 (m, 10H), 3.07 (d, J = 11.1 Hz, 3H), 2.97-2.73 (m, 3H), 2.63-2.55 (m, 6H), 2.40-2.30 (m, 2H), 2.08-1.97 (m, 1H), 1.73 (d, J = 12.2 Hz, 2H), 1.51-1.18 (m, 5H), 1.00 (s, 2H), 0.95-0.86 (m, 2H).
D119	LCMS (ESI) m/z: [M + H] ⁺ = 766.25	¹ H NMR (400 MHz, DMSO-d6) δ 11.06 (s, 1H), 8.95 (s, 1H), 7.73-7.61 (m, 2H), 6.94 (d, J = 2.2 Hz, 1H), 6.86 (dd, J = 8.6, 2.1 Hz, 1H), 6.74 (s, 2H), 6.70 (d, J = 7.2 Hz, 1H), 5.06 (dd, J = 12.8, 5.4 Hz, 1H), 4.28 (s, 2H), 4.22 (s, 2H), 3.88 (s, 7H), 3.59 (t, J = 9.6 Hz, 1H), 3.55-3.48 (m, 5H), 3.45 (t, J = 5.5 Hz, 2H), 3.28-3.23 (m, 1H), 2.97-2.82 (m, 2H), 2.75 (s, 6H), 2.71-2.65 (m, 1H), 2.62-2.53 (m, 3H), 2.13-1.94 (m, 3H), 1.71-1.59 (m, 1H), 1.55-1.41 (m, 1H).
D120	LCMS (ESI) m/z: [M + H] ⁺ = 810.20	
D121	LCMS (ESI) m/z: [M + H] ⁺ = 810.45	
D122	LCMS (ESI) m/z: [M + H] ⁺ = 780.35	
D123	LCMS (ESI) m/z: [M + H] ⁺ = 780.25	
D124	LCMS (ESI) m/z: [M + H] ⁺ = 849.30	¹ H NMR (300 MHz, Methanol-d4) δ 7.65 (d, J = 8.3 Hz, 1H), 7.57 (s, 1H), 6.83 (d, J = 2.0 Hz, 1H), 6.73 (s, 2H), 6.66 (dd, J = 8.4, 2.1 Hz, 1H), 5.07 (dd, J = 12.2, 5.5 Hz, 1H), 4.38 (d, J = 15.8 Hz, 4H), 4.02 (d, J = 9.2 Hz, 2H), 3.97 (s, 6H), 3.79 (s, 3H), 3.67-3.63 (m, 4H), 3.55 (t, J = 5.5 Hz, 2H), 2.92-2.69 (m, 7H), 2.67-2.54 (m, 6H), 2.16-2.08 (m, 1H), 1.89 (s, 4H), 1.15 (s, 6H).
D125		¹ H NMR (300 MHz, DMSO-d6, D20) δ 7.91-7.80 (m, 1H), 7.59 (s, 1H), 7.36-7.25 (m, 2H), 6.70 (s, 2H), 5.11 (dd, J = 12.8, 5.4 Hz, 1H), 4.75 (t, J = 6.8 Hz, 1H), 4.30-4.09 (m, 4H), 3.85 (s, 6H), 3.61-3.60 (m, 5H), 3.47-3.35 (m, 5H), 3.19-2.77 (m, 8H), 2.66-2.57 (m, 5H), 2.12-1.74 (m, 5H), 1.55-1.34 (m, 2H), 1.32-1.16 (m, 6H), 1.05 (t, J = 7.0 Hz, 1H).
D126	LCMS (ESI) m/z: [M + H] ⁺ = 818.45	¹ H NMR (300 MHz, DMSO-d6) δ 11.14 (s, 1H), 8.25 (s, 1H, FA), 7.91 (d, J = 8.1 Hz, 1H), 7.88-7.80 (m, 2H), 7.61 (s, 1H), 6.57 (s, 3H), 5.17 (dd, J = 12.9, 5.4 Hz, 1H), 4.21 (s, 2H), 3.77 (s, 6H), 3.62 (s, 3H),

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Compound No.	LCMS	¹ H NMR
D127	LCMS (ESI) m/z: [M + H] ⁺ = 821.50	¹ H NMR (400 MHz, Methanol-d4) δ 8.49 (s, 2H), 7.72 (d, J = 8.4 Hz, 1H), 7.58 (s, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.27 (dd, J = 8.5, 2.4 Hz, 1H), 6.73 (s, 2H), 5.61-5.54 (m, 1H), 5.09 (dd, J = 12.5, 5.4 Hz, 1H), 4.36 (s, 4H), 3.95 (s, 6H), 3.64 (s, 4H), 3.56-3.49 (m, 6H), 3.28-3.22 (m, 2H), 3.18-3.13 (m, 2H), 2.91-2.83 (m, 1H), 2.78 (s, 4H), 2.75-2.40 (m, 12H), 2.16-2.08 (m, 1H).
D128	LCMS (ESI) m/z: [M + H] ⁺ = 878.44	¹ H NMR (400 MHz, DMSO-d6) δ 11.10 (s, 1H), 8.16 (s, 1H, FA), 7.83 (d, J = 8.1 Hz, 1H), 7.63 (s, 1H), 7.31-7.25 (m, 2H), 6.63 (s, 2H), 6.58 (q, J = 4.4 Hz, 1H), 5.12 (dd, J = 12.9, 5.4 Hz, 1H), 4.98 (p, J = 6.7 Hz, 1H), 4.22 (s, 2H), 3.81 (s, 6H), 3.74 (s, 2H), 3.50 (s, 3H), 3.41 (t, J = 5.6 Hz, 7H), 3.01 (d, J = 10.0 Hz, 2H), 2.94-2.86 (m, 1H), 2.62-2.57 (m, 4H), 2.46-2.38 (m, 3H), 2.31-2.13 (m, 4H), 2.09-2.00 (m, 1H), 1.96-1.87 (m, 1H), 1.84-1.75 (m, 2H), 1.68-1.47 (m, 5H), 1.41-1.29 (m, 1H), 1.25-1.08 (m, 2H), 0.84 (d, J = 6.4 Hz, 3H).
D129	LCMS (ESI) m/z: [M + H] ⁺ = 821.35	¹ H NMR (400 MHz, DMSO-d6) δ 11.09 (s, 1H), 8.27 (s, 1H, FA), 7.69 (d, J = 8.5 Hz, 1H), 7.64 (s, 1H), 7.34 (d, J = 2.3 Hz, 1H), 7.26 (dd, J = 8.7, 2.2 Hz, 1H), 6.69-6.58 (m, 3H), 5.08 (dd, J = 12.9, 5.4 Hz, 1H), 4.22 (s, 2H), 3.96-3.87 (m, 2H), 3.83 (s, 8H), 3.50 (s, 3H), 3.46-3.39 (m, 8H), 3.14-2.98 (m, 2H), 2.94-2.74 (m, 3H), 2.60 (d, J = 4.2 Hz, 3H), 2.57-2.54 (m, 2H), 2.46-2.41 (m, 2H), 2.38-2.29 (m, 2H), 2.20 (s, 1H), 2.06-1.98 (m, 1H), 1.85-1.78 (m, 1H), 1.76-1.68 (n, 1H), 1.57-1.48 (m, 1H), 1.43-1.32 (m, 1H).
D130	LCMS (ESI) m/z: [M + H] ⁺ = 823.25	¹ H NMR (300 MHz, Methanol-d4) δ 7.63 (d, J = 8.5 Hz, 1H), 7.43 (d, J = 2.6 Hz, 1H), 7.28 (dd, J = 5.9, 2.1 Hz, 2H), 7.20 (d, J = 8.4 Hz, 1H), 6.56 (s, 2H), 5.09 (dd, J = 12.3, 5.4 Hz, 1H), 4.68-4.57 (m, 1H), 4.41-4.14 (m, 2H), 3.88 (d, J = 1.1 Hz, 6H), 3.72-3.60 (m, 3H), 3.59-3.49 (m, 4H), 3.30-3.18 (m, 4H), 3.06-2.86 (m, 4H), 2.90-2.76 (m, 5H), 2.78-2.36 (m, 10H), 2.30-2.11 (m, 2H), 2.07-1.76 (m, 3H), 1.44-1.28 (m, 1H).
D131	712.49	
D132	767.52	
D133	746.3	
D134	774.3	¹ H NMR (400 MHz, DMSO-d6) δ 11.10 (s, 1H), 8.13 (s, 1H), 7.95-7.84 (m, 2H), 7.83 (s, 2H), 7.60 (s, 1H), 6.56 (s, 3H), 5.73 (s, 2H), 5.13 (dd, J = 12.7, 5.4 Hz, 1H), 4.19 (s, 2H), 3.47 (s, 4H), 3.38 (t, J = 5.6 Hz, 2H), 3.30 (d, J = 8.7 Hz, 1H), 3.28 (s, 4H), 2.87 (td, J = 16.8, 15.2, 5.3 Hz, 1H), 2.57 (d, J = 4.2 Hz, 4H), 2.51 (s, 1H), 2.18 (t, J = 10.0 Hz, 2H), 2.05 (dd, J = 10.4, 4.7 Hz, 1H), 1.94-1.84 (m, 2H), 1.54 (d, J = 5.9 Hz, 4H).
D135	762.4	¹ H NMR (400 MHz, DMSO-d6) δ 11.10 (s, 1H), 8.12 (s, 1H), 7.95-7.84 (m, 1H), 7.82 (dd, J = 7.4, 3.8 Hz, 2H), 7.60 (d, J = 7.0 Hz, 1H), 6.68 (s, 1H), 6.61 (d, J = 1.8 Hz, 2H), 6.56 (d, J = 4.3 Hz, 1H), 5.73 (s, 1H), 5.13 (dd, J = 12.8, 5.3 Hz, 1H), 4.19 (s, 2H), 3.86-3.78 (m, 7H), 3.48 (t, J = 3.1 Hz, 3H), 3.39 (t, J = 5.6 Hz, 2H), 3.24 (dd, J = 16.5, 8.3 Hz, 1H), 2.93-2.80 (m, 3H), 2.73 (s, 1H), 2.57 (dd, J = 4.2, 1.5 Hz, 4H), 2.38 (dt, J = 26.0, 9.7 Hz, 2H), 2.19 (dt, J = 20.1, 9.5 Hz, 2H), 2.08-2.00 (m, 1H), 1.95 (dd, J = 13.3, 7.0 Hz, 2H).
D136	LCMS (ESI) m/z: [M + H] ⁺ = 849.60	¹ H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.21 (s, 2H, FA), 7.64 (t, J = 4.1 Hz, 2H), 6.78 (d, J = 2.1 Hz, 1H), 6.68-6.57 (m, 4H), 5.05 (dd, J = 12.9, 5.4 Hz, 1H), 4.22 (s, 2H), 3.81 (s, 6H), 3.77-3.68 (m, 6H), 3.50 (s, 3H), 3.41 (t, J = 5.6 Hz, 2H), 2.98 (s, 2H), 2.94-2.83 (m, 1H), 2.63-2.52 (m, 7H), 2.47-2.19 (m, 6H), 2.10 (d, J = 7.0 Hz, 2H), 2.04-1.95 (m, 1H), 1.80-1.72 (m, 4H), 1.68 (d, J = 12.7 Hz, 2H), 1.61-1.50 (m, 1H), 1.23-1.10 (m, 2H).
D137	LCMS (ESI) m/z: [M + H] ⁺ = 832.40	¹ H NMR (400 MHz, DMSO-d6) δ 11.15 (s, 1H), 8.21 (s, 1H FA), 7.91 (dd, J = 7.6, 0.9 Hz, 1H), 7.88-7.81 (m, 2H), 7.63 (s, 1H), 6.66-6.51 (m, 3H), 5.17 (dd, J = 12.8, 5.4 Hz, 1H), 4.21 (s, 2H), 3.77 (s, 6H), 3.40 (t, J = 5.5 Hz, 4H), 2.94-2.85 (m, 1H), 2.77 (t, J = 6.8 Hz, 2H), 2.63-2.54 (m, 7H), 2.42 (s, 4H), 2.12-2.00 (m, 1H), 1.62-1.44 (m, 6H), 1.41 (s, 6H).
D138	LCMS (ESI) m/z: [M + H] ⁺ = 835.41	¹ H NMR (400 MHz, DMSO-d6) δ 11.09 (s, 1H), 8.25 (s, 1H, FA), 7.69 (d, J = 8.6 Hz, 1H), 7.64 (s, 1H), 7.35 (d, J = 2.3 Hz, 1H), 7.27 (dd, J = 12.9, 5.3 Hz, 1H), 4.22 (s, 2H), 4.00-3.92 (m, 1H), 3.92-3.78 (m, 8H), 3.50 (s, 5H), 3.47-3.38 (m, 9H), 3.13-3.05 (m, 1H), 2.94-2.82 (m, 2H), 2.63-2.55 (m, 5H), 2.44-2.24 (m, 4H), 2.07-1.99 (m, 1H), 1.95-1.72 (m, 3H), 1.66-1.49 (m, 3H), 1.41-1.30 (m, 1H).
D139	LCMS (ESI) m/z: [M + H] ⁺ = 824.50	¹ H NMR (300 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.18 (s, 2H, FA), 7.71-7.60 (m, 2H), 7.34 (d, J = 2.1 Hz, 1H), 7.29-7.22 (m, 1H), 6.62-6.55 (m, 3H), 5.07 (dd, J = 12.6, 5.3 Hz, 1H), 4.22 (s, 2H), 3.78 (s, 6H), 3.56-3.49 (m, 6H), 3.45-3.38 (m, 8H), 2.93-2.82 (m, 1H), 2.66-2.53 (m, 8H), 2.47-2.31 (m, 12H), 2.06-1.98 (m, 1H).

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Compound No.	LCMS	¹ H NMR
D140	LCMS (ESI) m/z: [M + H] ⁺ = 908.55.	¹ H NMR (300 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.15 (s, 1H, FA), 7.72-7.62 (m, 2H), 7.34 (d, J = 2.2 Hz, 1H), 7.26 (d, J = 8.8 Hz, 1H), 6.67-6.56 (m, 3H), 5.07 (dd, J = 12.7, 5.3 Hz, 1H), 4.22 (s, 2H), 3.84-3.73 (m, 8H), 3.60 (s, 2H), 3.50 (s, 3H), 3.46-3.38 (m, 9H), 2.95-2.83 (m, 1H), 2.76-2.65 (m, 3H), 2.64-2.53 (m, 9H), 2.40-2.23 (m, 6H), 2.17 (s, 2H), 2.08-1.98 (m, 1H), 1.91-1.80 (m, 2H), 1.67-1.51 (m, 4H).
D141	LCMS (ESI) m/z: [M + H] ⁺ = 851.51	¹ H NMR (400 MHz, DMSO-d6) δ 11.04 (s, 1H), 8.18 (s, 2H), 7.74-7.47 (m, 2H), 7.26 (d, J = 2.2 Hz, 1H), 7.19 (dd, J = 8.7, 2.3 Hz, 1H), 6.54 (s, 3H), 5.03 (dd, J = 12.9, 5.4 Hz, 1H), 4.19 (s, 2H), 3.99 (d, J = 13.0 Hz, 2H), 3.81 (s, 2H), 3.74 (s, 6H), 3.46 (s, 3H), 3.37 (d, J = 5.7 Hz, 2H), 2.95-2.83 (m, 3H), 2.57 (d, J = 4.3 Hz, 3H), 2.14 (t, J = 7.5 Hz, 2H), 2.03-1.95 (m, 1H), 1.75-1.64 (m, 4H), 1.07 (d, J = 5.7 Hz, 7H), 1.00 (d, J = 6.6 Hz, 2H).
D142	LCMS (ESI) m/z: [M + H] ⁺ = 707.34	¹ H NMR (400 MHz, DMSO-d6) δ 11.10 (s, 1H), 8.14 (s, 1H), 7.91-7.81 (m, 2H), 7.60 (s, 1H), 6.56 (d, J = 3.9 Hz, 3H), 5.13 (dd, J = 12.7, 5.4 Hz, 1H), 4.19 (s, 2H), 3.77 (s, 5H), 3.55 (s, 2H), 3.48 (d, J = 10.1 Hz, 5H), 3.37 (t, J = 5.7 Hz, 3H), 3.19-3.14 (m, 2H), 2.87 (ddd, J = 16.7, 13.6, 5.4 Hz, 1H), 2.67-2.59 (m, 1H), 2.57 (d, J = 4.2 Hz, 3H), 2.11-1.98 (m, 1H).
D143	LCMS (ESI) m/z: [M + H] ⁺ = 735.38	
D144	LCMS (ESI) m/z: [M + H] ⁺ = 821.5	¹ H NMR (300 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.22 (s, 1H, FA), 7.70-7.59 (m, 2H), 6.91 (d, J = 2.1 Hz, 1H), 6.81 (dd, J = 8.6, 2.2 Hz, 1H), 6.63-6.53 (m, 3H), 5.06 (dd, J = 12.6, 5.4 Hz, 1H), 4.21 (s, 2H), 4.00 (q, J = 8.5 Hz, 2H), 3.88-3.81 (m, 2H), 3.78 (s, 6H), 3.68-3.57 (m, 3H), 3.54-3.45 (m, 8H), 3.25-3.16 (m, 4H), 3.10 (q, J = 7.3 Hz, 2H), 2.95-2.81 (m, 1H), 2.62-2.55 (m, 6H), 2.26-2.17 (m, 2H), 2.07-1.96 (m, 1H).
D145	LCMS (ESI) m/z: [M + H] ⁺ = 851.65	¹ H NMR (300 MHz, Methanol-d4) δ 7.82-7.76 (m, 1H), 7.58 (s, 1H), 7.51 (d, J = 2.3 Hz, 1H), 7.38 (dd, J = 8.5, 2.2 Hz, 1H), 6.73 (s, 2H), 5.11 (dd, J = 12.4, 5.4 Hz, 1H), 4.37 (d, J = 4.6 Hz, 4H), 4.25 (d, J = 13.6 Hz, 2H), 3.96 (d, J = 3.5 Hz, 6H), 3.75-3.60 (m, 6H), 3.60-3.52 (m, 3H), 3.51-3.41 (m, 2H), 3.24-3.07 (m, 4H), 2.92-2.70 (m, 6H), 2.63 (s, 2H), 2.18-1.85 (m, 4H), 1.84-1.58 (m, 4H), 1.57-1.48 (m, 6H).
D146	LCMS (ESI) m/z: [M + H] ⁺ = 807.55.	¹ H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.17 (s, 1H, FA), 7.68 (d, J = 8.5 Hz, 1H), 7.63 (s, 1H), 7.34 (d, J = 2.2 Hz, 1H), 7.25 (dd, J = 8.7, 2.3 Hz, 1H), 6.66-6.56 (m, 3H), 5.07 (dd, J = 12.9, 5.4 Hz, 1H), 4.22 (s, 2H), 3.84 (s, 2H), 3.82 (s, 6H), 3.59 (s, 2H), 3.50 (s, 4H), 3.48 (s, 2H), 3.43-3.39 (m, 8H), 2.93-2.84 (m, 1H), 2.62-2.58 (m, 4H), 2.58-2.55 (m, 1H), 2.35 (t, J = 4.9 Hz, 4H), 2.27-2.19 (m, 2H), 2.06-1.99 (m, 1H), 1.95 (t, J = 10.1 Hz, 2H).
D147	LCMS (ESI) m/z: [M + H] ⁺ = 827.35	¹ H NMR (400 MHz, DMSO-d6) δ 11.09 (s, 1H), 8.15 (s, 1H, FA), 7.68 (d, J = 8.4 Hz, 1H), 7.64 (s, 1H), 7.34 (s, 1H), 7.25 (dd, J = 8.9, 2.3 Hz, 1H), 6.59 (s, 3H), 5.07 (dd, J = 12.8, 5.4 Hz, 1H), 4.22 (s, 2H), 3.79 (s, 6H), 3.57 (s, 2H), 3.50 (s, 3H), 3.46-3.37 (m, 10H), 2.94-2.82 (m, 1H), 2.65-2.55 (m, 11H), 2.38-2.30 (m, 2H), 2.06-1.98 (m, 1H), 1.81 (t, J = 12.2 Hz, 2H), 1.74-1.54 (m, 2H).
D148	LCMS (ESI) m/z: [M + H] ⁺ = 809.35	¹ H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.18 (s, 1H, FA), 7.68 (d, J = 8.5 Hz, 1H), 7.63 (s, 1H), 7.34 (d, J = 2.2 Hz, 1H), 7.26 (dd, J = 8.8, 2.3 Hz, 1H), 6.64 (s, 2H), 6.59 (q, J = 4.4 Hz, 1H), 5.07 (dd, J = 12.9, 5.4 Hz, 1H), 4.21 (s, 2H), 3.90 (s, 2H), 3.82 (s, 6H), 3.50 (s, 3H), 3.44-3.39 (m, 8H), 3.37-3.28 (m, 5H), 3.08 (t, J = 8.9 Hz, 2H), 2.94-2.80 (m, 3H), 2.62-2.56 (m, 4H), 2.30 (t, J = 7.2 Hz, 2H), 2.21-2.13 (m, 1H), 2.06-1.94 (m, 2H), 1.61-1.49 (m, 2H), 1.48-1.39 (m, 1H).
D149	LCMS (ESI) m/z: [M + H] ⁺ = 824.75	¹ H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 8.23 (s, 2H, FA), 7.83 (dd, J = 8.2, 2.8 Hz, 1H), 7.63 (s, 1H), 7.34-7.23 (m, 2H), 6.66-6.57 (m, 3H), 5.12 (dd, J = 12.9, 5.4 Hz, 1H), 4.98-4.90 (m, 1H), 4.69 (p, J = 7.1 Hz, 1H), 4.22 (s, 2H), 3.80 (d, J = 4.7 Hz, 6H), 3.71 (s, 2H), 3.50 (s, 3H), 3.40 (t, J = 5.5 Hz, 2H), 3.01-2.92 (m, 2H), 2.92-2.84 (m, 1H), 2.74-2.68 (m, 1H), 2.65-2.57 (m, 4H), 2.56-2.52 (m, 2H), 2.42-2.25 (m, 3H), 2.22-2.14 (m, 1H), 2.10-1.98 (m, 6H), 1.93-1.57 (m, 4H), 1.49 (s, 1H), 1.25-1.07 (m, 2H).
D150	LCMS (ESI) m/z: [M + H] ⁺ = 769.45	¹ H NMR (400 MHz, DMSO-d6) δ 11.09 (s, 1H), 8.21 (s, 2H, FA), 7.68 (d, J = 8.5 Hz, 1H), 7.64 (s, 1H), 7.34 (d, J = 2.2 Hz, 1H), 7.26 (dd, J = 8.7, 2.3 Hz, 1H), 6.66 (t, J = 5.5 Hz, 1H), 6.60 (s, 2H), 5.08 (dd, J = 12.9, 5.4 Hz, 1H), 4.23 (s, 2H), 3.79 (s, 6H), 3.54 (s, 2H), 3.50 (s, 3H), 3.46-3.39 (m, 7H), 3.22 (q, J = 6.5 Hz, 3H), 2.93-2.83 (m, 1H), 2.64-2.53 (m, 6H), 2.43 (t, J = 7.1 Hz, 2H), 2.21 (s, 6H), 2.06-1.98 (m, 1H).
D151	LCMS (ESI) m/z: [M + H] ⁺ = 839.55	¹ H NMR (300 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.15 (s, 2H), 7.68 (d, J = 8.5 Hz, 1H), 7.63 (s, 1H), 7.34 (d, J = 2.2 Hz, 1H), 7.25 (dd, J = 8.6, 2.2 Hz, 1H), 6.59 (s, 3H), 5.08 (dd, J = 12.7, 5.3 Hz, 1H), 4.21 (s, 2H),

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Compound No.	LCMS m/z:	¹ H NMR
D152	LCMS (ESI) [M + H] ⁺ = 825.70.	¹ H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.14 (s, 1H, FA), 7.68 (d, J = 8.5 Hz, 1H), 7.63 (s, 1H), 7.35 (s, 1H), 7.26 (dd, J = 8.7, 2.3 Hz, 1H), 6.62 (s, 2H), 6.61-6.57 (m, 1H), 5.08 (dd, J = 12.9, 5.3 Hz, 1H), 4.21 (s, 2H), 3.81 (s, 6H), 3.78-3.73 (m, 1H), 3.65 (s, 2H), 3.50 (s, 4H), 3.47-3.42 (m, 6H), 3.42-3.37 (m, 5H), 2.95-2.82 (m, 2H), 2.74-2.69 (m, 1H), 2.60 (d, J = 4.3 Hz, 5H), 2.58-2.54 (m, 4H), 2.31-2.21 (m, 1H), 2.12-1.97 (m, 2H), 1.68-1.51 (m, 2H).
D153	LCMS (ESI) [M + H] ⁺ = 835.60.	¹ H NMR (400 MHz, Methanol-d4) δ 8.49 (s, 2H, FA), 7.74 (dd, J = 16.5, 8.4 Hz, 1H), 7.57 (s, 1H), 7.27 (s, 1H), 7.13 (d, J = 8.8 Hz, 1H), 6.70 (s, 2H), 5.11 (dd, J = 12.7, 5.4 Hz, 1H), 4.34 (d, J = 11.5 Hz, 4H), 4.05-3.88 (m, 8H), 3.78 (d, J = 12.0 Hz, 2H), 3.71-3.61 (m, 5H), 3.57-3.40 (m, 5H), 3.12-2.99 (m, 2H), 2.89-2.68 (m, 9H), 2.62 (s, 3H), 2.18-2.09 (m, 1H), 1.93 (d, J = 13.8 Hz, 2H), 1.84-1.78 (m, 1H), 1.73-1.63 (m, 1H), 1.52 (s, 3H), 1.39-1.27 (m, 1H).
D154	LCMS (ESI) [M + H] ⁺ = 859.75.	¹ H NMR (300 MHz, Methanol-d4) δ 8.51 (s, 2H), 7.70 (d, J = 8.5 Hz, 1H), 7.57 (s, 1H), 7.37 (d, J = 2.2 Hz, 1H), 7.25 (dd, J = 8.6, 2.3 Hz, 1H), 6.72 (s, 2H), 5.09 (dd, J = 12.3, 5.4 Hz, 1H), 4.37 (d, J = 9.4 Hz, 4H), 3.95 (s, 6H), 3.70-3.62 (m, 4H), 3.60-3.45 (m, 7H), 3.18 (t, J = 12.6 Hz, 2H), 2.95-2.69 (m, 12H), 2.68-2.59 (m, 2H), 2.58-2.46 (m, 1H), 2.19-2.07 (m, 3H), 2.03-1.86 (m, 2H).
D155	LCMS (ESI) [M + H] ⁺ = 859.50.	¹ H NMR (300 MHz, Methanol-d4) δ 7.79 (d, J = 8.4 Hz, 1H), 7.59 (s, 1H), 7.50 (d, J = 2.1 Hz, 1H), 7.41-7.34 (m, 1H), 6.75 (s, 2H), 5.12 (dd, J = 12.4, 5.4 Hz, 1H), 4.50 (s, 2H), 4.36 (s, 2H), 3.96 (s, 6H), 3.94 (3.74 (m, 3H), 3.70-3.62 (m, 5H), 3.61-3.39 (m, 8H), 3.39-3.35 (m, 2H), 3.23-3.19 (m, 1H), 2.87-2.71 (m, 6H), 2.68-2.61 (m, 2H), 2.40-2.21 (m, 3H), 2.18-2.09 (m, 1H), 1.96-1.80 (m, 2H).
D156	737.88	
D157	723.39	
D158	738.37	
D159	751.46	
D161	751.39	NA
D162	751.32	NA
D163	765.39	NA
D164	766.4	¹ H NMR (400 MHz, DMSO-d6) δ 11.04 (s, 1H), 8.13 (s, 1H), 7.65-7.57 (m, 2H), 6.75 (d, J = 2.1 Hz, 1H), 6.61 (dd, J = 8.4, 2.1 Hz, 1H), 6.56 (s, 2H), 6.54 (d, J = 4.5 Hz, 1H), 5.03 (dd, J = 12.9, 5.4 Hz, 1H), 4.19 (s, 2H), 4.05 (t, J = 7.7 Hz, 2H), 3.80 (dd, J = 8.9, 4.9 Hz, 2H), 3.76 (s, 5H), 3.54 (s, 2H), 3.47 (s, 3H), 3.37 (s, 1H), 3.25 (q, J = 5.9 Hz, 1H), 3.15 (s, 1H), 2.86 (ddd, J = 17.6, 13.9, 5.4 Hz, 1H), 2.61-2.50 (m, 4H), 2.47-2.42 (m, 4H), 2.34-2.29 (m, 4H), 1.99 (dp, J = 12.2, 4.6, 4.0 Hz, 1H).
D165	737.4	¹ H NMR (400 MHz, DMSO-d6) δ 11.03 (s, 1H), 8.15 (s, 1H), 7.61 (d, J = 8.8 Hz, 2H), 6.76 (d, J = 2.1 Hz, 1H), 6.62 (dd, J = 8.4, 2.1 Hz, 1H), 6.57 (s, 2H), 6.54 (dd, J = 5.8, 3.3 Hz, 1H), 5.03 (dd, J = 12.9, 5.4 Hz, 1H), 4.19 (s, 2H), 3.90 (q, J = 8.4 Hz, 4H), 3.77 (s, 6H), 3.47 (s, 3H), 3.38 (t, J = 5.5 Hz, 2H), 3.15 (s, 1H), 3.10 (s, 0H), 2.86 (ddd, J = 17.4, 13.9, 5.5 Hz, 1H), 2.77 (s, 2H), 2.61-2.48 (m, 6H), 2.05-1.93 (m, 3H).
D166	737.4	¹ H NMR (400 MHz, DMSO-d6) δ 11.04 (s, 1H), 8.13 (s, 1H), 7.65-7.58 (m, 2H), 6.80 (d, J = 2.0 Hz, 1H), 6.72 (dd, J = 8.3, 2.0 Hz, 1H), 6.56 (d, J = 12.0 Hz, 3H), 5.03 (dd, J = 12.9, 5.4 Hz, 1H), 4.28 (dt, J = 8.3, 4.2 Hz, 1H), 4.19 (s, 2H), 3.77 (s, 6H), 3.78-3.66 (m, 2H), 3.47 (s, 3H), 3.38 (t, J = 5.6 Hz, 2H), 3.15 (s, 1H), 2.96-2.79 (m, 2H), 2.72 (s, 1H), 2.57 (d, J = 4.3 Hz, 4H), 2.51 (s, 1H), 2.45 (s, 0H), 2.03-1.85 (m, 2H).
D167	LCMS (ESI) m/z: [M + H] ⁺ = 807.	¹ H NMR (300 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.24 (s, 2H, FA), 7.69-7.59 (m, 2H), 6.89 (d, J = 2.1 Hz, 1H), 6.80 (dd, J = 8.6, 2.2 Hz, 1H), 6.60 (s, 3H), 5.05 (dd, J = 12.5, 5.4 Hz, 1H), 4.21 (s, 2H), 3.79 (s, 6H), 3.70-3.63 (m, 4H), 3.54-3.47 (m, 7H), 3.43-3.37 (m, 6H), 3.18-3.10 (m, 4H), 3.04 (s, 2H), 2.91-2.82 (m, 1H), 2.63-2.56 (m, 5H), 2.39-2.31 (m, 1H), 2.15 (t, J = 6.8 Hz, 2H), 2.06-1.95 (m, 1H).
D168	LCMS (ESI) m/z: [M + H] ⁺ = 981.35.	¹ H NMR (400 MHz, DMSO-d6) δ 11.09 (s, 1H), 7.69 (d, J = 8.5 Hz, 1H), 7.64 (s, 1H), 7.35 (d, J = 2.3 Hz, 1H), 7.26 (dd, J = 8.7, 2.3 Hz, 1H), 6.69 (s, 2H), 6.60 (q, J = 4.4 Hz, 1H), 5.08 (dd, J = 12.9, 5.4 Hz, 1H), 4.22 (s, 2H), 4.14 (s, 2H), 4.00-3.91 (m, 2H), 3.86 (s, 6H), 3.70-3.56 (m, 2H), 3.50 (s, 3H), 3.45-3.39 (m, 6H), 2.94-2.83 (m, 2H), 2.63-2.56 (m, 6H), 2.50-2.42 (m, 7H), 2.06-1.97 (m, 1H).
D169	LCMS (ESI) m/z: [M + H] ⁺ = 795.35.	¹ H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.21 (s, 1H, FA), 7.68 (d, J = 8.5 Hz, 1H), 7.63 (s, 1H), 7.34 (d, J = 2.3 Hz, 1H), 7.26 (dd, J = 8.7, 2.3 Hz, 1H), 6.64-6.54 (m, 3H), 5.07 (dd, J = 12.9, 5.4 Hz, 1H), 4.22 (s, 2H), 3.80 (s, 6H), 3.73 (s, 2H), 3.50 (s, 4H), 3.45-3.37 (m, 8H), 2.95-2.79 (m, 2H), 2.66-2.56 (m, 6H), 2.49-2.44 (m, 3H),

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Compound No.	LCMS	¹ H NMR
D170	LCMS (ESI) m/z: [M + H] ⁺ = 795.35	2.40-2.32 (m, 3H), 2.31-2.26 (m, 2H), 2.07-1.96 (m, 1H), 1.91-1.81 (m, 1H), 1.46-1.34 (m, 1H). ¹ H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.19 (s, 1H, FA), 7.68-7.61 (m, 2H), 7.32 (d, J = 2.3 Hz, 1H), 7.24 (dd, J = 8.7, 2.3 Hz, 1H), 6.58 (s, 3H), 5.07 (dd, J = 12.9, 5.4 Hz, 1H), 4.21 (s, 2H), 4.04 (d, J = 12.7 Hz, 2H), 3.77 (s, 6H), 3.51 (d, J = 11.7 Hz, 6H), 3.40 (t, J = 5.6 Hz, 4H), 2.98-2.86 (m, 3H), 2.63-2.55 (m, 5H), 2.48-2.37 (m, 8H), 2.06-1.97 (m, 1H), 1.83 (d, J = 12.1 Hz, 2H), 1.43 (q, J = 11.7, 11.0 Hz, 2H).
D171	LCMS (ESI) m/z: [M + H] ⁺ = 823.55	¹ H NMR (300 MHz, Methanol-d4) δ 7.73 (d, J = 8.2 Hz, 1H), 7.57 (s, 1H), 6.96 (d, J = 2.1 Hz, 1H), 6.81 (dd, J = 8.2, 2.1 Hz, 1H), 6.73 (d, J = 4.1 Hz, 2H), 5.09 (dd, J = 12.3, 5.4 Hz, 1H), 4.50-4.20 (m, 9H), 3.96 (d, J = 4.8 Hz, 6H), 3.64 (s, 3H), 3.62-3.52 (m, 4H), 3.25-3.02 (m, 4H), 2.96-2.82 (m, 4H), 2.81-2.69 (m, 5H), 2.67-2.60 (m, 2H), 2.18-1.86 (m, 4H), 1.80-1.52 (m, 4H).
D172	LCMS (ESI) m/z: [M + H] ⁺ = 835.80	¹ H NMR (300 MHz, Methanol-d4) δ 8.45 (s, 2H, FA), 7.68 (d, J = 8.4 Hz, 1H), 7.58 (s, 1H), 7.09 (d, J = 2.1 Hz, 1H), 6.94 (dd, J = 8.5, 2.2 Hz, 1H), 6.71 (s, 2H), 5.08 (dd, J = 12.4, 5.4 Hz, 1H), 4.74 (s, 1H), 4.35 (s, 4H), 4.14 (s, 1H), 3.93 (s, 6H), 3.71-3.60 (m, 5H), 3.58-3.44 (m, 4H), 3.24 (d, J = 10.4 Hz, 1H), 3.16-3.01 (m, 3H), 2.97-2.70 (m, 8H), 2.63 (t, J = 5.7 Hz, 2H), 2.28-2.07 (m, 3H), 1.96 (d, J = 13.4 Hz, 2H), 1.75-1.49 (m, 5H).
D173	LCMS (ESI) m/z: [M + H] ⁺ = 851.40	¹ H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.20 (s, 2H, FA), 7.69-7.61 (m, 2H), 7.27 (d, J = 2.2 Hz, 1H), 7.21 (dd, J = 8.8, 2.4 Hz, 1H), 6.69-6.54 (m, 3H), 5.07 (dd, J = 12.9, 5.4 Hz, 1H), 4.22 (s, 2H), 4.03-3.93 (m, 3H), 3.79 (s, 7H), 3.63 (s, 3H), 3.50 (s, 3H), 3.40 (t, J = 5.5 Hz, 2H), 2.99-2.84 (m, 5H), 2.59 (d, J = 4.3 Hz, 3H), 2.58-2.53 (m, 4H), 2.25 (s, 3H), 2.23-2.15 (m, 2H), 2.06-1.97 (m, 1H), 1.88-1.71 (m, 2H), 1.63 (d, J = 12.5 Hz, 2H), 1.56-1.43 (m, 2H), 1.31 (s, 3H), 1.21-1.07 (m, 2H).
D174	LCMS (ESI) m/z: [M + H] ⁺ = 849.35	¹ H NMR (300 MHz, DMSO-d6) δ 11.09 (s, 1H), 8.18 (s, 1H, FA), 7.68 (d, J = 8.5 Hz, 1H), 7.62 (s, 1H), 7.34 (d, J = 2.2 Hz, 1H), 7.25 (dd, J = 8.7, 2.0 Hz, 1H), 6.59 (s, 3H), 5.07 (dd, J = 12.8, 5.4 Hz, 1H), 4.21 (s, 2H), 3.78 (s, 6H), 3.60-3.37 (m, 15H), 2.96-2.80 (m, 4H), 2.63-2.53 (m, 6H), 2.20 (s, 2H), 2.13-1.95 (m, 3H), 1.60-1.50 (m, 2H), 1.45-1.31 (m, 2H), 1.28-1.13 (m, 1H), 0.39 (s, 2H), 0.17 (s, 2H).
D175	LCMS (ESI) m/z: [M + H] ⁺ = 922.35	¹ H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.19 (s, 1H, FA), 7.70-7.66 (m, 1H), 7.63 (d, J = 2.7 Hz, 1H), 7.35 (s, 1H), 7.26 (t, J = 7.9 Hz, 1H), 6.62-6.56 (m, 3H), 5.07 (dd, J = 13.0, 5.4 Hz, 1H), 4.21 (s, 2H), 3.77 (d, J = 2.7 Hz, 6H), 3.61 (s, 2H), 3.57-3.52 (m, 4H), 3.50-3.47 (m, 4H), 3.44-3.40 (m, 7H), 3.34-3.30 (m, 3H), 2.94-2.84 (m, 1H), 2.63-2.58 (m, 6H), 2.57-2.54 (m, 5H), 2.48-2.41 (m, 3H), 2.41-2.23 (m, 2H), 2.06-1.97 (m, 1H), 1.72-1.58 (m, 2H), 1.56-1.41 (m, 2H).
D176	792.29	¹ H NMR (400 MHz, DMSO-d6) δ 11.10 (d, J = 15.8 Hz, 1H), 8.14 (s, 2H), 7.78 (d, J = 16.8 Hz, 2H), 7.60 (s, 1H), 6.57 (d, J = 15.8 Hz, 3H), 5.20-4.89 (m, 2H), 4.19 (s, 2H), 3.96 (s, 3H), 3.79 (d, J = 3.5 Hz, 7H), 3.48 (s, 3H), 2.57 (d, J = 4.2 Hz, 3H), 1.88-1.64 (m, 1H), 1.45-1.24 (m, 2H).
D177	764.92	
D178	794.46	
D179	LCMS (ESI) m/z: [M + H] ⁺ = 780.46	
D180	LCMS (ESI) m/z: [M + H] ⁺ = 766.39	
D181	LCMS (ESI) m/z: [M + H] ⁺ = 820.5	
D182	LCMS (ESI) m/z: [M + H] ⁺ = 792.91	
D183	LCMS (ESI) m/z: [M + H] ⁺ = 767.92	
D184	LCMS (ESI) m/z: [M + H] ⁺ = 781.45	¹ H NMR (300 MHz, DMSO-d6) δ 11.06 (s, 1H), 8.20 (s, 2H, FA), 7.79-7.50 (m, 2H), 6.76 (d, J = 2.0 Hz, 1H), 6.67 (d, J = 7.8 Hz, 1H), 6.62 (s, 2H), 5.05 (dd, J = 12.6, 5.4 Hz, 1H), 4.88 (t, J = 5.4 Hz, 1H), 4.24 (s, 2H), 4.21-4.10 (m, 1H), 4.00 (d, J = 9.7 Hz, 1H), 3.80 (s, 6H), 3.75-3.59 (m, 4H), 3.51 (s, 4H), 3.46-3.37 (m, 3H), 3.20 (d, J = 6.2 Hz, 2H), 3.08 (t, J = 8.0 Hz, 1H), 2.98-2.80 (m, 1H), 2.71-2.59 (m, 3H), 2.58-2.54 (m, 2H), 2.29 (s, 6H), 2.08-1.91 (m, 2H), 1.76 (d, J = 12.4 Hz, 1H).

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Compound No.	LCMS	¹ H NMR
D185	LCMS (ESI) m/z: [M + H] ⁺ = 795.25	
D186	LCMS (ESI) m/z: [M + H] ⁺ = 867.6	
D187	LCMS (ESI) m/z: [M + H] ⁺ = 795.55	¹ H NMR (300 MHz, DMSO-d6) δ 11.06 (s, 1H), 8.22 (s, 3H, FA), 7.66-6.64-6.56 (m, 3H), 5.05 (dd, J = 12.8, 5.4 Hz, 1H), 4.40-4.31 (m, 1H), 4.22 (s, 2H), 3.80 (s, 8H), 3.62 (s, 2H), 3.50 (s, 3H), 3.41 (t, J = 5.5 Hz, 2H), 3.20 (d, J = 6.7 Hz, 2H), 2.96-2.77 (m, 3H), 2.63-2.53 (m, 6H), 2.44 (t, J = 6.5 Hz, 3H), 2.31-2.25 (m, 6H), 2.07-1.90 (m, 3H).
D188	LCMS (ESI) m/z: [M + H] ⁺ = 809.65	
D189	LCMS (ESI) m/z: [M + H] ⁺ = 795.6	¹ H NMR (300 MHz, DMSO-d6) δ 11.06 (s, 1H), 8.23 (s, 3H, FA), 7.76-7.55 (m, 2H), 6.79 (d, J = 2.1 Hz, 1H), 6.71-6.60 (m, 2H), 6.60 (s, 2H), 5.06 (dd, J = 12.7, 5.3 Hz, 1H), 4.23 (s, 2H), 4.06-3.87 (m, 4H), 3.79 (s, 6H), 3.51 (s, 5H), 3.47-3.37 (m, 2H), 3.24-3.13 (m, 2H), 2.98-2.75 (m, 4H), 2.68-2.51 (m, 7H), 2.19 (s, 6H), 2.04 (q, J = 12.6, 9.6 Hz, 3H).
D190	LCMS (ESI) m/z: [M + H] ⁺ = 809.65	
D191	LCMS (ESI) m/z: [M + H] ⁺ = 809.45	
D192	LCMS (ESI) m/z: [M + H] ⁺ = 781.7	
D193	LCMS (ESI) m/z: [M + H] ⁺ = 936.55	
D194	LCMS (ESI) m/z: [M + H] ⁺ = 824.35	¹ H NMR (300 MHz, DMSO-d6) δ 11.10 (s, 1H), 8.19 (s, 2H, FA), 7.83 (d, J = 8.3 Hz, 1H), 7.64 (s, 1H), 7.42 (d, J = 2.2 Hz, 1H), 7.34 (dd, J = 8.3, 2.3 Hz, 1H), 6.68 (t, J = 5.7 Hz, 1H), 6.61 (s, 2H), 5.12 (dd, J = 12.9, 5.4 Hz, 1H), 4.25-4.13 (m, 4H), 3.80 (s, 6H), 3.63 (s, 3H), 3.50 (s, 4H), 3.40 (t, J = 5.5 Hz, 2H), 3.30 (s, 2H), 3.24 (s, 2H), 3.03 (t, J = 6.2 Hz, 2H), 2.96-2.81 (m, 1H), 2.66-2.55 (m, 4H), 2.28 (s, 7H), 2.15-2.03 (m, 3H), 1.86-1.71 (m, 4H)
D195	LCMS (ESI) m/z: [M + H] ⁺ = 837.65	¹ H NMR (300 MHz, DMSO-d6) δ 11.07 (s, 1H), 8.15 (s, 1H), 7.67 (d, J = 8.5 Hz, 1H), 7.63 (s, 1H), 7.32 (d, J = 2.2 Hz, 1H), 7.25 (dd, J = 8.6, 5.4 Hz, 1H), 6.69 (s, 2H), 6.59 (q, J = 4.4 Hz, 1H), 5.06 (dd, J = 12.8, 3.48 (m, 7H), 3.03-2.89 (m, 4H), 2.86-2.67 (m, 4H), 2.63-2.57 (m, 4H), 2.31-2.25 (m, 2H), 2.21 (s, 3H), 2.10-1.95 (m, 2H), 1.85-1.71 (m, 4H), 1.69-1.59 (m, 1H), 1.54-1.40 (m, 2H), 1.37-1.23 (m, 2H).
D196	LCMS (ESI) m/z: [M + H] ⁺ = 849.60	¹ H NMR (300 MHz, DMSO-d6) δ 11.07 (s, 1H), 8.18 (s, 2H, FA), 7.69-7.61 (m, 2H), 6.95 (d, J = 2.1 Hz, 1H), 6.86 (dd, J = 8.6, 2.2 Hz, 1H), 6.64-6.55 (m, 3H), 5.06 (dd, J = 12.6, 5.4 Hz, 1H), 4.21 (s, 2H), 3.79 (s, 6H), 3.70-3.61 (m, 4H), 3.50 (s, 3H), 3.40 (t, J = 5.6 Hz, 2H), 3.30 (dd, J = 11.0, 2.6 Hz, 2H), 3.00-2.91 (m, 4H), 2.91-2.76 (m, 2H), 2.65-2.52 (m, 10H), 2.44-2.38 (m, 2H), 2.32-2.23 (m, 2H), 2.04-1.94 (m, 1H), 1.63 (d, J = 12.2 Hz, 2H), 1.38-1.12 (m, 5H).
D197	LCMS (ESI) m/z: [M + H] ⁺ = 837.42	¹ H NMR (300 MHz, DMSO-d6) δ 11.06 (s, 1H), 8.19 (s, 2H, FA), 7.68-7.61 (m, 2H), 6.95 (d, J = 2.1 Hz, 1H), 6.87-6.81 (m, 1H), 6.59 (s, 3H), 5.06 (dd, J = 12.4, 5.4 Hz, 1H), 4.22 (s, 2H), 3.78 (s, 6H), 3.66-3.53 (m, 5H), 3.50 (s, 4H), 3.41 (s, 2H), 3.21-3.10 (m, 4H), 2.90-2.80 (m, 3H), 2.60 (d, J = 4.2 Hz, 3H), 2.43-2.39 (m, 2H), 2.18 (s, 3H), 2.13-1.98 (m, 4H), 1.90-1.79 (m, 1H), 1.62 (d, J = 11.9 Hz, 2H), 1.38-1.04 (m, 6H).
D198	LCMS (ESI) m/z: [M + H] ⁺ = 837.65	¹ H NMR (400 MHz, DMSO-d6) δ 11.07 (s, 1H), 8.20 (s, 2H, FA), 7.66-7.61 (m, 2H), 7.11 (d, J = 2.3 Hz, 1H), 7.03 (dd, J = 8.8, 2.4 Hz, 1H), 6.63-6.57 (m, 3H), 5.06 (dd, J = 12.9, 5.4 Hz, 1H), 4.22 (s, 2H), 3.79 (s, 6H), 3.69-3.59 (m, 7H), 3.50 (s, 3H), 3.40 (t, J = 5.5 Hz, 2H), 2.99-2.80 (m, 4H), 2.73 (t, J = 5.1 Hz, 2H), 2.62-2.54 (m, 6H), 2.44 (t, J = 7.2 Hz, 2H), 2.19 (t, J = 11.0 Hz, 2H), 2.06-1.95 (m, 1H), 1.85 (p, J = 6.2, 5.6 Hz, 2H), 1.59 (d, J = 11.9 Hz, 2H), 1.38-1.01 (m, 6H).
D199	LCMS (ESI) m/z: [M + H] ⁺ = 835.60	¹ H NMR (300 MHz, Methanol-d4) δ 8.54 (s, 1H), 7.66 (d, J = 8.3 Hz, 1H), 7.58 (s, 1H), 6.84 (d, J = 2.1 Hz, 1H), 6.74-6.66 (m, 3H), 5.07 (dd, J = 12.3, 5.4 Hz, 1H), 4.36 (s, 2H), 4.33 (s, 2H), 4.17 (s, 4H), 3.95 (s, 6H), 3.71-3.62 (m, 4H), 3.60-3.52 (m, 6H), 3.51-3.42 (m, 2H),

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Compound No.	LCMS	¹ H NMR
D200	LCMS (ESI) m/z: [M + H] ⁺ = 851.95	¹ H NMR (300 MHz, DMSO-d6) δ 11.06 (s, 1H), 8.16 (s, 1H, FA), 7.69-3.12-2.99 (m, 2H), 2.88-2.71 (m, 6H), 2.68-2.59 (m, 4H), 2.17-2.07 (m, 1H), 1.95 (d, J = 13.5 Hz, 2H), 1.73-1.53 (m, 2H), 1.46-1.36 (m, 2H).
D201	LCMS (ESI) m/z: [M + H] ⁺ = 795.75	¹ H NMR (300 MHz, DMSO-d6) δ 11.07 (s, 1H), 8.19 (s, 1H, FA), 7.67 (d, J = 8.5 Hz, 1H), 7.63 (s, 1H), 7.33 (d, J = 2.1 Hz, 1H), 7.24 (dd, J = 8.7, 2.3 Hz, 1H), 6.64-6.54 (m, 3H), 5.07 (dd, J = 12.7, 5.4 Hz, 1H), 4.22 (s, 2H), 4.10 (d, J = 13.0 Hz, 2H), 3.80 (s, 6H), 3.69 (s, 2H), 3.50 (s, 3H), 3.44-3.37 (m, 5H), 3.00-2.87 (m, 5H), 2.84-2.66 (m, 2H), 2.63-2.56 (m, 4H), 2.47-2.44 (m, 1H), 2.30-2.17 (m, 5H), 2.06-1.98 (m, 1H), 1.79 (d, J = 12.3 Hz, 2H), 1.65 (d, J = 12.3 Hz, 2H), 1.55-1.41 (m, 2H), 1.39-1.16 (m, 5H).
D202	LCMS (ESI) m/z: [M + H] ⁺ = 894.55	¹ H NMR (300 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.14 (s, 1H, FA), 7.70 (d, J = 8.5 Hz, 1H), 7.64 (s, 1H), 7.35 (d, J = 2.3 Hz, 1H), 7.27 (dd, J = 8.8, 2.2 Hz, 1H), 6.72 (s, 2H), 6.60 (q, J = 4.2 Hz, 1H), 5.08 (dd, J = 12.7, 5.4 Hz, 1H), 4.28-4.11 (m, 4H), 3.87 (s, 6H), 3.64 (s, 2H), 3.51 (s, 3H), 3.49-3.40 (m, 9H), 3.15-3.00 (m, 4H), 2.97-2.82 (m, 2H), 2.65-2.54 (m, 10H), 2.47-2.28 (m, 6H), 2.12-1.96 (m, 3H), 1.85-1.54 (m, 2H).
D203	LCMS (ESI) m/z: [M + H] ⁺ = 868.50	¹ H NMR (300 MHz, DMSO-d6) δ 11.11 (s, 1H), 8.17 (s, 1H FA), 7.84 (dd, J = 8.4, 4.2 Hz, 1H), 7.63 (d, J = 3.5 Hz, 1H), 7.43 (s, 1H), 7.36 (d, J = 8.4 Hz, 1H), 6.65-6.53 (m, 3H), 5.12 (dd, J = 12.9, 5.4 Hz, 1H), 4.25-4.15 (m, 4H), 3.79 (d, J = 3.3 Hz, 6H), 3.69-3.54 (m, 5H), 3.50 (s, 3H), 3.45-3.29 (m, 8H), 2.97-2.83 (m, 1H), 2.65-2.54 (m, 7H), 2.47-2.32 (m, 3H), 2.07-1.93 (m, 3H), 1.75-1.60 (m, 2H), 1.59-1.44 (m, 2H).
D204	853.65	
D205	LCMS (ESI) m/z: [M + H] ⁺ = 837.75	¹ H NMR (300 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.19 (s, 2H, FA), 7.68-7.62 (m, 2H), 7.31 (d, J = 2.2 Hz, 1H), 7.23 (dd, J = 8.7, 2.3 Hz, 1H), 6.66 (t, J = 5.1 Hz, 1H), 6.60 (s, 2H), 5.07 (dd, J = 12.7, 5.4 Hz, 1H), 4.22 (s, 2H), 4.12-4.01 (m, 2H), 3.79 (s, 6H), 3.59 (s, 2H), 3.50 (s, 3H), 3.41 (t, J = 5.4 Hz, 4H), 3.22-3.13 (m, 4H), 2.95-2.81 (m, 4H), 2.65-2.55 (m, 3H), 2.25 (s, 8H), 2.05-1.96 (m, 1H), 1.89-1.67 (m, 4H), 1.53-1.36 (m, 2H), 1.27-1.12 (m, 2H).
D206	LCMS (ESI) m/z: [M + H] ⁺ = 867.65	
D207	LCMS (ESI) m/z: [M + H] ⁺ = 809.7	¹ H NMR (300 MHz, DMSO-d6) δ 11.06 (s, 1H), 8.24 (s, 2H, FA), 7.64 (d, J = 5.9 Hz, 2H), 6.96-6.41 (m, 5H), 5.20-4.86 (m, 1H), 4.46-4.12 (m, 2H), 3.96 (t, J = 6.6 Hz, 6H), 3.79 (s, 6H), 3.65-3.30 (m, 9H), 3.11 (d, J = 6.9 Hz, 2H), 2.77 (s, 4H), 2.23 (s, 6H), 2.15-1.92 (m, 3H), 1.75-1.55 (m, 2H), 1.25-0.97 (m, 3H).
D208	LCMS (ESI) m/z: [M + H] ⁺ = 823.6	
D209	LCMS (ESI) m/z: [M + H] ⁺ = 823.45	
D210	LCMS (ESI) m/z: [M + H] ⁺ = 809.45	
D211	LCMS (ESI) m/z: [M + H] ⁺ = 795.55	
D212	LCMS (ESI) m/z: [M + H] ⁺ = 809.35	
D213	LCMS (ESI) m/z: [M + H] ⁺ = 840.4	
D214	LCMS (ESI) m/z: [M + H] ⁺ = 920.4	
D215	LCMS (ESI) m/z: [M + H] ⁺ = 824.4	
D216	LCMS (ESI) m/z: [M + H] ⁺ = 920.4	

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Compound No.	LCMS	¹ H NMR
D217	LCMS (ESI) m/z: [M + H] ⁺ = 950.5	
D218	LCMS (ESI) m/z: [M + H] ⁺ = 934.55	
D219	LCMS (ESI) m/z: [M + H] ⁺ = 906.5	
D220	LCMS (ESI) m/z: [M + H] ⁺ = 920.5	¹ H NMR (300 MHz, Methanol-d4) δ 8.47 (s, 2H, FA), 7.71-7.57 (m, 2H), 7.36 (s, 1H), 7.24 (d, J = 8.6 Hz, 1H), 6.71 (s, 2H), 5.07 (dd, J = 12.3, 5.4 Hz, 1H), 4.38 (s, 4H), 4.10 (t, J = 9.0 Hz, 1H), 3.95 (s, 6H), 3.63 (s, 4H), 3.51 (s, 5H), 3.45-3.39 (m, 1H), 3.23-3.04 (m, 4H), 3.01-2.81 (m, 8H), 2.80-2.60 (m, 8H), 2.58-2.50 (m, 2H), 2.36-2.22 (m, 1H), 2.20-2.03 (m, 3H), 2.00-1.76 (m, 6H), 1.75-1.58 (m, 3H).
D221	LCMS (ESI) m/z: [M + H] ⁺ = 906.5	
D222	NA	¹ H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 8.15 (s, 2H, FA), 7.84 (d, J = 8.3 Hz, 1H), 7.64 (s, 1H), 7.43 (d, J = 2.3 Hz, 1H), 7.35 (dd, J = 8.4, 2.3 Hz, 1H), 6.67-6.56 (m, 3H), 5.12 (dd, J = 12.9, 5.3 Hz, 1H), 4.39-4.35 (m, 1H), 4.25-4.17 (m, 4H), 3.81 (s, 6H), 3.59 (t, J = 4.2 Hz, 2H), 3.50 (s, 4H), 3.41-3.38 (m, 3H), 2.94-2.85 (m, 1H), 2.67-2.57 (m, 7H), 2.37-2.25 (m, 5H), 2.18 (s, 2H), 2.10-2.01 (m, 1H), 1.90-1.73 (m, 4H), 1.63-1.51 (m, 4H), 1.46-1.39 (m, 2H).
D223	LCMS (ESI) m/z: [M + H] ⁺ = 881.4	
D224	LCMS (ESI) m/z: [M + H] ⁺ = 824.4	
D225	LCMS (ESI) m/z: [M + H] ⁺ = 824.4	
D226	LCMS (ESI) m/z: [M + H] ⁺ = 906.45	
D227	LCMS (ESI) m/z: [M + H] ⁺ = 851.6	¹ H NMR (300 MHz, Methanol-d4) δ 8.55 (s, 2H, FA), 7.66 (d, J = 8.5 Hz, 1H), 7.61 (s, 1H), 7.33 (d, J = 2.1 Hz, 1H), 7.22 (dd, J = 8.7, 2.2 Hz, 1H), 6.72 (s, 2H), 5.08 (dd, J = 12.3, 5.4 Hz, 1H), 4.44-4.34 (m, 4H), 4.13-4.00 (m, 2H), 3.95 (s, 6H), 3.64 (s, 3H), 3.57 (t, J = 5.4 Hz, 3H), 3.47-3.34 (m, 4H), 3.22 (t, J = 7.0 Hz, 2H), 3.13-2.94 (m, 3H), 2.88 (s, 7H), 2.78-2.62 (m, 4H), 2.24 (s, 2H), 2.16-2.07 (m, 1H), 2.03-1.77 (m, 5H), 1.62 (s, 1H), 1.46-1.29 (m, 2H).
D228	LCMS (ESI) m/z: [M + H] ⁺ = 810.7	
D229	LCMS (ESI) m/z: [M + H] ⁺ = 881.6	
D230	LCMS (ESI) m/z: [M + H] ⁺ = 892.5	¹ H NMR (300 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.17 (s, 2H, FA), 7.69 (d, J = 8.5 Hz, 1H), 7.65 (s, 1H), 7.35 (s, 1H), 7.31-7.23 (m, 1H), 6.82 (d, J = 7.4 Hz, 1H), 6.63 (s, 2H), 5.08 (dd, J = 12.8, 5.2 Hz, 1H), 4.22 (s, 2H), 4.03 (q, J = 7.9 Hz, 1H), 3.81 (s, 6H), 3.77-3.70 (m, 4H), 3.61 (s, 2H), 3.50 (s, 3H), 3.47-3.38 (m, 10H), 2.94-2.76 (m, 3H), 2.60-2.54 (m, 2H), 2.45-2.29 (m, 12H), 2.15 (t, J = 10.2 Hz, 2H), 2.08-1.97 (m, 1H), 1.51-1.33 (m, 4H).
D231	LCMS (ESI) m/z: [M + H] ⁺ = 809.45	
D232	LCMS (ESI) m/z: [M + H] ⁺ = 920.45	
D233	LCMS (ESI) m/z: [M + H] ⁺ = 868.45	
D234	LCMS (ESI) m/z: [M + H] ⁺ = 823.45	¹ H NMR (400 MHz, DMSO-d6) δ 11.07 (s, 1H), 8.18 (s, 1H, FA), 7.67-7.59 (m, 2H), 6.93-6.85 (m, 2H), 6.77-6.71 (m, 1H), 6.60 (s, 2H), 5.04 (dd, J = 12.8, 5.4 Hz, 1H), 4.23 (s, 2H), 4.14-4.04 (m, 1H), 3.79 (s, 6H), 3.59 (s, 2H), 3.53-3.47 (m, 5H), 3.45-3.41 (m, 3H), 3.41 (s, 2H), 3.13-3.04 (m, 3H), 2.94-2.83 (m, 1H), 2.74-2.69 (m, 1H), 2.62-2.57 (m, 1H), 2.47-2.34 (m, 3H), 2.25 (s, 6H), 2.15 (t, J = 10.9 Hz, 1H), 2.05-1.89 (m, 4H), 1.79-1.68 (m, 2H), 1.65-1.56 (m, 2H).

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Compound No.	LCMS	¹ H NMR
D235	LCMS (ESI) m/z: [M + H] ⁺ = 852.45	
D236	LCMS (ESI) m/z: [M + H] ⁺ = 837.45	
D237	LCMS (ESI) m/z: [M + H] ⁺ = 838.4	
D238	LCMS (ESI) m/z: [M + H] ⁺ = 823.45	
D239	LCMS (ESI) m/z: [M + H] ⁺ = 824.85	
D240	LCMS (ESI) m/z: [M + H] ⁺ = 920.5	
D241	LCMS (ESI) m/z: [M + H] ⁺ = 795.4	
D242	LCMS (ESI) m/z: [M + H] ⁺ = 838.45	
D243	LCMS (ESI) m/z: [M + H] ⁺ = (d, J = 8.5 Hz, 1H), 7.64 (s, 1H), 7.34 (s, 1H), 7.26 (d, J = 8.7 Hz, 1H), 892.45 6.77 (s, 1H), 6.58 (s, 2H), 5.08 (dd, J = 12.8, 5.5 Hz, 1H), 4.28 (d, J = 5.9 Hz, 2H), 4.02-3.94 (m, 1H), 3.78 (s, 6H), 3.61-3.50 (m, 4H), 3.50-3.42 (m, 12H), 2.95-2.85 (m, 2H), 2.79-2.67 (m, 3H), 2.64-2.56 (m, 3H), 2.40-2.25 (m, 4H), 2.14 (s, 6H), 2.05-1.81 (m, 3H), 1.76-1.67 (m, 1H), 1.63-1.47 (m, 5H).	
D244	LCMS (ESI) m/z: [M + H] ⁺ = 824.45	
D245	LCMS (ESI) m/z: [M + H] ⁺ = 906.45	
D246	LCMS (ESI) m/z: [M + H] ⁺ = 9.04 (s, 1H), 7.69 (t, J = 4.1 Hz, 2H), 6.93 (s, 1H, TFA), 6.75 (d, J = 8.2 Hz, 3H), 6.65 (d, J = 8.3 Hz, 1H), 5.06 (dd, J = 12.8, 5.3 Hz, 1H), 823.45 4.31-4.09 (m, 4H), 3.89 (d, J = 6.6 Hz, 8H), 3.83 (s, 2H), 3.52 (s, 3H), 3.45 (s, 4H), 3.25-2.79 (m, 8H), 2.76 (d, J = 4.8 Hz, 6H), 2.66-2.60 (m, 3H), 2.16 (d, J = 13.7 Hz, 2H), 1.95 (dd, J = 34.7, 19.8 Hz, 5H).	
D247	LCMS (ESI) m/z: [M + H] ⁺ = 892.6	
D248	LCMS (ESI) m/z: [M + H] ⁺ = 810.4	
D249	LCMS (ESI) m/z: [M + H] ⁺ = 796.35	
D250	LCMS (ESI) m/z: [M + H] ⁺ = 838.35	¹ H NMR (400 MHz, DMSO-d6) δ 8.42 (s, 2H, FA), 7.90 (d, J = 8.2 Hz, 1H), 7.67 (s, 1H), 7.50 (d, J = 2.2 Hz, 1H), 7.39 (dd, J = 8.3, 2.3 Hz, 1H), 6.78 (s, 2H), 6.59 (d, J = 7.1 Hz, 1H), 5.13 (dd, J = 12.9, 5.4 Hz, 1H), 4.48 (s, 2H), 4.31 (t, J = 5.7 Hz, 2H), 4.25 (s, 2H), 4.06 (q, J = 7.5 Hz, 1H), 3.88 (s, 6H), 3.52 (s, 6H), 3.46-3.39 (m, 2H), 3.11-3.05 (m, 2H), 3.01 (s, 6H), 2.93 (s, 2H), 2.92-2.80 (m, 1H), 2.63 (s, 1H), 2.61-2.53 (m, 2H), 2.35 (s, 2H), 2.10-2.04 (m, 1H), 1.94-1.83 (m, 2H), 1.70 (t, J = 6.8 Hz, 3H), 1.60-1.44 (m, 3H).
D251	LCMS (ESI) m/z: [M + H] ⁺ = 878.85	¹ H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 8.17 (s, 1H, FA), 7.83 (d, J = 8.2 Hz, 1H), 7.63 (s, 1H), 7.33-7.25 (m, 2H), 6.65-6.57 (m, 3H), 5.12 (dd, J = 12.8, 5.4 Hz, 1H), 4.98 (q, J = 6.8 Hz, 1H), 4.22 (s, 2H), 3.79 (s, 6H), 3.63 (s, 2H), 3.50 (s, 3H), 3.41 (t, J = 5.5 Hz, 3H), 2.95-2.84 (m, 3H), 2.64-2.56 (m, 6H), 2.48-2.34 (m, 8H), 2.26-2.15 (m, 2H), 2.09-2.00 (m, 1H), 1.87-1.78 (m, 2H), 1.70-1.55 (m, 6H), 1.42-1.32 (m, 2H), 1.31-1.10 (m, 3H).

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Compound No.	LCMS	¹ H NMR
D252	LCMS (ESI) m/z: [M + H] ⁺ = 838.35	¹ H NMR (300 MHz, DMSO-d6) δ 11.12 (s, 1H), 8.17 (s, 1H, FA), 7.83 (d, J = 8.1 Hz, 1H), 7.64 (s, 1H), 7.35-7.23 (m, 2H), 6.68-6.55 (m, 3H), 5.12 (dd, J = 12.9, 5.4 Hz, 1H), 5.04-4.93 (m, 1H), 4.22 (s, 2H), 3.81 (s, 6H), 3.73 (s, 2H), 3.50 (s, 3H), 3.43-3.41 (m, 3H), 3.01-2.93 (m, 2H), 2.92-2.77 (m, 2H), 2.64-2.56 (m, 6H), 2.45-2.26 (m, 7H), 2.15-1.99 (m, 3H), 1.86-1.76 (m, 2H), 1.71-1.53 (m, 7H), 1.26-1.08 (m, 2H).
D253	LCMS (ESI) m/z: [M + H] ⁺ = 864.85.	¹ H NMR (300 MHz, DMSO-d6) δ 11.12 (s, 1H), 8.21 (s, 1H, FA), 7.84 (d, J = 8.3 Hz, 1H), 7.63 (s, 1H), 7.34-7.26 (m, 2H), 6.65-6.56 (m, 3H), 5.12 (dd, J = 12.8, 5.4 Hz, 1H), 5.03 (t, J = 6.9 Hz, 1H), 4.22 (s, 2H), 3.78 (s, 6H), 3.53-3.49 (m, 6H), 3.43-3.39 (m, 6H), 2.96-2.78 (m, 4H), 2.64-2.56 (m, 5H), 2.47-2.44 (m, 1H), 2.15-2.00 (m, 4H), 1.92-1.82 (m, 2H), 1.67-1.43 (m, 9H).
D254	LCMS (ESI) m/z: [M + H] ⁺ = 878.65	¹ H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 8.21 (s, 1H, FA), 7.84 (d, J = 8.3 Hz, 1H), 7.63 (s, 1H), 7.34-7.26 (m, 2H), 6.65-6.56 (m, 3H), 5.12 (dd, J = 12.8, 5.4 Hz, 1H), 5.03 (t, J = 6.9 Hz, 1H), 4.22 (s, 2H), 3.78 (s, 6H), 3.53-3.49 (m, 6H), 3.43-3.39 (m, 6H), 2.96-2.78 (m, 4H), 2.64-2.56 (m, 5H), 2.47-2.44 (m, 1H), 2.15-2.00 (m, 4H), 1.92-1.82 (m, 2H), 1.67-1.43 (m, 9H).
D255	LCMS (ESI) m/z: [M + H] ⁺ = 835.45	¹ H-NMR (400 MHz, DMSO-d6) δ 11.09 (s, 1H), 8.15 (s, 1H, FA), 7.69 (d, J = 8.5 Hz, 1H), 7.64 (s, 1H), 7.35 (d, J = 2.2 Hz, 1H), 7.27 (dd, J = 12.9, 2.3 Hz, 1H), 6.69 (s, 2H), 6.61 (q, J = 4.3 Hz, 1H), 5.08 (dd, J = 12.9, 5.4 Hz, 1H), 4.22 (s, 2H), 4.04 (s, 2H), 3.86 (s, 6H), 3.51 (s, 3H), 3.48-3.38 (m, 7H), 3.10-2.83 (m, 5H), 2.73 (t, J = 7.6 Hz, 1H), 2.64-2.53 (m, 6H), 2.39 (s, 4H), 2.08-1.95 (m, 3H), 1.76 (s, 2H), 1.73-1.57 (m, 4H).
D256	LCMS (ESI) m/z: [M + H] ⁺ = 809.	¹ H NMR (300 MHz, DMSO) δ 11.08 (s, 1H), 8.20 (d, FA, 2H), 7.73-7.61 (m, 2H), 7.39-7.18 (m, 2H), 6.60 (d, 3H), 5.07 (dd, 1H), 4.22 (s, 2H), 3.80 (s, 7H), 3.63 (d, 3H), 3.50 (s, 3H), 3.42 (d, 6H), 2.98-2.80 (m, 3H), 2.60 (d, 4H), 2.51-2.39 (m, 5H), 2.22-2.12 (m, 4H), 2.16-1.95 (m, 1H), 1.69 (d, 2H), 1.60-1.45 (m, 1H), 1.22-1.05 (m, 2H);
D257	LCMS (ESI) m/z: [M + H] ⁺ = 809.50	¹ H NMR (400 MHz, Methanol-d4) δ 8.49 (s, 3H, FA), 7.81 (d, J = 8.4 Hz, 1H), 7.56-7.48 (m, 2H), 7.39 (d, J = 8.6 Hz, 1H), 6.64 (s, 2H), 5.12 (dd, J = 12.6, 5.4 Hz, 1H), 4.35 (s, 2H), 4.10-4.02 (m, 3H), 3.90 (s, 6H), 3.89-3.85 (m, 3H), 3.84-3.62 (m, 9H), 3.55-3.48 (m, 3H), 3.08-3.01 (m, 1H), 2.98-2.83 (m, 2H), 2.78 (s, 3H), 2.76-2.70 (m, 2H), 2.64-2.57 (m, 2H), 2.44 (s, 1H), 2.17-1.98 (m, 4H), 1.39-1.27 (m, 2H).
D258	LCMS (ESI) m/z: [M + H] ⁺ = 795.40	¹ H NMR (400 MHz, DMSO-d6) δ 11.11 (s, 1H), 8.37 (s, 1H, FA), 7.79 (d, J = 8.3 Hz, 1H), 7.56 (d, J = 30.9 Hz, 2H), 7.47-7.31 (m, 1H), 6.61 (d, J = 5.4 Hz, 3H), 5.10 (dd, J = 13.0, 5.4 Hz, 1H), 4.21 (s, 2H), 3.91 (d, J = 8.9 Hz, 1H), 3.81 (s, 10H), 3.76-3.57 (m, 12H), 3.40 (t, J = 5.6 Hz, 4H), 3.26 (t, J = 10.7 Hz, 2H), 2.98-2.82 (m, 1H), 2.71 (s, 1H), 2.66-2.54 (m, 5H), 2.28-2.20 (m, 1H), 2.09-1.98 (m, 1H), 1.84-1.79 (s, 1H).
D259	LCMS (ESI) m/z: [M + H] ⁺ = 854.4	¹ H NMR (300 MHz, Methanol-d4) δ 8.48 (s, 1H, FA), 7.84 (d, J = 8.3 Hz, 1H), 7.60 (s, 1H), 7.46 (s, 1H), 7.40-7.34 (m, 1H), 6.72 (s, 2H), 5.13 (dd, J = 12.4, 5.4 Hz, 1H), 4.44-4.35 (m, 6H), 4.19-4.09 (m, 1H), 3.95 (s, 6H), 3.69-3.48 (m, 8H), 3.43-3.38 (m, 1H), 3.18-3.11 (m, 2H), 2.92-2.72 (m, 13H), 2.65 (s, 2H), 2.21-2.10 (m, 1H), 1.98 (dd, J = 12.8, 7.2 Hz, 1H), 1.82-1.71 (m, 4H), 1.58-1.47 (m, 1H).
D260	LCMS (ESI) m/z: [M + H] ⁺ = 795.4	
D261	LCMS (ESI) m/z: [M + H] ⁺ = 809.45	
D262	LCMS (ESI) m/z: [M + H] ⁺ = 824.4	¹ H NMR (400 MHz, DMSO-d6) δ 8.43 (s, 2H, FA), 7.90 (d, J = 8.4 Hz, 1H), 7.68 (s, 1H), 7.50 (d, J = 2.2 Hz, 1H), 7.39 (dd, J = 8.4, 2.3 Hz, 1H), 6.88 (d, J = 6.7 Hz, 1H), 6.77 (s, 2H), 5.14 (dd, J = 12.8, 5.4 Hz, 1H), 4.48 (s, 2H), 4.31 (t, J = 5.2 Hz, 4H), 4.25 (s, 2H), 4.13 (dq, J = 16.8, 8.2 Hz, 1H), 3.88 (s, 6H), 3.52 (s, 6H), 3.42 (t, J = 4.7 Hz, 2H), 3.01 (s, 6H), 2.96-2.84 (m, 4H), 2.63 (d, J = 3.8 Hz, 1H), 2.61-2.53 (m, 3H), 2.40-2.33 (m, 1H), 2.27-1.96 (m, 6H), 1.87-1.82 (m, 1H), 1.81-1.74 (m, 1H).
D263	LCMS (ESI) m/z: [M + H] ⁺ = 810.45	
D264	LCMS (ESI) m/z: [M + H] ⁺ = 796.7	
D265	LCMS (ESI) m/z: [M + H] ⁺ = 838.45	¹ H NMR (400 MHz, DMSO-d6 with a drop of D ₂ O) δ 8.40 (s, 2H, FA), 7.88 (d, J = 8.3 Hz, 1H), 7.66 (s, 1H), 7.48 (d, J = 2.3 Hz, 1H), 7.39 (dd, J = 8.4, 2.3 Hz, 1H), 6.74 (s, 2H), 5.12 (dd, J = 12.8, 5.4 Hz, 1H),

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Compound No.	LCMS	¹ H NMR
D266	LCMS (ESI) m/z: [M + H] ⁺ = 824.4	4.47 (s, 2H), 4.30 (t, J = 6.1 Hz, 2H), 4.23 (s, 2H), 3.86 (s, 6H), 3.55-3.48 (m, 5H), 3.41 (s, 2H), 3.25 (s, 1H), 3.07-2.97 (m, 9H), 2.96-2.81 (m, 3H), 2.75-2.70 (m, 1H), 2.66-2.55 (m, 5H), 2.34 (s, 1H), 2.24-2.14 (m, 1H), 2.09-1.94 (m, 3H), 1.52-1.42 (m, 2H), 1.03-0.97 (m, 1H).
D267	LCMS (ESI) m/z: [M + H] ⁺ = 838.4	
D268	LCMS (ESI) m/z: [M + H] ⁺ = 810.7	
D269	LCMS (ESI) m/z: [M + H] ⁺ = 824.45	¹ H NMR (400 MHz, Methanol-d4) δ 8.51 (s, 2H, FA), 7.81 (d, J = 8.2 Hz, 1H), 7.60 (s, 1H), 7.46 (s, 1H), 7.37 (d, J = 8.2 Hz, 1H), 6.71 (s, 2H), 5.12 (dd, J = 12.4, 5.4 Hz, 1H), 4.49 (s, 2H), 4.37 (d, J = 2.8 Hz, 4H), 3.95 (s, 6H), 3.63 (s, 3H), 3.58-3.52 (m, 2H), 3.37 (s, 2H), 3.27 (d, J = 7.3 Hz, 2H), 3.15 (s, 4H), 2.88 (s, 7H), 2.80-2.58 (m, 4H), 2.17-2.07 (m, 1H), 1.97-1.55 (m, 4H), 1.18-1.06 (m, 1H), 0.70-0.60 (m, 1H), 0.37 (t, J = 5.1 Hz, 1H).
D270	LCMS (ESI) m/z: [M + H] ⁺ = 810.4	
D271	LCMS (ESI) m/z: [M + H] ⁺ = 810.45	
D272	LCMS (ESI) m/z: [M + H] ⁺ = 824.4	
D273	LCMS (ESI) m/z: [M + H] ⁺ = 810.4	
D274	LCMS (ESI) m/z: [M + H] ⁺ = 796.35	¹ H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 8.18 (s, 2H, FA), 7.84 (d, J = 8.3 Hz, 1H), 7.64 (s, 1H), 7.46 (dd, J = 4.0, 2.2 Hz, 1H), 7.37 (dt, J = 8.3, 2.3 Hz, 1H), 6.63 (s, 2H), 6.58 (d, J = 4.9 Hz, 1H), 5.12 (dd, J = 12.9, 5.4 Hz, 1H), 4.26 (d, J = 11.7 Hz, 4H), 3.89 (s, 1H), 3.80 (d, J = 1.9 Hz, 6H), 3.74-3.54 (m, 4H), 3.50 (s, 3H), 3.44 (d, J = 5.7 Hz, 2H), 3.18-3.10 (m, 2H), 3.03-2.98 (m, 1H), 2.92-2.84 (m, 3H), 2.74-2.69 (m, 1H), 2.32 (s, 5H), 2.22 (d, J = 13.6 Hz, 2H), 2.09-2.04 (s, 2H), 1.80 (t, J = 11.3 Hz, 1H), 1.74-1.61 (m, 2H), 1.46 (d, J = 10.2 Hz, 1H). LCMS (ESI) m/z: [M + H] ⁺ = 796.35
D275	LCMS (ESI) m/z: [M + H] ⁺ = 864.45	¹ H NMR (400 MHz, Methanol-d4) δ 8.56 (br s, 1H, FA), 7.82 (d, J = 8.3 Hz, 1H), 7.58 (s, 1H), 7.30 (s, 1H), 7.25 (dd, J = 8.2, 2.2 Hz, 1H), 6.72 (s, 2H), 5.12 (dd, J = 12.7, 5.4 Hz, 1H), 4.97 (t, J = 6.6 Hz, 1H), 4.47 (s, 2H), 4.36 (s, 2H), 4.25 (t, J = 9.5 Hz, 2H), 4.01-3.90 (m, 8H), 3.64 (s, 3H), 3.60-3.49 (m, 5H), 3.47-3.42 (m, 1H), 3.23-3.17 (m, 1H), 2.95-2.82 (m, 3H), 2.80-2.67 (m, 5H), 2.64-2.54 (m, 4H), 2.18-2.10 (m, 1H), 2.03 (dd, J = 12.7, 6.2 Hz, 2H), 1.80-1.60 (m, 4H).
D276	LCMS (ESI) m/z: [M + H] ⁺ = 852.39	¹ H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 7.84 (d, J = 8.3 Hz, 1H), 7.70 (t, J = 5.8 Hz, 1H), 7.62 (s, 1H), 7.44 (d, J = 2.3 Hz, 1H), 7.36 (dd, J = 8.3, 2.3 Hz, 1H), 6.62-6.57 (m, 1H), 6.56 (s, 2H), 5.12 (dd, J = 12.9, 5.4 Hz, 1H), 4.19 (dd, J = 13.0, 6.6 Hz, 4H), 3.77 (s, 6H), 3.50 (s, 3H), 3.44 (s, 2H), 3.40 (t, J = 5.5 Hz, 2H), 3.40-3.35 (m, 2H), 3.07 (q, J = 6.5 Hz, 2H), 2.95-2.84 (m, 1H), 2.63-2.54 (m, 5H), 2.09-1.97 (m, 4H), 1.90 (s, 6H), 1.81-1.71 (m, 2H), 1.54-1.35 (m, 4H).
D277	LCMS (ESI) m/z: [M + H] ⁺ = 820.55	¹ H NMR (300 MHz, DMSO-d6) δ 11.12 (s, 1H), 8.23 (s, 1H, FA), 7.84 (d, J = 8.3 Hz, 1H), 7.61 (s, 1H), 7.43 (d, J = 2.2 Hz, 1H), 7.35 (dd, J = 8.3, 2.3 Hz, 1H), 7.25 (t, J = 5.8 Hz, 1H), 6.64-6.54 (m, 3H), 5.13 (dd, J = 12.9, 5.4 Hz, 1H), 4.25-4.15 (m, 4H), 4.02-3.85 (m, 2H), 3.77 (s, 6H), 3.57 (s, 2H), 3.49 (s, 3H), 3.43-3.38 (m, 6H), 3.11 (q, J = 6.5 Hz, 2H), 2.96-2.82 (m, 1H), 2.66-2.52 (m, 6H), 2.10-1.99 (m, 1H), 1.97-1.85 (m, 2H).
D278	LCMS (ESI) m/z: [M + H] ⁺ = 834.15	¹ H NMR (400 MHz, Methanol-d4) δ 8.48 (s, 1H, FA), 7.80 (d, J = 8.3 Hz, 1H), 7.55 (s, 1H), 7.40 (d, J = 2.3 Hz, 1H), 7.32 (dd, J = 8.4, 2.3 Hz, 1H), 6.63 (s, 2H), 5.11 (dd, J = 12.5, 5.4 Hz, 1H), 4.35 (s, 2H), 4.20 (t, J = 6.2 Hz, 2H), 4.16-4.06 (m, 1H), 4.02 (s, 2H), 3.88 (s, 6H), 3.88-3.83 (m, 4H), 3.63 (s, 3H), 3.53 (t, J = 5.6 Hz, 2H), 3.14 (t, J = 6.9 Hz, 2H), 2.95-2.83 (m, 1H), 2.80-2.67 (m, 5H), 2.65-2.60 (m, 2H), 2.18-2.09 (m, 1H), 1.97-1.86 (m, 2H), 1.80-1.67 (m, 2H).
D279	LCMS (ESI) m/z: [M + H] ⁺ = 806.45	¹ H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 7.86 (d, J = 8.3 Hz, 1H), 7.61 (s, 1H), 7.51 (s, 1H), 7.46 (d, J = 2.3 Hz, 1H), 7.37 (dd, J = 8.3, 2.3 Hz, 1H), 6.62-6.53 (m, 3H), 5.13 (dd, J = 12.9, 5.3 Hz, 1H), 4.24-4.16 (m, 4H), 4.04 (s, 1H), 3.78 (s, 6H), 3.59 (s, 2H), 3.49 (s,

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Compound No.	LCMS	¹ H NMR
D280	LCMS (ESI) m/z: [M + H] ⁺ = 820.60.	¹ H NMR (300 MHz, DMSO-d6) δ 11.12 (s, 1H), 7.83 (dd, J = 8.5, 7.2 Hz, 1H), 7.62 (s, 1H), 7.53 (d, J = 8.5 Hz, 1H), 7.47 (d, J = 7.2 Hz, 1H), 6.75-6.58 (m, 3H), 5.09 (dd, J = 12.8, 5.4 Hz, 1H), 4.28-4.19 (m, 4H), 3.96-3.61 (m, 8H), 3.50 (s, 3H), 3.40 (t, J = 5.5 Hz, 2H), 3.38 (s, 6H), 3.24-3.14 (m, 2H), 2.97-2.82 (m, 1H), 2.64-2.54 (m, 6H), 2.09-1.88 (m, 3H).
D281	LCMS (ESI) m/z: [M + H] ⁺ = 834.10	¹ H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 10.08 (s, 1H, TFA), 7.83 (dd, J = 8.5, 7.2 Hz, 1H), 7.69 (s, 1H), 7.64 (s, 1H), 7.53 (d, J = 8.5 Hz, 1H), 7.47 (d, J = 7.3 Hz, 1H), 6.71 (s, 2H), 6.61 (q, J = 4.3 Hz, 1H), 5.09 (dd, J = 12.7, 5.5 Hz, 1H), 4.66-4.29 (m, 5H), 4.26-4.14 (m, 5H), 3.86 (s, 6H), 3.51 (s, 3H), 3.44-3.39 (m, 4H), 3.11-3.01 (m, 2H), 2.94-2.81 (m, 1H), 2.64-2.53 (m, 6H), 2.07-1.98 (m, 1H), 1.85-1.76 (m, 2H), 1.70-1.60 (m, 2H).
D282	LCMS (ESI) m/z: [M + H] ⁺ = 806.60.	¹ H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 7.84 (t, J = 7.8 Hz, 1H), 7.62 (s, 1H), 7.55 (d, J = 8.6 Hz, 1H), 7.50 (d, J = 7.2 Hz, 1H), 6.69-6.53 (m, 3H), 5.11 (dd, J = 12.8, 5.4 Hz, 1H), 4.49-4.00 (m, 7H), 3.79 (s, 7H), 3.56-3.47 (m, 4H), 3.44-3.37 (m, 5H), 2.94-2.83 (m, 1H), 2.59 (d, J = 4.2 Hz, 4H), 2.57-2.53 (m, 4H), 2.07-1.98 (m, 1H).
D283	LCMS (ESI) m/z: [M + H] ⁺ = 852.39.	¹ H NMR (400 MHz, DMSO-d6) δ 11.11 (s, 1H), 7.82 (dd, J = 8.5, 7.3 Hz, 1H), 7.69 (t, J = 5.8 Hz, 1H), 7.62 (s, 1H), 7.53 (d, J = 8.6 Hz, 1H), 7.45 (d, J = 7.2 Hz, 1H), 6.59 (d, J = 4.4 Hz, 1H), 6.56 (s, 2H), 5.08 (dd, J = 12.9, 5.4 Hz, 1H), 4.24-4.17 (m, 4H), 3.77 (s, 6H), 3.50 (s, 3H), 3.44 (s, 2H), 3.40 (t, J = 5.6 Hz, 2H), 3.37 (s, 2H), 3.11-3.03 (m, 2H), 2.93-2.81 (m, 1H), 2.61-2.55 (m, 5H), 2.07-1.98 (m, 4H), 1.90 (s, 6H), 1.81-1.73 (m, 2H), 1.54-1.38 (m, 4H).
D284	LCMS (ESI) m/z: [M + H] ⁺ = 813.45	¹ H NMR (400 MHz, DMSO-d6) δ 11.09 (s, 1H), 8.15 (s, 1H, FA), 7.67 (d, J = 8.5 Hz, 1H), 7.63 (s, 1H), 7.33 (d, J = 2.3 Hz, 1H), 7.25 (dd, J = 8.7, 2.3 Hz, 1H), 6.61 (d, J = 6.9 Hz, 3H), 5.07 (dd, J = 12.9, 5.4 Hz, 1H), 4.21 (s, 2H), 3.84-3.77 (m, 7H), 3.71 (s, 2H), 3.64-3.53 (m, 5H), 3.52-3.46 (m, 4H), 3.43-3.38 (m, 7H), 2.95-2.83 (m, 1H), 2.72 (s, 2H), 2.60-2.53 (m, 9H), 2.28 (s, 3H), 2.06-1.97 (m, 1H).
D285	LCMS (ESI) m/z: [M - H] ⁺ = 774.37.	¹ H NMR (300 MHz, Methanol-d4) δ 8.56 (br s, 1.7H, FA), 7.55 (s, 1H), 7.24 (t, J = 7.7 Hz, 1H), 7.09 (d, J = 7.6 Hz, 1H), 6.91 (d, J = 7.9 Hz, 1H), 6.71 (s, 2H), 5.19 (dd, J = 13.4, 5.1 Hz, 1H), 4.39-4.27 (m, 5H), 4.09-3.98 (m, 2H), 3.94 (s, 6H), 3.67-3.50 (m, 14H), 3.40 (t, J = 5.4 Hz, 2H), 3.04-2.91 (m, 2H), 2.85 (s, 6H), 2.61 (s, 2H), 2.53-2.39 (m, 1H), 2.24-2.12 (m, 1H).
D286	LCMS (ESI) m/z: [M + H] ⁺ = 866.30.	¹ H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 8.18 (s, 1.0H, FA), 7.83 (d, J = 8.3 Hz, 1H), 7.68-7.62 (m, 2H), 7.43 (d, J = 2.3 Hz, 1H), 7.35 (dd, J = 8.3, 2.3 Hz, 1H), 6.62-6.56 (m, 3H), 5.12 (dd, J = 12.9, 5.4 Hz, 1H), 4.25-4.13 (m, 4H), 3.78 (s, 6H), 3.54 (s, 2H), 3.50 (s, 3H), 3.42-3.38 (m, 3H), 3.05 (q, J = 6.6 Hz, 2H), 2.94-2.84 (m, 1H), 2.64-2.53 (m, 6H), 2.48 (s, 2H), 2.11 (s, 3H), 2.08-2.01 (m, 1H), 1.85 (s, 6H), 1.80-1.71 (m, 2H), 1.51-1.35 (m, 4H).
D287	LCMS (ESI) m/z: [M + H] ⁺ = 874.35.	¹ H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.16 (s, 0.7H, FA), 7.68 (d, J = 8.5 Hz, 1H), 7.61 (s, 1H), 7.35 (d, J = 2.3 Hz, 1H), 7.26 (dd, J = 8.6, 2.3 Hz, 1H), 7.08 (t, J = 5.8 Hz, 1H), 6.58 (s, 3H), 5.07 (dd, J = 12.9, 5.3 Hz, 1H), 4.21 (s, 2H), 4.07-3.95 (m, 1H), 3.78 (s, 6H), 3.58 (s, 2H), 3.49 (s, 3H), 3.47-3.34 (m, 14H), 3.08 (q, J = 6.5 Hz, 2H), 2.94-2.82 (m, 1H), 2.59 (d, J = 4.2 Hz, 5H), 2.54 (s, 2H), 2.42 (t, J = 6.7 Hz, 2H), 2.07-1.99 (m, 1H).
D288	LCMS (ESI) m/z: [M + H] ⁺ = 866.25.	¹ H NMR (400 MHz, DMSO-d6) δ 11.14 (s, 1H), 8.19 (s, 0.9H, FA), 7.81 (dd, J = 8.6, 7.3 Hz, 1H), 7.68-7.61 (m, 2H), 7.52 (d, J = 8.6 Hz, 1H), 7.45 (d, J = 7.2 Hz, 1H), 6.64-6.54 (m, 3H), 5.08 (dd, J = 12.9, 5.4 Hz, 1H), 4.26-4.13 (m, 4H), 3.78 (s, 6H), 3.55-3.47 (m, 6H), 3.40 (t, J = 5.5 Hz, 2H), 3.08-3.01 (m, 2H), 2.93-2.82 (m, 1H), 2.63-2.52 (m, 6H), 2.47 (s, 2H), 2.10 (s, 3H), 2.06-1.99 (m, 1H), 1.84 (s, 6H), 1.81-1.73 (m, 2H), 1.51-1.39 (m, 4H).
D289	LCMS (ESI) m/z: [M + H] ⁺ = 854.70.	¹ H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 8.19 (s, 0.9H, FA), 7.83 (d, J = 8.3 Hz, 1H), 7.63 (s, 1H), 7.44 (d, J = 2.3 Hz, 1H), 7.36 (d, J = 8.4 Hz, 1H), 6.58 (s, 3H), 5.12 (dd, J = 12.9, 5.4 Hz, 1H), 4.33-4.26 (m, 2H), 4.21 (s, 2H), 3.97-3.89 (m, 1H), 3.76 (s, 8H), 3.70-3.67 (m, 2H), 3.59 (s, 3H), 3.49 (s, 4H), 2.95-2.76 (m, 5H), 2.63-2.52 (m, 10H), 2.29-2.19 (m, 1H), 2.18-2.10 (m, 1H), 2.09-1.99 (m, 1H), 1.52-1.28 (m, 2H).
D290	LCMS (ESI) m/z: [M + H] ⁺ = 815.50.	¹ H NMR (400 MHz, DMSO-d6, D2O) δ 8.53 (t, J = 5.8 Hz, TFA salt), 7.84 (d, J = 8.3 Hz, 1H), 7.66 (s, 1H), 7.46 (d, J = 2.3 Hz, 1H), 7.40 (dd, J = 8.3, 2.3 Hz, 1H), 6.68 (s, 2H), 5.11 (dd, J = 12.9, 5.4 Hz, 1H), 4.77 (s, 2H), 4.22 (d, J = 4.7 Hz, 4H), 3.86 (s, 6H), 3.58-3.52 (m, 2H), 3.50 (s, 3H), 3.44-3.14 (m, 8H), 2.94-2.83 (m, 4H), 2.75 (s, 6H), 2.65-2.53 (m, 4H), 2.08-1.96 (m, 1H).
D291	LCMS (ESI) m/z:	¹ H-NMR (400 MHz, DMSO-d6) δ 11.01 (s, 1H), 8.31 (t, J = 5.3 Hz, 1H), 8.22 (s, 0.8H, FA), 7.64 (s, 1H), 7.48 (t, J = 8.1 Hz, 1H), 6.68-

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Compound No.	LCMS m/z:	¹ H NMR
	[M + H] ⁺ = 797.55.	6.59 (m, 4H), 6.49 (d, J = 8.3 Hz, 1H), 5.18 (dd, J = 11.5, 5.6 Hz, 1H), 4.22 (s, 2H), 3.79 (s, 6H), 3.62 (s, 2H), 3.50 (s, 3H), 3.40 (t, J = 5.5 Hz, 2H), 3.14 (q, J = 6.6 Hz, 2H), 3.03 (q, J = 6.5 Hz, 2H), 2.90-2.76 (m, 1H), 2.70-2.58 (m, 2H), 2.58-2.52 (m, 5H), 2.27 (s, 6H), 2.20-2.08 (m, 1H), 1.65-1.54 (m, 2H), 1.44-1.38 (m, 2H), 1.37-1.18 (m, 8H).
D292	LCMS (ESI) [M + H] ⁺ = 801.50.	1H-NMR (400 MHz, Methanol-d4) δ 8.55 (brs, 0.9H, FA), 7.53 (s, 1H), 7.43 (t, J = 8.1 Hz, 1H), 6.70-6.63 (m, 3H), 6.51 (d, J = 8.3 Hz, 1H), 5.20-5.13 (m, 1H), 4.41-4.25 (m, 4H), 3.94 (s, 6H), 3.82-3.77 (m, 2H), 3.68 (s, 4H), 3.62-3.57 (m, 5H), 3.56-3.35 (m, 6H), 2.93-2.79 (m, 8H), 2.78-2.69 (m, 1H), 2.62 (s, 3H), 2.58-2.50 (m, 2H), 2.23-2.14 (m, 1H).
D293	764.3	¹ H NMR (400 MHz, DMSO-d6) δ 7.72 (s, 1H), 7.41 (d, J = 8.6 Hz, 1H), 6.75-6.62 (m, 4H), 5.06 (dd, J = 13.2, 5.0 Hz, 1H), 4.35 (t, J = 18.7 Hz, 4H), 4.27-4.16 (m, 3H), 4.11-3.98 (m, 3H), 3.88 (s, 6H), 3.75-3.62 (m, 5H), 3.53 (s, 3H), 3.31-3.12 (m, 3H), 3.05-2.82 (m, 8H), 2.81-2.73 (m, 1H), 2.70-2.56 (m, 3H), 2.42-2.32 (m, 1H), 2.18-2.05 (m, 2H), 2.04-1.84 (m, 3H).
D294	866.45	¹ H NMR (400 MHz, DMSO-d6) δ 11.13 (s, 1H), 8.20 (s, 0.9H, FA), 7.81 (dd, J = 8.5, 7.2 Hz, 1H), 7.64 (t, J = 5.8 Hz, 1H), 7.58-7.49 (m, 2H), 7.44 (d, J = 7.2 Hz, 1H), 6.58 (s, 2H), 6.54 (q, J = 4.3 Hz, 1H), 5.08 (dd, J = 12.9, 5.4 Hz, 1H), 4.26 (s, 2H), 4.20 (t, J = 6.4 Hz, 2H), 3.79 (s, 6H), 3.56-3.49 (m, 4H), 3.47 (s, 3H), 3.05 (q, J = 6.4 Hz, 2H), 2.88 (ddd, J = 17.3, 14.1, 5.4 Hz, 1H), 2.63-2.55 (m, 1H), 2.55-2.51 (m, 4H), 2.50-2.46 (m, 4H), 2.11 (s, 3H), 2.07-1.99 (m, 1H), 1.85 (s, 6H), 1.77 (t, J = 6.9 Hz, 2H), 1.50-1.39 (m, 4H).
D295	854.7	¹ H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 8.15 (s, 0.7H, FA), 7.83 (d, J = 8.3 Hz, 1H), 7.56 (s, 1H), 7.45 (d, J = 2.2 Hz, 1H), 7.36 (dd, J = 8.3, 2.3 Hz, 1H), 6.61 (s, 2H), 6.55 (q, J = 4.4 Hz, 1H), 5.12 (dd, J = 12.9, 5.4 Hz, 1H), 4.31-4.27 (m, 2H), 4.25 (s, 2H), 3.94-3.88 (m, 1H), 3.79 (s, 8H), 3.75 (s, 2H), 3.72-3.68 (m, 3H), 3.47 (s, 4H), 3.10-3.01 (m, 2H), 2.99-2.81 (m, 3H), 2.69-2.52 (m, 10H), 2.41-2.32 (m, 1H), 2.31-2.21 (m, 1H), 2.08-1.97 (m, 1H), 1.64-1.39 (m, 2H).
D296	813.45	¹ H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.16 (s, 1.1H, FA), 7.67 (d, J = 8.5 Hz, 1H), 7.56 (s, 1H), 7.34 (d, J = 2.3 Hz, 1H), 7.25 (dd, J = 8.7, 2.3 Hz, 1H), 6.63 (s, 2H), 6.54 (d, J = 4.5 Hz, 1H), 5.07 (dd, J = 12.9, 5.4 Hz, 1H), 4.27 (s, 2H), 3.82 (s, 6H), 3.73 (s, 2H), 3.63-3.55 (m, 4H), 3.52 (t, J = 5.9 Hz, 2H), 3.46 (s, 3H), 3.45-3.38 (m, 8H), 2.94-2.84 (m, 1H), 2.75 (s, 2H), 2.64-2.54 (m, 9H), 2.35-2.25 (m, 3H), 2.08-1.97 (m, 1H).
D297	802.55	¹ H NMR (400 MHz, DMSO-d6) δ 11.10 (s, 1H), 8.19 (s, 0.8H, FA), 7.82-7.72 (m, 2H), 7.54 (s, 1H), 7.48 (d, J = 8.6 Hz, 1H), 7.43 (d, J = 7.2 Hz, 1H), 6.57 (s, 2H), 6.56-6.51 (m, 1H), 5.08 (dd, J = 12.9, 5.4 Hz, 1H), 4.37-4.29 (m, 2H), 4.25 (s, 2H), 3.85-3.77 (m, 8H), 3.59 (t, J = 5.7 Hz, 2H), 3.54-3.50 (m, 4H), 3.46 (s, 3H), 3.34 (q, J = 5.9 Hz, 4H), 2.94 (s, 2H), 2.91-2.83 (m, 1H), 2.62-2.52 (m, 5H), 2.10 (s, 3H), 2.05-1.96 (m, 1H).
D298	827.5	¹ H-NMR (400 MHz, Methanol-d4) δ 8.47 (brs, 1.4H, FA), 7.69 (d, J = 8.5 Hz, 1H), 7.50 (s, 1H), 7.34 (d, J = 2.3 Hz, 1H), 7.24 (dd, J = 8.6, 2.3 Hz, 1H), 6.77 (s, 2H), 5.08 (dd, J = 12.4, 5.5 Hz, 1H), 4.50 (s, 2H), 4.09 (s, 2H), 3.97 (s, 6H), 3.92-3.87 (m, 2H), 3.76 (t, J = 5.2 Hz, 2H), 3.61 (s, 3H), 3.51-3.45 (m, 8H), 2.90-2.86 (m, 4H), 2.83 (s, 6H), 2.79-2.71 (m, 10H), 2.17-2.07 (m, 1H).
D299	809.94	¹ H NMR (400 MHz, DMSO-d6) δ 11.04 (s, 1H), 8.13 (s, 2H), 7.87 (s, 1H), 7.65 (d, J = 8.5 Hz, 1H), 7.31 (d, J = 2.3 Hz, 1H), 7.23 (dd, J = 8.7, 2.3 Hz, 1H), 6.68 (s, 2H), 6.33 (d, J = 4.5 Hz, 1H), 5.05 (dd, J = 12.9, 5.4 Hz, 1H), 3.81 (s, 5H), 3.65 (d, J = 3.1 Hz, 2H), 3.52 (s, 3H), 3.39 (d, J = 5.4 Hz, 4H), 3.15 (s, 2H), 2.97-2.78 (m, 3H), 2.58 (d, J = 4.3 Hz, 3H), 2.00 (dd, J = 9.2, 4.2 Hz, 1H), 1.64 (d, J = 12.6 Hz, 2H), 1.35 (s, 1H).
D300	738.82	¹ H NMR (400 MHz, DMSO-d6) δ 11.03 (s, 1H), 8.14 (s, 1H), 7.85 (d, J = 11.1 Hz, 1H), 7.60 (d, J = 8.3 Hz, 1H), 6.70-6.56 (m, 3H), 5.02 (dd, J = 12.9, 5.4 Hz, 1H), 4.68-4.54 (m, 2H), 4.38 (s, 2H), 3.80 (s, 6H), 3.73 (d, J = 19.6 Hz, 4H), 3.52 (s, 3H), 3.47 (s, 2H), 2.93-2.74 (m, 1H), 2.58 (dd, J = 4.4, 2.9 Hz, 4H), 2.37 (s, 4H), 2.05-1.91 (m, 1H), 1.69 (s, 4H).
D301	749.15	¹ H NMR (400 MHz, Methanol-d4) δ 7.41 (d, J = 7.8 Hz, 2H), 6.88 (d, J = 2.2 Hz, 1H), 6.80 (dd, J = 8.2, 2.2 Hz, 1H), 6.70 (s, 2H), 5.14 (dd, J = 13.3, 5.2 Hz, 1H), 4.51 (s, 2H), 4.47-4.20 (m, 4H), 4.15 (s, 2H), 3.95 (s, 6H), 3.77 (s, 4H), 3.61 (s, 3H), 3.55-3.35 (m, 5H), 3.15 (s, 1H), 3.29-3.01 (m, 1H), 2.98-2.85 (m, 1H), 2.80 (d, J = 17.6 Hz, 1H), 2.60 (t, J = 6.4 Hz, 2H), 2.51-2.47 (m, 3H), 2.25-2.04 (m, 5H), 1.85-1.79 (m, 2H), 1.72-1.67 (m, 2H).
D302	737.4	¹ H NMR (400 MHz, Methanol-d4) δ 8.33 (s, 2H, FA), 7.91 (s, 1H), 7.39 (d, J = 8.2 Hz, 1H), 6.85 (d, J = 2.2 Hz, 1H), 6.81-6.74 (m, 3H),

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-continued

Compound No.	LCMS	¹ H NMR
DD1	LCMS (ESI) m/z: [M + H] ⁺ = 878.5.	5.23 (t, J = 3.4 Hz, 2H), 5.14 (dd, J = 13.3, 5.2 Hz, 1H), 5.07 (t, J = 3.4 Hz, 2H), 4.45 (s, 2H), 4.42 (d, J = 16.5 Hz, 1H), 4.36 (d, J = 16.5 Hz, 1H), 4.22 (t, J = 9.4 Hz, 2H), 3.98 (s, 6H), 3.95 (d, J = 10.0 Hz, 2H), 3.71 (s, 3H), 3.68 (s, 4H), 3.20-3.10 (m, 1H), 2.98-2.86 (m, 1H), 2.84-2.69 (m, 3H), 2.61-2.42 (m, 5H), 2.23-2.13 (m, 1H), 1.94-1.96 (m, 4H). ¹ H NMR (400 MHz, Methanol-d4) δ 8.56 (s, 1H, FA), 7.55 (s, 1H), 7.49 (td, J = 8.6, 5.9 Hz, 1H), 7.28-7.20 (m, 1H), 7.19-7.12 (m, 1H), 6.63 (s, 2H), 4.36 (s, 2H), 3.96-3.82 (m, 8H), 3.64 (s, 3H), 3.59-3.49 (m, 4H), 3.31-3.24(m, 2H), 2.94-2.74 (m, 8H), 2.69-2.45 (m, 7H), 1.79 (d, J = 10.9 Hz, 2H), 1.62-1.46 (m, 5H).

Example 67—Preparation of Compounds D303-D375

In analogy to the procedures described in the examples above, compounds D303-D375 were prepared using the appropriate starting materials ²⁰

Compound No.	LCMS	¹ H NMR
D303	669.2	¹ H NMR (400 MHz, DMSO-d6) δ 11.07 (s, 1H), 7.67 (d, J = 8.3 Hz, 1H), 7.60 (s, 1H), 6.82 (d, J = 2.1 Hz, 1H), 6.73-6.66 (m, 1H), 6.63-6.53 (m, 3H), 5.06 (dd, J = 12.9, 5.4 Hz, 1H), 4.44-4.36 (m, 3H), 4.20 (s, 2H), 4.16 (s, 2H), 3.73 (s, 6H), 3.48 (s, 3H), 3.42-3.35 (m, 2H), 2.95-2.81 (m, 1H), 2.63-2.57 (m, 4H), 2.57-2.51 (m, 3H), 2.07-1.96 (m, 1H).
D304	752.45	¹ H NMR (300 MHz, DMSO-d6) δ 10.97 (s, 1H), 7.65 (s, 1H), 7.38 (d, J = 8.2 Hz, 1H), 6.69 (d, J = 7.5 Hz, 2H), 6.61 (d, J = 5.1 Hz, 3H), 5.08 (dd, J = 13.2, 5.1 Hz, 1H), 4.39-4.11 (m, 4H), 3.81 (s, 6H), 3.79-3.53 (m, 4H), 3.54-3.44 (m, 5H), 3.47-3.36 (m, 3H), 3.00-2.80 (m, 1H), 2.72-2.51 (m, 6H), 2.50-2.10 (m, 4H), 2.05-1.61 (m, 4H), 0.95 (d, J = 6.7 Hz, 3H).
D305	823.45	¹ H NMR (400 MHz, DMSO-d6) δ 8.14 (s, 1H, FA), 7.62 (s, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.26 (dd, J = 8.4, 2.4 Hz, 1H), 7.16 (d, J = 2.3 Hz, 1H), 6.67-6.58 (m, 2H), 6.54 (s, 1H), 5.16 (dd, J = 13.5, 5.1 Hz, 1H), 4.37-4.16 (m, 4H), 3.84-3.70 (m, 10H), 3.50 (s, 3H), 3.40 (t, J = 5.7 Hz, 2H), 3.31 (s, 3H), 3.07-2.92 (m, 5H), 2.82-2.66 (m, 8H), 2.63-2.58 (m, 4H), 2.38 (dd, 2H), 2.05-1.93 (m, 1H), 1.75 (d, J = 12.5 Hz, 2H), 1.48 (s, 3H), 1.35-1.12 (m, 3H).
D306	774.4	¹ H NMR (300 MHz, DMSO-d6) δ 10.98 (s, 1H), 7.65 (s, 1H), 7.42 (d, J = 8.6 Hz, 1H), 6.75-6.65 (m, 4H), 6.61 (s, 1H), 5.08 (dd, J = 13.3, 5.0 Hz, 1H), 4.38-4.15 (m, 5H), 3.92 (s, 3H), 3.86 (s, 7H), 3.75 (s, 3H), 3.51 (s, 3H), 2.98-2.83 (m, 2H), 2.60 (s, 7H), 2.43-2.34 (m, 3H), 2.25-2.07 (m, 2H), 2.02-1.92 (m, 1H).
D307	693.2	¹ H NMR (300 MHz, DMSO-d6) δ 10.97 (s, 1H), 7.65 (s, 1H), 7.36 (d, J = 9.2 Hz, 1H), 7.17-7.07 (m, 3H), 6.65-6.60 (m, 2H), 6.23-5.73 (m, 1H), 5.08 (dd, J = 13.3, 5.1 Hz, 1H), 4.50 (s, 2H), 4.36-4.12 (m, 4H), 3.83 (s, 6H), 3.49 (s, 3H), 3.43 (d, J = 5.0 Hz, 4H), 2.90 (s, 4H), 2.62 (s, 2H), 2.44-2.29 (m, 2H), 1.98 (d, J = 12.6 Hz, 1H).
D308	738.45	¹ H NMR (400 MHz, DMSO-d6) δ 10.97 (s, 1H), 8.18 (s, 1H, FA), 7.65 (s, 1H), 7.37 (d, J = 8.1 Hz, 1H), 6.77-6.65 (m, 2H), 6.63-6.53 (m, 3H), 5.08 (m, J = 13.3, 5.1 Hz, 1H), 4.39-4.12 (m, 4H), 3.79 (s, 6H), 3.57 (s, 4H), 3.50 (d, J = 4.1 Hz, 4H), 3.41 (m, J = 4.9 Hz, 4H), 2.91 (m, J = 17.6, 13.6, 5.3 Hz, 1H), 2.59 (d, J = 4.2 Hz, 6H), 2.44-2.33 (m, 4H), 2.03-1.95 (m, 1H), 1.71 (m, J = 5.3 Hz, 4H).
D309	837.6	¹ H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 7.63 (s, 1H), 7.42 (d, J = 8.5 Hz, 1H), 7.26 (dd, J = 8.5, 2.4 Hz, 1H), 7.15 (d, J = 2.3 Hz, 1H), 6.76-6.50 (m, 3H), 5.10 (dd, J = 13.3, 5.1 Hz, 1H), 4.39-4.14 (m, 4H), 3.98-3.66 (m, 8H), 3.50 (s, 3H), 3.45-3.38 (m, 2H), 3.33-3.26 (m, 4H), 3.00-2.82 (m, 2H), 2.81-2.64 (m, 3H), 2.64-2.56 (m, 5H), 2.56-2.52 (m, 2H), 2.49-2.27 (m, 3H), 2.20 (s, 1H), 2.06-1.90 (m, 1H), 1.83-1.67 (m, 2H), 1.62-1.35 (m, 5H), 1.35-0.94 (m, 6H).
D310	835.5	¹ H NMR (400 MHz, Methanol-d4) δ 7.68-7.61 (m, 1H), 7.54 (s, 1H), 7.10 (d, J = 8.0 Hz, 2H), 6.61 (s, 2H), 5.12 (dd, J = 13.3, 5.1 Hz, 1H), 4.63 (s, 1H), 4.49-4.38 (m, 2H), 4.36 (s, 2H), 4.22 (s, 1H), 3.97 (d, J = 12.8 Hz, 2H), 3.87 (s, 7H), 3.63 (s, 4H), 3.53 (t, J = 5.6 Hz, 3H), 3.23 (s, 2H), 3.09 (s, 2H), 2.99-2.86 (m, 3H), 2.85-2.71 (m, 5H), 2.62 (d, J = 6.1 Hz, 2H), 2.54-2.41 (m, 1H), 2.22-2.13 (m, 1H), 1.89 (d, J = 12.5 Hz, 2H), 1.79-1.71 (m, 2H), 1.66 (s, 1H), 1.44 (q, J = 11.2 Hz, 2H), 1.09-0.87 (m, 2H), 0.80 (s, 2H).
D311	885.45	¹ H NMR (400 MHz, DMSO-d6) δ 10.96 (s, 1H), 8.20 (s, 1H, FA), 7.61 (s, 1H), 7.50 (d, J = 8.5 Hz, 1H), 7.13 (t, J = 5.8 Hz, 1H), 7.08-6.99 (m, 2H),

Compound No.	LCMS	^1H NMR
D312	885.45	6.55 (s, 2H), 6.17-5.76 (m, 1H), 5.05 (dd, $J = 13.3, 5.1$ Hz, 1H), 4.39-4.11 (m, 5H), 3.87 (d, $J = 12.3$ Hz, 2H), 3.76 (s, 8H), 3.49 (s, 4H), 3.47-3.33 (m, 6H), 2.98-2.76 (m, 4H), 2.73-2.69 (m, 2H), 2.66-2.54 (m, 3H), 2.57-2.52 (m, 1H), 2.41-2.32 (m, 1H), 2.00-1.92 (m, 1H), 1.76 (d, $J = 12.5$ Hz, 2H), 1.63-1.39 (m, 3H), 1.30-1.17 (m, 2H), 0.68-0.63 (m, 2H), 0.48 (s, 2H).
D313	887.65	^1H NMR (400 MHz, DMSO-d6) δ 10.96 (s, 1H), 8.21 (s, 2H, TFA), 7.62 (s, 1H), 7.42 (d, $J = 8.4$ Hz, 1H), 7.26 (dd, $J = 8.6, 2.4$ Hz, 1H), 7.18-7.09 (m, 2H), 6.55 (s, 2H), 6.17-5.79 (m, 1H), 5.10 (dd, $J = 13.3, 5.1$ Hz, 1H), 4.45-4.13 (m, 5H), 3.86-3.66 (m, 10H), 3.55-3.48 (m, 5H), 3.48-3.41 (m, 4H), 3.40-3.36 (m, 1H), 2.98-2.85 (m, 1H), 2.76-2.66 (m, 6H), 2.65-2.55 (m, 3H), 2.45-2.34 (m, 1H), 2.03-1.96 (m, 1H), 1.77 (d, $J = 12.3$ Hz, 2H), 1.51-1.47 (m, 3H), 1.28 (d, $J = 11.7$ Hz, 2H), 0.69-0.65 (m, 2H), 0.51 (s, 2H).
D314	835.5	^1H NMR (400 MHz, Methanol-d4) δ 7.81 (s, 1H), 7.71 (s, 2H), 7.58 (s, 1H), 6.73 (s, 2H), 5.90 (tt, $J = 56.7, 4.2$ Hz, 1H), 5.18 (dd, $J = 13.3, 5.2$ Hz, 1H), 4.77-4.45 (m, 3H), 4.41 (s, 2H), 4.30-4.01 (m, 1H), 3.95 (s, 6H), 3.80 (d, $J = 12.1$ Hz, 2H), 3.65 (s, 3H), 3.62-3.49 (m, 4H), 3.42 (s, 2H), 3.16 (br s, 1H), 3.00-2.76 (m, 3H), 2.75-2.61 (m, 5H), 2.61-2.42 (m, 2H), 2.26-2.16 (m, 1H), 2.08 (d, $J = 13.6$ Hz, 2H), 1.82 (s, 1H), 1.67 (s, 10H).
D315	871.6	^1H NMR (300 MHz, DMSO-d6) δ 10.98 (s, 1H), 8.18 (s, 1H, FA), 7.64 (s, 1H), 7.41 (d, $J = 8.8$ Hz, 1H), 6.76-6.68 (m, 2H), 6.63-6.58 (m, 3H), 5.10 (dd, 1H), 4.39-4.13 (m, 4H), 3.89 (d, $J = 7.9$ Hz, 2H), 3.79 (s, 6H), 3.69 (d, $J = 8.0$ Hz, 2H), 3.60 (s, 2H), 3.50 (s, 3H), 3.41 (s, 2H), 3.40 (s, 2H), 2.98-2.82 (m, 3H), 2.59 (d, $J = 4.2$ Hz, 5H), 2.44-2.34 (m, 4H), 2.18 (d, $J = 7.2$ Hz, 4H), 2.00 (s, 3H), 1.63 (d, $J = 12.6$ Hz, 2H), 1.50 (s, 1H), 1.17-1.02 (m, 2H).
D316	862.5	^1H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 7.63 (s, 1H), 7.42 (d, $J = 8.4$ Hz, 1H), 7.26 (dd, $J = 8.5, 2.4$ Hz, 1H), 7.15 (dd, $J = 9.2, 4.1$ Hz, 2H), 6.64 (s, 2H), 5.99 (t, $J = 4.2$ Hz, 1H), 5.09 (dd, $J = 13.3, 5.1$ Hz, 1H), 4.43-4.10 (m, 5H), 3.78 (d, $J = 27.4$ Hz, 9H), 3.61 (s, 1H), 3.11 (s, 6H), 2.92 (s, 2H), 2.98-2.85 (m, 4H), 2.72 (d, $J = 11.9$ Hz, 2H), 2.62 (s, 3H), 2.55 (s, 3H), 2.46-2.30 (m, 3H), 2.06-1.89 (m, 1H), 1.82-1.68 (m, 2H), 1.53 (d, $J = 40.7$ Hz, 3H), 1.35-1.20 (m, 2H)..
D317	862.35	^1H NMR (400 MHz, DMSO-d6) δ 10.95 (s, 1H), 8.16 (s, 1H, FA), 7.65 (s, 1H), 7.49 (d, $J = 8.6$ Hz, 1H), 7.13 (t, $J = 5.7$ Hz, 1H), 7.04 (s, 2H), 6.59 (s, 2H), 6.15-5.81 (m, 1H), 5.09-4.99 (m, 1H), 4.37-4.12 (m, 4H), 3.85 (d, $J = 12.6$ Hz, 2H), 3.78 (s, 6H), 3.53 (s, 2H), 3.49-3.39 (m, 6H), 2.95-2.74 (m, 1H), 2.71-2.63 (m, 2H), 2.63-2.57 (m, 1H), 2.57-2.54 (m, 3H), 2.47-2.40 (m, 3H), 2.40-2.37 (m, 1H), 2.37-2.28 (m, 4H), 2.03-1.88 (m, 1H), 1.73 (d, $J = 13.8$ Hz, 2H), 1.50 (s, 1H), 1.42-1.31 (m, 2H), 1.27-1.12 (m, 2H),..
D318	840.55	^1H NMR (300 MHz, DMSO-d6) δ 10.96 (s, 1H), 8.22 (s, 1H, FA), 7.63 (s, 1H), 7.50 (d, $J = 8.8$ Hz, 1H), 7.12-6.99 (m, 2H), 6.65-6.58 (m, 1H), 6.56 (s, 2H), 5.05 (dd, $J = 13.2, 5.1$ Hz, 1H), 4.38-4.12 (m, 4H), 3.92-3.81 (m, 4H), 3.78 (s, 6H), 3.49-3.34 (m, 4H), 3.00-2.70 (m, 5H), 2.65-2.54 (m, 4H), 2.41-2.15 (m, 5H), 2.14-1.91 (m, 3H), 1.80-1.67 (m, 2H), 1.60-1.45 (m, 1H), 1.43-1.30 (m, 2H), 1.28-1.17 (m, 2H), 1.16-1.06 (m, 6H).
D319	840.55	^1H NMR (300 MHz, Methanol-d4) δ 7.80-7.53 (m, 4H), 6.75 (s, 2H), 5.18 (dd, $J = 13.3, 5.1$ Hz, 1H), 4.62-4.42 (m, 4H), 4.36 (s, 2H), 3.98 (s, 6H), 3.93-3.72 (m, 5H), 3.61-3.50 (m, 3H), 3.29-3.21 (m, 3H), 3.02-2.81 (m, 4H), 2.78 (s, 4H), 2.69-2.60 (m, 2H), 2.57-2.44 (m, 1H), 2.30-2.15 (m, 1H), 2.12-1.97 (m, 2H), 1.91-1.69 (m, 4H), 1.66-1.51 (m, 7H).
D320	887.45	^1H NMR (400 MHz, Methanol-d4) δ 7.68 (d, $J = 9.2$ Hz, 1H), 7.58 (s, 1H), 7.20-7.17 (m, 2H), 6.73 (s, 2H), 5.90 (tt, $J = 56.6, 4.2$ Hz, 1H), 5.13 (dd, $J = 13.3, 5.1$ Hz, 1H), 4.62 (s, 1H), 4.53-4.33 (m, 4H), 4.13 (s, 1H), 3.95 (s, 7H), 3.92 (s, 1H), 3.64 (s, 3H), 3.60-3.54 (m, 3H), 3.53-3.49 (m, 1H), 3.47 (s, 2H), 3.15 (s, 1H), 3.05-2.93 (m, 3H), 2.96-2.86 (m, 1H), 2.85-2.75 (m, 4H), 2.64 (t, $J = 5.2$ Hz, 3H), 2.48 (qd, $J = 13.2, 4.7$ Hz, 1H), 2.23-2.12 (m, 1H), 1.90 (d, $J = 12.6$ Hz, 2H), 1.68 (s, 7H), 1.66-1.59 (m, 2H), 1.51-1.37 (m, 2H).
D321	849.55	^1H NMR (400 MHz, DMSO-d6) δ 10.96 (s, 1H), 7.62 (s, 1H), 7.54 (d, $J = 8.3$ Hz, 1H), 7.11 (s, 2H), 6.72 (s, 2H), 5.04 (dd, $J = 13.2, 5.1$ Hz, 1H), 4.58 (s, 1H), 4.38-4.14 (m, 4H), 3.97 (s, 3H), 3.89 (s, 7H), 3.62-3.57 (m, 4H), 3.51 (s, 3H), 3.41 (t, $J = 5.6$ Hz, 2H), 3.34-3.15 (m, 4H), 2.97-2.78 (m, 3H), 2.67-2.55 (m, 6H), 2.56-2.50 (m, 2H), 2.45-2.29 (m, 1H), 2.22 (s, 1H), 2.03-1.81 (m, 3H), 1.82-1.68 (m, 4H), 1.64-1.55 (m, 1H), 1.31 (q, $J = 10.7$ Hz, 2H).

Compound No.	LCMS	¹ H NMR
D322	899.5	¹ H NMR (300 MHz, Methanol-d4) δ 7.69 (d, J = 9.1 Hz, 1H), 7.59 (s, 1H), 7.20 (d, J = 7.1 Hz, 2H), 6.74 (s, 2H), 6.16-5.65 (m, 1H), 5.12 (dd, J = 13.2, 5.1 Hz, 1H), 4.58-4.26 (m, 6H), 4.06-3.86 (m, 9H), 3.76-3.65 (m, 4H), 3.67-3.46 (m, 7H), 3.40 (s, 2H), 3.24 (s, 2H), 3.03 (t, J = 12.2 Hz, 2H), 2.94-2.78 (m, 2H), 2.78-2.69 (m, 2H), 2.67-2.61 (m, 2H), 2.57-2.34 (m, 2H), 2.22-2.02 (m, 3H), 1.94 (d, J = 12.5 Hz, 2H), 1.74 (d, J = 33.3 Hz, 3H), 1.61-1.38 (m, 2H).
D323	840.5	¹ H NMR (300 MHz, Methanol-d4) δ 8.49 (s, 2H, FA), 7.58 (s, 1H), 7.45 (d, J = 8.2 Hz, 1H), 7.37-7.30 (m, 2H), 6.73 (s, 2H), 5.15 (dd, J = 13.3, 5.1 Hz, 1H), 4.54-4.46 (m, 1H), 4.43-4.29 (m, 5H), 3.96 (s, 6H), 3.84-3.68 (m, 4H), 3.64 (s, 3H), 3.55 (t, J = 5.3 Hz, 2H), 3.37 (s, 1H), 2.96-2.72 (m, 6H), 2.64 (s, 3H), 2.58-2.44 (m, 3H), 2.24-2.12 (m, 1H), 1.95-1.83 (m, 2H), 1.62-1.42 (m, 9H), 1.42-1.22 (m, 2H).
D324	840.5	¹ H NMR (400 MHz, Methanol-d4) δ 7.68 (d, J = 9.3 Hz, 1H), 7.58 (s, 1H), 7.20-7.17 (m, 2H), 6.74 (s, 2H), 5.13 (dd, J = 13.3, 5.1 Hz, 1H), 4.59 (d, J = 13.5 Hz, 1H), 4.50-4.41 (m, 3H), 4.36 (s, 2H), 4.04-3.88 (m, 10H), 3.64 (s, 4H), 3.55 (t, J = 5.6 Hz, 2H), 3.37 (s, 1H), 3.24-3.13 (m, 1H), 3.08-2.84 (m, 6H), 2.83-2.75 (m, 1H), 2.68-2.59 (m, 2H), 2.52-2.41 (m, 1H), 2.23-2.12 (m, 1H), 1.91 (d, J = 12.9 Hz, 2H), 1.77-1.67 (m, 3H), 1.61 (d, J = 6.6 Hz, 6H), 1.52-1.40 (m, 2H).
D325	837.4	¹ H NMR (400 MHz, Methanol-d4) δ 8.57 (s, 1H, FA), 7.63 (d, J = 8.6 Hz, 1H), 7.57 (s, 1H), 7.11-7.05 (m, 2H), 6.72 (s, 2H), 5.11 (dd, J = 13.3, 5.1 Hz, 1H), 4.94-4.89 (m, 1H), 4.44 (s, 1H), 4.46-4.37 (m, 2H), 4.36 (s, 3H), 3.97-3.91 (m, 8H), 3.73-3.66 (m, 1H), 3.64 (s, 3H), 3.55 (t, J = 5.6 Hz, 2H), 3.00-2.89 (m, 1H), 2.89-2.80 (m, 3H), 2.78 (s, 5H), 2.63 (t, J = 5.6 Hz, 3H), 2.60-2.39 (m, 4H), 2.21-2.10 (m, 1H), 1.92-1.83 (m, 2H), 1.65 (s, 1H), 1.58-1.48 (m, 8H), 1.44-1.29 (m, 3H).
D326	837.45	¹ H NMR (400 MHz, Methanol-d4) δ 8.57 (s, 1H, FA), 7.58 (s, 1H), 7.45 (d, J = 8.4 Hz, 1H), 7.39-7.26 (m, 2H), 6.73 (s, 2H), 5.15 (dd, J = 13.3, 5.1 Hz, 1H), 4.49-4.34 (m, 3H), 4.36 (s, 3H), 3.96 (s, 6H), 3.77 (d, J = 12.3 Hz, 2H), 3.74-3.66 (m, 1H), 3.64 (s, 3H), 3.55 (t, J = 5.6 Hz, 2H), 3.01-2.86 (m, 2H), 2.86-2.76 (m, 6H), 2.75 (s, 1H), 2.64 (t, J = 5.7 Hz, 3H), 2.60-2.42 (m, 4H), 2.26-2.13 (m, 1H), 1.89 (s, 2H), 1.52 (d, J = 6.6 Hz, 9H), 1.48-1.35 (m, 3H).
D327	807.55	¹ H NMR (300 MHz, DMSO-d6) δ 10.99 (s, 1H), 8.19 (s, 1H), 7.61 (s, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.25 (d, J = 8.1 Hz, 1H), 7.15 (s, 1H), 6.76 (s, 2H), 6.60 (d, J = 4.2 Hz, 1H), 5.10 (dd, J = 13.2, 4.8 Hz, 1H), 4.33 (d, J = 17.1 Hz, 1H), 4.25-4.14 (m, 3H), 3.90-3.70 (m, 7H), 3.49 (s, 3H), 3.39 (s, 4H), 2.99-2.84 (m, 2H), 2.78-2.65 (m, 4H), 2.65-2.55 (m, 4H), 2.44-2.30 (m, 10H), 2.04-1.93 (m, 1H), 1.75 (d, J = 11.7 Hz, 2H), 1.55-1.35 (m, 3H), 1.35-1.12 (m, 5H).
D328	876.3	¹ H NMR (300 MHz, DMSO-d6) δ 11.09 (s, 1H), 7.65 (t, J = 4.3 Hz, 2H), 7.32-7.09 (m, 3H), 6.58 (s, 2H), 5.99 (tt, J = 56.7, 4.3 Hz, 1H), 5.07 (dd, J = 12.8, 5.4 Hz, 1H), 4.26 (s, 2H), 4.03 (d, J = 12.7 Hz, 2H), 3.77 (s, 6H), 3.51 (s, 2H), 3.46 (m, 2H), 3.44 (m, 2H), 3.43 (m, 2H), 2.91 (q, J = 14.2, 13.3 Hz, 4H), 2.61 (d, J = 3.6 Hz, 1H), 2.35 (d, J = 30.3 Hz, 10H), 2.01 (d, J = 11.0 Hz, 1H), 1.74 (d, J = 12.6 Hz, 2H), 1.57 (s, 1H), 1.35 (d, J = 7.3 Hz, 2H), 1.19 (dd, J = 20.1, 9.1 Hz, 2H).
D329	853.4	¹ H NMR (400 MHz, DMSO-d6) δ 10.96 (s, 1H), 7.63 (s, 1H), 7.52 (d, J = 8.5 Hz, 1H), 7.10-7.04 (m, 2H), 6.70 (s, 2H), 6.62 (s, 1H), 5.05 (dd, J = 13.3, 5.1 Hz, 1H), 4.32 (d, J = 16.9 Hz, 1H), 4.25-4.15 (m, 4H), 3.85-3.83 (m, 2H), 3.81-3.73 (m, 8H), 3.72-3.58 (m, 4H), 3.51 (s, 4H), 3.42 (s, 6H), 3.27-2.99 (m, 5H), 2.98-2.84 (m, 4H), 2.64-2.56 (m, 4H), 2.45-2.28 (m, 1H), 2.02-1.89 (m, 1H), 1.75 (d, J = 12.4 Hz, 2H), 1.65-1.48 (m, 3H), 1.33-1.17 (m, 2H).
D330	845.4	¹ H NMR (300 MHz, DMSO-d6) δ 10.96 (s, 1H), 8.24 (s, 2H, FA), 7.64 (s, 1H), 7.52 (d, J = 8.4 Hz, 1H), 7.17-7.06 (m, 2H), 6.59 (s, 3H), 5.05 (dd, J = 13.2, 5.0 Hz, 1H), 4.37-4.29 (m, 1H), 4.25-4.19 (m, 3H), 4.11-4.07 (m, 1H), 3.90-3.86 (m, 2H), 3.78 (s, 6H), 3.54-3.47 (m, 5H), 3.40 (t, J = 5.6 Hz, 3H), 3.24 (dd, J = 30.5, 13.2 Hz, 2H), 3.05-2.84 (m, 2H), 2.64-2.57 (m, 4H), 2.47-2.26 (m, 10H), 2.15-2.06 (m, 1H), 2.01-1.81 (m, 3H), 1.53-1.40 (m, 1H), 1.37-1.18 (m, 1H).
D331	655.4	¹ H NMR (400 MHz, DMSO-d6) δ 10.94 (s, 1H), 7.60 (s, 1H), 7.51 (d, J = 8.3 Hz, 1H), 6.64-6.49 (m, 5H), 5.04 (dd, J = 13.3, 5.1 Hz, 1H), 4.36-4.28 (m, 4H), 4.24-4.15 (m, 3H), 4.03-3.97 (m, 2H), 3.73 (s, 6H), 3.48 (s, 3H), 3.38 (t, J = 5.5 Hz, 2H), 2.97-2.83 (m, 1H), 2.63-2.53 (m, 6H), 2.42-2.27 (m, 1H), 1.99-1.92 (m, 1H).
D332	849.5	¹ H NMR (400 MHz, DMSO-d6) δ 10.99 (s, 1H), 7.62 (s, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.38 (dd, J = 8.5, 2.3 Hz, 1H), 7.32 (d, J = 2.3 Hz, 1H), 6.73 (s, 2H), 5.09 (dd, J = 13.3, 5.1 Hz, 1H), 4.65-4.43 (m, 1H), 4.44-4.15 (m, 4H), 3.89 (s, 6H), 3.81-3.76 (m, 4H), 3.57-3.31 (m, 4H), 3.41-3.30 (m, 3H), 3.24-3.06 (m, 5H), 2.94-2.84 (m, 4H), 2.75-2.63 (m, 5H), 2.61-2.57 (m, 3H), 2.56-2.52 (m, 1H), 2.14-2.05 (m, 1H), 2.04-1.96 (m, 1H), 1.96-1.79 (m, 4H), 1.74-1.69 (m, 2H), 1.60-1.56 (m, 1H), 1.46-1.36 (m, 2H).

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Compound No.	LCMS	¹ H NMR
D333	899.5	¹ H NMR (300 MHz, Methanol-d4) δ 7.72-7.56 (m, 4H), 6.74 (s, 2H), 6.16-5.60 (m, 1H), 5.24-5.08 (m, 1H), 4.62-4.22 (m, 6H), 3.97 (s, 6H), 3.80 (d, J = 12.0 Hz, 2H), 3.70-3.46 (m, 8H), 3.44-3.33 (m, 4H), 3.29-3.16 (m, 4H), 3.06 (s, 2H), 2.96-2.68 (m, 2H), 2.68-2.59 (m, 4H), 2.57-2.46 (m, 1H), 2.41 (s, 1H), 2.12 (dt, J = 45.4, 6.8 Hz, 5H), 1.83-1.47 (m, 5H).
D334	875.4	¹ H NMR (300 MHz, Methanol-d4) δ 7.59 (s, 1H), 7.39 (d, J = 8.2 Hz, 1H), 7.04-6.67 (m, 4H), 5.14 (dd, J = 13.1, 5.1 Hz, 1H), 4.66-4.48 (m, 2H), 4.45-4.31 (m, 4H), 4.31-4.12 (m, 4H), 3.97 (s, 6H), 3.93-3.89 (m, 2H), 3.87-3.57 (m, 9H), 3.55 (t, J = 5.6 Hz, 3H), 2.98-2.80 (m, 3H), 2.78 (s, 3H), 2.76-2.66 (m, 2H), 2.66-2.60 (m, 2H), 2.57-2.43 (m, 1H), 2.26-2.13 (m, 1H), 2.11-1.98 (m, 1H), 1.93-1.70 (m, 3H).
D335	868.55	¹ H NMR (300 MHz, DMSO-d6) δ 10.98 (s, 1H), 8.14 (s, 0.4H, FA), 7.65 (s, 1H), 7.39 (d, J = 8.3 Hz, 1H), 7.33-7.25 (m, 1H), 7.20 (d, J = 8.0 Hz, 1H), 6.73-6.64 (m, 2H), 6.57 (s, 2H), 5.39 (d, J = 8.0 Hz, 1H), 5.08 (dd, J = 13.3, 5.1 Hz, 1H), 4.61 (s, 2H), 4.36-4.16 (m, 2H), 3.80 (s, 6H), 3.72-3.57 (m, 6H), 3.48 (s, 3H), 3.14-2.81 (m, 5H), 2.70-2.56 (m, 5H), 2.49-2.30 (m, 4H), 2.27-2.05 (m, 3H), 2.04-1.58 (m, 6H), 1.51-1.32 (m, 1H).
D336	885.4	¹ H NMR (400 MHz, MeOD) δ 8.47 (s, 2FA, 2H), 7.59 (s, 1H), 7.40 (d, J = 8.2 Hz, 1H), 6.86 (d, J = 2.2 Hz, 1H), 6.78 (dd, J = 8.2, 2.2 Hz, 1H), 6.73 (s, 2H), 6.07-5.71 (m, 1H), 5.14 (dd, J = 13.3, 5.1 Hz, 1H), 4.47-4.32 (m, 6H), 3.95 (s, 6H), 3.67 (d, J = 18.9 Hz, 7H), 3.61-3.48 (m, 6H), 3.15-3.10 (m, 2H), 2.98-2.57 (m, 8H), 2.56-2.42 (m, 3H), 2.21-2.14 (m, 1H), 2.09-2.0 (m, 3H), 1.99-1.93 (m, 5H), 1.58-1.53 (m, 2H).
D337	837.5	¹ H NMR (300 MHz, DMSO-d6) δ 7.65 (d, J = 8.5 Hz, 1H), 7.29-7.16 (m, 2H), 6.50 (s, 2H), 4.99 (dd, J = 12.7, 5.5 Hz, 1H), 4.19 (d, J = 16.7 Hz, 4H), 3.96 (s, 3H), 3.77 (s, 6H), 3.50 (s, 4H), 3.34 (s, 8H), 3.10 (s, 2H), 2.94 (t, J = 12.3 Hz, 2H), 2.84-2.72 (m, 1H), 2.63 (d, J = 3.4 Hz, 1H), 2.55 (s, 3H), 2.4-2.5 (m, 1H), 2.18 (s, 2H), 2.10 (s, 3H), 2.06-1.96 (m, 1H), 1.73 (d, J = 12.4 Hz, 2H), 1.57 (s, 3H), 1.17 (d, J = 12.4 Hz, 2H).
D338	900.45	¹ H NMR (400 MHz, DMSO-d6) δ 11.13 (s, 1H), 8.03 (t, 1H), 7.86-7.71 (m, 1H), 7.57 (s, 1H), 7.35-7.21 (m, 2H), 6.73-6.59 (m, 3H), 5.12 (dd, J = 12.8, 5.4 Hz, 1H), 4.98 (t, J = 6.8 Hz, 1H), 4.25 (s, 2H), 3.79 (s, 6H), 3.59 (s, 3H), 3.42 (t, J = 5.5 Hz, 3H), 2.99-2.81 (m, 3H), 2.66-2.57 (m, 5H), 2.46-2.37 (m, 2H), 2.37-1.98 (m, 9H), 1.80 (dd, J = 12.3, 6.3 Hz, 2H), 1.70-1.59 (m, 4H), 1.56 (t, J = 5.1 Hz, 2H), 1.48 (s, 1H), 1.17-0.98 (m, 2H).
D339	871.5	¹ H NMR (400 MHz, Methanol-d4) δ 8.53 (s, 1H, FA), 7.65-7.54 (m, 2H), 6.70 (s, 2H), 6.61-6.51 (m, 2H), 5.09 (dd, J = 13.2, 5.1 Hz, 1H), 4.61 (s, 2H), 4.47-4.27 (m, 6H), 4.05 (d, J = 7.9 Hz, 2H), 3.93 (s, 6H), 3.74 (d, J = 8.0 Hz, 2H), 3.63 (s, 3H), 3.53 (t, J = 5.6 Hz, 4H), 3.17-3.01 (m, 2H), 2.95-2.85 (m, 1H), 2.82-2.73 (m, 4H), 2.72-2.58 (m, 3H), 2.57-2.39 (m, 3H), 2.37-2.27 (m, 2H), 2.18-2.07 (m, 3H), 2.05-1.97 (m, 2H), 1.96-1.83 (m, 1H), 1.51-1.40 (m, 1H).
D340	853.4	¹ H NMR (400 MHz, DMSO-d6) δ 10.99 (s, 1H), 7.63 (s, 1H), 7.44 (d, J = 8.5 Hz, 1H), 7.33-7.26 (m, 1H), 7.20 (s, 1H), 6.70 (s, 2H), 6.62 (s, 1H), 5.10 (dd, J = 13.3, 5.1 Hz, 1H), 4.34 (d, J = 16.8 Hz, 1H), 4.25-4.17 (m, 4H), 3.81-3.77 (m, 8H), 3.76-3.72 (m, 6H), 3.51 (s, 3H), 3.40 (s, 6H), 3.24-3.00 (m, 4H), 2.98-2.85 (m, 3H), 2.76 (t, J = 11.9 Hz, 3H), 2.65-2.52 (m, 4H), 2.43-2.34 (m, 1H), 2.04-1.94 (m, 1H), 1.78 (d, J = 12.3 Hz, 2H), 1.66-1.45 (m, 3H), 1.39-1.23 (m, 2H).
D341	812.45	¹ H NMR (300 MHz, MeOD) δ 8.52 (s, FA, 1H), 7.57 (s, 1H), 7.45 (d, J = 8.3 Hz, 1H), 7.38-7.27 (m, 2H), 6.68 (s, 2H), 5.15 (dd, J = 13.2, 5.1 Hz, 1H), 4.51-4.33 (m, 4H), 4.11 (s, 2H), 3.91 (s, 6H), 3.77 (d, J = 12.2 Hz, 2H), 3.64 (s, 3H), 3.54 (t, J = 5.7, 5.7 Hz, 2H), 3.15-3.03 (m, 4H), 3.00-2.85 (m, 4H), 2.85-2.68 (m, 6H), 2.66-2.61 (m, 2H), 2.59-2.42 (m, 1H), 2.23-2.13 (m, 1H), 1.87 (d, J = 12.3 Hz, 2H), 1.64-1.55 (m, 3H), 1.51-1.38 (m, 2H).
D342	850.35	¹ H NMR (400 MHz, Methanol-d4) δ 8.53 (s, 2H, FA), 8.10-7.81 (m, 3H), 7.59 (s, 1H), 6.73 (s, 2H), 5.16 (dd, J = 12.6, 5.4 Hz, 1H), 4.37 (d, J = 3.4 Hz, 4H), 4.26-4.09 (m, 1H), 3.95 (s, 6H), 3.80-3.65 (m, 4H), 3.59-3.36 (m, 6H), 3.11 (s, 3H), 2.90 (ddd, J = 17.6, 14.3, 5.1 Hz, 1H), 2.83-2.69 (m, 5H), 2.64 (t, J = 5.5 Hz, 2H), 2.30 (t, J = 13.5 Hz, 1H), 2.21-2.09 (m, 2H), 2.04 (d, J = 12.7 Hz, 3H), 1.96 (s, 1H), 1.78 (s, 3H), 1.65 (s, 2H), 1.58-1.49 (m, 3H), 1.45 (d, J = 6.2 Hz, 3H).
D343	932.4	¹ H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 8.19 (s, FA, 1H), 7.82 (d, J = 8.2 Hz, 1H), 7.62 (s, 1H), 7.32-7.24 (m, 2H), 6.64-6.55 (m, 3H), 5.12 (dd, J = 12.8, 5.4 Hz, 1H), 5.01-4.94 (m, 1H), 4.21 (s, 2H), 3.86-3.71 (m, 8H), 3.54-3.47 (m, 5H), 3.05-2.90 (m, 2H), 2.90-2.76 (m, 5H), 2.73-2.68 (m, 1H), 2.64-2.55 (m, 5H), 2.45-2.40 (m, 4H), 2.07-2.06 (m, 3H), 1.92-1.75 (m, 3H), 1.64-1.45 (m, 6H), 1.32-1.11 (m, 2H).
D344	859.45	¹ H NMR (400 MHz, Methanol-d4) δ 7.69 (d, J = 2.1 Hz, 1H), 7.66-7.57 (m, 3H), 6.74 (s, 2H), 6.13-5.65 (m, 1H), 5.22-5.13 (m, 1H), 4.62-4.37 (m, 6H), 3.95 (s, 6H), 3.88-3.74 (m, 3H), 3.65 (s, 3H), 3.60-3.55 (m, 7H), 3.53-3.49 (m, 1H), 3.44 (s, 3H), 3.27-3.20 (m, 2H), 3.19-3.09 (m, 2H).

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Compound No.	LCMS	¹ H NMR
D345	918.45	¹ H NMR (400 MHz, Methanol-d4) δ 7.58 (s, 1H), 7.48 (d, J = 8.3 Hz, 1H), 7.20 (d, J = 2.5 Hz, 1H), 7.15 (dd, J = 8.3, 2.4 Hz, 1H), 6.74 (d, J = 4.1 Hz, 2H), 5.16 (dd, J = 13.3, 5.1 Hz, 1H), 4.79 (t, J = 6.7 Hz, 1H), 4.50-4.42 (m, 2H), 4.36 (s, 4H), 3.96 (s, 6H), 3.69-3.59 (m, 5H), 3.55 (t, J = 5.6 Hz, 2H), 3.38-3.35 (m, 1H), 3.20-3.08 (m, 2H), 3.00-2.84 (m, 4H), 2.84-2.81 (m, 1H), 2.78 (s, 3H), 2.68-2.58 (m, 3H), 2.57-2.45 (m, 4H), 2.37 (d, J = 14.8 Hz, 1H), 2.24-2.01 (m, 4H), 1.96-1.87 (m, 2H), 1.74-1.52 (m, 6H).
D346	845.4	¹ H NMR (300 MHz, DMSO-d6) δ 10.99 (s, 1H), 8.36 (s, 3H, FA), 7.64 (s, 1H), 7.44 (d, J = 8.3 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 7.20 (s, 1H), 6.58 (s, 3H), 5.10 (dd, J = 13.4, 4.9 Hz, 1H), 4.40-4.31 (m, 1H), 4.25-4.16 (m, 3H), 4.02-3.89 (m, 3H), 3.78 (s, 6H), 3.52-3.49 (m, 5H), 3.42-3.37 (m, 3H), 3.23-3.14 (m, 1H), 3.14-3.05 (m, 1H), 2.97-2.84 (m, 2H), 2.62-2.56 (m, 4H), 2.44-2.28 (m, 10H), 2.05-1.94 (m, 2H), 1.92-1.72 (m, 2H), 1.57-1.44 (m, 1H), 1.36-1.22 (m, 1H).
D347	882.4	¹ H NMR (300 MHz, DMSO-d6) δ 11.14 (s, 1H), 9.21 (d, J = 73.7 Hz, TFA, 2H), 7.86 (d, J = 8.3 Hz, 1H), 7.77 (s, 1H), 7.34 (d, J = 2.3 Hz, 1H), 7.30 (d, J = 8.3 Hz, 1H), 6.77 (s, 2H), 6.66 (d, J = 4.5 Hz, 1H), 6.13 (s, 1H), 5.96 (s, 1H), 5.13 (dd, J = 12.9, 5.3 Hz, 1H), 5.05-4.97 (m, 1H), 4.23 (d, J = 14.7 Hz, 4H), 3.88 (s, 6H), 3.18 (s, 2H), 3.07-2.78 (m, 7H), 2.60 (d, J = 4.1 Hz, 8H), 2.18-1.69 (m, 11H), 1.63-1.39 (m, 2H).
D348	737.4	1H, 7.61-7.55 (m, 2H), 7.51 (dd, J = 8.4, 2.2 Hz, 1H), 6.80 (s, 2H), 5.17 (dd, J = 13.3, 5.2 Hz, 1H), 4.54-4.43 (m, 2H), 4.40 (s, 2H), 3.97 (s, 6H), 3.79 (d, J = 12.1 Hz, 2H), 3.67 (s, 3H), 3.48-3.42 (m, 5H), 3.32-3.24 (m, 3H), 3.15-3.01 (m, 6H), 2.92-2.84 (m, 3H), 2.84-2.74 (m, 1H), 2.60-2.42 (m, 1H), 2.24-2.07 (m, 3H), 2.03-1.94 (m, 2H), 1.75-1.67 (m, 3H), 1.60-1.50 (m, 2H).
D349	796.25	¹ H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 10.30-9.27 (m, 2H, TFA), 7.63 (d, J = 7.4 Hz, 1H), 7.41 (d, J = 8.8 Hz, 1H), 6.80-6.67 (m, 4H), 5.07 (dd, J = 13.2, 5.1 Hz, 1H), 4.43-4.26 (m, 6H), 4.24-4.18 (m, 2H), 4.10-3.94 (m, 3H), 3.89 (d, J = 3.2 Hz, 6H), 3.76-3.70 (m, 2H), 3.69-3.59 (m, 5H), 3.51 (s, 3H), 3.27-3.08 (m, 2H), 3.05-2.84 (m, 3H), 2.70-2.56 (m, 4H), 2.45-2.36 (m, 1H), 2.17-2.06 (m, 2H), 2.03-1.88 (m, 3H).
D350	736.25	¹ H NMR (300 MHz, DMSO-d6) δ 7.68 (s, 1H), 7.41 (d, J = 8.8 Hz, 1H), 6.79-6.66 (m, 4H), 5.04 (dd, J = 13.2, 5.1 Hz, 1H), 4.34 (dd, J = 17.0, 5.4 Hz, 3H), 4.25-4.14 (m, 3H), 4.04-3.92 (m, 2H), 3.89 (s, 6H), 3.71 (s, 2H), 3.57-3.49 (m, 3H), 3.42 (s, 5H), 3.36 (s, 3H), 3.26-3.10 (m, 1H), 3.05-2.92 (m, 3H), 2.82 (q, J = 11.6, 9.6 Hz, 2H), 2.60 (d, J = 16.7 Hz, 1H), 2.36 (dt, J = 13.5, 6.6 Hz, 1H), 2.11 (d, J = 13.7 Hz, 2H), 1.93 (td, J = 17.8, 16.9, 9.8 Hz, 3H).
D351	695.25	¹ H NMR (400 MHz, Methanol-d4) δ 8.56 (s, 1H, FA), 7.66 (d, J = 8.2 Hz, 1H), 6.88 (s, 1H), 6.86 (d, J = 2.1 Hz, 1H), 6.69 (dd, J = 8.4, 2.1 Hz, 1H), 6.65 (s, 2H), 5.08 (dd, J = 12.5, 5.4 Hz, 1H), 4.10-3.98 (m, 2H), 3.98-3.88 (m, 6H), 3.89-3.80 (m, 4H), 3.62 (s, 3H), 3.40 (t, J = 5.6 Hz, 2H), 3.05-2.81 (m, 4H), 2.81-2.68 (m, 3H), 2.56 (t, J = 6.2 Hz, 2H), 2.19-1.97 (m, 5H), 1.85 (q, J = 5.9 Hz, 2H).
D352	750.3	¹ H NMR (400 MHz, DMSO-d6) δ 10.97 (s, 1H), 8.21 (s, 2H, FA), 7.47 (s, 1H), 7.37 (d, J = 8.0 Hz, 1H), 6.68 (d, J = 10.2 Hz, 2H), 6.63 (s, 2H), 5.08 (dd, J = 13.3, 5.1 Hz, 1H), 4.38-4.14 (m, 2H), 3.81 (s, 7H), 3.57 (s, 6H), 3.40 (d, J = 16.8 Hz, 4H), 3.29 (dd, J = 6.9, 4.7 Hz, 1H), 3.15 (s, 3H), 2.98-2.84 (m, 1H), 2.77-2.68 (m, 2H), 2.59 (d, J = 16.1 Hz, 2H), 2.42 (d, J = 6.8 Hz, 2H), 2.39 (s, 3H), 2.28 (s, 4H), 1.98 (d, J = 12.0 Hz, 1H), 1.72 (t, J = 5.3 Hz, 4H).
D353	763.6	¹ H NMR (300 MHz, MeOD) δ 7.71 (s, 1H), 7.42 (d, J = 8.2 Hz, 1H), 6.88 (d, J = 2.2 Hz, 1H), 6.80 (d, J = 3.3 Hz, 3H), 5.14 (dd, J = 13.2, 5.1 Hz, 1H), 4.53-4.31 (m, 4H), 3.98 (d, J = 3.5 Hz, 6H), 3.78 (d, J = 23.5 Hz, 4H), 3.70-3.58 (m, 7H), 3.31-3.25 (m, 1H), 3.24-2.96 (m, 7H), 2.96-2.74 (m, 4H), 2.59-2.42 (m, 1H), 2.34-2.00 (m, 10H), 1.78-1.55 (m, 2H).
D354	807.45	¹ H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 8.87 (s, 1H), 8.23 (s, 2H, FA), 7.64-7.47 (m, 2H), 7.07-6.92 (m, 2H), 6.59 (s, 2H), 5.07 (dd, J = 13.4, 5.1 Hz, 1H), 4.86-4.78 (m, 1H), 4.38 (d, J = 17.2 Hz, 1H), 4.25 (d, J = 17.3 Hz, 1H), 3.79 (s, 6H), 3.55 (s, 3H), 3.53 (s, 2H), 2.93-2.77 (m, 5H), 2.64-2.59 (m, 1H), 2.45-2.36 (m, 5H), 2.29-2.17 (m, 4H), 2.08-1.99 (m, 5H), 1.80-1.75 (m, 2H), 1.61-1.51 (m, 6H), 1.45-1.41 (m, 1H), 1.07-0.99 (m, 2H).
D355	868.55	¹ H NMR (300 MHz, DMSO-d6) δ 10.98 (s, 1H), 8.14 (s, 0.4H, FA), 7.65 (s, 1H), 7.39 (d, J = 8.3 Hz, 1H), 7.33-7.25 (m, 1H), 7.20 (d, J = 8.0 Hz, 1H), 6.73-6.64 (m, 2H), 6.57 (s, 2H), 5.39 (d, J = 8.0 Hz, 1H), 5.08 (dd, J = 13.3, 5.1 Hz, 1H), 4.61 (s, 2H), 4.36-4.16 (m, 2H), 3.80 (s, 6H), 3.72-3.57 (m, 6H), 3.48 (s, 3H), 3.14-2.81 (m, 5H), 2.70-2.56 (m, 5H), 2.49-2.30 (m, 4H), 2.27-2.05 (m, 3H), 2.04-1.58 (m, 6H), 1.51-1.32 (m, 1H).

Compound No.	LCMS	^1H NMR
D356	666.4	^1H NMR (300 MHz, DMSO-d6) δ 10.98 (s, 1H), 8.20 (s, 1H, FA), 7.76 (s, 1H), 7.37 (d, J = 8.1 Hz, 1H), 6.73-6.62 (m, 4H), 5.08 (dd, J = 13.2, 5.0 Hz, 1H), 4.38-4.12 (m, 2H), 3.82 (s, 6H), 3.56 (s, 3H), 3.53-3.47 (m, 6H), 3.02-2.82 (m, 3H), 2.72 (t, J = 7.5 Hz, 2H), 2.65-2.56 (m, 1H), 2.45-2.27 (m, 5H), 2.05-1.94 (m, 3H), 1.81-1.63 (m, 4H).
D357	668.25	^1H NMR (300 MHz, DMSO-d6) δ 8.24 (s, 1H, FA), 7.98 (s, 1H), 7.37 (d, J = 8.1 Hz, 1H), 6.73-6.62 (m, 4H), 5.20 (s, 2H), 5.06 (dd, J = 13.2, 5.1 Hz, 1H), 4.93 (s, 2H), 4.38-4.12 (m, 2H), 3.82 (s, 6H), 3.60-3.51 (m, 9H), 2.98-2.80 (m, 1H), 2.65-2.53 (m, 3H), 2.42-2.26 (m, 3H), 2.03-1.93 (m, 1H), 1.79-1.69 (m, 4H).
D358	682.25	^1H NMR (300 MHz, DMSO-d6) δ 8.22 (s, 1H, FA), 7.98 (s, 1H), 7.62 (d, J = 8.2 Hz, 1H), 6.76 (d, J = 2.0 Hz, 1H), 6.64 (s, 3H), 5.20 (s, 2H), 5.04 (dd, J = 12.8, 5.3 Hz, 1H), 4.93 (s, 2H), 3.81 (s, 6H), 3.72 (s, 4H), 3.56 (s, 3H), 3.53 (s, 2H), 2.90-2.78 (m, 1H), 2.64-2.52 (m, 2H), 2.47-2.35 (m, 4H), 2.05-1.95 (m, 1H), 1.76-1.70 (m, 4H).
D359	668.25	^1H NMR (300 MHz, DMSO-d6) δ 8.22 (s, 1H, FA), 7.98 (s, 1H), 7.48 (d, J = 8.2 Hz, 1H), 6.65 (s, 2H), 6.54-6.43 (m, 2H), 5.20 (s, 2H), 5.01 (dd, J = 13.3, 5.0 Hz, 1H), 4.92 (s, 2H), 4.36-4.02 (m, 2H), 3.82 (s, 6H), 3.61 (s, 9H), 2.88 (t, J = 14.3 Hz, 1H), 2.68-2.50 (m, 5H), 2.40-2.29 (m, 1H), 2.00-1.91 (m, 1H), 1.79-1.73 (m, 4H).
D360	681.4	^1H NMR (400 MHz, DMSO-d6) δ 10.95 (s, 1H), 8.14 (s, 0.2H, FA), 7.50 (d, J = 8.2 Hz, 1H), 6.90 (s, 1H), 6.64 (s, 2H), 6.57-6.45 (m, 2H), 5.49 (s, 1H), 5.04 (dd, J = 13.3, 5.1 Hz, 1H), 4.35-4.16 (m, 2H), 4.10-3.78 (m, 8H), 3.69 (s, 4H), 3.48 (s, 3H), 3.26 (s, 3H), 3.01-2.79 (m, 3H), 2.65-2.55 (m, 2H), 2.48-2.43 (m, 2H), 2.41-2.35 (m, 1H), 2.05-1.77 (m, 5H), 1.69 (s, 2H),
D361	681.35	^1H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 8.15 (s, 0.2H, FA), 7.39 (d, J = 8.1 Hz, 1H), 6.90 (s, 1H), 6.69 (d, J = 7.6 Hz, 2H), 6.66-6.52 (m, 2H), 5.47 (d, J = 2.8 Hz, 1H), 5.08 (dd, J = 13.3, 5.1 Hz, 1H), 4.35-4.16 (m, 2H), 3.91-3.74 (m, 8H), 3.62 (s, 4H), 3.48 (s, 3H), 3.26 (s, 4H), 2.96-2.87 (m, 1H), 2.85-2.70 (m, 2H), 2.64-2.55 (m, 1H), 2.50-2.45 (m, 2H), 2.43-2.33 (m, 1H), 2.03-1.94 (m, 1H), 1.84 (s, 4H), 1.70 (s, 2H).
D362	627.2	^1H NMR (300 MHz, DMSO-d6) δ 11.12 (s, 1H), 7.88-7.80 (m, 1H), 7.76 (s, 1H), 7.27 (d, J = 7.4 Hz, 2H), 6.67 (s, 2H), 5.12 (dd, J = 12.8, 5.3 Hz, 1H), 4.97 (s, 1H), 3.81 (s, 9H), 3.51 (s, 3H), 3.28-3.12 (m, 3H), 3.01-2.80 (m, 3H), 2.70 (d, J = 7.6 Hz, 2H), 2.60 (d, J = 13.7 Hz, 2H), 2.00 (q, J = 7.5 Hz, 3H).
D363	680.2	^1H NMR (300 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.18 (s, 1H, FA), 7.76 (s, 1H), 7.63 (d, J = 8.3 Hz, 1H), 6.78 (d, J = 2.1 Hz, 1H), 6.69-6.60 (m, 3H), 5.05 (dd, J = 12.8, 5.3 Hz, 1H), 3.81 (s, 6H), 3.73 (s, 3H), 3.51 (s, 5H), 2.96 (t, J = 7.5 Hz, 3H), 2.90-2.80 (m, 1H), 2.78-2.55 (m, 4H), 2.41 (s, 4H), 1.99 (t, J = 7.7 Hz, 3H), 1.72 (s, 4H).
D364	626.25	^1H NMR (300 MHz, DMSO-d6) δ 10.98 (s, 1H), 7.77 (s, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.29-7.20 (m, 1H), 7.13 (d, J = 2.3 Hz, 1H), 6.67 (s, 2H), 5.09 (dd, J = 13.2, 5.1 Hz, 1H), 4.39-4.13 (m, 2H), 3.83 (s, 6H), 3.60 (s, 2H), 3.51 (s, 3H), 3.16 (s, 4H), 3.01-2.83 (m, 3H), 2.70 (d, J = 7.4 Hz, 2H), 2.58 (s, 5H), 2.41-2.30 (m, 1H), 1.98 (d, J = 8.4 Hz, 3H).
D365	621.35	^1H NMR (400 MHz, Methanol-d4) δ 8.53 (s, 1H, FA), 7.83 (s, 1H), 7.76-7.66 (m, 2H), 7.60 (d, J = 7.9 Hz, 1H), 6.79 (s, 2H), 5.17 (dd, J = 13.3, 5.2 Hz, 1H), 4.60-4.45 (m, 2H), 4.41-4.27 (m, 4H), 4.10 (q, J = 7.6 Hz, 2H), 3.97 (s, 6H), 3.85 (q, J = 8.2 Hz, 1H), 3.66 (s, 3H), 3.06-2.75 (m, 6H), 2.51 (qd, J = 13.2, 4.7 Hz, 1H), 2.24-2.18 (m, 1H), 2.15-2.02 (m, 2H).
D366	640.3	^1H NMR (300 MHz, DMSO-d6) δ 11.09 (s, 1H), 7.76 (s, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.32 (s, 1H), 7.23 (d, J = 8.6 Hz, 1H), 6.68 (s, 2H), 5.07 (dd, J = 13.1, 5.3 Hz, 1H), 3.83 (s, 6H), 3.67-3.57 (m, 2H), 3.51 (s, 3H), 3.40 (s, 5H), 2.96 (t, J = 7.3 Hz, 2H), 2.86 (d, J = 14.5 Hz, 1H), 2.70 (d, J = 7.5 Hz, 2H), 2.63-2.55 (m, 5H), 1.98 (q, J = 8.7, 7.2 Hz, 3H).
D367	623.15	^1H NMR (300 MHz, DMSO-d6) δ 11.02 (s, 1H), 8.14 (s, 0.4H, FA), 8.01 (s, 1H), 7.74-7.58 (m, 3H), 6.69 (s, 2H), 5.20 (t, J = 3.5 Hz, 2H), 5.11 (dd, J = 13.2, 5.1 Hz, 1H), 4.92 (t, J = 3.4 Hz, 2H), 4.57-4.30 (m, 2H), 4.02-3.89 (m, 4H), 3.86 (s, 6H), 3.67-3.53 (m, 6H), 3.01-2.83 (m, 1H), 2.67-2.55 (m, 1H), 2.49-2.30 (m, 1H), 2.08-1.96 (m, 1H).
D368	623.2	^1H NMR (300 MHz, DMSO-d6 with a drop of D2O) δ 8.17 (s, 0.4H, FA), 7.96 (s, 1H), 7.70 (dd, J = 7.9, 0.7 Hz, 1H), 7.64 (t, J = 1.1 Hz, 1H), 7.52 (dd, J = 7.9, 1.4 Hz, 1H), 6.64 (s, 2H), 5.17 (d, J = 3.5 Hz, 2H), 5.08 (dd, J = 13.2, 5.1 Hz, 1H), 4.92 (d, J = 3.3 Hz, 2H), 4.50-4.19 (m, 2H), 3.82 (s, 6H), 3.71-3.61 (m, 4H), 3.55 (s, 3H), 3.40 (q, J = 7.2 Hz, 1H), 3.29 (t, J = 7.0 Hz, 2H), 2.98-2.80 (m, 1H), 2.67-2.55 (m, 1H), 2.48-2.27 (m, 1H), 2.06-1.96 (m, 1H).
D369	621.3	^1H NMR (300 MHz, DMSO-d6) δ 11.02 (s, 1H), 10.1 (d, 2H, TFA), 7.77 (dd, J = 11.4, 7.3 Hz, 2H), 7.69 (s, 1H), 7.58 (d, J = 7.9 Hz, 1H), 6.78 (d, J = 3.3 Hz, 2H), 5.13 (dd, J = 13.2, 5.1 Hz, 1H), 4.53-4.08 (m, 9H), 3.90 (s, 6H), 3.51 (s, 3H), 2.93 (q, J = 9.5 Hz, 3H), 2.77-2.56 (m, 3H), 2.40-2.24 (m, 1H), 1.99 (q, J = 7.5 Hz, 3H).
D370	651.3	^1H NMR (300 MHz, DMSO-d6) δ 11.01 (s, 1H), 8.15 (.1.0 FA, s, 1H), 7.99 (s, 1H), 7.73-7.54 (m, 3H), 6.67 (s, 2H), 5.32-5.05 (m, 3H), 5.00-4.86

Compound No.	LCMS ^1H NMR
D371 649.35	^1H NMR (300 MHz, DMSO-d6) δ 11.01 (s, 1H), 8.19 (.1.0 FA, s, 1H), 7.75 (s, 1H), 7.68-7.55 (m, 3H), 6.66 (s, 2H), 5.11 (dd, J = 13.2, 5.1 Hz, 1H), 4.59-4.25 (m, 2H), 3.81 (s, 6H), 3.54 (s, 2H), 3.51 (s, 3H), 3.01-2.87 (m, 3H), 2.82-2.67 (m, 4H), 2.67-2.54 (m, 2H), 2.48-2.34 (m, 1H), 2.34-2.17 (m, 2H), 2.08-1.91 (m, 3H), 1.91-1.77 (m, 2H), 1.69-1.50 (m, 2H).
D372 765.6	^1H NMR (300 MHz, DMSO-d6) δ 10.97 (s, 1H), 8.17 (s, FA, 1H), 7.99 (s, 1H), 7.37 (d, J = 8.2 Hz, 1H), 6.67 (s, 4H), 5.21 (s, 2H), 5.08 (dd, J = 13.2, 5.0 Hz, 1H), 4.94 (s, 2H), 4.35-4.14 (m, 2H), 3.83 (s, 6H), 3.67 (s, 2H), 3.57 (d, J = 3.8 Hz, 7H), 3.05-2.79 (m, 4H), 2.64-2.55 (m, 1H), 2.42-2.17 (m, 6H), 2.17-2.06 (m, 2H), 2.04-1.91 (m, 1H), 1.84-1.58 (m, 6H), 1.58-1.47 (m, 1H), 1.28-0.95 (m, 2H).
D373 642.2	^1H NMR (300 MHz, DMSO-d6) δ 11.09 (s, 1H), 8.14 (s, FA, 0.2H), 8.00 (s, 1H), 7.68 (d, J = 8.5 Hz, 1H), 7.38-7.17 (m, 2H), 6.68 (s, 2H), 5.21 (s, 2H), 5.07 (dd, J = 12.7, 5.4 Hz, 1H), 4.93 (s, 2H), 3.85 (s, 6H), 3.56 (s, 5H), 3.50-3.38 (m, 4H), 2.97-2.80 (m, 1H), 2.69-2.54 (m, 4H), 2.50-2.40 (m, 2H), 2.11-1.95 (m, 1H).
D374 528.1	^1H NMR (300 MHz, DMSO-d6) δ 11.00 (s, 1H), 7.82 (s, 1H), 7.67-7.42 (m, 3H), 6.78 (s, 2H), 5.13 (dd, 1H), 4.53-4.29 (m, 2H), 3.73 (s, 6H), 3.53 (s, 3H), 3.08-2.99 (m, 2H), 2.69 (d, 4H), 2.28 (s, 1H), 2.13-1.96 (m, 3H).
D375 612.25	^1H NMR (400 MHz, DMSO-d6) δ 10.28 (s, 1H), 8.22 (s, 2H, FA), 7.74 (s, 1H), 7.14 (t, J = 8.0 Hz, 1H), 6.64 (s, 2H), 6.58 (d, J = 7.9 Hz, 1H), 6.35 (s, 1H), 6.28 (d, J = 8.4 Hz, 1H), 3.80 (s, 6H), 3.72 (t, J = 6.7 Hz, 2H), 3.50 (d, J = 3.4 Hz, 6H), 2.96 (t, J = 7.5 Hz, 2H), 2.81-2.66 (m, 5H), 2.66-2.59 (m, 1H), 2.40 (s, 4H), 2.03-1.92 (m, 3H), 1.69 (t, J = 5.5 Hz, 4H).

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Example 68—BRD9 bromodomain TR-FRET Competition Binding Assay

This example demonstrates the ability of the compounds of the disclosure to biochemically inhibit BRD9 bromodomain in a competition binding assay. 35

Procedure: His-Flag-BRD9 (P133-K239; Swiss Prot Q9H8M2; SEQ ID NO:1 mgsshhhhhlyfq/gdykddddkgslevlfqg/PAFNEST-PIQQLLEHFLRQLQRKDPHGFFAPVTDAIAGYSMII KHPMDFGTMKDKIVANEYKSVTTEFKADFJKLMCD-NAMTYNRPDTVYYKLAKKILHAGFKMMSK) was cloned, expressed, purified, and then treated with TEV protease. Cleaved His tag was removed by purification. The binding of a biotinylated small molecule ligand of BRD9 45 was assessed via the LANCE® TR-FRET platform (PerkinElmer), and the compounds were assayed for inhibitory activity against this interaction.

Results: A mixture of biotinylated-ligand and SureLight™ Allophycocyanin-Streptavidin (APC-SA, PerkinElmer AD0201) in 50 mM HEPES (pH 7.4), 50 mM NaCl, 1 mM TCEP (pH 7), 0.01% (v/v) Tween-20, 0.01% (w/v) bovine serum albumin was added to a white 384-well PerkinElmer Proxiplate Plus plate. DMSO or 3-fold serially diluted compounds were then added to the Proxiplate followed by addition of Flag-BRD9. After a 10-minute incubation at room temperature, Eu—W1024 anti-FLAG (PerkinElmer, AD0273) was added. The final reaction mixture that contained 3.75 nM biotinylated ligand, 3 nM Flag-BRD9, 7.5 nM SureLight™ Allophycocyanin-Streptavidin, and 0.2 nM Eu—W1024 anti-FLAG was incubated at room temperature for 90 minutes. 55

The plates were then read on a PerkinElmer Envision plate reader to determine the ratio of emission at 665 nm over 615 nm. Data was normalized to a DMSO control 65 (100%) and a no protein control (0%) and then fit to a four parameter, non-linear curve fit to calculate an IC₅₀ (μM) as

shown in Table 5. As shown by the results in Table 5, a number of compounds of the present disclosure exhibit an IC₅₀ value of <1 μM for BRD9 binding, indicating their affinity for targeting BRD9.

TABLE 5

Compound No.	Bromodomain TR-FRET Binding	
	Bromodomain TR-FRET	BRD9 IC ₅₀ (nM)
B1		NT
B2	+	
B3	+	
B4	+	
B5	++++	
B6	++	
B7	++++	
B8	+++	
B9	++++	
B10	+	
B11	+	
B12	+	
B13	+++	
B14	+	
B15	+	
B16	+	
B17	+	
B18	+++	
B19	+++	
B20	+++	
B21	++	
D1	NT	
D2	NT	
D3	NT	
D4	NT	
D5	NT	
D6	NT	
D7	NT	
D8	NT	
D9	NT	
D10	NT	
D11	NT	

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TABLE 5-continued

Bromodomain TR-FRET Binding	
Compound No.	Bromodomain TR-FRET BRD9 IC ₅₀ (nM)
D12	NT
D13	NT
D14	+++
D15	+++
D16	NT
D17	+++
D18	+++
D19	+
D20	+
D21	+++
D22	++++
D23	++
D24	++
D25	NT
D26	++++
D27	++
D28	++++
D29	++++
D30	++
D31	++++
D32	++
D33	+++
D34	+++
D35	+++
D36	+++
D37	++++
D38	++++

“+” indicates inhibitory effect of ≥1000 nM;

“++” indicates inhibitory effect of ≥100 nM;

“+++” indicates inhibitory effect of ≥10 nM;

“++++” indicates inhibitory effect of <10 nM;

“NT” indicates not tested

Example 69—SYO1 BRD9 NanoLuc Degradation Assay

This example demonstrates the ability of the compounds of the disclosure to degrade a Nanoluciferase-BRD9 fusion protein in a cell-based degradation assay.

Procedure: A stable SYO-1 cell line expressing 3xFLAG-NLuc-BRD9 was generated. On day 0 cells were seeded in 30 µL media into each well of 384-well cell culture plates. The seeding density was 8000 cells/well. On day 1, cells were treated with 30 nL DMSO or 30 nL of 3-fold serially DMSO-diluted compounds (10 points in duplicates with 1 µM as final top dose). Subsequently plates were incubated for 6 hours in a standard tissue culture incubator and equilibrated at room temperature for 15 minutes. Nanoluciferase activity was measured by adding 15 µL of freshly prepared Nano-Glo Luciferase Assay Reagent (Promega N1130), shaking the plates for 10 minutes and reading the bioluminescence using an EnVision reader.

Results: The Inhibition % was calculated using the following formula: % Inhibition=100×(Lum_{HC}−Lum_{Sample})/(Lum_{HC}−Lum_{LC}). DMSO treated cells are employed as High Control (HC) and 1 µM of a known BRD9 degrader standard treated cells are employed as Low Control (LC). The data was fit to a four parameter, non-linear curve fit to calculate IC₅₀ (µM) values as shown in Table 6A, Table 6B, and Table 6C. As shown by the results in Table 6A, Table 6B, and Table 6C, a number of compounds of the present disclosure exhibit an IC₅₀ value of <1 µM for the degradation of BRD9, indicating their use as compounds for reducing the levels and/or activity of BRD9 and their potential for treating BRD9-related disorders.

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TABLE 6A

SYO1 BRD9-NanoLuc Degradation	
Compound No.	SYO1 BRD9-NanoLuc degradation IC ₅₀ (nM)
5 D1	+++
5 D2	+++
5 D3	++
5 D4	+++
5 D5	+
10 D6	++
10 D7	+++
10 D8	++
10 D9	++++
10 D10	++
10 D11	+++
15 D12	+++
15 D13	+
15 D14	++
15 D15	++
15 D16	+++
15 D17	+++
15 D18	+++
20 D19	+
20 D20	+
20 D21	+++
20 D22	++++
20 D23	+
20 D24	+
25 D25	++++
25 D26	NT
25 D27	NT
25 D28	++++
25 D29	++++
30 D30	+
30 D31	+++
30 D32	++
30 D33	+
30 D34	NT
30 D35	NT
30 D36	NT
35 D37	+++
35 D38	+++

“+” indicates inhibitory effect of ≥1000 nM;

“++” indicates inhibitory effect of ≥100 nM;

“+++” indicates inhibitory effect of ≥10 nM;

“++++” indicates inhibitory effect of <10 nM;

“NT” indicates not tested

TABLE 6B

SYO1 BRD9-NanoLuc Degradation	
Compound No.	SYO1 BRD9-NanoLuc degradation IC ₅₀ (nM)
50 B22	+
50 B23	+
50 B24	NT
50 D39	++++
50 D40	++++
50 D41	++++
50 D42	++++
50 D43	++++
50 D44	++++
50 D45	++++
50 D46	++++
50 D47	++++
50 D48	++++
50 D49	++++
50 D50	+++
50 D51	++++
50 D52	++++
50 D53	+++
50 D54	+
50 D55	++++
50 D56	++++
50 D57	+++

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TABLE 6B-continued

SYO1 BRD9-NanoLuc Degradation	
Compound No.	SYO1 BRD9-NanoLuc degradation IC ₅₀ (nM)
D58	++++
D59	+++
D60	++
D61	++
D62	+
D63	++++
D64	++++
D65	++
D66	++++
D67	++
D68	++++
D69	++++
D70	+
D71	++++
D72	++++
D73	++++
D74	+
D75	+++
D76	++++
D77	+++
D78	++++
D79	+
D80	++++
D81	++++
D82	++++
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D84	++++
D85	++++
D86	++++
D87	++++
D88	++++
D89	++++
D90	+++
D91	++++
D92	+++
D93	++++
D94	NT
D95	++++
D96	++++
D97	++++
D98	++++
D99	++++
D100	++++
D101	++++
D102	++++
D103	++++
D104	++++
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D114	++++
D115	++++
D116	++++
D117	++++
D118	++++
D119	++++
D120	++
D121	++++
D122	+++
D123	++++
D124	++++
D125	++++
D126	++
D127	++++
D128	++++
D129	+++
D130	++++
D131	++++
D132	++++
D133	++++

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TABLE 6B-continued

SYO1 BRD9-NanoLuc Degradation	
Compound No.	SYO1 BRD9-NanoLuc degradation IC ₅₀ (nM)
D134	++++
D135	++++
D136	++++
D137	++
D138	++++
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D200	++++
D201	++++
D202	+++
D203	+++
D204	++
D205	+++
D206	++
D207	+++
D208	+++
D209	+++

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TABLE 6B-continued

SYO1 BRD9-NanoLuc Degradation	
Compound No.	SYO1 BRD9-NanoLuc degradation IC ₅₀ (nM)
D210	+++
D211	++
D212	+++
D213	++
D214	++
D215	++
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D217	+
D218	+++
D219	++
D220	++
D221	++
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D268	+++
D269	+++
D270	++
D271	+++
D272	++
D273	++
D274	++
D275	+++
D276	+++
D277	++
D278	+++
D279	++
D280	++
D281	+++
D282	++
D283	++++
D284	+++

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TABLE 6B-continued

SYO1 BRD9-NanoLuc Degradation	
Compound No.	SYO1 BRD9-NanoLuc degradation IC ₅₀ (nM)
D285	NT
D286	++
D287	++
D288	++
D289	+++
D290	+
D291	+++
D292	++
D293	++
D294	+
D295	++
D296	+
D297	+
D298	+
D299	++++
D300	++++
D301	++++
D302	++++
DD1	++++

“+” indicates inhibitory effect of ≥ 1000 nM;
 “++” indicates inhibitory effect of ≥ 100 nM;
 “+++” indicates inhibitory effect of ≥ 10 nM;
 “++++” indicates inhibitory effect of < 10 nM;
 “NT” indicates not tested

TABLE 6C

SYO1 BRD9-NanoLuc Degradation	
Compound No.	SYO1 BRD9-NanoLuc degradation IC ₅₀ (nM)
D303	++++
D304	++++
D305	+
D306	++++
D307	++++
D308	++++
D309	++++
D310	++++
D311	++++
D312	++++
D313	+
D314	++++
D315	++++
D316	+
D317	++++
D318	++++
D319	++++
D320	++++
D321	++++
D322	++++
D323	++++
D324	++++
D325	++++
D326	++++
D327	++++
D328	+
D329	++++
D330	++++
D331	+++
D332	++++
D333	++++
D334	++++
D335	++++
D336	++++
D337	+
D338	++++
D339	++++
D340	++++
D341	++++
D342	++++

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TABLE 6C-continued

SYO1 BRD9-NanoLuc Degradation

Compound No.	SYO1 BRD9-NanoLuc degradation IC ₅₀ (nM)
D343	+
D344	++++
D345	++++
D346	++++
D347	++++
D348	++++
D349	+++
D350	++++
D351	+++
D352	+++
D353	++++
D354	++++
D355	++++
D356	++++
D357	++++
D358	++++
D359	++++
D360	++++
D361	++++
D362	++++
D363	++++
D364	++++
D365	++++
D366	++++
D367	++++
D368	++++
D369	++++
D370	++++
D371	++++
D372	++++
D373	++++

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TABLE 6C-continued

SYO1 BRD9-NanoLuc Degradation		
	Compound No.	SYO1 BRD9-NanoLuc degradation IC ₅₀ (nM)
5	D374	++++
	D375	+

"+" indicates inhibitory effect of ≥ 1000 nM;
"++" indicates inhibitory effect of ≥ 100 nM;
"+++" indicates inhibitory effect of ≥ 10 nM;
"++++" indicates inhibitory effect of < 10 nM;
"NT" indicates not tested

Other Embodiments

All publications, patents, and patent applications mentioned in this specification are incorporated herein by reference in their entirety to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference in its entirety. Where a term in the present application is found to be defined differently in a document incorporated herein by reference, the definition provided herein is to serve as the definition for the term.

herein is to serve as the definition for the term.

25 While the invention has been described in connection with specific embodiments thereof, it will be understood that invention is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure that come within known or customary practice within the art to which the invention pertains and may be applied to the essential features hereinbefore set forth, and follows in the scope of the claims.

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Other embodiments are in the claims.

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acttgtactg gtacaacctc

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<400> SEQUENCE: 289

ttggcagttt ctacttgtac

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ccgggttcctc ccaggcgcca

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tccttttag atagcccatc

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tgggctatctc gaagaggaaac

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<400> SEQUENCE: 319

gctctacagc gtggtaaca

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<220> FEATURE:

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<400> SEQUENCE: 328

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gcgagctcaa gtccaccggg

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gagagcgcgac tcaagtccac

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<212> TYPE: DNA

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<220> FEATURE:

<223> OTHER INFORMATION: Synthetic Construct

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<210> SEQ ID NO 342

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gagctgtct actcagccata

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cacgcctgta tcatctccgt

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tcagcctacg gagatgagac

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aggagtttgt gaaggatgct

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gacctcctgg accagatcac

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cctccagatg aagccaagg

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gaaggctcca gatgaaggcca

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tccttagggtg tccccaacct

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<400> SEQUENCE: 375

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<400> SEQUENCE: 376

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<210> SEQ ID NO 377
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tgtgtctgtc tccacaggtt

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ccacaggttg gggacaccct

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agagctgctg ctgtctccata

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cagagctgct gctgtctccat

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agacagcagc agctctgttc	20
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atctccatgc tcagctctct 20

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tatctccatg ctcagctctc 20

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atgtcctgtt tacacaggga 20

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ttcacacaggg aaggtgaaga 20

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agttcaaatg gctgtcgta 20

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<400> SEQUENCE: 418

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<400> SEQUENCE: 419

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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 420

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<210> SEQ ID NO 421
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic Construct
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<400> SEQUENCE: 422

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taggggtcgt g ggtgacgtc

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ggagactgaa gaaaactcata

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<400> SEQUENCE: 428

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<400> SEQUENCE: 430

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ctagagtttag gtcttggcag

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ggtgtgtctag agttaggtct

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<220> FEATURE:
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<400> SEQUENCE: 434

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<400> SEQUENCE: 436

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gaatctaccg cagcggttcg

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<400> SEQUENCE: 447

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<400> SEQUENCE: 448

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gcagctcgta tgtcgtactc

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gtatcctgac ctacgcgctg

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<210> SEQ ID NO 454

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<211> LENGTH: 20
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<400> SEQUENCE: 454

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<400> SEQUENCE: 455

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<400> SEQUENCE: 456

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<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 457

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<400> SEQUENCE: 459

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gtagcgcgtaggagtggc 20

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<400> SEQUENCE: 461

gtcacacctgc attcgtaac 20

<210> SEQ ID NO 462
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<212> TYPE: DNA
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<400> SEQUENCE: 462

gcacacacctatcgaaatg 20

<210> SEQ ID NO 463
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<212> TYPE: DNA
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<400> SEQUENCE: 463

gttgatcaac gcgcttcgac 20

<210> SEQ ID NO 464
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 464

gcgtctcaactactccatcg 20

<210> SEQ ID NO 465
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<400> SEQUENCE: 465

gccgaccacac gtcagcgta 20

<210> SEQ ID NO 466
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<400> SEQUENCE: 466

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<210> SEQ ID NO 467
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<213> ORGANISM: Artificial Sequence
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<400> SEQUENCE: 467

gaatccagtg gggcgacaa 20

<210> SEQ ID NO 468
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<212> TYPE: DNA
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<400> SEQUENCE: 468

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<210> SEQ ID NO 469
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<212> TYPE: DNA
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gcgatcctca agtatgctca 20

<210> SEQ ID NO 470
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<400> SEQUENCE: 470

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<210> SEQ ID NO 471
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<400> SEQUENCE: 471

ggagatgcatt cgaagtgcatt 20

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ggatgcactc catctcgatct 20

<210> SEQ ID NO 473
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<400> SEQUENCE: 473

tgcccgagta ataacgcgag 20

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<400> SEQUENCE: 474

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<210> SEQ ID NO 476
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<220> FEATURE:
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<400> SEQUENCE: 476

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<210> SEQ ID NO 477
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 477

gttcacacgg tgtcgatag

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<210> SEQ ID NO 478
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Construct

<400> SEQUENCE: 478

ggatagggtga ccttagtacg

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gtatggtgag tagtcgcttg

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gcgtgcgtcc cgggttaccc

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<210> SEQ ID NO 560

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gatggcgctt cagtcgtcgg

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cgacgctagg taacgtagag 20

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atctgtccta attcgatcg 20

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gtacggggcg atcatccaca 20

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<223> OTHER INFORMATION: Synthetic Construct

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<210> SEQ ID NO 658
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gaacaagcaa cacctaaaag 20

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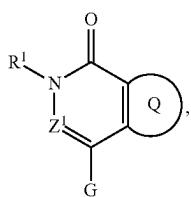
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The invention claimed is:

1. A compound having the structure of Formula I:

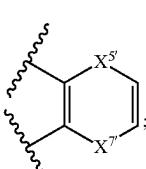
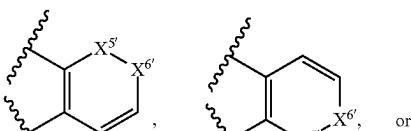


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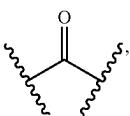
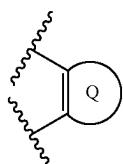
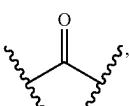


wherein

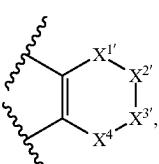
R¹ is H, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₁-C₆ heteroalkyl, or optionally substituted C₃-C₁₀ carbocyclyl;

Z¹ is CR² or N;

R² is H, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, or optionally substituted C₂-C₉ heteroaryl;

X¹ is a bond, O, NR^{3a},or CR^{4a}R^{5a};X² is O, NR^{3b},

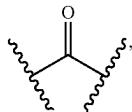
is



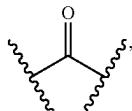
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or $\text{CR}^{4b}\text{R}^{5b}$;
 X^3 is O, NR^{3c} ,



or $\text{CR}^{4c}\text{R}^{5c}$;
 X^4 is a bond, O, NR^{3d} ,



or $\text{CR}^{4d}\text{R}^{5d}$;
 X^5 is O or NR^{3e} and X^6 is $\text{CR}^{4f}\text{R}^{5f}$, or X^5 is $\text{CR}^{4g}\text{R}^{5g}$ and
 X^6 is O or NR^{3f} ;

X^7 is O, NR^{3g} , or $\text{CR}^{4h}\text{R}^{5h}$;
 X^8 is O, NR^{3h} , or $\text{CR}^{4i}\text{R}^{5i}$;

each of R^{3a} , R^{3b} , R^{3c} , and R^{3d} is, independently, H, halogen, hydroxyl, optionally substituted $\text{C}_1\text{-C}_6$ alkyl, optionally substituted $\text{C}_1\text{-C}_6$ heteroalkyl, optionally substituted $\text{C}_3\text{-C}_{10}$ carbocyclyl, optionally substituted $\text{C}_2\text{-C}_9$ heterocyclyl, optionally substituted $\text{C}_6\text{-C}_{10}$ aryl, optionally substituted $\text{C}_2\text{-C}_9$ heteroaryl, optionally substituted $\text{C}_2\text{-C}_6$ alkenyl, optionally substituted $\text{C}_2\text{-C}_6$ heteroalkenyl, optionally substituted $\text{C}_1\text{-C}_6$ acyl, thiol, optionally substituted sulfone, optionally substituted sulfonamide, or optionally substituted amino, or R^{3a} and R^{4b} , R^{4a} and R^{3b} , R^{4b} and R^{4a} , R^{3b} and R^{4c} , R^{4b} and R^{4c} , R^{3c} and R^{4b} , R^{3c} and R^{4d} , R^{4c} and R^{4d} , and/or R^{3d} and R^{4c} , together with the atoms to which each is attached, combine to form optionally substituted $\text{C}_2\text{-C}_9$ heterocyclyl;

each of R^{4a} , R^{4b} , R^{4c} , and R^{4d} is, independently, H, halogen, hydroxyl, optionally substituted $\text{C}_1\text{-C}_6$ alkyl, optionally substituted $\text{C}_1\text{-C}_6$ heteroalkyl, optionally substituted $\text{C}_3\text{-C}_{10}$ carbocyclyl, optionally substituted $\text{C}_2\text{-C}_9$ heterocyclyl, optionally substituted $\text{C}_6\text{-C}_{10}$ aryl, optionally substituted $\text{C}_2\text{-C}_9$ heteroaryl, optionally substituted $\text{C}_2\text{-C}_6$ alkenyl, optionally substituted $\text{C}_2\text{-C}_6$ heteroalkenyl, optionally substituted $\text{C}_1\text{-C}_6$ acyl, thiol, optionally substituted sulfone, or optionally substituted amino, or R^{3a} and R^{4b} , R^{4a} and R^{3b} , R^{4b} and R^{4a} , R^{3b} and R^{4c} , R^{4b} and R^{4c} , R^{3c} and R^{4b} , R^{3c} and R^{4d} , R^{4c} and R^{4d} , and/or R^{3d} and R^{4c} , together with the atoms to which each is attached, combine to form optionally substituted $\text{C}_2\text{-C}_9$ heterocyclyl;

each of R^{5a} , R^{5b} , R^{5c} , and R^{5d} is, independently, H, halogen, hydroxyl, optionally substituted $\text{C}_1\text{-C}_6$ alkyl, optionally substituted $\text{C}_1\text{-C}_6$ heteroalkyl, optionally substituted $\text{C}_3\text{-C}_{10}$ carbocyclyl, optionally substituted $\text{C}_2\text{-C}_9$ heterocyclyl, optionally substituted $\text{C}_6\text{-C}_{10}$ aryl, optionally substituted $\text{C}_2\text{-C}_9$ heteroaryl, optionally substituted $\text{C}_2\text{-C}_6$ alkenyl, optionally substituted $\text{C}_2\text{-C}_6$ heteroalkenyl, hydroxyl, thiol, or optionally substituted amino;

each of R^{3e} , R^{3f} , R^{3g} , and R^{3h} is, independently, H, halogen, hydroxyl, optionally substituted $\text{C}_1\text{-C}_6$ alkyl, optionally substituted $\text{C}_1\text{-C}_6$ heteroalkyl, optionally substituted $\text{C}_3\text{-C}_{10}$ carbocyclyl, optionally substituted

$\text{C}_2\text{-C}_9$ heterocyclyl, optionally substituted $\text{C}_6\text{-C}_{10}$ aryl, optionally substituted $\text{C}_2\text{-C}_9$ heteroaryl, optionally substituted $\text{C}_2\text{-C}_6$ alkenyl, optionally substituted $\text{C}_2\text{-C}_6$ heteroalkenyl, optionally substituted $\text{C}_1\text{-C}_6$ acyl, thiol, optionally substituted sulfone, optionally substituted sulfonamide, or optionally substituted amino, or R^{3e} and R^{4f} or R^{4e} and R^{3f} , together with the atoms to which each is attached, combine to form optionally substituted heterocyclyl;

each of R^{4e} , R^{4f} , R^{4g} , and R^{4h} is, independently, H, halogen, hydroxyl, optionally substituted $\text{C}_1\text{-C}_6$ alkyl, optionally substituted $\text{C}_1\text{-C}_6$ heteroalkyl, optionally substituted $\text{C}_3\text{-C}_{10}$ carbocyclyl, optionally substituted $\text{C}_2\text{-C}_9$ heterocyclyl, optionally substituted $\text{C}_6\text{-C}_{10}$ aryl, optionally substituted $\text{C}_2\text{-C}_9$ heteroaryl, optionally substituted $\text{C}_2\text{-C}_6$ alkenyl, optionally substituted $\text{C}_2\text{-C}_6$ heteroalkenyl, optionally substituted $\text{C}_1\text{-C}_6$ acyl, thiol, optionally substituted sulfone, optionally substituted sulfonamide, or optionally substituted amino, or R^{3e} and R^{4f} or R^{4e} and R^{3f} , together with the atoms to which each is attached, combine to form optionally substituted heterocyclyl;

each of R^{5e} , R^{5f} , R^{5g} , and R^{5h} is, independently, H, halogen, hydroxyl, optionally substituted $\text{C}_1\text{-C}_6$ alkyl, optionally substituted $\text{C}_1\text{-C}_6$ heteroalkyl, optionally substituted $\text{C}_3\text{-C}_{10}$ carbocyclyl, optionally substituted $\text{C}_2\text{-C}_9$ heterocyclyl, optionally substituted $\text{C}_6\text{-C}_{10}$ aryl, optionally substituted $\text{C}_2\text{-C}_9$ heteroaryl, optionally substituted $\text{C}_2\text{-C}_6$ alkenyl, optionally substituted $\text{C}_2\text{-C}_6$ heteroalkenyl, hydroxyl, thiol, or optionally substituted amino; and

G is optionally substituted $\text{C}_6\text{-C}_{10}$ aryl, optionally substituted $\text{C}_3\text{-C}_{10}$ carbocyclyl, optionally substituted $\text{C}_2\text{-C}_9$ heteroaryl, or $\text{C}_2\text{-C}_9$ heterocyclyl,

or a pharmaceutically acceptable salt thereof.

2. A compound having the structure of Formula II:

A-L-B

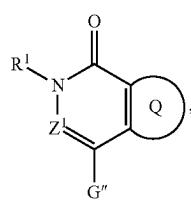
Formula II,

where

B is a degradation moiety,

L is a linker, and

A has the structure of Formula III:



Formula III

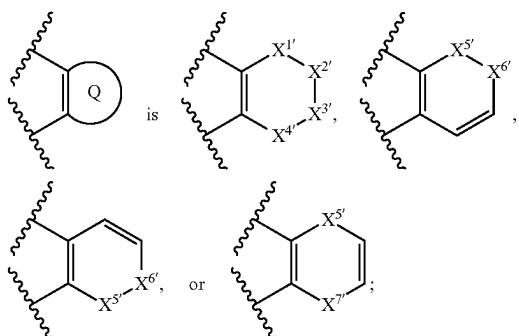
where

R^1 is H, optionally substituted $\text{C}_1\text{-C}_6$ alkyl, optionally substituted $\text{C}_2\text{-C}_6$ alkenyl, optionally substituted $\text{C}_1\text{-C}_6$ heteroalkyl, or optionally substituted $\text{C}_3\text{-C}_{10}$ carbocyclyl;

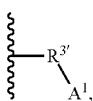
Z^1 is CR^2 or N;

R^2 is H, halogen, optionally substituted $\text{C}_1\text{-C}_6$ alkyl, optionally substituted $\text{C}_1\text{-C}_6$ heteroalkyl, optionally substituted $\text{C}_3\text{-C}_1\text{O}$ carbocyclyl, optionally substituted $\text{C}_2\text{-C}_9$ heterocyclyl, optionally substituted $\text{C}_6\text{-C}_{10}$ aryl, or optionally substituted $\text{C}_2\text{-C}_9$ heteroaryl;

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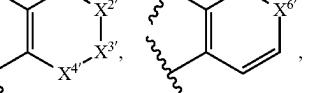


X^{1t} is a bond, O, NR^{3a} , or $CR^{4a}R^{5a}$;
 X^{2t} is O, NR^{3b} , or $CR^{4b}R^{5b}$;
 X^{3t} is O, NR^{3c} , or $CR^{4c}R^{5c}$;
 X^{4t} is a bond, O, NR^{3d} , or $CR^{4d}R^{5d}$;
 X^{5t} is O, NR^{3e} , or $CR^{4e}R^{5e}$;
 X^{6t} is O, NR^{3f} , or $CR^{4f}R^{5f}$;
 X^{7t} is O, NR^{3g} , or $CR^{4g}R^{5g}$;
each of R^{3a} , R^{3b} , R^{3c} , and R^{3d} is, independently, H,

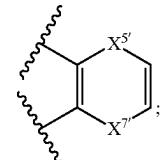


halogen, hydroxyl, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heterocyclyl, optionally substituted C_6 - C_{10} aryl, optionally substituted C_2 - C_9 heteroaryl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 heteroalkenyl, optionally substituted C_1 - C_6 acyl, thiol, optionally substituted sulfone, optionally substituted sulfonamide, or optionally substituted amino, or R^{3a} and R^{4b} , R^{4a} and R^{3b} , R^{4b} and R^{4a} , R^{3b} and R^{4c} , R^{4b} and R^{4c} , R^{3c} and R^{4b} , R^{3c} and R^{4d} , R^{4c} and R^{4d} , and/or R^{3d} and R^{4c} , together with the atoms to which each is attached, combine to form optionally substituted C_2 - C_9 heterocyclyl;

R^{3t} is absent, optionally substituted C_1 - C_6 alkylene, optionally substituted C_1 - C_6 heteroalkylene, optionally substituted C_3 - C_{10} carbocyclylene, optionally substituted C_2 - C_9 heterocyclylene, optionally substituted C_6 - C_{10} arylene, optionally substituted C_2 - C_9 heteroarylene, optionally substituted C_2 - C_6 alkenylene, optionally substituted C_2 - C_6 heteroalkenylene, optionally substituted sulfone, optionally substituted sulfonamide, or optionally substituted amino; each of R^{4a} , R^{4b} , R^{4c} , and R^{4d} is, independently, H, halogen, hydroxyl, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heterocyclyl, optionally substituted C_6 - C_{10} aryl, optionally substituted C_2 - C_9 heteroaryl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 heteroalkenyl, thiol, optionally substituted sulfone, or optionally substituted amino, or R^{3a} and R^{4b} , R^{4a} and R^{3b} , R^{4b} and R^{4a} , R^{3b} and R^{4c} , R^{4b} and R^{4c} , R^{3c} and R^{4b} , R^{3c} and R^{4d} , R^{4c} and R^{4d} , and/or R^{3d} and R^{4c} , together with the atoms to which each is attached, combine to form optionally substituted C_2 - C_9 heterocyclyl;



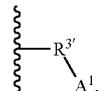
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each of R^{3e} , R^{3f} , and R^{3g} is, independently, H,



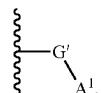
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halogen, hydroxyl, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heterocyclyl, optionally substituted C_6 - C_{10} aryl, optionally substituted C_2 - C_9 heteroaryl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 heteroalkenyl, optionally substituted C_1 - C_6 acyl, thiol, optionally substituted sulfone, optionally substituted sulfonamide, or optionally substituted amino, or R^{3e} and R^{4f} or R^{4e} and R^{3f} , together with the atoms to which each is attached, combine to form optionally substituted heterocyclyl;

each of R^{4e} , R^{4f} , and R^{4g} is, independently, H, halogen, hydroxyl, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heterocyclyl, optionally substituted C_6 - C_{10} aryl, optionally substituted C_2 - C_9 heteroaryl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 heteroalkenyl, optionally substituted C_1 - C_6 acyl, thiol, optionally substituted sulfone, optionally substituted sulfonamide, or optionally substituted amino, or R^{3e} and R^{4f} or R^{4e} and R^{3f} , together with the atoms to which each is attached, combine to form optionally substituted heterocyclyl;

each of R^{5e} , R^{5f} , and R^{5g} is, independently, H, halogen, hydroxyl, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heterocyclyl, optionally substituted C_6 - C_{10} aryl, optionally substituted C_2 - C_9 heteroaryl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 heteroalkenyl, hydroxyl, thiol, or optionally substituted amino;

G'' is



optionally substituted C_6 - C_{10} aryl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heteroaryl, or C_2 - C_9 heterocyclyl;

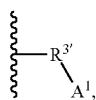
G' is optionally substituted C_3 - C_{10} carbocyclylene, C_2 - C_9 heterocyclylene, optionally substituted C_6 - C_{10} arylene, or optionally substituted C_2 - C_9 heteroarylene; and

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each of R^{5a} , R^{5b} , R^{5c} , and R^{5d} is, independently, H, halogen, hydroxyl, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted C_3 - C_{10} carbocyclyl, optionally substituted C_2 - C_9 heterocyclyl, optionally substituted C_6 - C_{10} aryl, optionally substituted C_2 - C_9 heteroaryl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 heteroalkenyl, hydroxyl, thiol, or optionally substituted amino;

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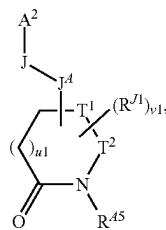
A^1 is a bond between A and the linker, where one of R^{3a1} , R^{3b1} , R^{3c1} , R^{3d1} , R^{3e1} , R^{3f1} , and R^{3g1} is



or G'' is



wherein B has the structure of Formula Y:



Formula Y

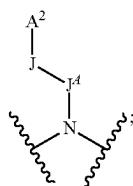
where

A^2 is a bond between the degradation moiety and the linker;

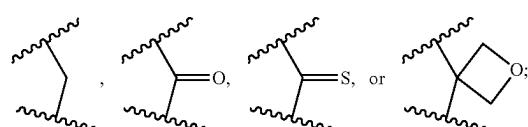
$v1$ is 0, 1, 2, 3, 4, or 5;

$u1$ is 1, 2, or 3;

T^1 is a bond or



T^2 is



R^{5A} is H, optionally substituted C_1 - C_6 alkyl, or optionally substituted C_1 - C_6 heteroalkyl;

each R^{J1} is, independently, halogen, optionally substituted C_1 - C_6 alkyl, or optionally substituted C_1 - C_6 heteroalkyl;

J^4 is absent, O, optionally substituted amino, optionally substituted C_1 - C_6 alkyl, or optionally substituted C_1 - C_6 heteroalkyl; and

J is absent, optionally substituted C_3 - C_{10} carbocyclene, optionally substituted C_6 - C_{10} arylene, optionally substituted C_2 - C_9 heterocyclene, or optionally substituted C_2 - C_9 heteroarylene;

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wherein L has the structure of Formula V:

A^1 -(E¹)-(F¹)—(C³)_m-(E³)_n-(F³)_{o1}—(F³)_{o2}-(E²)_p-A², Formula V

wherein

A^1 is a bond between the linker and A;

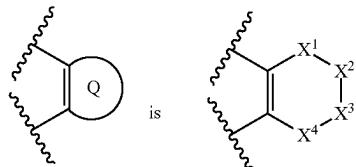
A^2 is a bond between B and the linker; each of m, n, o1, o2, and p is, independently, 0 or 1; each of E¹ and E² is, independently, O, S, NR^N, optionally substituted C_{1-10} alkylene, optionally substituted C_{2-10} alkenylene, optionally substituted C_{2-10} alkynylene, optionally substituted C_2 - C_{10} polyethylene glycol, or optionally substituted C_{1-10} heteroalkylene;

E³ is optionally substituted C_1 - C_6 alkylene, optionally substituted C_1 - C_6 heteroalkylene, O, S, or NR^N; each R^N is, independently, H, optionally substituted C_{1-4} alkyl, optionally substituted C_{2-4} alkenyl, optionally substituted C_{2-4} alkynyl, optionally substituted C_{2-6} heterocycl, optionally substituted C_{6-12} aryl, or optionally substituted C_{1-7} heteroalkyl;

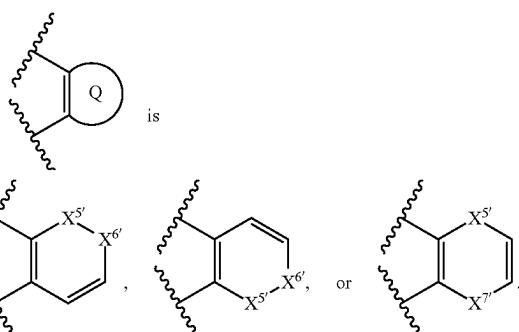
C³ is carbonyl, thiocarbonyl, sulphonyl, or phosphoryl; and

each of F¹, F², and F³ is, independently, optionally substituted C_3 - C_{10} carbocyclene, optionally substituted C_{2-10} heterocyclene, optionally substituted C_6 - C_{10} arylene, or optionally substituted C_2 - C_9 heteroarylene; or a pharmaceutically acceptable salt thereof.

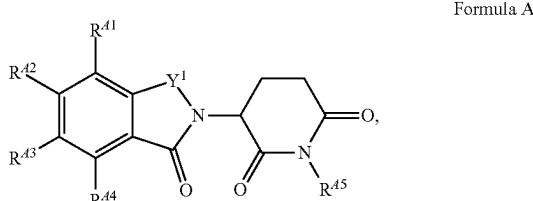
3. The compound of claim 2, wherein



4. The compound of claim 3, wherein

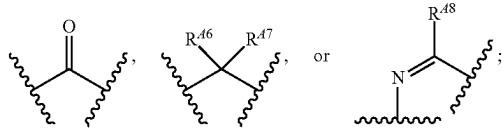


5. The compound of claim 2, wherein the structure of Formula Y has the structure of Formula A:



Formula A

wherein in
Y¹ is

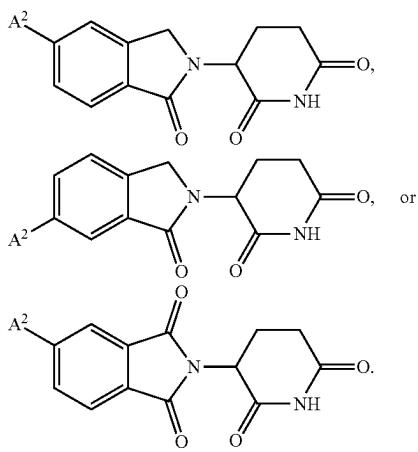


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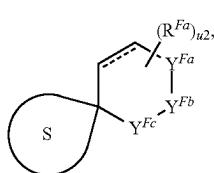
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R⁴⁵ is H, optionally substituted C₁-C₆ alkyl, or optionally substituted C₁-C₆ heteroalkyl;
R⁴⁶ is H or optionally substituted C₁-C₆ alkyl; and R⁴⁷ is H or optionally substituted C₁-C₆ alkyl; or R⁴⁶ and R⁴⁷, together with the carbon atom to which each is bound, combine to form optionally substituted C₃-C₆ carbocyclyl or optionally substituted C₂-C₅ heterocyclyl; or R⁴⁶ and R⁴⁷, together with the carbon atom to which each is bound, combine to form optionally substituted C₃-C₆ carbocyclyl or optionally substituted C₂-C₅ heterocyclyl;
R⁴⁸ is H, optionally substituted C₁-C₆ alkyl, or optionally substituted C₁-C₆ heteroalkyl;
each of R⁴¹, R⁴², R⁴³, and R⁴⁴ is, independently, H, A², halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ heteroalkenyl, optionally substituted —O—C₃-C₆ carbocyclyl, hydroxyl, thiol, or optionally substituted amino; or R⁴¹ and R⁴², R⁴² and R⁴³, and/or R⁴³ and R⁴⁴, together with the carbon atoms to which each is attached, combine to form (N); and
(N) is optionally substituted C₆-C₁₀ aryl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heteroaryl, or C₂-C₉ heterocyclyl, any of which is optionally substituted with A², wherein one of R⁴¹, R⁴², R⁴³, and R⁴⁴ is A², or (N) is substituted with A², or a pharmaceutically acceptable salt thereof.

6. The compound of claim 5, wherein the structure of Formula A is

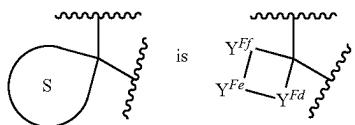


7. The compound of claim 2, wherein the degradation moiety comprises the structure of Formula FA:



Formula FA

where



or a bicyclic moiety which is substituted with A² and substituted with one or more groups independently selected from H, R^{FF1}, and oxo;

---- is a single bond or a double bond;
u2 is 0, 1, 2, or 3;

A² is a bond between the degrader and the linker;

Y^{Fa} is CR^{Fb}R^{Fc}, C=O, C=S, C=CH₂, SO₂, S(O), P(O)Oalkyl, P(O)NHalkyl, P(O)N(alkyl)₂, P(O)alkyl, P(O)OH, P(O)NH₂;

Y^{Fb} is NH, NR^{FF1}, CH₂, CHR^{FF1}, C(R^{FF1})₂, O, or S;

Y^{Fc} is CR^{Fd}R^{Fe}, C=O, C=S, C=CH₂, SO₂, S(O), P(O)Oalkyl, P(O)NHalkyl, P(O)N(alkyl)₂, P(O)alkyl, P(O)OH, P(O)NH₂;

each of R^{Fb}, R^{Fc}, R^{Fe}, and R^{Fd} is, independently, H, alkyl, aliphatic, heteroaliphatic, aryl, heteroaryl, carbocyclyl, hydroxyl, alkoxy, amino, —NHalkyl, or —Nalkyl₂; or R^{Fb} and R^{Fc}, together with the carbon atom to which each is attached, combine to form a 3-, 4-, 5-, or 6-membered spirocarbocyclylene, or a 4-, 5-, or 6-membered spiroheterocyclene comprising 1 or 2 heteroatoms selected from N and O;

or R^{Fe} and R^{Fd}, together with the carbon atom to which each is attached, combine to form a 3-, 4-, 5-, or 6-membered spirocarbocyclylene, or a 4-, 5-, or 6-membered spiroheterocyclene comprising 1 or 2 heteroatoms selected from N and O; and

or R^{Fd} and R^{Fb}, together with the carbon atoms to which each is attached, combine to form a 1, 2, 3, or 4 carbon bridged ring;

each of Y^{Fd} and Y^{Fe} is, independently, CH₂, CHR^{FF2}, C(R^{FF2})₂, C(O), N, NH, NR^{FF3}, O, S, or S(O);

Y^{Fe} is a bond or a divalent moiety attached to Y^{Fd} and Y^{Fe} that contains 1 to 5 contiguous carbon atoms that form a 3 to 8-membered ring,

wherein 1, 2, or 3 carbon atoms can be replaced with a nitrogen, oxygen, or sulfur atom;

wherein one of the ring atoms is substituted with A² and the others are substituted with one or more groups independently selected from H and R^{FF1}; and wherein the contiguous atoms of Y^{Fe} can be attached through a single or double bond;

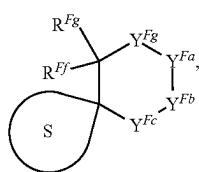
each R^{FF1} is, independently, H, alkyl, alkenyl, alkynyl, aliphatic, heteroaliphatic, carbocyclyl, halogen, hydroxyl, amino, cyano, alkoxy, aryl, heteroaryl, heterocyclyl, alkylamino, alkylhydroxyl, or haloalkyl;

each R^{FF2} is, independently, alkyl, alkene, alkyne, halogen, hydroxyl, alkoxy, azide, amino, —C(O)H, —C(O)OH, —C(O)(aliphatic, including alkyl), —C(O)O(aliphatic,

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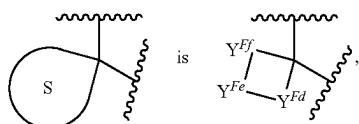
phatic, including alkyl), —NH(aliphatic, including alkyl), —N(aliphatic including alkyl)(aliphatic including alkyl), —NHSO₂alkyl, —N(alkyl)SO₂alkyl, —NHSO₂aryl, —N(alkyl)SO₂aryl, —NHSO₂alkenyl, —N(alkyl)SO₂alkenyl, —NHSO₂alkynyl, —N(alkyl)SO₂alkynyl, aliphatic, heteroaliphatic, aryl, heteroaryl, heterocyclic, carbocyclic, cyano, nitro, nitroso, —SH, —Salkyl, or haloalkyl; and R^{FF3} is alkyl, alkenyl, alkynyl, —C(O)H, —C(O)OH, —C(O)alkyl, or —C(O)Oalkyl, wherein if Y^{Fd} or Y^{Ff} is substituted with A², then Y^{Fe} is a bond, or a pharmaceutically acceptable salt thereof.

8. The compound of claim 2, wherein the degradation moiety comprises the structure of Formula FB:



Formula FB

where



or a bicyclic moiety which is substituted with A² and substituted with one or more groups independently selected from H, R^{FF1}, and oxo;

A² is a bond between the degrader and the linker; Y^{Fa} is CR^{Fb}R^{Fc}, C=O, C=S, C=CH₂, SO₂, S(O), P(O)Oalkyl, P(O)NHalkyl, P(O)N(alkyl)₂, P(O)alkyl, P(O)OH, P(O)NH₂; each of Y^{Fb} and Y^{Fg} is, independently, NH, NR^{FF1}, CH₂, CHR^{FF1}, C(R^{FF1})₂, O, or S;

Y^{Fc} is CR^{Fd}R^{Fe}, C=O, C=S, C=CH₂, SO₂, S(O), P(O)Oalkyl, P(O)NHalkyl, P(O)N(alkyl)₂, P(O)alkyl, P(O)OH, P(O)NH₂; each of R^{Fb}, R^{Fc}, R^{Fd}, R^{Fe}, R^{Ff}, and R^{Fg} is, independently, H, alkyl, aliphatic, heteroaliphatic, aryl, heteroaryl, carbocyclic, hydroxyl, alkoxy, amino, —NHalkyl, or —Nalkyl₂;

or R^{Fb} and R^{Fc}, together with the carbon atom to which each is attached, combine to form a 3-, 4-, 5-, or 6-membered spirocarbocyclene, or a 4-, 5-, or 6-membered spiroheterocyclene comprising 1 or 2 heteroatoms selected from N and O;

or R^{Fd} and R^{Fe}, together with the carbon atom to which each is attached, combine to form a 3-, 4-, 5-, or 6-membered spirocarbocyclene, or a 4-, 5-, or 6-membered spiroheterocyclene comprising 1 or 2 heteroatoms selected from N and O;

or R^{Ff} and R^{Fg}, together with the carbon atom to which each is attached, combine to form a 3-, 4-, 5-, or 6-membered spirocarbocyclene, or a 4-, 5-, or 6-membered spiroheterocyclene comprising 1 or 2 heteroatoms selected from N and O;

or R^{Fd} and R^{Fb}, together with the carbon atoms to which each is attached, combine to form a 1, 2, 3, or 4 carbon bridged ring;

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or R^{Fd} and R^{Ff}, together with the carbon atoms to which each is attached, combine to form a 1, 2, 3, or 4 carbon bridged ring;

or R^{Fb} and R^{Fg}, together with the carbon atoms to which each is attached, combine to form a 1, 2, 3, or 4 carbon bridged ring;

each of Y^{Fd} and Y^{Ff} is, independently, CH₂, CHR^{FF2}, C(R^{FF2})₂, C(O), N, NH, NR^{FF3}, O, S, or S(O);

Y^{Fe} is a bond or a divalent moiety attached to Y^{Fd} and Y^{Ff} that contains 1 to 5 contiguous carbon atoms that form a 3 to 8-membered ring,

wherein 1, 2, or 3 carbon atoms can be replaced with a nitrogen, oxygen, or sulfur atom;

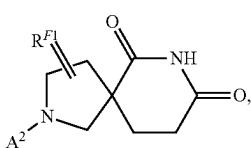
wherein one of the ring atoms is substituted with A² and the others are substituted with one or more groups independently selected from H and R^{FF1}; and

wherein the contiguous atoms of Y^{Fe} can be attached through a single or double bond;

each R^{FF1} is, independently, H, alkyl, alkenyl, alkynyl, aliphatic, heteroaliphatic, carbocyclic, halogen, hydroxyl, amino, cyano, alkoxy, aryl, heteroaryl, heterocyclic, alkylamino, alkylhydroxyl, or haloalkyl;

each R^{FF2} is, independently, alkyl, alkene, alkyne, halogen, hydroxyl, alkoxy, azide, amino, —C(O)H, —C(O)OH, —C(O)alkyl, or —C(O)Oalkyl, wherein if Y^{Fd} or Y^{Ff} is substituted with A², then Y^{Fe} is a bond, or a pharmaceutically acceptable salt thereof.

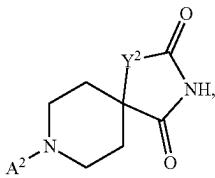
9. The compound of claim 2, wherein the degradation moiety comprises the structure of Formula F1:



Formula F1

wherein A² is a bond between the degrader and the linker; and R^{FF1} is absent or O, or a pharmaceutically acceptable salt thereof.

10. The compound of claim 2, wherein the degradation moiety comprises the structure of Formula F2:

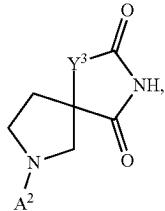


Formula F2

841

wherein
 A^2 is a bond between the degrader and the linker; and
 R^{F1} is absent or O,
or a pharmaceutically acceptable salt thereof.

11. The compound of claim 2, wherein the degradation moiety comprises the structure of Formula G:

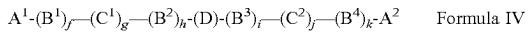


Formula G

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wherein
 A^2 is a bond between the degrader and the linker; and
 R^{F1} is absent or O,
or a pharmaceutically acceptable salt thereof.

12. The compound of claim 2, wherein the linker has the structure of Formula IV:

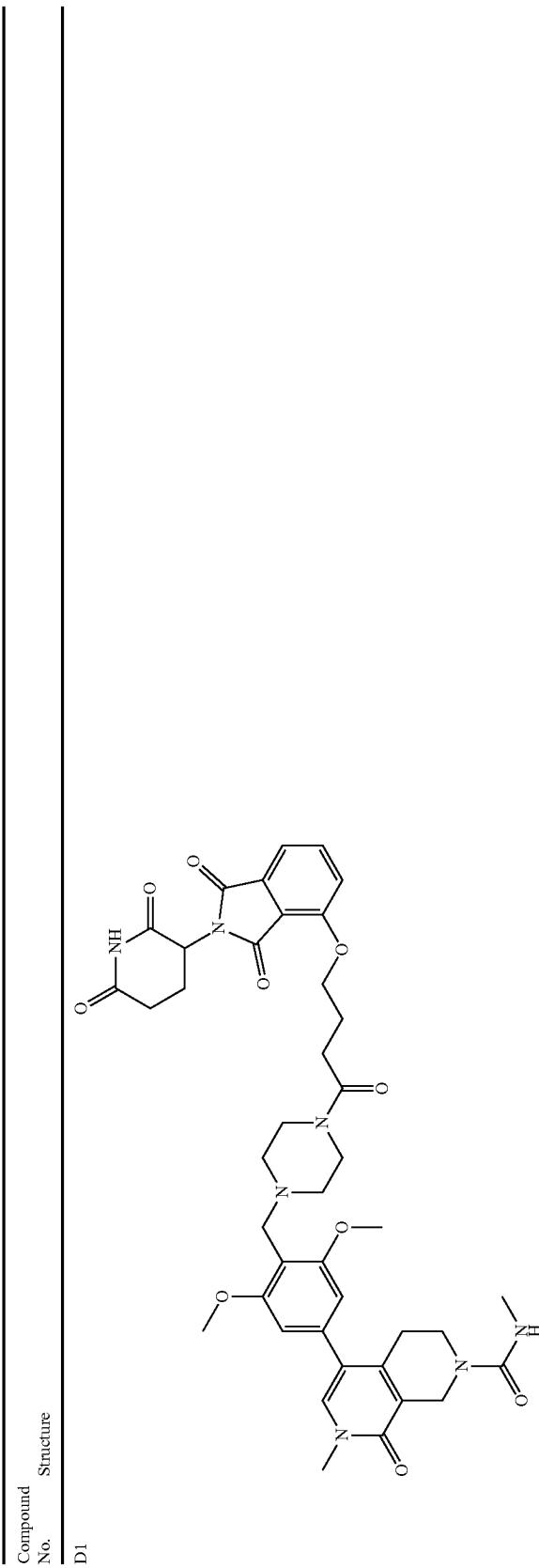


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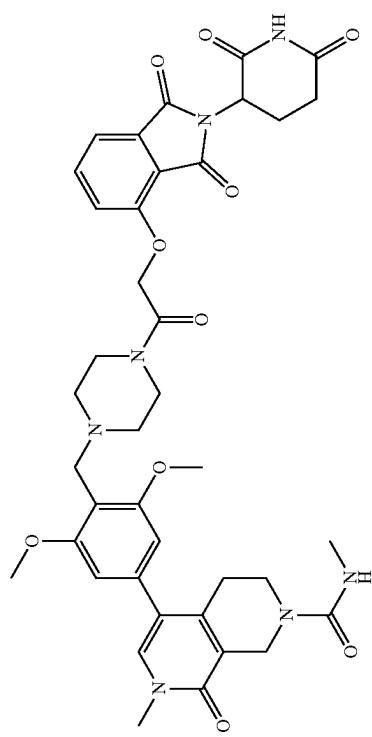
wherein
 A^1 is a bond between the linker and A;
 A^2 is a bond between B and the linker;
each of B^1 , B^2 , B^3 , and B^4 is, independently, optionally substituted C_1 - C_2 alkyl, optionally substituted C_1 - C_3 heteroalkyl, O, S, $S(O)_2$, or NR^N ;
each R^N is, independently, H, optionally substituted C_{1-4} alkyl, optionally substituted C_{2-4} alkenyl, optionally substituted C_{2-4} alkynyl, optionally substituted C_{2-6} heterocycl, optionally substituted C_{6-12} aryl, or optionally substituted C_{1-7} heteroalkyl;
each of C^1 and C^2 is, independently, carbonyl, thiocarbonyl, sulphonyl, or phosphoryl;
each of f, g, h, i, j, and k is, independently, 0 or 1; and D is optionally substituted C_{1-10} alkyl, optionally substituted C_{2-10} alkenyl, optionally substituted C_{2-10} alkynyl, optionally substituted C_{2-6} heterocycl, optionally substituted C_{6-12} aryl, optionally substituted C_2 - C_{10} polyethylene glycol, or optionally substituted C_{1-10} heteroalkyl, or a chemical bond linking $A^1-(B^1)_f-(C^1)_g-(B^2)_h-$ to $-(B^3)_i-(C^2)_j-(B^4)_k-A^2$.

13. The compound of claim 2, wherein the compound has the structure of A any one of compounds D1-D31, D32-D211, and D212-D343, or a pharmaceutically acceptable salt thereof

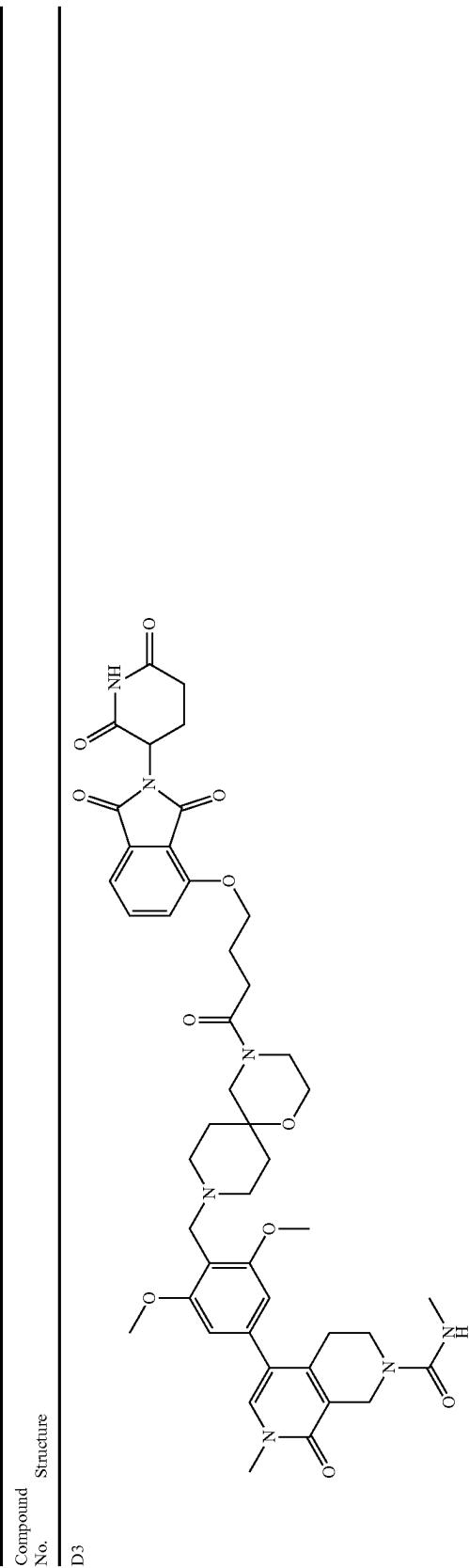
Compound
No.
Structure



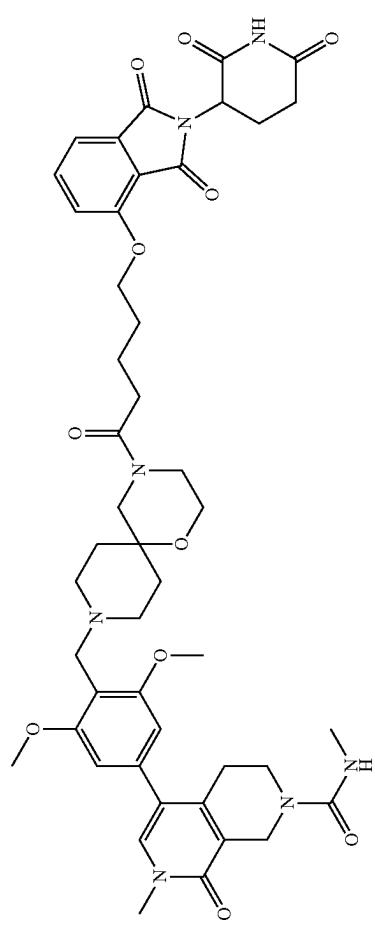
D2



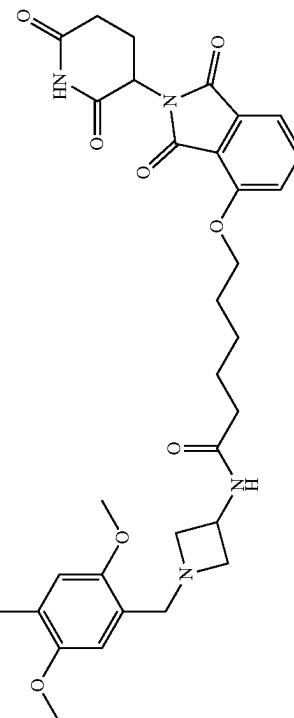
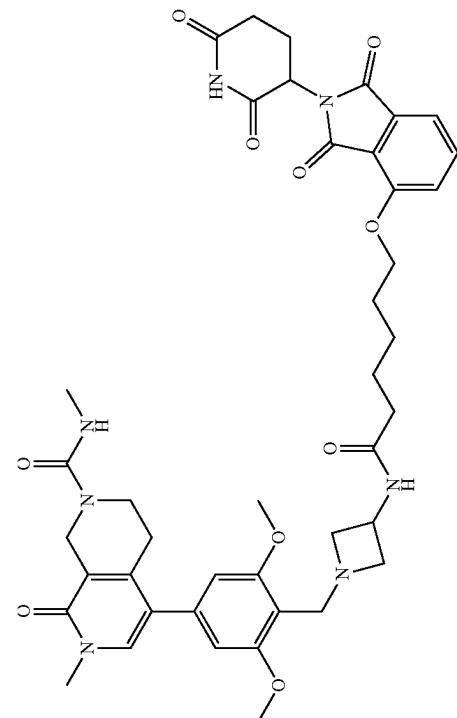
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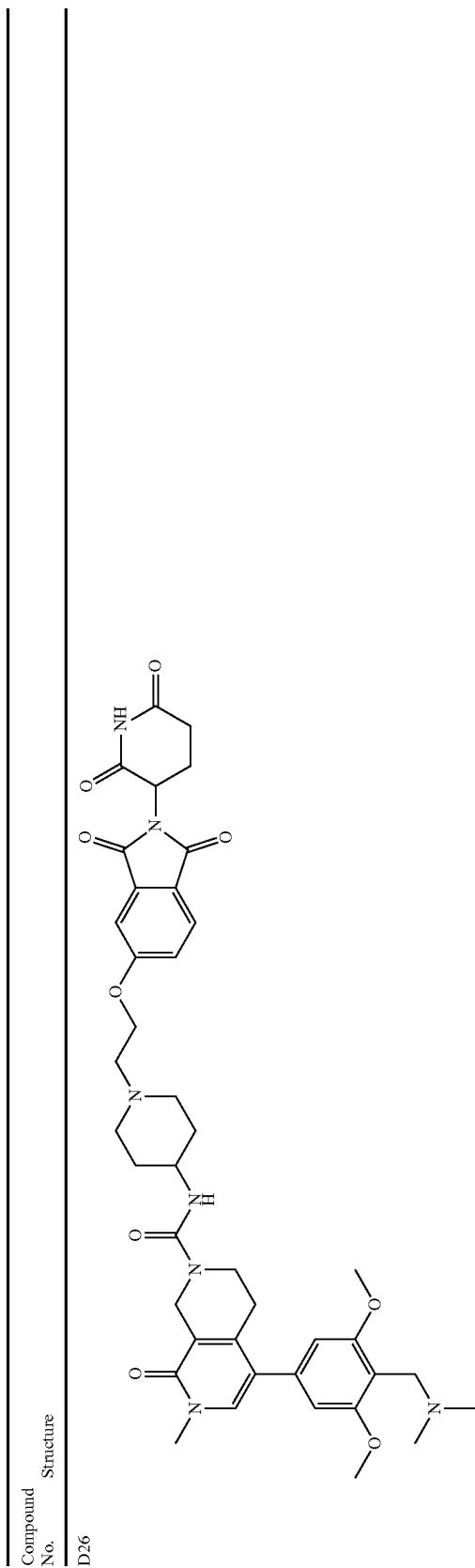
D4



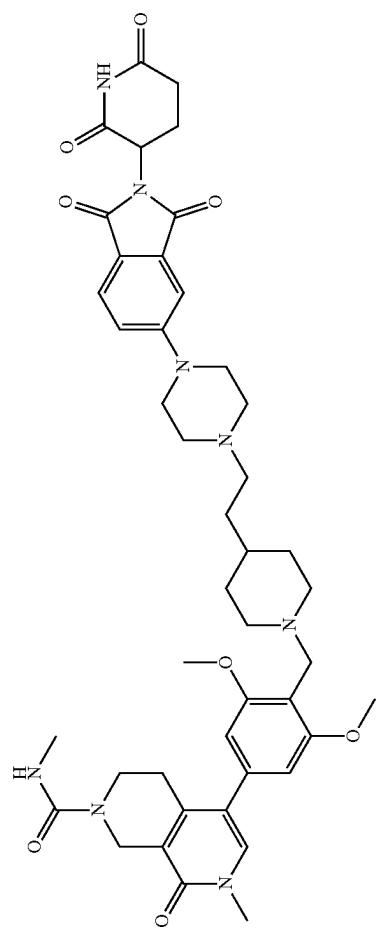
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Compound No.	Structure
D15	
D16	

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D28



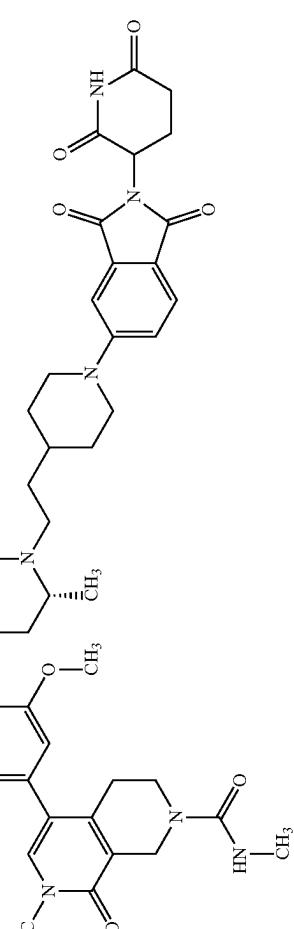
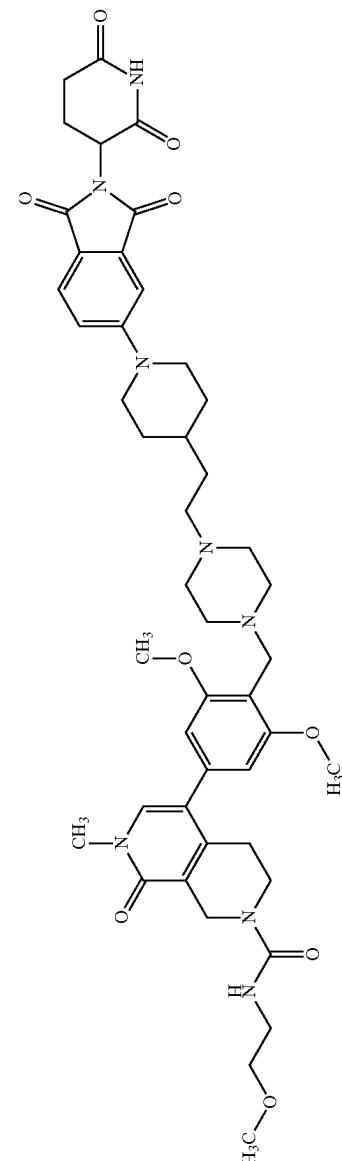
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Compound No.	Structure
D31	
D39	

-continued

Compound No.	Structure
D40	
D41	

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Compound No.	Structure
D42	
D43	

-continued

Compound No.	Structure
D44	
D45	

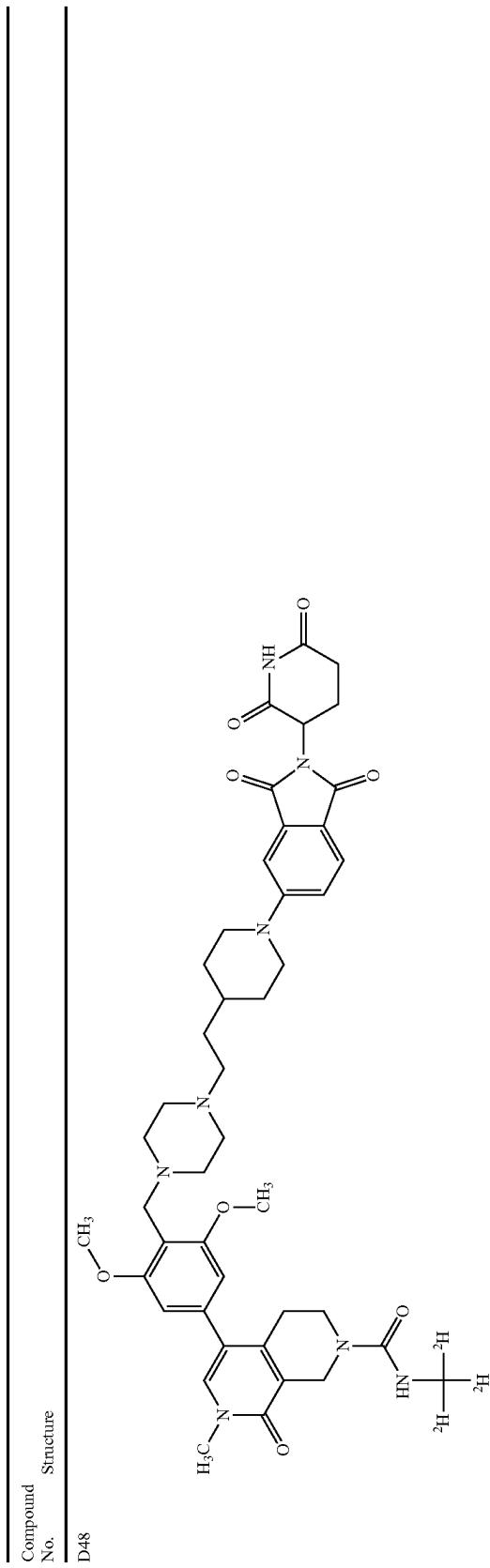
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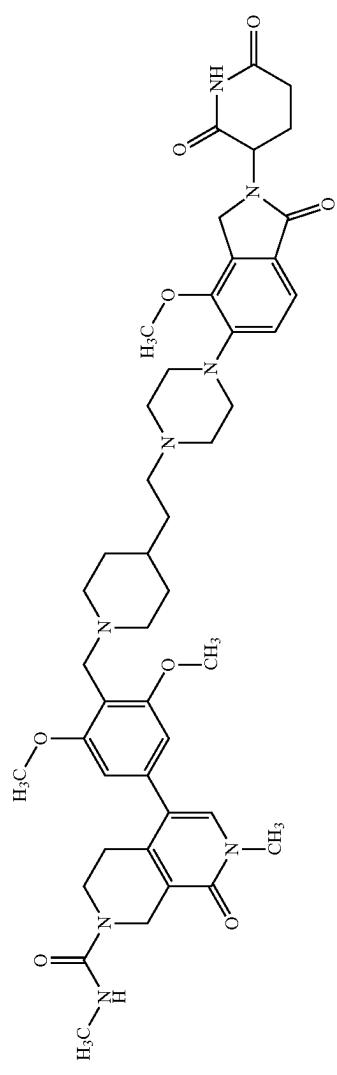
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Compound No.	Structure
D46	
D47	

-continued



D49



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Compound No.	Structure
D50	
D51	
D52	

-continued

Compound No.	Structure
D53	
D54	
D55	

-continued

Compound No.	Structure
D56	
D57	
D58	

-continued

Compound No.	Structure
D59	
D60	
D61	

-continued

Compound No.	Structure
D62	
D63	

-continued

Compound No.	Structure
D64	
D65	
D66	

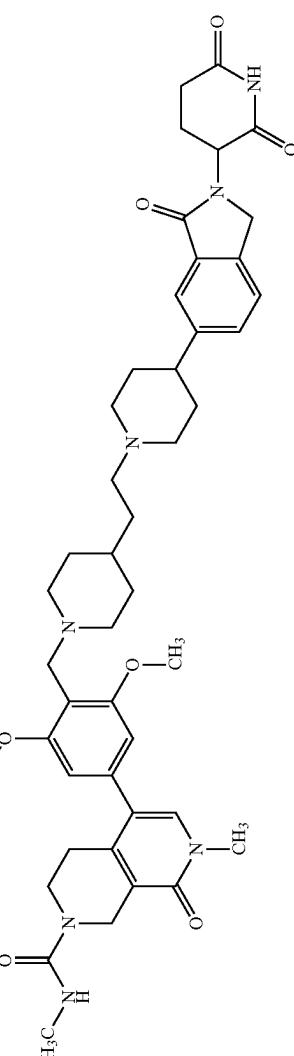
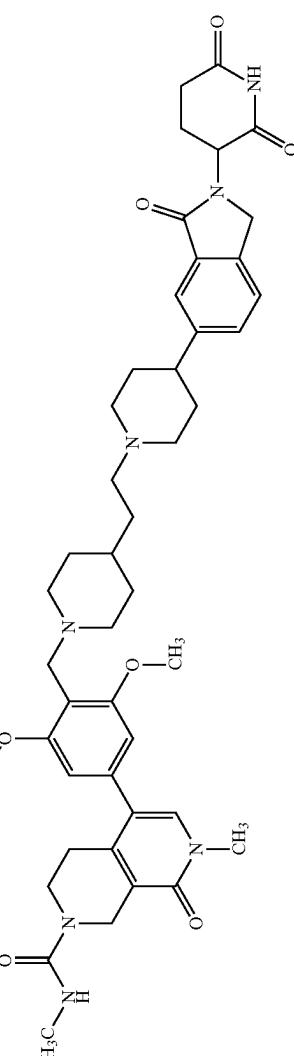
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Compound No.	Structure
D67	
D68	
D69	

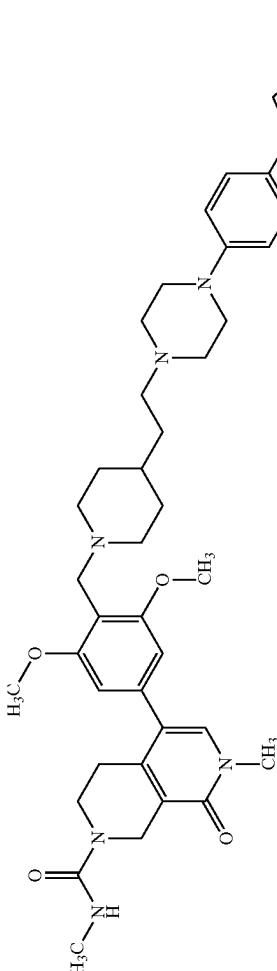
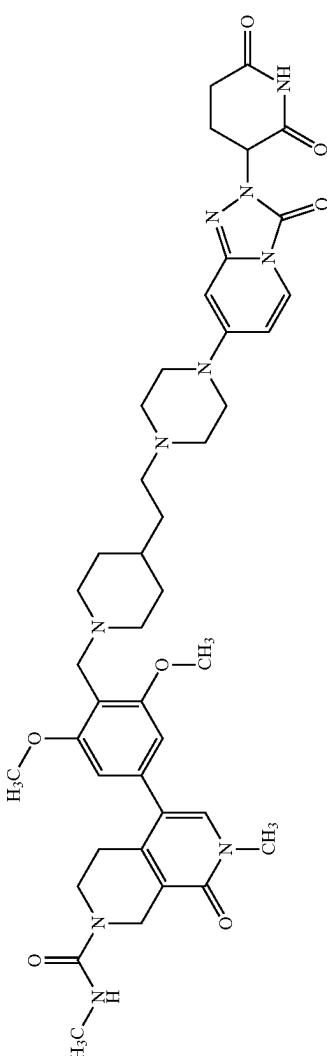
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Compound No.	Structure
D70	
D71	
D72	

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Compound No.	Structure
D73	 

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Compound No.	Structure
D76	
	

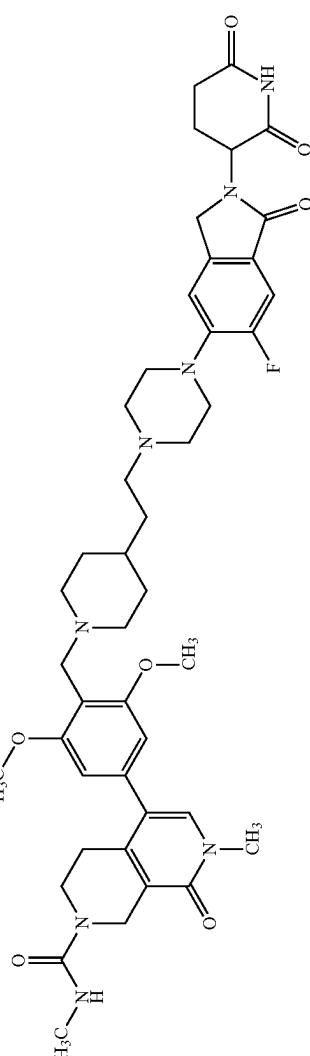
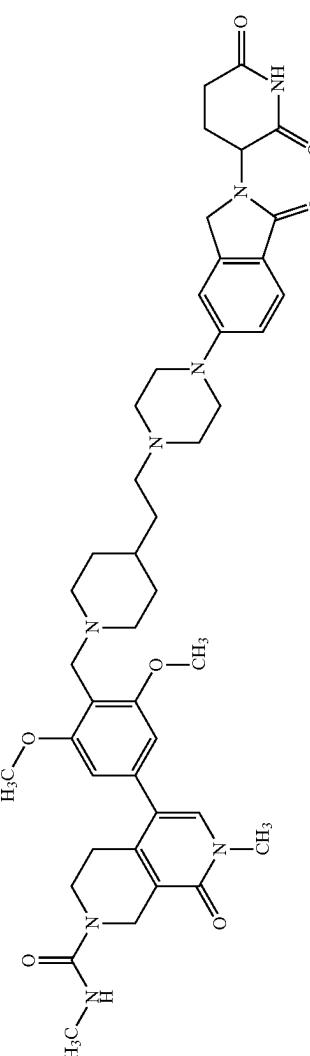
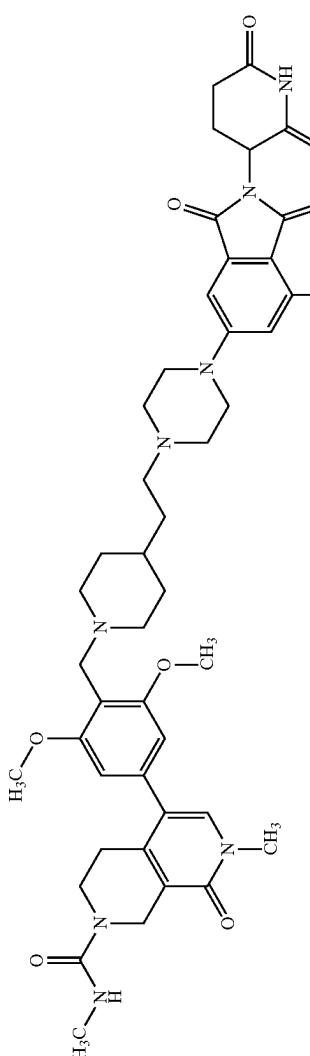
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Compound No.	Structure
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D79	
D81	

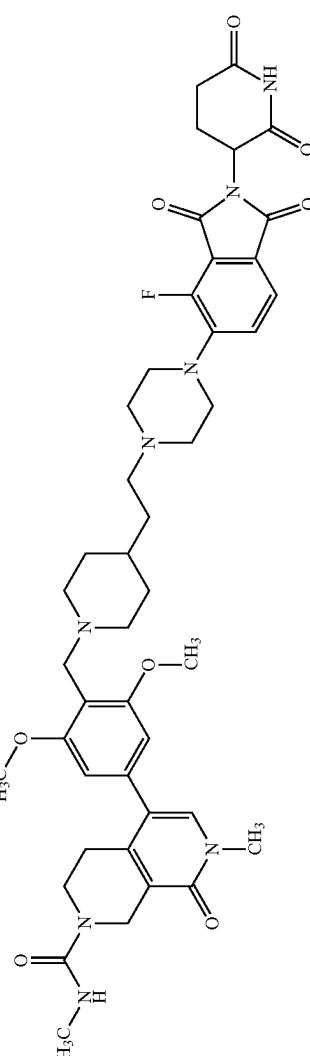
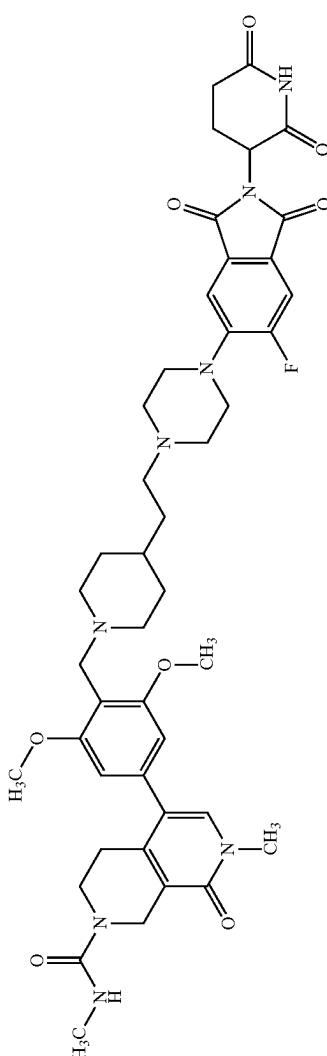
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Compound No.	Structure
D82	

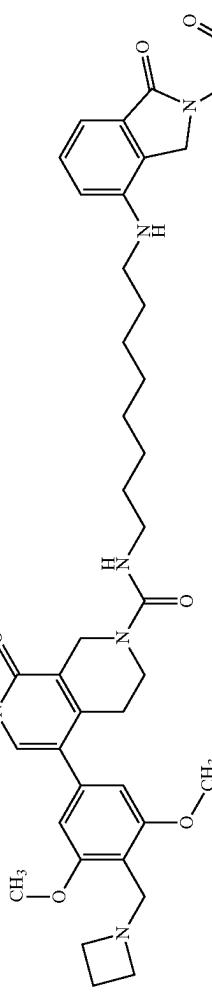
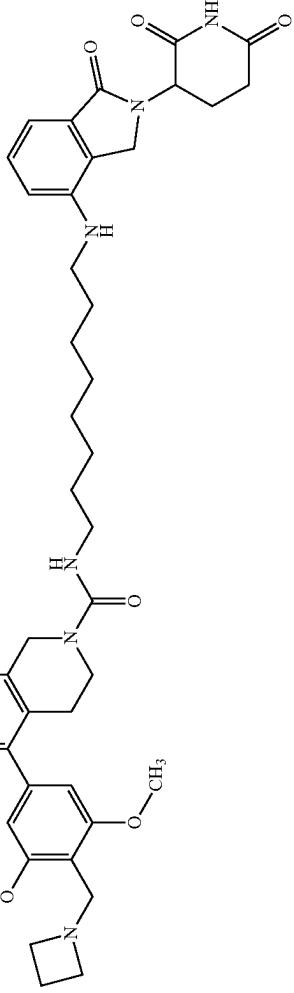
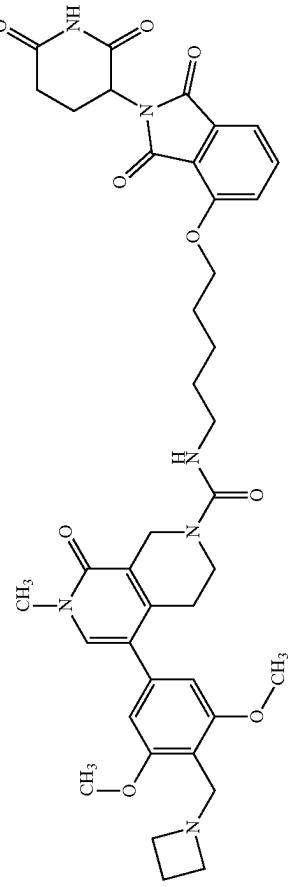
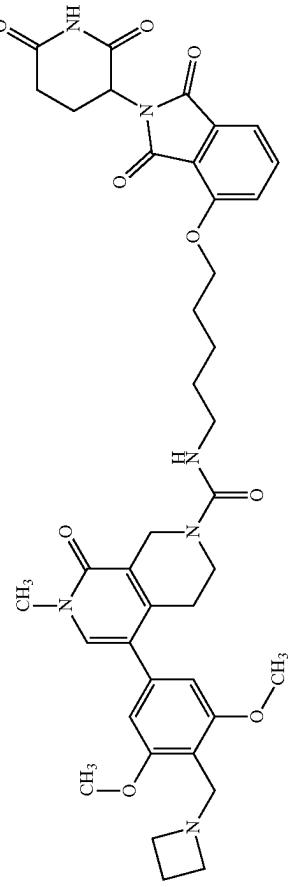
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Compound No.	Structure
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D85	
D86	

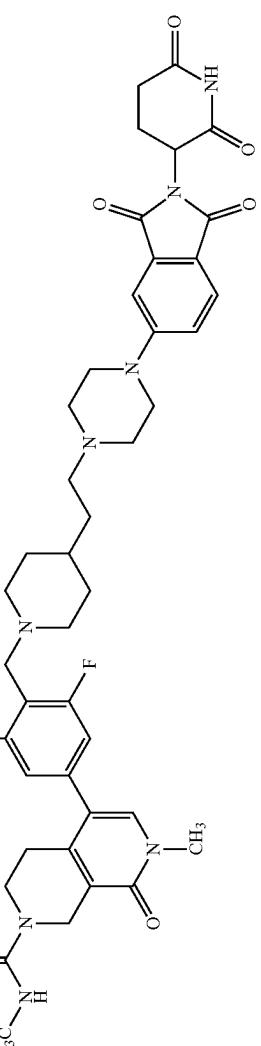
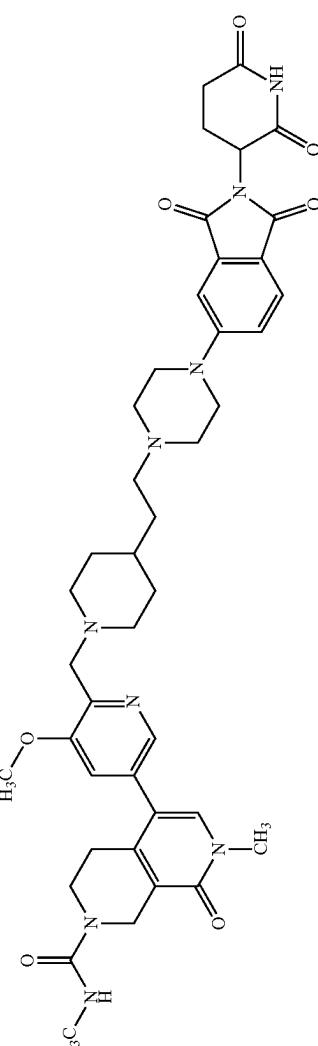
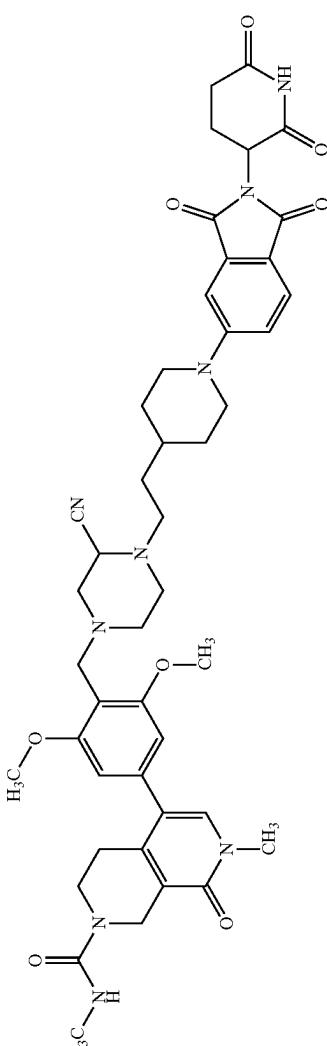
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Compound No.	Structure
D87	
	

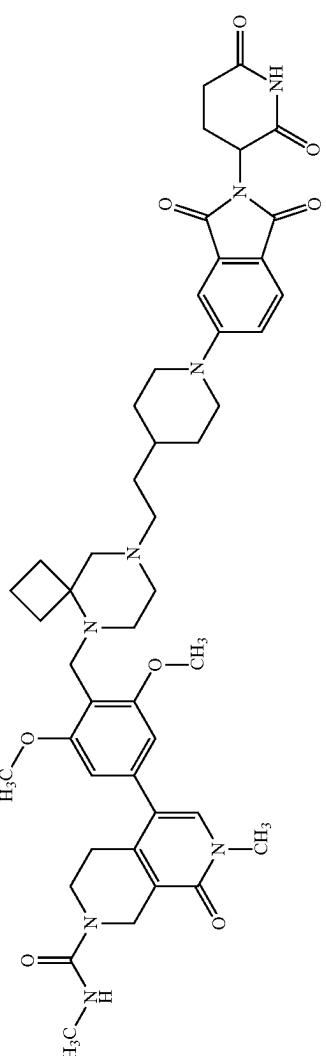
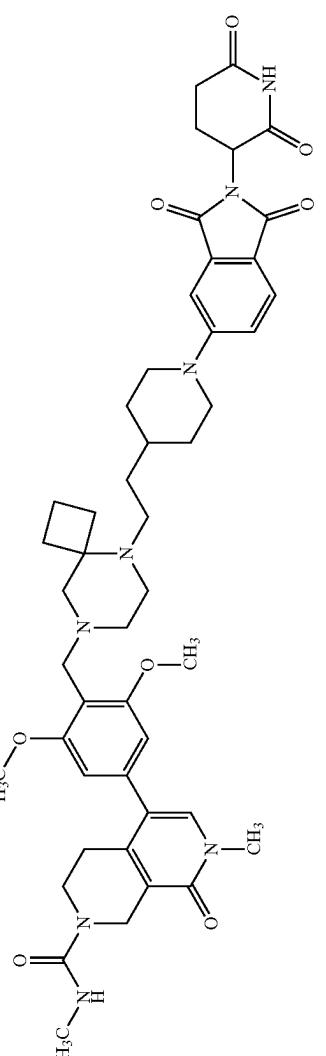
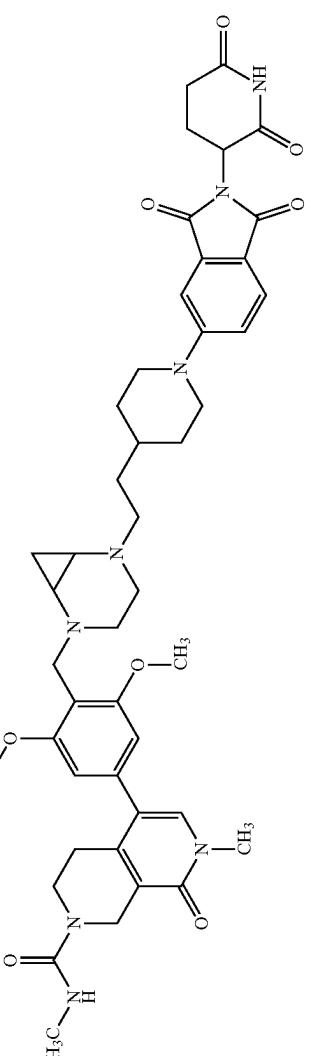
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Compound No.	Structure
D89	
891	
D90	
892	

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Compound No.	Structure
D91	
D92	
D93	

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Compound No.	Structure
D94	
D95	
D96	

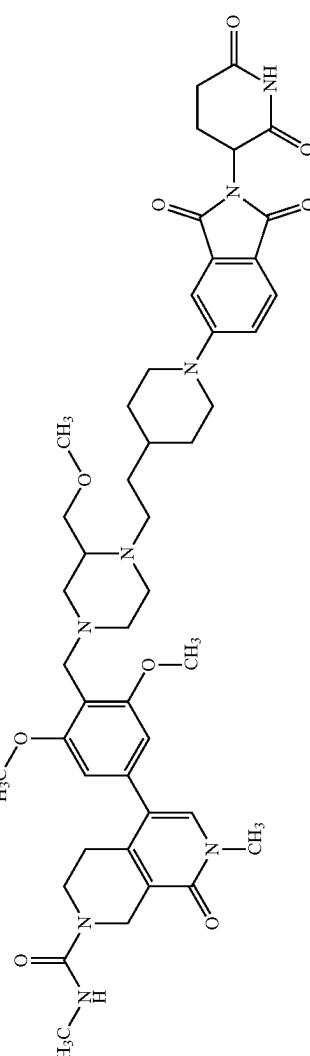
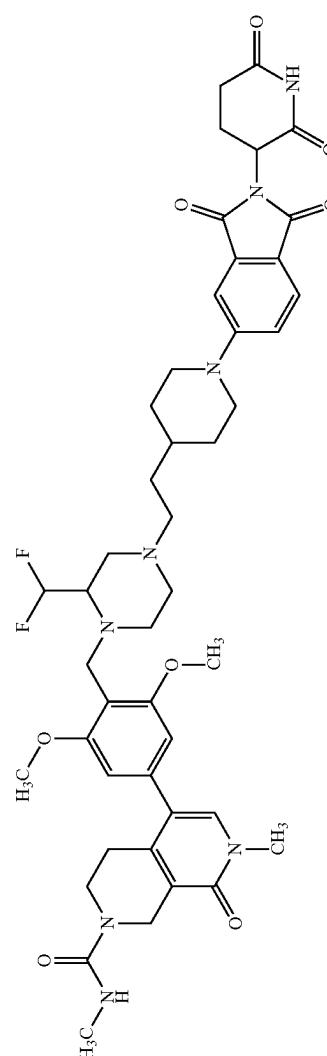
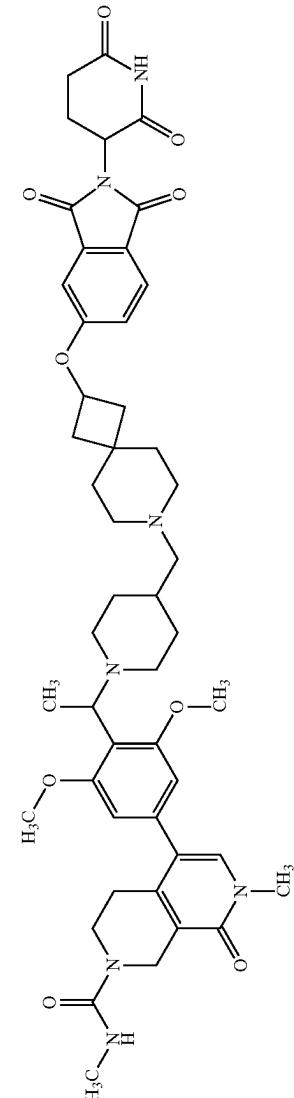
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Compound No.	Structure
D97	
D98	
D99	

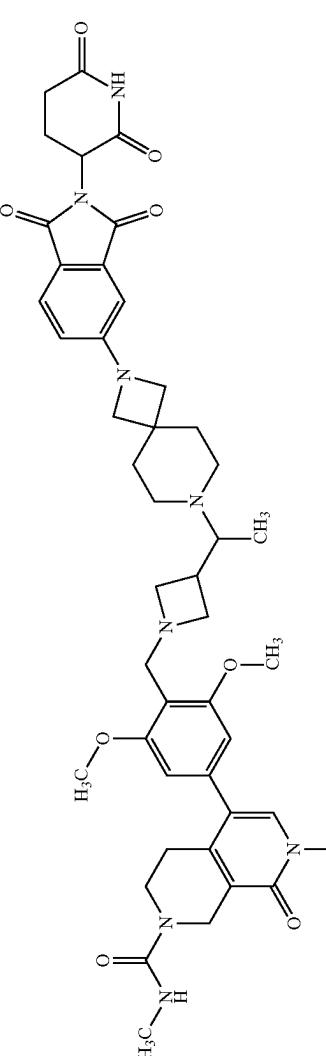
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Compound No.	Structure
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D101	
D102	

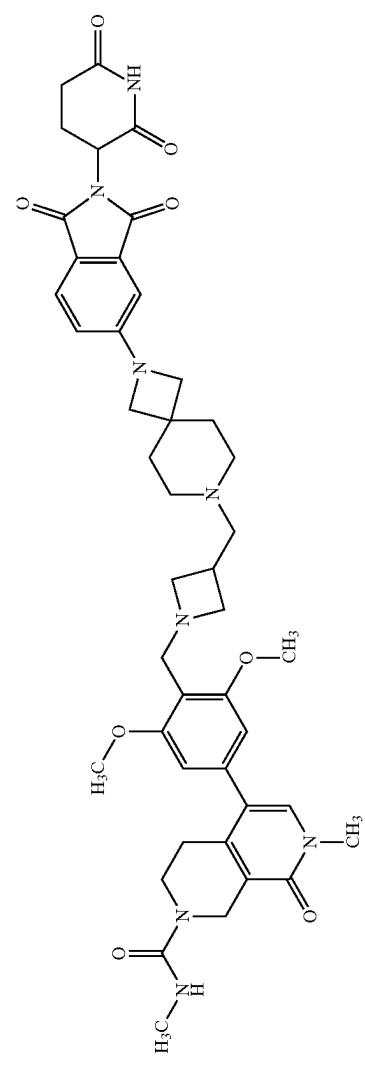
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Compound No.	Structure
D103	
D104	
D106	

-continued

Compound No.	Structure
D107	

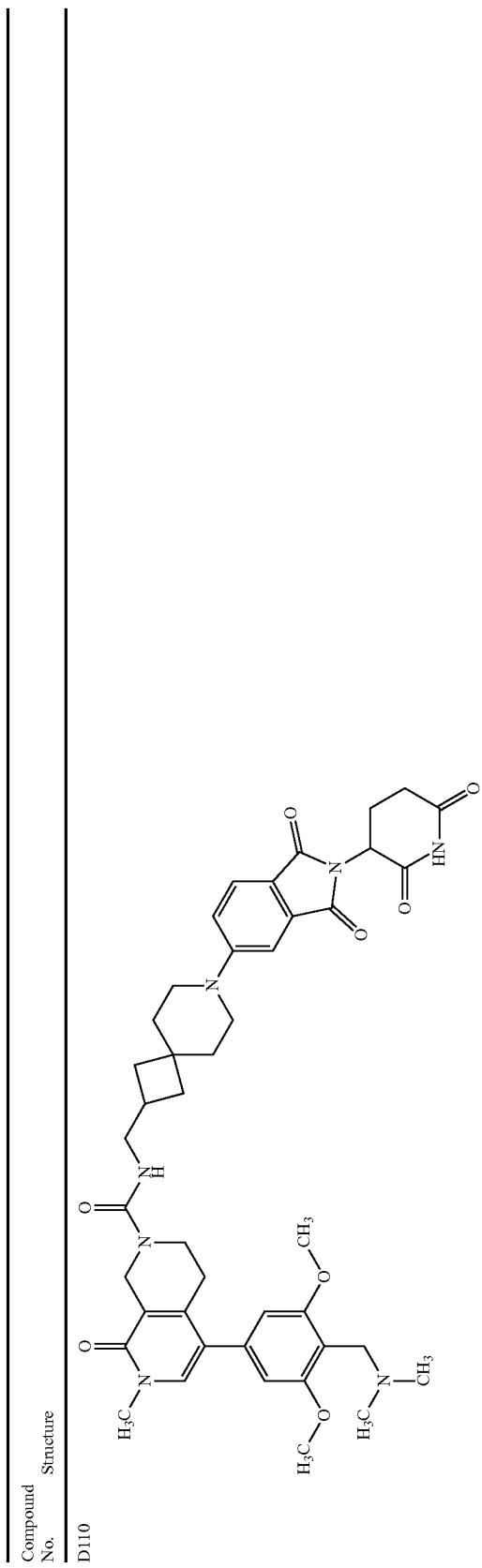
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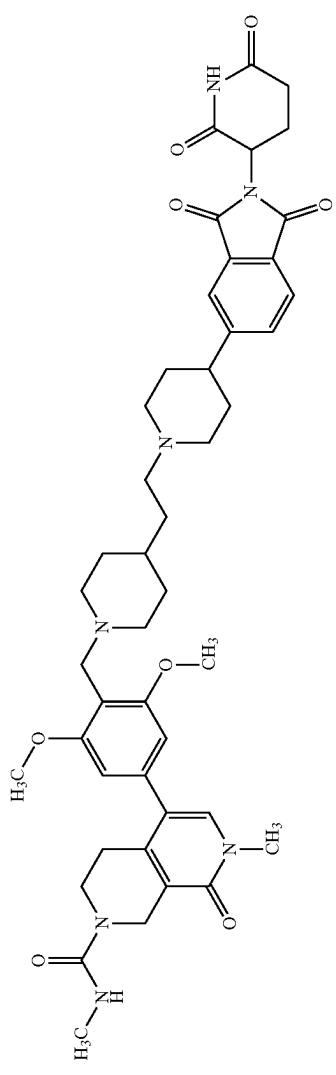
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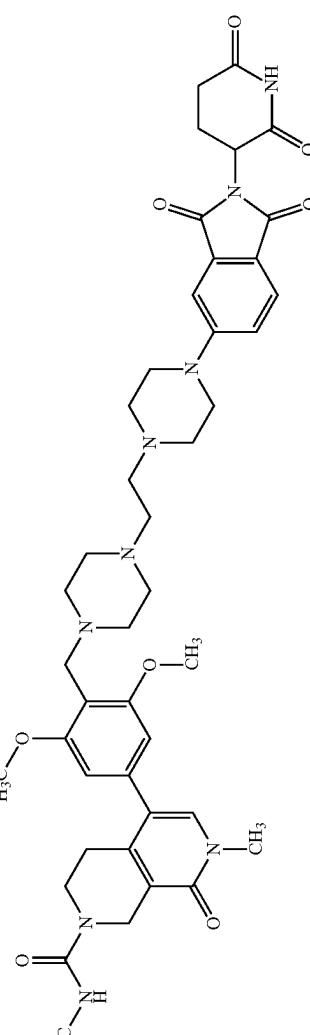
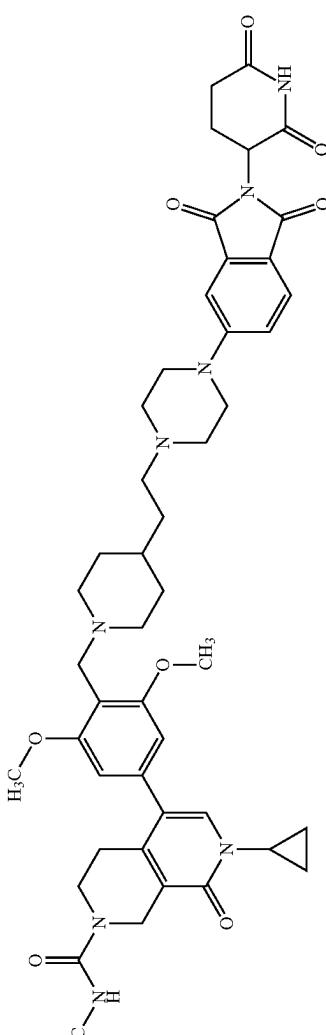
D113



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Compound No.	Structure
D114	
D115	
D116	

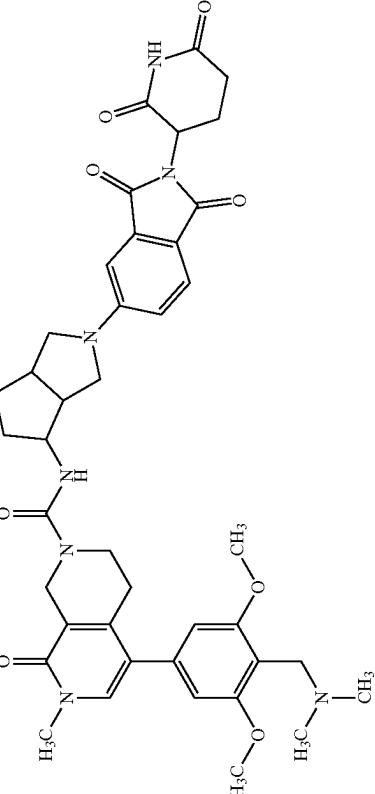
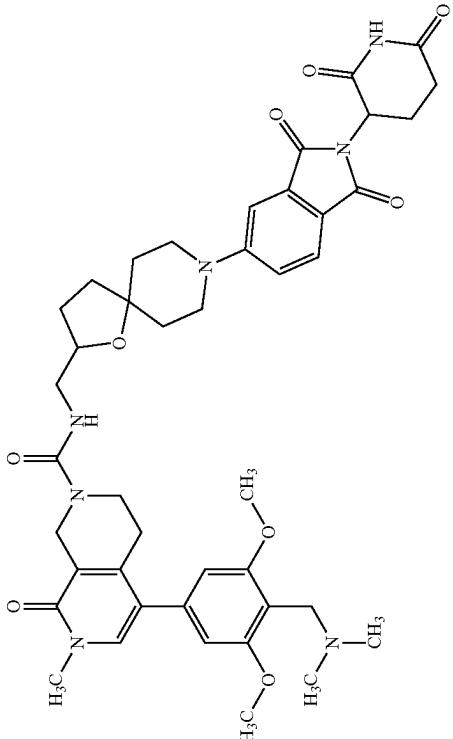
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Compound No.	Structure
D117	
D118	

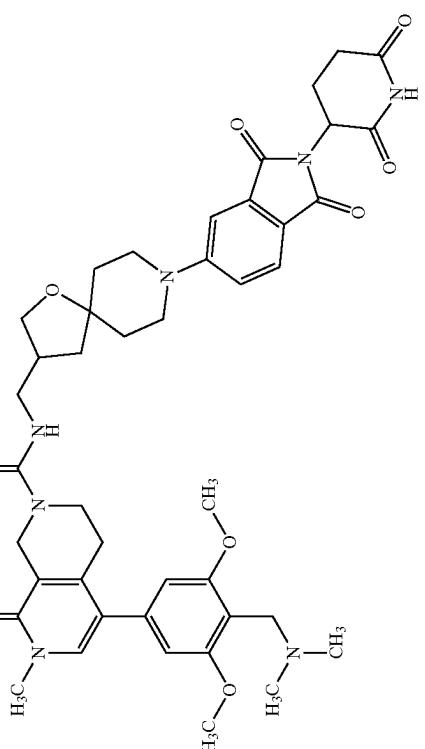
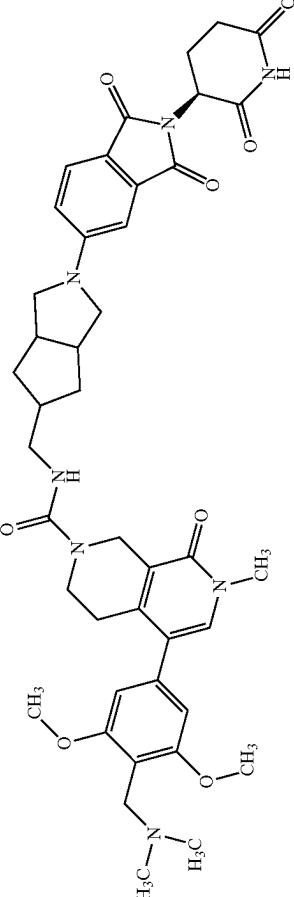
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912

-continued

Compound No.	Structure
D119	
D120	

-continued

Compound No.	Structure
D121	
D122	

-continued

Compound No.	Structure
D123	
D124	
D125	

-continued

Compound No.	Structure
D126	
D127	
D128	

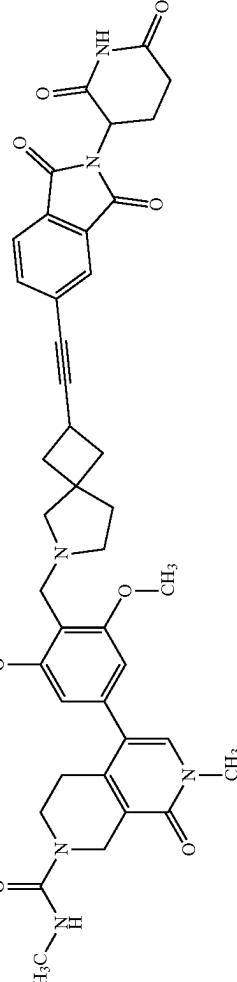
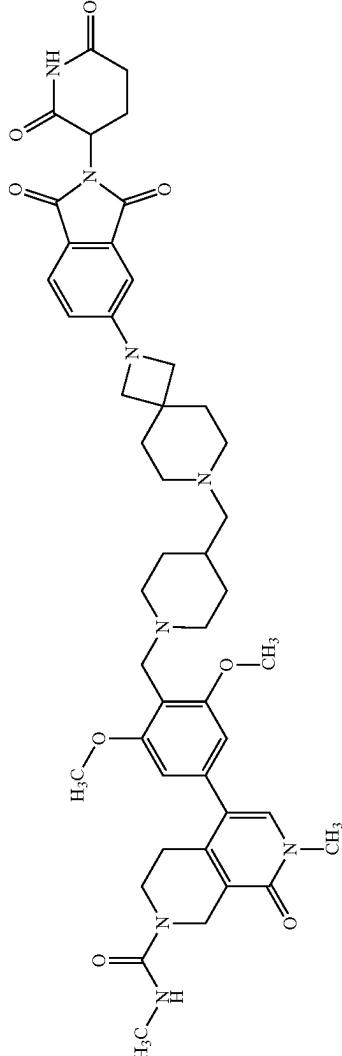
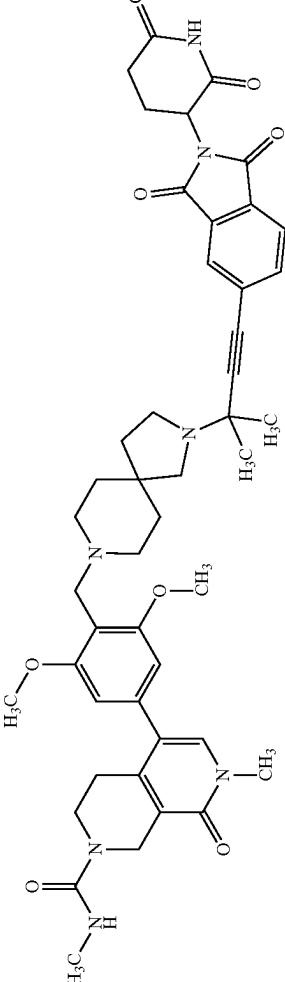
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Compound No.	Structure
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D130	
D131	

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Compound No.	Structure
D132	
D133	
D134	

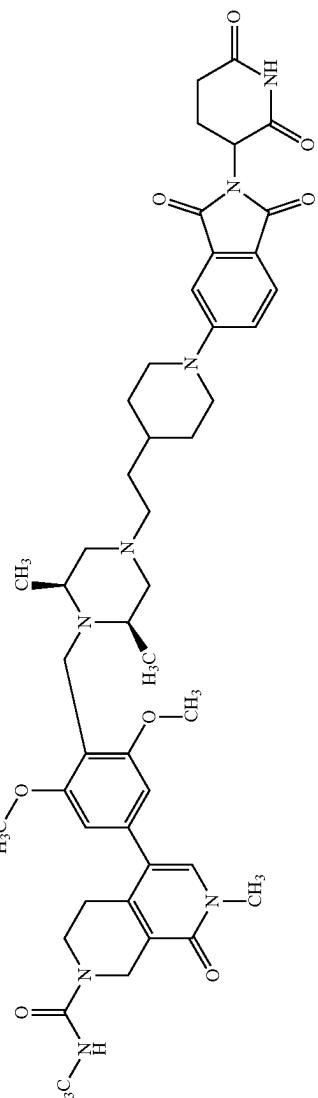
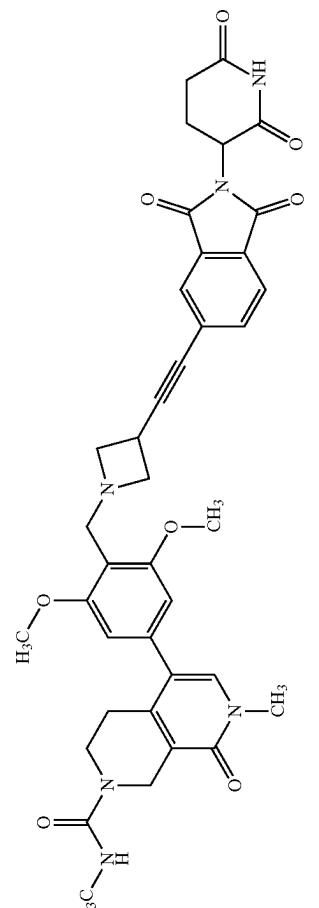
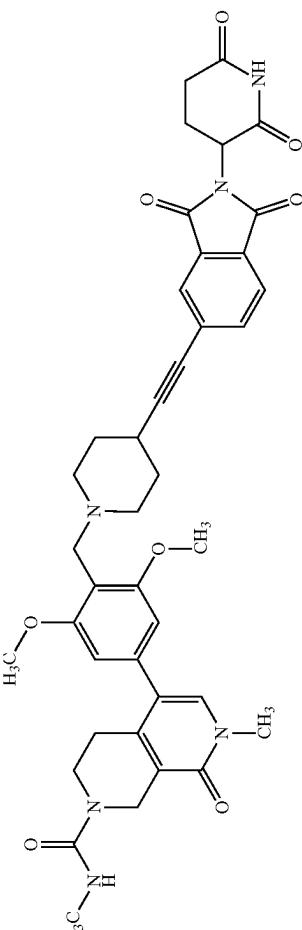
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Compound No.	Structure
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D136	
D137	

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Compound No.	Structure
D138	
D139	
D140	

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Compound No.	Structure
D141	
D142	
D143	

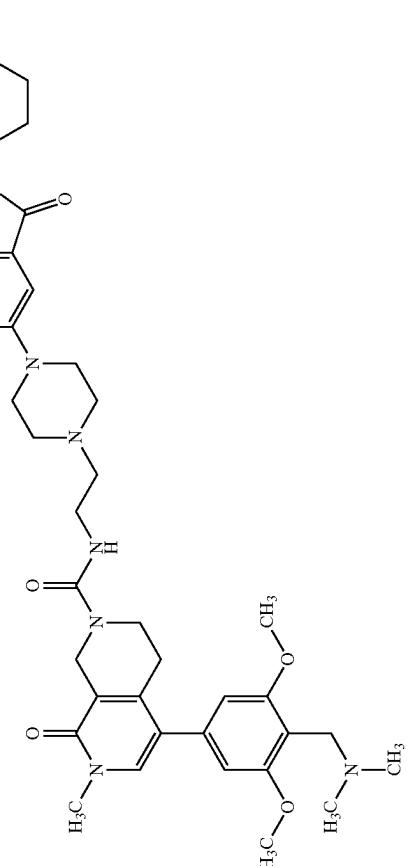
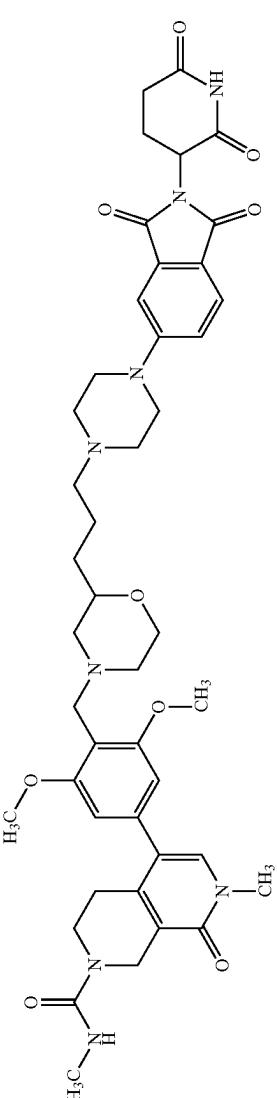
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Compound No.	Structure
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D145	
D146	

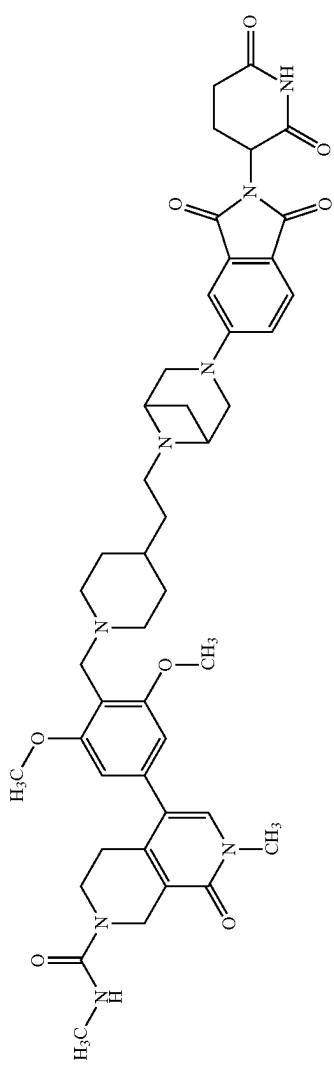
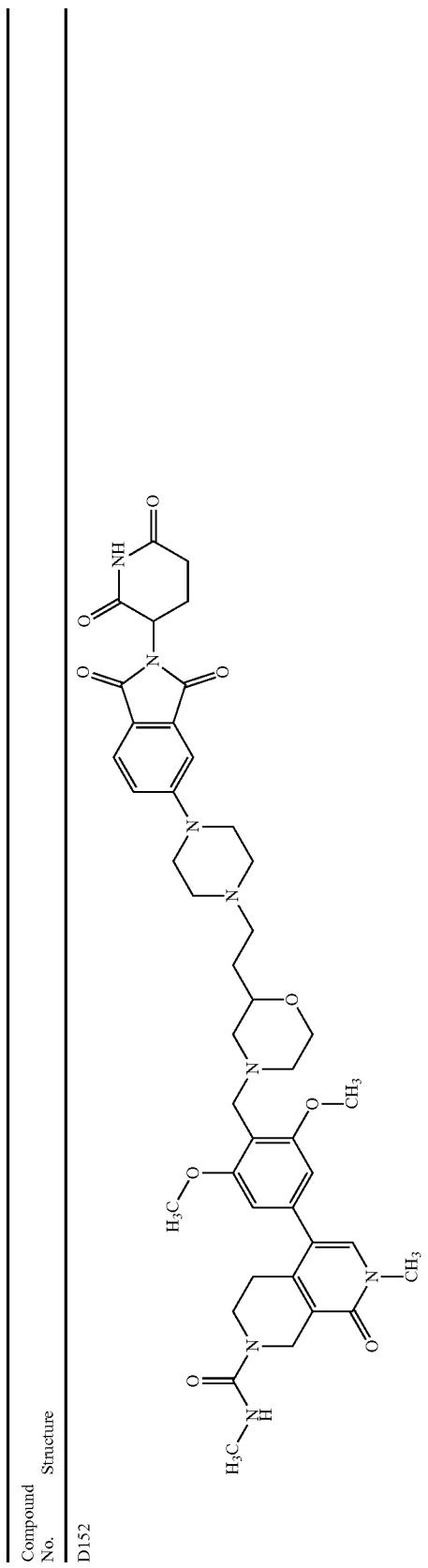
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Compound No.	Structure
D147	
D148	
D149	

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Compound No.	Structure
D150	
D151	

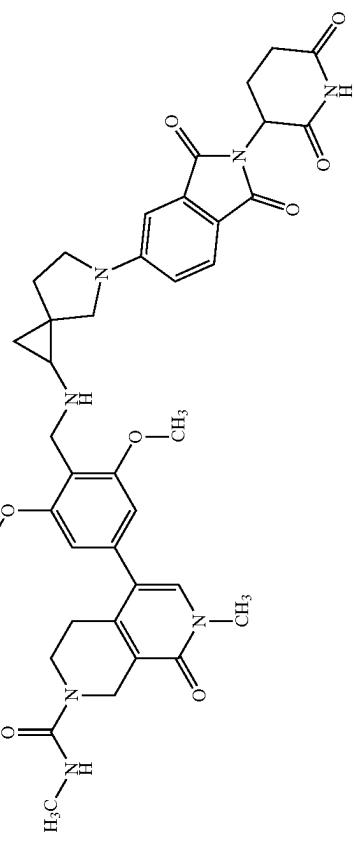
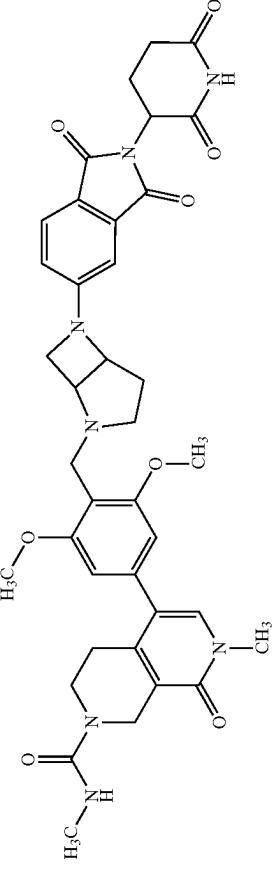
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Compound No.	Structure
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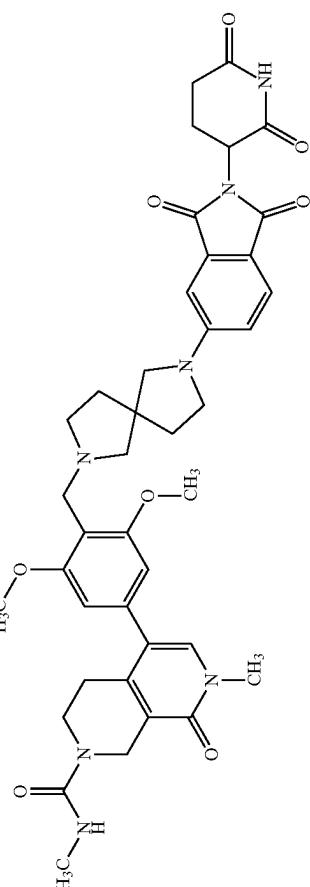
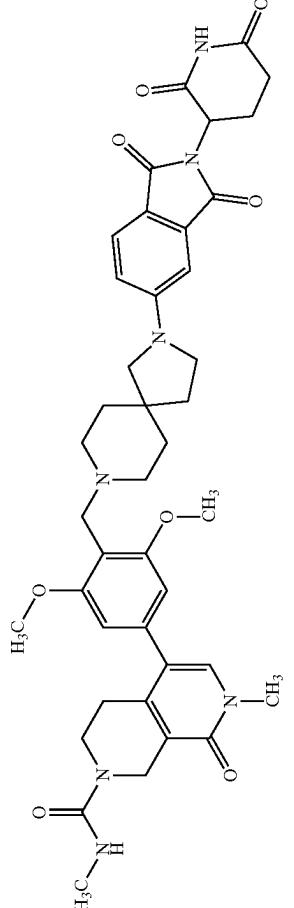
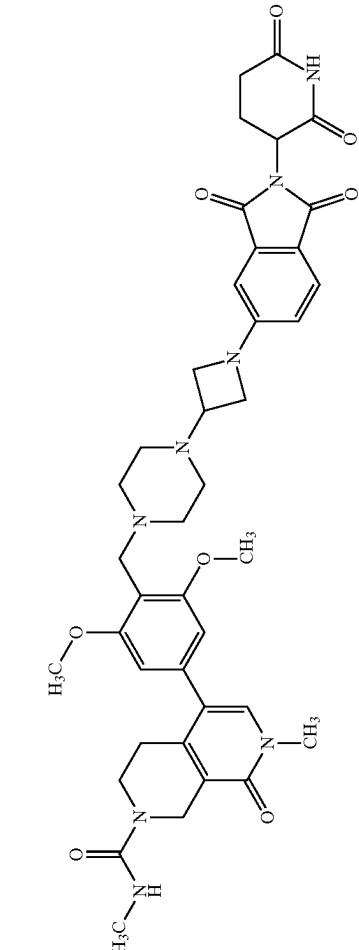
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Compound No.	Structure
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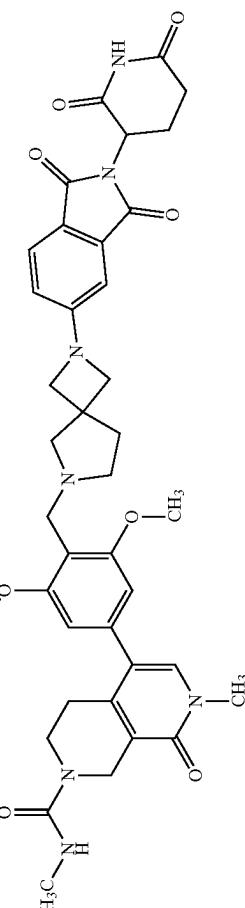
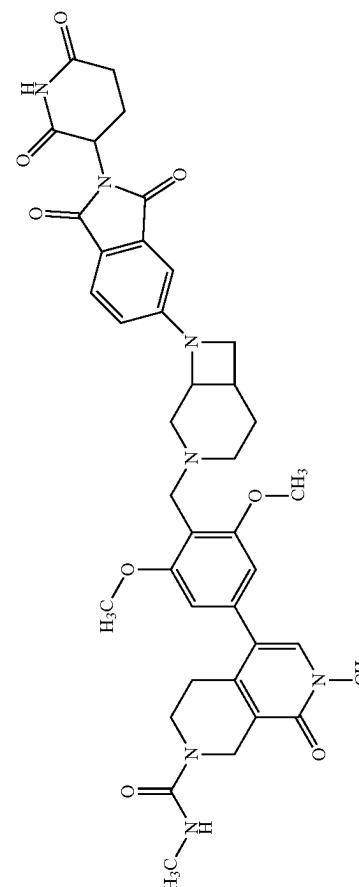
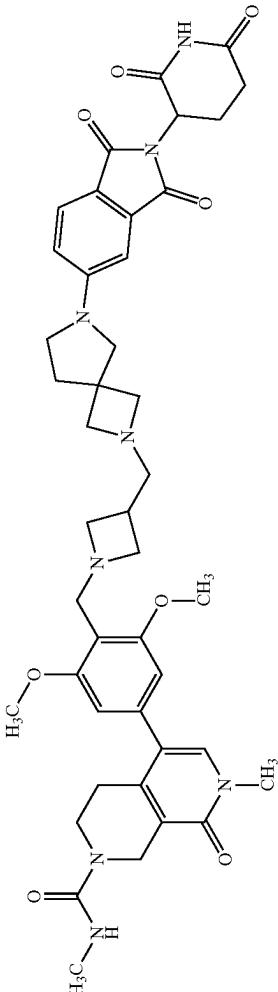
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Compound No.	Structure
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D159	
D161	

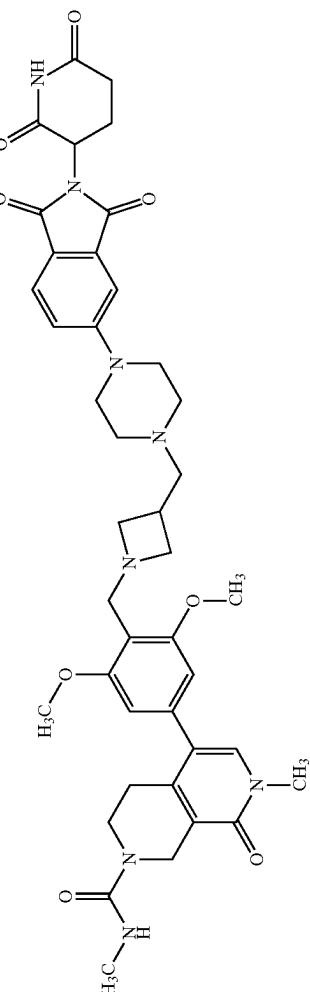
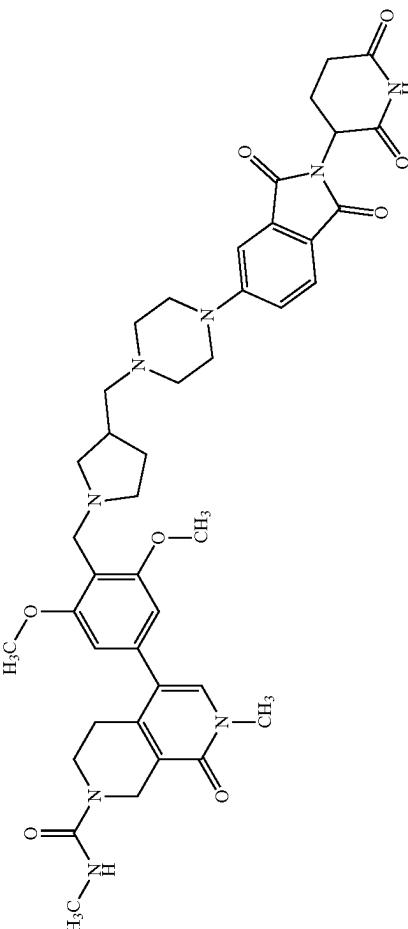
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Compound No.	Structure
D162	
D163	
D164	

-continued

Compound No.	Structure
D165	
D166	
D167	

-continued

Compound No.	Structure
D168	
D169	

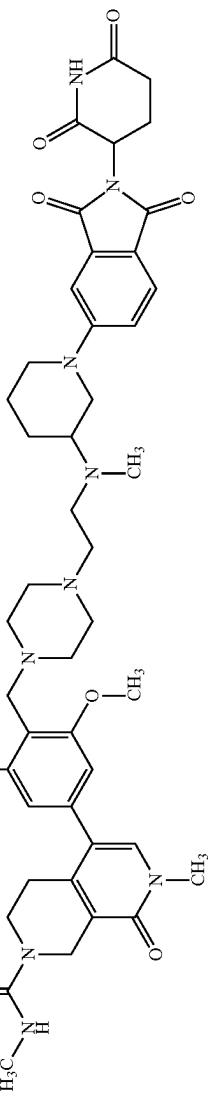
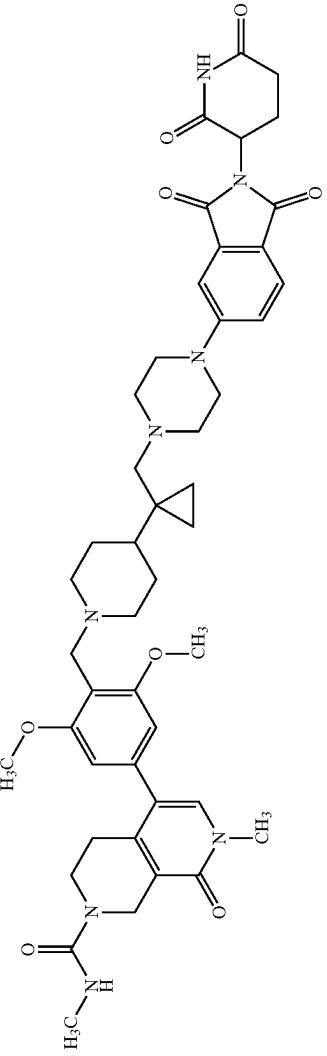
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Compound No.	Structure
D170	
D171	
D172	

951

952

-continued

Compound No.	Structure
D173	
D174	

-continued

Compound No.	Structure
D175	
D176	

955

956

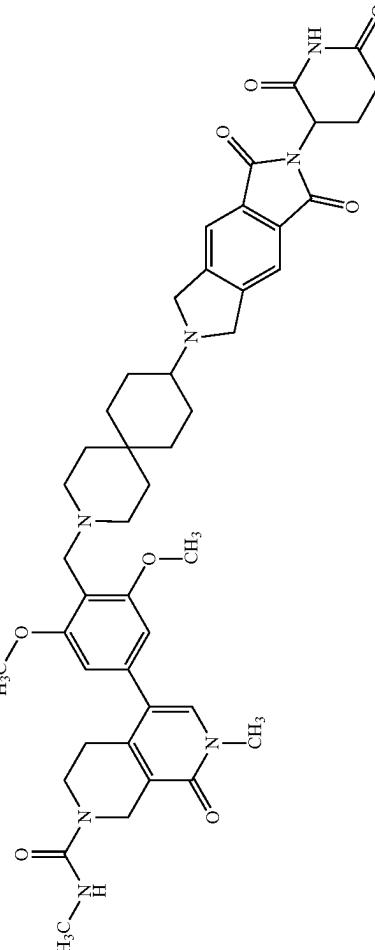
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Compound No.	Structure
D177	
D178	

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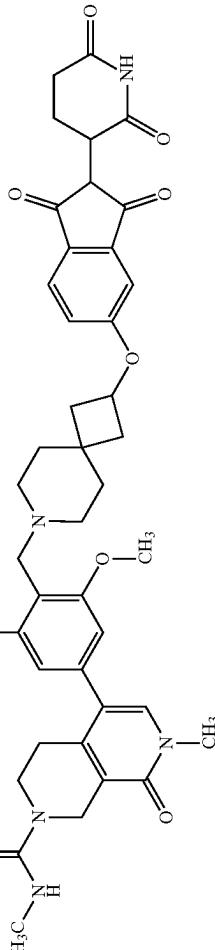
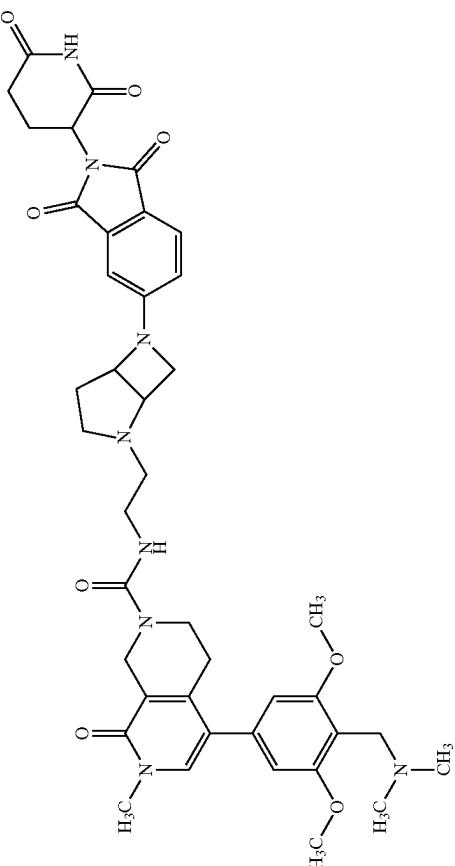
Compound No.	Structure
D179	
D180	

-continued

Compound No.	Structure
D181	

961**962**

-continued

Compound No.	Structure
D183	
D184	

-continued

Compound No.	Structure
D185	
D186	

965

966

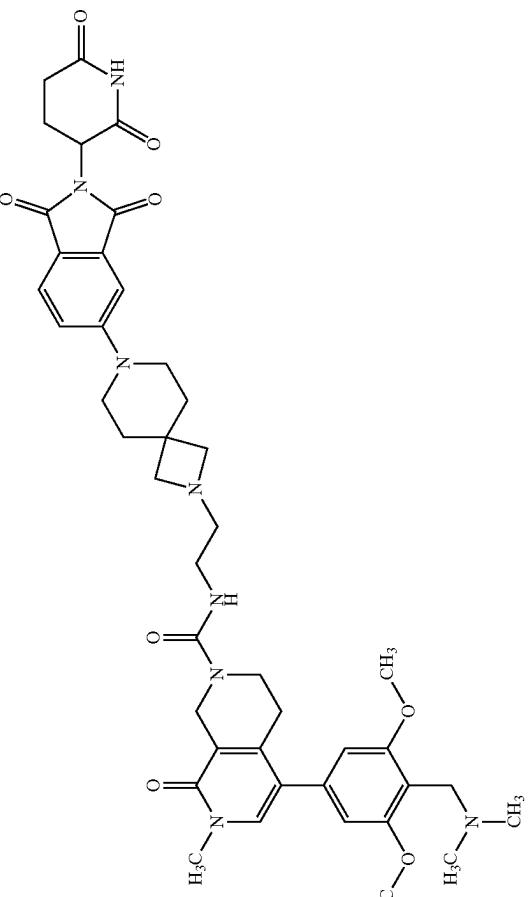
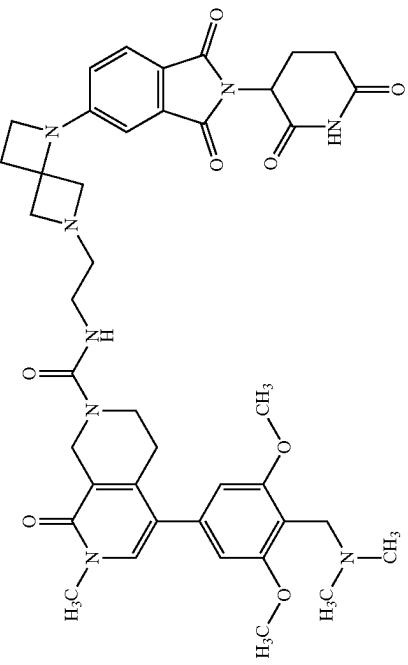
-continued

Compound No.	Structure
D187	<p>Chemical structure of compound D187:</p> <p>The structure features a 2,6-dimethyl-4-(methylamino)-4H-pyran-4-one core. Attached to the 4-position of the pyran ring is a 2-(4-(dimethylamino)phenyl)-2-methyl-1,3-dihydro-1,3-dioxolane-4-carbohydrazide side chain. The side chain includes a phenyl ring substituted with a dimethylaminophenoxy group (-O-CH₂-C₆H₃(CH₃)₂-N(CH₃)₂).</p>
D188	<p>Chemical structure of compound D188:</p> <p>The structure is identical to compound D187, featuring a 2,6-dimethyl-4-(methylamino)-4H-pyran-4-one core attached to a 2-(4-(dimethylamino)phenyl)-2-methyl-1,3-dihydro-1,3-dioxolane-4-carbohydrazide side chain.</p>

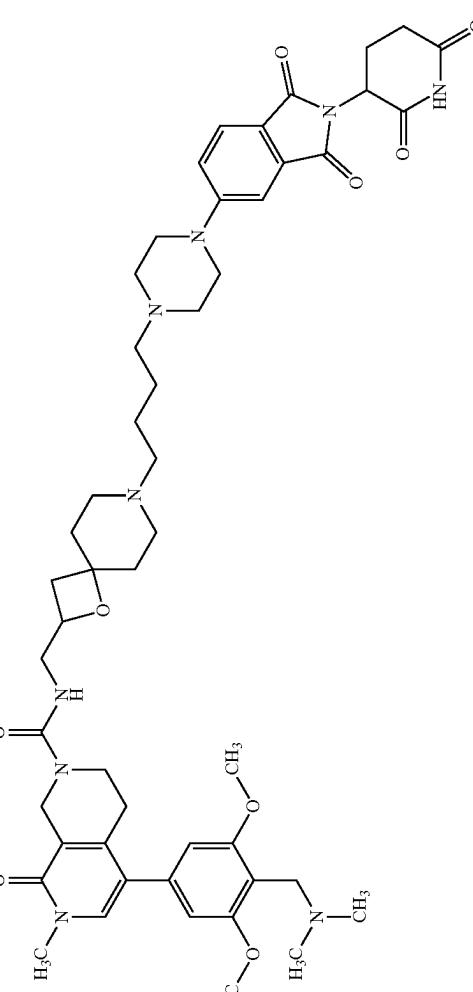
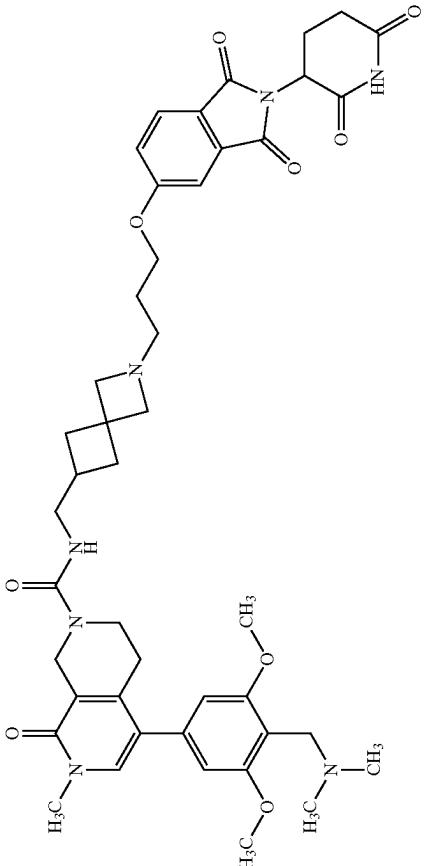
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Compound No.	Structure
D189	
D190	

-continued

Compound No.	Structure
D191	
D192	

-continued

Compound No.	Structure
D193	
D194	

-continued

Compound No.	Structure
D195	
D196	
D197	

-continued

Compound No.	Structure
D198	
D199	
D200	

-continued

Compound No.	Structure
D201	
D202	
D203	

979

980

-continued

Compound No.	Structure
D204	
D205	

-continued

Compound No.	Structure
D206	
D207	

983**984**

-continued

Compound No.	Structure
D208	
D209	

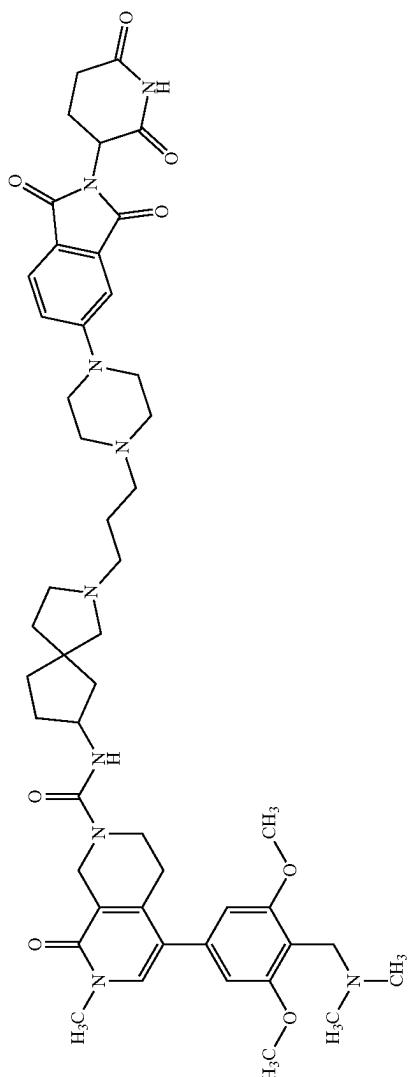
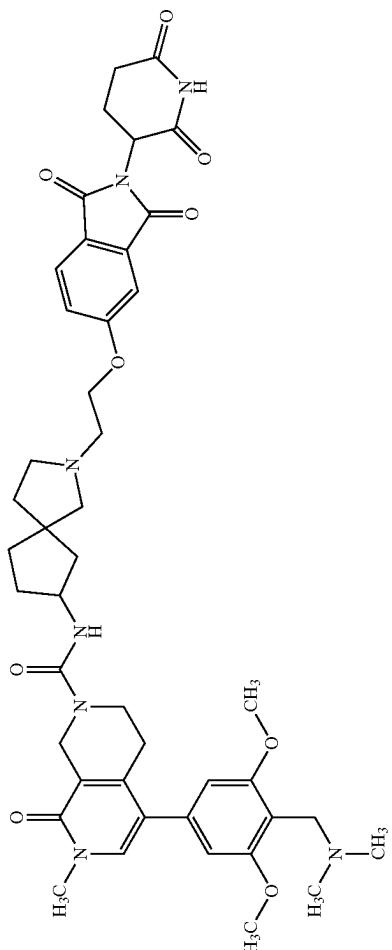
-continued

Compound No.	Structure
D210	
D211	

-continued

Compound No.	Structure
D212	<p>Chemical structure of compound D212:</p> <p>This compound features a complex multi-ring system. At the top is a 4-oxo-4,5-dihydroimidazolidine ring fused to a 2,3-dihydro-1H-pyridine ring. This is further fused to a 1,2-dihydro-1,4-dioxin ring. The 4-position of the pyridine ring is substituted with a 4-(cyclobutylmethyl)piperazine-1-carboxamide group. The 2-position of the pyridine ring is substituted with a 4-(dimethylaminomethoxy)phenyl group.</p>

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Compound No.	Structure
D214	
D215	

-continued

Compound No.	Structure
D216	
991	
D217	
992	

-continued

Compound No.	Structure
D218	
D219	

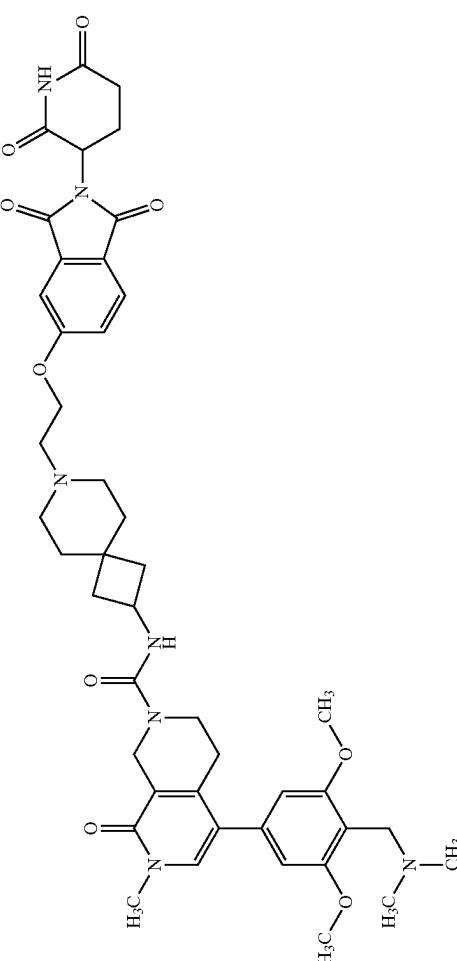
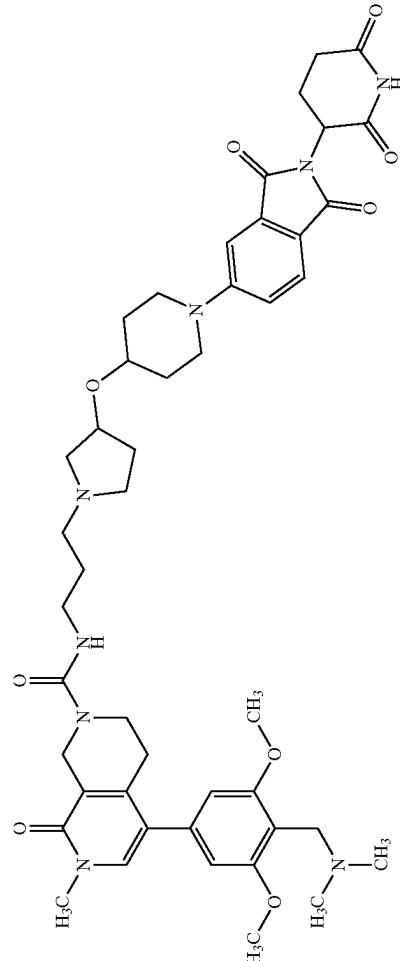
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Compound No.	Structure
D220	
D221	

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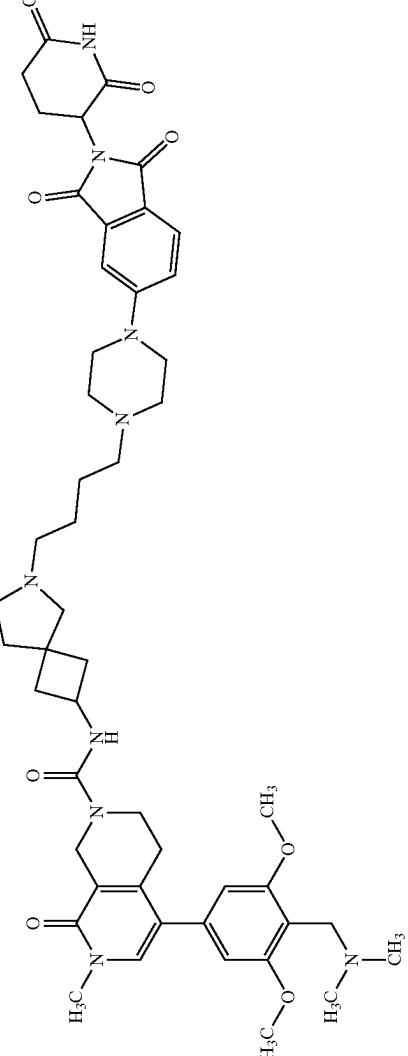
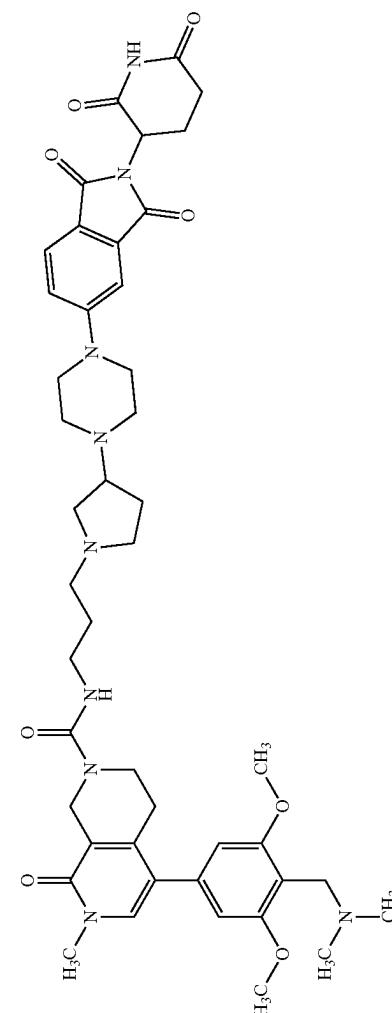
Compound No.	Structure
D222	
D223	

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Compound No.	Structure
D224	
D225	

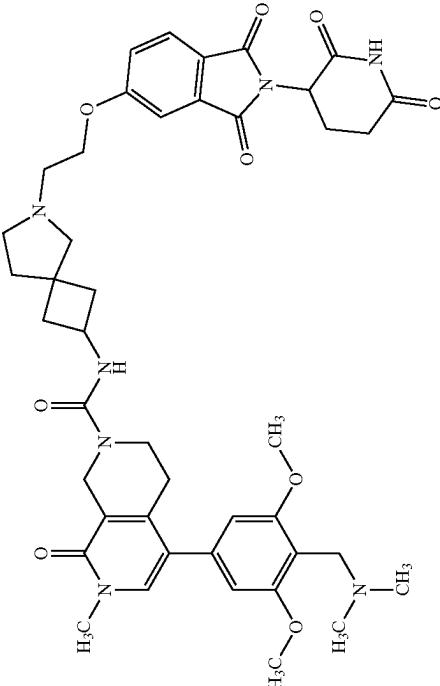
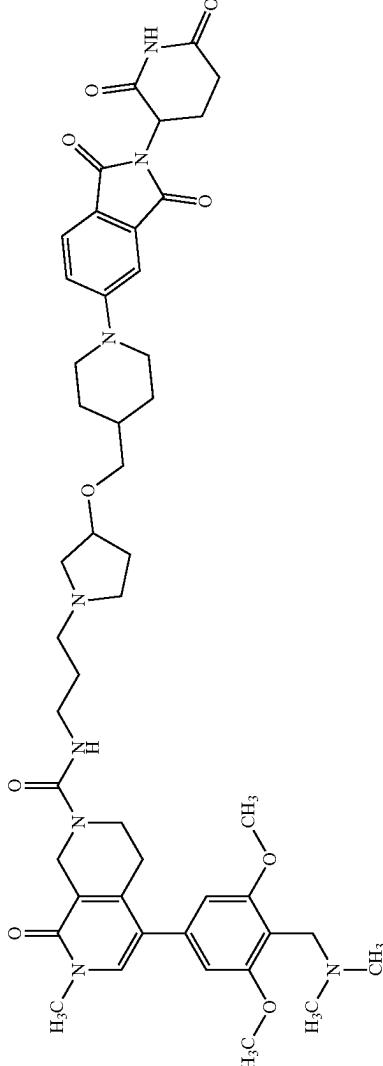
1001**1002**

-continued

Compound No.	Structure
D226	
D227	

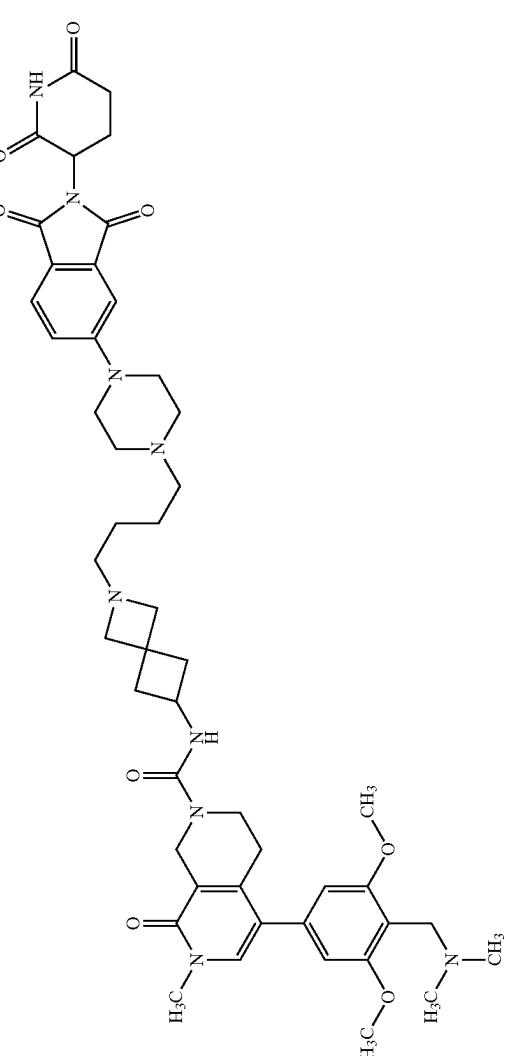
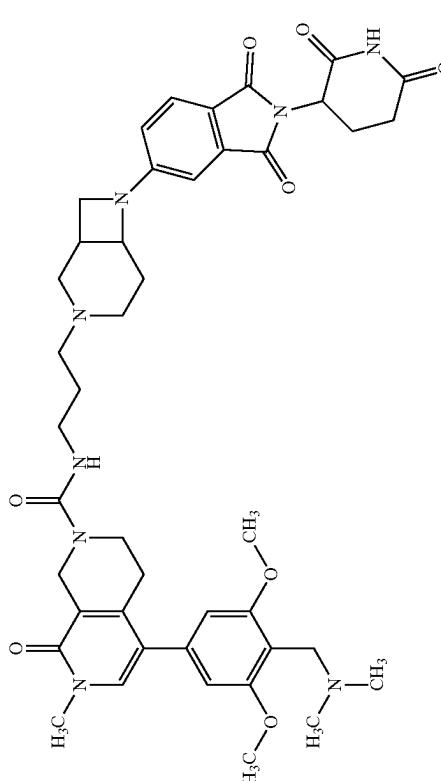
1003**1004**

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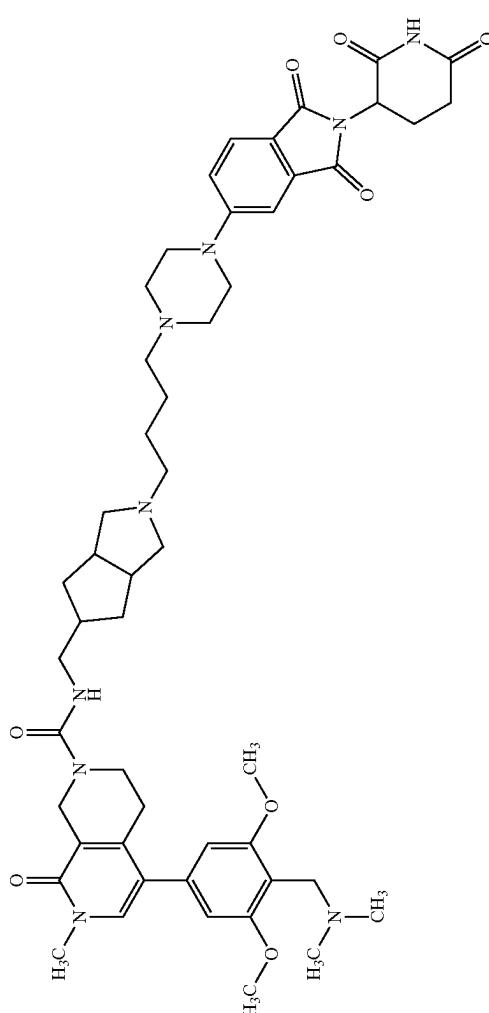
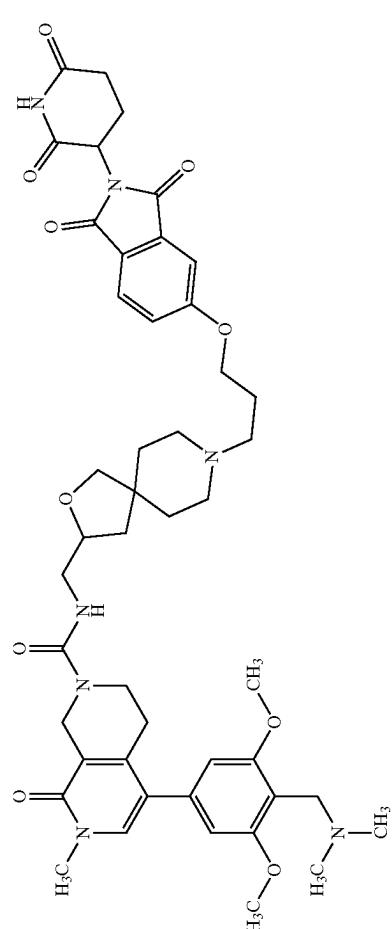
Compound No.	Structure
D228	
D229	

1005**1006**

-continued

Compound No.	Structure
D230	 <p>Chemical structure of compound D230:</p> <p>It features a 4-methyl-2-piperidinone core. This core is fused to a 4-(4-methyl-1-methoxybutyl)-2-methyl-1,3-dihydro-2H-1,4-benzodiazepine-2-one ring system. The benzodiazepine ring has a 4-methyl group and a 2-methyl group at the 2-position. The 4-position of the benzodiazepine ring is substituted with a 4-methyl-1-methoxybutyl group.</p>
D231	 <p>Chemical structure of compound D231:</p> <p>It features a 4-methyl-2-piperidinone core. This core is fused to a 4-(4-methyl-1-methoxybutyl)-2-methyl-1,3-dihydro-2H-1,4-benzodiazepine-2-one ring system. The benzodiazepine ring has a 4-methyl group and a 2-methyl group at the 2-position. The 4-position of the benzodiazepine ring is substituted with a 4-methyl-1-methoxybutyl group.</p>

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Compound No.	Structure
D232	
D233	

1009**1010**

-continued

Compound No.	Structure
D234	
D235	

1011**1012**

-continued

Compound No.	Structure
D236	
D237	

1013**1014**

-continued

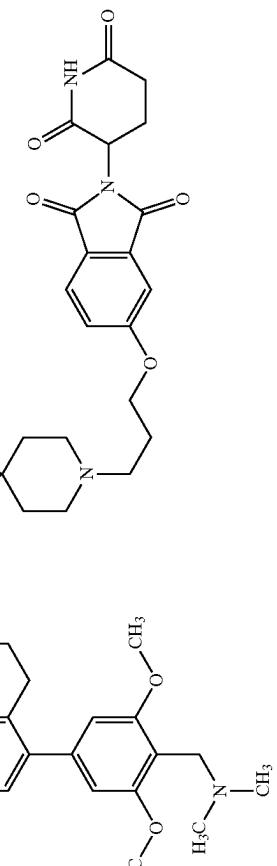
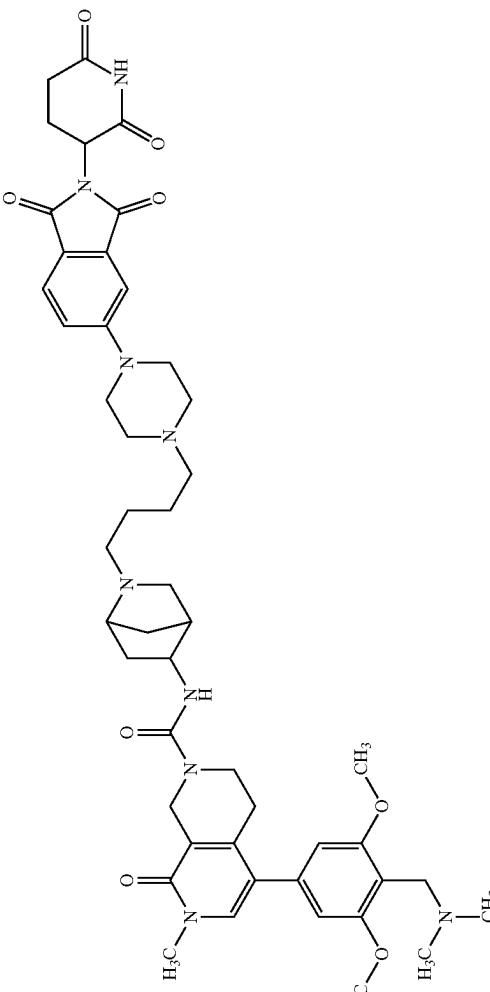
Compound No.	Structure
D238	
D239	

1015**1016**

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Compound No.	Structure
D240	
D241	

-continued

Compound No.	Structure
D242	
D243	

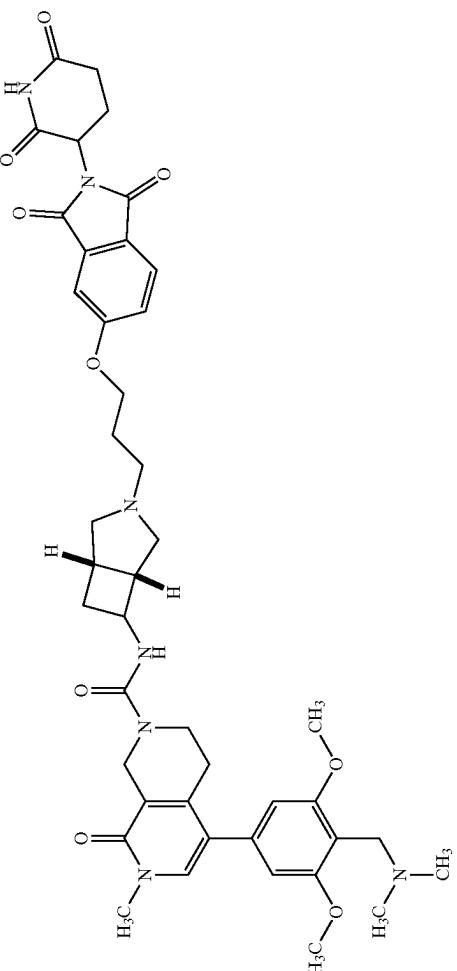
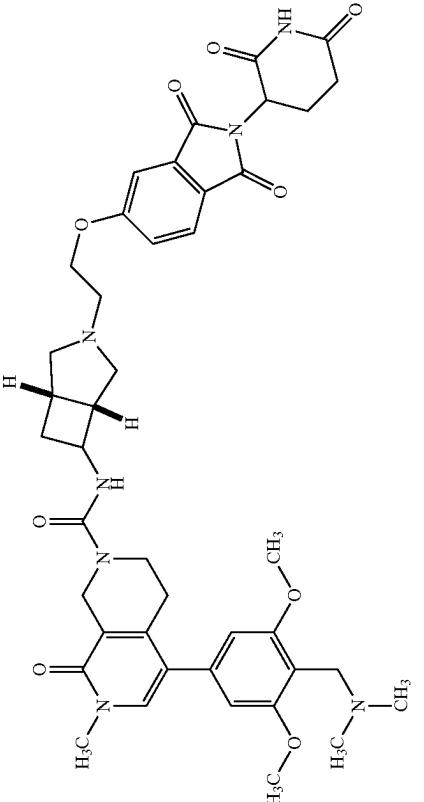
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Compound No.	Structure
D244	
D245	

-continued

Compound No.	Structure
D246	
D247	

-continued

Compound No.	Structure
D248	
D249	

-continued

Compound No.	Structure
D250	
D251	

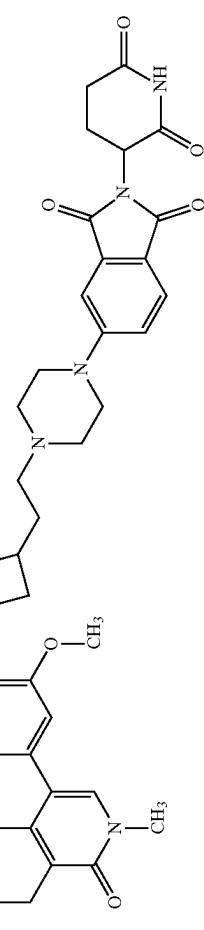
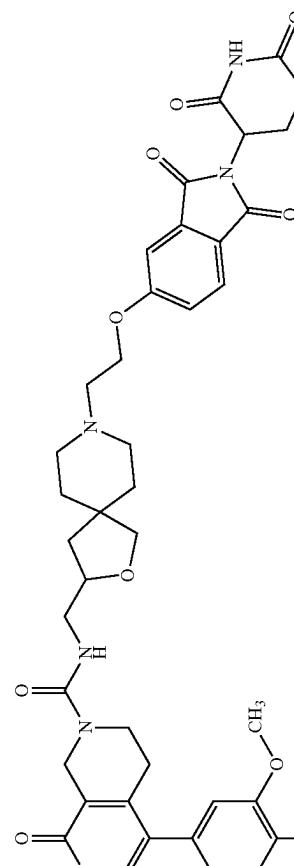
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Compound No.	Structure
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D253	
D254	

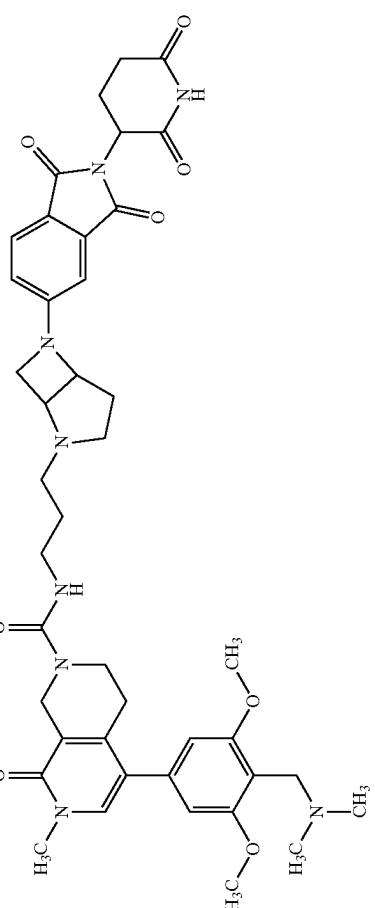
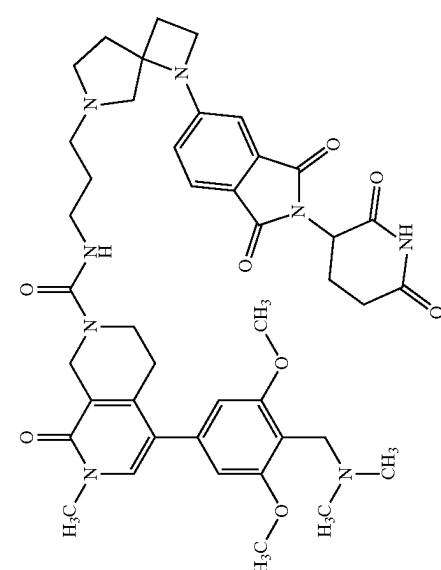
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Compound No.	Structure
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D256	
D257	

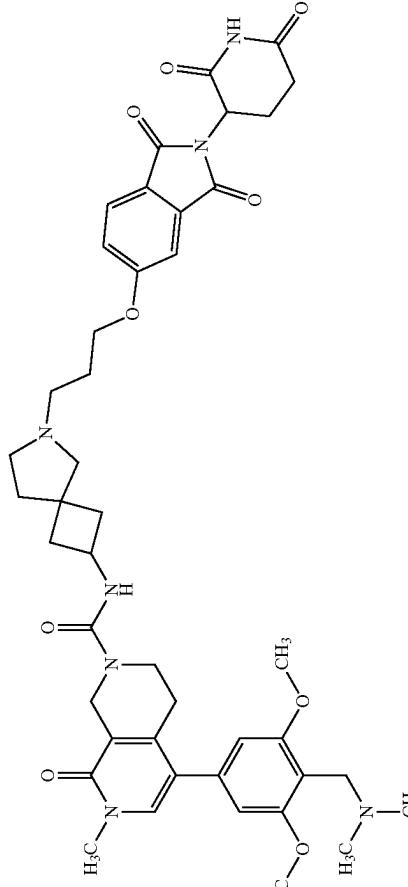
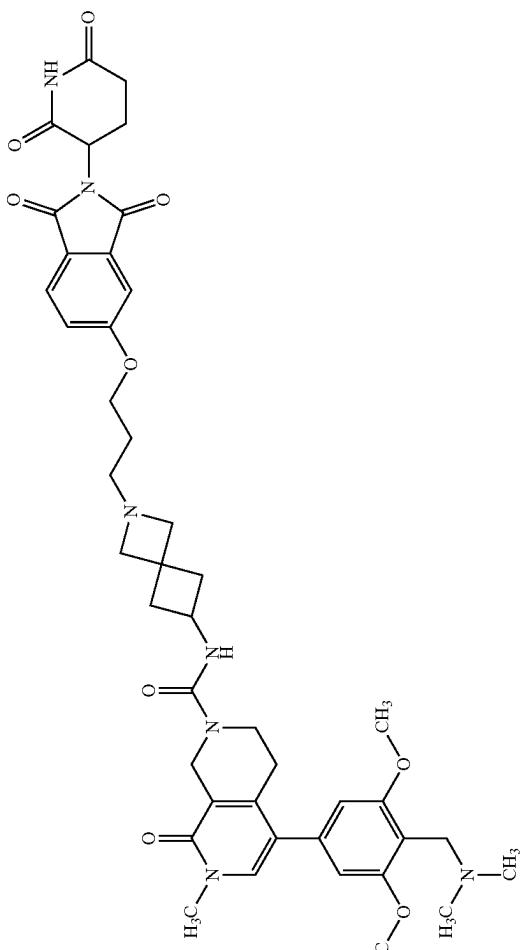
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Compound No.	Structure
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D259	

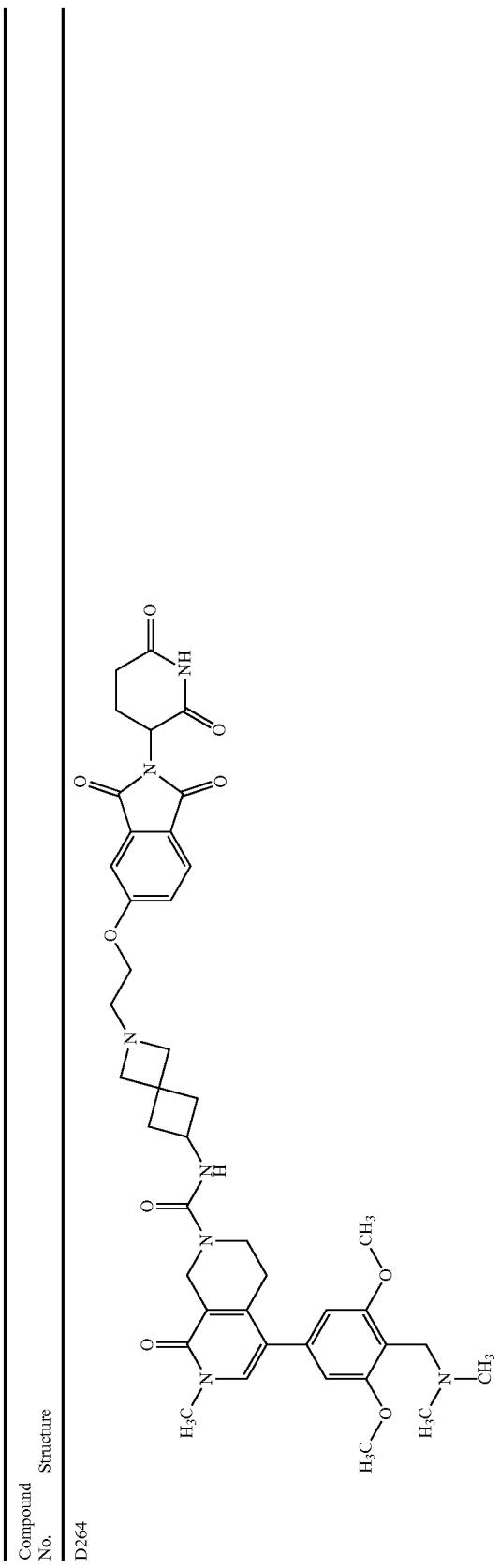
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Compound No.	Structure
D260	
D261	

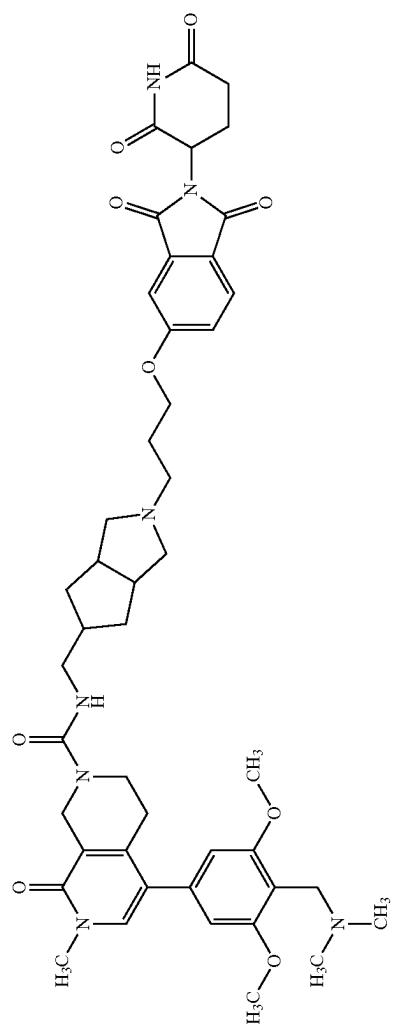
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Compound No.	Structure
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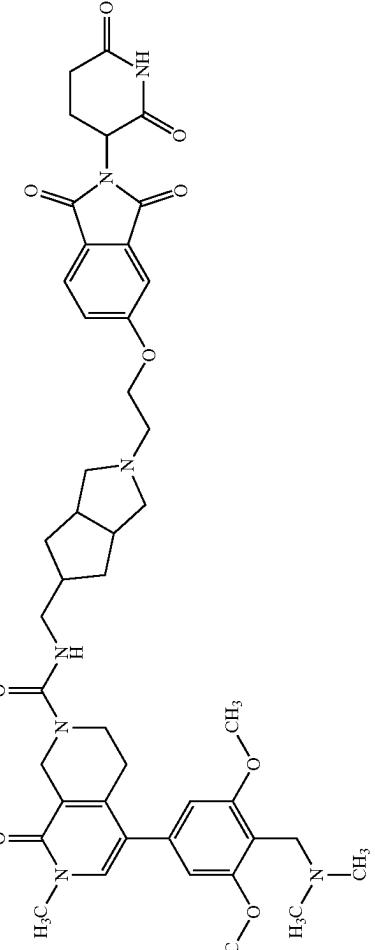
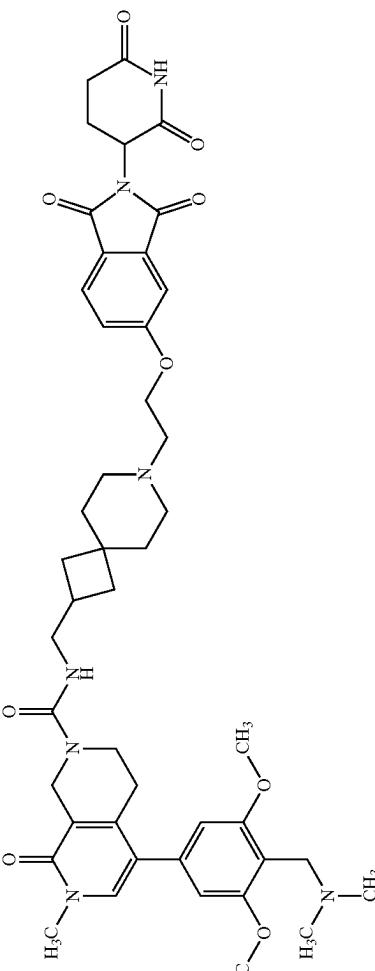
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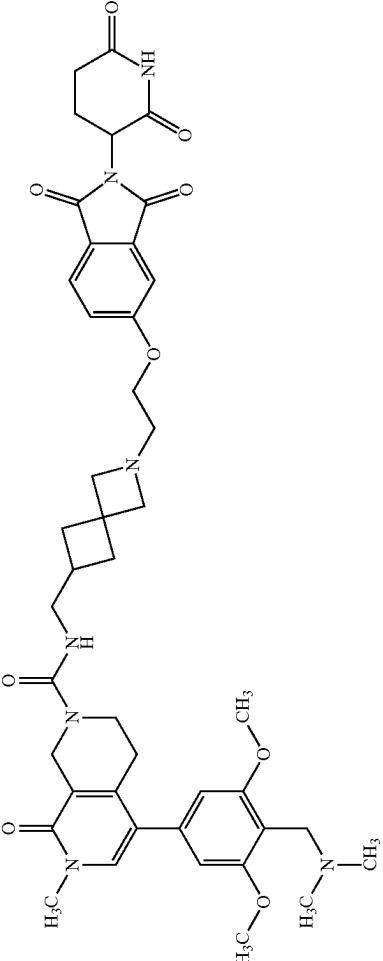
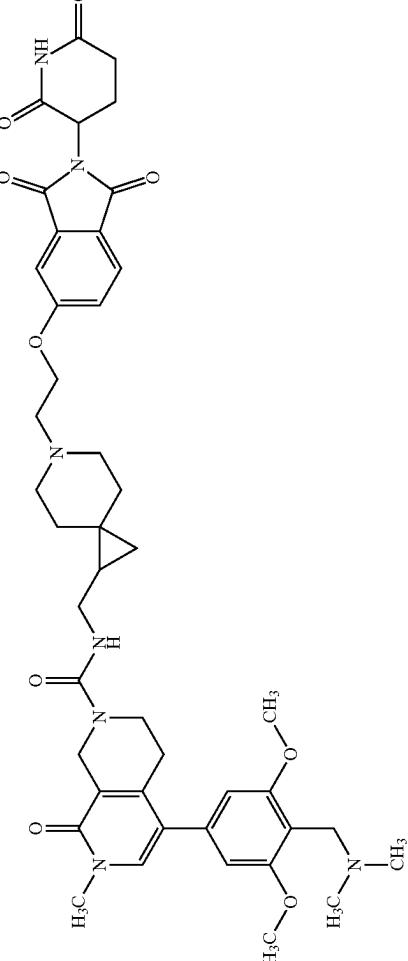
D265



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Compound No.	Structure
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D267	

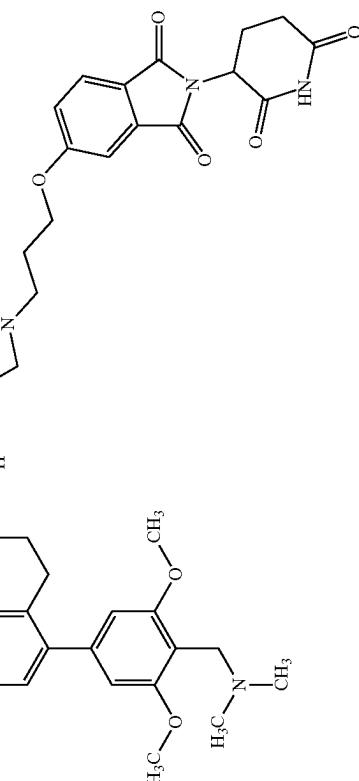
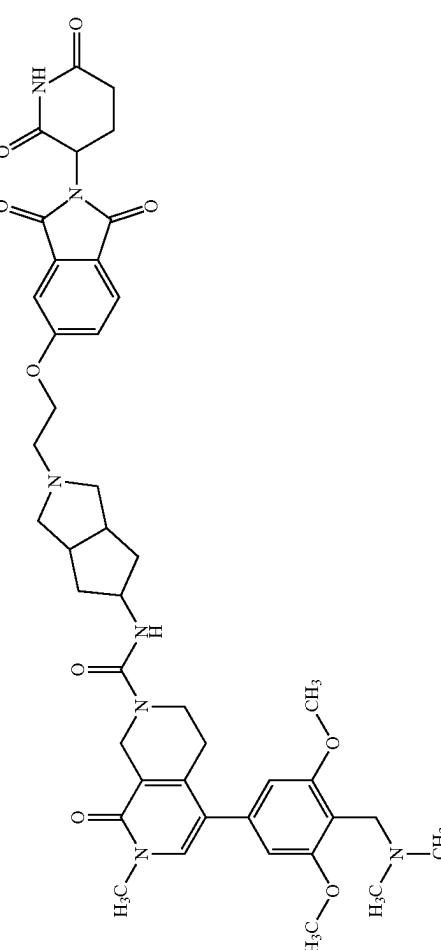
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Compound No.	Structure
D268	
D269	

-continued

Compound No.	Structure
D270	
D271	

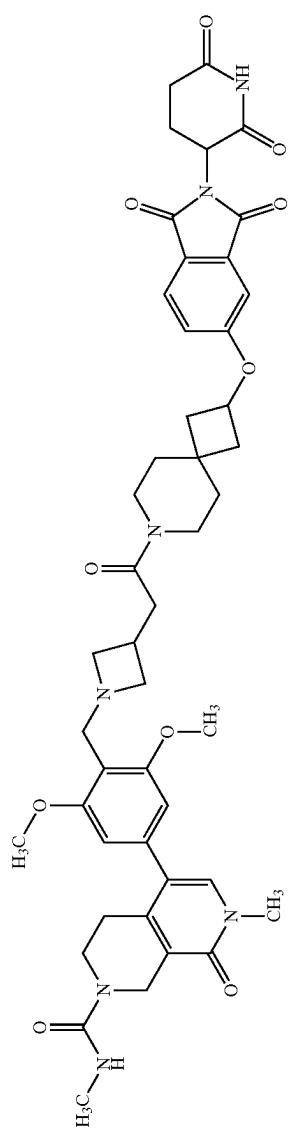
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Compound No.	Structure
D272	
D273	

-continued

Compound No.	Structure
D274	

D275



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Compound No.	Structure
D276	
D277	

-continued

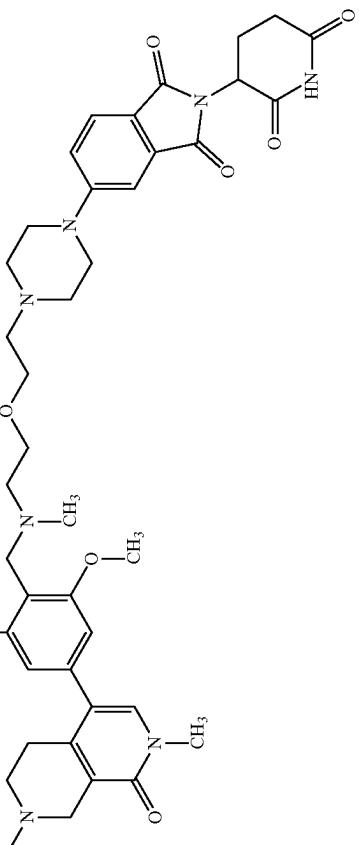
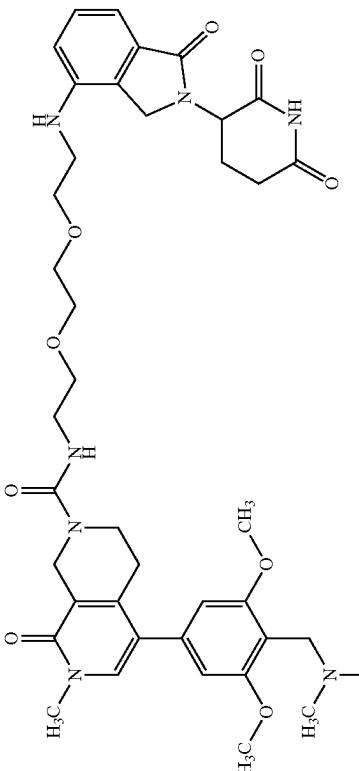
Compound No.	Structure
D278	
D279	
D280	

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Compound No.	Structure
D281	
D282	
D283	

1055**1056**

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Compound No.	Structure
D284	
D285	

D285

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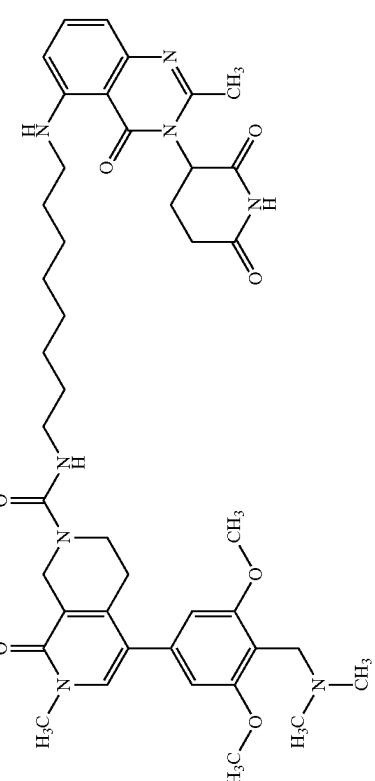
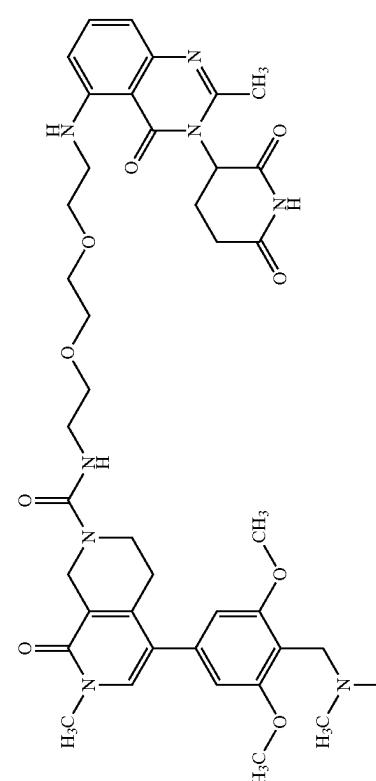
Compound No.	Structure
D286	
D287	
D288	

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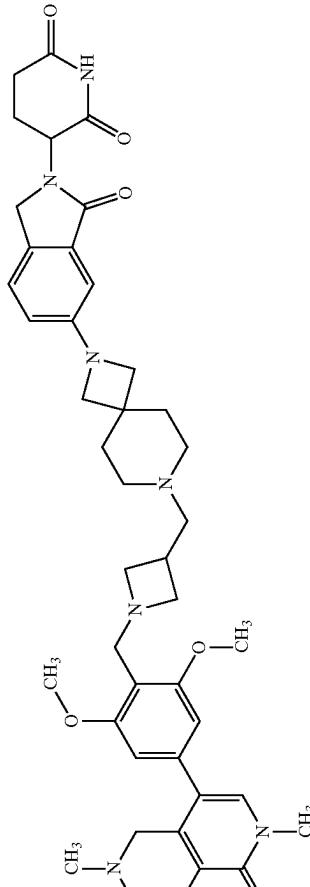
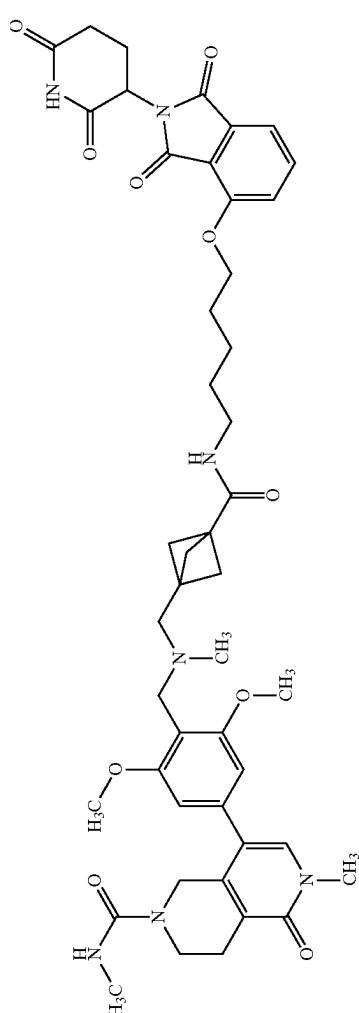
Compound No.	Structure
D289	
D290	

1061**1062**

-continued

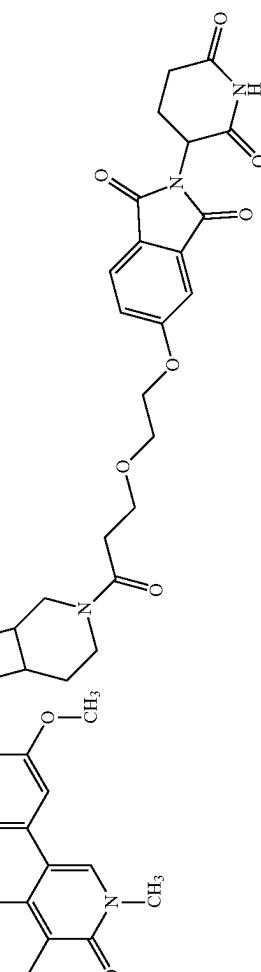
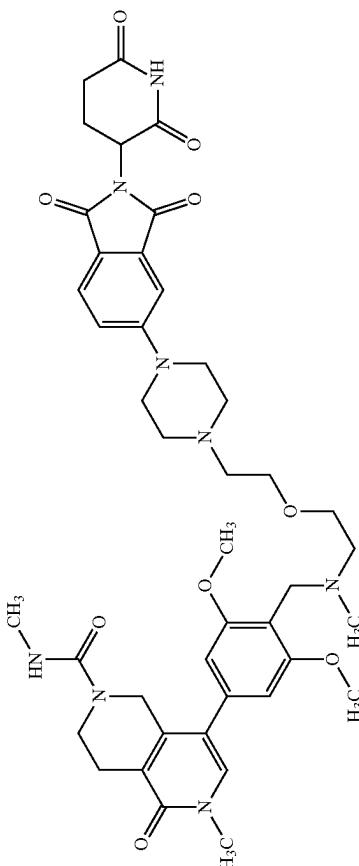
Compound No.	Structure
D291	
D292	

-continued

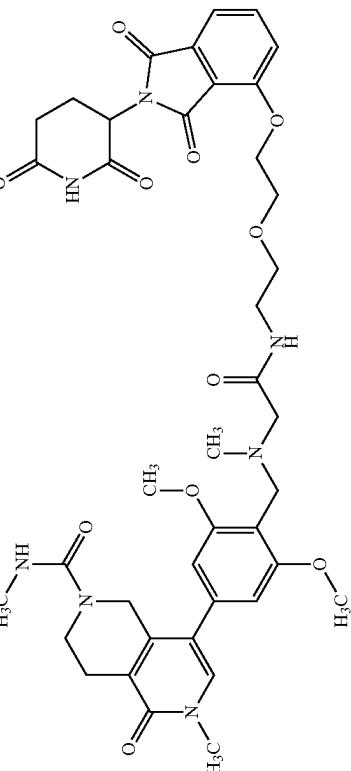
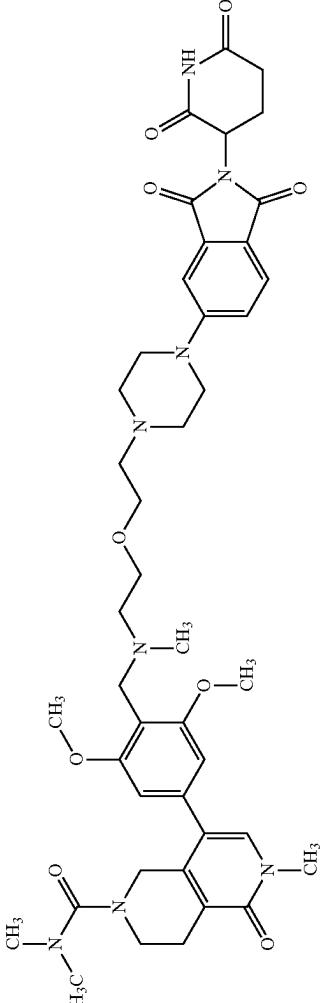
Compound No.	Structure
D293	
D294	

1065**1066**

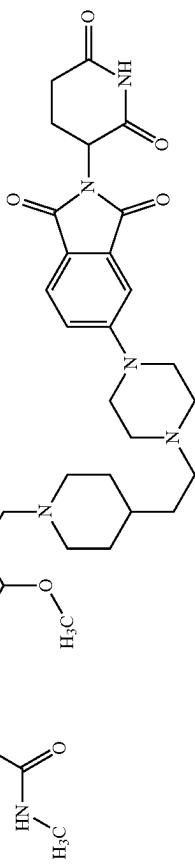
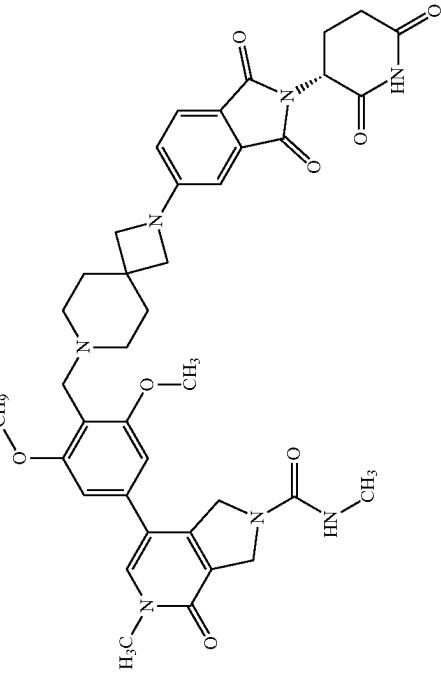
-continued

Compound No.	Structure
D295	
D296	

-continued

Compound No.	Structure
D297	
D298	

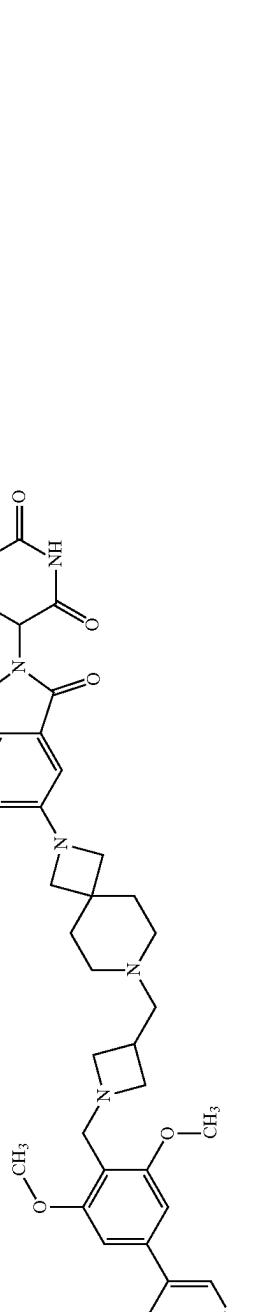
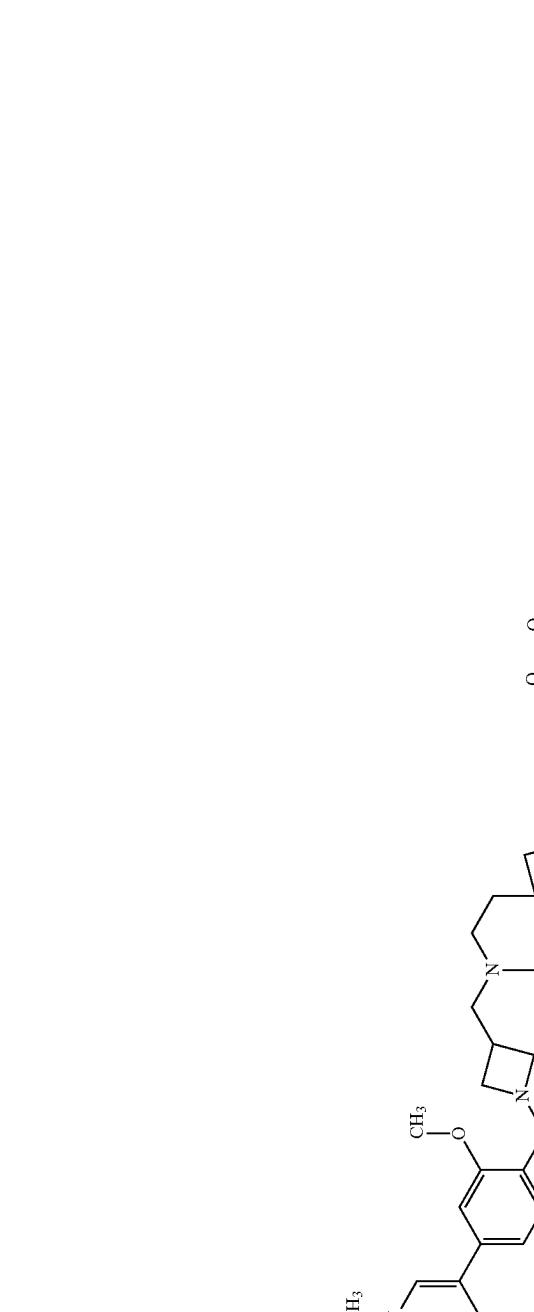
-continued

Compound No.	Structure
D299	
D300	

1071

1072

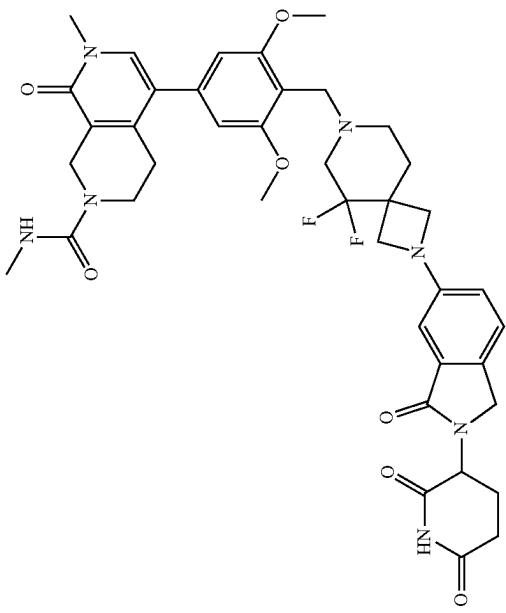
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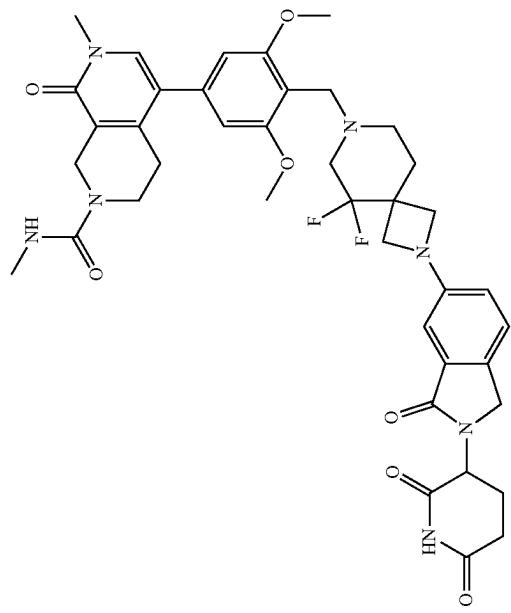
Compound No.	Structure
D301	
D302	

-continued

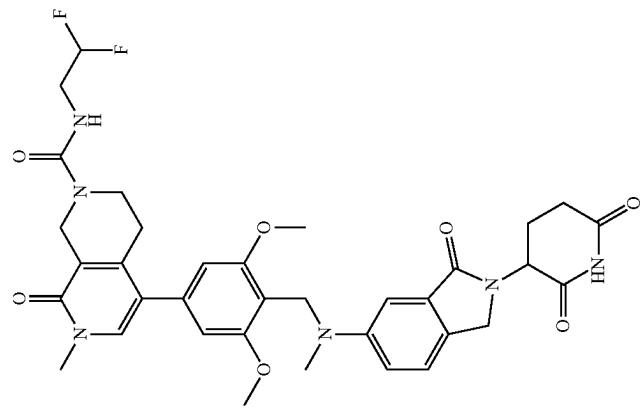
Compound No.	Structure
D304	
D305	

-continued

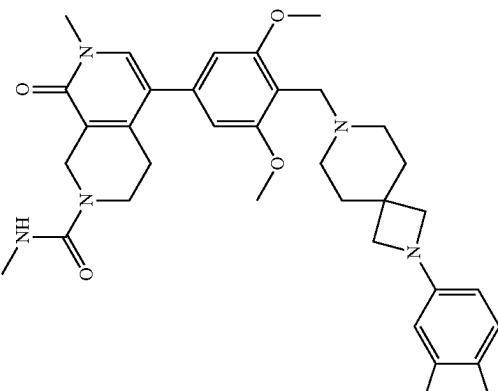
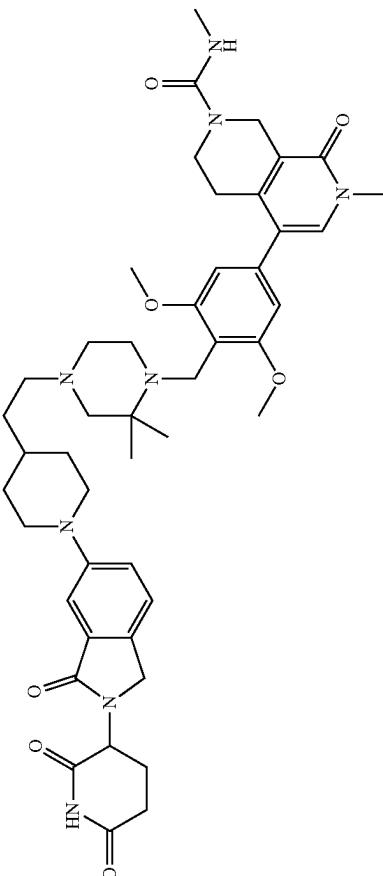
Compound No.	Structure
D306	



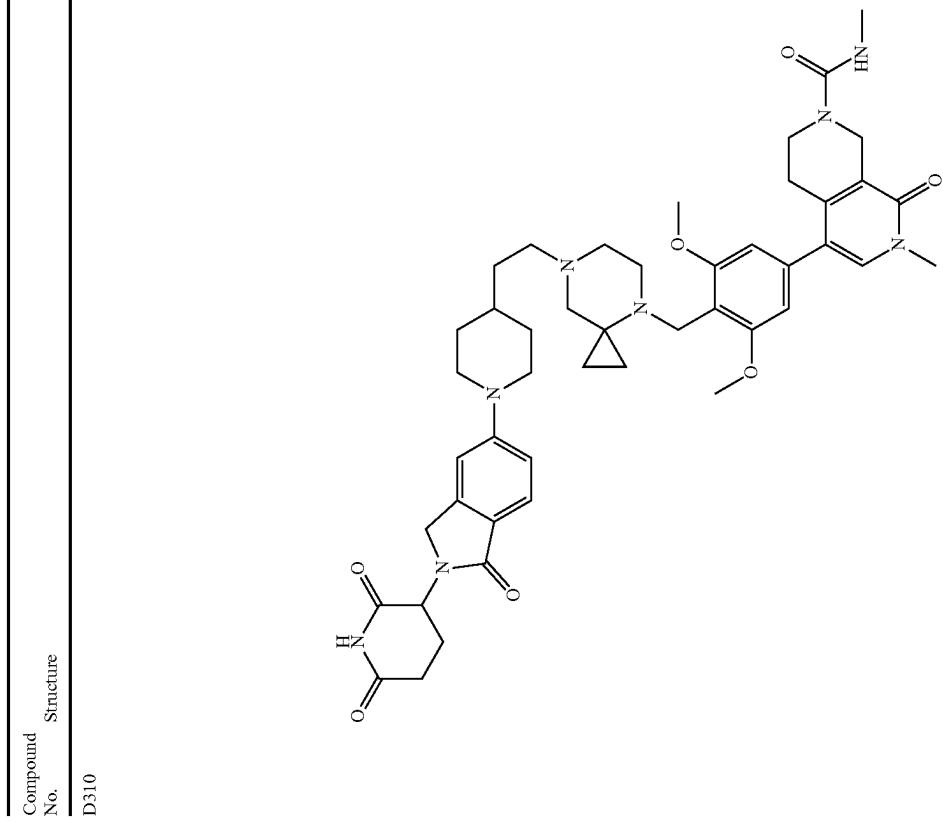
-continued

Compound
No. Structure
D307

-continued

Compound No.	Structure
D308	
D309	

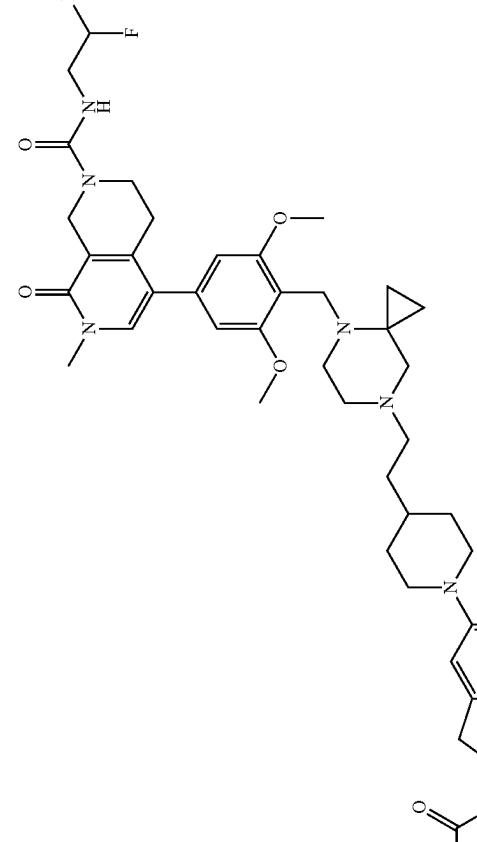
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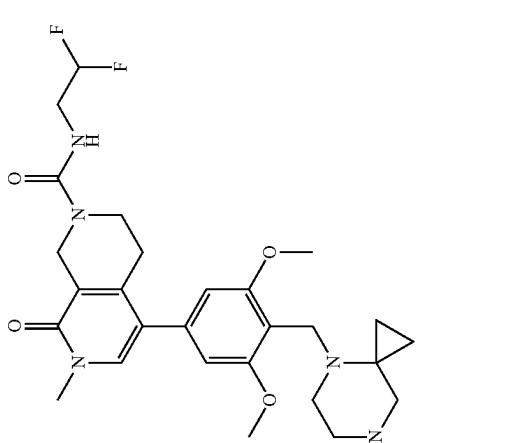
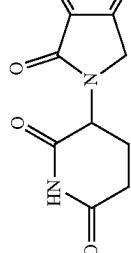
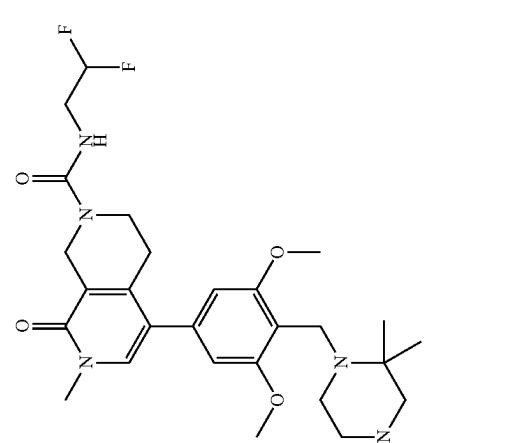
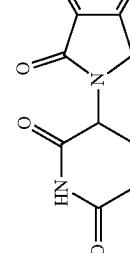
1083

1084

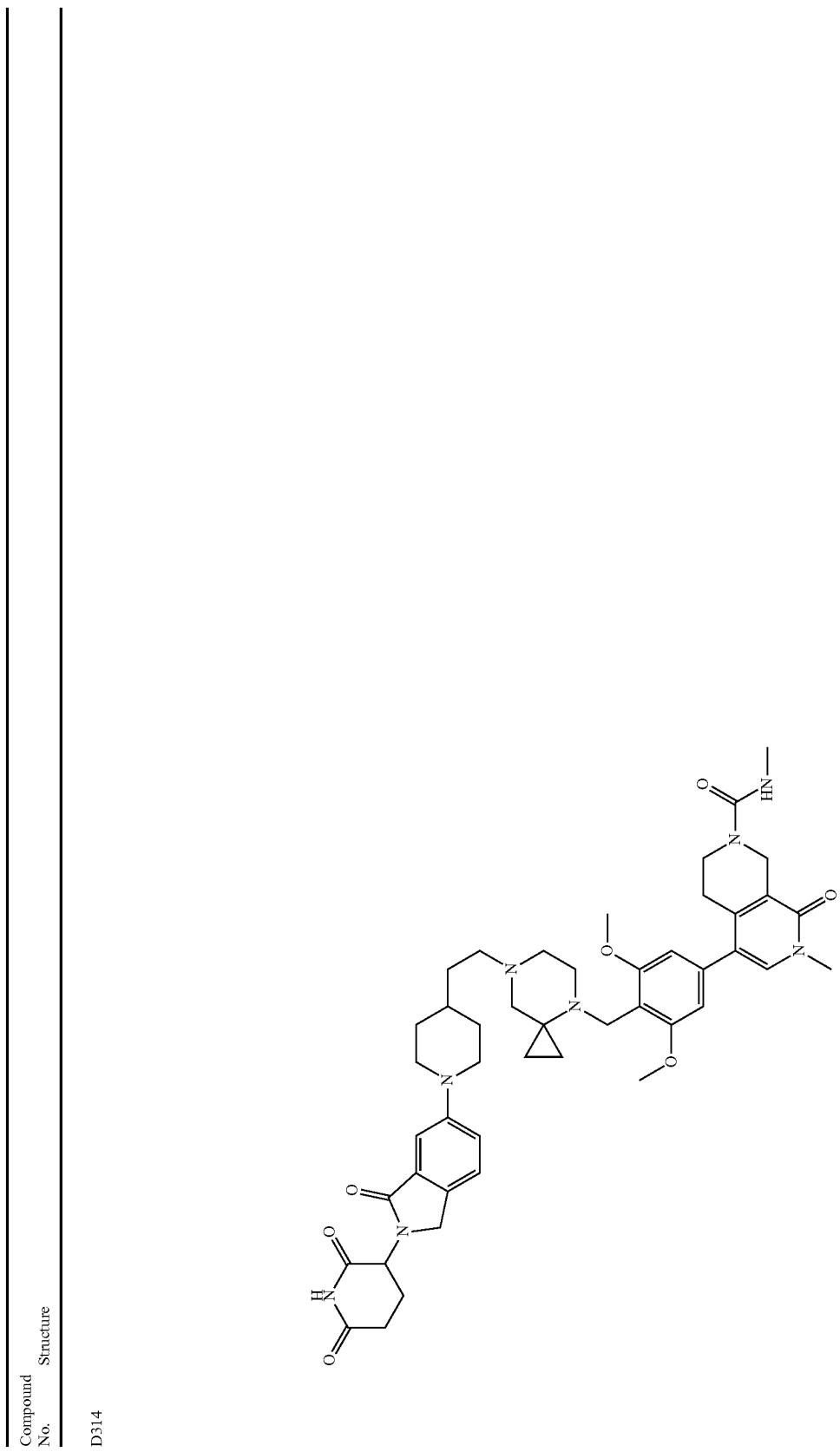
-continued

Compound No.	Structure
D311	

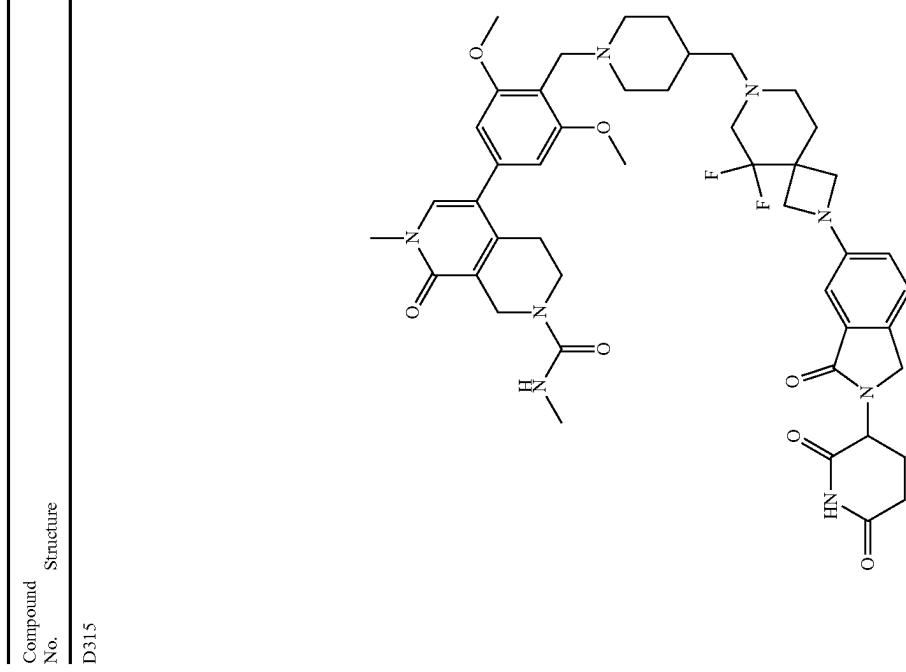
-continued

Compound No.	Structure
D312	 
D313	 

-continued



-continued



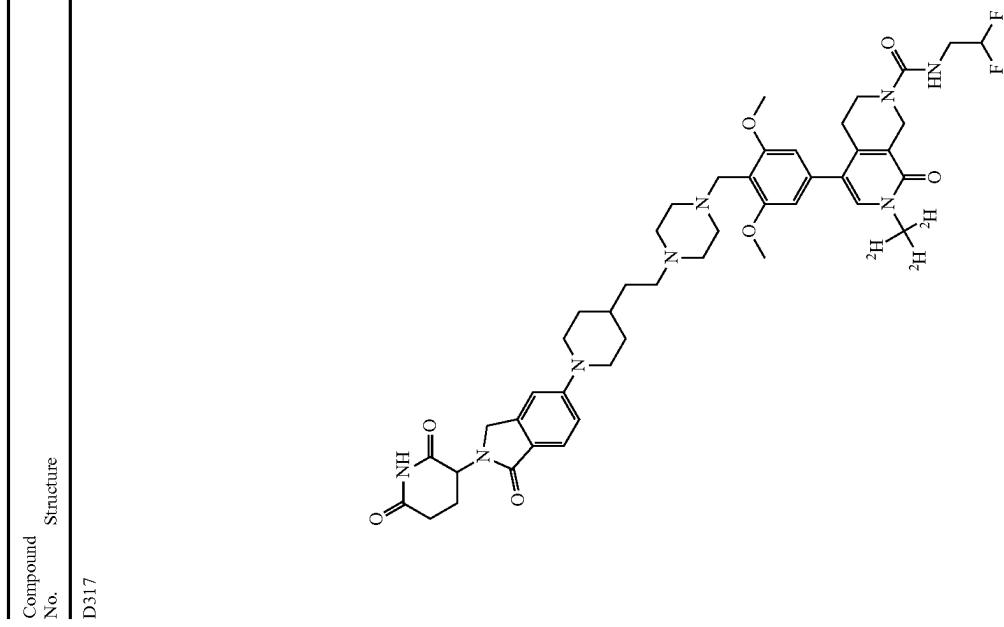
US 12,384,776 B2

1091

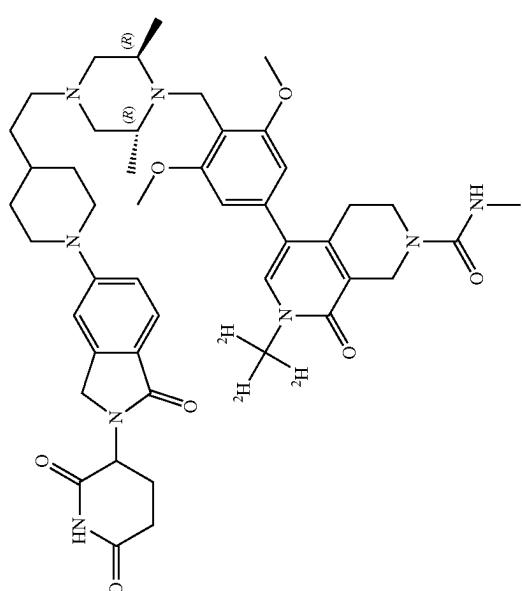
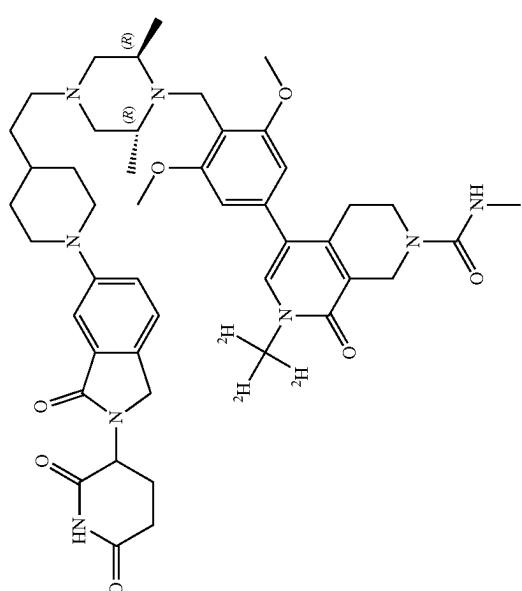
1092

-continued

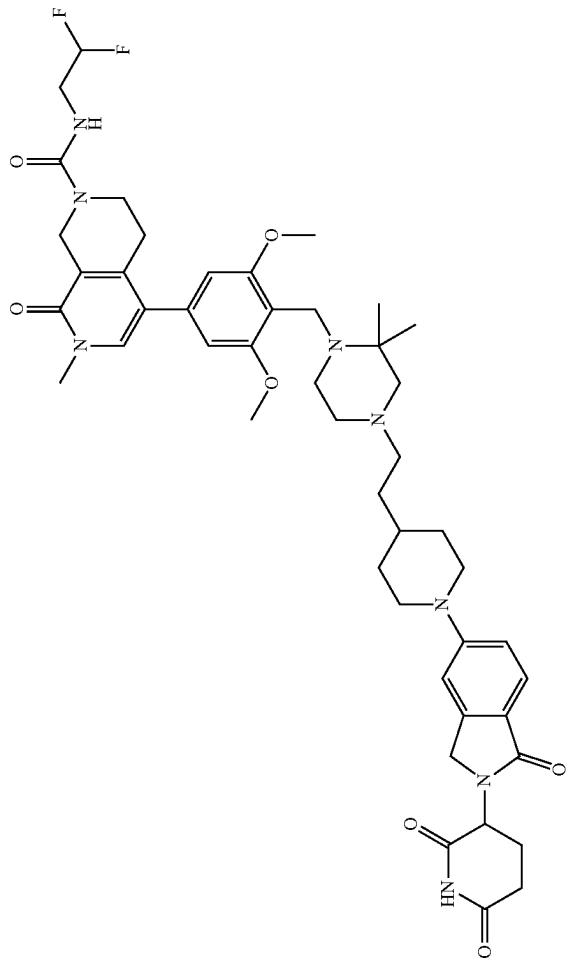
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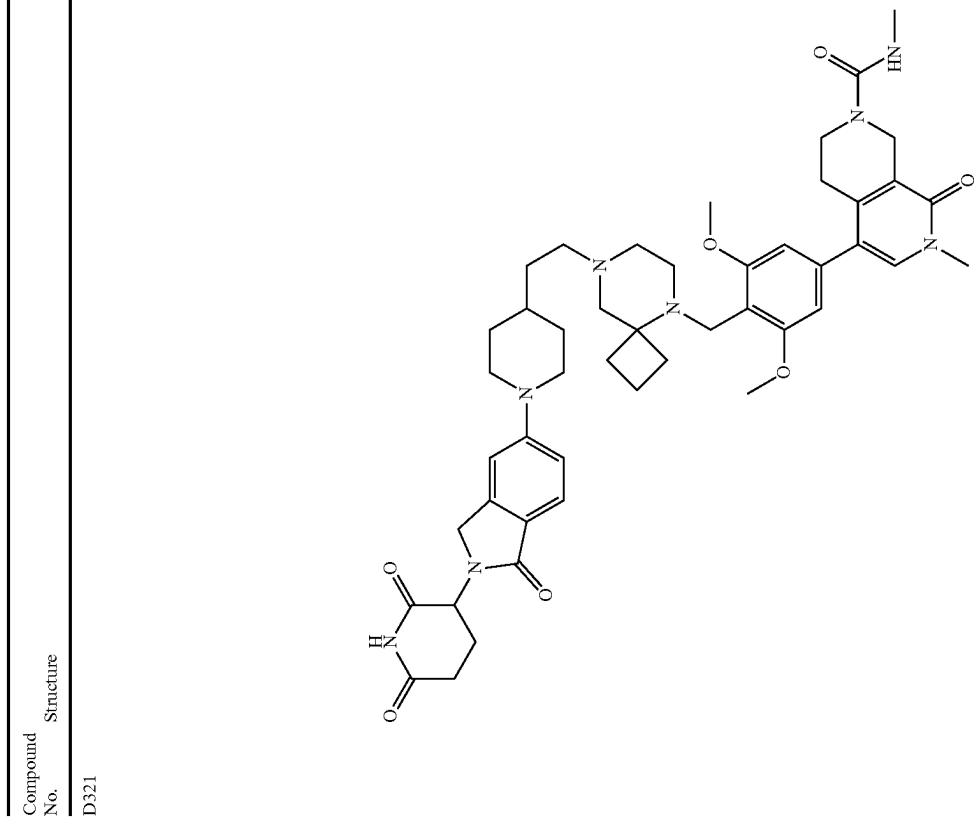
-continued

Compound No.	Structure
D318	
D319	

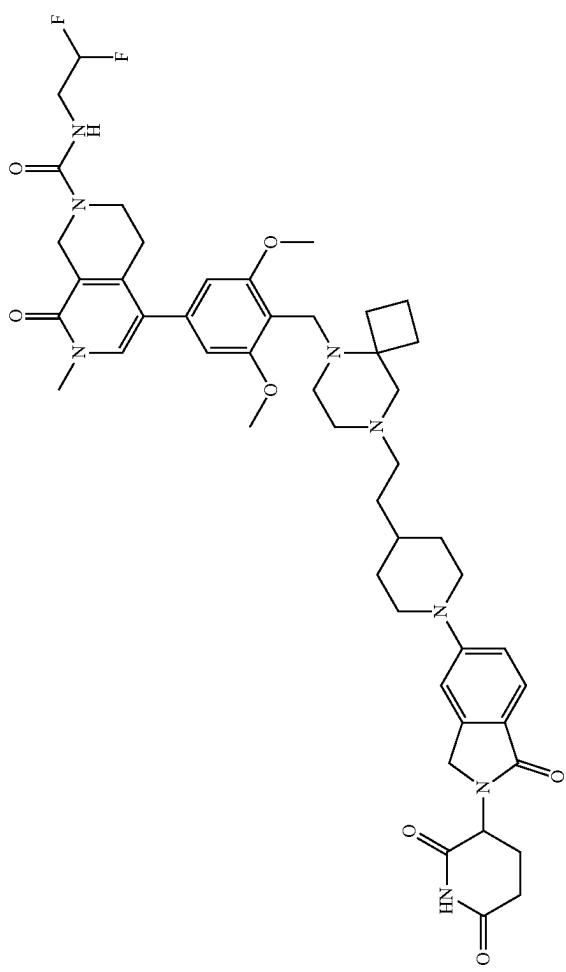
-continued

Compound No.	Structure
D320	

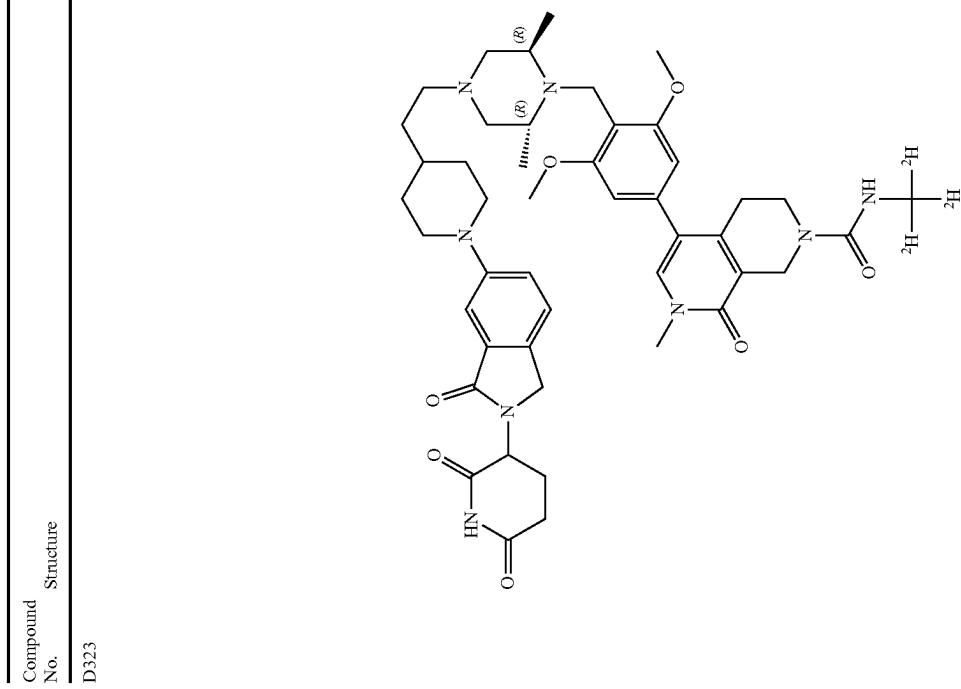
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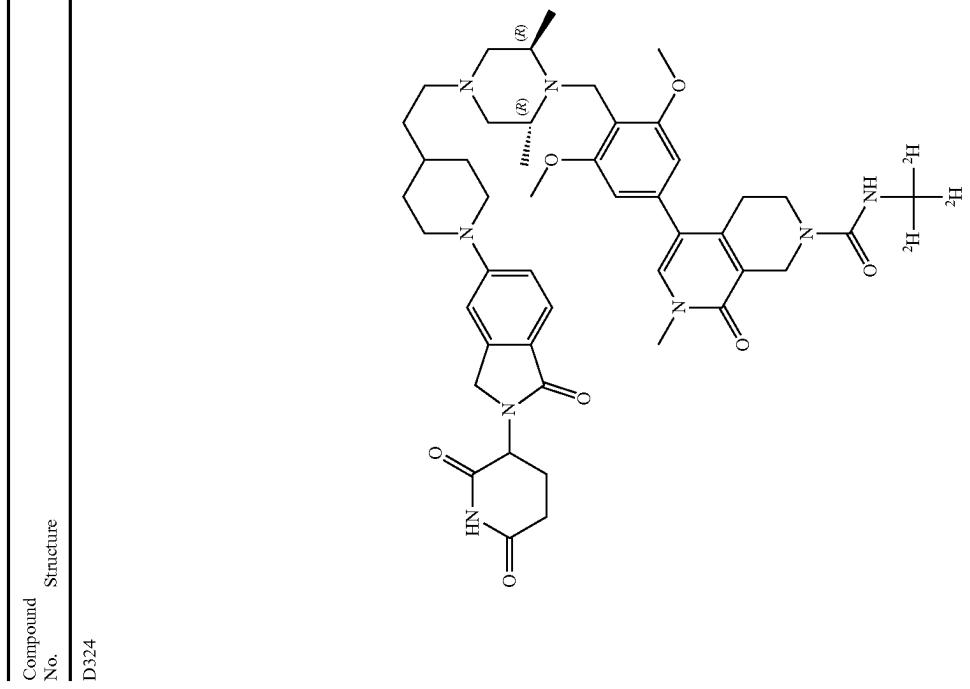
-continued

Compound No.	Structure
D322	 The structure consists of a central benzene ring substituted with a 4-(dimethylaminophenoxy)butyl group. This group is further substituted with a 4-(cyclobutylmethyl)piperazine ring, which is connected via a methylene bridge to a 4-(cyclohexylmethyl)piperazine ring. The latter is also connected via a methylene bridge to a 4-(cyclopentylmethyl)piperazine ring. The final part of the structure is a 4-(2,2-difluoroethylamino)phthalimide moiety.

-continued



-continued



-continued

Compound No.	Structure
D325	

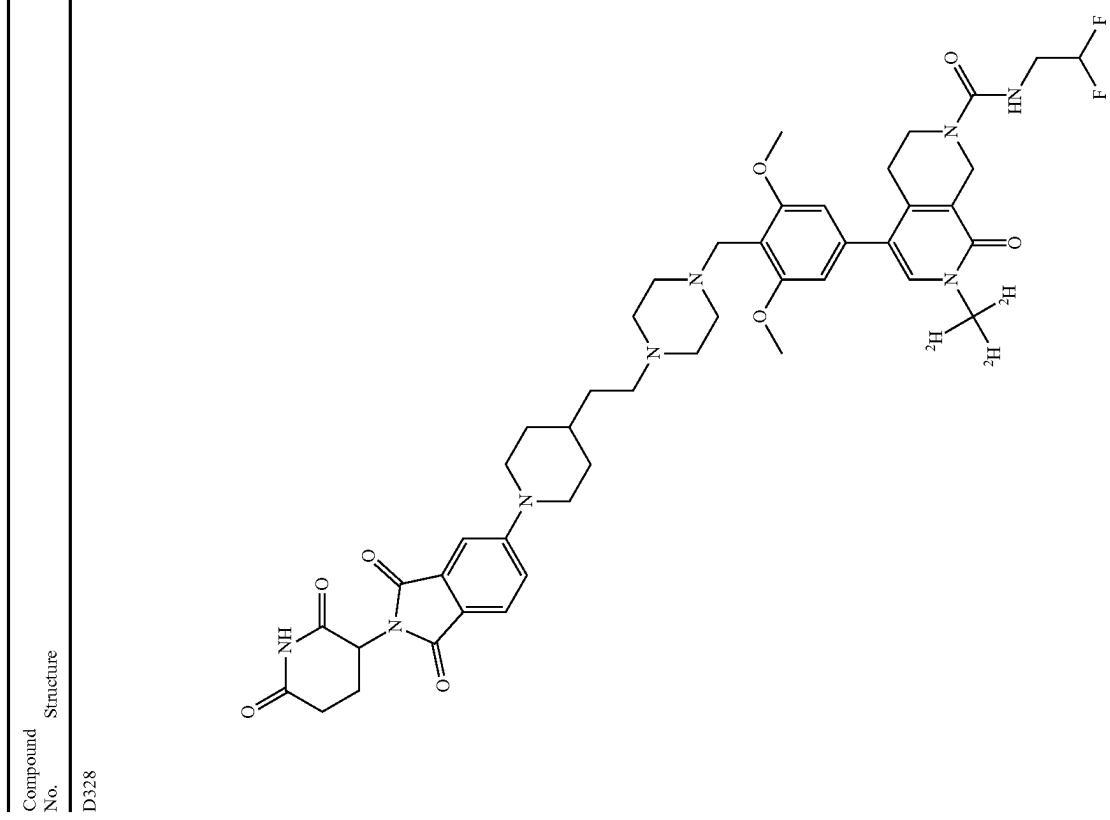
-continued

Compound No.	Structure
D327	

D327

1111**1112**

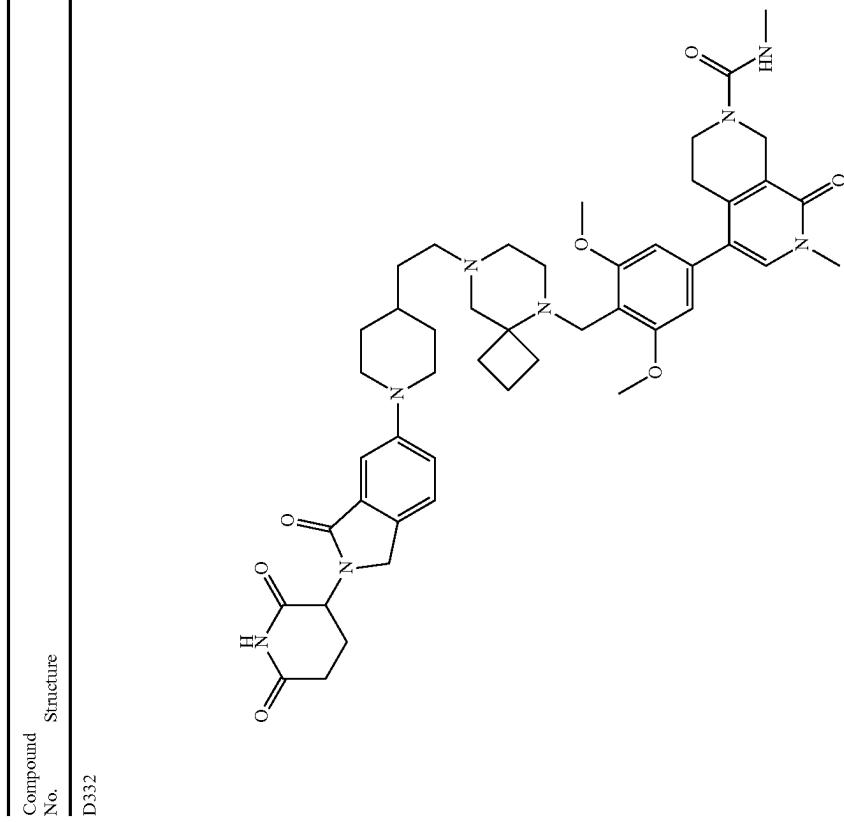
-continued



-continued

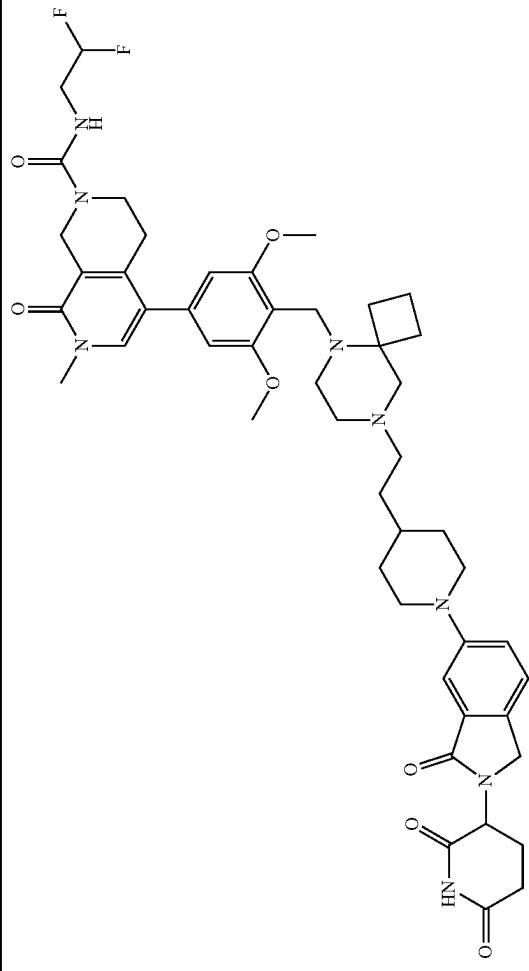
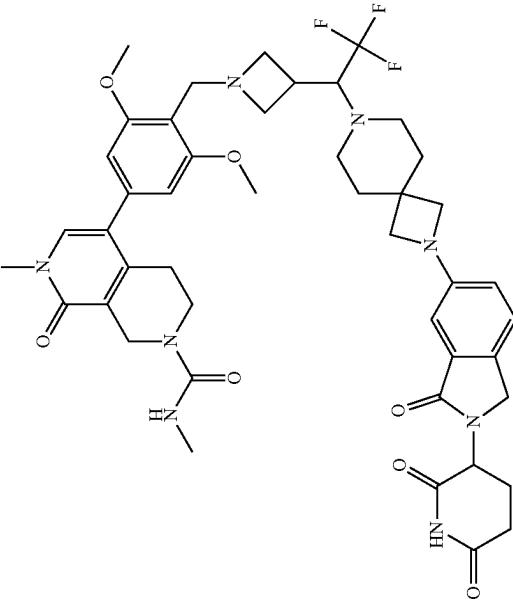
Compound No.	Structure
D329	
D330	

-continued

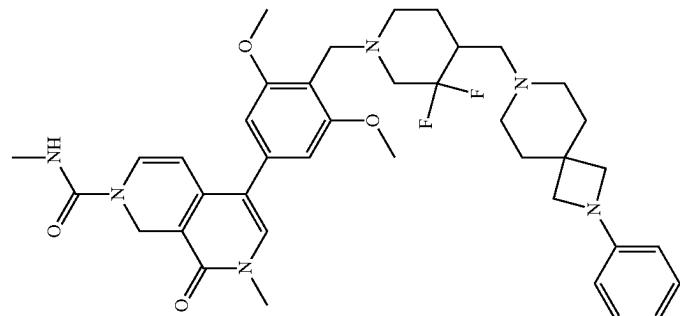


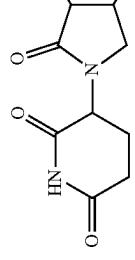
1117**1118**

-continued

Compound No.	Structure
D333	
D334	

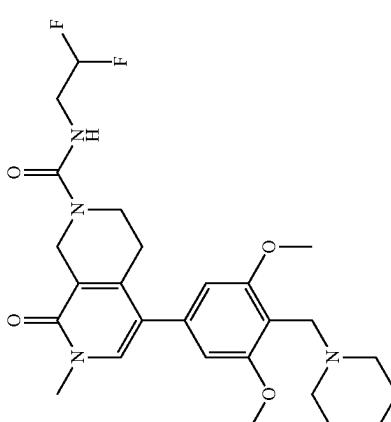
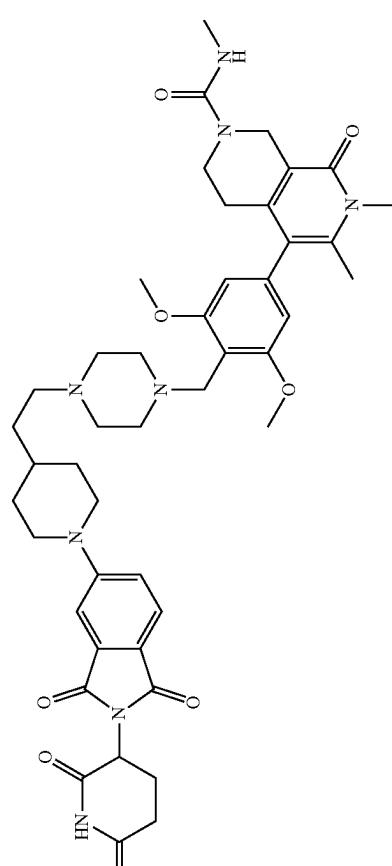
-continued

Compound No.	Structure
D335	

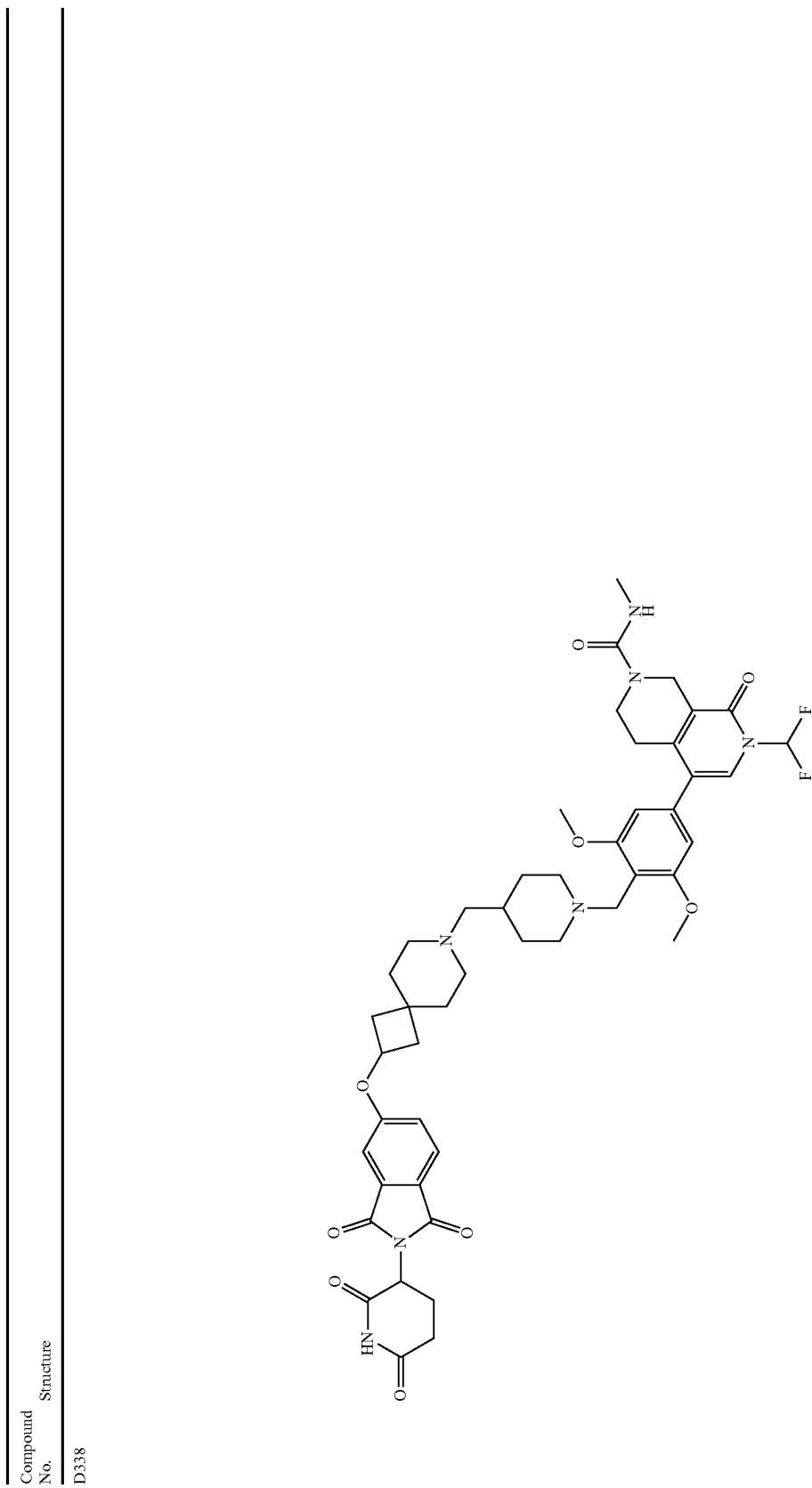


1121**1122**

-continued

Compound No.	Structure
D336	
D337	

-continued



-continued

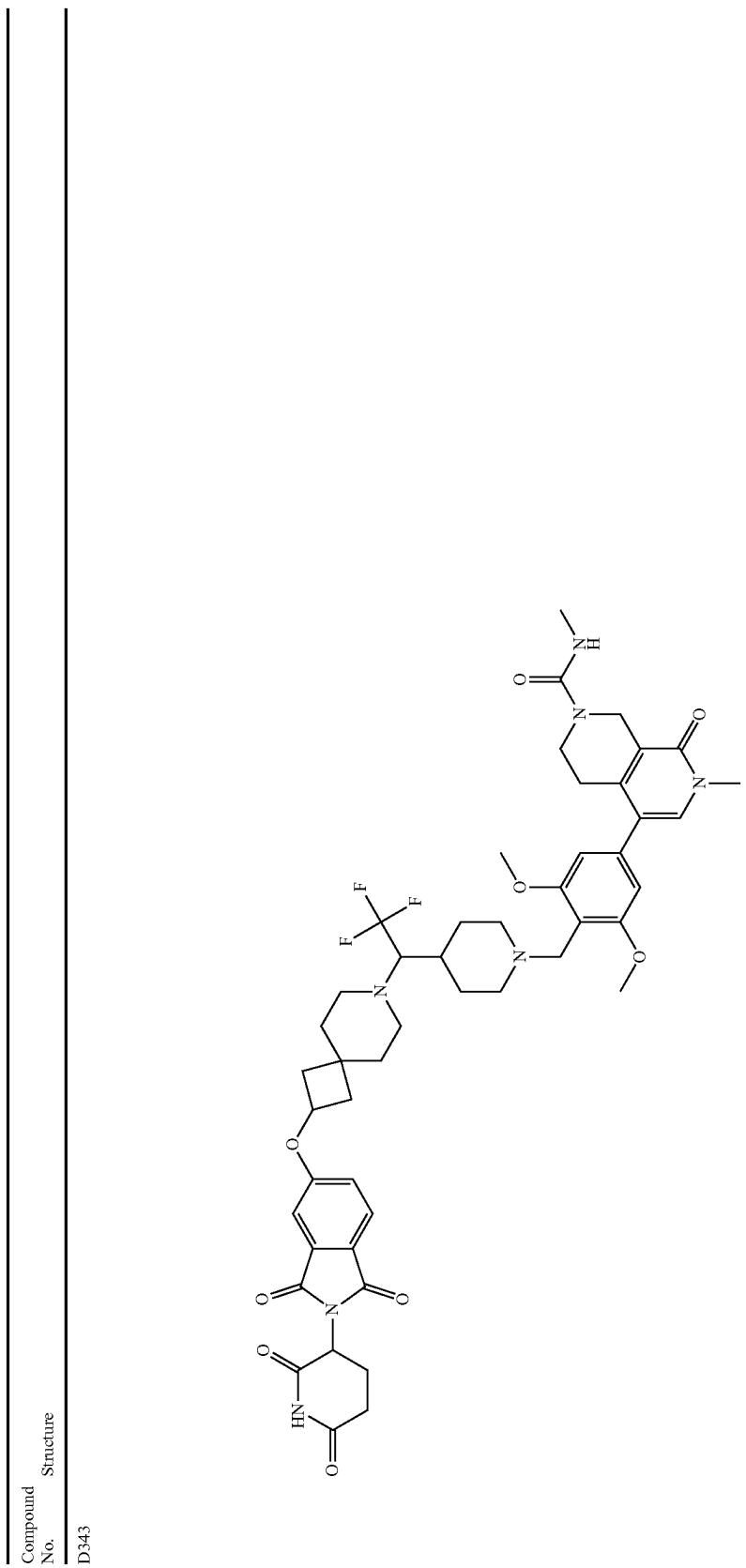
Compound No.	Structure
D339	
D340	

-continued

Compound No.	Structure
D341	
D342	

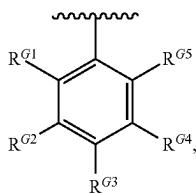
1129**1130**

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1131

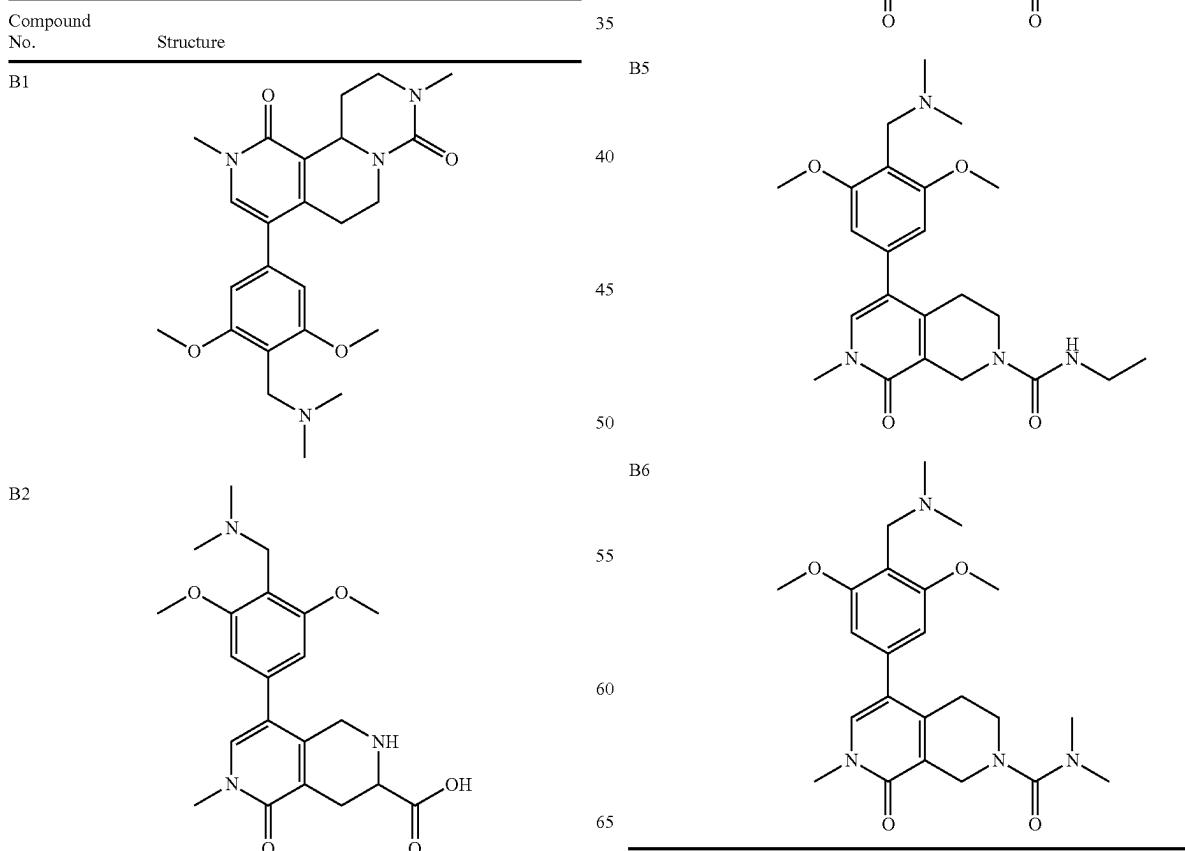
14. The compound of claim 1, wherein Gⁿ is



wherein each of R^{G1}, R^{G2}, R^{G3}, R^{G4}, and R^{G5} is, independently, H, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ heteroalkyl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heterocyclyl, optionally substituted C₆-C₁₀ aryl, optionally substituted C₂-C₉ heteroaryl, optionally substituted C₂-C₆ heteroalkenyl, optionally substituted C₂-C₆ carbocyclyl, optionally substituted C₁-C₃ alkyl-C₃-C₆ carbocyclyl, optionally substituted C₁-C₃ alkyl-C₂-C₅ heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R^{G1} and R^{G2}, R^{G2} and R^{G3}, R^{G3} and R^{G4}, and/or R^{G4} and R^{G5}, together with the carbon atoms to which each is attached, combine to form optionally substituted C₆-C₁₀ aryl, optionally substituted C₃-C₁₀ carbocyclyl, optionally substituted C₂-C₉ heteroaryl, or optionally substituted C₂-C₉ heterocyclyl.

15. The compound of claim 1, wherein the compound has the structure of any one of compounds B1-B6 in the below table, or a pharmaceutically acceptable salt thereof

Compound No.	Structure
5	
10	B3
15	
20	
25	B4
30	
35	B5
40	
45	
50	
55	B6
60	
65	

**1132**

-continued

1133

16. A pharmaceutical composition comprising the compound of claim 2, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

17. A method of treating a synovial cancer in a subject having synovial cancer the method including administering to the subject having synovial cancer an effective amount of a compound of claim 2 or a pharmaceutically acceptable salt thereof. 5

1134

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