

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(10) International Publication Number

WO 2022/086892 A1

(43) International Publication Date
28 April 2022 (28.04.2022)

(51) International Patent Classification:

<i>C07D 239/80</i> (2022.01)	<i>C07D 403/10</i> (2022.01)
<i>A61P 35/00</i> (2022.01)	<i>C07D 403/12</i> (2022.01)
<i>A61K 31/551</i> (2022.01)	<i>C07D 405/10</i> (2022.01)
<i>A61K 31/517</i> (2022.01)	<i>C07D 405/12</i> (2022.01)
<i>A61K 45/06</i> (2022.01)	<i>C07D 413/04</i> (2022.01)
<i>C07D 495/04</i> (2022.01)	<i>C07D 413/10</i> (2022.01)
<i>C07D 401/04</i> (2022.01)	<i>C07D 413/12</i> (2022.01)
<i>C07D 403/04</i> (2022.01)	<i>C07D 243/04</i> (2022.01)

UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

(21) International Application Number:

PCT/US2021/055504

(22) International Filing Date:

19 October 2021 (19.10.2021)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

63/094,617 21 October 2020 (21.10.2020) US



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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ,

(54) Title: INTERLEUKIN 4 (IL4)-INDUCED GENE 1 INHIBITORS AND METHODS OF USE THEREOF

(57) Abstract: The invention relates to novel heterocyclic compounds and pharmaceutical preparations thereof. The invention further relates to methods of treating or preventing cancer using the novel heterocyclic compounds of the invention.

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Interleukin 4 (IL4)-induced gene 1 Inhibitors and Methods of Use Thereof

RELATED APPLICATION

This application claims the benefit of priority to U.S. Provisional Patent Application No. 63/094,617, filed October 21, 2020, which application is hereby incorporated by reference in its entirety.

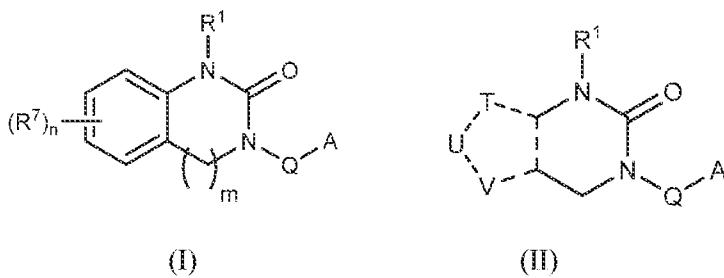
BACKGROUND

Interleukin 4 (IL4)-induced gene 1 (IL4I1) is a flavin adenine dinucleotide (FAD)-dependent amino acid oxidase that metabolizes aromatic amino acids L-phenylalanine, L-tryptophan, and L-tyrosine and produces hydrogen peroxide, ammonia, and the corresponding alpha-ketoacid. In normal human tissues, IL4I1 is expressed and secreted by several specialized cells of the immune system, including antigen presenting cells, macrophages, and B cells. In addition, IL4I1 is highly expressed in the tumors of several types of human cancers, including B-cell lymphoma, melanoma, and ovarian cancer. While the precise role of IL4I1 in human physiology is currently emerging, IL4I1 is believed to regulate several aspects of the human immune system. For example, through its enzymatic activity, IL4I1 inhibits the function of cytotoxic and memory T cells. These observations have led to the hypothesis that in the disease state of cancer, IL4I1 promotes tumor growth by suppressing the anti-tumor immune system of the human host. Consistent with this idea, genetic knockout of IL4I1 slows tumor growth in mouse models of melanoma. IL4I1 has therefore emerged as a potential therapeutic target for the treatment of human cancers. However, to date, there are no inhibitors of IL4I1 enzymatic activity with suitable potency and pharmacological properties to serve as therapies for cancer.

Many of the current cancer treatments agents fail to successfully treat all patients or all symptoms in treated patients, and many of these treatments are associated with undesirable side effects. As certain cancers develop resistance to various chemotherapeutic agents, alternate cancer therapies are needed. Thus, there is a need for additional compounds and methods for treating cancer and other diseases.

SUMMARY

Disclosed herein are compounds of Formula (I) or (II), or a pharmaceutically acceptable salt or prodrug thereof:



wherein

R^1 is selected from H, unsubstituted alkyl, hydroxyalkyl, cycloalkyl, and cycloalkylalkyl;

R^7 is selected from halo, CN, nitro, hydroxy, alkyl, alkenyl, alkoxy, amino, amido, carboxy, and acyloxy;

m is 1 or 2;

n is 0, 1, or 2;

T is S or CR⁸;

U is S or CR^9 ,

V is S or CR^{10} ,

wherein one and only one of T, U and V is S;

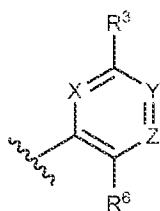
---- bond indicates a single or double bond as valency permits where up to two non-consecutive ---- bonds are double bonds;

Q is a bond, CH_2 , $\text{CH}(\text{CH}_3)$, CH_2CH_2 , - $\text{C}_2(\text{alkyl})\text{NR}^{11}$ - or - $\text{C}_2(\text{alkyl})\text{O}-$;

wherein C₂(alkyl) is optionally substituted with one or more alkyl groups;

A is selected from aryl, heteroaryl, cycloalkyl or heterocyclyl;

provided that if the compound is of Formula (I), and Q is a bond and m = 1, then A is:



wherein

X is N or CR^2 ,

Y is N or CR^4 .

Z is N or CR^5 .

R^2 , R^3 , R^4 and R^5 are each independently selected from H, halo, CN, nitro, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, acyloxy, azido, carboxy, amino, amido, sulfone, $-SO_2NR^aR^b$, heteroaralkyl, aralkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl;

R^6 is selected from H, halo, CN, alkyl, hydroxy, alkoxy, sulfone, cycloalkyl, heterocyclyl, aryl, and heteroaryl; or

R^5 and R^6 , taken together with the atoms to which they are attached, may form a 5- or 6-membered aryl, cycloalkyl, heterocyclyl or heteroaryl;

R^8 , R^9 and R^{10} are each independently selected from H, halo and unsubstituted alkyl;

R^{11} is H or alkyl;

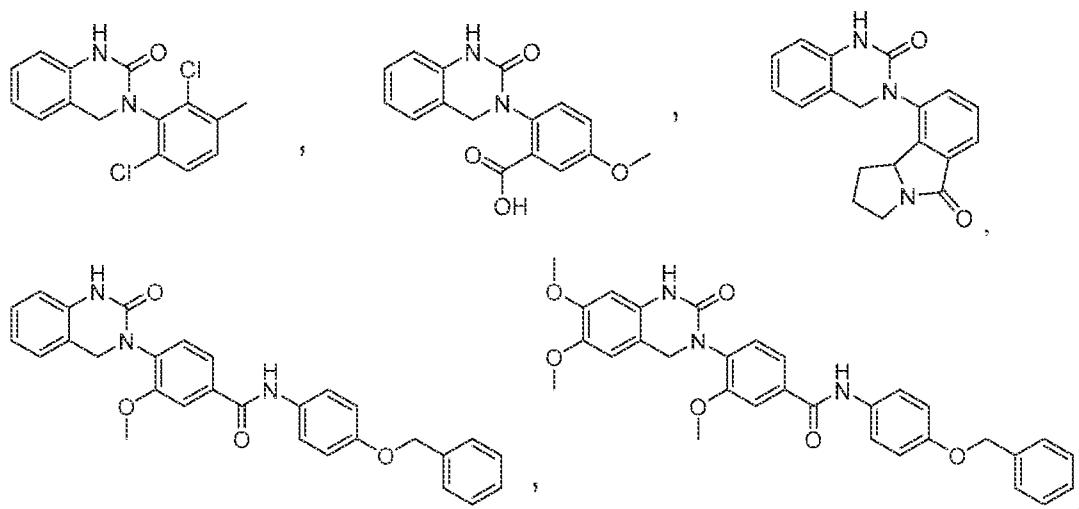
R^a and R^b are each H or alkyl;

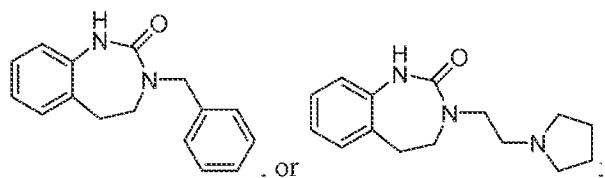
provided that:

if Q is a bond and m is 1, then:

- if R^6 is Cl or methyl, then at least one of R^2 , R^3 , R^4 and R^5 is not H;
- R^3 or R^5 is not aralkoxy or heteroaralkoxy;
- R^4 and R^6 are not both methyl or methoxy;
- R^2 and R^6 are not both ethyl;
- R^2 , R^3 , R^4 , R^5 , and R^6 are not each H;
- if R^2 and R^6 are each H, then Y is CR^4 and R^4 is H;
- if R^2 and R^6 are each H, then R^3 is not methyl, trifluoromethyl, pyridinyl, or methoxy;

the compound of Formula (I) is not





if Q is CH_2 or CH_2CH_2 and m=1, then R^7 is 6-fluoro;

if Q is CH_2 and m=2, then A is not cycloalkyl;

if Q is $\text{CH}(\text{CH}_3)$ and m = 1, then R^7 is not amido;

if the compound is of Formula (II), and Q is a bond, then A is not heterocyclyl; and

if Q is a bond and m is 2, then A is aryl or heteroaryl, and A is not substituted with sulfone, alkylthio, difluoromethoxy, or 1,1-difluoroethyl.

In certain embodiments, the present invention provides a pharmaceutical composition suitable for use in a subject in the treatment or prevention of cancer comprising an effective amount of any of the compounds described herein (e.g., a compound of the invention, such as a compound of Formula (I) or (II)), or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients. In certain embodiments, the pharmaceutical preparations may be for use in treating or preventing a condition or disease as described herein.

Disclosed herein are methods of treating diseases and conditions that benefit from the inhibition of IL4II, comprising administering to a subject in need thereof an effective amount of a compound as disclosed herein (e.g., a compound of Formula (I) or (II) or any of the embodiments thereof disclosed herein). In certain embodiments, the human subject is in need of such treatment. These diseases include, but are not limited to cancers.

Provided herein are combination therapies of compounds of Formula (I) or (II) with monoclonal antibodies and other chemotherapeutic agents that can enhance the therapeutic benefit beyond the ability of the adjuvant therapy alone.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 is a graph showing tumor volume development over time in a mouse B-cell lymphoma xenograft model dosed orally with a compound of the invention.

FIG. 2 is a graph showing tumor volume development over time in a mouse melanoma xenograft model dosed orally with a compound of the invention.

FIG. 3 is a graph showing tumor volume development over time in a mouse melanoma xenograft model dosed orally with a compound of the invention.

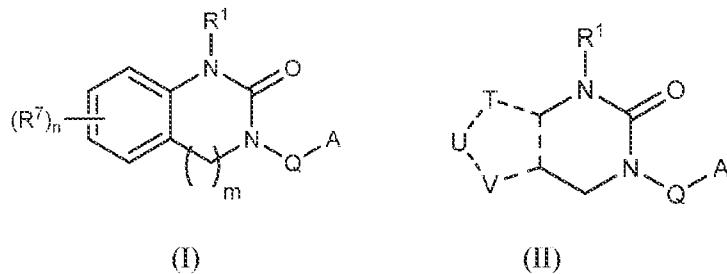
FIG. 4 is a graph showing tumor volume development over time in a mouse T-cell lymphoma xenograft model dosed orally with a compound of the invention.

FIG. 5 is a graph showing tumor volume development over time in a mouse B-cell lymphoma xenograft model with established tumors dosed orally with a compound of the invention.

FIG. 6 is a graph showing tumor volume development over time in a mouse melanoma xenograft model dosed orally with a compound of the invention, dosed with an anti-PD-L1 antibody, and dosed with a combination of a compound of the invention and an anti-PD-L1 antibody.

DETAILED DESCRIPTION

In some embodiments, the invention provides a compound of Formula (I) or (II) or a pharmaceutically acceptable salt or prodrug thereof:



wherein

R¹ is selected from H, unsubstituted alkyl, hydroxyalkyl, cycloalkyl, and cycloalkylalkyl;

R⁷ is selected from halo, CN, nitro, hydroxy, alkyl, alkenyl, alkoxy, amino, amido, carboxy, and acyloxy;

m is 1 or 2;

n is 0, 1, or 2;

T is S or CR⁸;

U is S or CR⁹;

V is S or CR¹⁰;

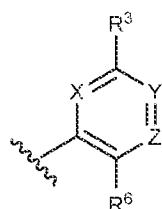
wherein one and only one of T, U and V is S;

---- bond indicates a single or double bond as valency permits where up to two non-consecutive ---- bonds are double bonds;

Q is a bond, CH₂, CH(CH₃), CH₂CH₂, -C₂(alkyl)NR¹¹- or -C₂(alkyl)O-; wherein C₂(alkyl) is optionally substituted with one or more alkyl groups;

A is selected from aryl, heteroaryl, cycloalkyl or heterocyclyl;

provided that if the compound is of Formula (I), and Q is a bond and m = 1, then A is:



wherein

X is N or CR²;

Y is N or CR⁴;

Z is N or CR⁵;

R², R³, R⁴ and R⁵ are each independently selected from H, halo, CN, nitro, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, acyloxy, azido, carboxy, amino, amido, sulfone, -SO₂NR^aR^b, heteroaralkyl, aralkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl;

R⁶ is selected from H, halo, CN, alkyl, hydroxy, alkoxy, sulfone, cycloalkyl, heterocyclyl, aryl, and heteroaryl; or

R⁵ and R⁶, taken together with the atoms to which they are attached, may form a 5- or 6-membered aryl, cycloalkyl, heterocyclyl or heteroaryl;

R⁸, R⁹ and R¹⁰ are each independently selected from H, halo and unsubstituted alkyl;

R¹¹ is H or alkyl;

R^a and R^b are each H or alkyl;

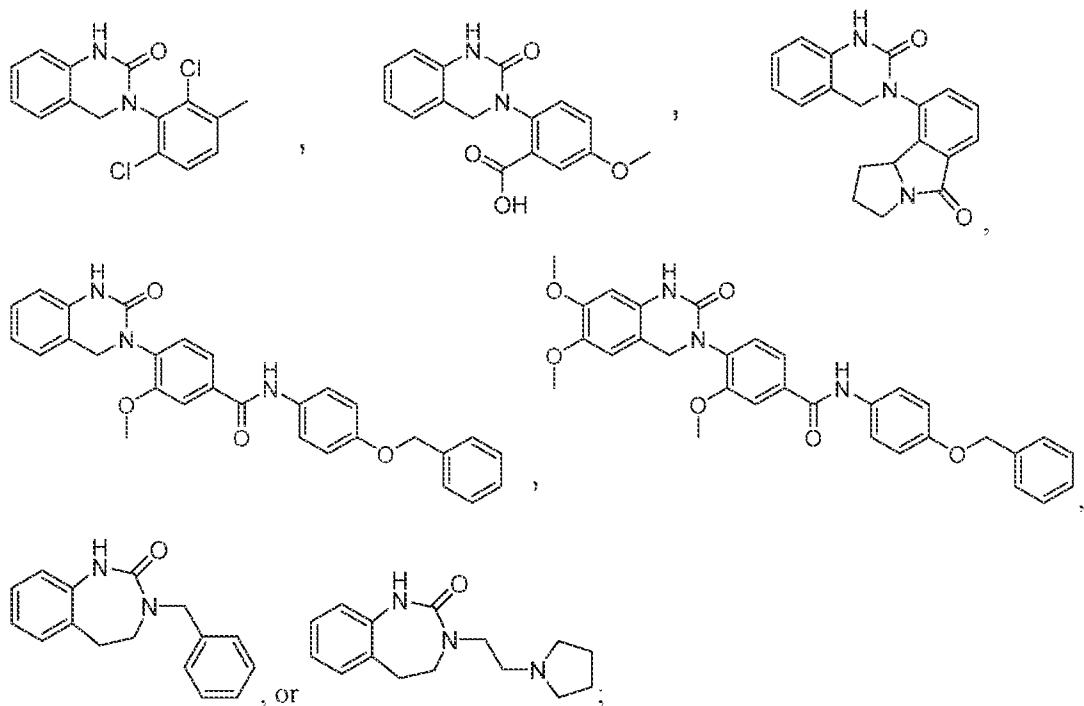
provided that:

if Q is a bond and m is 1, then:

- a) if R⁶ is Cl or methyl, then at least one of R², R³, R⁴ and R⁵ is not H;
- b) R³ or R⁵ is not aralkoxy or heteroaralkoxy;
- c) R⁴ and R⁶ are not both methyl or methoxy;
- d) R² and R⁶ are not both ethyl;

- e) R², R³, R⁴, R⁵, and R⁶ are not each H;
- f) if R² and R⁶ are each H, then Y is CR⁴ and R⁴ is H;
- g) if R² and R⁶ are each H, then R³ is not methyl, trifluoromethyl, pyridinyl, or methoxy;

the compound of Formula (I) is not



if Q is CH₂ or CH₂CH₂ and m=1, then R⁷ is 6-fluoro;

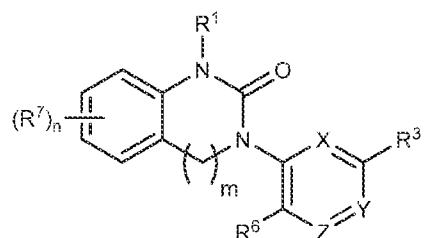
if Q is CH₂ and m=2, then A is not cycloalkyl;

if Q is CH(CH₃) and m = 1, then R⁷ is not amido;

if the compound is of Formula (II), and Q is a bond, then A is not heterocyclyl; and

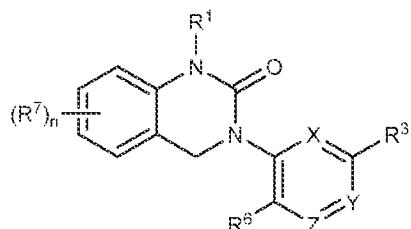
if Q is a bond and m is 2, then A is aryl or heteroaryl, and A is not substituted with sulfone, alkylthio, difluoromethoxy, or 1,1-difluoroethyl.

In certain embodiments, the compound is of Formula (IA):



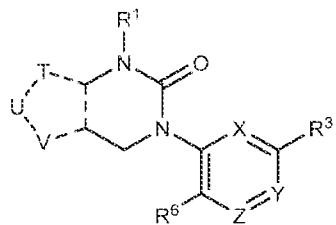
(IA).

In certain embodiments, the compound is of Formula (IB):



(IB).

In certain embodiments, the compound is of Formula (IIA):



(IIA).

In certain embodiments, T is S, U is CR⁹, R⁹ is H, and V is CH. In certain embodiments, T is S, U is CR⁹, R⁹ is chloro, and V is CH. In certain embodiments, T is CH, U is CH, and V is S.

In certain embodiments, m is 2. In certain embodiments, R¹ is H. In certain embodiments, wherein R¹ is methyl. In certain embodiments, X is N. In certain embodiments, X is CR². In certain embodiments, Y is N. In certain embodiments, Y is CR⁴. In certain embodiments, Z is N. In certain embodiments, Z is CR⁵.

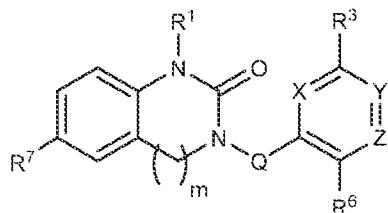
In certain embodiments, R², R³, R⁴ and R⁵ are each independently selected from H, halo, CN, nitro, alkyl, alkenyl, alkynyl, alkoxy, carboxy, amino, amido, and aryl. In certain embodiments, R², R³, R⁴ and R⁵ are each independently selected from H, halo, hydroxy, alkoxy and aralkyl. In certain embodiments, R² is selected from H, fluoro, bromo, CN and methyl. In certain embodiments, R² is H. In certain embodiments, R² is fluoro or CN.

In certain embodiments, R³ is selected from H, fluoro, chloro, bromo, hydroxy, CN, NO₂, NH₂, methyl, methoxy, ethoxy, -C(O)NMe₂, -CH₂OH, -CH₂CH₂OH, -(CH₂)₄OH, -CH₂CO₂H, -CH₂CONH₂, -CH₂CONMe₂, -CH₂CONEt₂, -CH₂CONHCH₂CH₂NEt₂, -CH₂-oxazolyl, -CH₂CH₂-imidazolyl, -(CH₂)₂CO₂H, -(CH₂)₂CO₂Et, -(CH₂)₂CONH(CH₂)₂OH, -CH₂CO₂Me, -CH₂CO-morpholino, -CH₂CO-pyrroloidinyl, -CH₂CH₂CO-morpholino, -CH=CH-COOH, -CH=CH-COOEt, -C≡C-(CH₂)₂OH, -CO₂H, -CO₂Me, -CONH-cyclopentyl, -CO-pyrrolidinyl, -CO-3-fluoropyrrolidinyl, -O(CH₂)₂-OH, -O(CH₂)₂OCH₃; -O(CH₂)₂OCH₂CH₃, -OCH₂-CO₂H, -OCH₂-CO₂Et, -O(CH₂)₂-pyrrolidinyl, -OCH₂-CO-pyrrolidinyl, -OCH₂-CO-morpholino, -OCH₂-CONH-CH₂CH₂phenyl, -OCH₂-CONH-4-chlorophenyl, 3-methoxyphenyl and ethyl 5-furylcarboxylate.

In certain embodiments, R⁴ is selected from H, fluoro, chloro, bromo, iodo, CN, and -NH₂. In certain embodiments, R⁵ is selected from H, fluoro, CN, nitro, and amino. In certain embodiments, R⁶ is fluoro. In certain embodiments, R⁶ is chloro or bromo. In certain embodiments, R⁶ is cyano. In certain embodiments, R⁶ is methyl or isopropyl. In certain embodiments, R⁶ is selected from hydroxy, methoxy, ethoxy, -OCH₂-CO₂Et, and -OCH₂-CO₂H. In certain embodiments, R⁶ is sulfone.

In certain embodiments, Q is -CH₂CH₂-NH- and each of R², R³, R⁴, R⁵, and R⁶ are H. In certain embodiments, Q is -CH₂CH₂-O- and each of R², R³, R⁴, R⁵, and R⁶ are H.

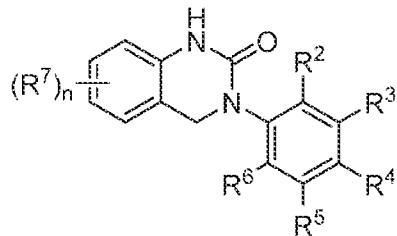
In certain embodiments, the compound is of Formula (IC):



(IC)

In certain such embodiments, R⁷ is H, fluoro, chloro, methyl or methoxy.

In certain embodiments, the compound is of Formula (ID):



wherein, R² and R⁶ are each independently selected from H, halo, CN and methyl; R³ and R⁵ are each independently selected from H, halo, hydroxyl, alkyl, alkoxy and aralkyl; R⁴ is selected from H, halo, and NH₂; R⁷ is fluoro or chloro; and n = 0 or 1. In certain such embodiments, R³ is selected from H, halo and methyl; R⁴ and R⁵ are each H; and R⁷ is fluoro. In certain such embodiments, R² is selected from fluoro, chloro and CN; R⁶ is selected from H, fluoro and chloro; and R³ is H.

In certain embodiments, the compound is of Formula (I); R¹ is selected from H and unsubstituted alkyl; Q is selected from CH₂, CH(CH₃), CH₂CH₂, -CH₂CH₂NH- and -CH₂CH₂O-; A is selected from aryl and cycloalkyl; wherein, A is optionally substituted one or more halo, alkoxy or alkyl substituents; m = 1; and n = 0 or 1. In certain such embodiments, R¹ is H; Q is selected from CH₂, CH(CH₃), CH₂CH₂, and -CH₂CH₂O-; A is aryl; wherein, A is optionally substituted one or more halo or alkoxy substituents.

Definitions

Unless defined otherwise, all technical and scientific terms used herein have the meaning commonly understood by a person skilled in the art of the present disclosure. The following references provide one of skill with a general definition of many of the terms used in this disclosure: Singleton et al., Dictionary of Microbiology and Molecular Biology (2nd ed. 1994); The Cambridge Dictionary of Science and Technology (Walker ed., 1988); The Glossary of Genetics, 5th Ed., R. Rieger et al. (eds.), Springer Verlag (1991); and Hale & Marham, The Harper Collins Dictionary of Biology (1991). As used herein, the following terms have the meanings ascribed to them below, unless specified otherwise.

In some embodiments, chemical structures are disclosed with a corresponding chemical name. In case of conflict, the chemical structure controls the meaning, rather than the name.

In this disclosure, "comprises," "comprising," "containing" and "having" and the like can have the meaning ascribed to them in U.S. Patent law and can mean "includes," "including," and the like; "consisting essentially of" or "consists essentially" likewise has the meaning ascribed in U.S. Patent law and the term is open-ended, allowing for the presence of more than that which is recited so long as basic or novel characteristics of that which is recited are not substantially changed by the presence of more than that which is recited, but excludes prior art embodiments.

Unless specifically stated or obvious from context, as used herein, the term "or" is understood to be inclusive. Unless specifically stated or obvious from context otherwise, as used herein, the terms "a", "an", and "the" are understood to be singular or plural.

The term "acyl" is art-recognized and refers to a group represented by the general formula hydrocarbylC(O)-, preferably alkylC(O)-.

The term "acylamino" is art-recognized and refers to an amino group substituted with an acyl group and may be represented, for example, by the formula hydrocarbylC(O)NH-.

The term "acyloxy" is art-recognized and refers to a group represented by the general formula hydrocarbylC(O)O-, preferably alkylC(O)O-.

The term "alkoxy" refers to an alkyl group, preferably a lower alkyl group, having an oxygen attached thereto. Representative alkoxy groups include methoxy, ethoxy, propoxy, tert-butoxy and the like.

The term "alkoxyalkyl" refers to an alkyl group substituted with an alkoxy group and may be represented by the general formula alkyl-O-alkyl.

The term "aralkoxy" refers to an alkyl group substituted with an aryl group and an alkoxy group and may be represented by the general formula O-alkyl-aryl. Representative aralkoxy groups include benzyloxy.

The term "heteroarylalkoxy" refers to a heteroaryl group substituted with an alkoxy group and may be represented by the general formula alkyl-O-heteroaryl.

The term "alkenyl", as used herein, refers to an aliphatic group containing at least one double bond and is intended to include both "unsubstituted alkenyls" and "substituted alkenyls", the latter of which refers to alkenyl moieties having substituents replacing a hydrogen on one or more carbons of the alkenyl group. Such substituents may occur on one or more carbons that are included or not included in one or more double bonds. Moreover, such substituents include all those contemplated for alkyl groups, as discussed below, except

where stability is prohibitive. For example, substitution of alkenyl groups by one or more alkyl, carbocyclyl, aryl, heterocyclyl, or heteroaryl groups is contemplated.

An "alkyl" group or "alkane" is a straight chained or branched non-aromatic hydrocarbon which is completely saturated. Typically, a straight chained or branched alkyl group has from 1 to about 20 carbon atoms, preferably from 1 to about 10 unless otherwise defined. Examples of straight chained and branched alkyl groups include methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, tert-butyl, pentyl, hexyl, pentyl and octyl. A C₁-C₆ straight chained or branched alkyl group is also referred to as a "lower alkyl" group.

Moreover, the term "alkyl" (or "lower alkyl") as used throughout the specification, examples, and claims is intended to include both "unsubstituted alkyls" and "substituted alkyls", the latter of which refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents, if not otherwise specified, can include, for example, a halogen, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxy carbonyl, a formyl, or an acyl), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an alkoxy, a phosphoryl, a phosphate, a phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclyl, an aralkyl, or an aromatic or heteroaromatic moiety. It will be understood by those skilled in the art that the moieties substituted on the hydrocarbon chain can themselves be substituted, if appropriate. For instance, the substituents of a substituted alkyl may include substituted and unsubstituted forms of amino, azido, imino, amido, phosphoryl (including phosphonate and phosphinate), sulfonyl (including sulfate, sulfonamido, sulfamoyl and sulfonate), and silyl groups, as well as ethers, alkylthios, carbonyls (including ketones, aldehydes, carboxylates, and esters), -CF₃, -CN and the like. Exemplary substituted alkyls are described below. Cycloalkyls can be further substituted with alkyls, alkenyls, alkoxy, alkylthios, aminoalkyls, carbonyl-substituted alkyls, -CF₃, -CN, and the like.

The term " C_{x-y} " when used in conjunction with a chemical moiety, such as, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy is meant to include groups that contain from x to y carbons in the chain. For example, the term " C_{x-y} alkyl" refers to substituted or unsubstituted saturated hydrocarbon groups, including straight-chain alkyl and branched-chain alkyl groups that contain from x to y carbons in the chain, including haloalkyl groups such as trifluoromethyl and 2,2,2-trifluoroethyl, etc. C₀ alkyl indicates a hydrogen where the group is

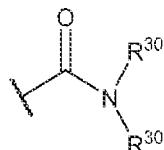
in a terminal position, a bond if internal. The terms “C₂-alkenyl” and “C₂-alkynyl” refer to substituted or unsubstituted unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond respectively.

The term “alkylamino”, as used herein, refers to an amino group substituted with at least one alkyl group.

The term “alkylthio”, as used herein, refers to a thiol group substituted with an alkyl group and may be represented by the general formula alkylS-.

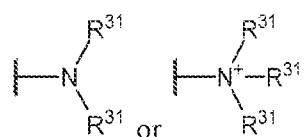
The term “alkynyl”, as used herein, refers to an aliphatic group containing at least one triple bond and is intended to include both “unsubstituted alkynyls” and “substituted alkynyls”, the latter of which refers to alkynyl moieties having substituents replacing a hydrogen on one or more carbons of the alkynyl group. Such substituents may occur on one or more carbons that are included or not included in one or more triple bonds. Moreover, such substituents include all those contemplated for alkyl groups, as discussed above, except where stability is prohibitive. For example, substitution of alkynyl groups by one or more alkyl, carbocyclyl, aryl, heterocyclyl, or heteroaryl groups is contemplated.

The terms “amide” and “amido”, as used herein, refer to a group



wherein each R³⁰ independently represents a hydrogen or hydrocarbyl group, or two R³⁰ are taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure.

The terms “amine” and “amino” are art-recognized and refer to both unsubstituted and substituted amines and salts thereof, e.g., a moiety that can be represented by



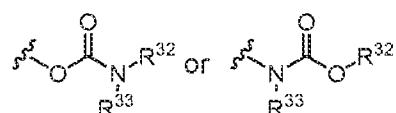
wherein each R³¹ independently represents a hydrogen or a hydrocarbyl group, or two R³¹ are taken together with the N atom to which they are attached complete a heterocycle

having from 4 to 8 atoms in the ring structure. The term “aminoalkyl”, as used herein, refers to an alkyl group substituted with an amino group.

The term “aralkyl”, as used herein, refers to an alkyl group substituted with an aryl group.

The term “aryl” as used herein include substituted or unsubstituted single-ring aromatic groups in which each atom of the ring is carbon. Preferably, the ring is a 5- to 7-membered ring, more preferably a 6-membered ring. The term “aryl” also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is aromatic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocycls. Aryl groups include benzene, naphthalene, phenanthrene, phenol, aniline, and the like.

The term “carbamate” is art-recognized and refers to a group



wherein R³² and R³³ independently represent hydrogen or a hydrocarbyl group, such as an alkyl group, or R³² and R³³ taken together with the intervening atom(s) complete a heterocycle having from 4 to 8 atoms in the ring structure.

The terms “carbocycle”, and “carbocyclic”, as used herein, refers to a saturated or unsaturated ring in which each atom of the ring is carbon. The term carbocycle includes both aromatic carbocycles and non-aromatic carbocycles. Non-aromatic carbocycles include both cycloalkane rings, in which all carbon atoms are saturated, and cycloalkene rings, which contain at least one double bond.

The term “carbocycle” includes 5-7 membered monocyclic and 8-12 membered bicyclic rings. Each ring of a bicyclic carbocycle may be selected from saturated, unsaturated and aromatic rings. Carbocycle includes bicyclic molecules in which one, two or three or more atoms are shared between the two rings. The term “fused carbocycle” refers to a bicyclic carbocycle in which each of the rings shares two adjacent atoms with the other ring. Each ring of a fused carbocycle may be selected from saturated, unsaturated and aromatic rings. In an exemplary embodiment, an aromatic ring, e.g., phenyl, may be fused to a saturated or unsaturated ring, e.g., cyclohexane, cyclopentane, or cyclohexene. Any

combination of saturated, unsaturated and aromatic bicyclic rings, as valence permits, is included in the definition of carbocyclic. Exemplary “carbocycles” include cyclopentane, cyclohexane, bicyclo[2.2.1]heptane, 1,5-cyclooctadiene, 1,2,3,4-tetrahydronaphthalene, bicyclo[4.2.0]oct-3-ene, naphthalene and adamantane. Exemplary fused carbocycles include decalin, naphthalene, 1,2,3,4-tetrahydronaphthalene, bicyclo[4.2.0]octane, 4,5,6,7-tetrahydro-1H-indene and bicyclo[4.1.0]hept-3-ene. “Carbocycles” may be substituted at any one or more positions capable of bearing a hydrogen atom.

A “cycloalkyl” group is a cyclic hydrocarbon which is completely saturated. “Cycloalkyl” includes monocyclic and bicyclic rings. Typically, a monocyclic cycloalkyl group has from 3 to about 10 carbon atoms, more typically 3 to 8 carbon atoms unless otherwise defined. The second ring of a bicyclic cycloalkyl may be selected from saturated, unsaturated and aromatic rings. Cycloalkyl includes bicyclic molecules in which one, two or three or more atoms are shared between the two rings. The term “fused cycloalkyl” refers to a bicyclic cycloalkyl in which each of the rings shares two adjacent atoms with the other ring. The second ring of a fused bicyclic cycloalkyl may be selected from saturated, unsaturated and aromatic rings. A “cycloalkenyl” group is a cyclic hydrocarbon containing one or more double bonds.

The term “carbocyclalkyl”, as used herein, refers to an alkyl group substituted with a carbocycle group.

The term “carbonate” is art-recognized and refers to a group $\text{-OCO}_2\text{R}^{34}$, wherein R^{34} represents a hydrocarbyl group.

The term “carboxy”, as used herein, refers to a group represented by the formula $\text{-CO}_2\text{H}$.

The term “ester”, as used herein, refers to a group -C(O)OR^{35} wherein R^{35} represents a hydrocarbyl group.

The term “ether”, as used herein, refers to a hydrocarbyl group linked through an oxygen to another hydrocarbyl group. Accordingly, an ether substituent of a hydrocarbyl group may be hydrocarbyl-O-. Ethers may be either symmetrical or unsymmetrical. Examples of ethers include, but are not limited to, heterocycle-O-heterocycle and aryl-O-heterocycle. Ethers include “alkoxyalkyl” groups, which may be represented by the general formula alkyl-O-alkyl.

The terms “halo” and “halogen” as used herein means halogen and includes chloro, fluoro, bromo, and iodo.

The terms “hetarylalkyl” and “heteroaralkyl”, as used herein, refers to an alkyl group substituted with a hetaryl group.

The term “heteroalkyl”, as used herein, refers to a saturated or unsaturated chain of carbon atoms and at least one heteroatom, wherein no two heteroatoms are adjacent.

The terms “heteroaryl” and “hetaryl” include substituted or unsubstituted aromatic single ring structures, preferably 5- to 7-membered rings, more preferably 5- to 6-membered rings, whose ring structures include at least one heteroatom, preferably one to four heteroatoms, more preferably one or two heteroatoms. The terms “heteroaryl” and “hetaryl” also include polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is heteroaromatic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocycls. Heteroaryl groups include, for example, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, pyrazole, pyridine, pyrazine, pyridazine, and pyrimidine, and the like.

The term “heteroatom” as used herein means an atom of any element other than carbon or hydrogen. Preferred heteroatoms are nitrogen, oxygen, and sulfur.

The terms “heterocycl”, “heterocycle”, and “heterocyclic” refer to substituted or unsubstituted non-aromatic ring structures, preferably 3- to 10-membered rings, more preferably 3- to 7-membered rings, whose ring structures include at least one heteroatom, preferably one to four heteroatoms, more preferably one or two heteroatoms. The terms “heterocycl” and “heterocyclic” also include polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is heterocyclic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocycls. Heterocycl groups include, for example, piperidine, piperazine, pyrrolidine, morpholine, lactones, lactams, and the like.

The term “heterocyclalkyl”, as used herein, refers to an alkyl group substituted with a heterocycle group.

The term “hydrocarbyl”, as used herein, refers to a group that is bonded through a carbon atom that does not have a =O or =S substituent, and typically has at least one carbon-

hydrogen bond and a primarily carbon backbone, but may optionally include heteroatoms. Thus, groups like methyl, ethoxyethyl, 2-pyridyl, and trifluoromethyl are considered to be hydrocarbyl for the purposes of this application, but substituents such as acetyl (which has a =O substituent on the linking carbon) and ethoxy (which is linked through oxygen, not carbon) are not. Hydrocarbyl groups include, but are not limited to aryl, heteroaryl, carbocycle, heterocyclyl, alkyl, alkenyl, alkynyl, and combinations thereof.

The term “hydroxyalkyl”, as used herein, refers to an alkyl group substituted with a hydroxy group.

The term “lower” when used in conjunction with a chemical moiety, such as, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy is meant to include groups where there are ten or fewer non-hydrogen atoms in the substituent, preferably six or fewer. A “lower alkyl”, for example, refers to an alkyl group that contains ten or fewer carbon atoms, preferably six or fewer. In certain embodiments, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy substituents defined herein are respectively lower acyl, lower acyloxy, lower alkyl, lower alkenyl, lower alkynyl, or lower alkoxy, whether they appear alone or in combination with other substituents, such as in the recitations hydroxyalkyl and aralkyl (in which case, for example, the atoms within the aryl group are not counted when counting the carbon atoms in the alkyl substituent).

The terms “polycyclyl”, “polycycle”, and “polycyclic” refer to two or more rings (e.g., cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls) in which two or more atoms are common to two adjoining rings, e.g., the rings are “fused rings”. Each of the rings of the polycycle can be substituted or unsubstituted. In certain embodiments, each ring of the polycycle contains from 3 to 10 atoms in the ring, preferably from 5 to 7.

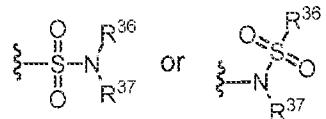
The term “silyl” refers to a silicon moiety with three hydrocarbyl moieties attached thereto.

The term “substituted” refers to moieties having substituents replacing a hydrogen on one or more carbons of the backbone. It will be understood that “substitution” or “substituted with” includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. As used herein, the term “substituted” is

contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and non-aromatic substituents of organic compounds. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. Substituents can include any substituents described herein, for example, a halogen, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxy carbonyl, a formyl, or an acyl), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an alkoxy, a phosphoryl, a phosphate, a phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulphydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclyl, an aralkyl, or an aromatic or heteroaromatic moiety. It will be understood by those skilled in the art that substituents can themselves be substituted, if appropriate. Unless specifically stated as “unsubstituted,” references to chemical moieties herein are understood to include substituted variants. For example, reference to an “aryl” group or moiety implicitly includes both substituted and unsubstituted variants.

The term “sulfate” is art-recognized and refers to the group $\text{-OSO}_3\text{H}$, or a pharmaceutically acceptable salt thereof.

The term “sulfonamide” is art-recognized and refers to the group represented by the general formulae



wherein R^{36} and R^{37} independently represent hydrogen or hydrocarbyl, such as alkyl, or R^{36} and R^{37} taken together with the intervening atom(s) complete a heterocycle having from 4 to 8 atoms in the ring structure.

The term “sulfoxide” is art-recognized and refers to the group -S(O)-R^{38} , wherein R^{38} represents a hydrocarbyl.

The term “sulfonate” is art-recognized and refers to the group SO_3H , or a pharmaceutically acceptable salt thereof.

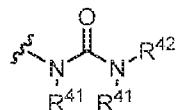
The term “sulfone” is art-recognized and refers to the group -S(O)₂-R³⁹, wherein R³⁹ represents a hydrocarbyl.

The term “thioalkyl”, as used herein, refers to an alkyl group substituted with a thiol group.

The term “thioester”, as used herein, refers to a group -C(O)SR⁴⁰ or -SC(O)R⁴⁰ wherein R¹⁰ represents a hydrocarbyl.

The term “thioether”, as used herein, is equivalent to an ether, wherein the oxygen is replaced with a sulfur.

The term “urea” is art-recognized and may be represented by the general formula



wherein R⁴¹ and R⁴² independently represent hydrogen or a hydrocarbyl, such as alkyl, or either occurrence of R⁴¹ taken together with R⁴² and the intervening atom(s)complete a heterocycle having from 4 to 8 atoms in the ring structure.

The term “protecting group” refers to a group of atoms that, when attached to a reactive functional group in a molecule, mask, reduce or prevent the reactivity of the functional group. Typically, a protecting group may be selectively removed as desired during the course of a synthesis. Examples of protecting groups can be found in Greene and Wuts, *Protective Groups in Organic Chemistry*, 3rd Ed., 1999, John Wiley & Sons, NY and Harrison et al., *Compendium of Synthetic Organic Methods*, Vols. 1-8, 1971-1996, John Wiley & Sons, NY. Representative nitrogen protecting groups include, but are not limited to, formyl, acetyl, trifluoroacetyl, benzyl, benzyloxycarbonyl (“CBZ”), tert-butoxycarbonyl (“Boc”), trimethylsilyl (“TMS”), 2-trimethylsilyl-ethanesulfonyl (“TES”), trityl and substituted trityl groups, allyloxycarbonyl, 9-fluorenylmethyloxycarbonyl (“Fmoc”), nitro-veratryloxycarbonyl (“NVOC”) and the like. Representative hydroxyl protecting groups include, but are not limited to, those where the hydroxyl group is either acylated (esterified) or alkylated such as benzyl and trityl ethers, as well as alkyl ethers, tetrahydropyranyl ethers, trialkylsilyl ethers (e.g., TMS or TIPS groups), glycol ethers, such as ethylene glycol and propylene glycol derivatives and allyl ethers.

In certain embodiments, compounds of the invention may be racemic. In certain embodiments, compounds of the invention may be enriched in one enantiomer. For example,

a compound of the invention may have greater than about 30% ee, about 40% ee, about 50% ee, about 60% ee, about 70% ee, about 80% ee, about 90% ee, or even about 95% or greater ee. In certain embodiments, compounds of the invention may have more than one stereocenter. In certain such embodiments, compounds of the invention may be enriched in one or more diastereomer. For example, a compound of the invention may have greater than about 30% de, about 40% de, about 50% de, about 60% de, about 70% de, about 80% de, about 90% de, or even about 95% or greater de.

In certain embodiments, the therapeutic preparation may be enriched to provide predominantly one enantiomer of a compound (e.g., of Formula (I) or (II)). An enantiomerically enriched mixture may comprise, for example, at least about 60 mol percent of one enantiomer, or more preferably at least about 75, about 90, about 95, or even about 99 mol percent. In certain embodiments, the compound enriched in one enantiomer is substantially free of the other enantiomer, wherein substantially free means that the substance in question makes up less than about 10%, or less than about 5%, or less than about 4%, or less than about 3%, or less than about 2%, or less than about 1% as compared to the amount of the other enantiomer, e.g., in the composition or compound mixture. For example, if a composition or compound mixture contains about 98 grams of a first enantiomer and about 2 grams of a second enantiomer, it would be said to contain about 98 mol percent of the first enantiomer and only about 2% of the second enantiomer.

In certain embodiments, the therapeutic preparation may be enriched to provide predominantly one diastereomer of a compound (e.g., of Formula (I) or (II)). A diastereomerically enriched mixture may comprise, for example, at least about 60 mol percent of one diastereomer, or more preferably at least about 75, about 90, about 95, or even about 99 mol percent.

The term "subject" to which administration is contemplated includes, but is not limited to, humans (i.e., a male or female of any age group, e.g., a pediatric subject (e.g., infant, child, adolescent) or adult subject (e.g., young adult, middle-aged adult or senior adult)) and/or other primates (e.g., cynomolgus monkeys, rhesus monkeys); mammals, including commercially relevant mammals such as cattle, pigs, horses, sheep, goats, cats, and/or dogs; and/or birds, including commercially relevant birds such as chickens, ducks, geese, quail, and/or turkeys. Preferred subjects are humans.

As used herein, a therapeutic that “prevents” a disorder or condition refers to a compound that, in a statistical sample, reduces the occurrence of the disorder or condition in the treated sample relative to an untreated control sample, or delays the onset or reduces the severity of one or more symptoms of the disorder or condition relative to the untreated control sample.

The term “treating” includes prophylactic and/or therapeutic treatments. The term “prophylactic or therapeutic” treatment is art-recognized and includes administration to the subject of one or more of the disclosed compositions. If it is administered prior to clinical manifestation of the unwanted condition (e.g., disease or other unwanted state of the subject) then the treatment is prophylactic (i.e., it protects the subject against developing the unwanted condition), whereas if it is administered after manifestation of the unwanted condition, the treatment is therapeutic, (i.e., it is intended to diminish, ameliorate, or stabilize the existing unwanted condition or side effects thereof).

The term “prodrug” is intended to encompass compounds which, under physiologic conditions, are converted into the therapeutically active agents of the present invention (e.g., a compound of Formula (I) or (II)). A common method for making a prodrug is to include one or more selected moieties which are hydrolyzed under physiologic conditions to reveal the desired molecule. In other embodiments, the prodrug is converted by an enzymatic activity of the subject. For example, esters or carbonates (e.g., esters or carbonates of alcohols or carboxylic acids) are preferred prodrugs of the present invention. In certain embodiments, some or all of the compounds of Formula (I) or (II) in a formulation represented above can be replaced with the corresponding suitable prodrug, e.g., wherein a hydroxyl in the parent compound is presented as an ester or a carbonate or carboxylic acid.

An “effective amount”, as used herein, refers to an amount that is sufficient to achieve a desired biological effect. A “therapeutically effective amount”, as used herein, refers to an amount that is sufficient to achieve a desired therapeutic effect. For example, a therapeutically effective amount can refer to an amount that is sufficient to improve at least one sign or symptom of cancer.

A “response” to a method of treatment can include a decrease in or amelioration of negative symptoms, a decrease in the progression of a disease or symptoms thereof, an increase in beneficial symptoms or clinical outcomes, a lessening of side effects, stabilization of disease, partial or complete remedy of disease, among others.

Methods of Use

Provided herein are methods of inhibiting IL4II in a cell, comprising contacting the cell with a compound of the invention, such as a compound of Formula (I) or (II), or a pharmaceutically acceptable salt thereof. In certain embodiments, contacting the cell occurs in a subject in need thereof, thereby treating a disease or disorder mediated by IL4II.

Also, disclosed herein are methods of treating a disease or a disorder mediated by IL4II comprising administering a compound the invention, such as a compound of Formula (I) or (II), or a pharmaceutically acceptable salt thereof. In some embodiments, disclosed herein are methods of treating cancer comprising administering a compound the invention, such as a compound of Formula (I) or (II), or a pharmaceutically acceptable salt thereof.

The methods described herein are useful for the treatment of a wide variety of cancers, including bladder cancer, bone cancer, brain cancer (including glioblastoma), breast cancer, cardiac cancer, cervical cancer, colon cancer, colorectal cancer, esophageal cancer, fibrosarcoma, gastric cancer, gastrointestinal cancer, glioma (including glioblastoma), head & neck cancer, Kaposi's sarcoma, kidney cancer (including renal cell adenocarcinoma), leukemia, liver cancer, lung cancer (including non-small cell lung cancer, small cell lung cancer, and mucoepidermoid pulmonary carcinoma), lymphoma, melanoma, myeloma, ovarian cancer (including ovarian adenocarcinoma), pancreatic cancer, penile cancer, prostate cancer, testicular germcell cancer, thymoma and thymic carcinoma.

In some embodiments, the subject has a cancer selected from breast cancer, brain cancer, colon cancer, fibrosarcoma, kidney cancer, lung cancer, melanoma, ovarian cancer, and prostate cancer. In certain embodiments, the subject has a cancer selected from breast cancer, colon cancer, fibrosarcoma, melanoma, ovarian cancer, and prostate cancer. In other embodiments, the subject has a cancer selected from brain cancer, breast cancer, kidney cancer, lung cancer, melanoma, and ovarian cancer. In some embodiments, the subject has head and neck squamous cell carcinoma, ovarian cancer, breast cancer or esophageal cancer. In other embodiments, the subject has pancreatic cancer, esophageal cancer, stomach cancer, head and neck cancer, colon cancer, lung cancer or kidney cancer. In yet other embodiments, the subject has breast cancer. In some embodiments, the breast cancer is breast adenocarcinoma. In certain embodiments, the breast cancer is triple-negative breast cancer.

In certain embodiments, the methods for treating or preventing cancer can be demonstrated by one or more responses such as increased apoptosis, inhibition of tumor

growth, reduction of tumor metastasis, inhibition of tumor metastasis, reduction of microvessel density, decreased neovascularization, inhibition of tumor migration, tumor regression, and increased survival of the subject.

In certain embodiments, the disease or the disorder mediated by IL4 is a disease or disorder mediated by IL4II activity. In some embodiments, the compounds of the invention, such as compounds of Formula (I) or (II), are useful as inhibitors of IL4II.

Combination Treatments

In some embodiments, the method of treating or preventing cancer may comprise administering a IL4II inhibitor conjointly with one or more other chemotherapeutic agent(s). In one embodiment, the IL4II inhibitor is a compound of the invention, such as a compound of Formula (I) or (II). Other chemotherapeutic agents can include IL4II-specific monoclonal antibodies which enhance the effects of other antibodies and therapies because of increased overall immune system activity (lower T-regulatory function and higher T-effector function, etc.) (Antonioli 2016).

In certain embodiments, the method of treating or preventing cancer may comprise administering a compound of the invention conjointly with one or more other chemotherapeutic agent(s).

Chemotherapeutic agents that may be conjointly administered with compounds of the invention include: 1-amino-4-phenylamino-9,10-dioxo-9,10-dihydroanthracene-2-sulfonate (acid blue 25), 1-amino-4-[4-hydroxyphenyl-amino]-9,10-dioxo-9,10-dihydroanthracene-2-sulfonate, 1-amino-4-[4-aminophenylamino]-9,10-dioxo-9,10-dihydroanthracene-2-sulfonate, 1-amino-4-[1-naphthylamino]-9,10-dioxo-9,10-dihydroanthracene-2-sulfonate, 1-amino-4-[4-fluoro-2-carboxyphenylamino]-9,10-dioxo-9,10-dihydroanthracene-2-sulfonate, ABT-263, afatinib dimaleate, axitinib, aminoglutethimide, amsacrine, anastrozole, APCP, asparaginase, AZD5363, Bacillus Calmette–Guérin vaccine (bcg), bicalutamide, bleomycin, bortezomib, β -methylene-ADP (AOPCP), buserelin, busulfan, cabazitaxel, cabozantinib, camptothecin, capecitabine, carboplatin, carfilzomib, carmustine, ceritinib, chlorambucil, chloroquine, cisplatin, cladribine, clodronate, cobimetinib, colchicine, crizotinib, cyclophosphamide, cyproterone, cytarabine, dacarbazine, dactinomycin, daunorubicin, demethoxyviridin, dexamethasone, dichloroacetate, dienestrol, diethylstilbestrol, docetaxel, doxorubicin,

epirubicin, eribulin, erlotinib, estradiol, estramustine, etoposide, everolimus, exemestane, filgrastim, fludarabine, fludrocortisone, fluorouracil, fluoxymesterone, flutamide, gefitinib, gemcitabine, genistein, goserelin, GSK1120212, hydroxyurea, idarubicin, ifosfamide, imatinib, interferon, irinotecan, ixabepilone, lenalidomide, letrozole, leucovorin, leuprolide, levamisole, lomustine, lonidamine, mechlorethamine, medroxyprogesterone, megestrol, melphalan, mercaptopurine, mesna, metformin, methotrexate, milt efosine, mitomycin, mitotane, mitoxantrone, MK-2206, mutamycin, N-(4-sulfamoylphenylcarbamothioyl) pivalamide, NF279, NF449, nilutamide, nocodazole, octreotide, olaparib, osimertinib, oxaliplatin, paclitaxel, palbociclib, pamidronate, pazopanib, pemexetred, pentostatin, perifosine, PF-04691502, plicamycin, pomalidomide, porfimer, PPADS, procarbazine, quercetin, raltitrexed, ramucirumab, reactive blue 2, rituximab, rolofylline, romidepsin, rucaparib, selumetinib, sirolimus, sodium 2,4-dinitrobenzenesulfonate, sorafenib, streptozocin, sunitinib, suramin, talazoparib, tamoxifen, temozolomide, temsirolimus, teniposide, testosterone, thalidomide, thioguanine, thiopeta, titanocene dichloride, tonapofylline, topotecan, trametinib, trastuzumab, tretinoin, veliparib, vinblastine, vincristine, vindesine, vinorelbine, and vorinostat (SAHA). In other embodiments, chemotherapeutic agents that may be conjointly administered with compounds of the invention include: ABT-263, dexamethasone, 5-fluorouracil, PF-04691502, romidepsin, and vorinostat (SAHA). In other embodiments, chemotherapeutic agents that may be conjointly administered with compounds of the invention include: 1-amino-4-phenylamino-9,10-dioxo-9,10-dihydroanthracene-2-sulfonate (acid blue 25), 1-amino-4-[4-hydroxyphenylamino]-9,10-dioxo-9,10-dihydroanthracene-2-sulfonate, 1-amino-4-[4-aminophenylamino]-9,10-dioxo-9,10-dihydroanthracene-2-sulfonate, 1-amino-4-[1-naphthylamino]-9,10-dioxo-9,10-dihydroanthracene-2-sulfonate, 1-amino-4-[4-fluoro-2-carboxyphenylamino]-9,10-dioxo-9,10-dihydroanthracene-2-sulfonate, 1-amino-4-[2-anthracynylamino]-9,10-dioxo-9,10-dihydroanthracene-2-sulfonate, APCP, β -methylene-ADP (AOPCP), capecitabine, cladribine, cytarabine, fludarabine, doxorubicin, gemcitabine, N-(4-sulfamoylphenylcarbamothioyl) pivalamide, NF279, NF449, PPADS, quercetin, reactive blue 2, rolofylline sodium 2,4-dinitrobenzenesulfonate, sumarin, and tonapofylline.

Chemotherapeutic agents that may be conjointly administered with compounds of the invention include: inhibitors of the MAPK/ERK pathway, such as KRAS inhibitors, SOS inhibitors, SHP2 inhibitors, Raf inhibitors and MEK inhibitors; immune checkpoint

inhibitors, such as PD-1 inhibitors, PD-L1 inhibitors, CTLA-4 inhibitors, CD20 inhibitors, CD47 inhibitors, GD2 inhibitors, LAG-3 inhibitors, TIM-3 inhibitors, TIGIT inhibitors, VISTA inhibitors, B7-H3 inhibitors, BTLA inhibitors, Siglec-15 inhibitors; and other immuno oncology agents, such as IDO inhibitors, interleukin-2 (IL-2), arginase inhibitors and inhibitors of the CD73/adenosine pathway. Chemotherapeutic agents that may be conjointly administered with compounds of the invention include: small molecules, antibodies, cytokines, and polypeptides. Many combination therapies have been developed for the treatment of cancer. In certain embodiments, compounds of the invention (e.g., compounds of Formula (I) or (II)) may be conjointly administered with a combination therapy. Examples of combination therapies with which compounds of the invention may be conjointly administered are included in Table 1.

Table 1: Exemplary combinatorial therapies for the treatment of cancer

Name	Therapeutic agents
ABV	Doxorubicin, Bleomycin, Vinblastine
ABVD	Doxorubicin, Bleomycin, Vinblastine, Dacarbazine
AC (Breast)	Doxorubicin, Cyclophosphamide
AC (Sarcoma)	Doxorubicin, Cisplatin
AC (Neuroblastoma)	Cyclophosphamide, Doxorubicin
ACE	Cyclophosphamide, Doxorubicin, Etoposide
ACe	Cyclophosphamide, Doxorubicin
AD	Doxorubicin, Dacarbazine
AP	Doxorubicin, Cisplatin
ARAC-DNR	Cytarabine, Daunorubicin
B-CAVe	Bleomycin, Lomustine, Doxorubicin, Vinblastine
BCVPP	Carmustine, Cyclophosphamide, Vinblastine, Procarbazine, Prednisone
BEACOPP	Bleomycin, Etoposide, Doxorubicin, Cyclophosphamide, Vincristine, Procarbazine, Prednisone, Filgrastim
BEP	Bleomycin, Etoposide, Cisplatin
BIP	Bleomycin, Cisplatin, Ifosfamide, Mesna

Name	Therapeutic agents
BOMP	Bleomycin, Vincristine, Cisplatin, Mitomycin
CA	Cytarabine, Asparaginase
CABO	Cisplatin, Methotrexate, Bleomycin, Vincristine
CAF	Cyclophosphamide, Doxorubicin, Fluorouracil
CAL-G	Cyclophosphamide, Daunorubicin, Vincristine, Prednisone, Asparaginase
CAMP	Cyclophosphamide, Doxorubicin, Methotrexate, Procarbazine
CAP	Cyclophosphamide, Doxorubicin, Cisplatin
CAV	Cyclophosphamide, Doxorubicin, Vincristine
CAVE ADD	CAV and Etoposide
CA-VP16	Cyclophosphamide, Doxorubicin, Etoposide
CC	Cyclophosphamide, Carboplatin
CDDP/VP-16	Cisplatin, Etoposide
CEF	Cyclophosphamide, Epirubicin, Fluorouracil
CEPP(B)	Cyclophosphamide, Etoposide, Prednisone, with or without/ Bleomycin
CEV	Cyclophosphamide, Etoposide, Vincristine
CF	Cisplatin, Fluorouracil or Carboplatin Fluorouracil
CHAP	Cyclophosphamide or Cyclophosphamide, Altretamine, Doxorubicin, Cisplatin
ChIVPP	Chlorambucil, Vinblastine, Procarbazine, Prednisone
CHOP	Cyclophosphamide, Doxorubicin, Vincristine, Prednisone
CHOP-BLEO	Add Bleomycin to CHOP
CISCA	Cyclophosphamide, Doxorubicin, Cisplatin
CLD-BOMP	Bleomycin, Cisplatin, Vincristine, Mitomycin
CMF	Methotrexate, Fluorouracil, Cyclophosphamide
CMFP	Cyclophosphamide, Methotrexate, Fluorouracil, Prednisone

Name	Therapeutic agents
CMFVP	Cyclophosphamide, Methotrexate, Fluorouracil, Vincristine, Prednisone
CMV	Cisplatin, Methotrexate, Vinblastine
CNF	Cyclophosphamide, Mitoxantrone, Fluorouracil
CNOP	Cyclophosphamide, Mitoxantrone, Vincristine, Prednisone
COB	Cisplatin, Vincristine, Bleomycin
CODE	Cisplatin, Vincristine, Doxorubicin, Etoposide
COMLA	Cyclophosphamide, Vincristine, Methotrexate, Leucovorin, Cytarabine
COMP	Cyclophosphamide, Vincristine, Methotrexate, Prednisone
Cooper Regimen	Cyclophosphamide, Methotrexate, Fluorouracil, Vincristine, Prednisone
COP	Cyclophosphamide, Vincristine, Prednisone
COPE	Cyclophosphamide, Vincristine, Cisplatin, Etoposide
COPP	Cyclophosphamide, Vincristine, Procarbazine, Prednisone
CP(Chronic lymphocytic leukemia)	Chlorambucil, Prednisone
CP (Ovarian Cancer)	Cyclophosphamide, Cisplatin
CVD	Cisplatin, Vinblastine, Dacarbazine
CVI	Carboplatin, Etoposide, Ifosfamide, Mesna
CVP	Cyclophosphamide, Vincristine, Prednisone
CVPP	Lomustine, Procarbazine, Prednisone
CYVADIC	Cyclophosphamide, Vincristine, Doxorubicin, Dacarbazine
DA	Daunorubicin, Cytarabine
DAT	Daunorubicin, Cytarabine, Thioguanine
DAV	Daunorubicin, Cytarabine, Etoposide
DCT	Daunorubicin, Cytarabine, Thioguanine
DHAP	Cisplatin, Cytarabine, Dexamethasone
DI	Doxorubicin, Ifosfamide

Name	Therapeutic agents
DTIC/Tamoxifen	Dacarbazine, Tamoxifen
DVP	Daunorubicin, Vincristine, Prednisone
EAP	Etoposide, Doxorubicin, Cisplatin
EC	Etoposide, Carboplatin
EFP	Etoposide, Fluorouracil, Cisplatin
ELF	Etoposide, Leucovorin, Fluorouracil
EMA 86	Mitoxantrone, Etoposide, Cytarabine
EP	Etoposide, Cisplatin
EVA	Etoposide, Vinblastine
FAC	Fluorouracil, Doxorubicin, Cyclophosphamide
FAM	Fluorouracil, Doxorubicin, Mitomycin
FAMTX	Methotrexate, Leucovorin, Doxorubicin
FAP	Fluorouracil, Doxorubicin, Cisplatin
F-CL	Fluorouracil, Leucovorin
FEC	Fluorouracil, Cyclophosphamide, Epirubicin
FED	Fluorouracil, Etoposide, Cisplatin
FL	Flutamide, Leuprolide
FZ	Flutamide, Goserelin acetate implant
HDMTX	Methotrexate, Leucovorin
Hexa-CAF	Altretamine, Cyclophosphamide, Methotrexate, Fluorouracil
IDMTX/6-MP	Methotrexate, Mercaptopurine, Leucovorin
IE	Ifosfamide, Etoposide, Mesna
IfoVP	Ifosfamide, Etoposide, Mesna
IPA	Ifosfamide, Cisplatin, Doxorubicin
M-2	Vincristine, Carmustine, Cyclophosphamide, Prednisone, Melphalan
MAC-III	Methotrexate, Leucovorin, Dactinomycin, Cyclophosphamide

Name	Therapeutic agents
MACC	Methotrexate, Doxorubicin, Cyclophosphamide, Lomustine
MACOP-B	Methotrexate, Leucovorin, Doxorubicin, Cyclophosphamide, Vincristine, Bleomycin, Prednisone
MAID	Mesna, Doxorubicin, Ifosfamide, Dacarbazine
m-BACOD	Bleomycin, Doxorubicin, Cyclophosphamide, Vincristine, Dexamethasone, Methotrexate, Leucovorin
MBC	Methotrexate, Bleomycin, Cisplatin
MC	Mitoxantrone, Cytarabine
MF	Methotrexate, Fluorouracil, Leucovorin
MICE	Ifosfamide, Carboplatin, Etoposide, Mesna
MINE	Mesna, Ifosfamide, Mitoxantrone, Etoposide
mini-BEAM	Carmustine, Etoposide, Cytarabine, Melphalan
MOBP	Bleomycin, Vincristine, Cisplatin, Mitomycin
MOP	Mechlorethamine, Vincristine, Procarbazine
MOPP	Mechlorethamine, Vincristine, Procarbazine, Prednisone
MOPP/ABV	Mechlorethamine, Vincristine, Procarbazine, Prednisone, Doxorubicin, Bleomycin, Vinblastine
MP (multiple myeloma)	Melphalan, Prednisone
MP (prostate cancer)	Mitoxantrone, Prednisone
MTX/6-MO	Methotrexate, Mercaptopurine
MTX/6-MP/VP	Methotrexate, Mercaptopurine, Vincristine, Prednisone
MTX-CDDPAdr	Methotrexate, Leucovorin, Cisplatin, Doxorubicin
MV (breast cancer)	Mitomycin, Vinblastine
MV (acute myelocytic leukemia)	Mitoxantrone, Etoposide
M-VAC Methotrexate	Vinblastine, Doxorubicin, Cisplatin
MVP Mitomycin	Vinblastine, Cisplatin
MVPP	Mechlorethamine, Vinblastine, Procarbazine, Prednisone

Name	Therapeutic agents
NFL	Mitoxantrone, Fluorouracil, Leucovorin
NOVP	Mitoxantrone, Vinblastine, Vincristine
OPA	Vincristine, Prednisone, Doxorubicin
OPPA	Add Procarbazine to OPA.
PAC	Cisplatin, Doxorubicin
PAC-I	Cisplatin, Doxorubicin, Cyclophosphamide
PA-CI	Cisplatin, Doxorubicin
PCV	Lomustine, Procarbazine, Vincristine
PFL	Cisplatin, Fluorouracil, Leucovorin
POC	Prednisone, Vincristine, Lomustine
ProMACE	Prednisone, Methotrexate, Leucovorin, Doxorubicin, Cyclophosphamide, Etoposide
ProMACE/cytaBOM	Prednisone, Doxorubicin, Cyclophosphamide, Etoposide, Cytarabine, Bleomycin, Vincristine, Methotrexate, Leucovorin, Cotrimoxazole
PRoMACE/MOPP	Prednisone, Doxorubicin, Cyclophosphamide, Etoposide, Mechlorethamine, Vincristine, Procarbazine, Methotrexate, Leucovorin
Pt/VM	Cisplatin, Teniposide
PVA	Prednisone, Vincristine, Asparaginase
PVB	Cisplatin, Vinblastine, Bleomycin
PVDA	Prednisone, Vincristine, Daunorubicin, Asparaginase
SMF	Streptozocin, Mitomycin, Fluorouracil
TAD	Mechlorethamine, Doxorubicin, Vinblastine, Vincristine, Bleomycin, Etoposide, Prednisone
TTT	Methotrexate, Cytarabine, Hydrocortisone
Topo/CTX	Cyclophosphamide, Topotecan, Mesna
VAB-6	Cyclophosphamide, Dactinomycin, Vinblastine, Cisplatin, Bleomycin
VAC	Vincristine, Dactinomycin, Cyclophosphamide

Name	Therapeutic agents
VACAdr	Vincristine, Cyclophosphamide, Doxorubicin, Dactinomycin, Vincristine
VAD	Vincristine, Doxorubicin, Dexamethasone
VATH	Vinblastine, Doxorubicin, Thiotepa, Flouxymesterone
VBAP	Vincristine, Carmustine, Doxorubicin, Prednisone
VBCMP	Vincristine, Carmustine, Melphalan, Cyclophosphamide, Prednisone
VC	Vinorelbine, Cisplatin
VCAP	Vincristine, Cyclophosphamide, Doxorubicin, Prednisone
VD	Vinorelbine, Doxorubicin
VelP	Vinblastine, Cisplatin, Ifosfamide, Mesna
VIP	Etoposide, Cisplatin, Ifosfamide, Mesna
VM	Mitomycin, Vinblastine
VMCP	Vincristine, Melphalan, Cyclophosphamide, Prednisone
VP	Etoposide, Cisplatin
V-TAD	Etoposide, Thioguanine, Daunorubicin, Cytarabine
5 + 2	Cytarabine, Daunorubicin, Mitoxantrone
7 + 3	Cytarabine with/, Daunorubicin or Idarubicin or Mitoxantrone
"8 in 1"	Methylprednisolone, Vincristine, Lomustine, Procarbazine, Hydroxyurea, Cisplatin, Cytarabine, Dacarbazine

In some embodiments, the chemotherapeutic agents that may be conjointly administered with compounds of the invention, such as a compound of Formula (I) or (II), include a IL4II inhibitor.

In other embodiments, the chemotherapeutic agents that may be conjointly administered with compounds of the invention, such as a compound of Formula (I) or (II), include known IL4II inhibitors.

In other embodiments, the chemotherapeutic agents that may be conjointly administered with compounds of the invention, such as a compound of Formula (I) or (II), include a nucleoside-based drug. In certain embodiments, the nucleoside-based drug is selected from gemcitabine, capecitabine, cytarabine, fludarabine and cladribine.

In further embodiments, the combination therapy comprises a compound of the invention, such as a compound of Formula (I) or (II), conjointly administered with an anthracycline. In other embodiments, the combination therapy comprises a compound of the invention, such as a compound of Formula (I) or (II), conjointly administered with doxorubicin.

In certain embodiments, the conjoint therapies of the invention comprise conjoint administration with other types of chemotherapeutic agents, such as immuno-oncology agents. Cancer cells often have specific cell surface antigens that can be recognized by the immune system. Thus, immuno-oncology agents, such as monoclonal antibodies, can selectively bind to cancer cell antigens and effect cell death. Other immuno-oncology agents can suppress tumor-mediated inhibition of the native immune response or otherwise activate the immune response and thus facilitate recognition of the tumor by the immune system. Exemplary antibody immuno-oncology agents, include, but are not limited to, abagovomab, adecatumumab, afutuzumab, alemtuzumab, anatumomab mafenatox, apolizumab, blinatumomab, BMS-936559, catumaxomab, durvalumab, epacadostat, epratuzumab, indoximod, inotuzumab ozogamicin, intelimumab, ipilimumab, isatuximab, lambrolizumab, MED14736, MPDL3280A, nivolumab, obinutuzumab, ocaratuzumab, ofatumumab, olatatumab, pembrolizumab, pidilizumab, rituximab, ticilimumab, samalizumab, and tremelimumab. Thus, in some embodiments, the methods of the invention comprise conjoint administration of one or more immuno-oncology agents, such as the agents mentioned above.

In some embodiments, the combination therapy comprises a compound of the invention, such as a compound of Formula (I) or (II), conjointly administered with anti-PD-1 therapy.

In some embodiments, the combination therapy comprises conjoint administration of a compound of the invention, such as a compound of Formula (I) or (II), with anti-PD-1 therapy. In certain embodiments, the combination therapy comprises conjoint administration of a compound of the invention, such as a compound of Formula (I) or (II), with oxaliplatin.

In other embodiments, the combination therapy comprises conjoint administration of a compound of the invention, such as a compound of Formula (I) or (II), with doxorubicin.

In certain embodiments, a compound of the invention may be conjointly administered with non-chemical methods of cancer treatment. In certain embodiments, a compound of the invention may be conjointly administered with radiation therapy. In certain embodiments, a compound of the invention may be conjointly administered with surgery, with thermoablation, with focused ultrasound therapy, with cryotherapy, or with any combination of these.

In certain embodiments, compounds of the invention may be conjointly administered with one or more other compounds of the invention. Moreover, such combinations may be conjointly administered with other therapeutic agents, such as other agents suitable for the treatment of cancer, such as the agents identified above. In certain embodiments, conjointly administering one or more additional chemotherapeutic agents with a compound of the invention provides a synergistic effect. In certain embodiments, conjointly administering one or more additional chemotherapeutic agents provides an additive effect.

Pharmaceutical Compositions

In certain embodiments, the present invention provides a pharmaceutical preparation suitable for use in a human patient, comprising any of the compounds shown above (e.g., a compound of the invention, such as a compound of Formula (I) or (II), and one or more pharmaceutically acceptable excipients. In certain embodiments, the pharmaceutical preparations may be for use in treating or preventing a condition or disease as described herein. Any of the disclosed compounds may be used in the manufacture of medicaments for the treatment of any diseases or conditions disclosed herein.

The compositions and methods of the present invention may be utilized to treat a subject in need thereof. In certain embodiments, the subject is a mammal such as a human, or a non-human mammal. When administered to subject, such as a human, the composition or the compound is preferably administered as a pharmaceutical composition comprising, for example, a compound of the invention and a pharmaceutically acceptable carrier. Pharmaceutically acceptable carriers are well known in the art and include, for example, aqueous solutions such as water or physiologically buffered saline or other solvents or vehicles such as glycols, glycerol, oils such as olive oil, or injectable organic esters. In a

preferred embodiment, when such pharmaceutical compositions are for human administration, particularly for invasive routes of administration (i.e., routes, such as injection or implantation, that circumvent transport or diffusion through an epithelial barrier), the aqueous solution is pyrogen-free, or substantially pyrogen-free. The excipients can be chosen, for example, to effect delayed release of an agent or to selectively target one or more cells, tissues or organs. The pharmaceutical composition can be in dosage unit form such as tablet, capsule (including sprinkle capsule and gelatin capsule), granule, lyophile for reconstitution, powder, solution, syrup, suppository, injection or the like. The composition can also be present in a transdermal delivery system, e.g., a skin patch. The composition can also be present in a solution suitable for topical administration, such as an eye drop.

A pharmaceutically acceptable carrier can contain physiologically acceptable agents that act, for example, to stabilize, increase solubility or to increase the absorption of a compound such as a compound of the invention. Such physiologically acceptable agents include, for example, carbohydrates, such as glucose, sucrose or dextrans, antioxidants, such as ascorbic acid or glutathione, chelating agents, low molecular weight proteins or other stabilizers or excipients. The choice of a pharmaceutically acceptable carrier, including a physiologically acceptable agent, depends, for example, on the route of administration of the composition. The preparation or pharmaceutical composition can be a self-emulsifying drug delivery system or a self-microemulsifying drug delivery system. The pharmaceutical composition (preparation) also can be a liposome or other polymer matrix, which can have incorporated therein, for example, a compound of the invention. Liposomes, for example, which comprise phospholipids or other lipids, are nontoxic, physiologically acceptable and metabolizable carriers that are relatively simple to make and administer.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of a subject without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The phrase "pharmaceutically acceptable carrier" as used herein means a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to

the subject. Some examples of materials which can serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations.

A pharmaceutical composition (preparation) can be administered to a subject by any of a number of routes of administration including, for example, orally (for example, drenches as in aqueous or non-aqueous solutions or suspensions, tablets, capsules (including sprinkle capsules and gelatin capsules), boluses, powders, granules, pastes for application to the tongue); absorption through the oral mucosa (e.g., sublingually); anally, rectally or vaginally (for example, as a pessary, cream or foam); parenterally (including intramuscularly, intravenously, subcutaneously or intrathecally as, for example, a sterile solution or suspension); nasally; intraperitoneally; subcutaneously; transdermally (for example as a patch applied to the skin); and topically (for example, as a cream, ointment or spray applied to the skin, or as an eye drop). The compound may also be formulated for inhalation. In certain embodiments, a compound may be simply dissolved or suspended in sterile water. Details of appropriate routes of administration and compositions suitable for same can be found in, for example, U.S. Pat. Nos. 6,110,973, 5,763,493, 5,731,000, 5,541,231, 5,427,798, 5,358,970 and 4,172,896, as well as in patents cited therein.

The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the subject being treated, the particular mode of administration. The amount of active ingredient that can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound which produces a therapeutic effect.

Generally, out of one hundred percent, this amount will range from about 1 percent to about ninety-nine percent of active ingredient, preferably from about 5 percent to about 70 percent, most preferably from about 10 percent to about 30 percent.

Methods of preparing these formulations or compositions include the step of bringing into association an active compound, such as a compound of the invention, with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound of the present invention with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

Formulations of the invention suitable for oral administration may be in the form of capsules (including sprinkle capsules and gelatin capsules), cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), lyophile, powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a compound of the present invention as an active ingredient. Compositions or compounds may also be administered as a bolus, electuary or paste.

To prepare solid dosage forms for oral administration (capsules (including sprinkle capsules and gelatin capsules), tablets, pills, dragees, powders, granules and the like), the active ingredient is mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, cetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; (10) complexing agents, such as, modified and unmodified cyclodextrins; and (11) coloring agents. In the case of capsules (including sprinkle capsules

and gelatin capsules), tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

The tablets, and other solid dosage forms of the pharmaceutical compositions, such as dragees, capsules (including sprinkle capsules and gelatin capsules), pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions that can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

Liquid dosage forms useful for oral administration include pharmaceutically acceptable emulsions, lyophiles for reconstitution, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, cyclodextrins and derivatives thereof, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ,

olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

Formulations of the pharmaceutical compositions for rectal, vaginal, or urethral administration may be presented as a suppository, which may be prepared by mixing one or more active compounds with one or more suitable nonirritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active compound.

Formulations of the pharmaceutical compositions for administration to the mouth may be presented as a mouthwash, or an oral spray, or an oral ointment.

Alternatively or additionally, compositions can be formulated for delivery via a catheter, stent, wire, or other intraluminal device. Delivery via such devices may be especially useful for delivery to the bladder, urethra, ureter, rectum, or intestine.

Formulations which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be appropriate.

Dosage forms for the topical or transdermal administration include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants that may be required.

The ointments, pastes, creams and gels may contain, in addition to an active compound, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to an active compound, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

Transdermal patches have the added advantage of providing controlled delivery of a compound of the present invention to the body. Such dosage forms can be made by dissolving or dispersing the active compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate of such flux can be controlled by either providing a rate controlling membrane or dispersing the compound in a polymer matrix or gel.

Ophthalmic formulations, eye ointments, powders, solutions and the like, are also contemplated as being within the scope of this invention. Exemplary ophthalmic formulations are described in U.S. Publication Nos. 2005/0080056, 2005/0059744, 2005/0031697 and 2005/004074 and U.S. Patent No. 6,583,124, the contents of which are incorporated herein by reference. If desired, liquid ophthalmic formulations have properties similar to that of lacrimal fluids, aqueous humor or vitreous humor or are compatible with such fluids. A preferred route of administration is local administration (*e.g.*, topical administration, such as eye drops, or administration via an implant).

The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrastemal injection and infusion.

Pharmaceutical compositions suitable for parenteral administration comprise one or more active compounds in combination with one or more pharmaceutically acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

Examples of suitable aqueous and nonaqueous carriers that may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents that delay absorption such as aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution, which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microencapsulated matrices of the subject compounds in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions that are compatible with body tissue.

For use in the methods of this invention, active compounds can be given per se or as a pharmaceutical composition containing, for example, 0.1 to 99.5% (more preferably, 0.5 to 90%) of active ingredient in combination with a pharmaceutically acceptable carrier.

Methods of introduction may also be provided by rechargeable or biodegradable devices. Various slow release polymeric devices have been developed and tested *in vivo* in

recent years for the controlled delivery of drugs, including proteinaceous biopharmaceuticals. A variety of biocompatible polymers (including hydrogels), including both biodegradable and non-degradable polymers, can be used to form an implant for the sustained release of a compound at a particular target site.

Actual dosage levels of the active ingredients in the pharmaceutical compositions may be varied so as to obtain an amount of the active ingredient that is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

The selected dosage level will depend upon a variety of factors including the activity of the particular compound or combination of compounds employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound(s) being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound(s) employed, the age, sex, weight, condition, general health and prior medical history of the subject being treated, and like factors well known in the medical arts.

A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the therapeutically effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the pharmaceutical composition or compound at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved. By "therapeutically effective amount" is meant the concentration of a compound that is sufficient to elicit the desired therapeutic effect. It is generally understood that the effective amount of the compound will vary according to the weight, sex, age, and medical history of the subject. Other factors which influence the effective amount may include, but are not limited to, the severity of the subject's condition, the disorder being treated, the stability of the compound, and, if desired, another type of therapeutic agent being administered with the compound of the invention. A larger total dose can be delivered by multiple administrations of the agent. Methods to determine efficacy and dosage are known to those skilled in the art (Isselbacher *et al.* (1996) Harrison's Principles of Internal Medicine 13 ed., 1814-1882, herein incorporated by reference).

In general, a suitable daily dose of an active compound used in the compositions and methods of the invention will be that amount of the compound that is the lowest dose

effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above.

If desired, the effective daily dose of the active compound may be administered as one, two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms. In certain embodiments of the present invention, the active compound may be administered two or three times daily. In preferred embodiments, the active compound will be administered once daily.

In certain embodiments, compounds of the invention may be used alone or conjointly administered with another type of therapeutic agent. As used herein, the phrase “conjoint administration” refers to any form of administration of two or more different therapeutic compounds such that the second compound is administered while the previously administered therapeutic compound is still effective in the body (e.g., the two compounds are simultaneously effective in the subject, which may include synergistic effects of the two compounds). For example, the different therapeutic compounds can be administered either in the same formulation or in a separate formulation, either concomitantly or sequentially. In certain embodiments, the different therapeutic compounds can be administered within one hour, 12 hours, 24 hours, 36 hours, 48 hours, 72 hours, or a week of one another. Thus, a subject who receives such treatment can benefit from a combined effect of different therapeutic compounds.

In certain embodiments, conjoint administration of compounds of the invention with one or more additional therapeutic agent(s) (e.g., one or more additional chemotherapeutic agent(s)) provides improved efficacy relative to each individual administration of the compound of the invention (e.g., compound of formula I or Ia) or the one or more additional therapeutic agent(s). In certain such embodiments, the conjoint administration provides an additive effect, wherein an additive effect refers to the sum of each of the effects of individual administration of the compound of the invention and the one or more additional therapeutic agent(s).

This invention includes the use of pharmaceutically acceptable salts of compounds of the invention in the compositions and methods of the present invention. In certain embodiments, contemplated salts of the invention include, but are not limited to, alkyl, dialkyl, trialkyl or tetra-alkyl ammonium salts. In certain embodiments, contemplated salts of the invention include, but are not limited to, L-arginine, benethamine, benzathine,

betaine, calcium hydroxide, choline, deanol, diethanolamine, diethylamine, 2-(diethylamino)ethanol, ethanolamine, ethylenediamine, N-methylglucamine, hydrabamine, 1H-imidazole, lithium, L-lysine, magnesium, 4-(2-hydroxyethyl)morpholine, piperazine, potassium, 1-(2-hydroxyethyl)pyrrolidine, sodium, triethanolamine, tromethamine, and zinc salts. In certain embodiments, contemplated salts of the invention include, but are not limited to, Na, Ca, K, Mg, Zn or other metal salts.

In certain embodiments, the pharmaceutically acceptable salt of the compound is selected from alkyl ammonium salts, dialkyl ammonium salts, trialkyl ammonium salts, tetraalkyl ammonium salts, L-arginine salts, benenthamine salts, benzathine salts, betaine salts, calcium hydroxide salts, choline salts, deanol salts, diethanolamine salts, diethylamine salts, 2-(diethylamino)ethanol salts, ethanolamine salts, ethylenediamine salts, N-methylglucamine salts, hydrabamine salts, 1H-imidazole salts, lithium salts, L-lysine salts, magnesium salts, 4-(2-hydroxyethyl)morpholine salts, piperazine salts, potassium salts, 1-(2-hydroxyethyl)pyrrolidine salts, sodium salts, triethanolamine salts, tromethamine salts, Na salts, Ca salts, K salts, Mg salts, and Zn salts.

The pharmaceutically acceptable acid addition salts can also exist as various solvates, such as with water, methanol, ethanol, dimethylformamide, and the like. Mixtures of such solvates can also be prepared. The source of such solvate can be from the solvent of crystallization, inherent in the solvent of preparation or crystallization, or adventitious to such solvent.

Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

Examples of pharmaceutically acceptable antioxidants include: (1) water-soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfite, sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and (3) metal-chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

The invention now being generally described, it will be more readily understood by reference to the following examples which are included merely for purposes of illustration of certain aspects and embodiments of the present invention, and are not intended to limit the invention.

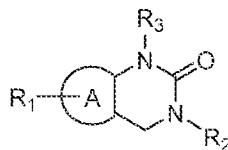
General Synthetic Procedures

Compound numbers A1-G5 as used in the general synthesis section below refer only to genus structures in this section and do not apply to compounds disclosed elsewhere in this application. Compounds disclosed herein can be made by methods depicted in the reaction schemes below.

The starting materials and reagents used in preparing these compounds are either available from commercial supplier such as Aldrich Chemical Co., Bachem, etc., or can be made by methods well known in the art. The schemes are merely illustrative of some methods by which the compounds disclosed herein can be synthesized and various modifications to these schemes can be made and will be suggested to POSITA having referred to this disclosure. The starting materials and the intermediates and the final products of the reacton may be isolated and purified if desired using conventional techniques, including but not limited to filtration, distillation, crystallization, chromatography, and the like and may be characterized using conventional means, including physical constants and spectral data.

Unless specified otherwise, the reactions described herein take place at atmospheric pressure over a temperature range from about -78 °C to about 150 °C.

General Synthetic Schemes

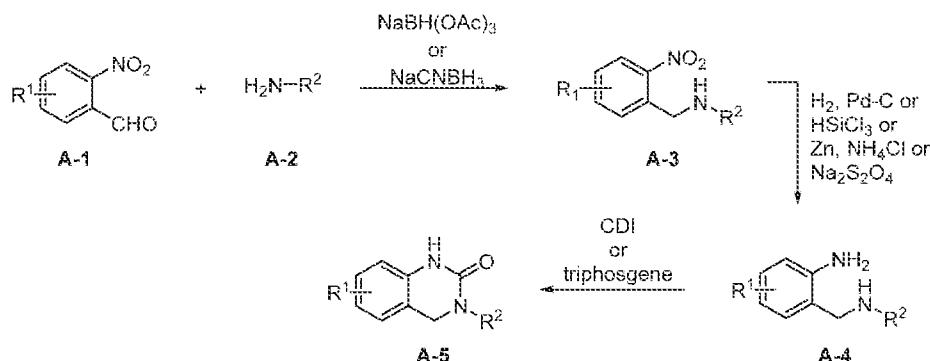


Formula (I)

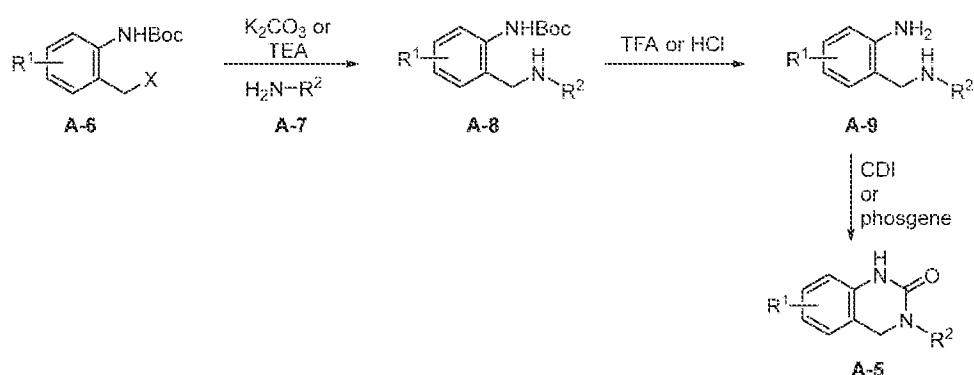
Compounds of the invention in Formula (I), can be conveniently prepared from the corresponding substituted 2-nitrobenzaldehyde (A-1) using general Scheme 1 set forth below. In this method, desired aldehyde A-1 where R¹ is H, halogen, CN, OH, amino, alkyl, alkoxy, N-alkyl or thiol ether group and amine A-2 where R² is alkyl, cycloalkyl, heterocyclic, aryl or heteroaryl, are treated with a reducing agent like sodium triacetoxyborohydride or sodium

cyanoborohydride in a reductive amination reaction to give amine A-3. In some instances, the reactions are slow and are best completed sequentially. For these examples, the aldehyde and amine are combined to form an imine and the reducing agent is added in a separate step, often after several hours. Formation of the imine may be facilitated by addition of either a Bronsted acid or a Lewis acid. In these reactions, a stronger reducing agent such as sodium borohydride or lithium borohydride is often preferred. Treatment of A-3 with a reducing agent like hydrogen gas and a palladium catalyst or trichlorosilane or Zn, Fe and NH₄Cl or Na₂S₂O₄ gives amine A-4. Subsequent treatment with carbonyldiimidazole (CDI), phosgene or triphosgene conveniently gives cyclized product A-5.

Scheme 1

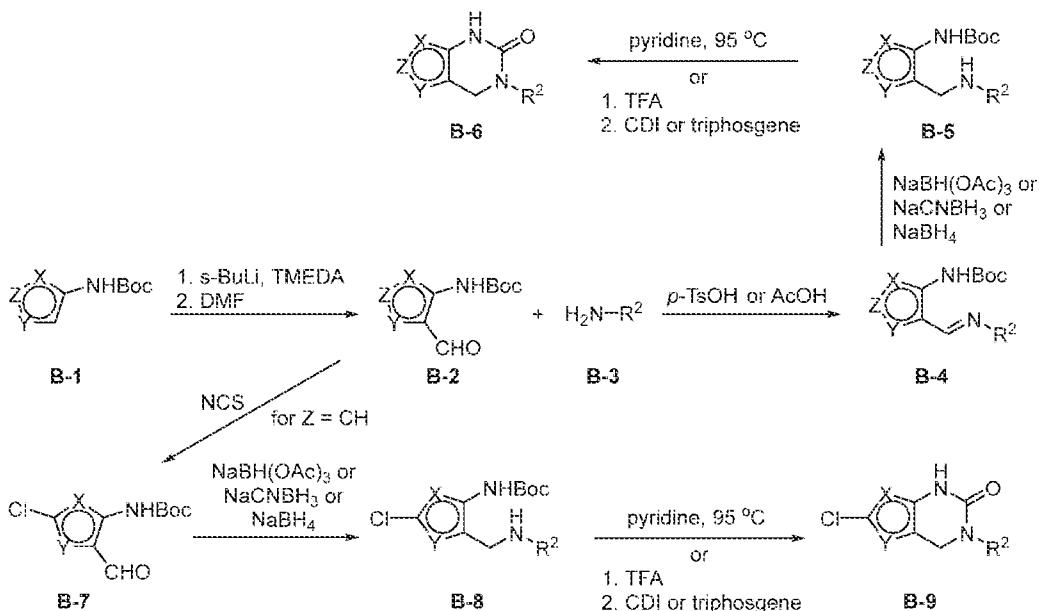


Compounds in formula (I) where R¹ is H, halogen, CN, OH, amino, alkyl, alkoxy, N-alkyl or thiol ether group and R² is alkyl, cycloalkyl, heterocyclic, aryl or heteroaryl, can be prepared as illustrated in Scheme 2. Intermediate A-8 can be assembled by an alkylation from 2-(*tert*-butyl carbamate)-benzyl halide A-6 where X is Cl, Br, I, OMs, OTs or OTf, and primary amine A-7 where R² is alkyl, cycloalkyl, heterocyclic, aryl or heteroaryl, under the influence of a base, such as K₂CO₃, Cs₂CO₃, Et₃N or i-PrNEt₂ in a solvent, such as DMF, DMSO, MeCN or THF. Removal of the Boc protecting group provides the requisite diamine A-9 in the presence of an acid, such as TFA or HCl. Treatment of A-9 with CDI, triphosgene or phosgene leads to the desired product A-5 as in formula (I).

Scheme 2

Heteroaryl compounds in formula (I) where X, Y and Z are chosen from C or N atom and R₂ is alkyl, cycloalkyl, heterocyclic, aryl or heteroaryl, can be prepared as illustrated in Scheme 3. The synthesis begins from an ortho-formylation of *tert*-butyl heteroaryl carbamate B-1 by the treatment of s-BuLi and TMEDA first and followed by DMF in THF at low temperature, such as -40 °C to give aldehyde B-2. Imine formation between aldehyde B-2 and amine B-3 can be achieved in the presence of a Lewis acid or Bronsted acid, such as TsOH or AcOH to give imine intermediate B-4. Reduce this resulting imine B-4 to B-5 by using a reducing reagent, such as Na(OAc)₂BH, NaCNBH₃ or NaBH₄, in a solvent such as CH₂Cl₂ or ClCH₂CH₂Cl. Converting B-5 into the final product B-6 as in formula (I) can be accomplished by either an one-pot intramolecular cyclization from treatment in pyridine at 95 °C or through a two-step sequence which first removing the Boc group by TFA and followed by the treatment of the resulting diamine with CDI, triphosgene or phosgene. Furthermore, a halogen such as Cl can be conveniently installed on the heteroaryl A ring in B-2 (where Z is CH) by the treatment of NCS to provide intermediate B-7. Final product B-9 as in Formula (I) can be obtained from B-7 through the similar process for B-6. Those familiar with organic synthesis will know that other halogens also can be introduced at B-2 and additional functional groups can be derived from these halogens depending on the specific target molecules.

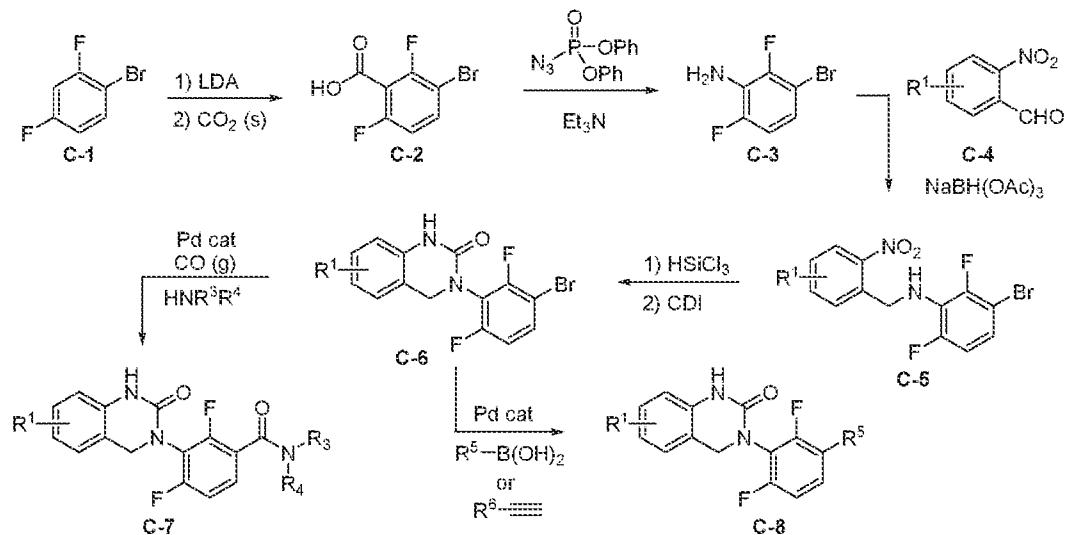
Scheme 3



Examples of general formula (I) where R¹ is H, halogen, CN, OH, amino, alkyl, alkoxy or thiol ether group and R² is 2,6-difluorophenyl with optional substituents in the 3-position can often be made using Scheme 4. In this method, 1-bromo-2,4-difluorobenzene (**C-1**) is deprotonated with a strong base like lithium diisopropyl-amide (LDA), lithium bis(trimethylsilyl)amide (LiHMDS) or sodium hydride (NaH), then quenched with carbon dioxide to give carboxylic acid **C-2**. Treatment with diphenyl phosphoryl azide (DPPA) with triethyl amine results in aniline **C-3** via the Curtius rearrangement. Reductive amination with substituted 2-nitrobenzaldehyde **C-4** using sodium triacetoxyborohydride in trifluoro-acetic acid gives benzyl amine **C-5**. The nitro group can be reduced to the corresponding amine using a wide variety of reducing agents, but hydrogen with a palladium catalyst or trichlorosilane with diisopropylethylamine or Zn or Fe are often preferred. The reduction product is transformed to heterocycle **C-6** by treatment with carbonyldiimidazole (CDI), phosgene or triphosgene. **C-6** is a convenient intermediate for a variety of reaction well-known to those skilled in the art of organic synthesis. Some of these include: (a) palladium catalyzed carbonylative coupling reaction with amine HNR³R⁴ to give amides **C-7**; (b) Suzuki coupling reactions with boronic acids R⁵-B(OH)₂ to give target compounds where R⁵ is an aryl ring (phenyl or heterocycle) **C-8**; (c) Sonogashira coupling reactions where an

alkyne is coupled with the bromide to give R⁵ is a triple bond linked to R⁶. It is understood, that the reactions illustrated in Scheme 4 are simply examples, and specific final targets may require additional steps.

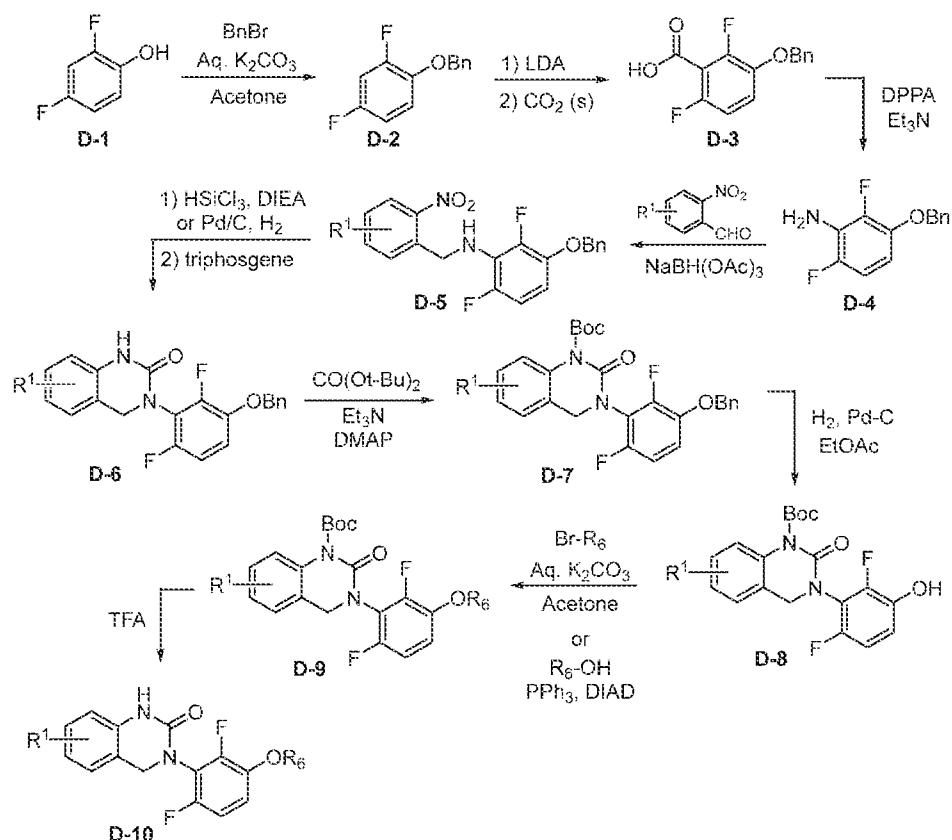
Scheme 4



Examples of general formula (I) where R² is 2,6-difluorophenyl with an oxygen-linked substituent in the 3-position can often be made using Scheme 5. In this method, the hydroxyl group of 2,4-difluorophenol (**D-1**) is initially protected with a suitable group like benzyl, methyl or benzyloxymethyl ether. The protected intermediate (**D-2**) is deprotonated with a strong base like lithium diisopropylamide (LDA), lithium bis(trimethylsilyl)amide (LiHMDS) or sodium hydride (NaH), then quenched with carbon dioxide to give carboxylic acid **D-3**. Treatment with diphenyl phosphoryl azide (DPPA) with triethyl amine results in aniline **D-4** via the Curtius rearrangement. Reductive amination with a substituted 2-nitrobenzaldehyde and sodium triacetoxyborohydride in trifluoroacetic acid gives benzyl amine **D-5**. The nitro group can be reduced to the corresponding amine using a wide variety of reducing agents, but hydrogen with a palladium catalyst or trichlorosilane with diisopropylethylamine are often convenient. The reduction product is transformed to heterocycle **D-6** by treatment with carbonyldiimidazole (CDI), phosgene or triphosgene. **D-6** can be used directly to make certain targets, but protection of the cyclic urea N-H is often preferable, depending on the reaction conditions used in subsequent reactions. Introduction of a Boc-group by treatment with di-*tert*-butyl decarbonate, triethylamine and dimethylaminopyridine

(DMAP) is often convenient (**D-7**). Deprotection of the benzyl protecting group with hydrogen gas gives intermediate **D-8** with the free phenolic OH. This hydroxyl group can be functionalized using a variety of reactions. For example, it can be alkylated with an alkyl halide ($\text{Br}-\text{R}^6$) or it can be coupled with alcohols using a Mitsunobu reaction. Once the R^6 group is incorporated, deprotection of the Boc-group with an acid such as trifluoroacetic acid (TFA) gives the target compounds.

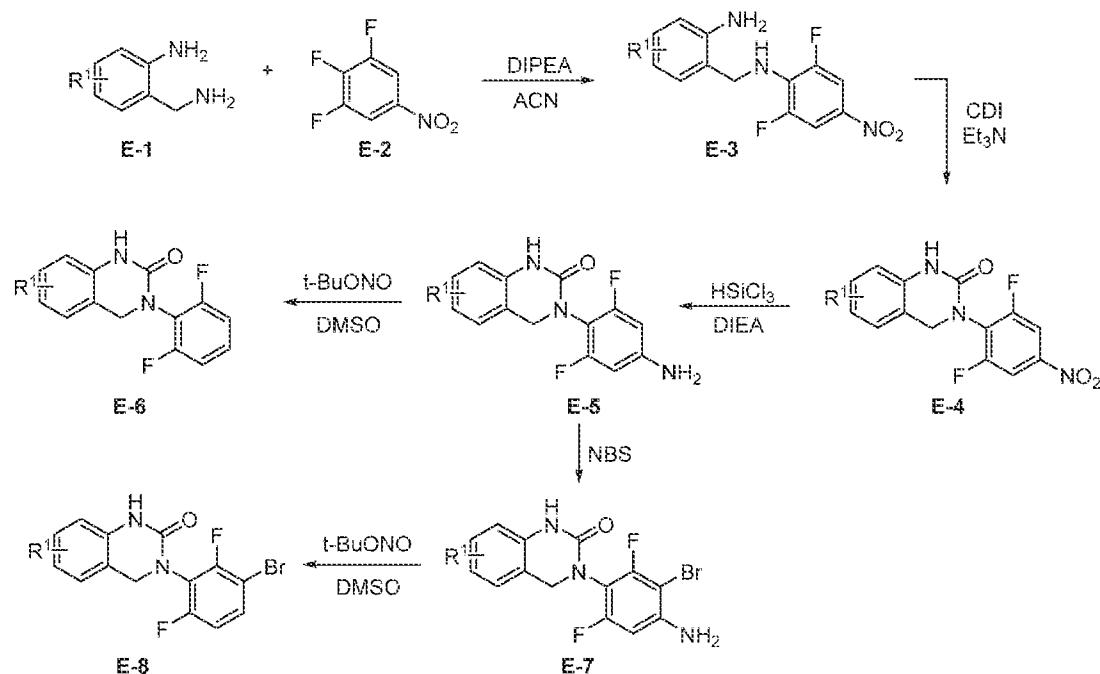
Scheme 5



A preferred method to make examples of Formula (I) where R^2 is 2,6-difluorophenyl with optional substituents in the 3-position can often be made using Scheme 6. In this method, diamine **E-1** is coupled with 1,2,3-trifluoro-5-nitrobenzene (**E-2**) in a nucleophilic aromatic substitution reaction to give amine **E-3**. Treatment with CDI gives 3,4-dihydroquinazolin-2(*H*)-one **E-4**. Reduction of the nitro group using hydrogen gas or trichlorosilane give aniline **E-5**. For targets where R^2 is 2,6-difluorophenyl (**E-6**), the amine can be removed using oxidizing it to a diazonium salt isoamyl nitrite in DMSO. Alternatively,

treatment of amine E-5 with bromine or *N*-Bromo succinimide (NBS) gives the bromo intermediate E-7. The amino group of E-7 can be eliminated as before to give bromide E-8. Those familiar with organic synthesis will know that each of these intermediates (e.g. E-5, E-7, E-8) can be used to introduce additional functional groups depending on the specific target molecules.

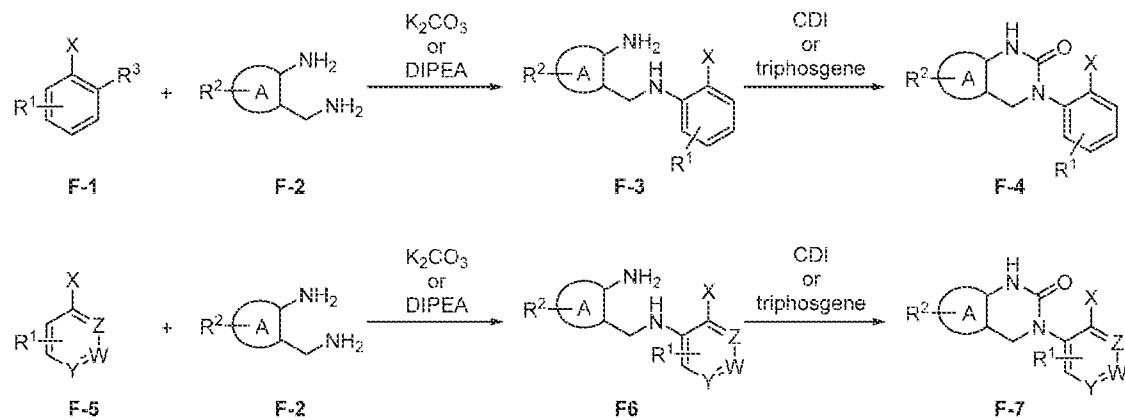
Scheme 6



Compounds in formula (I) where ring A is aryl or heteroaryl, R¹ is halogen, CN, ester, carboxylic acid, amide, sulfonamide, sulfone, alkyl, cycloalkyl, alkoxy, amino, *N*-alkyl, thiol ether, heterocyclic, aryl or heteroaryl and R₂ is H, halogen, CN, alkyl, alkoxy, thiol ether, amino or *N*-alkyl group, can be prepared as illustrated in Scheme 7. The synthesis starts from a nucleophilic displacement reaction between electrophile F-1 where X is halogen or OTf and R₃ is CN, SO₂Me, NO₂, CHO, and diamine nucleophile F-2 in the presence of a base, such as K₂CO₃, Cs₂CO₃, TEA or DIPEA, in solvent such as DMSO, DMF or MeCN gives intermediate F-3 which is then converted into F-4 as in Formula (I) by the treatment with CDI, triphosgene or phosgene either in the presence of a base, such as K₂CO₃ or TEA, or without. Additionally, Compounds F-7 as in Formula (I) can be prepared from a different electrophile F-5 where X is halogen or OTf, W is either C or N while either Y and Z can be a

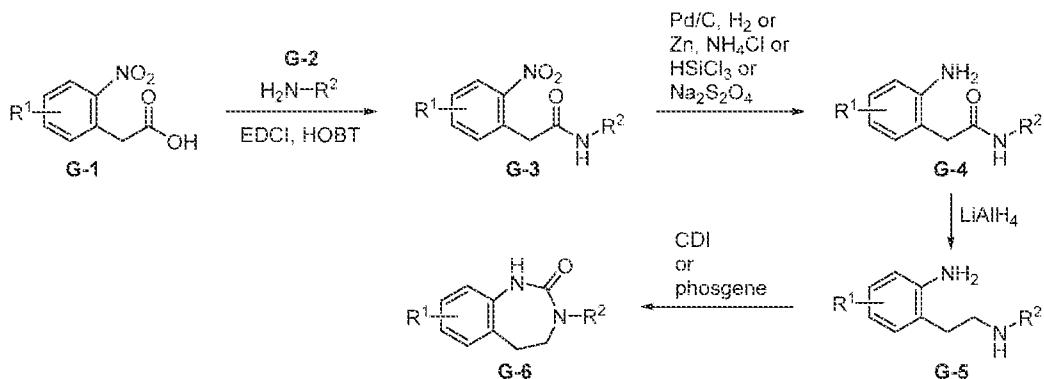
N atom selectively or both as N atoms that facilitates the nucleophilic displacement of the leaving group X.

Scheme 7



Compounds in formula (I) where R¹ is H, halogen, CN, OH, amino, alkyl, alkoxy, *N*-alkyl or thiol ether group and R² is alkyl, cycloalkyl, heterocyclic, aryl or heteroaryl, can be prepared as illustrated in Scheme 8. The synthesis starts from the amide coupling from 2-nitrophenyl-acetic acid precursor G-1 and amine G-2 with a peptide coupling reagent, such as EDCI-HOBt, DCC, DIC, HATU or T₃P, in solvent such as DMF, NMP or THF, leads to amide G-3. Reduction of the nitro group in G-3 to amine G-4 by a reducing reagent, such as Pd/C and H₂, HSiCl₃, Zn, Fe or Na₂S₂O₄. Conversion of the resulting amide moiety in G-4 by a reducing reagent, such as LAH or borane reagent, gives the diamine G-5. Finally, treatment of G-5 with CDI, triphosgene or phosgene leads to the desired G-6 as in Formula (I).

Scheme 8



Those having skill in the art will recognize that the starting materials and reaction conditions may be varied, the sequence of the reactions altered, and additional steps employed to produce compounds encompassed by the present invention, as demonstrated by the following examples. In some cases, protection of certain reactive functionalities may be necessary to achieve some of the above transformations. In general, the need for such protecting groups as well as the conditions necessary to attach and remove such groups will be apparent to those skilled in the art of organic synthesis.

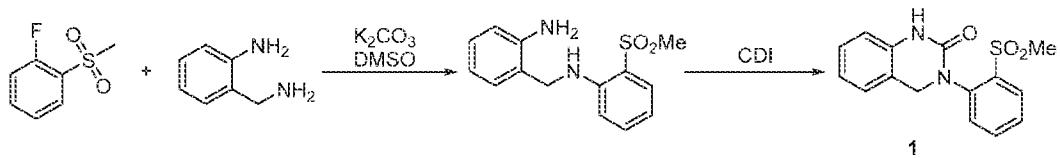
The disclosures of all articles and references mentioned in this application, including patents, are incorporated herein by reference.

The preparation of the compounds of the present invention is illustrated further by the following examples, which are not to be construed as limiting the invention in scope or spirit to the specific procedures and compounds described in them.

Synthetic Examples

Example 1

Synthesis of 3-(2-(methylsulfonyl)phenyl)-3,4-dihydroquinazolin-2(1*H*)-one



Step 1:

To a solution of 2-fluorophenylmethylsulfone (285 mg, 1.64 mmole) and 2-amino-4-aminobiphenyl (200 mg, 1.64 mmol) in DMSO (2 mL) was added K₂CO₃ (339 mg, 2.46 mmol) at room temperature. The resulting mixture was stirred at 80 °C overnight. It was allowed to cool to room temperature. The crude reaction mixture was diluted with EtOAc (10 mL) and water (8 mL). The aqueous layer was further extracted with EtOAc (2x10 mL). The combined organic layer was washed with brine, dried (MgSO₄) and concentrated. The crude residue was purified by flash SiO₂ column chromatography (0–8% EtOAc in hexane) to provide the desired product *N*-(2-aminobenzyl)-2-(methylsulfonyl)aniline.

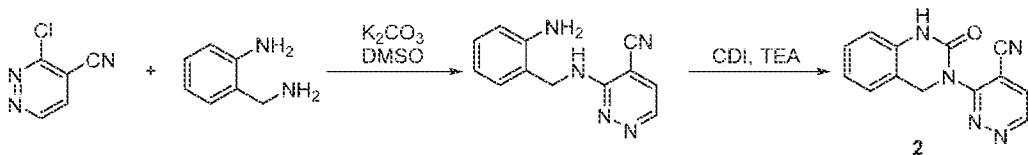
Step 2:

To a solution of *N*-(2-aminobenzyl)-2-(methylsulfonyl)aniline (180 mg, 0.60 mmol) in THF (2 mL) at room temperature was added CDI (126 mg, 0.78 mmol). The reaction mixture was stirred for 48 hours before it was diluted with EtOAc (10 mL) and water (8 mL). The aqueous layer was further extracted with EtOAc (2x10 mL). The combined organic layer was washed with brine, dried (MgSO_4) and concentrated. The crude was purified by flash SiO_2 column chromatography (0–8% EtOAc in hexane) to provide the desired product 3-(2-(methylsulfonyl)phenyl)-3,4-dihydroquinazolin-2(1*H*)-one as a white solid.

^1H NMR (CDCl_3 , 300 MHz) δ 8.55 (s, 1H), 8.30 (dd, $J=1.5, 7.9$ Hz, 1H), 7.87–7.93 (m, 1H), 7.62–7.77 (m, 2H), 7.07–7.29 (m, 3H), 6.80 (d, $J=7.8$ Hz, 1H), 4.98 (q, $J=13.9, 94.5$ Hz, 2H), 3.30 (s, 3H); LC/MS [M + H] = 303.0.

Example 2

Synthesis of 3-(2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)pyridazine-4-carbonitrile



Step 1:

To a solution of 3-chloropyridazine-4-carbonitrile (285 mg, 2.04 mmole) and 2-aminobenzylamine (249 mg, 2.04 mmol) in DMSO (2 mL) was added K_2CO_3 (419 mg, 3.06 mmol) at room temperature. The resulting mixture was stirred at 80 °C overnight. It was allowed to cool to room temperature. The crude reaction mixture was diluted with EtOAc (10 mL) and water (8 mL). The aqueous layer was further extracted with EtOAc (2x10 mL). The combined organic layer was washed with brine, dried (MgSO_4) and concentrated. The crude was purified by flash SiO_2 column chromatography (0–8% EtOAc in hexane) to provide the desired product 3-((2-aminobenzyl)amino)pyridazine-4-carbonitrile.

Step 2:

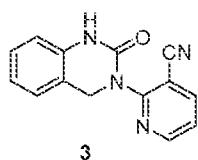
To a solution of 3-((2-aminobenzyl)amino)pyridazine-4-carbonitrile (180 mg, 0.81 mmol) in THF (2 mL) was added CDI (137 mg, 0.89 mmol) at room temperature, the reaction mixture was stirred for 48 hours before it was diluted with EtOAc and water. The aqueous layer was further extracted with EtOAc (2x10 mL). The combined organic layer was washed with brine, dried (MgSO_4) and concentrated. The crude was purified by flash SiO_2 column

chromatography (0–8% EtOAc in hexane) to provide the desired product 3-(2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)pyridazine-4-carbonitrile as a white solid.

¹H NMR (CDCl₃, 300 MHz) δ 9.24 (d, *J*=4.9 Hz, 1H), 7.74 (d, *J*=4.9 Hz, 1H) 7.09–7.34 (m, 3H), 6.88 (d, *J*=7.6 Hz, 1H), 5.24 (s, 2H); LC/MS [M + H] = 252.0.

Example 3

Synthesis of 2-(2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)nicotinonitrile

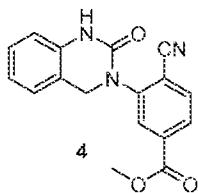


Proceeding as described in Example 2 above but substituting 3-chloropyridazine-4-carbonitrile with 2-fluoronicotinonitrile provided the title compound as a white solid.

¹H NMR (CDCl₃, 300 MHz) δ 8.68 (dd, *J*=1.3, 4.9 Hz, 1H), 8.03 (dd, *J*=1.9, 7.7 Hz, 1H), 7.95 (s, 1H), 7.02–7.31 (m, 4H), 6.90 (d, *J*=7.9 Hz, 1H), 5.02 (s, 2H); LC/MS [M + H] = 251.1.

Example 4

Synthesis of methyl 4-cyano-3-(2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)benzoate

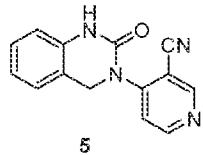


Proceeding as described in Example 2 above but substituting 3-chloropyridazine-4-carbonitrile with methyl 3-chloro-4-cyanobenzoate provided the title compound as a white solid.

¹H NMR (CDCl₃, 300 MHz) δ 8.06–8.09 (m, 2H), 7.83 (d, *J*=8.1 Hz, 1H) 7.49 (s, 1H), 7.23–7.28 (m, 1H), 7.01–7.13 (m, 2H), 6.80 (d, *J*=7.7 Hz, 1H), 4.92 (s, 2H), 3.98 (s, 3H); LC/MS [M + H] = 308.0.

Example 5

Synthesis of 4-(2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)nicotinonitrile

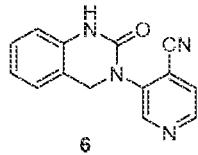


Proceeding as described in Example 2 above but substituting 3-chloropyridazine-4-carbonitrile with 4-chloronicotinonitrile provided the title compound as a white solid.

¹H NMR (CDCl₃, 300 MHz) δ 8.82–8.92 (m, 2H), 7.92 (s, 1H), 6.86–7.07 (m, 4H), 6.88 (d, J=7.8 Hz, 1H), 4.93 (s, 2H); LC/MS [M + H] = 251.0.

Example 6

Synthesis of 4-(2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)nicotinonitrile

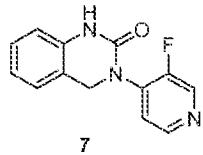


Proceeding as described in Example 2 above but substituting 3-chloropyridazine-4-carbonitrile with 3-chloroisomericotinonitrile provided the title compound as a white solid.

¹H NMR (CDCl₃, 300 MHz) δ 8.71–8.87 (m, 2H), 6.71–7.88 (m, 5H), 4.87 (s, 2H); LC/MS [M + H] = 251.0.

Example 7

Synthesis of 3-(3-fluoropyridin-4-yl)-3,4-dihydroquinazolin-2(1*H*)-one

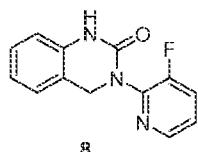


Proceeding as described in Example 2 above but substituting 3-chloropyridazine-4-carbonitrile with 3,4-difluoropyridine provided the title compound as a white solid.

¹H NMR (CDCl₃, 300 MHz) δ 8.75 (s, 1H), 8.04 (s, 1H), 7.06–7.38 (m, 5H), 6.84–6.87 (d, *J* = 7.8 Hz, 1H), 4.86 (s, 2H); LC/MS [M + H] = 244.0.

Example 8

Synthesis of 3-(3-fluoropyridin-2-yl)-3,4-dihydroquinazolin-2(1*H*)-one

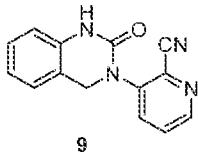


Proceeding as described in Example 2 above but substituting 3-chloropyridazine-4-carbonitrile with 2,3-difluoropyridine provided the title compound as a solid.

¹H NMR (CDCl₃, 300 MHz) δ 8.31 (s, 1H), 7.47–7.56 (m, 2H), 7.01–7.27 (m, 4H), 6.82 (d, *J*=7.8 Hz, 1H), 4.97 (s, 2H); LC/MS [M + H] = 244.0.

Example 9

Synthesis of 3-(2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)picolinonitrile

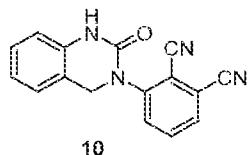


Proceeding as described in Example 2 above but substituting 3-chloropyridazine-4-carbonitrile with 3-chloropicolinonitrile provided the title compound as a solid.

¹H NMR (CDCl₃, 300 MHz) δ 8.67 (dd, *J*=1.3, 4.6 Hz, 1H), 7.89 (dd, *J*=1.4, 8.3 Hz, 1H), 7.60–7.64 (m, 1H), 7.49 (s, 1H), 7.03–7.30 (m, 3H), 6.82 (d, *J*=7.6 Hz, 1H), 4.94 (s, 2H); LC/MS [M + H] = 251.0.

Example 10

Synthesis of 3-(2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)phthalonitrile

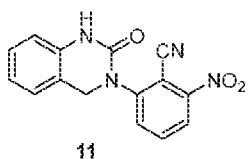


Proceeding as described in Example 2 above but substituting 3-chloropyridazine-4-carbonitrile with 3-fluorophthalonitrile provided the title compound as a white solid.

¹H NMR (DMSO-*d*6, 300 MHz); δ 10.08 (s, 1H), 7.98–8.12 (m, 3H), 7.25 (t, *J*=7.5 Hz, 1H), 7.19 (d, *J*=7.6 Hz, 1H), 6.99 (t, *J*=7.5 Hz, 1H), 6.93 (d, *J*=7.9 Hz, 1H), 4.92 (bs, 2H), LC/MS [M + H]⁺ = 275.1.

Example 11

Synthesis of 2-nitro-6-(2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)benzonitrile

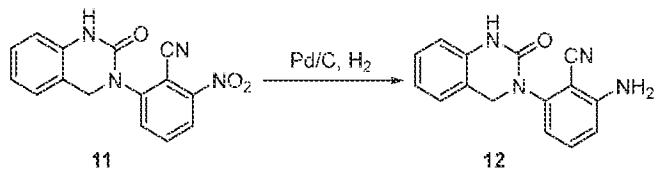


Proceeding as described in Example 2 above but substituting 3-chloropyridazine-4-carbonitrile with 2-fluoro-6-nitrobenzonitrile provided the title compound as a solid.

¹H NMR (DMSO-*d*6, 300 MHz); δ 10.05 (s, 1H), 8.32 (d, *J*=8.4 Hz, 1H), 8.17 (d, *J*=8.3 Hz, 1H), 8.06 (t, *J*=8.3 Hz, 1H), 7.25 (t, *J*=7.7 Hz, 1H), 7.19 (d *J*=7.2 Hz, 1H), 6.99 (t, *J*=7.6 Hz, 1H), 6.93 (d, *J*=8.2 Hz, 1H), 4.93 (bs, 2H); LC/MS [M + H]⁺ = 295.2.

Example 12

Synthesis of 2-amino-6-(2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)benzonitrile

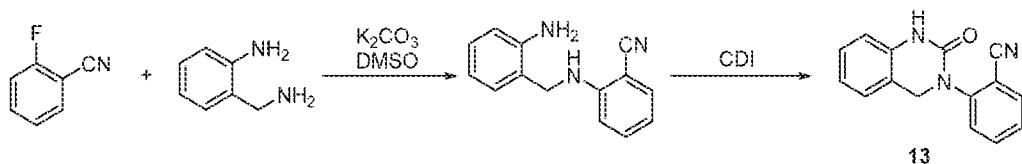


To a solution of 2-nitro-6-(2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)benzonitrile (210 mg; 0.714 mmol) in MeOH (4 mL) was added Pd/C (10% wt., 40 mg). The flask was evacuated and back filled with H₂ before it was stirred under H₂ (ballon). After it was stirred for 2 hrs, the catalyst was filtered through a short plug of celite and rinsed with 10% MeOH in DCM. The filtrate was concentrated and the residue was purified by trituration from hot DCM. The solid was collected by filtration to provide 2-amino-6-(2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)benzonitrile as a solid.

¹H NMR (DMSO-*d*6, 300 MHz); δ 9.70 (s, 1H), 7.30–7.39 (m, 1H), 7.13–7.25 (m, 2H), 6.93 (t, *J*=7.65 Hz, 1H), 6.87 (d, *J*=7.93 Hz, 1H), 6.64–6.76 (m, 2H), 6.10 (bs, 2H), 4.75 (bs, 2H); LC/MS [M + H] = 265.1.

Example 13

Synthesis of 2-(2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)benzonitrile



Step 1:

To a solution of 2-fluorobenzonitrile (218 mg, 2.0 mmol) and 2-aminobenzylamine (244 mg, 2.0 mmol) in DMSO (2.4 ml) was added K₂CO₃ (332 mg, 2.4 mmol) at room temperature. The resulting mixture was stirred at 85°C overnight. It was allowed to cool to room temperature. The crude reaction mixture was diluted with EtOAc (15 mL) and water (10 mL). The aqueous layer was extracted with EtOAc (2x15 mL). The combined organic layer was washed with brine, dried (MgSO₄) and concentrated. The crude 2-((2-amino-benzyl)amino)benzonitrile was used in the next step directly without further purification.

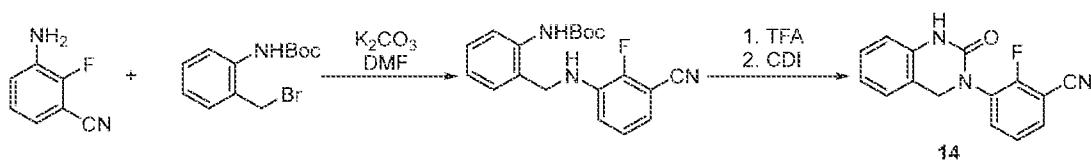
Step 2:

To a solution of crude 2-((2-aminobenzyl)amino)benzonitrile in DMF (2.4 mL) was added CDI (389 mg, 2.4 mmol) at room temperature, the reaction mixture was stirred for 48 hours before it was diluted with EtOAc (15 mL) and water (10 mL). The aqueous layer was extracted with EtOAc (2x15 mL). The combined organic layer was washed with brine, dried (MgSO₄) and concentrated. The crude was purified by flash SiO₂ column chromatography (0–20% EtOAc in Hexane) to provide the desired product 2-(2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)benzonitrile as a white solid.

¹H NMR (DMSO-*d*6, 300 MHz) δ 9.86 (s, 1H), 7.78–7.89 (m, 2H), 7.69–7.71 (d, *J* = 7.6 Hz, 1H), 7.47–7.52 (td, *J* = 15.3, 1.0 Hz 1H), 7.17–7.24 (m, 2H), 6.89–6.99 (m, 2H), 4.86 (s, 2H); LC/MS [M + H] = 250.2.

Example 14

Synthesis of 2-fluoro-3-(2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)benzonitrile



Step 1:

To a solution of *tert*-butyl (2-(bromomethyl)phenyl)carbamate (200 mg, 0.70 mmol) in dry diisopropylformamide (2 mL) was added 3-amino-2-fluorobenzonitrile (109 mg, 0.80 mmol) and followed by the addition of potassium carbonate (106 mg, 0.77 mmol). The mixture was stirred for 3 hours under argon atmosphere before the organic volatile was removed under reduced pressure. The crude residue was partitioned between EtOAc (25 mL) and water (25 mL). The organic layer was separated and concentrated. The resulting crude was purified by preparative TLC (eluting with 45% EtOAc in hexanes) to provide *tert*-butyl (2-(((3-cyano-2-fluorophenyl)amino)methyl)phenyl)carbamate (169 mg) as a viscous oil.

Step 2:

To a solution of *tert*-butyl (2-(((3-cyano-2-fluorophenyl)amino)methyl)phenyl)- carbamate (169 mg, 0.49 mmol) in DCM (2 mL) was added TFA (1.5 mL) dropwise. The mixture was stirred for 1.5 hours before it was concentrated under reduced pressure. The residue was taken up in DCM (10 mL) and concentrated again. The crude residue was taken up in DCM (20 mL) and 5% aqueous NaHCO₃ solution (20 mL). The organic layer was washed with H₂O (20 mL) and separated. The aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic layer was dried over Na₂SO₄, filtered and concentrated. The crude product was used directly in the next step without further purification.

Step 3:

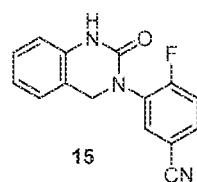
The crude diamine product obtained from the previous step was taken up in dry THF (2 mL) and Et₃N (0.2 mL, 1.49 mmol) followed by the addition of carbonyl diimidazole (195 mg, 1.20 mmol). The mixture was stirred under argon atmosphere overnight before it was diluted with EtOAc (25 mL) and washed with brine (25 mL). The organic phase was collected and the aqueous phase was extracted with EtOAc (2 x 25 mL). The combined organic phase was dried over Na₂SO₄, filtered and concentrated. The crude product was purified by preparative TLC (eluting first with 60% EtOAc in hexanes and then 1.5–3%

MeOH in DCM) to provide 2-fluoro-3-(2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)benzonitrile (62 mg) as a solid.

¹H NMR (CDCl₃, 300 MHz); δ 8.52 (bs, 1H), 7.67–7.75 (m, 1H), 7.58–7.65 (m, 1H), 7.31–7.38 (m, 1H), 7.19–7.28 (m, 1H), 7.08 (d, *J*=7.9 Hz, 1H), 6.98–7.05 (m, 1H), 6.80 (d, *J*=7.9 Hz, 1H), 4.81 (s, 2H); LC/MS [M + H] = 268.1.

Example 15

Synthesis of 4-fluoro-3-(2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)benzonitrile

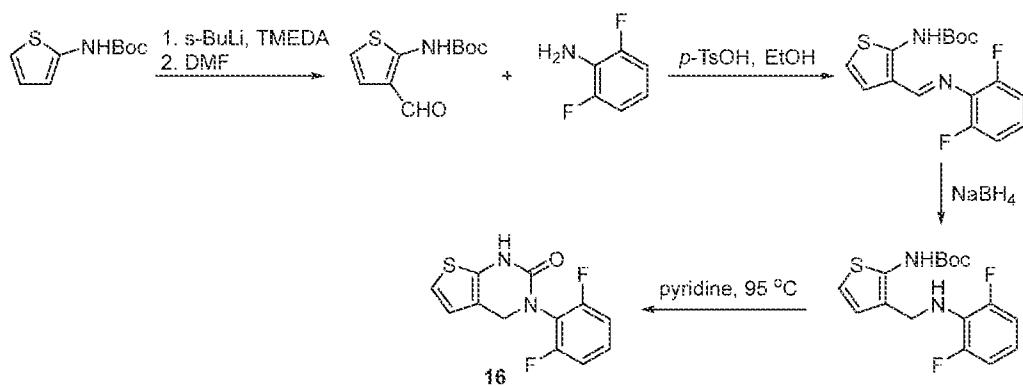


Proceeding as described in Example 14 above but substituting 3-amino-2-fluorobenzonitrile with 3-amino-4-fluorobenzonitrile provided the title compound as a solid.

¹H NMR (CDCl₃, 300 MHz); δ 8.27 (bs, 1H), 7.75 (dd, *J*=6.9, 2.1 Hz, 1H), 7.59–7.66 (m, 1H), 7.18–7.34 (m, 2H), 7.07 (d, *J*=6.6 Hz, 1H), 6.97–7.04 (m, 1H), 6.79 (d, *J*=7.9 Hz, 1H), 4.79 (s, 2H); LC/MS [M + H] = 268.1.

Example 16

Synthesis of 3-(2,6-difluorophenyl)-3,4-dihydrothieno[2,3-d]pyrimidin-2(1*H*)-one



Step 1:

An oven dried flask under argon atmosphere was charged with *tert*-butyl thiophen-2-ylcarbamate (1.5 g, 7.53 mmol) and TMEDA (2.82 mL, 18.82 mmol) in dry THF (15 mL).

The mixture was cooled to -40 °C and followed by addition of a solution of s-BuLi (15.7 mL;

1.2 M in cyclohexanes) dropwise. The reaction mixture was stirred and then allowed to warm up to -10 °C slowly over 1 h. The flask was again cooled back to -40 °C and followed by addition of DMF (1.57 mL; 20.33 mmol) dropwise. The mixture was then stirred and allowed to warm up to ambient temperature 16 hr. The reaction mixture was quenched via addition of a saturated aq. NH₄Cl solution (50 mL) and extracted with EtOAc (50 mL). The organic phase was collected and the aqueous phase was further extracted with EtOAc (2x40 mL). The combined organic phase was dried (MgSO₄), filtered and concentrated. The crude was purified by CombiFlash silica gel column chromatography (0–40% EtOAc in hexanes) to provide *tert*-butyl (3-formylthiophen-2-yl)carbamate (905 mg, 53%) as an oil.

Step 2:

To a solution of *tert*-butyl (3-formylthiophen-2-yl)carbamate (643 mg, 2.83 mmol) in absolute EtOH (3 mL) under argon atmosphere was added 2,6-difluoroaniline (0.82 mL, 5.49 mmol) and followed by *p*-toluene sulfonic acid monohydrate (10 mg). The reaction mixture was stirred for 30 minutes and then the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography (20% EtOAc in hexanes) to provide *tert*-butyl (*E*)-(3-(((2,6-difluorophenyl)imino)methyl)thiophen-2-yl)carbamate (990 mg) as an oil.

Step 3:

A solution of *tert*-butyl (*E*)-(3-(((2,6-difluorophenyl)imino)methyl)thiophen-2-yl)carbamate (985 mg, 2.81 mmol) in absolute EtOH (15 mL) was cooled to 0 °C. To this was added powdered NaBH₄ (1.5 g, 39.62 mmol) followed *p*-toluene sulfonic acid monohydrate (250 mg, 0.4 mmol). The mixture was stirred for 10 minutes and then warmed to ambient temperature and stirred further overnight. The reaction mixture was concentrated and the residue was partitioned between EtOAc (50 mL) and 50% diluted brine (50 mL). The organic phase collected and the aqueous phase was further extracted with EtOAc (2 x 40 mL). The combined organic phase was dried (MgSO₄), filtered and concentrated. The crude was purified by preparative TLC (eluting with 16% EtOAc in hexanes) to provide *tert*-butyl (3-(((2,6-difluorophenyl)amino)methyl)thiophen-2-yl)carbamate (865 mg) as a powder.

Step 4:

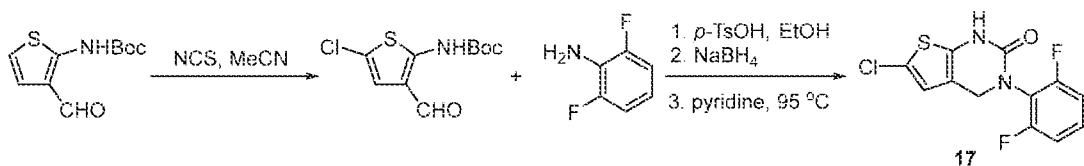
A solution of *tert*-butyl (3-(((2,6-difluorophenyl)amino)methyl)thiophen-2-yl)- carbamate (131 mg, 0.38 mmol) in dry pyridine (1 mL) under argon atmosphere was stirred at 95 °C for 45 hours before the solvent was removed under reduced pressure. The residue

was purified by preparative TLC (elute with 1.5–2% MeOH in DCM first and then 50% EtOAc in hexanes) to provide *tert*-butyl 3-(2,6-difluorophenyl)-3,4-dihydrothieno[2,3-d]pyrimidin-2(1*H*)-one (17 mg) as a solid.

¹H NMR (CDCl₃, 300 MHz); δ 8.60 (bs, 1H), 7.24–7.37 (m, 1H), 6.95–7.07 (m, 2H), 6.70 (d, J=5.4 Hz, 1H), 6.60 (d, J=5.3 Hz, 1H), 4.75 (s, 2H); LC/MS [M + H] = 267.1.

Example 17

Synthesis of 6-chloro-3-(2,6-difluorophenyl)-3,4-dihydrothieno[2,3-d]pyrimidin-2(1*H*)-one



Step 1:

To a solution of *tert*-butyl (3-formylthiophen-2-yl)carbamate (487 mg, 2.14 mmol) in dry CH₃CN (6 mL) under argon atmosphere was added *N*-chlorosuccinimide (316 mg, 2.37 mmol). The mixture was heated to 55 °C for 4 hours before it was concentrated. The crude residue was purified by preparative TLC (eluting with 16% EtOAc in hexane) to provide *tert*-butyl (5-chloro-3-formylthiophen-2-yl)carbamate (905 mg, 53%) as an oil.

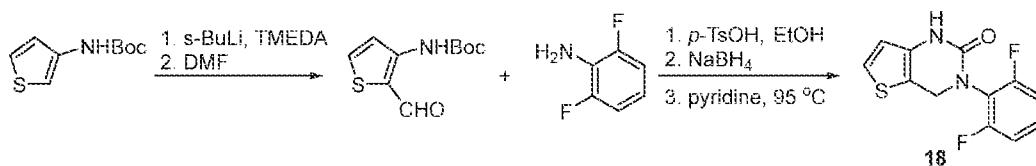
Steps 2 – 4:

Proceeding as described in Example 16 above but substituting *tert*-butyl (3-formylthiophen-2-yl)carbamate with *tert*-butyl (5-chloro-3-formylthiophen-2-yl)carbamate provided the title compound as a solid.

¹H NMR (CDCl₃, 300 MHz); δ 9.09 (s, 1H), 7.25–7.38 (m, 1H), 6.94–7.06 (m, 2H), 6.45 (s, 1H), 4.64 (s, 2H); LC/MS [M + H] = 301.1.

Example 18

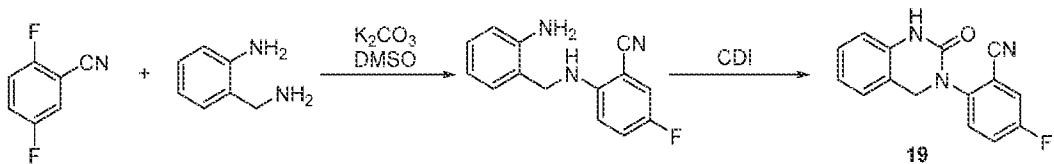
Synthesis of 3-(2,6-difluorophenyl)-3,4-dihydrothieno[3,2-d]pyrimidin-2(1*H*)-one



Proceeding as described in Example 16 above but substituting *tert*-butyl thiophen-2-ylcarbamate with *tert*-butyl thiophen-3-ylcarbamate provided the title compound as a solid. ¹H NMR (CDCl₃, 300 MHz); δ 8.67 (bs, 1H), 7.27–7.39 (m, 1H), 7.14 (d, *J*=5.2 Hz, 1H), 6.98–7.08 (m, 2H), 6.58 (d, *J*=5.2 Hz, 1H), 4.88 (s, 2H); LC/MS [M + H] = 267.1.

Example 19

Synthesis of 5-fluoro-2-(2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)benzonitrile



Step 1:

To a solution of 2,5-difluorobenzonitrile (278 mg, 2.0 mmol) and 2-aminobenzylamine (244 mg, 2.0 mmol) in DMSO (2.4 mL) was added K₂CO₃ (332 mg, 2.4 mmol) at room temperature. The resulting mixture was stirred at 85°C overnight before it was allowed to cool to room temperature and diluted with EtOAc (15 mL) and water (10 mL). The aqueous layer was extracted with EtOAc (2x15 mL). The combined organic layer was washed with brine, dried (MgSO₄) and concentrated. The crude 2-((2-amino-benzyl)amino)-5-fluorobenzonitrile was used in the next step with no purification.

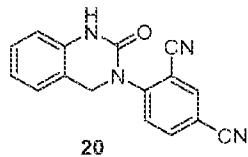
Step 2:

To a solution of crude 2-((2-aminobenzyl)amino)-5-fluorobenzonitrile in DMF (2.4 ml) was added CDI (389 mg, 2.4 mmole) at room temperature, the reaction mixture was stirred for 48 hours before it was diluted with EtOAc (15 mL) and water (10 mL). The aqueous layer was extracted with EtOAc (2x15 mL). The combined organic layer was washed with brine, dried (MgSO₄) and concentrated. The crude was purified by flash SiO₂ column chromatography (0 – 20% EtOAc in hexane) to provide the desired product 5-fluoro-2-(2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)benzonitrile as a white solid.

¹H NMR (DMSO-*d*6, 300 MHz) δ 9.87 (s, 1H), 7.90–7.93 (dd, *J* = 8.4, 2.6 Hz, 1H), 7.69–7.79 (m, 2H), 7.16–7.25 (m, 2H), 6.88–6.99 (m, 2H), 4.85 (s, 2H); LC/MS [M + H] = 268.1.

Example 20

Synthesis of 4-(2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)isophthalonitrile

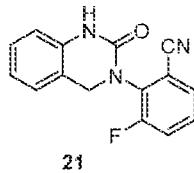


Proceeding as described in Example 19 above but substituting 2,5-difluorobenzo-nitrile with 2-fluoroterephthalonitrile provided the title compound as a white solid.

¹H NMR (DMSO-*d*6, 300 MHz) δ 10.13 (s, 1H), 8.48–8.49 (d, *J*=1.8 Hz, 1H), 8.27–8.30 (dd, *J*=8.6, 1.9 Hz, 1H), 7.85–7.88 (d, *J*=8.5 Hz, 1H), 7.19–7.27 (m, 2H), 6.91–7.02 (m, 2H), 4.94 (s, 2H); LC/MS [M + H] = 275.1.

Example 21

Synthesis of 3-fluoro-2-(2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)benzonitrile

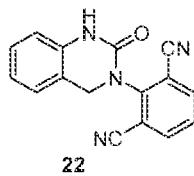


Proceeding as described in Example 19 above but substituting 2,5-difluorobenzo-nitrile with 2,3-difluorobenzonitrile provided the title compound as a white solid.

¹H NMR (DMSO-*d*6, 300 MHz) δ 9.91 (s, 1H), 7.76–7.83 (m, 2H), 7.60–7.67 (m, 1H), 7.16–7.26 (m, 2H), 6.90–7.00 (m, 2H), 4.86 (q, *J*=25.1,14.2 Hz, 2H); LC/MS [M + H] = 268.1.

Example 22

Synthesis of 2-(2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)isophthalonitrile

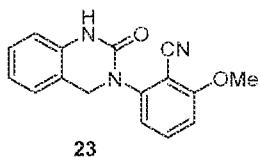


Proceeding as described in Example 19 above but substituting 2,5-difluorobenzo-nitrile with 2-chloroisophthalonitrile provided the title compound as a white solid.

¹H NMR (DMSO-*d*6, 300 MHz) δ 10.05 (s, 1H), 8.33–8.35 (d, *J*=7.9 Hz, 2H), 7.77–7.83 (t, *J*=8.1 Hz, 1H), 7.18–7.29 (m, 2H), 6.93–7.03 (m, 2H), 4.89 (s, 2H); LC/MS [M + H] = 275.1.

Example 23

Synthesis of 2-methoxy-6-(2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)benzonitrile

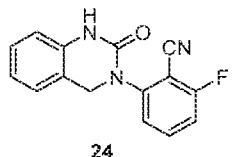


Proceeding as described in Example 19 above but substituting 2,5-difluorobenzonitrile with 2-fluoro-6-methoxybenzonitrile provided the title compound as a white solid.

¹H NMR (DMSO-*d*6, 300 MHz) δ 9.82 (s, 1H), 7.70–7.76 (t, *J*=8.24 Hz, 1H), 7.16–7.24 (m, 4H), 6.88–6.98 (m, 2H), 4.82 (s, 2H); LC/MS [M + H] = 280.1.

Example 24

Synthesis of 2-fluoro-6-(2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)benzonitrile

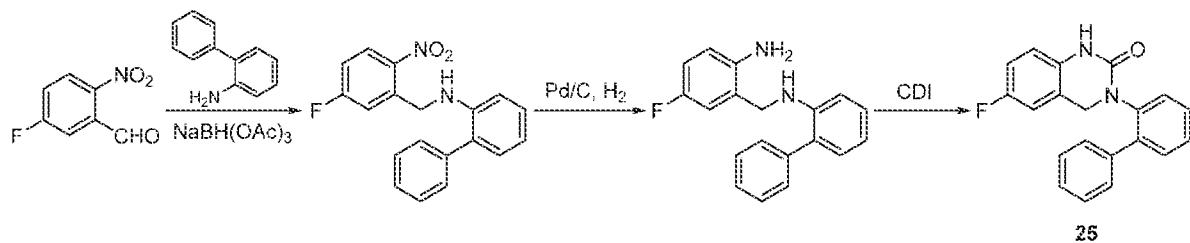


Proceeding as described in Example 19 above but substituting 2,5-difluorobenzonitrile with 2,6-difluorobenzonitrile provided the title compound as a solid.

¹H NMR (DMSO-*d*6, 300 MHz) δ 9.99 (s, 1H), 7.83–7.91 (q, *J*=15.6, 7.6 Hz, 1H), 7.56–7.57 (d, *J*=8.2 Hz, 1H), 7.43–7.49 (t, *J*=8.6 Hz, 1H), 7.18–7.26 (m, 2H), 6.91–7.00 (m, 2H), 4.90 (s, 2H); LC/MS [M + H] = 268.1.

Example 25

Synthesis of 3-([1,1'-biphenyl]-2-yl)-6-fluoro-3,4-dihydroquinazolin-2(1*H*)-one



Step 1:

While under nitrogen, a solution of 5-fluoro-2-nitrobenzaldehyde (240 mg, 1.4 mmol) and [1,1'-biphenyl]-2-amine (240 mg, 1.4 mmol) in dichloromethane (5 mL) was treated with acetic acid (0.09 mL, 1.6 mmol) and warmed to 50 °C for 3 h. After cooling to room temperature, sodium triacetoxyborohydride (449 mg, 2.1 mmol) was added and stirring was continued for approximately 16 h. Once complete, the reaction was quenched with saturated aqueous sodium bicarbonate (50 mL), extracted with ethyl acetate (3x 25 mL), washed with saturated aqueous sodium chloride (60 mL), dried over sodium sulfate, filtered and concentrated. Purification medium pressure liquid chromatography (MPLC) (silica, 25 g, 5-90% hexanes in ethyl acetate) gave *N*-(5-fluoro-2-nitrobenzyl)-[1,1'-biphenyl]-2-amine as a light yellow solid (330 mg, 72%).

Step 2:

A solution of *N*-(5-fluoro-2-nitrophenyl)methyl-[1,1'-biphenyl]-2-amine (320 mg, 0.99 mmol) and Pd/C (10% wt., 105 mg, 0.1 mmol) in ethyl acetate was purged with nitrogen, evacuated and treated with hydrogen (balloon). After stirring for 4 h, the reaction vessel was evacuated, purged with nitrogen and filtered through a pad of Celite. The Celite was washed with ethyl acetate and the combined filtrate was concentrated to give crude *N*-(2-amino-5-fluorobenzyl)-[1,1'-biphenyl]-2-amine as an off-white solid (280 mg, 96%) that was used in subsequent step without further purification.

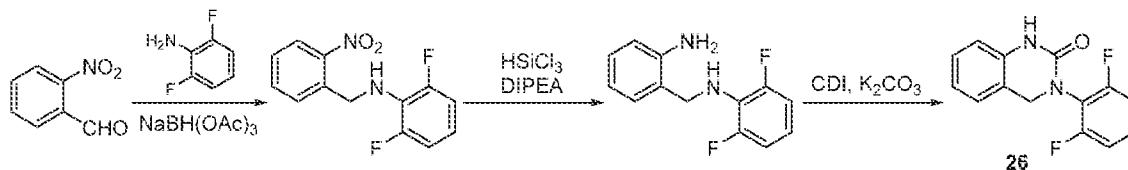
Step 3:

While under nitrogen, a solution of crude *N*-(2-amino-5-fluorophenyl)methyl-[1,1'-bi-phenyl]-2-amine (280 mg, 0.96 mmol) in THF (8 mL) was treated with 1,1'-carbonyldiimidazole (310 mg, 1.92 mmol) and warmed to 65 °C. After stirring for 14 h, the solution was allowed to cool to room temperature and concentrated. The resulting residue was purified by MPLC (5-50% ethyl acetate in hexanes) to give the title compound was isolated as off-white solid (220 mg, 72%).

¹H NMR (400 MHz, DMSO-*d*6) δ ppm 9.37 (s, 1H), 7.61–7.16 (m, 9H), 6.95 (td, *J*= 8.8, 2.9 Hz, 1H), 6.84 (dd, *J*= 9.0, 2.9 Hz, 1H), 6.75 (dd, *J*= 8.8, 4.8 Hz, 1H), 4.62 (d, *J*= 14.9 Hz, 1H), 4.13 (d, *J*= 14.8 Hz, 1H).

Example 26

Synthesis of 3-(2,6-difluorophenyl)-3,4-dihydroquinazolin-2(1*H*)-one



Step 1:

While under nitrogen, a solution of 2,6-difluoroaniline (0.834 mL, 7.75 mmol) in TFA (17.4 mL) was cooled to 0°C and treated with sodium triacetoxyborohydride (3.27 g, 15.5 mmol) as one portion. After stirring at for 10 min, 2-nitrobenzaldehyde (1.24 g, 8.22 mmol) was added and the ice-bath was removed. After stirring an additional 20 h, the reaction mixture was concentrated, and the residue poured into cold water and extracted with ethyl acetate. The combined organic solution was successively washed with water, saturated aqueous sodium bicarbonate and saturated aqueous ammonium chloride. The resulting solution was dried over anhydrous magnesium sulfate and concentrated. Purification by medium pressure liquid chromatography (MPLC) (Biotage column eluting with 0-15% ethyl acetate in hexanes) gave 2,6-difluoro-*N*-(2-nitrobenzyl)aniline as a pale yellow oil (2.02 g, 99% yield).

¹H NMR (400 MHz, CDCl₃) δ 8.10–7.99 (m, 1H), 7.63–7.51 (m, 2H), 7.42 (ddd, *J*=8.6, 6.2, 2.7 Hz, 1H), 6.78 (td, *J*=8.4, 7.9, 1.6 Hz, 2H), 6.72–6.58 (m, 1H), 4.76 (s, 2H).

Step 2:

While under nitrogen, a solution of 2,6-difluoro-*N*-(2-nitrophenyl)methylaniline (2.02 g, 7.645 mmol) and diisopropylethylamine (7.58 mL, 45.9 mmol) in dry DCM (57.3 mL) was cooled to 0 °C and treated with a separate solution of HSiCl₃ (3.86 mL, 38.22 mmol) in dry dichloromethane (28.7 mL) over 10 min. Once the addition was complete, the ice-bath was removed and stirring was continued at room temperature. After approximately 18 h, the reaction mixture was re-cooled with an ice-bath and carefully quenched with

saturated aqueous of Na₂CO₃ (60 mL). The biphasic mixture was stirred for 4 h, filtered through Celite. The resulting filtrate was extracted with ethyl acetate, dried over MgSO₄, filtered and concentrated to give *N*-(2-aminobenzyl)-2,6-difluoroaniline as a yellow solid (1.58 g, 88% yield).

¹H NMR (500 MHz, CDCl₃) δ 7.18–7.12 (m, 2H), 6.86 (td, *J*=8.3, 1.5 Hz, 2H), 6.81–6.72 (m, 3H), 4.39 (s, 2H).

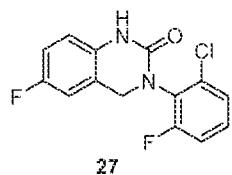
Step 3:

While under nitrogen, a solution of *N*-(2-aminobenzyl)-2,6-difluoroaniline (1.061 g, 4.53 mmol) and K₂CO₃ (868 mg, 6.28 mmol) in anhydrous THF (27.6 mL) was cooled in to 0 °C and carefully treated with a separate solution of triphosgene (1.400 g, 4.71 mmol) in THF (16.6 mL). Once the addition was complete, stirring was continued for 10 min at 0 °C, then 1 h at room temperature. The solution was concentrated, diluted with water and filtered. The resulting solid was washed successively with diethyl ether and aqueous acetonitrile to give the title compound as a white solid (1.005 g, 85% yield).

¹H NMR (500 MHz, DMSO-*d*₆) δ 9.75 (s, 1H), 7.50–7.40 (m, 1H), 7.22 (dt, *J*=12.2, 8.1 Hz, 3H), 7.14 (d, *J*=7.5 Hz, 1H), 6.95 (t, *J*=7.5 Hz, 1H), 6.88 (d, *J*=7.9 Hz, 1H), 4.72 (s, 2H); LC/MS [M + H] = 261.1.

Example 27

Synthesis of 3-(2-chloro-6-fluorophenyl)-6-fluoro-3,4-dihydroquinazolin-2(1*H*)-one

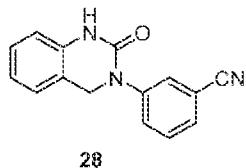


Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine with 2-chloro-6-fluoroaniline provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 9.74 (s, 1H), 7.46 (dd, *J*=3.7, 2.5 Hz, 2H), 7.39 (td, *J*=6.2, 2.8 Hz, 1H), 7.07 (t, *J*=8.4 Hz, 2H), 6.88 (ddd, *J*=8.0, 4.9, 1.3 Hz, 1H), 4.68 (s, 2H).

Example 28

Synthesis of 3-(2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)benzonitrile

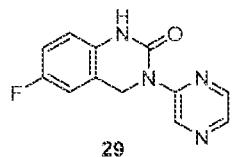


Proceeding as described in Example 26 above but substituting 2,6-difluoroaniline with 3-cyanoaniline provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 7.75 (bs, 1H), 7.72 (s, 1H), 7.70–7.65 (m, 1H), 7.54 (s, 1H), 7.53–7.52 (m, 1H), 7.27 (dt, *J*=1, 8.4 Hz, 1H), 7.13 (d, *J*=7.0 Hz, 1H), 7.04 (t, *J*=7.5 Hz, 1H), 6.82 (d, *J*=7.74 Hz, 1H); LC/MS [M + H] = 250.1.

Example 29

Synthesis of 6-fluoro-3-(pyrazin-2-yl)-3,4-dihydroquinazolin-2(1*H*)-one

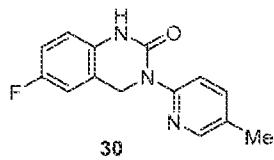


Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine with 2-amino-pyrazine provided the title compound as a solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 10.12 (s, 1H), 9.06 (s, 1H), 8.48 (s, 1H), 8.33 (s, 1H), 7.23 (s, 1H), 7.06 (t, *J*=8.0 Hz, 1H), 6.95–6.91 (m, 1H), 4.99 (s, 2H).

Example 30

Synthesis of 6-fluoro-3-(5-methylpyridin-2-yl)-3,4-dihydroquinazolin-2(1*H*)-one

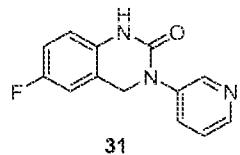


Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine with 2-amino-5-methylpyridine provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.84 (s, 1H), 8.24 (m, 1H), 7.59–7.62 (m 2H), 7.18–7.21 (m, 1H), 7.03–7.06 (m, 1H), 6.87–6.91 (m, 1H), 4.95 (s, 2H), 2.28 (s, 3H).

Example 31

Synthesis of 6-fluoro-3-(pyridin-3-yl)-3,4-dihydroquinazolin-2(*H*)-one

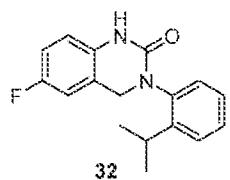


Proceeding as described in Example 25 above but substituting 2,6-difluoroaniline with 3-aminopyridine provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.78 (s, 1H), 8.62 (d, *J*=2.5 Hz, 1H), 8.40 (dd, *J*=4.7, 1.5 Hz, 1H), 7.81 (ddd, *J*=8.2, 2.7, 1.5 Hz, 1H), 7.43 (dd, *J*=8.2, 4.7 Hz, 1H), 7.07 (t, *J*=8.4 Hz, 2H), 6.89 (ddd, *J*=7.9, 4.9, 1.2 Hz, 1H), 4.88 (s, 2H).

Example 32

Synthesis of 6-fluoro-3-(2-isopropylphenyl)-3,4-dihydroquinazolin-2(*H*)-one

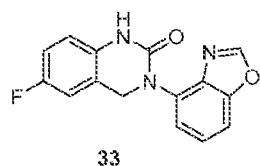


Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine with 2-isopropylaniline provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.49 (s, 1H), 7.56–7.16 (m, 4H), 7.04 (t, *J*=8.2 Hz, 2H), 6.90–6.71 (m, 1H), 4.84 (d, *J*=14.8 Hz, 1H), 4.44 (d, *J*=14.9 Hz, 1H), 3.10–2.84 (m, 1H), 1.13 (dd, *J*=6.9, 1.1 Hz, 6H).

Example 33

Synthesis of 3-(benzo[d]oxazol-4-yl)-6-fluoro-3,4-dihydroquinazolin-2(*H*)-one

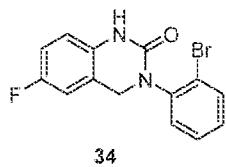


Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine with benzo[d]oxazol-4-amine provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.72 (s, 1H), 8.75 (s, 1H), 7.70 (dd, *J*=8.0, 1.1 Hz, 1H), 7.57–7.32 (m, 2H), 7.08 (d, *J*=9.1 Hz, 2H), 6.94–6.81 (m, 1H), 4.95 (s, 2H).

Example 34

Synthesis of 3-(2-bromophenyl)-6-fluoro-3,4-dihydroquinazolin-2(1*H*)-one

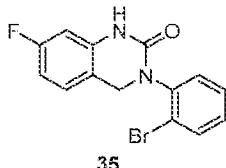


Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine with 2-bromoaniline provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.62 (s, 1H), 7.51–7.27 (m, 3H), 7.22 (td, *J*=6.6, 3.3 Hz, 1H), 7.06 (ddd, *J*=17.4, 8.9, 2.9 Hz, 2H), 6.87 (dd, *J*=8.6, 4.8 Hz, 1H), 4.81 (s, 2H).

Example 35

Synthesis of 3-(2-bromophenyl)-7-chloro-3,4-dihydroquinazolin-2(1*H*)-one

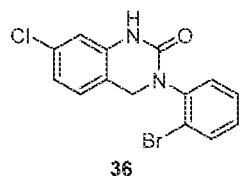


Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine and 5-fluoro-2-nitrobenzaldehyde with 2-bromoaniline and 4-fluoro-2-nitrobenzaldehyde provided the title compound as a white solid.

¹H NMR (300 MHz, DMSO-*d*6) δ 9.70 (s, 1H), 7.73 (dd, *J*=8.0, 1.5 Hz, 1H), 7.56 (dd, *J*=7.8, 1.7 Hz, 1H), 7.48 (dt, *J*=7.3, 1.3 Hz, 1H), 7.31 (dt, *J*=7.7, 1.7 Hz, 1H), 7.21–7.16 (m, 1H), 6.75 (dt, *J*=8.8, 2.8 Hz, 1H), 6.54 (dd, *J*=10.3, 2.5 Hz, 1H), 4.70 (dd, *J*=39.0, 13.7 Hz, 1H).

Example 36

Synthesis of 3-(2-bromophenyl)-7-chloro-3,4-dihydroquinazolin-2(1*H*)-one

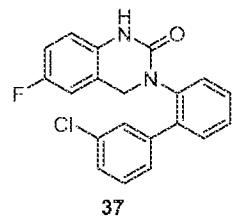


Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine and 5-fluoro-2-nitrobenzaldehyde with 2-bromoaniline and 4-chloro-2-nitrobenzaldehyde provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.71 (s, 1H), 7.73 (dd, *J*=8.0, 1.0 Hz, 1H), 7.45–7.57 (m, 2H), 7.29 (t, *J*=4.0 Hz, 1H), 7.18 (td, *J*=8.0, 4.0 Hz, 1H), 6.72–6.77 (m, 1H), 6.64 (d, *J*=8.0 Hz, 1H), 4.76 (d, *J*=12.0 Hz, 1H), 4.59 (d, *J*=12.0 Hz, 1H).

Example 37

Synthesis of 3-(3'-chloro-[1,1'-biphenyl]-2-yl)-6-fluoro-3,4-dihydroquinazolin-2(*1H*)-one

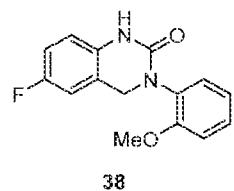


Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine with 3'-chloro-[1,1'-biphenyl]-2-amine provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.42 (s, 1H), 7.71–7.15 (m, 8H), 7.09–6.85 (m, 2H), 6.76 (dd, *J*=8.8, 4.8 Hz, 1H), 4.74 (d, *J*=14.8 Hz, 1H), 4.26 (d, *J*=14.8 Hz, 1H).

Example 38

Synthesis of 6-fluoro-3-(2-methoxyphenyl)-3,4-dihydroquinazolin-2(*1H*)-one

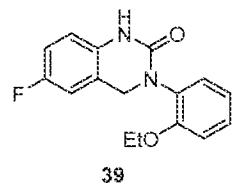


Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine with 2-methoxyaniline provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.42 (s, 1H), 7.37–7.20 (m, 2H), 7.10 (dd, *J*=8.3, 1.2 Hz, 1H), 7.03–6.92 (m, 3H), 6.83 (dd, *J*=9.6, 4.9 Hz, 1H), 4.62 (s, 2H), 3.78 (s, 3H).

Example 39

Synthesis of 6-fluoro-3-(2-ethoxyphenyl)-3,4-dihydroquinazolin-2(1*H*)-one

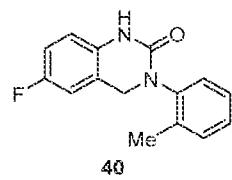


Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine with 2-ethoxyaniline provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.42 (s, 1H), 7.32–7.19 (m, 2H), 7.13–6.90 (m, 4H), 6.84 (dd, *J*=5.9, 3.5 Hz, 1H), 4.63 (s, 2H), 4.05 (q, *J*=7.0 Hz, 2H), 1.26 (t, *J*=7.0 Hz, 3H).

Example 40

Synthesis of 6-fluoro-3-(o-tolyl)-3,4-dihydroquinazolin-2(1*H*)-one

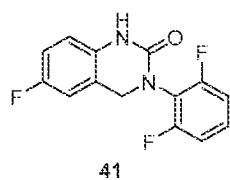


Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine with 2-methylaniline provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.50 (s, 1H), 7.41–7.17 (m, 4H), 7.04 (ddd, *J*=8.9, 4.7, 1.9 Hz, 2H), 6.95–6.76 (m, 1H), 4.84 (d, *J*=14.8 Hz, 1H), 4.52 (d, *J*=14.8 Hz, 1H), 2.14 (s, 3H); LC/MS [M + H] = 257.1.

Example 41

Synthesis of 3-(2,6-difluorophenyl)-6-fluoro-3,4-dihydroquinazolin-2(1*H*)-one

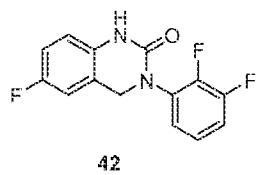


Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine with 2,6-difluoroaniline provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.80 (s, 1H), 7.57–7.38 (m, 1H), 7.24 (t, *J*=8.3 Hz, 2H), 7.06 (tt, *J*=8.2, 4.3 Hz, 2H), 6.88 (dd, *J*=8.6, 4.8 Hz, 1H), 4.72 (s, 2H); LC/MS [M + H] = 279.1.

Example 42

Synthesis of 3-(2,3-difluorophenyl)-6-fluoro-3,4-dihydroquinazolin-2(1*H*)-one

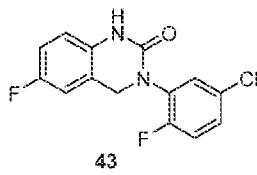


Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine with 2,3-difluoroaniline provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.81 (s, 1H), 7.49–7.32 (m, 2H), 7.31–7.22 (m, 1H), 7.13–7.01 (m, 2H), 6.88 (dd, *J*=9.6, 4.8 Hz, 1H), 4.80 (s, 2H).

Example 43

Synthesis of 3-(5-chloro-2-fluorophenyl)-6-fluoro-3,4-dihydroquinazolin-2(1*H*)-one

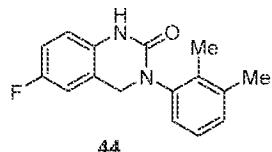


Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine with 3-chloro-6-fluoroaniline provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.71 (s, 1H), 7.69–7.48 (m, 2H), 7.28 (ddd, *J* = 8.9, 8.0, 3.1 Hz, 1H), 7.10–7.00 (m, 2H), 6.86 (dd, *J* = 9.6, 4.8 Hz, 1H), 5.00–4.46 (m, 2H).

Example 44

Synthesis of 3-(2,3-dimethylphenyl)-6-fluoro-3,4-dihydroquinazolin-2(1*H*)-one

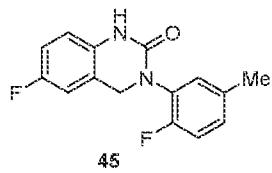


Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine with 2,3-dimethylaniline provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.47 (s, 1H), 7.26–7.09 (m, 3H), 7.09–6.95 (m, 2H), 6.85 (dd, *J* = 9.5, 4.9 Hz, 1H), 4.80 (d, *J* = 14.8 Hz, 1H), 4.49 (d, *J* = 14.9 Hz, 1H), 2.26 (s, 3H), 2.02 (s, 3H).

Example 45

Synthesis of 6-fluoro-3-(2-fluoro-5-methylphenyl)-3,4-dihydroquinazolin-2(1*H*)-one

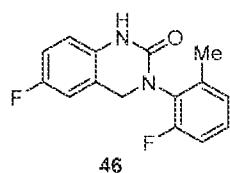


Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine with 2-fluoro-5-methylaniline provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.66 (s, 1H), 7.35–7.26 (m, 1H), 7.25–7.10 (m, 2H), 7.10–7.00 (m, 2H), 6.86 (dd, *J* = 9.6, 4.8 Hz, 1H), 4.73 (s, 2H), 2.30 (s, 3H).

Example 46

Synthesis of 6-fluoro-3-(2-fluoro-6-methylphenyl)-3,4-dihydroquinazolin-2(1*H*)-one

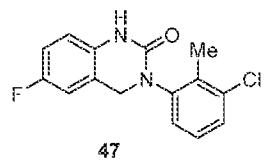


Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine with 2-fluoro-6-methylaniline provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.66 (s, 1H), 7.30 (t, *J*=7.6 Hz, 1H), 7.23 (t, *J*=6.9 Hz, 1H), 7.13 (t, *J*=7.7 Hz, 1H), 7.09–7.00 (m, 2H), 6.86 (dd, *J*=9.5, 4.9 Hz, 1H), 4.73 (s, 2H), 2.25 (s, 3H).

Example 47

Synthesis of 3-(3-chloro-2-methylphenyl)-6-fluoro-3,4-dihydroquinazolin-2(1*H*)-one

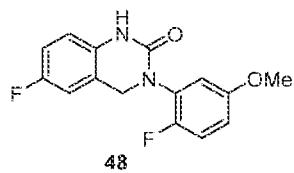


Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine with 3-chloro-2-methylaniline provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.60 (s, 1H), 7.43 (dd, *J*=8.0, 1.4 Hz, 1H), 7.38 (dd, *J*=8.0, 1.4 Hz, 1H), 7.30 (t, *J*=7.9 Hz, 1H), 7.09–6.99 (m, 2H), 6.92–6.79 (m, 1H), 4.87 (d, *J*=14.7 Hz, 1H), 4.54 (d, *J*=14.7 Hz, 1H), 2.16 (s, 3H).

Example 48

Synthesis of 6-fluoro-3-(2-fluoro-5-methoxyphenyl)-3,4-dihydroquinazolin-2(1*H*)-one

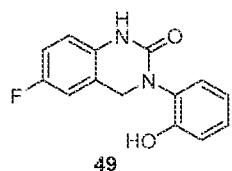


Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine with 2-fluoro-5-methoxyaniline provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.67 (s, 1H), 7.20 (dd, *J*=10.1, 9.1 Hz, 1H), 7.12–7.01 (m, 3H), 6.95–6.78 (m, 2H), 4.75 (s, 2H), 3.76 (s, 3H).

Example 49

Synthesis of 6-fluoro-3-(2-hydroxyphenyl)-3,4-dihydroquinazolin-2(1*H*)-one

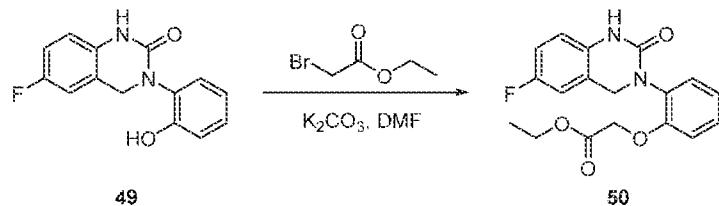


Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine with 2-hydroxyaniline provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.57 (s, 1H), 9.40 (s, 1H), 7.23–7.09 (m, 2H), 7.01 (dd, *J*=8.9, 7.0 Hz, 2H), 6.91 (dd, *J*=8.1, 1.4 Hz, 1H), 6.86–6.77 (m, 2H), 4.64 (s, 2H).

Example 50

Synthesis of ethyl 2-(2-(6-fluoro-2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)phenoxy)acetate

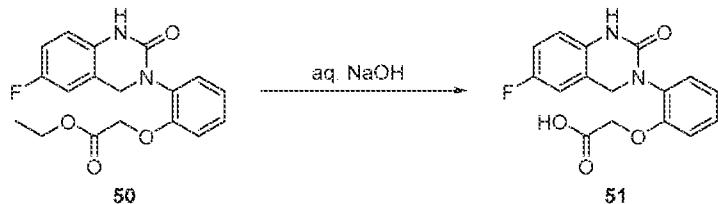


A solution of 6-fluoro-3-(2-hydroxyphenyl)-3,4-dihydroquinazolin-2(1*H*)-one (50 mg, 0.19 mmol) and ethyl bromoacetate (0.02 mL, 0.19 mmol) in DMF was treated with K₂CO₃ (40 mg, 0.29 mmol) and warmed to 65 °C. After stirring for 4 h, the heating bath was removed, and the reaction mixture cooled to room temperature. The solution was diluted with ethyl acetate and washed successively with water and saturated aqueous sodium chloride, dried over sodium sulfate, filtered and concentrated. Purification by MPLC (10–70% ethyl acetate in hexanes) gave the title compound as an off-white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.44 (s, 1H), 7.43–7.16 (m, 2H), 7.13–6.94 (m, 4H), 6.84 (ddd, *J*=7.7, 4.9, 1.5 Hz, 1H), 4.76 (d, *J*=46.2 Hz, 4H), 4.13 (q, *J*=7.1 Hz, 2H), 1.16 (t, *J*=7.1 Hz, 3H).

Example 51

Synthesis of 2-(2-(6-fluoro-2-oxo-1,4-dihydroquinazolin-3(2H)-yl)phenoxy)acetic acid



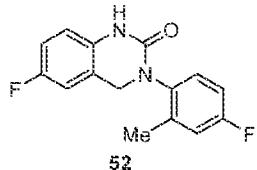
A solution of ethyl 2-(2-(6-fluoro-2-oxo-1,4-dihydroquinazolin-3(2H)-yl)phenoxy)-acetate in THF (30 mL) and methanol (15 mL) was treated with 2.0 N NaOH (15.1 mL).

After stirring for approximately 16 h, the reaction was quenched with 1 N HCl to pH 3 and the precipitated product was filtered to the title compound as white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 12.99 (s, 1H), 9.47 (s, 1H), 7.28 (t, *J*=7.6 Hz, 2H), 7.13–6.93 (m, 4H), 6.84 (dd, *J*=8.3, 4.8 Hz, 1H), 4.72 (d, *J*=8.2 Hz, 4H).

Example 52

Synthesis of 6-fluoro-3-(4-fluoro-2-methylphenyl)-3,4-dihydroquinazolin-2(1*H*)-one

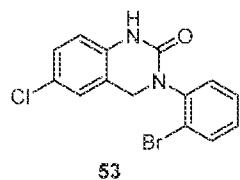


Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine with 4-fluoro-2-methylaniline provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.52 (s, 1H), 7.38 (dd, *J*=8.7, 5.6 Hz, 1H), 7.15 (dd, *J*=9.8, 3.0 Hz, 1H), 7.12–7.05 (m, 1H), 7.03 (d, *J*=8.8 Hz, 2H), 6.89–6.81 (m, 1H), 4.82 (d, *J*=14.7 Hz, 1H), 4.51 (d, *J*=14.8 Hz, 1H), 2.15 (s, 3H).

Example 53

Synthesis of 3-(2-bromophenyl)-6-chloro-3,4-dihydroquinazolin-2(1*H*)-one

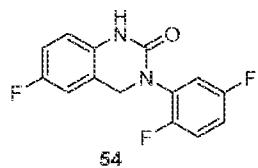


Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine and 5-fluoro-2-nitrobenzaldehyde with 2-bromoaniline and 5-chloro-2-nitrobenzaldehyde provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ ppm 9.71 (s, 1H), 7.73 (dd, *J*=8.0, 1.4 Hz, 1H), 7.55 (dd, *J*=7.9, 1.7 Hz, 1H), 7.47 (td, *J*=7.6, 1.5 Hz, 1H), 7.34–7.20 (m, 3H), 6.86 (d, *J*=8.3 Hz, 1H), 4.79 (d, *J*=14.6 Hz, 1H), 4.60 (d, *J*=14.6 Hz, 1H).

Example 54

Synthesis of 3-(2,5-difluorophenyl)-6-fluoro-3,4-dihydroquinazolin-2(*H*)-one

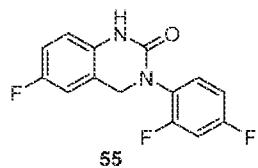


Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine with 2,5-difluoroaniline provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ ppm 9.77 (s, 1H), 7.48 (ddd, *J*=9.4, 6.1, 3.2 Hz, 1H), 7.35 (td, *J*=9.5, 5.1 Hz, 1H), 7.27–7.17 (m, 1H), 7.05 (d, *J*=8.8 Hz, 2H), 6.96–6.81 (m, 1H), 4.78 (s, 2H).

Example 55

Synthesis of 3-(2,4-difluorophenyl)-6-fluoro-3,4-dihydroquinazolin-2(*H*)-one

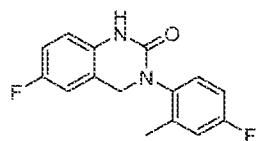


Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine with 2,4-difluoroaniline provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.70 (s, 1H), 7.58 (td, *J*=8.9, 6.1 Hz, 1H), 7.36 (ddd, *J*=10.7, 9.1, 2.9 Hz, 1H), 7.16 (ddt, *J*=10.3, 7.3, 1.5 Hz, 1H), 7.04 (d, *J*=8.7 Hz, 2H), 6.92–6.79 (m, 1H), 4.74 (s, 2H).

Example 56

Synthesis of 6-fluoro-3-(4-fluoro-2-methylphenyl)-3,4-dihydroquinazolin-2(*H*)-one

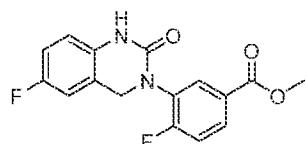


Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine with 2-methyl-4-fluoroaniline provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.52 (s, 1H), 7.38 (dd, *J*=8.7, 5.6 Hz, 1H), 7.15 (dd, *J*=9.8, 3.0 Hz, 1H), 7.12–7.05 (m, 1H), 7.03 (d, *J*=8.8 Hz, 2H), 6.89–6.81 (m, 1H), 4.82 (d, *J*=14.7 Hz, 1H), 4.51 (d, *J*=14.8 Hz, 1H), 2.15 (s, 3H).

Example 57

Synthesis of methyl 4-fluoro-3-(6-fluoro-2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)benzoate



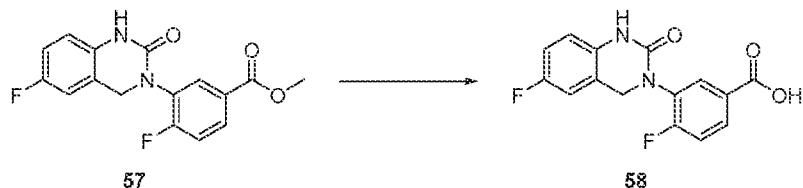
57

Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine with methyl 3-amino-4-fluorobenzoate provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.79 (s, 1H), 8.09 (dd, *J*=7.4, 2.2 Hz, 1H), 7.95 (ddd, *J*=8.6, 4.7, 2.2 Hz, 1H), 7.45 (dd, *J*=10.2, 8.6 Hz, 1H), 7.06 (d, *J*=8.8 Hz, 2H), 6.95–6.81 (m, 1H), 4.83 (s, 2H), 3.87 (s, 3H).

Example 58

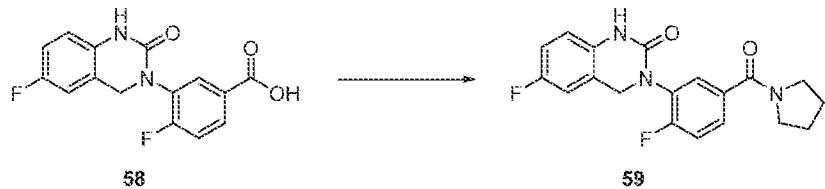
Synthesis of 4-fluoro-3-(6-fluoro-2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)benzoic acid



Proceeding as described in Example 51 above but substituting ethyl 2-(6-fluoro-2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)phenoxyacetate with methyl 4-fluoro-3-(6-fluoro-2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)benzoate provided the title compound as a white solid.
¹H NMR (400 MHz, DMSO-*d*6) δ 13.19 (s, 1H), 9.78 (s, 1H), 8.05 (dd, *J* = 7.5, 2.2 Hz, 1H), 7.92 (ddd, *J* = 8.6, 4.8, 2.2 Hz, 1H), 7.42 (dd, *J* = 10.2, 8.6 Hz, 1H), 7.06 (t, *J* = 7.9 Hz, 2H), 6.96–6.82 (m, 1H), 4.82 (s, 2H).

Example 59

Synthesis of 6-fluoro-3-(2-fluoro-5-(pyrrolidine-1-carbonyl)phenyl)-3,4-dihydroquinazolin-2(*H*)-one

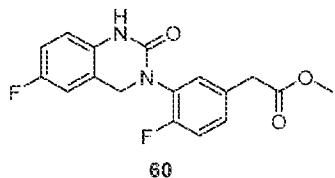


A solution of 4-fluoro-3-(6-fluoro-2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)benzoic acid (87 mg, 0.28 mmol) and piperidine (0.02 mL, 0.28 mmol) in DMF (2 mL) was treated with HATU (109 mg, 0.28 mmol) and *N*-methylmorpholine (0.09 mL, 0.86 mmol), and stirred at room temperature. After 15 h, the crude reaction mixture was diluted with ethyl acetate (70 mL) and washed successively with water and saturated aqueous sodium chloride, dried over sodium sulfate, filtered and concentrated. Purification by HPLC (10–70% ethyl acetate in hexanes) gave the title compound (70 mg, 69%) as an off-white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.74 (s, 1H), 7.68 (dd, *J* = 7.5, 2.2 Hz, 1H), 7.61–7.43 (m, 1H), 7.34 (dd, *J* = 10.3, 8.5 Hz, 1H), 7.06 (ddd, *J* = 9.1, 4.6, 1.9 Hz, 2H), 6.92–6.81 (m, 1H), 4.80 (s, 2H), 3.46 (dd, *J* = 14.2, 6.8 Hz, 4H), 1.85 (q, *J* = 6.1, 5.5 Hz, 4H).

Example 60

Synthesis of methyl 2-(4-fluoro-3-(6-fluoro-2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)phenyl)acetate

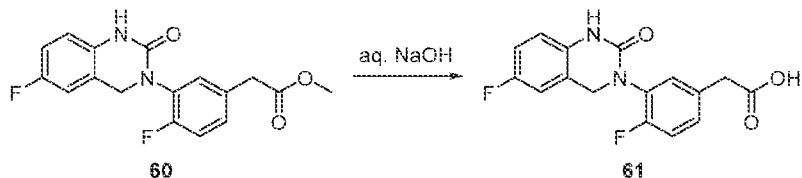


Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine with methyl 2-(3-amino-4-fluorophenyl)acetate provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.70 (s, 1H), 7.53–7.31 (m, 1H), 7.31–7.17 (m, 2H), 7.06 (dd, *J* = 8.9, 7.1 Hz, 2H), 6.91–6.83 (m, 1H), 4.74 (s, 2H), 3.71 (s, 2H), 3.63 (s, 3H).

Example 61

Synthesis of 2-(4-fluoro-3-(6-fluoro-2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)phenyl)acetic acid

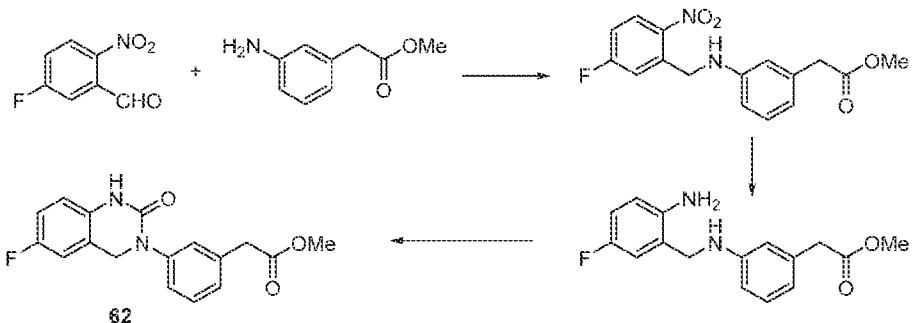


Proceeding as described in Example 51 above but substituting ethyl 2-(6-fluoro-2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)phenoxyacetate with methyl 2-(4-fluoro-3-(6-fluoro-2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)phenyl)acetate provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 12.43 (s, 1H), 9.69 (s, 1H), 7.50–7.32 (m, 1H), 7.23 (dd, *J* = 8.1, 1.3 Hz, 2H), 7.06 (dd, *J* = 8.7, 7.3 Hz, 2H), 6.91–6.78 (m, 1H), 4.74 (s, 2H), 3.59 (s, 2H).

Example 62

Synthesis of methyl 2-(3-(6-fluoro-2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)phenyl)acetate

**Step 1:**

While under nitrogen, a solution of 5-fluoro-2-nitrobenzaldehyde (1.53 g, 3.82 mmol) and 2-(*o*-aminophenyl)acetate (1.47 g, 3.82 mmol) in dichloroethane (12.5 mL) was treated with acetic acid (0.01 mL, 0.18 mmol) and warmed to 50 °C for 12 h. After cooling to room temperature, sodium triacetoxyborohydride (2.81 g, 5.73 mmol) was added and stirring was continued for an additional 16 h. Once complete, the reaction was quenched with saturated aqueous NaHCO₃, extracted with ethyl acetate, washed with saturated aqueous sodium chloride (60 mL), dried over sodium sulfate, filtered and concentrated. Purification by medium pressure liquid chromatography (MPLC) (silica, 25 g, 5–50% hexanes in ethyl acetate) gave methyl 2-(3-((5-fluoro-2-nitrobenzyl)amino)phenyl)acetate as a yellow oil (2.17 g, 77%).

Step 2:

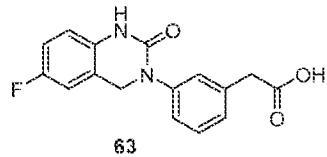
While under nitrogen, a solution of methyl 2-(3-((5-fluoro-2-nitrobenzyl)amino)phenyl)acetate (2.167 g, 2.20 mmol) and diisopropylethylamine (6.75 mL, 40.8 mmol) in dry dichloromethane (50 mL) was cooled to 0 °C (ice-bath) and treated with a separate solution of HSiCl₃ (3.44 mL, 34.0 mmol) in dry dichloromethane (20 mL) over 10 min. Once the addition was complete, the ice-bath was removed and stirring was continued at room temperature. After approximately 18 h, the reaction mixture was re-cooled with an ice-bath and carefully quenched with saturated aqueous of NaHCO₃ (50 mL). The biphasic mixture was stirred for 2 h, filtered through Celite. The resulting filtrate was extracted with ethyl acetate, dried over MgSO₄, filtered and concentrated to give methyl 2-(3-((2-amino-5-fluorobenzyl)amino)phenyl)acetate as a yellow solid which was used without further purification (1.96 g, 100% yield).

Step 3:

While under nitrogen, a solution of methyl 2-(3-((2-amino-5-fluorobenzyl)amino)phenyl)acetate (1.96 g, 6.80 mmol) in THF (50 mL) was treated with 1,1'-carbonyldiimidazole (1.38 g, 8.25 mmol) and warmed to 65 °C. After stirring for approximately 16 h, the solution was allowed to cool to room temperature and concentrated. Purification by MPLC (20-100% ethyl acetate in hexanes) gave methyl 2-(3-(6-fluoro-2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)phenyl)acetate (1.46 g, 68%) as an off-white solid.
¹H NMR (400 MHz, DMSO-*d*6) δ 9.62 (s, 1H), 7.38–7.29 (m, 1H), 7.29–7.22 (m, 2H), 7.16–7.00 (m, 3H), 6.87 (dd, *J*=8.7, 4.8 Hz, 1H), 4.80 (s, 2H), 3.70 (s, 2H), 3.62 (s, 3H).

Example 63

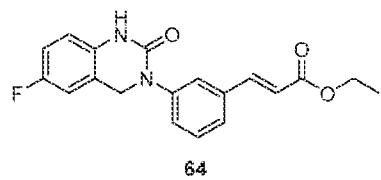
Synthesis of 2-(3-(6-fluoro-2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)phenyl)acetic acid



A solution of methyl 2-(3-((2-amino-5-fluorobenzyl)amino)phenyl)acetate (1.46 g, 4.65 mmol) in THF (30 mL) and methanol (15 mL) was treated with 2.0 N NaOH (15.1 mL, 32.2 mmol). After stirring for approximately 16 h, the reaction was quenched with 1 N HCl to pH 3 and the precipitated product was filtered to the title compound as a white solid (1.34 g, 96%). ¹H NMR (400 MHz, DMSO-*d*6) δ 12.35 (s, 1H), 9.62 (s, 1H), 7.32 (dd, *J*=8.3, 7.3 Hz, 1H), 7.28–7.21 (m, 2H), 7.15–7.00 (m, 3H), 6.87 (dd, *J*=8.7, 4.8 Hz, 1H), 4.80 (s, 2H), 3.58 (s, 2H).

Example 64

Synthesis of ethyl (*E*)-3-(3-(6-fluoro-2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)phenyl)acrylate

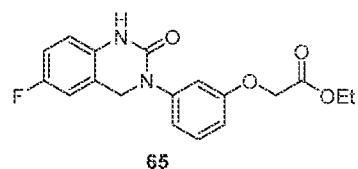


Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine with ethyl (*E*)-3-(3-aminophenyl)acrylate provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.69 (s, 1H), 7.76–7.72 (m, 1H), 7.66 (d, *J*=16.0 Hz, 1H), 7.56 (dt, *J*=6.4, 1.9 Hz, 1H), 7.48–7.38 (m, 2H), 7.12–7.00 (m, 2H), 6.88 (dd, *J*=8.5, 4.8 Hz, 1H), 6.69 (d, *J*=16.0 Hz, 1H), 4.86 (s, 2H), 4.20 (q, *J*=7.1 Hz, 2H), 1.26 (t, *J*=7.1 Hz, 3H).

Example 65

Synthesis of ethyl 2-(3-(6-fluoro-2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)phenoxy)acetate

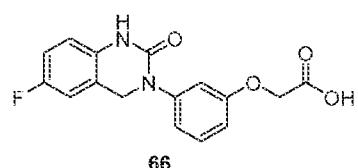


Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine with ethyl 2-(3-aminophenoxy)acetate provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.63 (s, 1H), 7.43–7.19 (m, 1H), 7.13–7.01 (m, 2H), 6.97 (dd, *J*=7.0, 1.3 Hz, 2H), 6.86 (dd, *J*=8.6, 4.8 Hz, 1H), 6.83–6.71 (m, 1H), 4.79 (d, *J*=9.2 Hz, 4H), 4.17 (q, *J*=7.1 Hz, 2H), 1.22 (t, *J*=7.1 Hz, 3H).

Example 66

Synthesis of 2-(3-(6-fluoro-2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)phenoxy)acetic acid

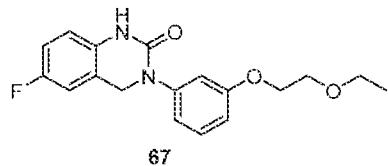


Proceeding as described in Example 51 above but substituting ethyl 2-(2-(6-fluoro-2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)phenoxy)acetate with ethyl 2-(3-(6-fluoro-2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)phenoxy)acetate provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 13.00 (s, 1H), 9.62 (s, 1H), 7.28 (t, *J*=8.3 Hz, 1H), 7.12–7.00 (m, 2H), 6.96 (dd, *J*=8.3, 1.7 Hz, 2H), 6.86 (dd, *J*=8.6, 4.8 Hz, 1H), 6.80–6.70 (m, 1H), 4.80 (s, 2H), 4.67 (s, 2H).

Example 67

Synthesis of 3-(3-(2-ethoxyethoxy)phenyl)-6-fluoro-3,4-dihydroquinazolin-2(1*H*)-one

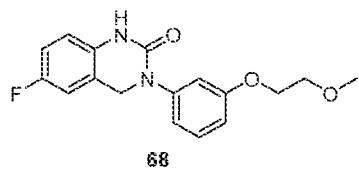


Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine with 1-(2-ethoxyethoxy)-3-nitrobenzene provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 7.43 (s, 1H), 7.29 (t, *J*=8.0 Hz, 1H), 6.95–6.88 (m, 3H), 6.84–6.77 (m, 2H), 6.71–6.68 (m, 1H), 4.76 (s, 2H), 4.12 (t, *J*=4.0 Hz, 2H), 3.78 (t, *J*=4.0 Hz, 2H), 3.59 (q, *J*=6.7 Hz, 2H), 1.23 (t, *J*=6.7 Hz, 3H).

Example 68

Synthesis of 6-fluoro-3-(3-(2-methoxyethoxy)phenyl)-3,4-dihydroquinazolin-2(1*H*)-one

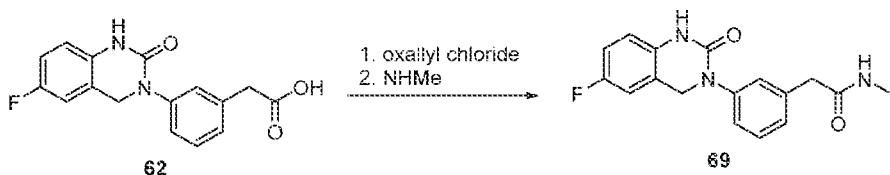


Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine with 3-(2-methoxyethoxy)aniline provided the title compound as a white solid.

¹H NMR (400 MHz, CDCl₃) δ 7.75 (s, 1H), 7.29 (t, *J*=8.2 Hz, 1H), 6.98–6.91 (m, 2H), 6.91–6.61 (m, 4H), 4.76 (s, 2H), 4.15–4.08 (m, 2H), 3.77–3.70 (m, 2H), 3.43 (s, 3H).

Example 69

Synthesis of 2-(3-(6-fluoro-2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)phenyl)-N-methylacetamide



Step 1:

While under nitrogen, a solution of 2-(3-(6-fluoro-2-oxo-1,4-dihydroquinazolin-3(2H)-yl)phenyl)acetic acid (200 mg, 0.67 mmol) in dichloromethane (3 mL) was treated with oxalyl chloride (0.114 mL, 1.33 mmol) and N,N-dimethylformamide (1 drop). After the reaction was complete, the solution was warmed to 40 °C for 1 h, cooled to room temperature and concentrated to give 2-(3-(6-fluoro-2-oxo-1,4-dihydroquinazolin-3(2H)-yl)phenyl)acetyl chloride as an off-white solid that was used without further purification (212 mg, 100%).

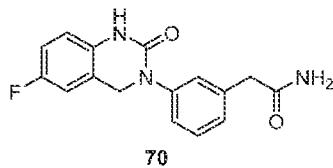
Step 2:

While under nitrogen, a solution of 2-(3-(6-fluoro-2-oxo-1,4-dihydroquinazolin-3(2H)-yl)phenyl)acetyl chloride (100 mg, 0.31 mmol) in dichloromethane (2 mL) was cooled to 0 °C and treated with methylamine (33% solution in ethanol, 0.3 mL). After the addition was complete, the reaction was stirred at room temperature for 16 h, concentrated, and washed with water. The organic phase was dried over MgSO₄, filtered and concentrated. Purification by Prep TLC (5% methanol in dichloromethane) gave the title compound as an off-white solid (99 mg, 100% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.36 (t, *J*=7.6 Hz, 1H), 7.24–7.10 (m, 3H), 6.88 (td, *J*=8.5, 2.7 Hz, 1H), 6.79–6.69 (m, 2H), 4.76 (s, 2H), 3.52 (s, 2H), 2.88 (brs, 4H), 2.69 (s, 3H).

Example 70

Synthesis of 2-(3-(6-fluoro-2-oxo-1,4-dihydroquinazolin-3(2H)-yl)phenyl)acetamide

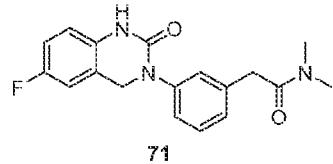


Proceeding as described in Example 69 above but substituting methylamine with aqueous NH₄OH provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.61 (s, 1H), 7.47 (s, 1H), 7.30 (t, *J*=7.7 Hz, 1H), 7.27–7.18 (m, 2H), 7.15–7.00 (m, 3H), 6.95–6.82 (M, 2H), 4.79 (s, 2H), 3.38 (s, 2H).

Example 71

Synthesis of 2-(3-(6-fluoro-2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)phenyl)-*N,N*-dimethylacetamide

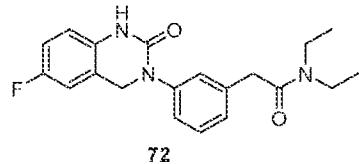


Proceeding as described in Example 69 above but substituting methylamine with dimethylamine provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.61 (s, 1H), 7.37–7.27 (m, 1H), 7.25–7.19 (m, 2H), 7.13–7.00 (m, 3H), 6.87 (dd, *J*=8.7, 4.8 Hz, 1H), 4.79 (s, 2H), 3.70 (s, 2H), 3.02 (s, 3H), 2.84 (s, 3H).

Example 72

Synthesis of *N,N*-diethyl-2-(3-(6-fluoro-2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)phenyl)acetamide

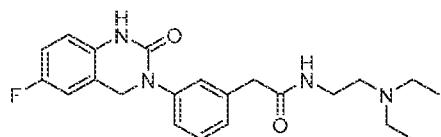


Proceeding as described in Example 69 above but substituting methylamine with *N,N*-diethylamine provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.61 (s, 1H), 7.31 (t, *J*=7.7 Hz, 1H), 7.25–7.18 (m, 2H), 7.13–6.98 (m, 3H), 6.86 (dd, *J*=8.7, 4.8 Hz, 1H), 4.78 (s, 2H), 3.67 (s, 2H), 3.38–3.31 (m, 2H), 3.27 (q, *J*=7.1 Hz, 2H), 1.07 (t, *J*=7.1 Hz, 3H), 1.02 (t, *J*=7.0 Hz, 3H).

Example 73

Synthesis of *N*-(2-(diethylamino)ethyl)-2-(3-(6-fluoro-2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)phenyl)acetamide



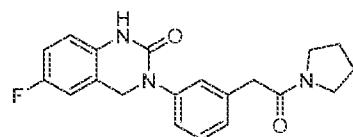
73

Proceeding as described in Example 69 above but substituting methylamine with *N¹,N¹*-diethylethane-1,2-diamine provided the title compound as a white solid.

¹H NMR (400 MHz, acetone-*d*6) δ 8.69 (s, 1H), 8.13 (s, 1H), 7.42 (s, 1H), 7.40–7.28 (m, 2H), 7.19 (dt, *J*=7.1, 1.7 Hz, 1H), 7.09–6.95 (m, 3H), 4.89 (s, 2H), 3.69 (q, *J*=5.4 Hz, 2H), 3.64 (s, 2H), 3.48–3.43 (m, 2H), 3.39 (q, *J*=7.3 Hz, 4H), 1.31 (t, *J*=7.3 Hz, 6H).

Example 74

Synthesis of 6-fluoro-3-(3-(2-oxo-2-(pyrrolidin-1-yl)ethyl)phenyl)-3,4-dihydroquinazolin-2(1*H*)-one



74

Proceeding as described in Example 69 above but substituting methylamine with pyrrolidine provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.61 (s, 1H), 7.31 (td, *J*=7.5, 1.1 Hz, 1H), 7.25–7.19 (m, 2H), 7.11–7.00 (m, 3H), 6.86 (dd, *J*=8.7, 4.8 Hz, 1H), 4.79 (s, 2H), 3.63 (s, 2H), 3.48 (t, *J*=6.8 Hz, 2H), 3.29 (t, *J*=6.9 Hz, 2H), 1.92–1.81 (m, 2H), 1.81–1.70 (m, 2H).

Example 75

Synthesis of 6-fluoro-3-(3-((3-methyl-1,2,4-oxadiazol-5-yl)methyl)phenyl)-3,4-dihydroquinazolin-2(1*H*)-one



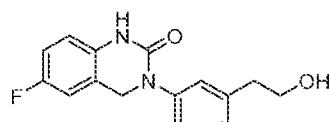
62

75

A solution of methyl 2-(3-(6-fluoro-2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)phenyl)-acetate (75 mg, 0.24 mmol) in toluene (3 mL) was treated with (*Z*)-*N'*-hydroxyacetimidamide (36.9 mg, 0.50 mmol) and potassium carbonate (68.9 mg, 0.50 mmol). The reaction was heated to reflux for 6 h, cooled to room temperature, diluted with ethyl acetate (5 mL), washed successively with water and saturated aqueous sodium chloride. The organic phase was dried over sodium sulfate, filtered and concentrated. Purification by MPLC (0–20% methanol in dichloromethane) gave the title compound (62 mg, 77%) as a white solid.
¹H NMR (400 MHz, CDCl₃) δ 7.44 (s, 1H), 7.40 (t, *J*=7.8 Hz, 1H), 7.35 (s, 1H), 7.33–7.28 (m, 1H), 7.23 (d, *J*=7.7 Hz, 1H), 6.94 (td, *J*=8.5, 2.8 Hz, 1H), 6.82 (dd, *J*=8.3, 2.7 Hz, 1H), 6.71 (dd, *J*=8.7, 4.5 Hz, 1H), 4.80 (s, 2H), 4.22 (s, 2H), 2.38 (s, 3H).

Example 76

Synthesis of 6-fluoro-3-(3-(2-hydroxyethyl)phenyl)-3,4-dihydroquinazolin-2(*H*)-one



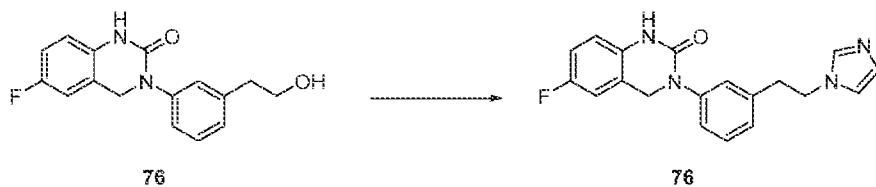
76

Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine with 2-(3-aminophenyl)ethanol provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.56 (s, 1H), 7.24 (t, *J*=7.7 Hz, 1H), 7.20–7.11 (m, 2H), 7.08–6.96 (m, 3H), 6.83 (dd, *J*=8.7, 4.8 Hz, 1H), 4.76 (s, 2H), 4.63 (t, *J*=5.2 Hz, 1H), 3.58 (td, *J*=7.1, 5.2 Hz, 2H), 2.69 (t, *J*=7.1 Hz, 2H).

Example 77

Synthesis of 3-(3-(2-(1*H*-imidazol-1-yl)ethyl)phenyl)-6-fluoro-3,4-dihydroquinazolin-2(*H*)-one



Step 1:

To a solution of 6-fluoro-3-(3-(2-hydroxyethyl)phenyl)-3,4-dihydroquinazolin-2(1*H*)-one (80 mg, 0.28 mmol) in DCM (1 mL) under N₂ atmosphere at 0 °C was added Et₃N (97 mL, 0.70 mmol) and MsCl (26 μL, 0.34 mmol). The reaction mixture was stirred from 0 – 25 °C over 2 hr before it was diluted with DCM (5 mL) and water (3 mL). The organic layer was dried over Na₂SO₄ and concentrated. The crude product was used in the following step without further purification.

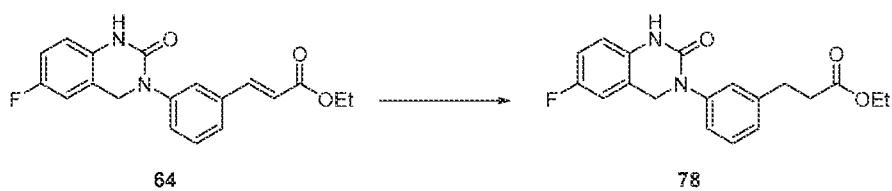
Step 2:

To a solution of crude 3-(6-fluoro-2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)phenethyl methanesulfonate in DMF (1 mL) at 25 °C was added imidazole (29 mg, 42 mmol) and K₂CO₃ (135 mg, 0.98 mmol). The reaction mixture was stirred for 24 hr before it was diluted with EtOAc (7 mL) and water (5 mL). The organic layer was washed with water (5 mL), brine (3 mL), dried over Na₂SO₄ and concentrated. The crude was purified by flash column chromatography over silica gel (5% methanol in dichloromethane with 0.5% acetic acid) gave the title compound (59 mg, 63%) as a white solid.

¹H NMR (400 MHz, CDCl₃) δ 8.30 (s, 1H), 7.64 (s, 1H), 7.44–7.32 (m, 2H), 7.31–7.19 (m, 2H), 7.17–7.05 (m, 2H), 6.91 (td, *J*=8.6, 2.8 Hz, 1H), 6.76 (ddd, *J*=21.9, 8.5, 3.6 Hz, 2H), 4.76 (s, 2H), 4.63 (t, *J*=6.7 Hz, 2H), 3.10 (t, *J*=6.7 Hz, 2H).

Example 78

Synthesis of ethyl 3-(3-(6-fluoro-2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)phenyl)propanoate



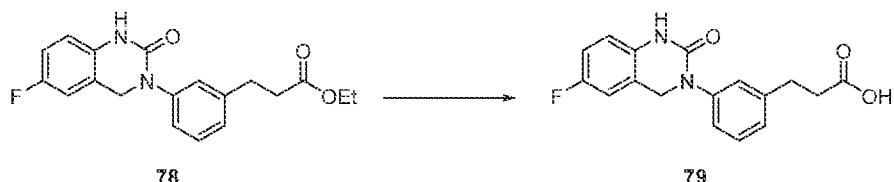
A suspension of ethyl (E)-3-(3-(6-fluoro-2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)-phenyl)acrylate (70 mg, 0.206 mmol) and 10% palladium on carbon (21.9 mg, 0.02 mmol) in methanol (1.5 mL) was purged with nitrogen, then treated with hydrogen (balloon) for 16 h. After the reaction was complete, the reaction mixture was purged with nitrogen, filtered through celite and concentrated to give the title compound (61.8 mg, 88%) as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.61 (s, 1H), 7.40–7.13 (m, 3H), 7.13–7.69 (m, 3H), 6.87

(dd, $J=8.6, 4.8$ Hz, 1H), 4.79 (s, 2H), 4.05 (q, $J=6.4$ Hz, 4H), 2.86 (t, $J=7.6$ Hz, 2H), 2.63 (t, $J=7.7$ Hz, 2H), 1.16 (t, $J=6.6$ Hz, 5H).

Example 79

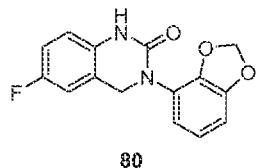
Synthesis of 3-(3-(6-fluoro-2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)phenyl)propanoic acid



Proceeding as described in Example 51 above but substituting ethyl 2-(6-fluoro-2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)phenoxyacetate with ethyl 3-(3-(6-fluoro-2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)phenyl)propanoate provided the title compound as a white solid.
¹H NMR (400 MHz, DMSO-*d*6) δ 12.15 (s, 1H), 9.60 (s, 1H), 7.28 (t, $J=7.7$ Hz, 1H), 7.23 (s, 1H), 7.18 (d, $J=8.2$ Hz, 1H), 7.11–7.00 (m, 3H), 6.86 (dd, $J=8.6, 4.8$ Hz, 1H), 4.79 (s, 2H), 2.83 (t, $J=7.7$ Hz, 2H), 2.55 (t, $J=7.7$ Hz, 2H).

Example 80

Synthesis of 3-(benzo[d][1,3]dioxol-4-yl)-6-fluoro-3,4-dihydroquinazolin-2(*H*)-one

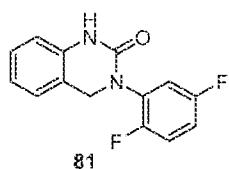


Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine with benzo[d][1,3]dioxol-4-amine provided the title compound as a white solid.

¹H NMR (300 MHz, DMSO-*d*6) δ 9.62 (s), 7.08–7.02 (m, 2H), 6.90–6.84 (m, 4H), 6.02 (s, 2H), 4.75 (s, 2H).

Example 81

Synthesis of 3-(2,5-difluorophenyl)-3,4-dihydroquinazolin-2(*H*)-one

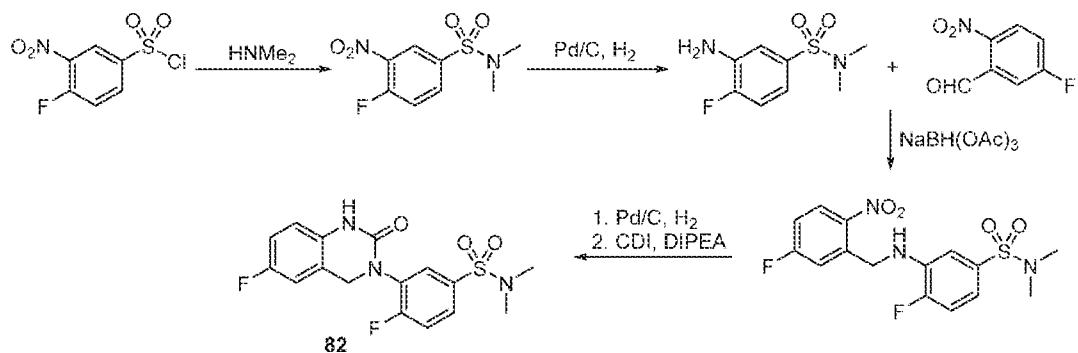


Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine and 3-fluoro-5-nitrobenzaldehyde with 2,5-difluoroaniline and 2-nitrobenzaldehyde provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.74 (s, 1H), 7.49 (ddd, *J* = 9.3, 6.1, 3.2 Hz, 1H), 7.34 (td, *J* = 9.6, 5.1 Hz, 1H), 7.25–7.09 (m, 3H), 6.94 (td, *J* = 7.5, 1.2 Hz, 1H), 6.87 (dd, *J* = 8.0, 1.1 Hz, 1H), 4.78 (s, 2H).

Example 82

Synthesis of 4-fluoro-3-(6-fluoro-2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)-*N,N*-dimethylbenzenesulfonamide



Step 1:

A solution of 4-fluoro-3-nitrobenzenesulfonyl chloride (2.39 g, 10 mmol), dimethylamine hydrochloride (815 mg, 10 mmol) in dichloromethane (15 mL) was cooled to 0 °C and treated with triethylamine (3.06 mL, 22 mmol). Once the addition was complete, the cooling bath was removed and the reaction slowly warmed to room temperature. After stirring an additional 2 h at room temperature, the reaction mixture was transferred to a separatory funnel, washed with water and crystallized from ethyl acetate to give 4-fluoro-*N,N*-dimethyl-3-nitrobenzenesulfonamide (1.2 g, 48%) as a pale yellow solid.

Step 2:

A solution of 4-fluoro-*N,N*-dimethyl-3-nitrobenzenesulfonamide (750 mg, 3.02 mmol), acetic acid (0.5 mL) and palladium on carbon (10%, 100 mg) in methanol (10 mL) was purged with nitrogen, cooled to 0 °C and treated with hydrogen (balloon). After 5 h, the reaction mixture was filtered through Celite, and concentrated to give 3-amino-4-fluoro-*N,N*-dimethylbenzenesulfonamide as a white solid (600 mg) that was used in the subsequent step without further purification.

Step 3:

A solution of 5-fluoro-2-nitrobenzaldehyde (465 mg, 2.75 mmol), 3-amino-4-fluoro-*N,N*-dimethylbenzenesulfonamide (600 mg, 2.75 mmol) and acetic acid (0.02 mL, 0.39 mmol) in dichloroethane (10 mL) was warmed to 70 °C. After stirring 5 h the solution was cooled to room temperature and treated with sodium triacetoxyborohydride (1.16 g, 5.50 mmol). After stirring an additional 10 h, the reaction was quenched with saturated aqueous sodium bicarbonate, extracted with ethyl acetate, dried over magnesium sulfate, filtered and concentrated. Purification by flash SiO₂ column chromatography (30% ethyl acetate in hexanes) gave 4-fluoro-3-((5-fluoro-2-nitrobenzyl)amino)-*N,N*-dimethylbenzenesulfonamide as a brown oil (990 mg, 97%).

Step 4:

A solution of 4-fluoro-3-((5-fluoro-2-nitrobenzyl)amino)-*N,N*-dimethylbenzenesulfonamide (323 mg, 0.869 mmol) and palladium on carbon (10%, 50 mg) in ethyl acetate (10 mL) was purged with nitrogen, cooled to 0 °C and treated with hydrogen (balloon). After 2 h, the reaction mixture was filtered through Celite, and concentrated to give 3-((2-amino-5-fluorobenzyl)amino)-4-fluoro-*N,N*-dimethylbenzenesulfonamide as a pale-yellow oil (295 mg) that was used in the subsequent step without further purification.

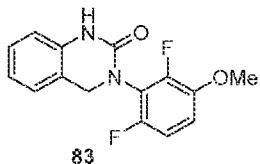
Step 5:

A solution of 3-((2-amino-5-fluorobenzyl)amino)-4-fluoro-*N,N*-dimethylbenzenesulfonamide (290 mg, 0.849 mmol) and diisopropylethylamine (0.28 mL, 1.69 mmol) in anhydrous THF (5 mL) was treated with carbonyldiimidazole (275 mg, 1.69 mmol) and warmed to 65 °C. After 22 h, the reaction mixture was cooled to room temperature, diluted with ethyl acetate and washed with water. Purification by crystallization (20% methanol in ethyl acetate) gave 4-fluoro-3-(6-fluoro-2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)-*N,N*-dimethylbenzenesulfonamide (170 mg, 54%) as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.81 (s, 1H), 7.89 (dd, *J* = 7.1, 2.3 Hz, 1H), 7.70 (ddd, *J* = 8.6, 4.4, 2.3 Hz, 1H), 7.55 (dd, *J* = 10.1, 8.7 Hz, 1H), 7.03 (ddt, *J* = 9.5, 5.0, 2.4 Hz, 2H), 6.85 (dd, *J* = 9.6, 4.8 Hz, 1H), 4.83 (s, 2H), 2.62 (s, 6H).

Example 83

Synthesis of 3-(2,6-difluoro-3-methoxyphenyl)-3,4-dihydroquinazolin-2(*1H*)-one

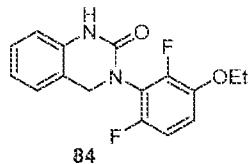


Proceeding as described in Example 26 above but substituting 2,6-difluoroaniline with 2,6-difluoro-3-methoxyaniline provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.76 (s, 1H), 7.32–7.04 (m, 4H), 7.00–6.81 (m, 2H), 4.71 (s, 2H), 3.86 (s, 3H).

Example 84

Synthesis of 3-(2,6-difluoro-3-ethoxyphenyl)-3,4-dihydroquinazolin-2(*1H*)-one

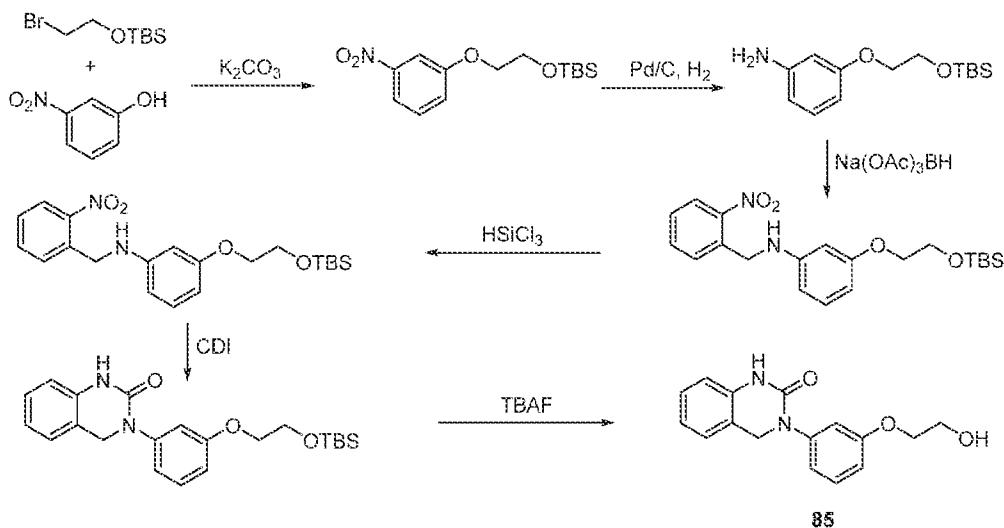


Proceeding as described in Example 26 above but substituting 2,6-difluoroaniline with 2,6-difluoro-3-ethoxyaniline provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ ppm 9.76 (s, 1H), 7.29–7.05 (m, 4H), 7.00–6.82 (m, 2H), 4.71 (s, 2H), 4.12 (q, *J*=7.0 Hz, 2H), 1.34 (t, *J*=7.0 Hz, 3H).

Example 85

Synthesis of 3-(3-(2-hydroxyethoxy)phenyl)-3,4-dihydroquinazolin-2(*1H*)-one



Step 1:

A solution of 3-nitrophenol (1.39 g, 10 mmol), potassium carbonate (1.79 g, 13 mmol), sodium iodide (1.79 g, 12.0 mmol) in dimethylformamide (9.6 mL) was treated with 2-bromoethoxy-tert-butyldimethylsilane (2.57 mL, 12.0 mmol) and warmed to 80 °C. After 19 h, the reaction mixture was cooled to room temperature, diluted with ethyl acetate and washed successively with water and saturated aqueous sodium chloride. The organic phase was dried over magnesium sulfate, filtered and concentrated. Purification by MPLC (0-15% ethyl acetate in hexanes) gave *tert*-butyldimethyl(2-(3-nitrophenoxy)ethoxy)silane (1.65 g, 55%) as a light brown oil.

Step 2:

A solution of *tert*-butyldimethyl(2-(3-nitrophenoxy)ethoxy)silane (550 mg, 1.85 mmol) and palladium on carbon (10% Wt. 196.8 mg, 0.18 mmol) in ethyl acetate (22 mL) was purged with nitrogen and treated with hydrogen (balloon). After stirring for 14 h, the reaction mixture was purged with nitrogen, filtered through Celite and concentrated to give 3-((*tert*-butyldimethylsilyl)oxy)ethoxyaniline (500 mg, 100%) as a light-brown oil that was used without further purification.

Step 3:

A solution of 3-((*tert*-butyldimethylsilyl)oxy)ethoxyaniline (500 mg, 1.87 mmol), 2-nitrobenzaldehyde (283 mg, 1.87 mmol) and acetic acid (0.16 mL, 2.8 mmol) was warmed to 60 °C. After 5 h, the reaction mixture was cooled to room temperature and treated with sodium triacetoxyborohydride (789 mg, 3.74 mmol) with continued stirring for 17 h. The

reaction was quenched with saturated aqueous NaHCO₃, extracted with ethyl acetate and washed with saturated aqueous sodium chloride. The organic phase was dried over magnesium sulfate, filtered and concentrated. Purification by MPLC (0-20% ethyl acetate in hexanes) gave 3-(2-((*tert*-butyldimethylsilyl)oxy)ethoxy)-N-(2-nitrobenzyl)aniline (439 mg, 58%) as a light brown oil.

Step 3:

A solution of 3-(2-((*tert*-butyldimethylsilyl)oxy)ethoxy)-N-(2-nitrobenzyl)aniline (219 mg, 0.54 mmol) and diisopropylethylamine (0.54 mL, 3.26 mmol) in anhydrous dichloromethane (4 mL) was cooled to 0 °C (ice-bath) treated with a second solution of trichlorosilane (0.272 mL, 2.72 mmol) in anhydrous dichloromethane (2.03 mL) dropwise over 10 min. After the addition was complete, the ice-bath was removed and stirring was continued for 18 h. The reaction mixture was quenched with saturated aqueous NaHCO₃ and stirring was continued for an additional 30 min. The resulting bi-phasic solution was extracted with ethyl acetate, dried over magnesium sulfate, filtered and concentrated to give N-(2-aminobenzyl)-3-(2-((*tert*-butyldimethylsilyl)oxy)ethoxy)aniline (162 mg, 80%) that was used without further purification.

Step 5:

A solution of N-(2-aminobenzyl)-3-(2-((*tert*-butyldimethylsilyl)oxy)ethoxy)aniline (162 mg, 0.435 mmol) in THF (4.2 mL) was treated with 1,1'-Carbonyldiimidazole (106 mg, 0.652 mmol) and warmed to 65 °C. After 18 h, the reaction mixture was cooled to room temperature, concentrated and purified via MPLC (0-20% ethyl acetate in hexanes) to give 3-(3-(2-((*tert*-butyldimethylsilyl)oxy)ethoxy)phenyl)-3,4-dihydroquinazolin-2(1*H*)-one (54.4 mg, 31%) as a light-brown oil.

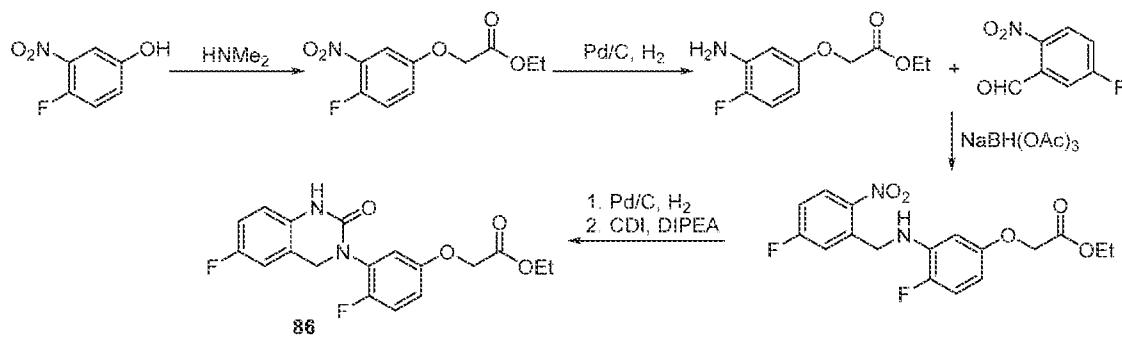
Step 6:

A solution of 3-(3-(2-((*tert*-butyldimethylsilyl)oxy)ethoxy)phenyl)-3,4-dihydro-quinazolin-2(1*H*)-one (54.4 mg, 0.136 mmol) in THF (1.4 mL) was cooled to 0 °C (ice-bath) and treated with a THF solution of tetrabutylammoniumfluoride (1M, 0.164 mL, 0.164 mmol). After stirring for 4 h, the reaction mixture was concentrated and purified via MPLC (0-10% methanol in dichloromethane) to give the title compound (23 mg, 59%) as an off-white solid.

¹H NMR (400 MHz, Methanol-*d*4) δ 7.32 (t, *J*=8.1 Hz, 1H), 7.21 (td, *J*=7.7, 1.4 Hz, 1H), 7.16–7.11 (m, 1H), 7.03–6.93 (m, 3H), 6.91–6.85 (m, 2H), 4.84 (s, 2H), 4.07 (dd, *J*=5.3, 4.2 Hz, 2H), 3.87 (t, *J*=4.7 Hz, 2H).

Example 86

Synthesis of ethyl 2-(4-fluoro-3-(6-fluoro-2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)phenoxy)acetate



Step 1:

A solution of 3-nitrophenol (1.57 g, 10 mmol) and potassium carbonate (2.76 g, 20 mmol) in acetonitrile (10 mL) was treated with iodoacetate (2.38 mL, 20 mmol). After stirring for 15 h, the reaction mixture was diluted with ethyl acetate and washed successively with water and saturated aqueous sodium chloride, dried over magnesium sulfate, filtered and concentrated. Purification via MPLC (0-25% ethyl acetate in hexanes gave ethyl 2-(4-fluoro-3-nitrophenoxy)acetate (2.22 g, 91%) as a light brown oil.

Step 2:

A solution of ethyl 2-(3-nitrophenoxy)acetate (0.552 g, 2.27 mmol) and palladium on carbon (10%, 242 mg, 0.227 mmol) in ethyl acetate (27 mL) was purged with nitrogen and treated with hydrogen (balloon). After 15 h, the reaction was purged with nitrogen, filtered through Celite and concentrated to give the title compound as a light brown oil that was used in the subsequent step without further purification.

Step 3:

A solution of 2-nitrobenzaldehyde (326 mg, 2.15 mmol), ethyl 2-(4-fluoro-3-nitrophenoxy)acetate (460 mg, 2.16 mmol) and acetic acid (0.18 mL, 3.23 mmol) in dichloroethane (10 mL) was warmed to 70 °C. After stirring 5 h, the solution was cooled to room temperature and treated with sodium triacetoxyborohydride (910 mg, 4.32 mmol).

After stirring an additional 19 h, the reaction was quenched with saturated aqueous sodium bicarbonate, extracted with ethyl acetate, dried over magnesium sulfate, filtered and concentrated. Purification by MPLC (0–30% ethyl acetate in hexanes) gave ethyl 2-(4-fluoro-3-((2-nitrobenzyl)amino)phenoxy)acetate as a brown oil (194 mg, 26%).

Step 4:

While under nitrogen, a solution of ethyl 2-(4-fluoro-3-((2-nitrobenzyl)amino)phenoxy)acetate (194 mg, 0.557 mmol) and diisopropylethylamine (0.552 mL, 3.34 mmol) in dry dichloromethane (4.2 mL) was cooled to 0 °C (ice-bath) and treated with a separate solution of HSiCl₃ (0.282 mL, 2.79 mmol) in dry dichloromethane over 10 min. Once the addition was complete, the ice-bath was removed and stirring was continued at room temperature. After approximately 18 h, the reaction mixture was re-cooled with an ice-bath and carefully quenched with saturated aqueous of Na₂CO₃ (4 mL). The biphasic mixture was stirred for 4 h, filtered through Celite. The resulting filtrate was extracted with ethyl acetate, dried over MgSO₄, filtered and concentrated to give ethyl 2-(3-((2-aminobenzyl)amino)-4-fluorophenoxy)acetate as a yellow solid (130 mg, 73% yield).

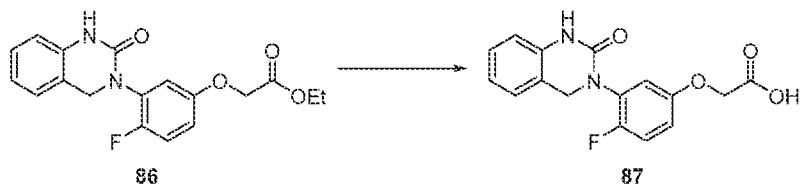
Step 5:

While under nitrogen, a solution of ethyl 2-(3-((2-aminobenzyl)amino)-4-fluorophenoxy)acetate (129 mg, 0.40 mmol) and diisopropylethylamine (0.135 mL, 0.82 mmol) in THF (3.9 mL) was treated with 1,1'-carbonyldiimidazole (132 mg, 0.816 mmol) and warmed to 70 °C. After stirring for 16 h, the solution was allowed to cool to room temperature and concentrated. The resulting residue was purified by MPLC (0-30% ethyl acetate in hexanes) to give ethyl 2-(4-fluoro-3-(2-oxo-1,4-dihydroquinazolin-3(2H)-yl)phenoxy)acetate (134 mg) as an off-white solid.

¹H NMR (500 MHz, DMSO-*d*6) δ 9.64 (s, 1H), 7.19 (td, *J* = 8.9, 8.3, 3.2 Hz, 2H), 7.13 (dd, *J* = 6.6, 3.5 Hz, 2H), 6.93 (td, *J* = 7.5, 1.1 Hz, 1H), 6.90–6.84 (m, 2H), 4.79 (s, 2H), 4.75 (s, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 1.22 (t, *J* = 7.1 Hz, 3H).

Example 87

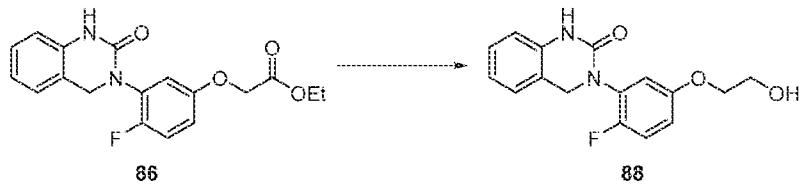
Synthesis of 2-(4-fluoro-3-(2-oxo-1,4-dihydroquinazolin-3(2H)-yl)phenoxy)acetic acid



Proceeding as described in Example 51 above but substituting ethyl 2-(2-(6-fluoro-2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)phenoxy)acetate with ethyl 2-(4-fluoro-3-(2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)phenoxy)acetate provided the title compound as a white solid.
¹H NMR (400 MHz, DMSO-*d*6) δ 13.02 (s, 1H), 9.65 (s, 1H), 7.19 (t, *J* = 8.1 Hz, 2H), 7.16–7.09 (m, 2H), 6.93 (t, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 8.1 Hz, 2H), 4.75 (s, 2H), 4.68 (s, 2H).

Example 88

Synthesis of 3-(2-fluoro-5-(2-hydroxyethoxy)phenyl)-3,4-dihydroquinazolin-2(*H*)-one



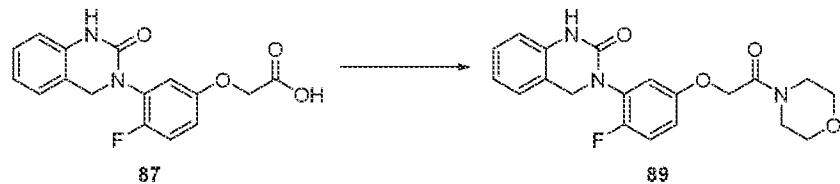
A solution of ethyl 2-(4-fluoro-3-(2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)phenoxy)-acetate (75.7 mg, 0.22 mmol) in ethanol (7 mL) was cooled to 0 °C and treated with lithium borohydride (47.92 mg, 0.22 mmol). After 1 h, the cooling bath was removed, the reaction warmed to room temperature with continued stirring for 15 h. After the reaction was complete, the mixture was re-cooled to 0 °C and quenched with 2 N HCl (until clear). After stirring an additional 30 min, the reaction mixture was diluted with ethyl acetate and washed successively with water and saturated aqueous sodium chloride and concentrated.

Purification by MPLC (2-20% methanol in dichloromethane) gave 3-(2-fluoro-5-(2-hydroxyethoxy)phenyl)-3,4-dihydroquinazolin-2(*H*)-one (46 mg, 69%) as a white solid.

¹H NMR (400 MHz, CDCl₃) δ 7.22 (d, *J* = 7.6 Hz, 1H), 7.15–7.04 (m, 3H), 7.00 (t, *J* = 7.5 Hz, 1H), 6.94 (dd, *J* = 6.2, 3.1 Hz, 1H), 6.85 (dt, *J* = 9.1, 3.4 Hz, 1H), 6.75 (d, *J* = 7.9 Hz, 1H), 4.79 (s, 2H), 4.09–4.03 (m, 2H), 3.95 (t, *J* = 4.4 Hz, 2H).

Example 89

Synthesis of 3-(2-fluoro-5-(2-morpholino-2-oxoethoxy)phenyl)-3,4-dihydroquinazolin-2(1*H*)-one

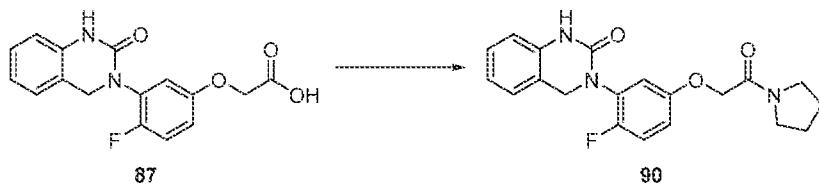


A solution of 2-(4-fluoro-3-(2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)phenoxy)acetic acid (79.1 mg, 0.25 mmol) and triethylamine (0.122 mL, 0.875 mmol) and morpholine (0.0324 mL, 0.375 mmol) in dimethylformamide (2 mL) was cooled to 0 °C (ice-bath) and treated with propylphosphonic anhydride (50% in ethyl acetate, 0.260 mL, 0.438 mmol). After stirring for 30 min, the cooling bath was removed and stirring was continued for 64 h. The reaction was quenched with water and the resulting precipitates was filtered, washed sequentially with water and acetonitrile to give the title compound (61.9 mg, 64%) as a white solid.

¹H NMR (500 MHz, DMSO-*d*6) δ ppm 9.64 (s, 1H), 7.19 (t, *J* = 8.7 Hz, 2H), 7.16–7.09 (m, 2H), 6.93 (t, *J* = 7.5 Hz, 1H), 6.87 (t, *J* = 7.4 Hz, 2H), 4.83 (s, 2H), 4.75 (s, 2H), 3.58 (dd, *J* = 17.3, 6.0 Hz, 4H), 3.46 (t, *J* = 4.7 Hz, 4H).

Example 90

Synthesis of 3-(2-fluoro-5-(2-oxo-2-(pyrrolidin-1-yl)ethoxy)phenyl)-3,4-dihydroquinazolin-2(1*H*)-one



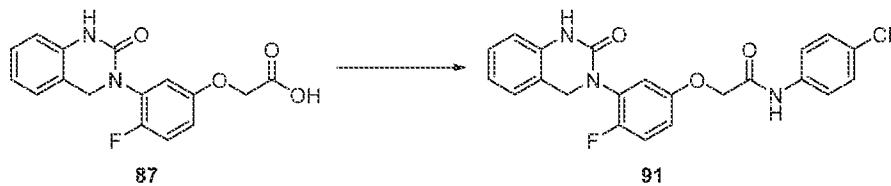
Proceeding as described in Example 89 above but substituting morpholine with pyrrolidine provided the title compound as a white solid.

¹H NMR (500 MHz, DMSO-*d*6) δ 9.63 (s, 1H), 7.19 (td, *J* = 9.6, 8.8, 4.1 Hz, 2H), 7.14 (d, *J* = 7.5 Hz, 1H), 7.10 (dd, *J* = 6.4, 3.1 Hz, 1H), 6.93 (t, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 7.9 Hz,

2H), 4.74 (s, 2H), 4.71 (s, 2H), 3.46 (t, $J = 6.8$ Hz, 2H), 3.32 (t, $J = 6.9$ Hz, 4H), 1.89 (p, $J = 6.8$ Hz, 2H), 1.77 (p, $J = 6.9$ Hz, 2H).

Example 91

Synthesis of *N*-(4-chlorophenyl)-2-(4-fluoro-3-(2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)phenoxy)acetamide

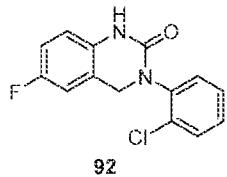


Proceeding as described in Example 89 above but substituting morpholine with 4-chloroaniline provided the title compound as a white solid.

^1H NMR (400 MHz, DMSO-*d*6) δ 10.22 (s, 1H), 9.68 (s, 1H), 7.72–7.65 (m, 2H), 7.42–7.35 (m, 2H), 7.27–7.16 (m, 3H), 7.13 (d, $J = 7.5$ Hz, 1H), 6.99–6.89 (m, 2H), 6.87 (d, $J = 7.9$ Hz, 1H), 4.75 (s, 2H), 4.71 (s, 2H).

Example 92

Synthesis of 3-(2-chlorophenyl)-6-fluoro-3,4-dihydroquinazolin-2(1*H*)-one

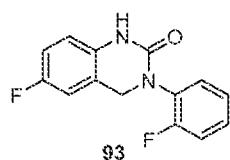


Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine with 2-chloroaniline provided the title compound as a white solid.

^1H NMR (400 MHz, DMSO-*d*6) δ 9.63 (s, 1H), 7.56 (td, $J = 7.3, 1.7$ Hz, 2H), 7.48–7.24 (m, 2H), 7.13–6.96 (m, 2H), 6.86 (dd, $J = 9.7, 4.8$ Hz, 1H), 4.81 (d, $J = 14.6$ Hz, 1H), 4.60 (d, $J = 14.6$ Hz, 1H).

Example 93

Synthesis of 6-fluoro-3-(2-fluorophenyl)-3,4-dihydroquinazolin-2(1*H*)-one

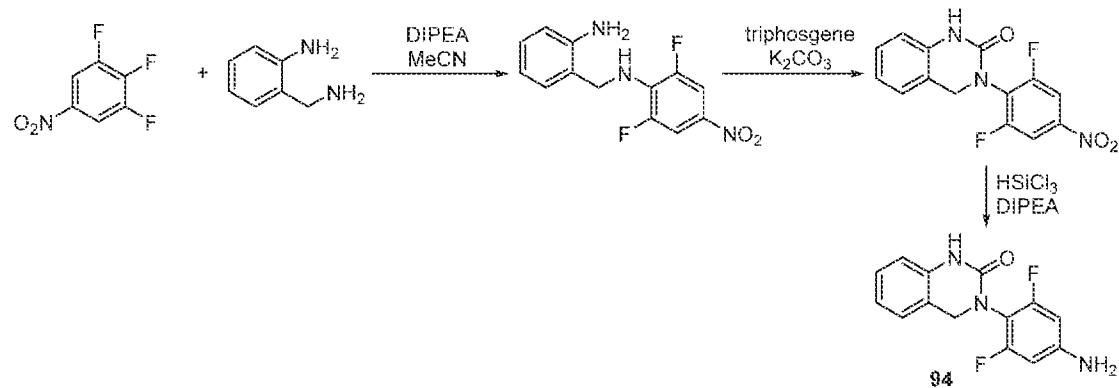


Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine with 2-fluoroaniline provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.69 (s, 1H), 7.50 (td, *J* = 7.9, 1.8 Hz, 1H), 7.42–7.17 (m, 3H), 7.05 (ddd, *J* = 8.9, 4.7, 1.9 Hz, 2H), 6.87 (dd, *J* = 9.6, 4.8 Hz, 1H), 4.76 (s, 2H).

Example 94

Synthesis of 3-(4-amino-2,6-difluorophenyl)-3,4-dihydroquinazolin-2(1*H*)-one



Step 1:

A solution of 2-(aminomethyl)aniline (7.33 g, 60 mmol) and diisopropylethylamine (3.97 mL, 24 mmol) in acetonitrile (60 mL) was treated with 1,2,3-trifluoro-5-nitrobenzene (10.6 g, 60 mmol) and warmed to 60 °C. After 14 h, the reaction mixture concentrated, precipitated with water, filtered and washed with water to give *N*-(2-aminobenzyl)-2,6-difluoro-4-nitroaniline (16.3 g, 96%) as a yellow solid.

Step 2:

A solution of *N*-(2-aminobenzyl)-2,6-difluoro-4-nitroaniline (16.1 g, 57.8 mmol) and potassium carbonate (11.1 g, 80.1 mmol) in anhydrous THF (260 mL) was cooled to 0 °C (ice-bath) and treated with triphosgene (17.8 g, 60.1 mmol). After 10 min, the cooling bath was removed and stirring was continued for 1 h. The reaction mixture was re-cooled to 0 °C and quenched with water and concentrated. The resulting precipitate was filtered and washed

with water to give 3-(2,6-difluoro-4-nitrophenyl)-3,4-dihydroquinazolin-2(1*H*)-one (17.5 g, 99%) as light yellow solid.

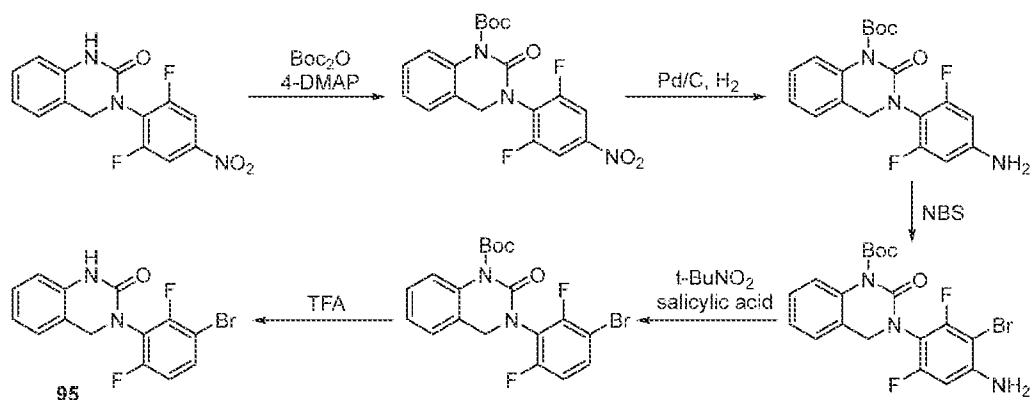
Step 3:

A solution of 3-(2,6-difluoro-4-nitrophenyl)-3,4-dihydroquinazolin-2(1*H*)-one (5.19 g, 17 mmol) and diisopropylethylamine (16.86 mL, 102 mmol) in dichloromethane (128 mL) was cooled to 0 °C and treated with trichlorosilane (8.59 mL, 85 mmol) in a dichloromethane (64 mL) at 0 °C over 10 min. After the addition was complete, stirring was continued for 16 h at room temperature. The reaction was quenched with saturated aqueous NaHCO₃ (128 mL) and saturated aqueous Na₂CO₃ (128 mL). The resulting biphasic mixture was stirred for 3 h, then extracted with ethyl acetate, dried over magnesium sulfate, filtered and concentrated to give 3-(4-amino-2,6-difluorophenyl)-3,4-dihydroquinazolin-2(1*H*)-one as an off-white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.51 (s, 1H), 7.24–7.04 (m, 2H), 6.99–6.77 (m, 2H), 6.27–6.17 (m, 2H), 5.76 (s, 2H), 4.55 (s, 2H).

Example 95

Synthesis of 3-(3-bromo-2,6-difluorophenyl)-3,4-dihydroquinazolin-2(1*H*)-one



Step 1:

A solution of 3-(2,6-difluoro-4-nitrophenyl)-3,4-dihydroquinazolin-2(1*H*)-one (2.50 g, 8.2 mmol) and di-tert-butyl decarbonate (3.58 g, 16.4 mmol) in THF (50 mL) was treated with dimethylaminopyridine (1.00 g, 8.2 mmol) and stirred at room temperature for 16 h. The crude product mixture was concentrated and purified directly by MPLC (0-20% ethyl

acetate in hexanes) to give *tert*-butyl 3-(2,6-difluoro-4-nitrophenyl)-2-oxo-3,4-dihydroquinazoline-1(2*H*)-carboxylate (3.34 g, 100%) as an off-white powder.

Step 2:

A solution of *tert*-butyl 3-(2,6-difluoro-4-nitrophenyl)-2-oxo-3,4-dihydroquinazoline-1(2*H*)-carboxylate (3.32 g, 8.2 mmol) and palladium on carbon (10% wt., 873 mg, 0.82 mmol) in ethyl acetate (83 mL) was purged with nitrogen, then treated with hydrogen (balloon). After stirring at room temperature for 18 h, the balloon was removed, the solution was purged with nitrogen, filtered through Celite and concentrated to give *tert*-butyl 3-(4-amino-2,6-difluorophenyl)-2-oxo-3,4-dihydroquinazoline-1(2*H*)-carboxylate (3.0 g, 97%) as a white solid.

Step 3:

A solution *tert*-butyl 3-(4-amino-2,6-difluorophenyl)-2-oxo-3,4-dihydroquinazoline-1(2*H*)-carboxylate (750.8 mg, 2 mmol) in dimethylformamide (1.55 mL) was treated with N-bromosuccinimide (373.8 mg, 2.1 mmol) and stirred at room temperature. After 2 h, the solution was diluted with water and the resulting precipitate was filtered and washed with water to give *tert*-butyl 3-(4-amino-3-bromo-2,6-difluorophenyl)-2-oxo-3,4-dihydroquinazoline-1(2*H*)-carboxylate (1.12 g) as a light-brown solid that was used in the subsequent step without further purification.

Step 4:

A solution of *tert*-butyl 3-(4-amino-3-bromo-2,6-difluorophenyl)-2-oxo-3,4-dihydroquinazoline-1(2*H*)-carboxylate (1.13 g, 2 mmol), salicylic acid (27.6 mg, 0.2 mmol) in THF (7 mL) was warmed to 65 °C and carefully treated with *tert*-butylnitrite (0.68 mL, 5.65 mmol). After the addition was complete, stirring was continued for 2 h. The solution was concentrated and purified via MPLC (0 – 20% ethyl acetate in hexanes) to give *tert*-butyl 3-(3-bromo-2,6-difluorophenyl)-2-oxo-3,4-dihydroquinazoline-1(2*H*)-carboxylate (687 mg, 78%) as a white powder.

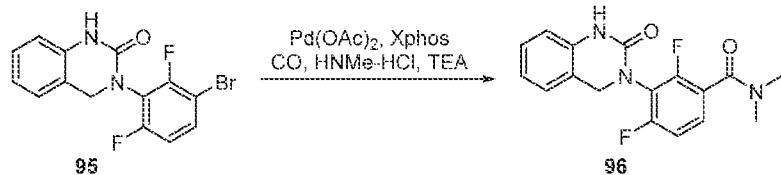
Step 5:

A solution of *tert*-butyl 3-(3-bromo-2,6-difluorophenyl)-2-oxo-3,4-dihydroquinazoline-1(2*H*)-carboxylate (687 mg, 1.56 mmol) in trifluoroacetic acid (3.8 mL) was stirred for 15 h, concentrated and diluted with saturated aqueous NaHCO₃. The precipitated product was filtered, washed with water and dried to give the title compound (470 mg, 89%) as a solid.

¹H NMR (500 MHz, DMSO-*d*6) δ 9.87 (s, 1H), 7.82 (ddd, *J* = 9.1, 7.8, 5.7 Hz, 1H), 7.31 (td, *J* = 9.3, 1.7 Hz, 1H), 7.27–7.20 (m, 1H), 7.16 (d, *J* = 7.5 Hz, 1H), 6.98 (td, *J* = 7.5, 1.1 Hz, 1H), 6.92 (d, *J* = 7.9 Hz, 1H), 4.77 (d, *J* = 2.4 Hz, 2H).

Example 96

Synthesis of 2,4-difluoro-*N,N*-dimethyl-3-(2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)benzamide

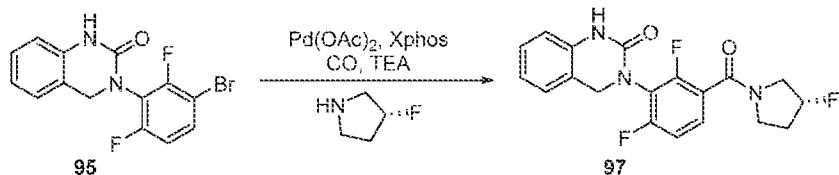


While under nitrogen, a solution of 3-(3-bromo-2,6-difluorophenyl)-3,4-dihydroquinazolin-2(1*H*)-one (100 mg, 0.295 mmol), xantphos (8.5 mg, 0.0147 mmol), palladium acetate (3.3 mg, 0.01474 mmol), triethylamine (0.2 mL, 1.474 mmol) and dimethylamine hydrochloride (120 mg, 1.474 mmol) in DMSO (1 mL) was treated with carbon monoxide (balloon). The solution was warmed to 75 °C with continued stirring for 12 h. The reaction mixture was diluted with ethyl acetate, washed with water and purified by preparative thin layer chromatography (20:1:0.1 = dichloromethane : methanol : acetic acid) to give the title compound (26 mg, 27%) as a white solid.

¹H NMR (400 MHz, Chloroform-*d*) δ 7.38 (ddd, *J* = 8.7, 7.1, 5.9 Hz, 1H), 7.23–7.14 (m, 2H), 7.11–7.00 (m, 2H), 6.98 (dd, *J* = 7.5, 1.1 Hz, 1H), 6.72 (d, *J* = 7.9 Hz, 1H), 4.82–4.69 (m, 2H), 3.10 (s, 3H), 2.97 (s, 3H).

Example 97

Synthesis of (*R*)-3-(2,6-difluoro-3-(3-fluoropyrrolidine-1-carbonyl)phenyl)-3,4-dihydroquinazolin-2(1*H*)-one

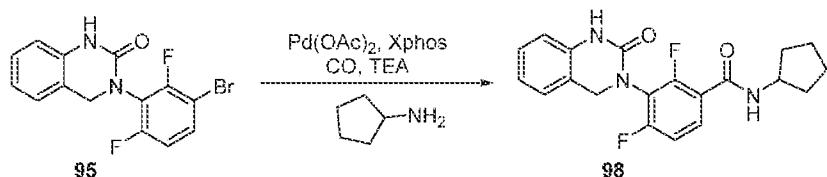


Proceeding as described in Example 96 above but substituting dimethylamine hydrochloride with (*R*)-3-fluoropyrrolidine provided the title compound as a white solid.

¹H NMR (400 MHz, Chloroform-*d*) δ 7.43 (dddd, *J* = 25.0, 20.9, 12.8, 5.0 Hz, 2H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.17–7.03 (m, 2H), 6.99 (t, *J* = 7.4 Hz, 1H), 6.72 (d, *J* = 7.9 Hz, 1H), 4.88–4.61 (m, 2H), 4.15–3.23 (m, 5H), 2.41–1.97 (m, 2H).

Example 98

Synthesis of *N*-cyclopentyl-2,4-difluoro-3-(2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)benzamide

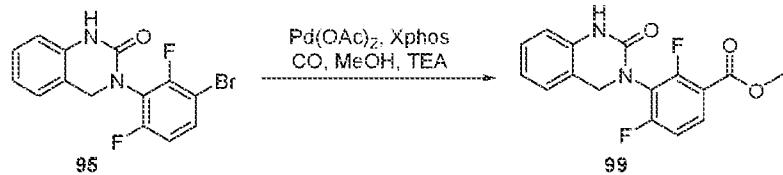


Proceeding as described in Example 96 above but substituting dimethylamine hydrochloride with cyclopentylamine provided the title compound as a white solid.

¹H NMR (400 MHz, Chloroform-*d*) δ 8.07 (td, *J* = 8.8, 6.3 Hz, 1H), 7.24–7.17 (m, 2H), 7.14–6.95 (m, 3H), 6.74 (d, *J* = 7.9 Hz, 1H), 6.57 (t, *J* = 9.2 Hz, 1H), 4.87–4.64 (m, 2H), 4.43–4.32 (m, 1H), 2.04 (dt, *J* = 12.5, 6.4 Hz, 2H), 1.66 (dddd, *J* = 12.5, 10.9, 8.4, 4.7 Hz, 4H), 1.46 (dt, *J* = 12.6, 6.1 Hz, 2H).

Example 99

Synthesis of methyl 2,4-difluoro-3-(2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)benzoate

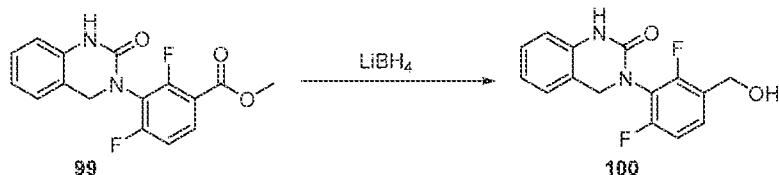


While under nitrogen, a solution of 3-(3-bromo-2,6-difluorophenyl)-3,4-dihydro-quinazolin-2(1*H*)-one (500 mg, 1.47 mmol), xantphos (42.6 mg, 0.74 mmol), palladium acetate (16.6 mg, 0.074 mmol), triethylamine (0.41 mL, 2.95 mmol) and methanol (0.48 mL, 11.8 mmol) in DMSO (5 mL) was treated with carbon monoxide (balloon). The solution was warmed to 75 °C with continued stirring for 12 h. The reaction mixture was diluted with ethyl acetate, washed with water and purified by flash column chromatography (30% ethyl acetate in hexanes) to give the title compound (265 mg, 56%) as a white solid.

¹H NMR (400 MHz, Chloroform-*d*) δ 7.97 (ddd, *J* = 9.0, 7.8, 6.2 Hz, 1H), 7.21 (td, *J* = 7.7, 1.5 Hz, 2H), 7.13–7.01 (m, 2H), 6.99 (td, *J* = 7.4, 1.1 Hz, 1H), 6.73 (dd, *J* = 8.0, 1.0 Hz, 1H), 4.80 (d, *J* = 13.9 Hz, 1H), 4.73 (d, *J* = 13.9 Hz, 1H), 3.91 (s, 3H).

Example 100

Synthesis of 3-(2,6-difluoro-3-(hydroxymethyl)phenyl)-3,4-dihydroquinazolin-2(1*H*)-one

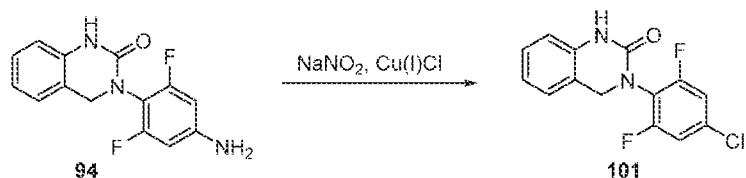


A solution of methyl 2,4-difluoro-3-(2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)benzoate (50 mg, 0.157 mmol) in THF was treated with lithium borohydride (6.8 mg, 0.314 mmol) and stirred at room temperature. After 30 min, the reaction was quenched with methanol and warmed to reflux for 1 h. After cooling to room temperature, the reaction was diluted with dichloromethane, washed with water and saturated aqueous sodium chloride. The resulting product was purified via preparative thin layer chromatography to give the title compound (33 mg, 72%) as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.72 (s, 1H), 7.44 (q, *J* = 8.2 Hz, 1H), 7.22–7.13 (m, 2H), 7.10 (d, *J* = 7.5 Hz, 1H), 6.91 (t, *J* = 7.4 Hz, 1H), 6.85 (d, *J* = 8.0 Hz, 1H), 5.35 (td, *J* = 5.8, 1.9 Hz, 1H), 4.67 (s, 2H), 4.50 (d, *J* = 5.8 Hz, 2H).

Example 101

Synthesis of 3-(4-chloro-2,6-difluorophenyl)-3,4-dihydroquinazolin-2(1*H*)-one



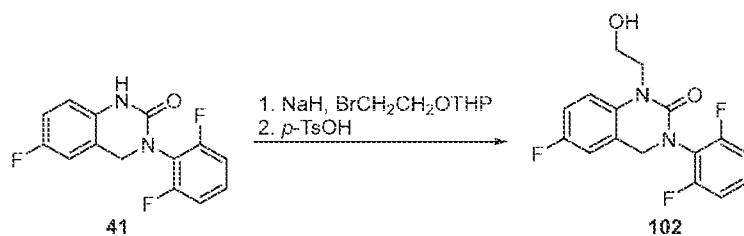
A solution of 3-(4-amino-2,6-difluorophenyl)-3,4-dihydroquinazolin-2(1H)-one (106 mg, 0.285 mmol) suspended in concentrated HCl (1 mL) and water (1 mL) was cooled to 0 °C and treated with NaNO₂ (40 mg, 0.578 mmol). After stirring for 30 min, copper (I) chloride (57.2 mg, 0.578 mmol) was added and stirring was continued for an additional 30

min, then warmed to 50 °C for 1 h. The reaction was diluted with ethyl acetate and washed with water. Purification by preparative thin layer chromatography gave the title compound (46 mg, 41%) as a white solid.

¹H NMR (400 MHz, Chloroform-*d*) δ 7.28 (s, 1H), 7.20 (td, *J* = 7.7, 1.6 Hz, 1H), 7.09–6.94 (m, 4H), 6.72 (dd, *J* = 7.9, 1.0 Hz, 1H), 4.74 (s, 2H).

Example 102

Synthesis of 3-(2,6-difluorophenyl)-6-fluoro-1-(2-hydroxyethyl)-3,4-dihydroquinazolin-2(1*H*)-one



Step 1:

To a solution of 3-(2,6-difluorophenyl)-6-fluoro-3,4-dihydroquinazolin-2(1*H*)-one (100 mg, 0.36 mmol) in DMF (3 mL) at 0 °C was added NaH (60%, 16 mg, 0.39 mmol). After stirring for 15 min, 2-(2-bromoethoxy)tetrahydro-2*H*-pyran (90 mg, 0.47 mmol) was added and stirring was continued for an additional 1 h. The reaction was diluted with water (1 mL) and extracted with ethyl acetate (10 mL). The organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated. Purification of the crude residue by flash column chromatography on SiO₂ gave 3-(2,6-difluorophenyl)-6-fluoro-1-(2-((tetrahydro-2*H*-pyran-2-yl)oxy)ethyl)-3,4-dihydroquinazolin-2(1*H*)-one (152 mg) as a white solid.

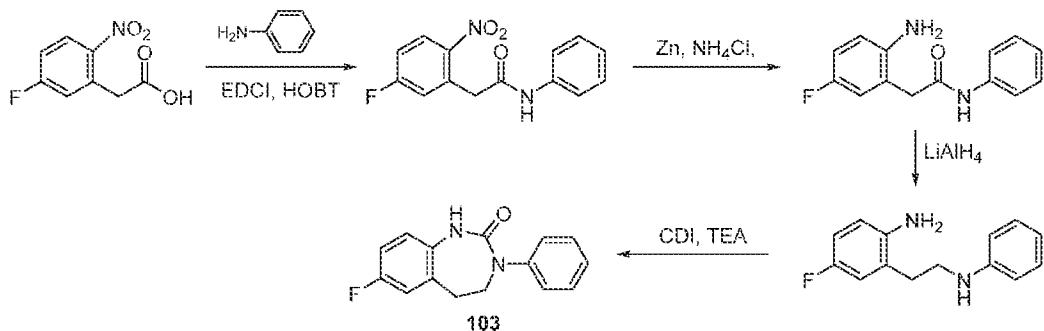
Step 2:

To a solution of 3-(2,6-difluorophenyl)-6-fluoro-1-(2-((tetrahydro-2*H*-pyran-2-yl)oxy)ethyl)-3,4-dihydroquinazolin-2(1*H*)-one (150 mg, 0.37 mmol) in MeOH (6 mL) at 25 °C was added p-TsOH monohydrate (7 mg, 0.04 mmol). The resulting reaction mixture was stirred at 25 °C for 8 h before it was concentrated. The residue was diluted with water (2 mL) and extracted with EtOAc (15 mL). The organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated. The crude residue was purified by flash column chromatography on SiO₂ gave 3-(2,6-di-fluorophenyl)-6-fluoro-1-(2-hydroxyethyl)-3,4-dihydroquinazolin-2(1*H*)-one as a solid.

¹H NMR (CDCl₃, 400 MHz) δ ppm 7.26–7.36 (m, 1H), 6.93–7.12 (m, 4H), 6.83 (dd, *J*=8.0, 2.7 Hz, 1H), 4.72 (s, 2H), 4.14 (t, *J*=5.0 Hz, 2H), 3.98 (t, *J*=5.0 Hz, 2H); LC/MS [M + H] = 323.1.

Example 103

Synthesis of 7-fluoro-3-phenyl-1,3,4,5-tetrahydro-2*H*-benzo[d][1,3]diazepin-2-one



Step 1:

To a solution of 2-(5-fluoro-2-nitrophenyl)acetic acid (500 mg, 2.51 mmol, 1 *eq*) and aniline (350.74 mg, 3.77 mmol, 1.5 *eq*) in DCM (10 mL) was added EDCI (962.66 mg, 5.02 mmol, 2 *eq*), HOBr (678.53 mg, 5.02 mmol, 2 *eq*) and TEA (1.40 mL, 10.04 mmol, 4 *eq*). The mixture was stirred at 20°C for 14 hrs before it was washed with water (30 mL). The aqueous phase was extracted with EtOAc (3x20 mL). The combined organic layer was washed with water (2x15 mL), brine (15 mL), dried over Na₂SO₄ and filtered and concentrated. The crude residue was purified by flash silica gel column chromatography (15–25% EtOAc in petroleum ether) to give 2-(5-fluoro-2-nitrophenyl)-*N*-phenylacetamide (590 mg, 85% yield) as a yellow solid.

Step 2:

To a solution of 2-(5-fluoro-2-nitrophenyl)-*N*-phenylacetamide (700 mg, 2.55 mmol, 1 *eq*) in MeOH (8 mL) and H₂O (2 mL) at 20°C was added NH₄Cl (1.37 g, 25.52 mmol, 10 *eq*) and then Zn (1.67 g, 25.52 mmol, 10 *eq*) in portions. Then the mixture was stirred at 50°C for 2 hrs before it was filtered. The filter cake was washed with MeOH (40 mL). The combined filtrate was concentrated to dryness. Then the mixture was co-evaporated with EtOH (2x15 mL) to give the crude product which was then re-taken up in EtOAc (30 mL), washed with water (2x5 mL), brine (2x5 mL), dried over anhydrous Na₂SO₄ and filtered.

The filtrate was concentrated to dryness to give 2-(2-amino-5-fluorophenyl)-*N*-phenylacetamide (560 mg) as a solid.

Step 3:

To a solution of 2-(2-amino-5-fluorophenyl)-*N*-phenylacetamide (430 mg, 1.76 mmol, 1 *eq*) in THF (4 mL) at 0°C was added LiAlH₄ (281.29 mg, 7.04 mmol, 4 *eq*). The reaction mixture was stirred at 70°C for 1.5 hrs before it was quenched with water (20 mL) at 0°C and then diluted with EtOAc (5 mL). The mixture was filtered through a pad of celite and the filter cake was washed with EtOAc (2x5 mL). The organic phase was separated and the aq. phase was extracted with EtOAc (2x8 mL). The combined organic phase was washed with water (2x5 mL), brine (2x5mL), dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated to dryness. The crude product was purified by flash silica gel column chromatography (20–25% EtOAc in petroleum ether) to give 4-fluoro-2-(phenylamino)-ethylaniline (270 mg, 57% yield) as an oil.

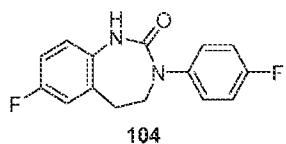
Step 4:

To a solution of 4-fluoro-2-(phenylamino)-ethylaniline (260 mg, 1.13 mmol, 1 *eq*) in THF (9 mL) at 15°C was added TEA (471.46 uL, 3.39 mmol, 3 *eq*) and CDI (219.69 mg, 1.35 mmol, 1.2 *eq*). The mixture was stirred at 30°C for 14 hrs before it was diluted with water (20 mL) and extracted with EtOAc (3x10 mL). The combined organic phase was washed with water (8 mL) and brine (8 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The crude solid was triturated with EtOAc (5 mL), MeOH (5 mL) and DMF (1 mL) and then collected by filtration. The solid was further triturated with MeOH (5 mL) and then with EtOAc (3 mL) and filtered to give 7-fluoro-3-phenyl-1,3,4,5-tetrahydro-2*H*-benzo[d][1,3]diazepin-2-one (47.9 mg, 16% yield) as a white solid.

¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.91 (s, 1H), 7.33–7.40 (m, 2H), 7.25–7.31 (m, 2H), 7.18–7.25 (m, 1H), 7.09–7.16 (m, 1H), 6.94–7.02 (m, 2H), 3.77–3.90 (t, *J*=5.2 Hz, 2H), 3.01–3.12 (t, *J*=4.8 Hz, 2H); LC/MS [M + H] = 256.8.

Example 104

Synthesis of 7-fluoro-3-(4-fluorophenyl)-1,3,4,5-tetrahydro-2*H*-benzo[d][1,3]diazepin-2-one

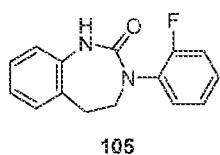


Proceeding as described in Example 103 above but substituting aniline with 4-fluoroaniline provided the title compound as a white solid.

¹H NMR (DMSO-*d*6, 400 MHz) δ ppm 8.93 (s, 1H), 7.29–7.35 (m, 2H), 7.15–7.23 (m, 2H), 7.10–7.15 (m, 1H), 6.94–7.01 (m, 2H), 3.77–3.82 (m, 2H), 3.05–3.10 (m, 2H); LC/MS [M + H] = 274.9.

Example 105

Synthesis of 3-(2-fluorophenyl)-1,3,4,5-tetrahydro-2*H*-benzo[d][1,3]diazepin-2-one

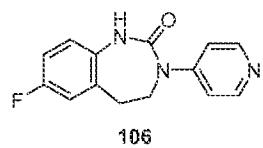


Proceeding as described in Example 103 above but substituting 2-(5-fluoro-2-nitrophenyl)acetic acid and aniline with 2-(2-nitrophenyl)acetic acid and 2-fluoroaniline provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ ppm 9.02 (s, 1H), 7.41 (td, *J*=7.9, 1.8 Hz, 1H), 7.25–7.36 (m, 2H), 7.19–7.25 (m, 1H), 7.08–7.14 (m, 3H), 6.89 (m, 1H), 3.73–3.81 (m, 2H), 3.03–3.10 (m, 2H); LC/MS [M + H] = 256.9.

Example 106

Synthesis of 7-fluoro-3-(pyridin-4-yl)-1,3,4,5-tetrahydro-2*H*-benzo[d][1,3]diazepin-2-one

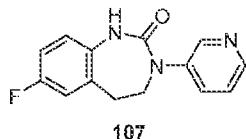


Proceeding as described in Example 103 above but substituting aniline with 4-aminopyridine provided the title compound as a white solid.

¹H NMR (DMSO-*d*6, 400 MHz) δ ppm 9.29 (s, 1H), 8.36–8.50 (m, 2H), 7.33–7.40 (m, 2H), 7.15 (dd, *J*=8.62, 5.20 Hz, 1H), 6.96–7.07 (m, 2H), 3.93–4.01 (m, 2H), 3.03–3.13 (m, 2H); LC/MS [M + H] = 257.9.

Example 107

Synthesis of 7-fluoro-3-(pyridin-3-yl)-1,3,4,5-tetrahydro-2*H*-benzo[*d*][1,3]diazepin-2-one

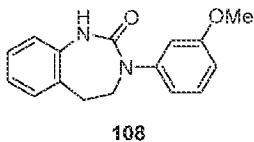


Proceeding as described in Example 103 above but substituting aniline with 3-aminopyridine provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.07 (s, 1H), 8.53 (d, *J*=2.1 Hz, 1H), 8.40 (d, *J*=4.6 Hz, 1H), 7.75 (br d, *J*=8.1 Hz, 1H), 7.41 (dd, *J*=8.1, 4.7 Hz, 1H), 7.14 (m, 1H), 6.95–7.05 (m, 2H), 3.83–3.92 (t, *J*=5.0 Hz, 2H), 3.06–3.14 (t, *J*=4.8 Hz, 2H); LC/MS [M + H]⁺ = 257.9.

Example 108

Synthesis of 3-(3-methoxyphenyl)-1,3,4,5-tetrahydro-2*H*-benzo[d][1,3]diazepin-2-one

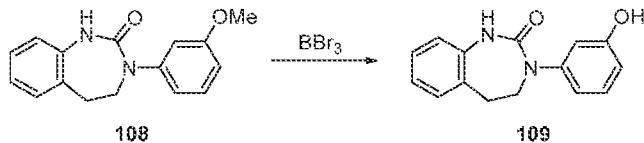


Proceeding as described in Example 103 above but aniline and 2-(5-fluoro-2-nitrophenyl)acetic acid with 3-methoxyaniline and 2-(2-nitrophenyl)acetic acid provided the title compound as a white solid.

¹H NMR (DMSO-*d*₆, 400 MHz) δ ppm 8.88 (s, 1H), 7.27 (t, *J*=8.03 Hz, 1H), 7.07–7.14 (m, 3H), 6.83–6.89 (m, 3H), 6.78–6.82 (m, 1H), 3.79–3.85 (m, 2H), 3.75 (s, 3H), 3.03–3.10 (m, 2H); LC/MS [M + H]⁺ = 269.0.

Example 109

Synthesis of 3-(3-hydroxyphenyl)-1,3,4,5-tetrahydro-2*H*-benzo[d][1,3]diazepin-2-one



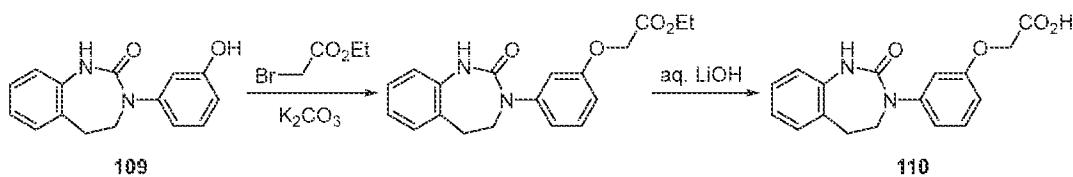
To a solution of 7-(3-methoxyphenyl)-1,3,4,5-tetrahydro-2*H*-benzo[*d*][1,3]diazepin-2-one (310 mg, 1.16 mmol, 1 eq) in DCM (7 mL) at 0°C was added BBr₃ (556.63 uL, 5.78

mmol, 5 *eq*). The reaction mixture was stirred at 0°C for 0.5 hr before it was quenched with addition of EtOH dropwise. The mixture was diluted with water (10 mL) and extracted with ethyl acetate (3x8 mL). The combined organic layer was washed with brine (20 mL), dried by Na₂SO₄, filtered and concentrated. The crude residue was purified by Combi-flash (silica gel, 0–15% MeOH in DCM) to give 3-(3-hydroxyphenyl)-1,3,4,5-tetrahydro-2*H*-benzo[d]-[1,3]diazepin-2-one as a white solid.

¹H NMR (DMSO-*d*₆, 400 MHz) δ ppm 9.49 (s, 1H), 8.84 (s, 1H), 7.06–7.17 (m, 4H), 6.80–6.92 (m, 1H), 6.66–6.72 (m, 2H), 6.60–6.64 (m, 1H), 3.74–3.84 (m, 2H), 3.00–3.08 (m, 2H); LC/MS [M + H] = 255.0.

Example 110

Synthesis of 2-(3-(2-oxo-1,2,4,5-tetrahydro-3*H*-benzo[d][1,3]diazepin-3-yl)phenoxy)acetic acid



Step 1:

To a solution of 3-(3-hydroxyphenyl)-1,3,4,5-tetrahydro-2*H*-benzo[d]-[1,3]diazepin-2-one (115 mg, 452.25 umol, 1 *eq*) in DMF (1 mL) was added K₂CO₃ (187.51 mg, 1.36 mmol, 3 *eq*) and ethyl 2-bromoacetate (83.08 mg, 497.48 umol, 1.1 *eq*). The mixture was stirred at 90°C for 16 hr before it was diluted with water (3 mL) and extracted with ethyl acetate (3x3 mL). The combined organic was washed with water (5 mL), dried by Na₂SO₄, filtered and concentrated. The crude was purified by Combi-flash (silica gel, 30–80% ethyl acetate in petrol ether) to give ethyl 2-(3-(2-oxo-1,2,4,5-tetrahydro-3*H*-benzo[d][1,3]-diazepin-3-yl)phenoxy)acetate (90.2 mg, 59% yield) as a white solid.

Step 2:

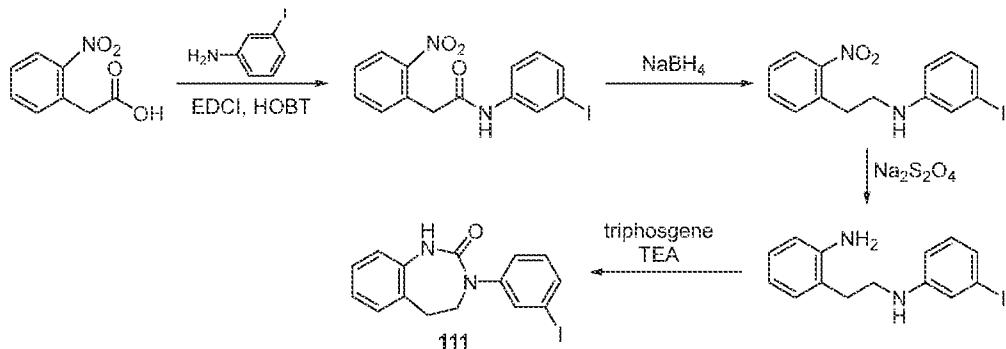
To a suspension of ethyl 2-(3-(2-oxo-1,2,4,5-tetrahydro-3*H*-benzo[d][1,3]diazepin-3-yl)phenoxy)acetate (85 mg, 249.73 umol, 1 *eq*) in THF (1.2 mL) was added LiOH (2 M, 0.4 mL, 3.20 *eq*). The mixture was stirred at 15°C for 0.5 hr before it was diluted with water (1.5 mL) and extracted with ethyl acetate (2x2 mL). The aq. layer was separated and acidified with

1N aq. HCl pH to 6 to generate precipitate. The solid was collected by filtration and rinsed with water (5 mL), dried to give 2-(3-(2-oxo-1,2,4,5-tetrahydro-3H-benzo[d][1,3]diazepin-3-yl)phenoxy)acetic acid (36.7 mg, 47% yield, 99.58%) as a white solid.

¹H NMR (DMSO-*d*₆, 400 MHz) δ ppm 12.99 (br s, 1H), 8.87 (s, 1H), 7.23–7.30 (m, 1H), 7.06–7.15 (m, 3H), 6.83–6.93 (m, 3H), 6.76 (dd, *J*=8.13, 1.90 Hz, 1H), 4.67 (s, 2H), 3.79–3.86 (m, 2H), 3.03–3.08 (m, 2H); LC/MS [M + H] = 312.9.

Example 111

Synthesis of 3-(3-iodophenyl)-1,3,4,5-tetrahydro-2*H*-benzo[d][1,3]diazepin-2-one



Steps 1 – 2:

Proceeding as described in Example 103 above but substituting aniline and 2-(5-fluoro-2-nitro-phenyl)acetic acid with 3-idoaniline and 2-(2-nitrophenyl)acetic acid provided 3-iodo-*N*-(2-nitrophenethyl)aniline.

Steps 3:

To a solution of 3-iodo-*N*-(2-nitrophenethyl)aniline (1.39 g, 3.78 mmol, 1 *eq*) in THF (15 mL) and H₂O (10 mL) was added Na₂S₂O₄ (6.57 g, 37.75 mmol, 8.22 mL, 10 *eq*) at 20–25°C. The reaction mixture was stirred at 20–25°C for 16 before it was extracted with EtOAc (3x10 mL). The combined organic layer was washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated. The crude was purified by flash silica gel column chromatography (0–25% EtOAc in petroleum ether) to provide *N*-(2-aminophen-ethyl)-3-iodoaniline (380 mg, 24% yield).

Steps 4:

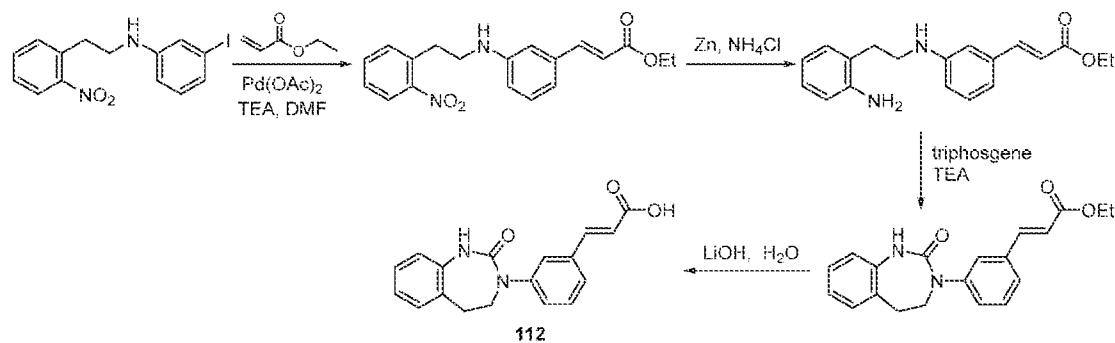
To a solution of *N*-(2-aminophen-ethyl)-3-iodoaniline (768.81 umol, 1 *eq*) in MeCN (5 mL) at 0°C was added TEA (107.01 uL, 768.81 umol, 1 *eq*) and bis(trichloromethyl) carbonate (91.26 mg, 307.52 umol, 0.4 *eq*). The reaction mixture was stirred at 0°C for 0.5 hr

and then stirred for 1hr at 15°C. The reaction mixture was diluted saturated NaHCO₃ aq. (10 mL) extracted with EtOAc (3x5 mL). The combined organic layer was washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated. The crude was purified by prep-TLC (petroleum ether: EtOAc = 1:1) to give a yellow solid. This solid was suspended in EtOAc (3 mL) and stirred for 3 hr to give a white suspension. The solid was collected by filtration and suspended in H₂O (2 mL) and then lyophilized to provide 3-(3-iodophenyl)-1,3,4,5-tetrahydro-2*H*-benzo[d][1,3]diazepin-2-one (15.0 mg, 5% yield) as a white solid.

¹H NMR (DMSO-*d*₆, 400 MHz) δ ppm 8.95 (s, 1H), 7.69 (t, *J*=1.75 Hz, 1H), 7.58 (d, *J*=8.00 Hz, 1H), 7.32 (br d, *J*=6.75 Hz, 1H), 7.14–7.20 (m, 1H), 7.07–7.13 (m, 3H), 6.84–6.91 (m, 1H), 3.79–3.86 (m, 2H), 3.04–3.10 (m, 2H); LC/MS [M + H]⁺ = 365.0.

Example 112

Synthesis of (*E*)-3-(3-(2-oxo-1,2,4,5-tetrahydro-3*H*-benzo[d][1,3]diazepin-3-yl)phenyl)acrylic acid



Step 1:

To a solution of 3-iodo-*N*-(2-nitrophenethyl)aniline (1.96 g, 5.32 mmol, 1 *eq*) in DMF (30 mL) at 15°C was added TEA (1.85 mL, 13.31 mmol, 2.5 *eq*), Pd(OAc)₂ (120 mg, 532.36 umol, 0.1 *eq*) and ethyl acrylate (1.33 g, 13.31 mmol, 2.5 *eq*). The mixture was stirred at 120°C for 27 hours before it was allowed to cool and diluted with H₂O (150 mL) extracted with ethyl acetate (3x50 mL). The combined organic layer was washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purification by flash silica gel column chromatography (0–30% ethyl acetate in petroleum ether) to provide ethyl (*E*)-3-(3-((2-nitrophenethyl)amino)phenyl)acrylate (1.55 g, 85% yield) as a yellow solid.

Step 2:

To a solution of ethyl (*E*)-3-((2-nitrophenethyl)amino)phenyl)acrylate (1.55 g, 4.55 mmol, 1 *eq*) in methanol (20 mL) was added Zn (2.38 g, 36.43 mmol, 8 *eq*), NH₄Cl (2.44 g, 45.54 mmol, 10 *eq*) and H₂O (5 mL). The mixture was stirred at 50°C for 2 hours and then was stirred at 65°C for additional 1 hour before solid was filtered off and the filtrate was concentrated under reduced pressure. The residue was dissolved with ethyl acetate (100 mL) and water (100 mL) and then extracted with ethyl acetate (3x40 mL). The combined organic layers were washed with water (100 mL) and brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give ethyl (*E*)-3-((2-aminophenethyl)amino)phenyl)acrylate as a brown gum (1.24 g, 88% yield). This crude product was used in the next step directly without further purification.

Step 3:

To a solution of ethyl (*E*)-3-((2-aminophenethyl)amino)phenyl)acrylate (400 mg, 1.29 mmol, 1 *eq*) in CH₃CN (16 mL) at 0°C was added TEA (179.37 uL, 1.29 mmol, 1 *eq*) then added triphosgene (152.97 mg, 515.48 umol, 0.4 *eq*). The mixture was stirred at 0°C for 30 min then warmed to 15°C and stirred additionally for 1.5 hour. The reaction mixture was quenched by addition of saturated aq. NH₄Cl (10 mL) and water (5 mL) then extracted with ethyl acetate (2x10 mL). The combined organic layers were dried over Na₂SO₄ and concentrated. The crude residue was purified by flash column chromatography on silica gel (0–25% ethyl acetate in petroleum ether) ethyl (*E*)-3-(3-(2-oxo-1,2,4,5-tetrahydro-3H-benzo[d][1,3]diazepin-3-yl)phenyl)acrylate (175 mg) was as a yellow gum.

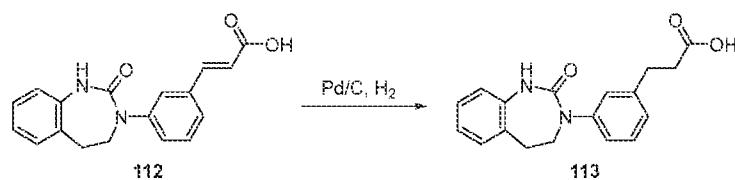
Step 4:

To a solution of ethyl (*E*)-3-(3-(2-oxo-1,2,4,5-tetrahydro-3H-benzo[d][1,3]diazepin-3-yl)phenyl)acrylate (175 mg) in THF (2 mL) at 15°C was added LiOH.H₂O (2 M, 780 uL). The mixture was stirred at 15 °C for 1 hour and then at 25°C for 14 hours. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (2x5 mL). The aqueous phase was acidified with 2M aq. HCl to pH 4 and then concentrated under reduced pressure. The crude residue was purified by prep-HPLC (column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: [water(0.05%HCl)-ACN]; B%: 23%-63%,10 min) and lyophilization to give (*E*)-3-(3-(2-oxo-1,2,4,5-tetrahydro-3H-benzo[d][1,3]diazepin-3-yl)phenyl)acrylic acid as a solid (70 mg, 18% yield for two steps).

¹H NMR (DMSO-*d*₆, 400 MHz) δ ppm 8.95 (s, 1H), 7.65 (s, 1H), 7.51–7.62 (m, 2H), 7.41 (t, *J*=7.8 Hz, 1H), 7.32–7.36 (m, 1H), 7.08–7.15 (m, 3H), 6.85–6.90 (m, 1H), 6.57 (d, *J*=16.1 Hz, 1 H), 3.83–3.90 (m, 2H), 3.06–3.11 (m, 2H); LC/MS [M + H]⁺ = 308.9.

Example 113

Synthesis of 3-(3-(2-oxo-1,2,4,5-tetrahydro-3*H*-benzo[d][1,3]diazepin-3-yl)phenyl)propanoic acid

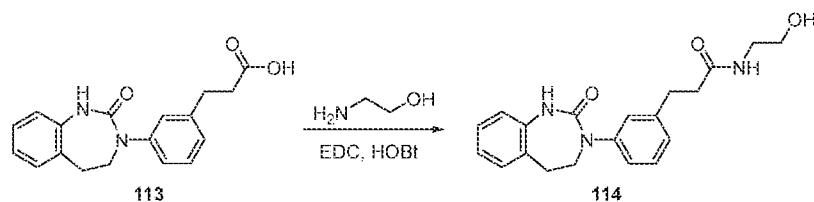


To a solution of (*E*)-3-(3-(2-oxo-1,2,4,5-tetrahydro-3*H*-benzo[d][1,3]diazepin-3-yl)phenyl)acrylic acid as a solid (50 mg, 162.16 umol, 1 *eq.*) in MeOH (3 mL) at 20 °C was added Pd/C (20 mg, 10% wt). The mixture under a H₂ atmosphere (30 Psi) was stirred at 20°C for 14 hours before the catalyst was filtered off. The filtrate was concentrated under reduced pressure to give 3-(3-(2-oxo-1,2,4,5-tetrahydro-3*H*-benzo[d][1,3]diazepin-3-yl)phenyl)propanoic acid as a white solid (20 mg).

¹H NMR (methanol-*d*₄, 400 MHz) δ ppm 7.28–7.37 (m, 1H), 7.12–1.17 (m, 5H), 7.00 (d, *J*=7.5 Hz, 1H), 6.92–6.97 (m, 1H), 3.89–3.94 (m, 2H), 3.14–3.19 (m, 2H), 2.90–2.97 (m, 2H), 2.62 (t, *J*=7.65 Hz, 2H).

Example 114

Synthesis of *N*-(2-hydroxyethyl)-3-(3-(2-oxo-1,2,4,5-tetrahydro-3*H*-benzo[d][1,3]diazepin-3-yl)phenyl)propanamide



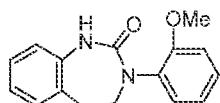
To a solution of 3-(3-(2-oxo-1,2,4,5-tetrahydro-3*H*-benzo[d][1,3]diazepin-3-yl)phenyl)propanoic acid (crude, 48.33 umol, 1 *eq.*) in THF (2 mL) was added TEA (10.09 uL, 72.50 umol, 1.5 *eq.*), EDCI (11.12 mg, 58.00 umol, 1.2 *eq.*) and HOBT (7.84 mg, 58.00 umol,

1.2 *eq*) then added aminoethanol (3.54 mg, 58.00 umol, 1.2 *eq*). The mixture was stirred at 15°C for 15 hours before it was diluted with water (10 mL) and extracted with a mixture of ethyl acetate and methanol (10:1 = v:v, 3x8 mL). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by preparative TLC (ethyl acetate : methanol=10:1). The product was then lyophilized to give *N*-(2-hydroxyethyl)-3-(3-(2-oxo-1,2,4,5-tetrahydro-3*H*-benzo[d][1,3]diazepin-3-yl)-phenyl)propanamide (5.0 mg, 29% yield for two steps) as a white solid.

¹H NMR (methanol-*d*4, 400 MHz) δ ppm 7.29–7.35 (m, 1H), 7.10–7.18 (m, 5H), 7.01 (d, *J*=8.00 Hz, 1H), 6.92–6.97 (m, 1H), 3.88–3.95 (m, 2H), 3.51 (t, *J*=5.82 Hz, 2H), 3.22–3.28 (m, 2H), 3.14–3.20 (m, 2H), 2.93 (t, *J*=7.57 Hz, 2H), 2.51 (t, *J*=7.57 Hz, 2H); LC/MS [M + H] = 353.8.

Example 115

Synthesis of 3-(2-methoxyphenyl)-1,3,4,5-tetrahydro-2*H*-benzo[d][1,3]diazepin-2-one



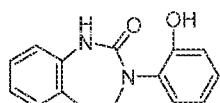
115

Proceeding as described in Example 103 above but substituting aniline and 2-(5-fluoro-2-nitro-phenyl)acetic acid with 2-methoxyaniline and 2-(2-nitrophenyl)acetic acid provided the title compound as a white solid.

¹H NMR (DMSO-*d*6, 400 MHz) δ ppm 8.79 (s, 1H), 7.27 (t, *J*=8.0 Hz, 1H), 7.16–7.18 (m, 1H), 7.07–7.16 (m, 4H), 6.84–6.94 (m, 2H), 3.77 (s, 3H), 3.62–3.64 (m, 2H), 3.03–3.06 (m, 2H); LC/MS [M + H] = 269.0.

Example 116

Synthesis of 3-(2-hydroxyphenyl)-1,3,4,5-tetrahydro-2*H*-benzo[d][1,3]diazepin-2-one

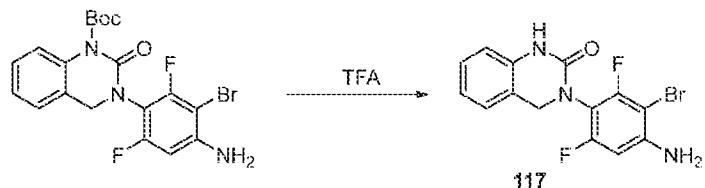


116

Proceeding as described in Example 109 above but substituting 3-(3-methoxyphenyl)-1,3,4,5-tetrahydro-2*H*-benzo[d][1,3]diazepin-2-one with 3-(2-methoxyphenyl)-1,3,4,5-tetrahydro-2*H*-benzo[d][1,3]diazepin-2-one provided the title compound as a white solid.
¹H NMR (DMSO-*d*₆, 400 MHz) δ ppm 8.76 (s, 1H), 7.07–7.11 (m, 5H), 6.78–6.90 (m, 3H), 3.64–3.66 (m, 2H), 3.05–3.07 (m, 2H); LC/MS [M + H] = 254.9.

Example 117

Synthesis of 3-(4-amino-3-bromo-2,6-difluorophenyl)-3,4-dihydroquinazolin-2(*H*)-one

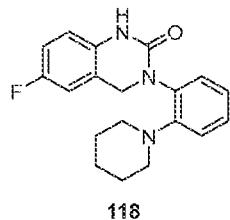


A mixture of *tert*-butyl 3-(4-amino-3-bromo-2,6-difluorophenyl)-2-oxo-3,4-dihydro-quinazoline-1(*H*)-carboxylate (100 mg) in DCM (2 mL) and TFA (1 mL) at 25 °C was stirred for 1 h before it was concentrated under reduced pressure. The residue was partitioned between EtOAc (8 mL) and saturated aq. NaHCO₃ solution (5 mL). The organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated to provide the title compound as a white solid.

¹H NMR (CDCl₃, 300 MHz) δ 7.21–7.26 (m, 1H), 6.98–7.08 (m, 2H), 6.78–6.80 (m, 1H), 6.73 (d, *J*=7.7 Hz, 1H), 6.43 (dd, *J*=11.3, 2.2 Hz, 2H), 4.74(s, 2H); LC/MS [M + H] = 354.0.

Example 118

Synthesis of 6-fluoro-3-(2-(piperidin-1-yl)phenyl)-3,4-dihydroquinazolin-2(*H*)-one

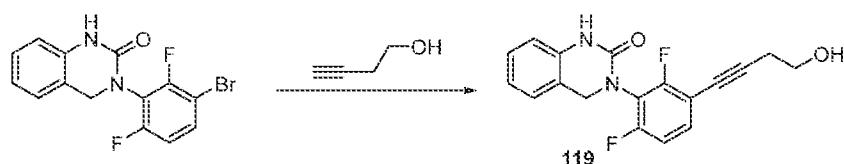


Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine with 2-(piperidin-1-yl)aniline provided the title compound as a white solid.

¹H NMR (CDCl₃, 300 MHz) δ 7.46 (s, 1H), 7.21–7.30 (m, 2H), 7.02–7.18 (m, 2H), 6.76–6.88 (m, 2H), 6.65–6.72 (m, 1H), 5.10 (bs, 1H), 4.42 (bs, 1H), 3.00 (bs, 2H), 2.75 (bs, 2H), 1.37–1.50 (m, 6H).

Example 119

Synthesis of 3-(2,6-difluoro-3-(4-hydroxybut-1-yn-1-yl)phenyl)-3,4-dihydroquinazolin-2(1*H*)-one

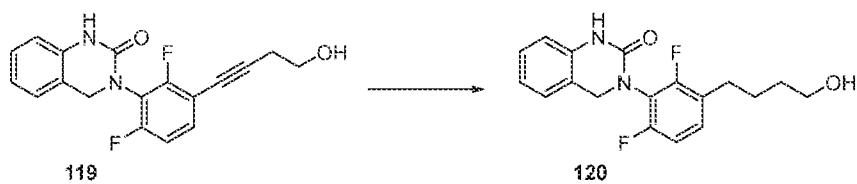


To a mixture of 3-(3-bromo-2,6-difluorophenyl)-3,4-dihydroquinazolin-2(1*H*)-one (400 mg, 1.18 mmol) and but-3-yn-1-ol (413 mg, 5.90 mmol) in DMF (5 mL) at 25 °C under a N₂ atmosphere was added Pd(PPh₃)₂Cl₂ catalyst (83 mg, 0.12 mmol), CuI (22 mg, 0.12 mmol) and Et₃N (1.64 mL, 11.79 mmol). The reaction mixture was heated at 75 °C for 16 h before it was allowed to cool to ambient temperature and filtered through a pad of Celite. The filtrate was diluted with EtOAc (10 mL) and water (10 mL). The organic layer was washed with diluted aq. HCl (5 mL), brine, dried (Na₂SO₄), filtered and concentrated. The crude residue was purified by flash column chromatography on SiO₂ (0–40% ethyl acetate in hexanes) to provide the title compound as a solid.

¹H NMR (DMSO-*d*6, 300 MHz) δ 9.80 (s, 1H), 7.50–7.57 (m, 2H), 7.19–7.26 (m, 1H), 7.13 (d, *J*=6.6 Hz, 1H), 6.96 (t, *J*=7.3 Hz, 1H), 6.89 (d, *J*=7.7 Hz, 1H), 4.80 (s, 2H), 3.72 (t, *J*=6.5 Hz, 2H), 2.30 (t, *J*=6.5 Hz, 2H); LC/MS [M + H] = 329.1.

Example 120

Synthesis of 3-(2,6-difluoro-3-(4-hydroxybutyl)phenyl)-3,4-dihydroquinazolin-2(1*H*)-one

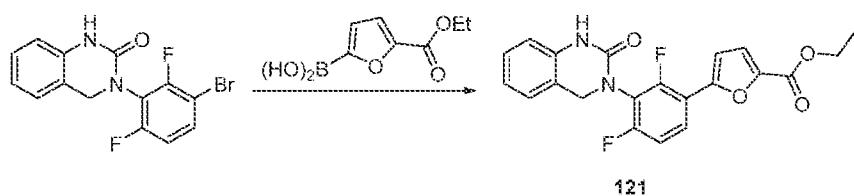


A mixture of 3-(2,6-difluoro-3-(4-hydroxybut-1-yn-1-yl)phenyl)-3,4-dihydroquinazolin-2(1*H*)-one (100 mg) and Pd/C (10% wt., 25 mg) in EtOAc (5 mL) under H₂ (balloon) for 2 h before the catalyst was filtered off. The filtrate was concentrated to provide 3-(2,6-difluoro-3-(4-hydroxybutyl)phenyl)-3,4-dihydroquinazolin-2(1*H*)-one as a solid.

¹H NMR (CDCl₃, 300 MHz) δ 8.55 (s, 1H), 7.51 (s, 1H), 7.13–7.28 (m, 2H), 6.91–7.08 (m, 3H), 6.75 (d, *J*=7.6 Hz, 1H), 4.79 (s, 2H), 3.68 (t, *J*=6.3 Hz, 2H), 2.69 (t, *J*=6.6 Hz, 2H), 1.62–1.74 (m, 4H); LC/MS [M + H]⁺ = 333.2.

Example 121

Synthesis of ethyl 5-(2,4-difluoro-3-(2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)phenyl)furan-2-carboxylate

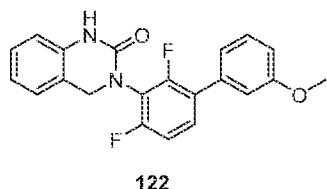


To a mixture of 3-(3-bromo-2,6-difluorophenyl)-3,4-dihydroquinazolin-2(1*H*)-one (220 mg, 0.64 mmol), (5-(ethoxycarbonyl)furan-2-yl)boronic acid (179 mg, 0.97 mmol) and Na₂CO₃ (407 mg, 2.59 mmol) in dioxane (6 mL) and H₂O (1 mL) under a N₂ atmosphere was added Pd(PPh₃)₄ catalyst (75 mg, 0.06 mmol) was heated at 100 °C for 7 h before it was allowed to cool to 25 °C and filtered. The filtrate was partitioned between EtOAc (20 mL) and water (10 mL). The organic layer was washed with brine, dried (Na₂SO₄), filtered and concentrated. The crude residue was purified by flash column chromatography on SiO₂ (0 – 30% ethyl acetate in hexanes) to provide the title compound as a white solid.

¹H NMR (DMSO-*d*6, 300 MHz) δ 9.84 (s, 1H), 7.89–7.94 (m, 1H), 7.39–7.47 (m, 2H), 7.14–7.26 (m, 2H), 7.05 (t, *J*=3.5 Hz, 1H), 6.88–6.99 (m, 2H), 4.78 (s, 2H), 4.33 (q, *J*=7.0 Hz, 2H), 1.33 (t, *J*=7.1 Hz, 2H); LC/MS [M + H]⁺ = 399.2.

Example 122

Synthesis of 3-(2,4-difluoro-3'-methoxy-[1,1'-biphenyl]-3-yl)-3,4-dihydroquinazolin-2(1*H*)-one

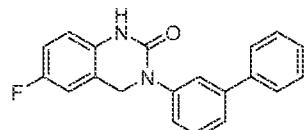


Proceeding as described in Example 121 above but substituting (5-(ethoxycarbonyl)furan-2-yl)boronic acid with 3-methoxyphenylboronic acid provided the title compound as a white solid.

¹H NMR (DMSO-*d*6, 300 MHz) δ 9.77 (s, 1H), 7.56–7.63 (m, 1H), 7.42 (t, *J*=7.8 Hz, 1H), 7.33 (t, *J*=6.3 Hz, 1H), 7.08–7.26 (m, 4H), 6.88–7.03 (m, 3H), 4.79 (s, 2H), 3.81 (s, 3H); LC/MS [M + H] = 367.2.

Example 123

Synthesis of 3-([1,1'-biphenyl]-3-yl)-6-fluoro-3,4-dihydroquinazolin-2(1*H*)-one



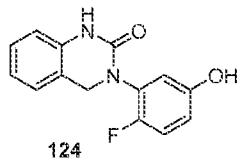
123

Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine with [1,1'-biphenyl]-3-amine provided the title compound as a white solid.

¹H NMR (DMSO-*d*6, 300 MHz) δ 9.66 (s, 1H) 7.96 (dd, *J*=8.3, 1.7 Hz, 2H) 7.64 (d, *J*=2.0 Hz, 1H) 7.54–7.43 (m, 4H) 7.42–7.33 (m, 2H) 7.10–7.05 (m, 2H) 6.88 (dd, *J*=8.6, 4.8 Hz, 1H) 4.90 (s, 2H).

Example 124

Synthesis of 3-(2-fluoro-5-hydroxyphenyl)-3,4-dihydroquinazolin-2(1*H*)-one

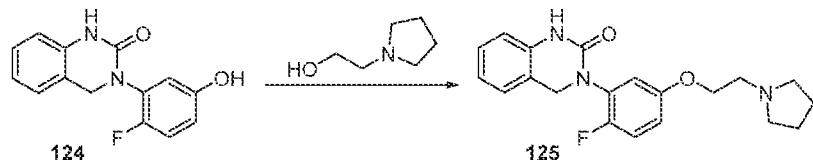


Proceeding as described in Example 26 above but substituting 2,6-difluoroaniline with 5-fluoro-3-hydroxyaniline provided the title compound as a white solid.

¹H NMR (DMSO-*d*6, 300 MHz) δ 9.62 (s, 1H), 9.51 (bs, 1H), 7.00–7.19 (m, 3H), 6.81–6.88 (m, 1H), 6.75–6.79 (m, 2H), 6.55–6.65 (m, 1H), 4.75 (s, 2H).

Example 125

Synthesis of 3-(2-fluoro-5-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-3,4-dihydroquinazolin-2(1*H*)-one

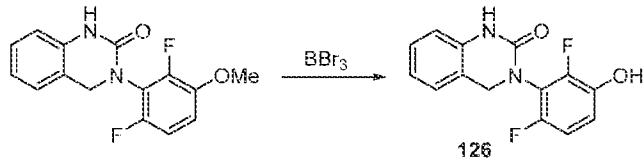


To a mixture of 3-(2-fluoro-5-hydroxyphenyl)-3,4-dihydroquinazolin-2(1*H*)-one (200 mg, 0.77 mmol), 2-(pyrrolidin-1-yl)ethanol (134 mg, 1.16 mmol) and Ph₃P (366 mg, 1.39 mmol) in dioxane (6 mL) in THF (1 mL) under a N₂ atmosphere at 0 °C was added a solution of DIAD (274 μ L, 1.39 mmol) dropwise. The resulting mixture was stirred from 0 – 25 °C over 24 h before it was concentrated. The crude mixture was purified by flash column chromatography on SiO₂ to provide the title compound as a solid.

¹H NMR (CDCl₃, 300 MHz) δ 7.58 (s, 1H), 7.22 (t, *J*=7.2 Hz, 1H), 6.93–7.09 (m, 4H), 6.84–6.88 (m, 1H), 6.78 (d, *J*=7.7 Hz, 1H), 4.78 (s, 2H), 4.21 (t, *J*=5.4 Hz, 2H), 3.08 (t, *J*=5.5 Hz, 2H), 2.88 (bs, 4H), 1.92 (bs, 4H); LC/MS [M + H] = 356.2.

Example 126

Synthesis of 3-(2,6-difluoro-3-hydroxyphenyl)-3,4-dihydroquinazolin-2(1*H*)-one

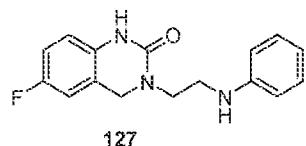


Proceeding as described in Example 109 above but substituting 7-(3-methoxyphenyl)-1,3,4,5-tetrahydro-2*H*-benzo[d][1,3]diazepin-2-one with 3-(2,6-difluoro-3-methoxyphenyl)-3,4-dihydroquinazolin-2(1*H*)-one provided the title compound as a white solid.

¹H NMR (DMSO-*d*6, 300 MHz) δ 9.97 (s, 1H), 9.70 (s, 1H), 7.13–7.23 (m, 2H), 6.87–7.04 (m, 4H), 4.70 (s, 2H); LC/MS [M + H] = 277.1.

Example 127

Synthesis of 6-fluoro-3-(2-(phenylamino)ethyl)-3,4-dihydroquinazolin-2(1*H*)-one

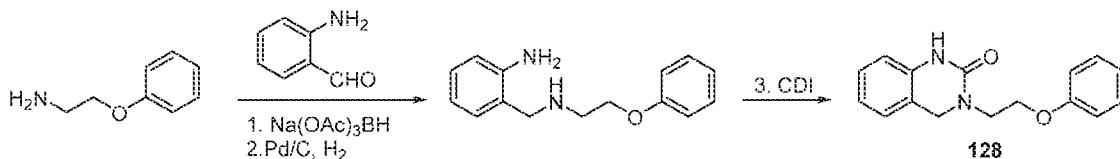


Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine with *N*¹-phenylethane-1,2-diamine provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.22 (s, 1H), 7.06 (dd, *J*=8.5, 7.2 Hz, 2H), 6.96 (dd, *J*=9.1, 2.8 Hz, 2H), 6.76 (dd, *J*=9.6, 4.9 Hz, 1H), 6.70–6.56 (m, 2H), 6.52 (t, *J*=7.2 Hz, 1H), 5.67 (t, *J*=5.9 Hz, 1H), 4.50 (s, 2H), 3.44 (t, *J*=6.8 Hz, 2H), 3.28–3.13 (m, 2H).

Example 128

Synthesis of 3-(2-phenoxyethyl)-3,4-dihydroquinazolin-2(1*H*)-one

**Step 1:**

While under nitrogen, a solution of 2-nitrobenzaldehyde (577 mg, 3.82 mmol) and 2-phenoxyethylamine (524 mg, 3.82 mmol) in dichloroethane (10 mL) was treated with acetic acid (0.24 mL, 4.2 mmol) and warmed to 50 °C for 3 h. After cooling to room temperature, sodium triacetoxyborohydride (1,208 mg, 5.73 mmol) was added and stirring was continued for approximately 16 h. Once complete, the reaction was quenched with saturated aqueous NaHCO₃ (50 mL), extracted with ethyl acetate (25 mL, 3x), washed with saturated aqueous sodium chloride (60 mL), dried over sodium sulfate, filtered and concentrated. Purification by medium pressure liquid chromatography (MPLC) (silica, 25 g, 5–90% hexanes in ethyl acetate) gave *N*-(2-nitrobenzyl)-2-phenoxyethan-1-amine as a pale yellow solid (650 mg, 62%).

Step 2:

A solution of *N*-(2-nitrobenzyl)-2-phenoxyethan-1-amine (600 mg, 2.20 mmol) and Pd/C (10% wt., 234 mg, 0.22 mmol) in ethyl acetate was purged with nitrogen, evacuated and treated with hydrogen (balloon). After stirring for 2 h, the reaction vessel was evacuated, purged with nitrogen and filtered through Celite. The Celite was washed with ethyl acetate and the combined filtrate was concentrated to give 2-(((2-phenoxyethyl)amino)methyl)aniline as an off-white solid (500 mg, 94%).

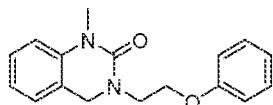
Step 3:

While under nitrogen, a solution of 2-(((2-phenoxyethyl)amino)methyl)aniline (500 mg, 2.06 mmol) in THF (10 mL) was treated with 1,1'-carbonyldiimidazole (669 mg, 4.13 mmol) and warmed to 65 °C. After stirring for approximately 16 h, the solution was allowed to cool to room temperature and concentrated. The resulting residue was suspended in a mixture of ethyl acetate and diethyl ether and filtered. The resulting solid was washed with ethyl acetate and dried to give the title compound as off-white solid (350 mg, 63%).

¹H NMR (400 MHz, DMSO-*d*6) δ 9.24 (s, 1H), 7.33–7.22 (m, 2H), 7.17–7.02 (m, 2H), 7.00–6.81 (m, 4H), 6.77 (dd, *J*=7.9, 1.1 Hz, 1H), 4.58 (s, 2H), 4.15 (t, *J*=5.8 Hz, 2H), 3.67 (t, *J*=5.8 Hz, 2H).

Example 129

Synthesis of 1-methyl-3-(2-phenoxyethyl)-3,4-dihydroquinazolin-2(1*H*)-one



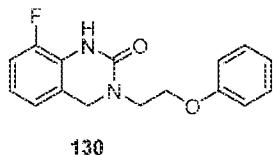
129

While under nitrogen, a solution of 3-(2-phenoxyethyl)-3,4-dihydroquinazolin-2(1*H*)-one (150 mg, 0.56 mmol) in DMF (5 mL) was cooled to 0 °C (ice bath), and treated with NaH (60% suspension oil, 16 mg, 0.67 mmol). After stirring for 1 hour, iodomethane (0.04 mL, 0.67 mmol) was added and the ice-bath was removed. After an additional 16 h, the reaction was quenched with saturated aqueous ammonium chloride (50 mL), extracted with diethyl ether (70 mL), washed with saturated aqueous sodium chloride (50 mL), dried over sodium sulfate and concentrated and filtered. The crude product was purified by MPLC (10-90% ethyl acetate in hexanes) to afford the title compound as off-white solid (120 mg, 76%).

¹H NMR (400 MHz, CDCl₃) δ 7.36–7.19 (m, 3H), 7.07 (dd, *J*=7.5, 1.4 Hz, 1H), 7.03–6.73 (m, 5H), 4.60 (s, 2H), 4.24 (t, *J*=5.2 Hz, 2H), 3.82 (t, *J*=5.2 Hz, 2H), 3.30 (s, 3H).

Example 130

Synthesis of 8-fluoro-3-(2-phenoxyethyl)-3,4-dihydroquinazolin-2(1*H*)-one

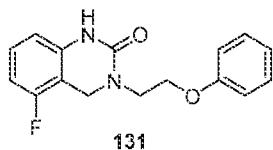


Proceeding as described in Example 128 above but substituting 2-nitrobenzaldehyde with 3-fluoro-2-nitrobenzaldehyde provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.28 (s, 1H), 7.28 (dd, *J*=8.7, 7.2 Hz, 2H), 7.11–6.99 (m, 1H), 7.02–6.78 (m, 5H), 4.63 (s, 2H), 4.17 (t, *J*=5.7 Hz, 2H), 3.69 (t, *J*=5.7 Hz, 2H).

Example 131

Synthesis of 5-fluoro-3-(2-phenoxyethyl)-3,4-dihydroquinazolin-2(1*H*)-one

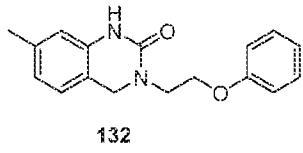


Proceeding as described in Example 128 above but substituting 2-nitrobenzaldehyde with 2-fluoro-6-nitrobenzaldehyde provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.47 (d, *J*=1.9 Hz, 1H), 7.28 (dd, *J*=8.7, 7.2 Hz, 2H), 7.16 (td, *J*=8.1, 6.2 Hz, 1H), 7.06–6.78 (m, 3H), 6.71 (ddd, *J*=9.4, 8.3, 1.0 Hz, 1H), 6.60 (d, *J*=8.0 Hz, 1H), 4.63 (s, 2H), 4.17 (t, *J*=5.7 Hz, 2H), 3.71 (t, *J*=5.7 Hz, 2H).

Example 132

Synthesis of 7-methyl-3-(2-phenoxyethyl)-3,4-dihydroquinazolin-2(1*H*)-one

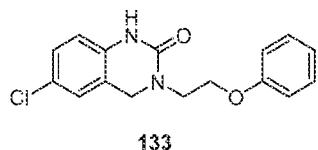


Proceeding as described in Example 128 above but substituting 2-nitrobenzaldehyde with 4-methyl-2-nitrobenzaldehyde provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.17 (s, 1H), 7.27 (dd, *J*=8.7, 7.2 Hz, 2H), 7.07–6.84 (m, 4H), 6.76–6.65 (m, 1H), 6.60–6.51 (m, 1H), 4.53 (s, 2H), 4.15 (t, *J*=5.8 Hz, 2H), 3.66 (t, *J*=5.8 Hz, 2H), 2.20 (s, 3H).

Example 133

Synthesis of 6-chloro-3-(2-phenoxyethyl)-3,4-dihydroquinazolin-2(1*H*)-one

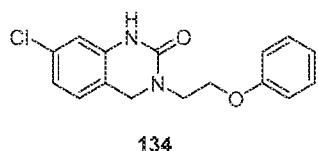


Proceeding as described in Example 128 above but substituting 2-nitrobenzaldehyde with 5-chloro-2-nitrobenzaldehyde provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.38 (s, 1H), 7.28 (dd, *J*=8.7, 7.2 Hz, 2H), 7.23–7.13 (m, 2H), 7.00–6.88 (m, 3H), 6.77 (d, *J*=8.4 Hz, 1H), 4.58 (s, 2H), 4.15 (t, *J*=5.6 Hz, 2H), 3.66 (t, *J*=5.6 Hz, 2H).

Example 134

Synthesis of 7-chloro-3-(2-phenoxyethyl)-3,4-dihydroquinazolin-2(1*H*)-one

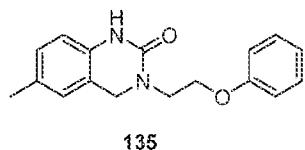


Proceeding as described in Example 128 above but substituting 2-nitrobenzaldehyde with 4-chloro-2-nitrobenzaldehyde provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.23 (s, 1H), 7.35–7.19 (m, 2H), 7.16–7.05 (m, 2H), 7.00–6.82 (m, 3H), 6.77 (dd, *J*=8.0, 1.1 Hz, 1H), 4.57 (s, 2H), 4.16 (t, *J*=5.8 Hz, 2H), 3.67 (t, *J*=5.8 Hz, 2H).

Example 135

Synthesis of 6-methyl-3-(2-phenoxyethyl)-3,4-dihydroquinazolin-2(*H*)-one

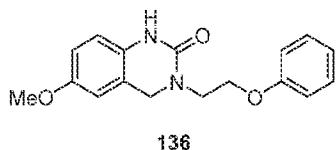


Proceeding as described in Example 128 above but substituting 2-nitrobenzaldehyde with 5-methyl-2-nitrobenzaldehyde provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.14 (s, 1H), 7.28 (dd, *J*=8.7, 7.2 Hz, 2H), 7.05–6.84 (m, 5H), 6.66 (d, *J*=8.0 Hz, 1H), 4.53 (s, 2H), 4.15 (t, *J*=5.8 Hz, 2H), 3.66 (t, *J*=5.8 Hz, 2H), 2.19 (s, 3H); LC/MS [M + Na] = 305.2.

Example 136

Synthesis of 6-methoxy-3-(2-phenoxyethyl)-3,4-dihydroquinazolin-2(*H*)-one

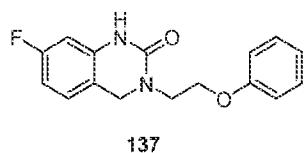


Proceeding as described in Example 128 above but substituting 2-nitrobenzaldehyde with 5-methoxy-2-nitrobenzaldehyde provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.07 (s, 1H), 7.28 (dd, *J*=8.6, 7.2 Hz, 2H), 7.03–6.84 (m, 3H), 6.71 (d, *J*=3.6 Hz, 3H), 4.54 (s, 2H), 4.15 (t, *J*=5.7 Hz, 2H), 3.67 (d, *J*=6.9 Hz, 5H).

Example 137

Synthesis of 7-fluoro-3-(2-phenoxyethyl)-3,4-dihydroquinazolin-2(*H*)-one

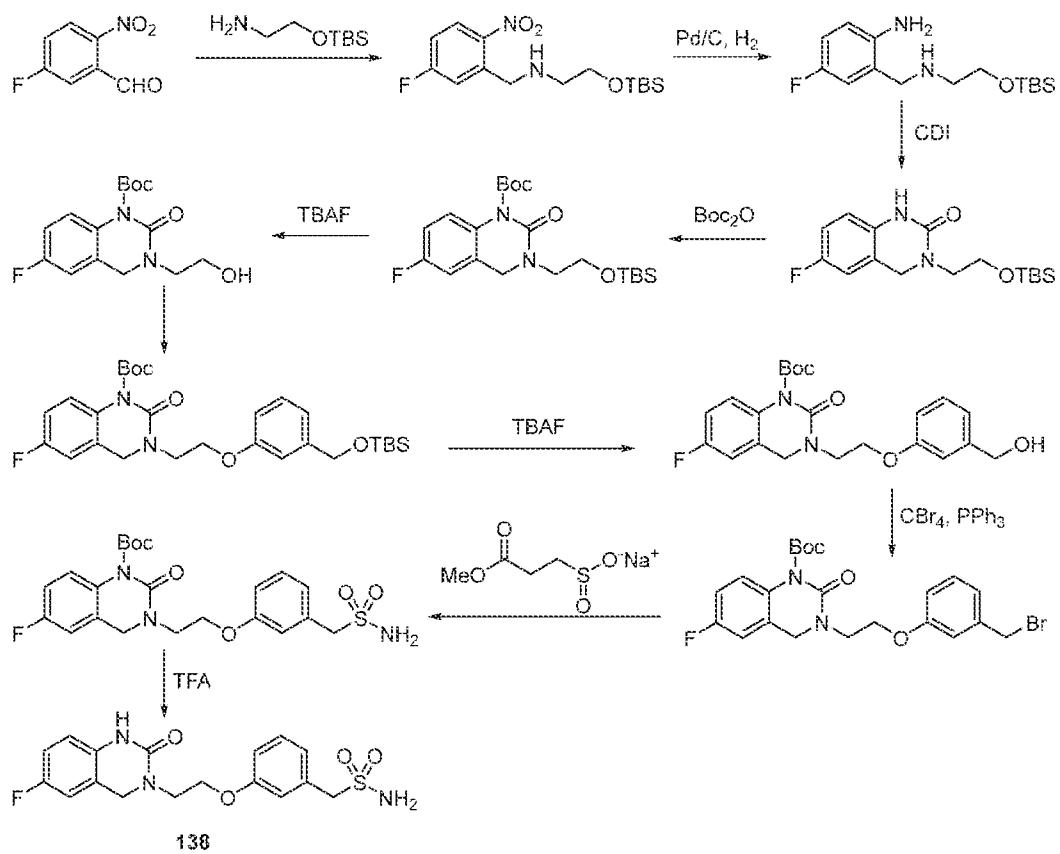


Proceeding as described in Example 128 above but substituting 2-nitrobenzaldehyde with 4-fluoro-2-nitrobenzaldehyde provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.38 (s, 1H), 7.28 (dd, *J*=8.7, 7.3 Hz, 2H), 7.13 (dd, *J*=8.4, 6.1 Hz, 1H), 6.93 (ddt, *J*=15.1, 7.3, 1.1 Hz, 3H), 6.69 (td, *J*=8.7, 2.6 Hz, 1H), 6.55 (dd, *J*=10.3, 2.6 Hz, 1H), 4.55 (s, 2H), 4.15 (t, *J*=5.7 Hz, 2H), 3.67 (t, *J*=5.7 Hz, 2H).

Example 138

Synthesis of (3-(2-(6-fluoro-2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)ethoxy)phenyl)methanesulfonamide



Step 1:

While under nitrogen, a solution of 5-fluoro-2-nitrobenzaldehyde (4.00 g, 23.6 mmol) and (2-aminoethoxy)-*tert*-butyl dimethylsilane (4.56 g, 26.0 mmol) in dichloroethane (10 mL) was treated with acetic acid (1.5 mL, 26.0 mmol) and warmed to 60 °C for 3 h. After cooling

to room temperature, sodium triacetoxyborohydride (10.0 g, 47.3 mmol) was added and stirring was continued for approximately 16 h. Once complete, the reaction was quenched with saturated aqueous NaHCO₃, extracted with ethyl acetate, washed with saturated aqueous sodium chloride (60 mL), dried over sodium sulfate, filtered and concentrated. Purification by medium pressure liquid chromatography (MPLC) (silica, 25 g, 0–50% hexanes in ethyl acetate) gave 2-((*tert*-butyldimethylsilyl)oxy)-*N*-(5-fluoro-2-nitrobenzyl)ethan-1-amine as a pale yellow solid (2.50 g, 32%).

Step 2:

A solution of 2-((*tert*-butyldimethylsilyl)oxy)-*N*-(5-fluoro-2-nitrobenzyl)ethan-1-amine (2.25 g, 6.85 mmol) and Pd/C (10% wt., 234 mg, 0.22 mmol) in ethyl acetate (26 mL) was purged with nitrogen, evacuated and treated with hydrogen (balloon). After stirring for 24 h, the reaction vessel was evacuated, purged with nitrogen and filtered through Celite. The Celite was washed with ethyl acetate and the combined filtrate was concentrated to give 2-(((2-((*tert*-butyldimethylsilyl)oxy)ethyl)amino)methyl)-4-fluoroaniline as an off-white solid that was used in the next step without further purification (2.04 g, 100%).

Step 3:

While under nitrogen, a solution of 2-(((2-((*tert*-butyldimethylsilyl)oxy)ethyl)amino)methyl)-4-fluoroaniline (2.04 g, 6.85 mmol) in THF (20 mL) was treated with 1,1'-carbonyldiimidazole (2.22 g, 13.67 mmol) and warmed to 60 °C. After stirring for approximately 16 h, the solution was allowed to cool to room temperature, diluted with water and extracted with ethyl acetate, dried over sodium sulfate, filtered and concentrated. The resulting 3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-6-fluoro-3,4-dihydroquinazolin-2(1*H*)-one as a light-yellow solid was used in the subsequent step without further purification.

Step 4:

While under nitrogen, a solution of 3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-6-fluoro-3,4-dihydroquinazolin-2(1*H*)-one (1.38 g, 4.25 mmol), triethylamine (1.77 mL, 12.76 mmol) and dimethylaminopyridine (260 mg, 2.21 mmol) in dichloromethane (20 mL) was cooled to 0 °C (ice-bath) and treated with di*tert*butyl decarbonate (0.96 g, 6.38 mmol). After the addition was complete, the ice-bath was removed and stirring was continued for approximately 16 h. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous

ammonium chloride, dried over MgSO₄, filtered and concentrated. Purification by MPLC (0-20% ethyl acetate in hexanes) gave 3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-6-fluoro-3,4-dihydroquinazolin-2(1*H*)-one as a pale-yellow oil (1.75 g, 97%).

Step 5:

A solution of 3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-6-fluoro-3,4-dihydroquinazolin-2(1*H*)-one (1.86 g, 4.4 mmol) in THF (25 mL) was cooled to 0 °C (ice-bath) and treated with a separate solution of tetrabutylammonium fluoride (1.0 M in THF, 8.76 mL, 8.76 mmol) and acetic acid (0.5 mL, 8.76 mmol). After the addition was complete, the ice-bath was removed and stirring was continued for approximately 16 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic phase was washed successively with saturated aqueous NaHCO₃ and saturated aqueous sodium chloride, then dried over sodium sulfate, filtered and concentrated. Purification by MPLC (5-50% ethyl acetate in hexanes) gave *tert*-butyl 6-fluoro-3-(2-hydroxyethyl)-2-oxo-3,4-dihydroquinoline-1(2*H*)-carboxylate as a white solid (1.18 g, 87%).

Step 6:

A solution of *tert*-butyl 6-fluoro-3-(2-hydroxyethyl)-2-oxo-3,4-dihydroquinazoline-1(2*H*)-carboxylate (250 mg, 0.81 mmol), 3-((*tert*-butyldimethylsilyl)oxy)methylphenol (231 mg, 0.97 mmol) and triphenylphosphine (296 mg, 1.13 mmol) in anhydrous THF (6 mL) was cooled to 0 °C (ice-bath) and treated with diisopropyl azodicarboxylate (0.22 mL, 1.13 mmol). After the addition was complete, the ice-bath was removed and stirring was continued for approximately 16 h. The reaction mixture was concentrated, and the crude reaction mixture was purified by MPLC (0-60% ethyl acetate in hexanes) to give *tert*-butyl 3-(2-(3-((*tert*-butyldimethylsilyl)oxy)methyl)phenoxy)ethyl)-6-fluoro-2-oxo-3,4-dihydroquinazoline-1(2*H*)-carboxylate as a clear oil (180 mg, 42%).

Step 7:

A solution of *tert*-butyl 3-(2-(3-((*tert*-butyldimethylsilyl)oxy)methyl)phenoxy)ethyl)-6-fluoro-2-oxo-3,4-dihydroquinazoline-1(2*H*)-carboxylate (170 mg, 0.32 mmol) in THF (5 mL) was cooled to 0 °C (ice-bath) and treated with a separate solution of tetrabutylammonium fluoride (1.0 M in THF, 0.64 mL, 0.64 mmol) and acetic acid (0.036 mL, 0.64 mmol). After the addition was complete, the ice-bath was removed and stirring was

continued for approximately 16 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic phase was washed successively with saturated aqueous NaHCO₃ and saturated aqueous sodium chloride, then dried over sodium sulfate, filtered and concentrated. Purification by MPLC (20-40% ethyl acetate in dichloromethane) gave *tert*-butyl 6-fluoro-3-(2-(3-(hydroxymethyl)phenoxy)ethyl)-2-oxo-3,4-dihydroquinazoline-1(2*H*)-carboxylate as a clear oil (120 mg, 90%).

Step 8:

A solution of *tert*-butyl 6-fluoro-3-(2-(3-(hydroxymethyl)phenoxy)ethyl)-2-oxo-3,4-dihydroquinazoline-1(2*H*)-carboxylate (120 mg, 0.28 mmol) and carbontetrabromide (115 mg, 0.35 mmol) in dichloromethane (4 mL) was cooled to 0 °C (ice-bath) and treated with triphenylphosphine (91 mg, 0.35 mmol). After 30 min, the reaction was concentrated. The crude reaction mixture was purified by MPLC (0-50% ethyl acetate in hexanes) to give *tert*-butyl 3-(2-(3-(bromomethyl)phenoxy)ethyl)-6-fluoro-2-oxo-3,4-dihydroquinazoline-1(2*H*)-carboxylate as a colorless oil (90 mg, 65%).

Step 9:

A solution of *tert*-butyl 3-(2-(3-(bromomethyl)phenoxy)ethyl)-6-fluoro-2-oxo-3,4-dihydroquinazoline-1(2*H*)-carboxylate (80 mg, 0.17 mmol) in anhydrous DMSO was treated with sodium 1-methyl-3-sulfinopropanoate (35 mg, 0.20 mmol). After stirring for 10 min, NaOMe (25% solution in methanol, 36 microL, 0.17 mmol) was added and stirring was continued for an additional 15 min. The solution was cooled to 0 °C (ice-bath) and treated with a separate solution of hydroxylamine-O-sulfonic acid (94 mg, 0.83 mmol) and sodium acetate (52 mg, 0.63 mmol) in water (3 mL). The resulting suspension stirred for about 16 h, gradually warming as the ice-bath melted. The reaction mixture was diluted with ethyl acetate and washed with saturated aqueous sodium chloride, dried over sodium sulfate, filtered and concentrated. Purification by MPLC (0-60% ethyl acetate in hexanes) gave *tert*-butyl 6-fluoro-2-oxo-3-(2-(3-(sulfamoylmethyl)phenoxy)ethyl)-3,4-dihydroquinazoline-1(2*H*)-carboxylate (35 mg, 44%).

Step 10:

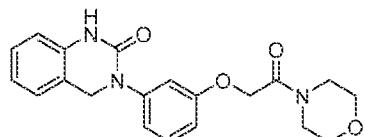
A solution of *tert*-butyl 6-fluoro-2-oxo-3-(2-(3-(sulfamoylmethyl)phenoxy)ethyl)-3,4-dihydroquinazoline-1(2*H*)-carboxylate (35 mg, 0.07 mmol) in dichloromethane (2 mL) was

treated with trifluoroacetic acid (0.5 mL, 6.73 mmol). After stirring for 16 h, the reaction mixture was concentrated, dissolved in toluene and re-concentrated to remove excess trifluoroacetic acid. The crude product was triturated in diethyl ether to give the title compound as an off-white solid.

¹H NMR (400 MHz, DMSO-d₆) δ 9.27 (s, 1H) 7.27 (t, *J*=7.8 Hz, 1H) 7.04–6.88 (m, 5H) 6.83–6.72 (m, 3H) 4.58 (s, 2H) 4.22 (s, 2H) 4.16 (t, *J*=5.7 Hz, 2H) 3.67 (t, *J*=5.6 Hz, 2H).

Example 139

Synthesis of 3-(3-(2-morpholino-2-oxoethoxy)phenyl)-3,4-dihydroquinazolin-2(1*H*)-one



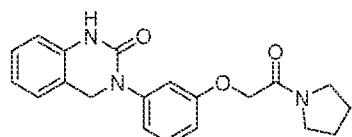
139

Proceeding as described in Example 89 above but substituting 2-(4-fluoro-3-(2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)phenoxy)acetic acid with 2-(3-(2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)phenoxy)acetic acid provided the title compound as a white solid.

¹H NMR (500 MHz, DMSO-d₆) δ 9.58 (s, 1H), 7.27 (t, *J*=8.1 Hz, 1H), 7.21–7.14 (m, 2H), 6.97 (dd, *J*=8.5, 1.7 Hz, 2H), 6.92 (t, *J*=7.5 Hz, 1H), 6.87 (d, *J*=7.9 Hz, 1H), 6.80–6.75 (m, 1H), 4.82 (s, 2H), 4.79 (s, 2H), 3.62–3.55 (m, 4H), 3.46 (t, *J*=5.4 Hz, 4H).

Example 140

Synthesis of 3-(3-(2-oxo-2-(pyrrolidin-1-yl)ethoxy)phenyl)-3,4-dihydroquinazolin-2(1*H*)-one



140

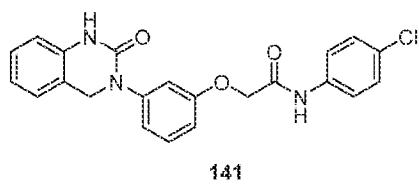
Proceeding as described in Example 89 above but substituting 2-(4-fluoro-3-(2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)phenoxy)acetic acid and morpholine with 2-(3-(2-oxo-1,4-

dihydroquinazolin-3(2*H*)-yl)phenoxy)acetic acid and pyrrolidine provided the title compound as a white solid.

¹H NMR (500 MHz, DMSO-*d*6) δ 9.57 (s, 1H), 7.27 (t, *J*=8.3 Hz, 1H), 7.21–7.13 (m, 2H), 6.96 (d, *J*=6.0 Hz, 2H), 6.92 (t, *J*=7.5 Hz, 1H), 6.87 (d, *J*=7.9 Hz, 1H), 6.79–6.75 (m, 1H), 4.79 (s, 2H), 4.71 (s, 2H), 3.47 (t, *J*=6.8 Hz, 2H), 3.32 (d, *J*=6.2 Hz, 2H), 1.94–1.83 (m, 2H), 1.82–1.71 (m, 2H).

Example 141

Synthesis of *N*-(4-chlorophenyl)-2-(3-(2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)phenoxy)acetamide

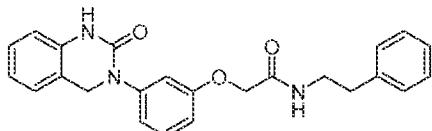


Proceeding as described in Example 89 above but substituting 2-(4-fluoro-3-(2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)phenoxy)acetic acid and morpholine with 2-(3-(2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)phenoxy)acetic acid and 4-chloroaniline provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 10.23 (s, 1H), 9.62 (s, 1H), 7.69 (d, *J*=8.8 Hz, 2H), 7.38 (d, *J*=8.8 Hz, 2H), 7.31 (t, *J*=8.1 Hz, 1H), 7.21–7.13 (m, 2H), 7.07 (d, *J*=2.3 Hz, 1H), 7.00 (dd, *J*=7.7, 1.9 Hz, 1H), 6.92 (t, *J*=7.5 Hz, 1H), 6.89–6.83 (m, 2H), 4.80 (s, 2H), 4.71 (s, 2H).

Example 142

Synthesis of 2-(3-(2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)phenoxy)-*N*-phenethylacetamide



142

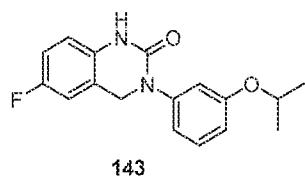
Proceeding as described in Example 89 above but substituting 2-(4-fluoro-3-(2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)phenoxy)acetic acid and morpholine with 2-(3-(2-oxo-1,4-

dihydroquinazolin-3(2*H*)-yl)phenoxy)acetic acid and 2-phenylethan-1-amine provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 7.56 (s, 1H), 7.37–7.17 (m, 7H), 7.09 (d, *J*=7.5 Hz, 1H), 7.05 (dd, *J*=8.0, 1.9 Hz, 1H), 7.00 (t, *J*=7.5 Hz, 1H), 6.95 (t, *J*=2.3 Hz, 1H), 6.79 (d, *J*=7.9 Hz, 1H), 6.75 (dd, *J*=8.3, 2.5 Hz, 1H), 6.65 (t, *J*=5.9 Hz, 1H), 4.82 (s, 2H), 4.49 (s, 2H), 3.61 (q, *J*=6.7 Hz, 2H), 2.86 (t, *J*=7.1 Hz, 2H).

Example 143

Synthesis of 6-fluoro-3-(3-isopropoxyphenyl)-3,4-dihydroquinazolin-2(*1H*)-one

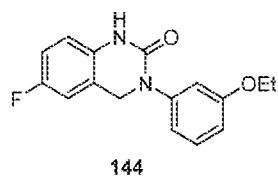


Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine with 3-isopropoxyaniline provided the title compound as a white solid.

¹H NMR (400 MHz, CDCl₃) δ 7.74 (s, 1H) 7.30 (t, *J*=8.1 Hz, 1H) 6.95–6.87 (m, 3H) 6.81–6.78 (m, 2H) 6.71 (dd, *J*=8.7, 4.5 Hz, 1H) 4.79 (s, 2H) 4.55 (p, *J*=6.1 Hz, 1H) 1.35 (d, *J*=6.0 Hz, 6H).

Example 144

Synthesis of 3-(3-ethoxyphenyl)-6-fluoro-3,4-dihydroquinazolin-2(*1H*)-one

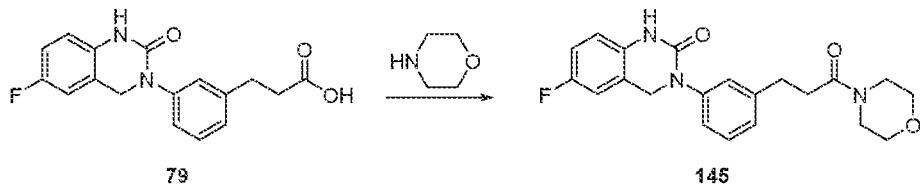


Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine with 3-ethoxyaniline provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.61 (s, 1H), 7.27 (t, *J*=8.4 Hz, 1H), 7.15–7.00 (m, 2H), 6.95–6.90 (m, 2H), 6.86 (dd, *J*=8.6, 4.8 Hz, 1H), 6.78 (ddd, *J*=8.3, 2.4, 1.0 Hz, 1H), 4.79 (s, 2H), 4.02 (q, *J*=7.0 Hz, 2H), 1.32 (t, *J*=7.0 Hz, 3H).

Example 145

Synthesis of 6-fluoro-3-(3-(3-morpholino-3-oxopropyl)phenyl)-3,4-dihydroquinazolin-2(1*H*)-one

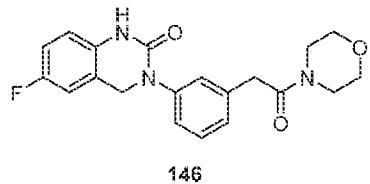


Proceeding as described in Example 89 above but substituting 2-(4-fluoro-3-(2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)phenoxy)acetic acid with 3-(3-(6-fluoro-2-oxo-1,4-dihydro-quinazolin-3(2*H*)-yl)phenyl)propanoic acid provided the title compound as a white solid.

¹H NMR (400 MHz, CDCl₃) δ 7.34 (t, *J*=7.8 Hz, 1H), 7.25–7.17 (m, 2H), 7.13 (d, *J*=7.2 Hz, 2H), 6.93 (td, *J*=8.5, 2.7 Hz, 1H), 6.82 (dd, *J*=8.2, 2.7 Hz, 1H), 6.70 (dd, *J*=8.7, 4.5 Hz, 1H), 4.79 (s, 2H), 3.63 (s, 4H), 3.55 (t, *J*=4.8 Hz, 2H), 3.39 (t, *J*=4.9 Hz, 2H), 3.01 (t, *J*=7.8 Hz, 2H), 2.67–2.60 (m, 2H).

Example 146

Synthesis of 6-fluoro-3-(3-(2-morpholino-2-oxoethyl)phenyl)-3,4-dihydroquinazolin-2(1*H*)-one

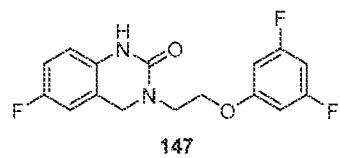


Proceeding as described in Example 69 above but substituting methylamine with morpholine provided the title compound as a white solid.

¹H NMR (400 MHz, CDCl₃) δ 7.38 (t, *J*=7.7 Hz, 1H), 7.30–7.23 (m, 2H), 7.14 (d, *J*=6.5 Hz, 2H), 6.93 (td, *J*=8.5, 2.8 Hz, 1H), 6.81 (dd, *J*=8.3, 2.7 Hz, 1H), 6.69 (dd, *J*=8.7, 4.5 Hz, 1H), 4.80 (s, 2H), 3.75 (s, 2H), 3.66 (s, 4H), 3.60–3.52 (m, 2H), 3.52–3.44 (m, 2H).

Example 147

Synthesis of 3-(2-(3,5-difluorophenoxy)ethyl)-6-fluoro-3,4-dihydroquinazolin-2(1*H*)-one

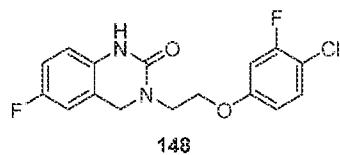


Proceeding as described in Example 128 above but substituting 2-nitrobenzaldehyde and 2-phenoxyethylamine with 2-nitro-5-fluorobenzaldehyde and 2-(3,5-difluorophenoxy)ethan-1-amine provided the title compound as a white solid.

¹H NMR (300 MHz, DMSO-*d*6) δ 9.27 (s, 1H), 7.01–6.95 (m, 2H), 6.79–6.74 (m, 4H), 4.56 (s, 2H), 4.20 (*t*, *J*=5.8 Hz, 2H), 3.66 (*t*, *J*=5.6 Hz, 2H).

Example 148

Synthesis of 3-(2-(4-chloro-3-fluorophenoxy)ethyl)-6-fluoro-3,4-dihydroquinazolin-2(1*H*)-one

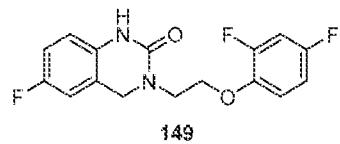


Proceeding as described in Example 128 above but substituting 2-nitrobenzaldehyde and 2-phenoxyethylamine with 2-nitro-5-fluorobenzaldehyde and 4-(2-aminoethoxy)-1-chloro-2-fluorobenzene provided the title compound as a white solid.

¹H NMR (300 MHz, DMSO-*d*6) δ 9.27 (s, 1H), 7.45 (*t*, *J*=8.6 Hz, 1H), 7.12 (dd, *J*=2.8, 11.5 Hz, 1H), 7.01–6.95 (m, 2H), 6.88–6.84 (m, 1H), 6.79–6.74 (m, 1H), 4.55 (s, 2H), 4.19 (*t*, *J*=5.9 Hz, 2H), 3.66 (*t*, *J*=5.6 Hz, 2H).

Example 149

Synthesis of 3-(2-(2,4-difluorophenoxy)ethyl)-6-fluoro-3,4-dihydroquinazolin-2(1*H*)-one

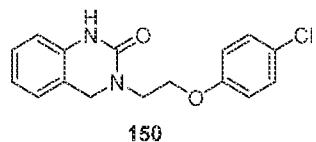


Proceeding as described in Example 128 above but substituting 2-nitrobenzaldehyde and 2-phenoxyethylamine with 2-nitro-5-fluorobenzaldehyde and 2-(2,4-difluorophenoxy)-ethanamine provided the title compound as a white solid.

¹H NMR (300 MHz, DMSO-*d*6) δ 9.27 (s, 1H), 7.31–7.20 (m, 2H), 7.03–6.96 (m, 3H), 6.77 (dd, *J*=4.8, 9.2 Hz, 1H), 4.57 (s, 2H), 4.22 (t, *J*=5.7 Hz, 2H), 3.67 (t, *J*=5.8 Hz, 2H).

Example 150

Synthesis of 3-(2-(4-chlorophenoxy)ethyl)-3,4-dihydroquinazolin-2(1*H*)-one

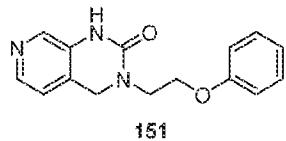


Proceeding as described in Example 128 above but substituting 2-phenoxyethylamine with 2-(4-chlorophenoxy)ethanamine provided the title compound as a white solid.

¹H NMR (300 MHz, DMSO-*d*6) δ 9.23 (s, 1H), 7.33–7.29 (m, 2H), 7.12 (t, *J*=7.5 Hz, 1H), 7.09 (d, *J*=6.9 Hz, 1H), 7.01–6.98 (m, 2H), 6.87 (t, *J*=7.5 Hz, 1H), 6.77 (d, *J*=7.8 Hz, 1H), 4.56 (s, 2H), 4.17 (t, *J*=5.6 Hz, 2H), 3.67 (t, *J*=5.7 Hz, 2H).

Example 151

Synthesis of 3-(2-phenoxyethyl)-3,4-dihdropyrido[3,4-d]pyrimidin-2(1*H*)-one

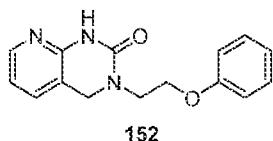


Proceeding as described in Example 128 above but substituting 2-nitrobenzaldehyde with 3-nitroisonicotinaldehyde provided the title compound as a white solid.

¹H NMR (300 MHz, DMSO-*d*6) δ 9.46 (s, 1H), 8.08 (d, *J*=4.8 Hz, 1H), 8.05 (s, 1H), 7.31–7.25 (m, 2H), 7.14 (d, *J*=4.6 Hz, 1H), 6.97–6.91 (m, 3H), 4.64 (s, 2H), 4.17 (t, *J*=5.7 Hz, 2H), 3.68 (t, *J*=5.6 Hz, 2H).

Example 152

Synthesis of 3-(2-phenoxyethyl)-3,4-dihydropyrido[2,3-d]pyrimidin-2(1*H*)-one

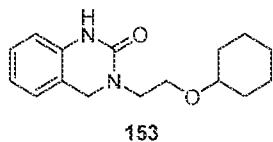


Proceeding as described in Example 128 above but substituting 2-nitrobenzaldehyde with 2-nitropyridine-3-carbaldehyde provided the title compound as a white solid.

¹H NMR (300 MHz, DMSO-*d*6) δ 9.67 (s, 1H), 8.07 (dd, *J*=1.0, 4.7 Hz, 1H), 7.51 (d, *J*=7.1 Hz, 1H), 7.31–7.26 (m, 2H), 6.98–6.89 (m, 4H), 4.61 (s, 2H), 4.17 (t, *J*=5.7 Hz, 2H), 3.69 (t, *J*=5.7 Hz, 2H).

Example 153

Synthesis of 3-(2-(cyclohexyloxy)ethyl)-3,4-dihydroquinazolin-2(1*H*)-one

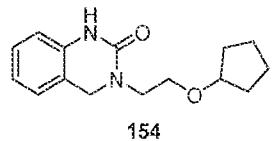


Proceeding as described in Example 128 above but substituting 2-phenoxyethylamine with 2-(cyclohexyloxy)ethanamine provided the title compound as a white solid.

¹H NMR (300 MHz, DMSO-*d*6) δ 9.13 (s, 1H), 7.14–7.05 (m, 2H), 6.86 (t, *J*=7.3 Hz, 1H), 6.76 (d, *J*=7.7 Hz, 1H), 4.50 (s, 2H), 3.57 (t, *J*=5.9 Hz, 2H), 3.43 (t, *J*=5.5 Hz, 2H), 3.29–3.23 (m, 1H), 1.83–1.76 (m, 2H), 1.64–1.62 (m, 2H), 1.46–1.43 (m, 1H), 1.25–1.16 (m, 5H).

Example 154

Synthesis of 3-(2-(cyclopentyloxy)ethyl)-3,4-dihydroquinazolin-2(1*H*)-one

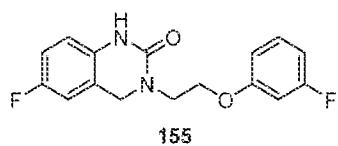


Proceeding as described in Example 128 above but substituting 2-phenoxyethylamine with 2-(cyclopentyloxy)ethanamine provided the title compound as a white solid.

¹H NMR (300 MHz, DMSO-*d*6) δ 9.13 (s, 1H), 7.14–7.05 (m, 2H), 6.86 (dt, *J*=1.1, 7.7 Hz, 1H), 6.76 (d, *J*=7.8 Hz, 1H), 4.48 (s, 2H), 3.90–3.88 (m, 1H), 3.53–3.40 (m, 4H), 1.65–1.45 (m, 8H).

Example 155

Synthesis of 6-fluoro-3-(2-(3-fluorophenoxy)ethyl)-3,4-dihydroquinazolin-2(1*H*)-one

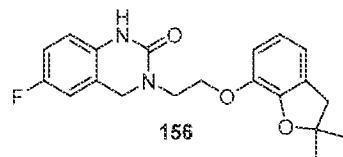


Proceeding as described in Example 128 above but substituting 2-nitrobenzaldehyde and 2-phenoxyethylamine with 2-nitro-5-fluorobenzaldehyde and 2-(3-fluorophenoxy)ethanamine provided the title compound as a white solid.

¹H NMR (300 MHz, DMSO-*d*6) δ 9.23 (s, 1H), 7.34–7.26 (m, 1H), 7.15–7.08 (m, 2H), 6.89–6.72 (m, 4H), 4.57 (s, 2H), 4.18 (d, *J*=5.7 Hz, 1H), 3.68 (d, *J*=5.7 Hz, 1H),.

Example 156

Synthesis of 3-(2-((2,2-dimethyl-2,3-dihydrobenzofuran-7-yl)oxy)ethyl)-6-fluoro-3,4-dihydroquinazolin-2(1*H*)-one

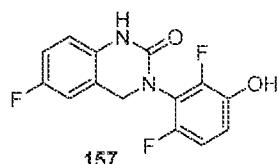


Proceeding as described in Example 128 above but substituting 2-nitrobenzaldehyde and 2-phenoxyethylamine with 2-nitro-5-fluorobenzaldehyde and 2-[(2,2-dimethyl-2,3-dihydro-1-benzofuran-7-yl)oxy]ethan-1-amine provided the title compound as a white solid.

¹H NMR (300 MHz, DMSO-*d*6) δ 9.24 (s, 1H), 7.01–6.94 (m, 2H), 6.83–6.68 (m, 4H), 4.58 (s, 2H), 4.15 (d, *J*=5.6 Hz, 1H), 3.63 (d, *J*=5.9 Hz, 1H), 2.98 (s, 2H), 1.39 (s, 6H).

Example 157

Synthesis of 3-(2,6-difluoro-3-hydroxyphenyl)-6-fluoro-3,4-dihydroquinazolin-2(1*H*)-one

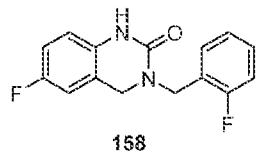


Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine with 3-amino-2,6-difluorophenol provided the title compound as a white solid.

¹H NMR (300 MHz, DMSO-*d*6) δ 9.98 (s, 1H), 9.70 (s, 1H), 7.21 (t, *J*=7.8 Hz, 1H), 7.14 (d, *J*=7.3 Hz, 1H), 7.01–6.91 (m, 2H), 6.88 (d, *J*=8.2 Hz, 1H), 4.70 (s, 2H).

Example 158

Synthesis of 6-fluoro-3-(2-fluorobenzyl)-3,4-dihydroquinazolin-2(1*H*)-one

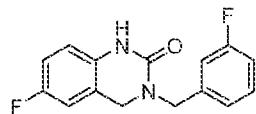


Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine with 2-fluorobenzylamine provided the title compound as a white solid.

¹H NMR (300 MHz, DMSO-*d*6) δ 9.37 (s, 1H), 7.37–7.32 (m, 2H), 7.24–7.17 (m, 2H), 7.01–6.96 (m, 2H), 6.80 (q, *J*=4.74 Hz, 1H), 4.60 (s, 2H), 4.37 (s, 2H).

Example 159

Synthesis of 6-fluoro-3-(3-fluorobenzyl)-3,4-dihydroquinazolin-2(1*H*)-one



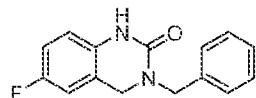
169

Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine with 3-fluorobenzylamine provided the title compound as a white solid.

¹H NMR (400 MHz, methanol-*d*4) δ 7.36 (td, *J*=7.9, 5.9 Hz, 1H), 7.15 (d, *J*=7.6 Hz, 1H), 7.08 (dt, *J*=9.8, 2.1 Hz, 1H), 7.04–6.95 (m, 1H), 6.90 (td, *J*=8.7, 2.9 Hz, 1H), 6.81 (ddd, *J*=15.3, 8.8, 3.8 Hz, 2H), 4.62 (s, 2H), 4.37 (s, 2H).

Example 160

Synthesis of 3-benzyl-6-fluoro-3,4-dihydroquinazolin-2(1*H*)-one



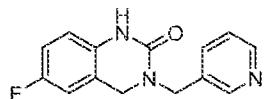
160

Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine with benzylamine provided the title compound as a white solid.

¹H NMR (400 MHz, methanol-*d*4) δ 7.34 (d, *J*=3.7 Hz, 4H), 7.30–7.25 (m, 1H), 6.95–6.84 (m, 1H), 6.83–6.73 (m, 2H), 4.62 (s, 2H), 4.34 (s, 2H).

Example 161

Synthesis of 6-fluoro-3-(pyridin-3-ylmethyl)-3,4-dihydroquinazolin-2(1*H*)-one



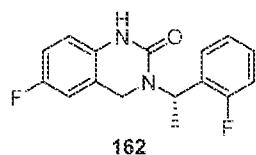
161

Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine with 3-picollylamine provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.40 (s, 1H), 8.72–8.36 (m, 2H), 7.71 (dt, *J*=7.9, 2.0 Hz, 1H), 7.38 (ddd, *J*=7.8, 4.8, 0.9 Hz, 1H), 6.97 (ddt, *J*=11.9, 5.2, 2.9 Hz, 2H), 6.79 (dd, *J*=8.5, 4.9 Hz, 1H), 4.56 (s, 2H), 4.34 (s, 2H).

Example 162

Synthesis of (*S*)-6-fluoro-3-(1-(2-fluorophenyl)ethyl)-3,4-dihydroquinazolin-2(1*H*)-one

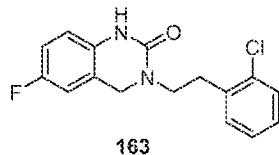


Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine with (*S*)-1-(2-fluorophenyl)ethan-1-amine provided the title compound as a white solid.

¹H NMR (300 MHz, DMSO-*d*6) δ 9.27 (s, 1H), 7.50–7.45 (m, 1H), 7.39–7.34 (m, 1H), 7.26–7.13 (m, 2H), 7.00–6.93 (m, 2H), 6.80–6.75 (m, 1H), 5.86 (q, *J*=7.23 Hz, 1H), 4.38 (d, *J*=14.67 Hz, 2H), 3.95 (d, *J*=14.67 Hz, 1H), 1.52 (d, *J*=7.2 Hz, 3H).

Example 163

Synthesis of 3-(2-chlorophenethyl)-6-fluoro-3,4-dihydroquinazolin-2(1*H*)-one

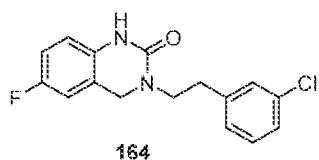


Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine with 2-(2-chlorophenyl)ethan-1-amine provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.19 (s, 1H), 7.46–7.38 (m, 1H), 7.37–7.30 (m, 1H), 7.29–7.19 (m, 2H), 6.97 (ddd, *J*=8.9, 4.6, 1.9 Hz, 2H), 6.75 (dd, *J*=9.6, 4.9 Hz, 1H), 4.41 (s, 2H), 3.67–3.44 (m, 2H), 3.09–2.88 (m, 2H).

Example 164

Synthesis of 3-(3-chlorophenethyl)-6-fluoro-3,4-dihydroquinazolin-2(1*H*)-one

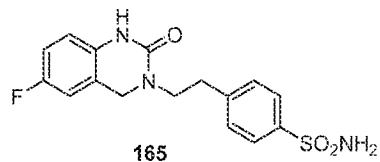


Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine with 2-(3-chlorophenyl)ethan-1-amine provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.19 (s, 1H), 7.42–7.11 (m, 4H), 7.04–6.90 (m, 2H), 6.75 (dd, *J*=8.6, 4.9 Hz, 1H), 4.40 (s, 2H), 3.67–3.42 (m, 2H), 2.85 (dd, *J*=8.5, 6.5 Hz, 2H).

Example 165

Synthesis of 4-(2-(6-fluoro-2-oxo-1,4-dihydroquinazolin-3(2H)-yl)ethyl)benzenesulfonamide

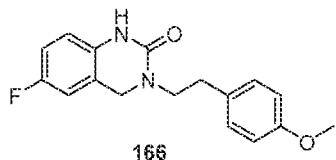


Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine with 4-(2-aminoethyl)benzenesulfonamide provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.20 (s, 1H), 7.94–7.60 (m, 2H), 7.43 (d, *J*=8.2 Hz, 2H), 7.28 (s, 2H), 6.97 (t, *J*=8.4 Hz, 2H), 6.82–6.69 (m, 1H), 4.44 (s, 2H), 3.62–3.47 (m, 2H), 2.93 (t, *J*=7.6 Hz, 2H).

Example 166

Synthesis of 6-fluoro-3-(4-methoxyphenethyl)-3,4-dihydroquinazolin-2(1*H*)-one

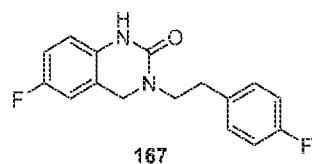


Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine with 2-(4-methoxyphenyl)ethan-1-amine provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.17 (s, 1H), 7.14 (d, *J*=8.6 Hz, 2H), 6.95 (dq, *J*=8.7, 2.9 Hz, 2H), 6.84 (d, *J*=8.6 Hz, 2H), 6.75 (dd, *J*=8.5, 4.9 Hz, 1H), 4.39 (s, 2H), 3.71 (s, 3H), 3.55–3.34 (m, 2H), 2.87–2.67 (m, 2H).

Example 167

Synthesis of 6-fluoro-3-(4-fluorophenethyl)-3,4-dihydroquinazolin-2(1*H*)-one

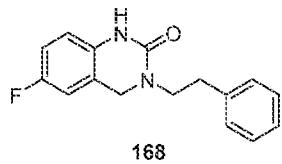


Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine with 2-(4-fluorophenyl)ethan-1-amine provided the title compound as a white solid.

¹H NMR (400 MHz, DMSO-*d*6) δ 9.18 (s, 1H), 7.27 (dd, *J*=8.5, 5.7 Hz, 2H), 7.10 (t, *J*=8.9 Hz, 2H), 7.00–6.89 (m, 2H), 6.75 (dd, *J*=8.6, 4.9 Hz, 1H), 4.40 (s, 2H), 3.70–3.43 (m, 2H), 2.83 (dd, *J*=8.6, 6.5 Hz, 2H).

Example 168

Synthesis of 6-fluoro-3-phenethyl-3,4-dihydroquinazolin-2(1*H*)-one

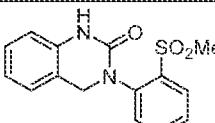
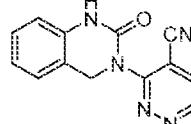
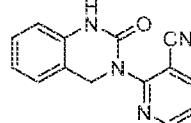
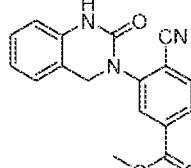
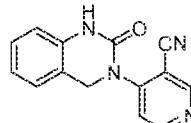
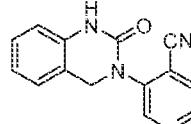


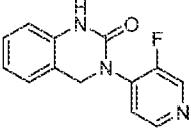
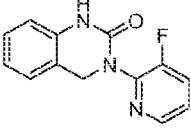
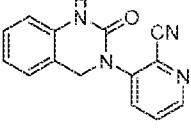
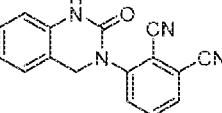
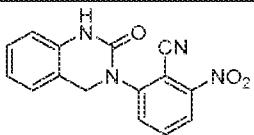
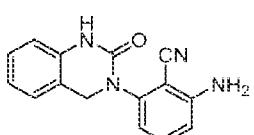
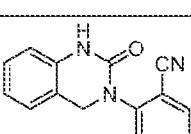
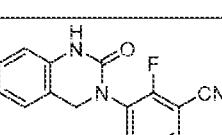
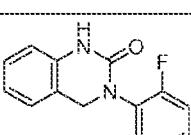
Proceeding as described in Example 25 above but substituting [1,1'-biphenyl]-2-amine with 2-phenylethan-1-amine provided the title compound as a white solid.

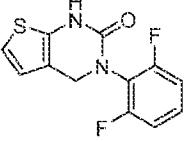
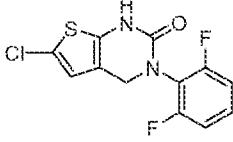
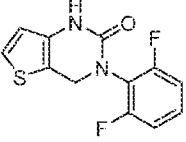
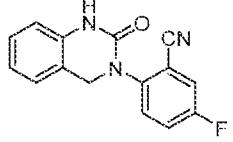
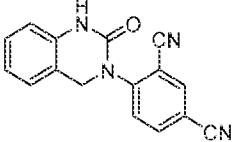
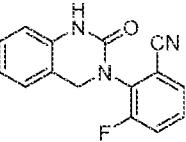
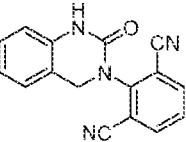
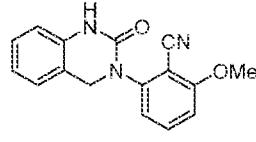
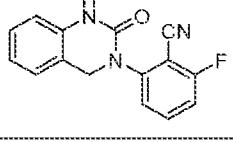
¹H NMR (300 MHz, DMSO-*d*6) δ 9.18 (s, 1H), 7.32–7.18 (m, 5H), 7.00–6.93 (m, 2H), 6.78–6.74 (dd, *J*=4.9, 8.7 Hz, 1H), 4.40 (s, 2H), 3.51 (t, *J*=7.3 Hz, 2H), 2.84 (t, *J*=8.3 Hz, 2H).

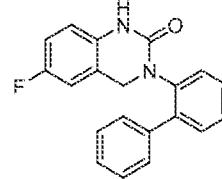
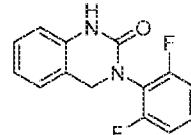
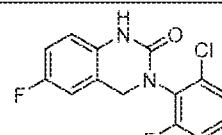
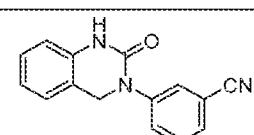
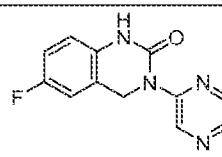
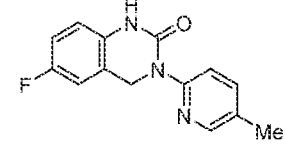
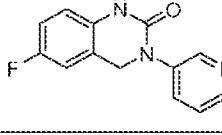
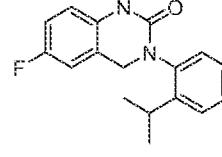
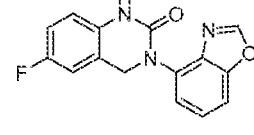
IL4II Enzyme Activity

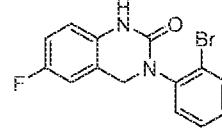
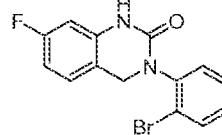
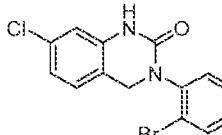
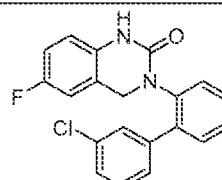
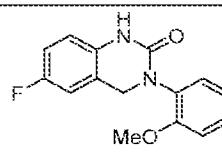
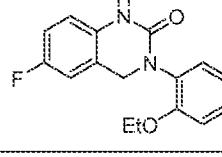
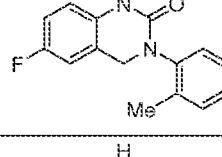
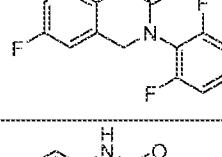
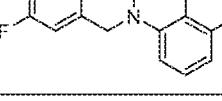
For measurement of IL4II enzyme activity, recombinant human IL4II was obtained from R&D Systems, Cat. No. 5684-AO-020. Serial dilutions of test compound were incubated with recombinant human IL4II and L-phenylalanine in reaction buffer (50 mM NaPO₄ pH 7.0, 100 mM NaCl, 0.05% TX-100, 0.05 mg/mL bovine serum albumin, 0.25 Units/mL horseradish peroxidase, 25 µM Amplex red). The final reaction volume was 30 µL and the final concentration of IL4II, L-phenylalanine and DMSO were 5 nM, 1 mM, and 1% respectively. Reactions were monitored continuously by fluorescence (Ex 535 nm, Em 587 nm) in a microplate spectrophotometer for 30 minutes at room temperature.

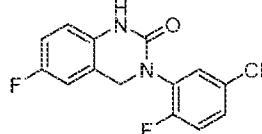
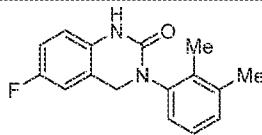
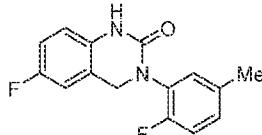
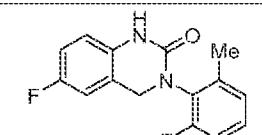
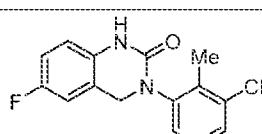
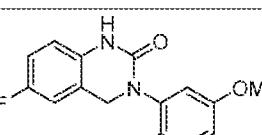
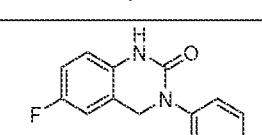
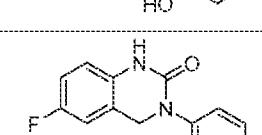
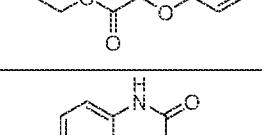
Example	Structure	Human IL4II IC ₅₀ (µM)
1		3.18
2		2.68
3		0.460
4		1.44
5		3.38
6		0.730

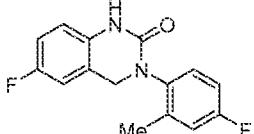
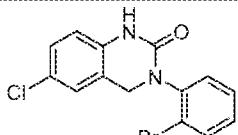
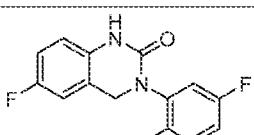
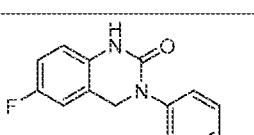
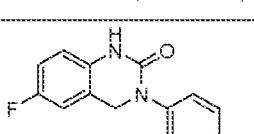
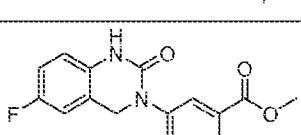
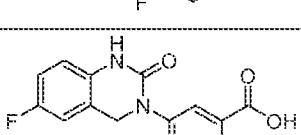
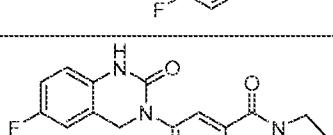
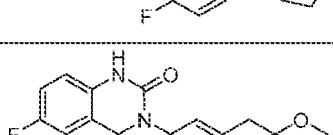
7		>10
8		0.263
9		2.92
10		>10
11		8.47
12		0.153
13		0.177
14		2.22
15		1.74

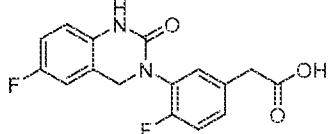
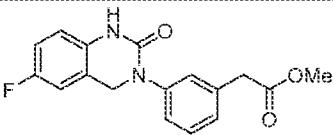
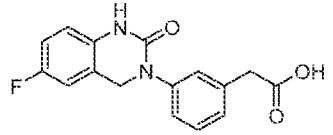
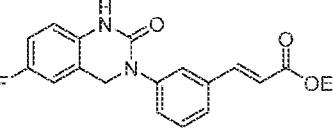
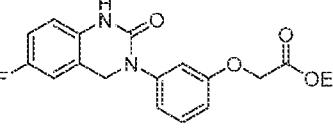
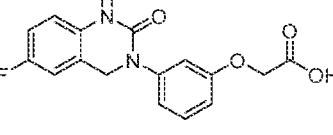
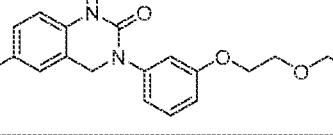
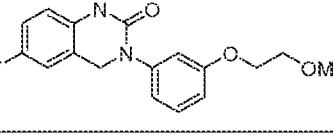
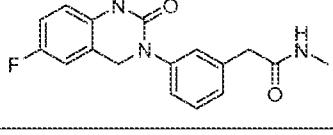
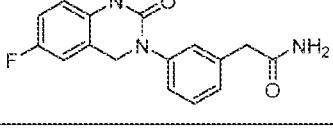
16		0.084
17		0.038
18		0.065
19		0.382
20		>10
21		0.197
22		0.243
23		>10
24		0.161

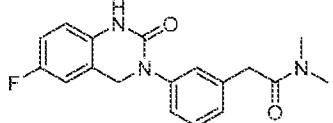
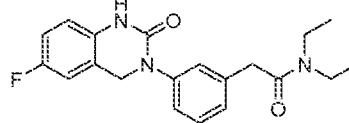
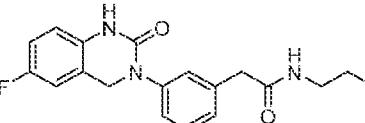
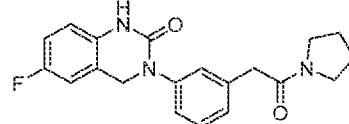
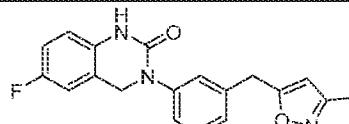
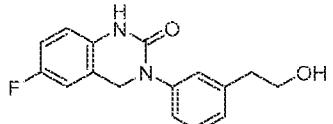
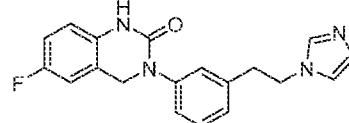
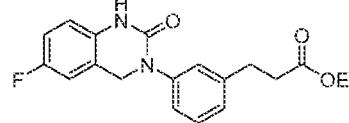
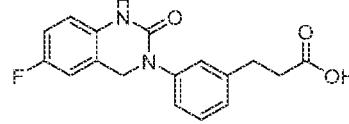
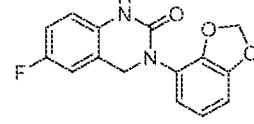
25		2.59
26		0.100
27		0.251
28		5.46
29		>10
30		>10
31		2.24
32		1.01
33		0.251

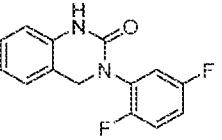
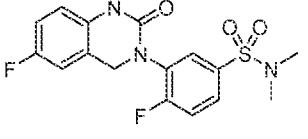
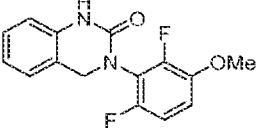
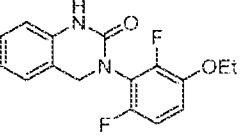
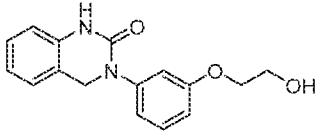
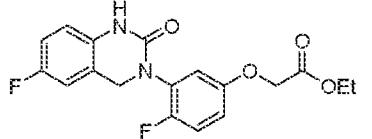
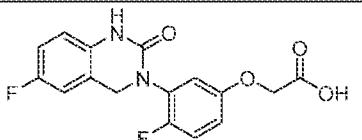
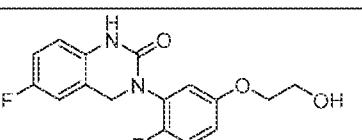
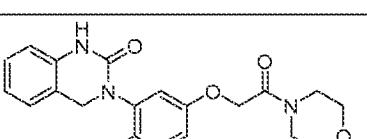
34		0.051
35		2.19
36		>10
37		4.12
38		0.348
39		0.296
40		0.261
41		0.092
42		0.124

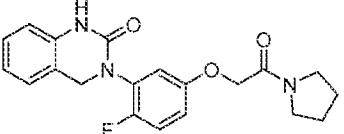
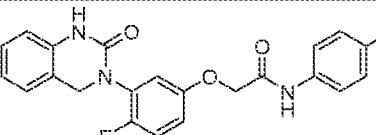
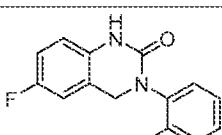
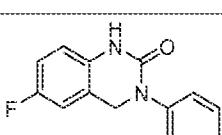
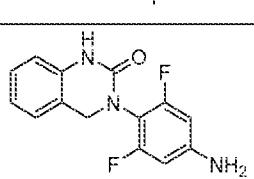
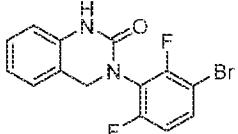
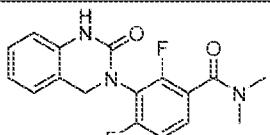
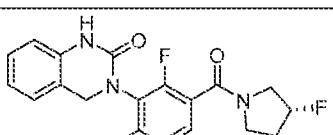
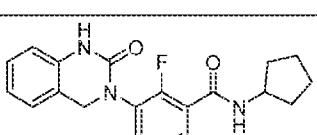
43		0.202
44		0.432
45		0.127
46		0.170
47		0.526
48		0.282
49		0.162
50		1.34
51		3.89

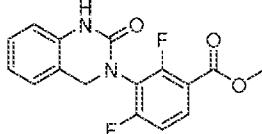
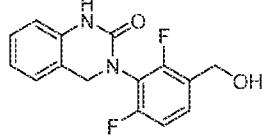
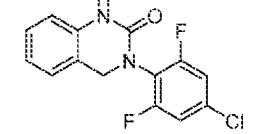
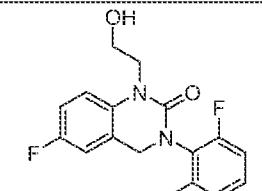
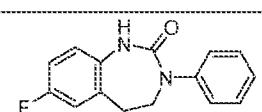
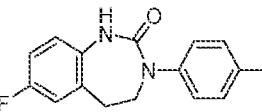
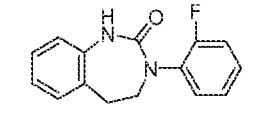
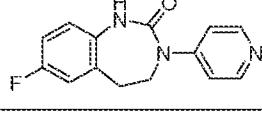
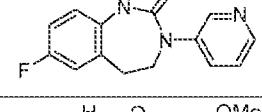
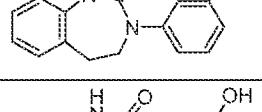
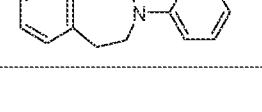
52		0.615
53		0.395
54		0.105
55		0.184
56		0.615
57		0.918
58		5.96
59		1.27
60		0.268

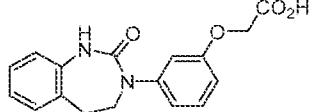
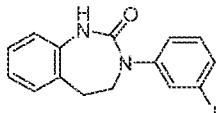
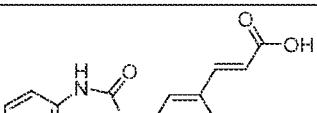
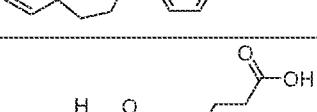
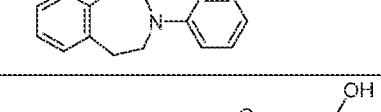
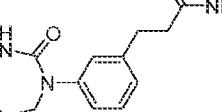
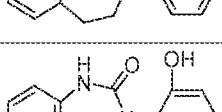
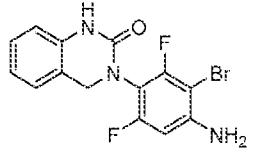
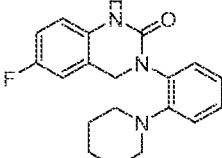
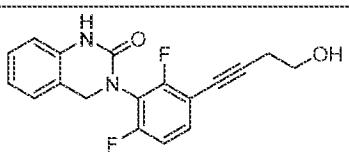
61		1.06
62		0.038
63		2.57
64		1.61
65		0.082
66		3.56
67		0.457
68		0.418
69		0.438
70		0.226

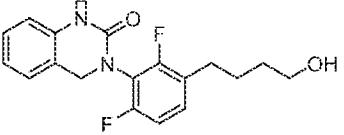
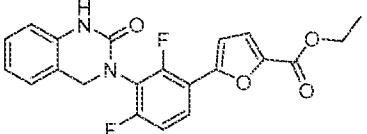
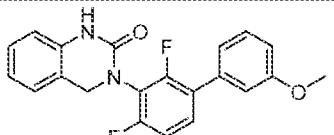
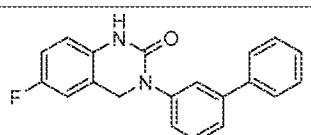
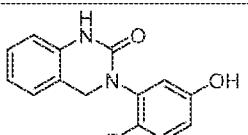
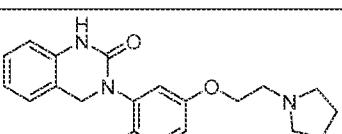
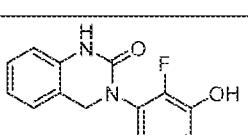
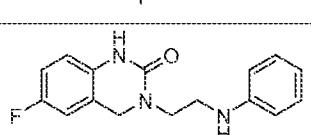
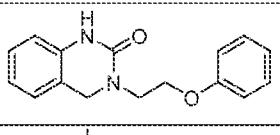
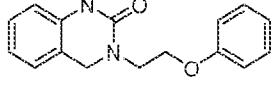
71		0.473
72		0.483
73		4.36
74		0.675
75		0.663
76		0.243
77		0.858
78		0.690
79		8.91
80		0.181

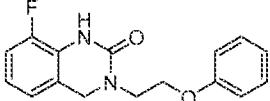
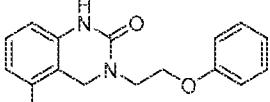
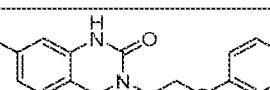
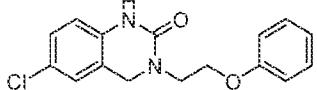
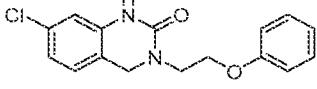
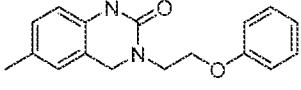
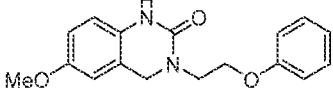
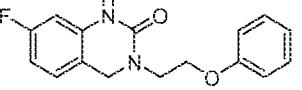
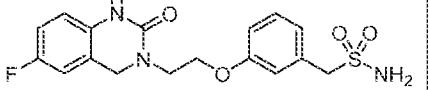
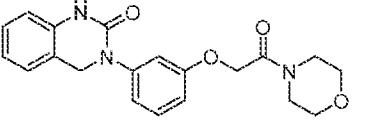
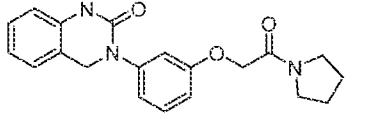
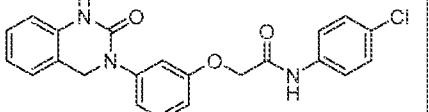
81		0.119
82		2.31
83		1.60
84		0.572
85		2.41
86		0.264
87		1.99
88		0.713
89		2.00

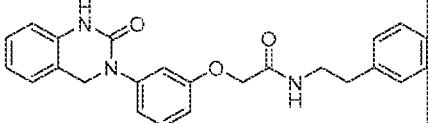
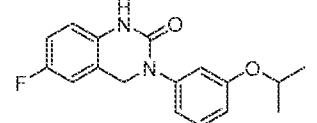
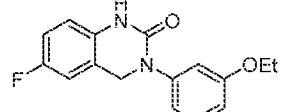
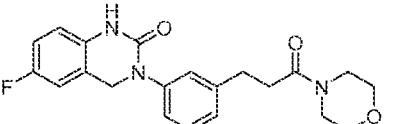
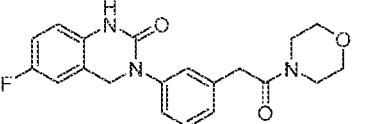
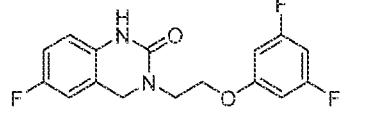
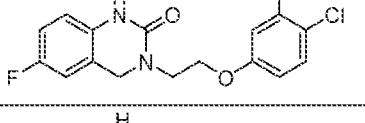
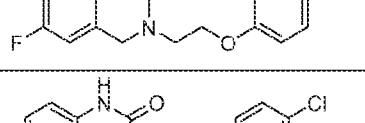
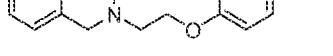
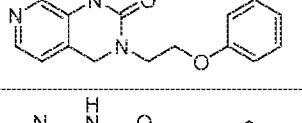
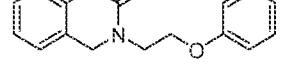
90		0.731
91		3.50
92		0.134
93		0.047
94		0.097
95		0.231
96		3.57
97		2.43
98		2.43

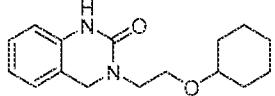
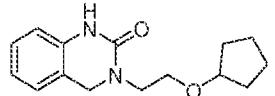
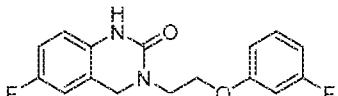
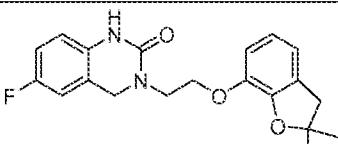
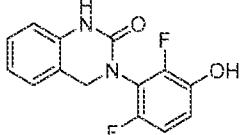
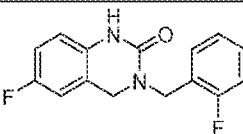
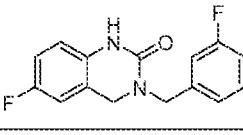
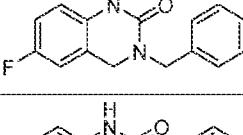
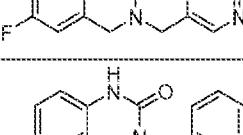
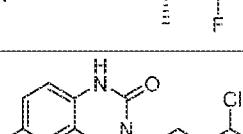
99		1.04
100		0.508
101		1.52
102		0.256
103		0.578
104		5.71
105		1.27
106		>10
107		>10
108		>10
109		8.64

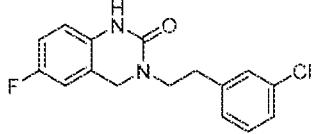
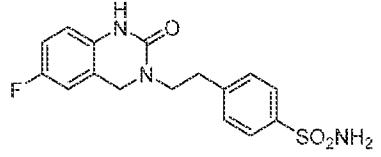
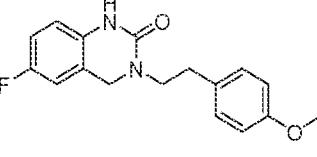
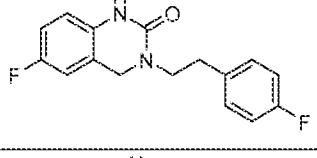
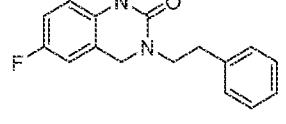
110		>10
111		4.73
112		>10
113		>10
114		>10
115		0.568
116		2.07
117		0.514
118		1.63
119		1.55

120		0.845
121		0.298
122		0.303
123		1.73
124		0.532
125		>10
126		0.517
127		0.439
128		0.030
129		0.174

130		1.02
131		3.55
132		5.07
133		0.449
134		0.074
135		3.51
136		0.911
137		1.12
138		0.737
139		1.10
140		0.345
141		4.38

142		0.853
143		0.166
144		0.320
145		1.65
146		1.09
147		0.114
148		0.404
149		0.140
150		0.301
151		0.733
152		8.53

153		0.052
154		0.137
155		0.093
156		0.243
157		0.571
158		0.271
159		0.159
160		0.377
161		1.575
162		0.210
163		0.394

164		0.069
165		1.203
166		0.744
167		1.764
168		0.158

Xenograft in vivo Studies

A20 efficacy study

Female BALB/c mice (N=20), age 7-8 weeks, were implanted subcutaneously with 1×10^7 A20 B-cell lymphoma cells per mouse suspended in phosphate buffered saline and mixed 1:1 with matrigel. Mice were randomized into the following two groups of N=10 mice per group: 1) vehicle control (aqueous 0.5% carboxymethylcellulose/0.1% polysorbate-80) and 2) compound of the invention (Example 41) dosed orally at 50 mg/kg (formulated at 5 mg/mL in 0.5% carboxymethylcellulose/0.1% polysorbate-80). For both groups, dosing was initiated one day post-implantation (Study Day 1) and continued orally twice daily for 23 days. Tumors were measured with calipers starting on Study Day 7 and then every 3 or 4 days thereafter. Tumor volume was calculated using the following formula: tumor volume (mm^3) = $(a \times b^2/2)$ where 'a' is the largest perpendicular diameter and 'b' is the smallest perpendicular diameter. *P value < 0.05 (Two-tailed T test). Results are shown in Figure 1.

B16-F10 efficacy study

Female C57BL/6 mice (N=20), age 7-8 weeks, were implanted subcutaneously with 1×10^6 B16-F10 melanoma cells per mouse suspended in phosphate buffered saline. Mice were randomized into the following two groups of N=10 mice per group: 1) vehicle control (aqueous 0.5% carboxymethylcellulose/0.1% polysorbate-80) and 2) compound of the invention (Example 41) dosed orally at 50 mg/kg (formulated at 5 mg/mL in aqueous 0.5% carboxymethylcellulose/0.1% polysorbate-80). For both groups, dosing was initiated one day post-implantation (Study Day 1) and continued orally twice daily for 14 days. Tumors were measured with calipers on Study Days 6, 9, 12, and 14. Tumor volume was calculated using the following formula: tumor volume (mm^3) = ($a \times b^2/2$) where 'a' is the largest perpendicular diameter and 'b' is the smallest perpendicular diameter. **P value<0.01 (Two-tailed T test). Results are shown in Figure 2.

B16.OVA.hIL4II efficacy study

Female C57BL/6 mice (N=20), age 7-8 weeks, were implanted subcutaneously with 2×10^6 B16.OVA.hIL4II melanoma cells per mouse suspended in phosphate buffered saline. B16.OVA.hIL4II are B16-F10 cells that have been engineered to express both the ovalbumin antigen and human IL4II. Mice were randomized into the following two groups of N=10 mice per group: 1) vehicle control (aqueous 0.5% carboxymethylcellulose/0.1% polysorbate-80) and 2) compound of the invention (Example 41) dosed orally at 50 mg/kg (formulated at 5 mg/mL in aqueous 0.5% carboxymethylcellulose/0.1% polysorbate-80). For both groups, dosing was initiated one day post-implantation (Study Day 1) and continued orally twice daily for 22 days. Tumors were measured with calipers starting on Study Day 8 and then every 3 or 4 days thereafter. Tumor volume was calculated using the following formula: tumor volume (mm^3) = ($a \times b^2/2$) where 'a' is the largest perpendicular diameter and 'b' is the smallest perpendicular diameter. *P value<0.05 (Two-tailed T test). Results are shown in Figure 3.

E.G7-OVA efficacy study

Female C57BL/6 mice (N=20), age 7-8 weeks, were implanted subcutaneously with 1×10^6 E.G7-OVA T-cell lymphoma cells per mouse suspended in phosphate buffered saline. Mice were randomized into the following two groups of N=10 mice per group: 1) vehicle control

(aqueous 0.5% carboxymethylcellulose/0.1% polysorbate-80) and 2) compound of the invention (Example 41) dosed orally at 50 mg/kg (formulated at 5 mg/mL in aqueous 0.5% carboxymethylcellulose/0.1% polysorbate-80). For both groups, dosing was initiated one day post-implantation (Study Day 1) and continued orally twice daily for 21 days. Tumors were measured with calipers starting on Study Day 7 and then every 3 or 4 days thereafter. Tumor volume was calculated using the following formula: tumor volume (mm^3) = ($a \times b^2/2$) where ‘a’ is the largest perpendicular diameter and ‘b’ is the smallest perpendicular diameter. * P value<0.05 (Two-tailed T test). Results are shown in Figure 4.

A20 efficacy with delayed dosing study

Female BALB/c mice (N=20), age 7-8 weeks, were implanted subcutaneously with 1×10^7 A20 B-cell lymphoma cells per mouse suspended in phosphate buffered saline and mixed 1:1 with matrigel. Mice, N=10 mice per group, were administered either 1) vehicle control (aqueous 0.5% carboxymethylcellulose/0.1% polysorbate-80) or 2) compound of the invention (Example 41) dosed orally at 50 mg/kg (formulated at 5 mg/mL in aqueous 0.5% carboxymethylcellulose/0.1% polysorbate-80). All mice were orally administered vehicle twice daily from Study Days 1 to 6 and then randomized into two groups of equivalent mean tumor volumes. Group 1 continued with oral administration of vehicle twice daily until Study Day 23. Group 2 was orally administered compound of the invention twice daily from Study Days 7 to 23. Tumors were measured with calipers starting on Study Day 9 and then every 3 or 4 days thereafter. Tumor volume was calculated using the following formula: tumor volume (mm^3) = ($a \times b^2/2$) where ‘a’ is the largest perpendicular diameter and ‘b’ is the smallest perpendicular diameter. ** P value<0.01 (Two-tailed T test). Results are shown in Figure 5.

B16-F10 efficacy study in combination with anti-PD-L1

Female C57BL/6 mice (N=40), age 7-8 weeks, were implanted subcutaneously with 1×10^6 B16-F10 melanoma cells per mouse suspended in phosphate buffered saline. Mice were randomized into the following four groups of N=10 mice per group: 1) vehicle control (aqueous 0.5% carboxymethylcellulose/0.1% polysorbate-80); 2) compound of the invention (Example 41) dosed orally at 50 mg/kg (formulated at 5 mg/mL in aqueous 0.5% carboxymethylcellulose/0.1% polysorbate-80); 3) anti-PD-L1 antibody clone 10F.9G2 dosed

intraperitoneally at 5 mg/kg (formulated at 0.5 mg/mL in saline); and 4) compound of the invention plus anti-PD-L1. For vehicle and compound of the invention, dosing was initiated one day post-implantation (Study Day 1) and continued orally twice daily for 15 days. For anti-PD-L1 antibody, mice were dosed on Study Days 5, 7, 9, 11, and 13. Tumors were measured with calipers on Study Days 7, 11, 13, and 15. Tumor volume was calculated using the following formula: tumor volume (mm³) = (a x b²/2) where 'a' is the largest perpendicular diameter and 'b' is the smallest perpendicular diameter. *P value<0.05 (Two-way ANOVA). Results are shown in Figure 6.

Incorporation by Reference

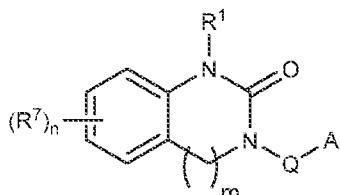
All publications and patents mentioned herein are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

Equivalents

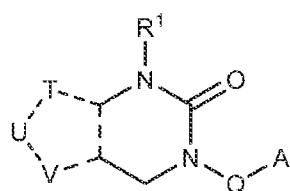
While specific embodiments of the subject invention have been discussed, the above specification is illustrative and not restrictive. Many variations of the invention will become apparent to those skilled in the art upon review of this specification and the claims below. The full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

What is claimed is:

1. A compound of Formula (I) or (II), or a pharmaceutically acceptable salt or prodrug thereof:



(I)



(II)

wherein

R¹ is selected from H, unsubstituted alkyl, hydroxyalkyl, cycloalkyl, and cycloalkylalkyl;

R⁷ is selected from halo, CN, nitro, hydroxy, alkyl, alkenyl, alkoxy, amino, amido, carboxy, and acyloxy;

m is 1 or 2;

n is 0, 1, or 2;

T is S or CR⁸;

U is S or CR⁹;

V is S or CR¹⁰;

wherein one and only one of T, U and V is S;

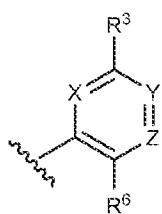
---- bond indicates a single or double bond as valency permits where up to two non-consecutive ---- bonds are double bonds;

Q is a bond, CH₂, CH(CH₃), CH₂CH₂, -C₂(alkyl)NR¹¹- or -C₂(alkyl)O-;

wherein C₂(alkyl) is optionally substituted with one or more alkyl groups;

A is selected from aryl, heteroaryl, cycloalkyl or heterocyclyl;

provided that if the compound is of Formula (I), and Q is a bond and m = 1, then A is:



wherein

X is N or CR²;

Y is N or CR⁴;

Z is N or CR⁵;

R², R³, R⁴ and R⁵ are each independently selected from H, halo, CN, nitro, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, acyloxy, azido, carboxy, amino, amido, sulfone, -SO₂NR^aR^b, heteroaralkyl, aralkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl;

R⁶ is selected from H, halo, CN, alkyl, hydroxy, alkoxy, sulfone, cycloalkyl, heterocyclyl, aryl, and heteroaryl; or

R⁵ and R⁶, taken together with the atoms to which they are attached, may form a 5- or 6-membered aryl, cycloalkyl, heterocyclyl or heteroaryl;

R⁸, R⁹ and R¹⁰ are each independently selected from H, halo and unsubstituted alkyl;

R¹¹ is H or alkyl;

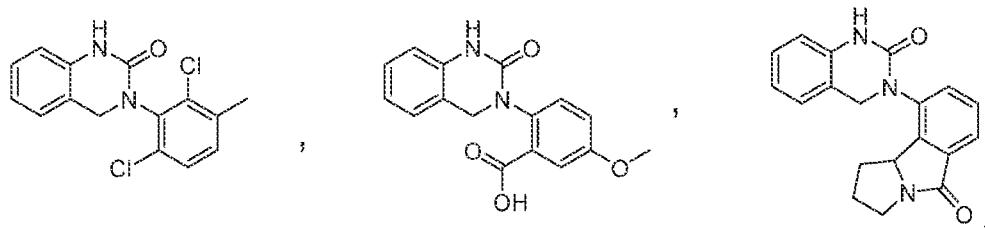
R^a and R^b are each H or alkyl;

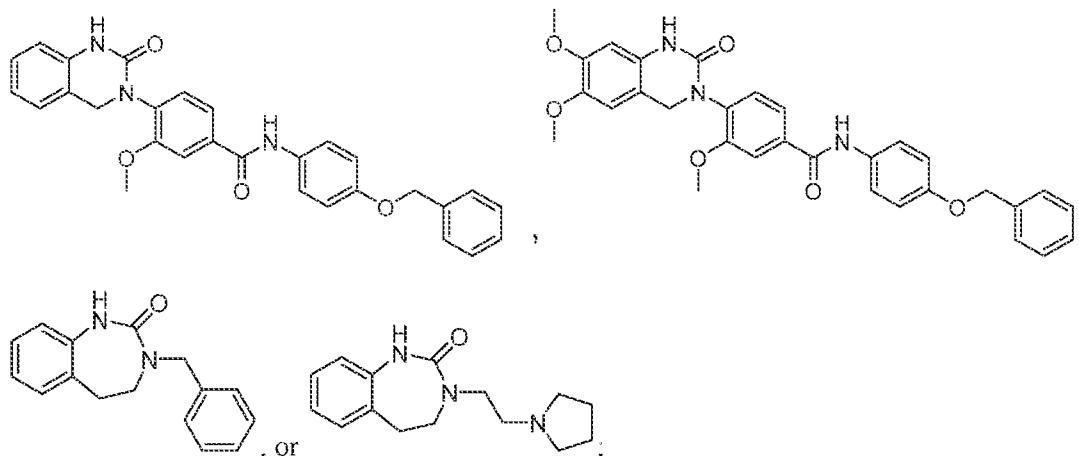
provided that:

if Q is a bond and m is 1, then:

- a) if R⁶ is Cl or methyl, then at least one of R², R³, R⁴ and R⁵ is not H;
- b) R³ or R⁵ is not aralkoxy or heteroaralkoxy;
- c) R⁴ and R⁶ are not both methyl or methoxy;
- d) R² and R⁶ are not both ethyl;
- e) R², R³, R⁴, R⁵, and R⁶ are not each H;
- f) if R² and R⁶ are each H, then Y is CR⁴ and R⁴ is H;
- g) if R² and R⁶ are each H, then R³ is not methyl, trifluoromethyl, pyridinyl, or methoxy;

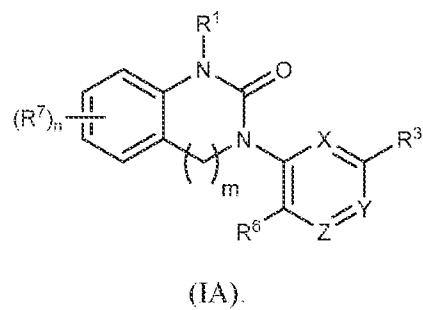
the compound of Formula (I) is not



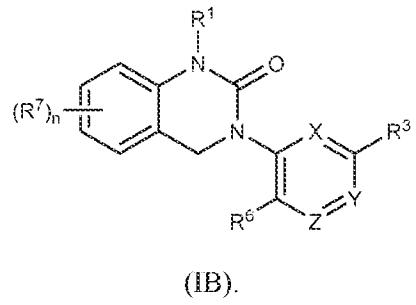


if Q is CH_2 or CH_2CH_2 and m=1, then R^7 is 6-fluoro;
 if Q is CH_2 and m=2, then A is not cycloalkyl;
 if Q is $\text{CH}(\text{CH}_3)$ and m = 1, then R^7 is not amido;
 if the compound is of Formula (II), and Q is a bond, then A is not heterocyclyl; and
 if Q is a bond and m is 2, then A is aryl or heteroaryl, and A is not substituted with sulfone, alkylthio, difluoromethoxy, or 1,1-difluoroethyl.

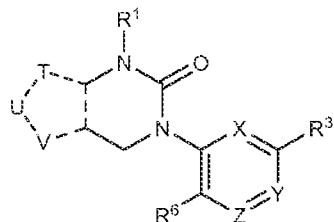
2. The compound of claim 1, wherein the compound is of Formula (IA):



3. The compound of claim 1 or 2, wherein the compound is of Formula (IB):



4. The compound of claim 1, wherein the compound is of Formula (IIA):



(IIA).

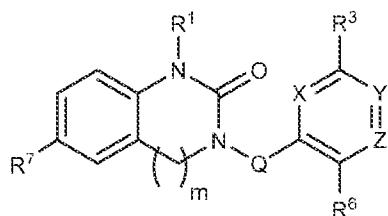
5. The compound of claim 4, wherein T is S, U is CR⁹, R⁹ is H, and V is CH.
6. The compound of claim 4, wherein T is S, U is CR⁹, R⁹ is chloro, and V is CH.
7. The compound of claim 4, wherein T is CH, U is CH, and V is S.
8. The compound of claim 1 or 2, wherein m is 2.
9. The compound of any one of claims 1-8, wherein R¹ is H.
10. The compound of any one of claims 1-8, wherein R¹ is methyl.
11. The compound of any one of claims 1-10, wherein X is N.
12. The compound of any one of claims 1-10, wherein X is CR².
13. The compound of any one of claims 1-12, wherein Y is N.
14. The compound of any one of claims 1-12, wherein Y is CR⁴.
15. The compound of any one of claims 1-14, wherein Z is N.
16. The compound of any one of claims 1-14, wherein Z is CR⁵.
17. The compound of any one of claims 1-16, wherein R², R³, R⁴ and R⁵ are each independently selected from H, halo, CN, nitro, alkyl, alkenyl, alkynyl, alkoxy, carboxy, amino, amido, and aryl.
18. The compound of any one of claims 1-17, wherein R², R³, R⁴ and R⁵ are each independently selected from H, halo, hydroxy, alkoxy and aralkyl.

19. The compound of any one of claims 1-17, wherein R² is selected from H, fluoro, bromo, CN and methyl.
20. The compound of any one of claims 1-19, wherein R² is H.
21. The compound of any one of claims 1-19, wherein R² is fluoro or CN.
22. The compound of any one of claims 1-17, wherein R³ is selected from H, fluoro, chloro, bromo, hydroxy, CN, NO₂, NH₂, methyl, methoxy, ethoxy, -C(O)NMe₂, -CH₂OH, -CH₂CH₂OH, -(CH₂)₄OH, -CH₂CO₂H, -CH₂CONH₂, -CH₂CONMe₂, -CH₂CONEt₂, -CH₂CONHCH₂CH₂NET₂, -CH₂-oxazolyl, -CH₂CH₂-imidazolyl, -(CH₂)₂CO₂H, -(CH₂)₂CO₂Et, -(CH₂)₂CONH(CH₂)₂OH, -CH₂CO₂Me, -CH₂CO-morpholino, -CH₂CO-pyrrolidinyl, -CH₂CH₂CO-morpholino, -CH=CH-COOH, -CH=CH-COOEt, -C≡C-(CH₂)₂OH, -CO₂H, -CO₂Me, -CONH-cyclopentyl, -CO-pyrrolidinyl, -CO-3-fluoropyrrolidinyl, -O(CH₂)₂-OH, -O(CH₂)₂OCH₃; -O(CH₂)₂OCH₂CH₃, -OCH₂-CO₂H, -OCH₂-CO₂Et, -O(CH₂)₂-pyrrolidinyl, -OCH₂-CO-pyrrolidinyl, -OCH₂-CO-morpholino, -OCH₂-CONH-CH₂CH₂phenyl, -OCH₂-CONH-4-chlorophenyl, 3-methoxyphenyl and ethyl 5-furylcarboxylate.
23. The compound of any one of claims 1-22, wherein R⁴ is selected from H, fluoro, chloro, bromo, iodo, CN, and -NH₂.
24. The compound of any one of claims 1-23, wherein R⁵ is selected from H, fluoro, CN, nitro, and amino.
25. The compound of any one of claims 1-24, wherein R⁶ is fluoro.
26. The compound of any one of claims 1-24, wherein R⁶ is chloro or bromo.
27. The compound of any one of claims 1-24, wherein R⁶ is cyano.
28. The compound of any one of claims 1-24, wherein R⁶ is methyl or isopropyl.
29. The compound of any one of claims 1-24, wherein R⁶ is selected from hydroxy, methoxy, ethoxy, -OCH₂-CO₂Et, and -OCH₂-CO₂H.
30. The compound of any one of claims 1-24, wherein R⁶ is sulfone.

31. The compound of any one of claims 1-30, wherein Q is -CH₂CH₂-NH- and each of R², R³, R⁴, R⁵, and R⁶ are H.

32. The compound of any one of claims 1-30, wherein Q is -CH₂CH₂-O- and each of R², R³, R⁴, R⁵, and R⁶ are H.

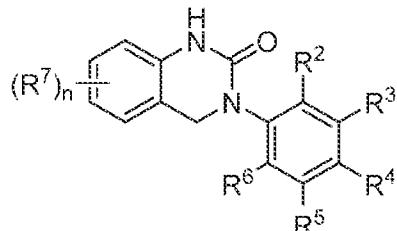
33. The compound of claim 1, wherein the compound is of Formula (IC):



(IC)

34. The compound of claim 33, wherein R⁷ is H, fluoro, chloro, methyl or methoxy.

35. The compound of claim 1, wherein the compound is of Formula (ID):



(ID)

wherein,

R² and R⁶ are each independently selected from H, halo, CN and methyl;

R³ and R⁵ are each independently selected from H, halo, hydroxyl, alkyl, alkoxy and aralkyl;

R⁴ is selected from H, halo, and NH₂;

R⁷ is fluoro or chloro; and

n = 0 or 1.

36. The compound of claim 35, wherein

R³ is selected from H, halo and methyl;

R⁴ and R⁵ are each H; and

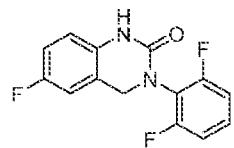
R⁷ is fluoro.

37. The compound of claim 36, wherein
R² is selected from fluoro, chloro and CN;
R⁶ is selected from H, fluoro and chloro; and
R³ is H.

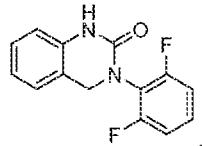
38. The compound of claim 1, wherein,
the compound is of Formula (I);
R¹ is selected from H and unsubstituted alkyl;
Q is selected from CH₂, CH(CH₃), CH₂CH₂, -CH₂CH₂NH- and -CH₂CH₂O-;
A is selected from aryl and cycloalkyl; wherein,
A is optionally substituted one or more halo, alkoxy or alkyl substituents;
m = 1; and
n = 0 or 1.

39. The compound of claim 37, wherein,
R¹ is H;
Q is selected from CH₂, CH(CH₃), CH₂CH₂, and -CH₂CH₂O-;
A is aryl; wherein,
A is optionally substituted one or more halo or alkoxy substituents.

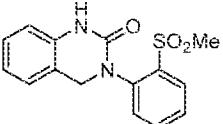
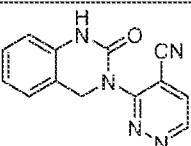
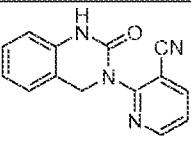
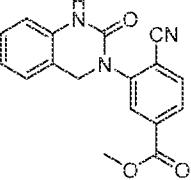
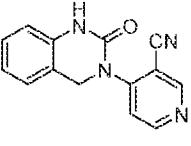
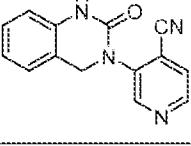
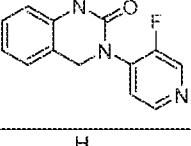
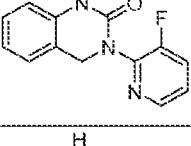
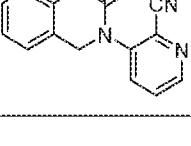
40. The compound of claim 1, having the structure:

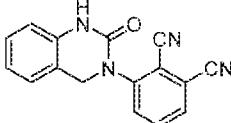
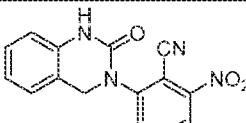
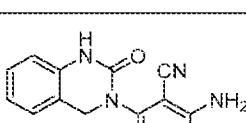
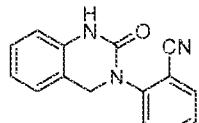
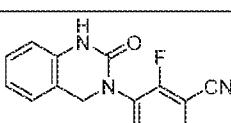
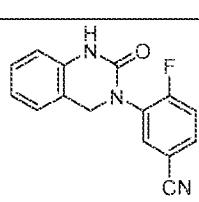
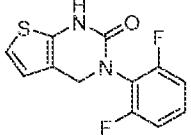
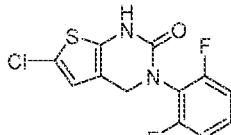
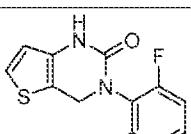


41. The compound of claim 1, having the structure:

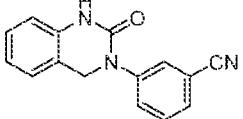
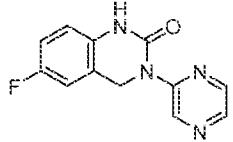
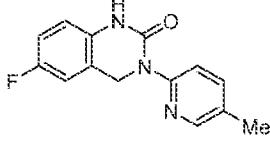
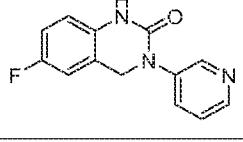
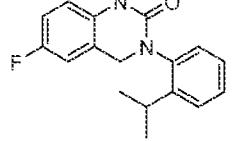
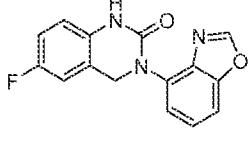
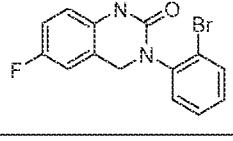
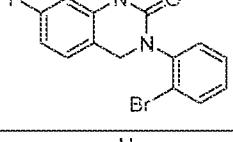
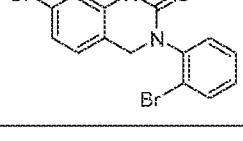


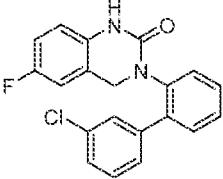
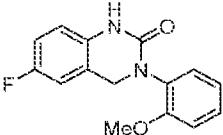
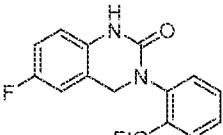
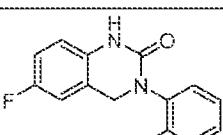
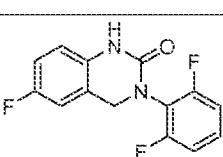
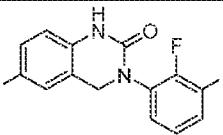
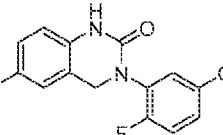
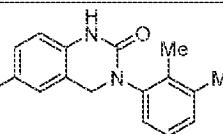
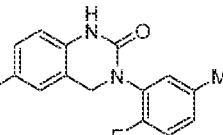
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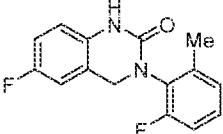
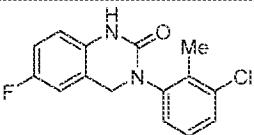
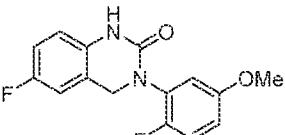
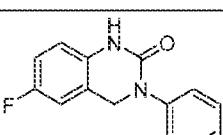
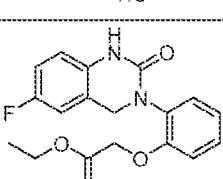
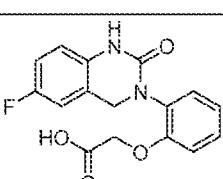
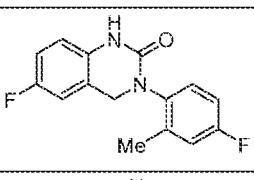
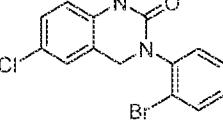
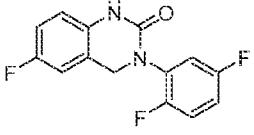
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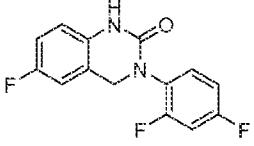
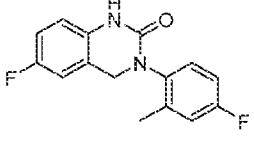
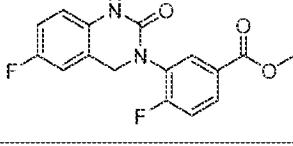
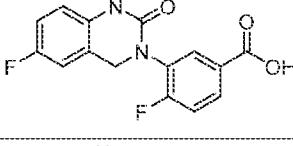
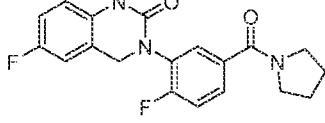
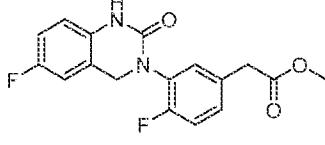
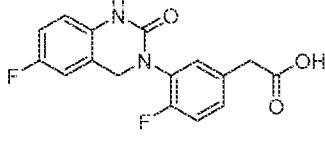
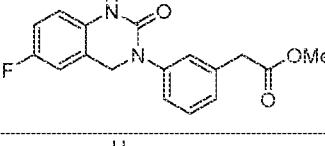
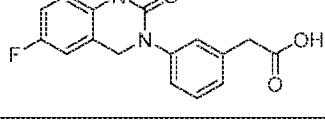
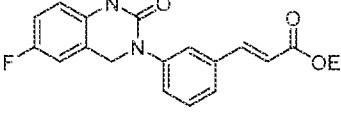
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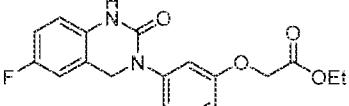
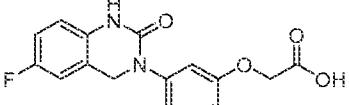
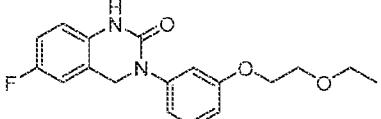
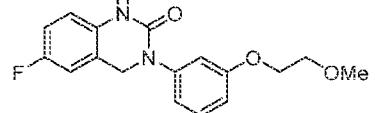
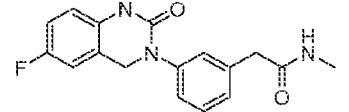
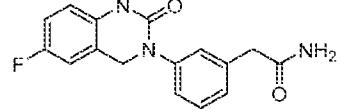
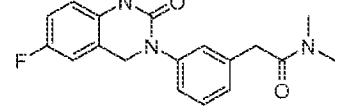
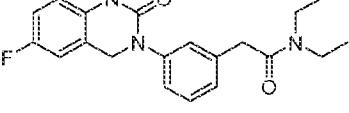
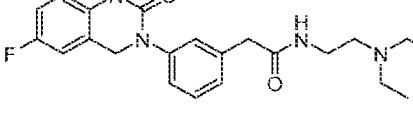
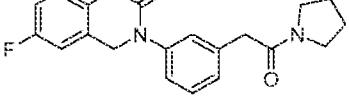
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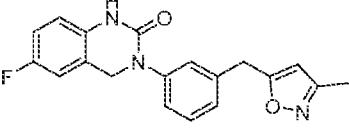
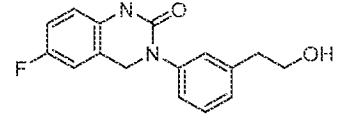
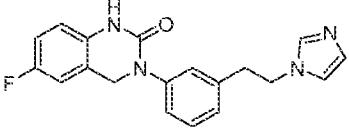
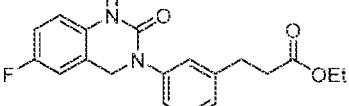
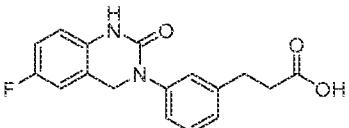
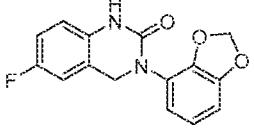
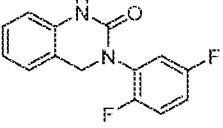
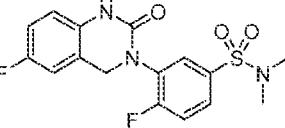
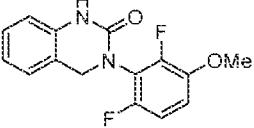
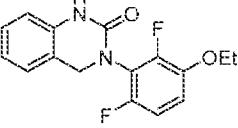
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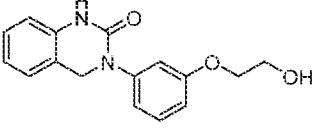
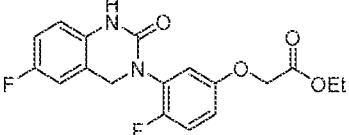
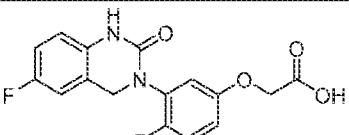
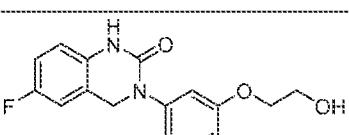
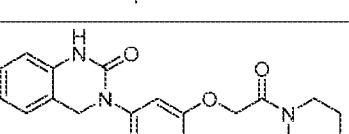
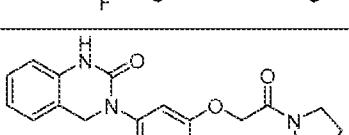
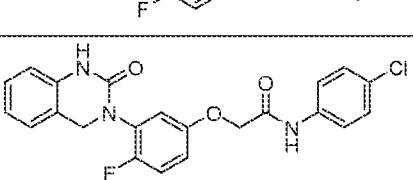
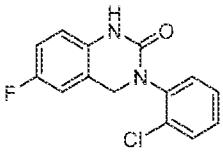
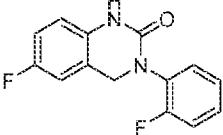
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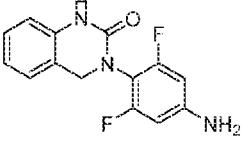
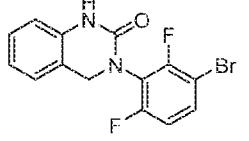
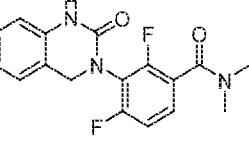
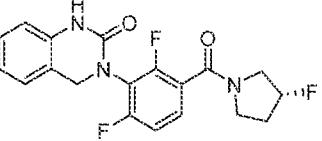
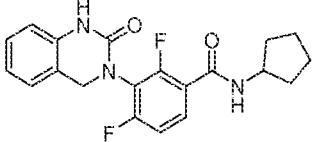
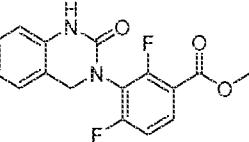
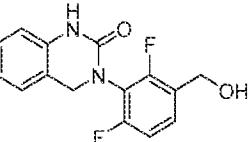
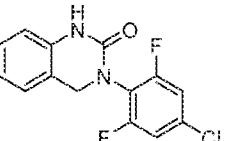
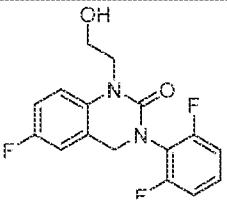
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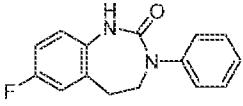
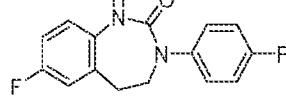
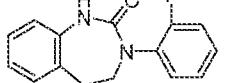
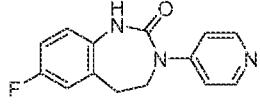
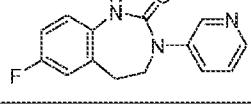
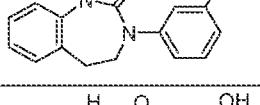
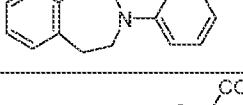
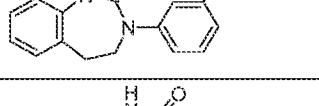
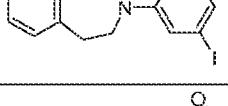
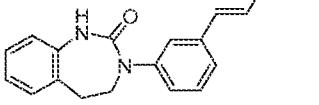
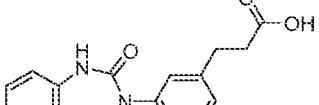
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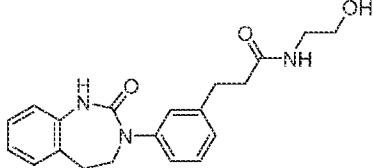
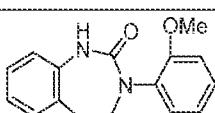
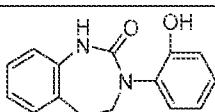
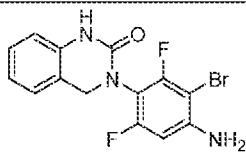
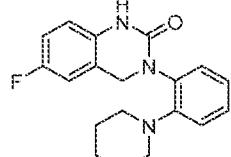
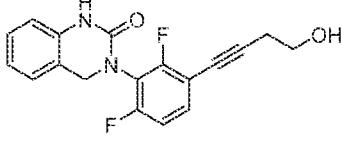
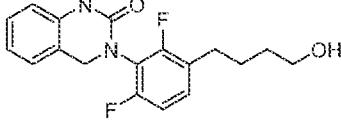
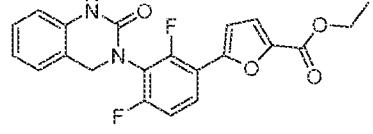
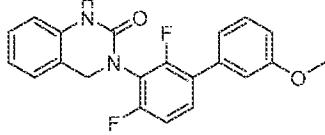
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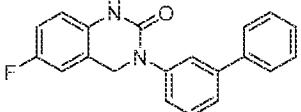
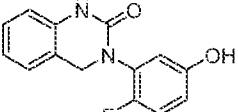
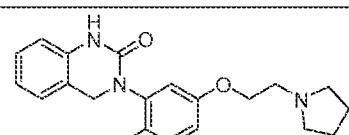
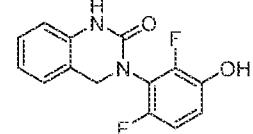
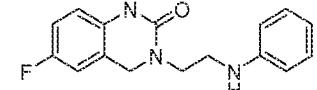
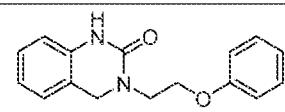
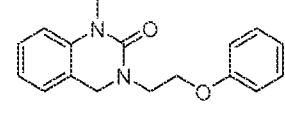
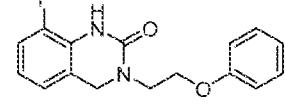
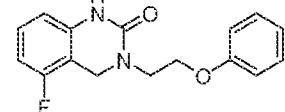
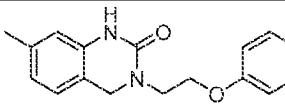
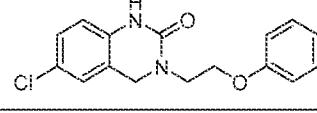
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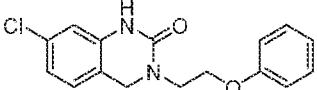
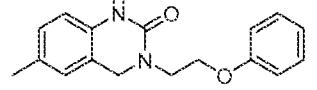
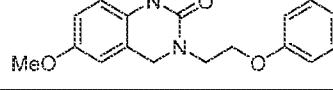
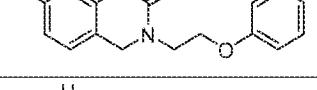
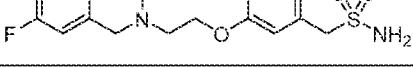
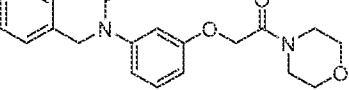
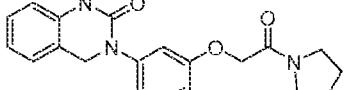
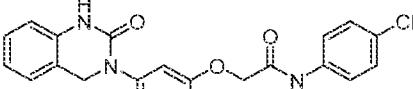
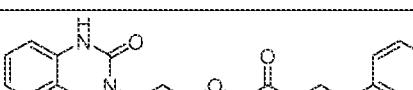
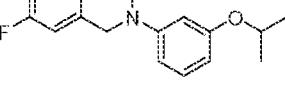
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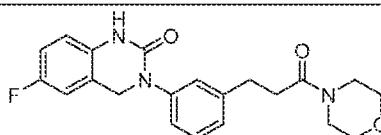
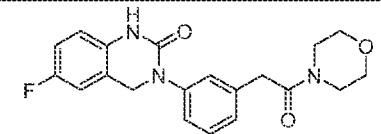
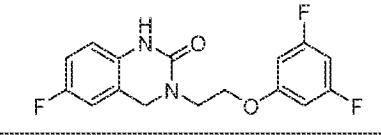
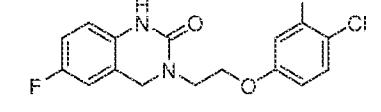
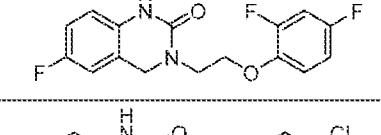
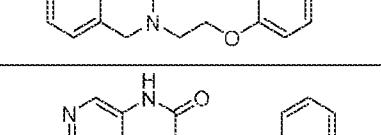
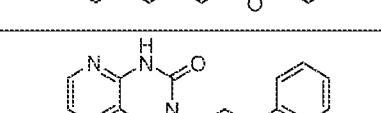
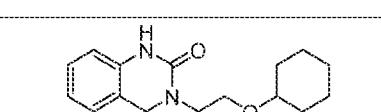
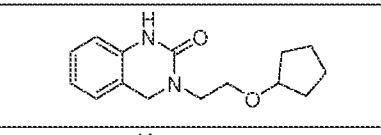
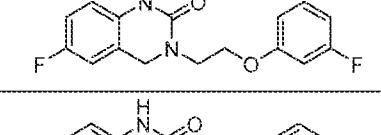
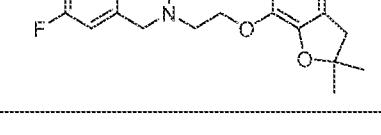
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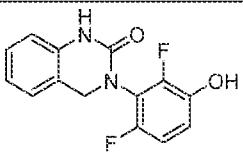
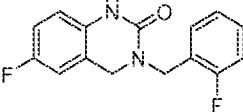
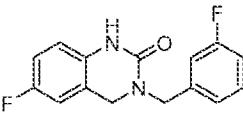
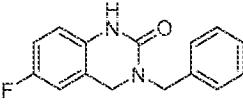
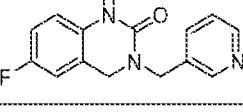
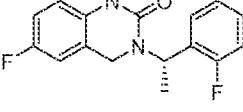
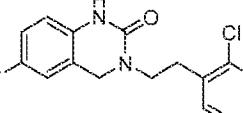
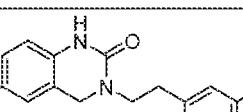
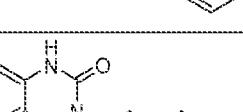
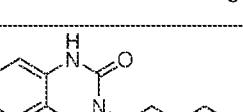
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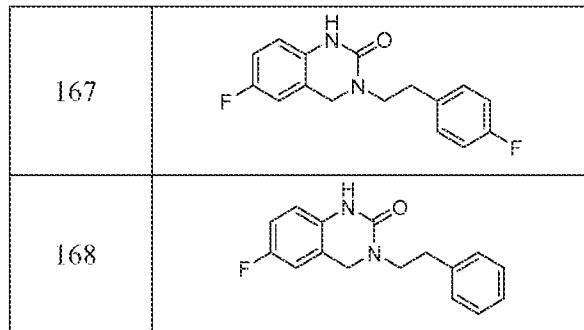
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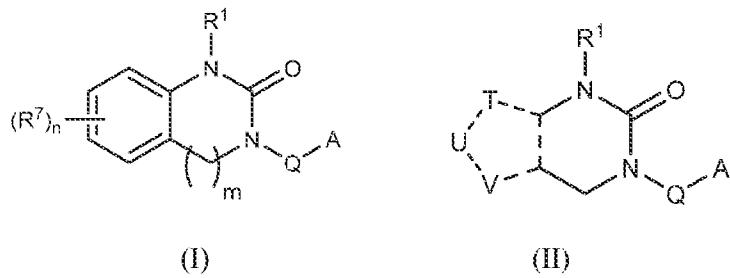
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or a pharmaceutically acceptable salt thereof.

43. A pharmaceutical composition comprising a compound according to any one of claims 1-42, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

44. A method of treating or preventing cancer, comprising administering to a subject in need thereof a compound of Formula (I) or (II), or a pharmaceutically acceptable salt or prodrug thereof:



wherein

R¹ is selected from H, unsubstituted alkyl, hydroxyalkyl, cycloalkyl, and cycloalkylalkyl;

R⁷ is selected from halo, CN, nitro, hydroxy, alkyl, alkenyl, alkoxy, amino, amido, carboxy, and acyloxy;

m is 1 or 2;

n is 0, 1, or 2;

T is S or CR⁸;

U is S or CR⁹;

V is S or CR¹⁰;

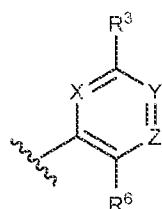
wherein one and only one of T, U and V is S;

---- bond indicates a single or double bond as valency permits where up to two non-consecutive ---- bonds are double bonds;

Q is a bond, CH₂, CH(CH₃), CH₂CH₂, -C₂(alkyl)NR¹¹⁻ or -C₂(alkyl)O-; wherein C₂(alkyl) is optionally substituted with one or more alkyl groups;

A is selected from aryl, heteroaryl, cycloalkyl or heterocyclyl;

provided that if the compound is of Formula (I), and Q is a bond and m = 1, then A is:



wherein

X is N or CR²;

Y is N or CR⁴;

Z is N or CR⁵;

R², R³, R⁴ and R⁵ are each independently selected from H, halo, CN, nitro, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, acyloxy, azido, carboxy, amino, amido, sulfone, -SO₂NR^aR^b, heteroaralkyl, aralkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl;

R⁶ is selected from H, halo, CN, alkyl, hydroxy, alkoxy, sulfone, cycloalkyl, heterocyclyl, aryl, and heteroaryl; or

R⁵ and R⁶, taken together with the atoms to which they are attached, may form a 5- or 6-membered aryl, cycloalkyl, heterocyclyl or heteroaryl;

R⁸, R⁹ and R¹⁰ are each independently selected from H, halo and unsubstituted alkyl;

R¹¹ is H or alkyl;

R^a and R^b are each H or alkyl;

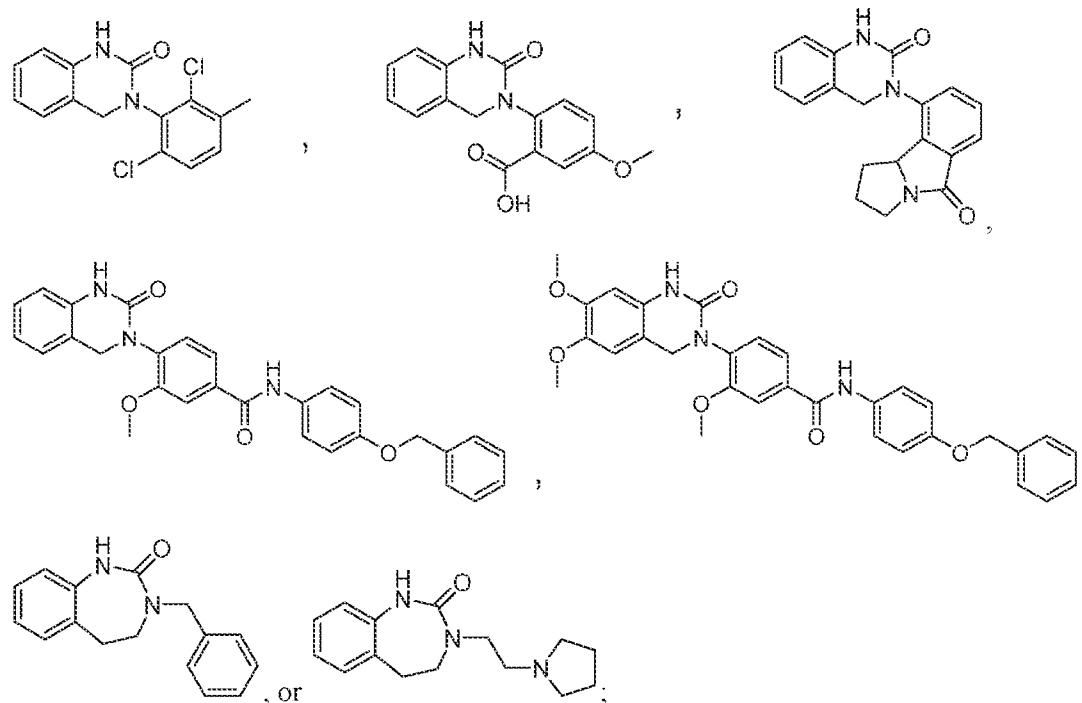
provided that:

if Q is a bond and m is 1, then:

- a) if R⁶ is Cl or methyl, then at least one of R², R³, R⁴ and R⁵ is not H;
- b) R³ or R⁵ is not aralkoxy or heteroaralkoxy;
- c) R⁴ and R⁶ are not both methyl or methoxy;
- d) R² and R⁶ are not both ethyl;
- e) R², R³, R⁴, R⁵, and R⁶ are not each H;

- f) if R² and R⁶ are each H, then Y is CR⁴ and R⁴ is H;
- g) if R² and R⁶ are each H, then R³ is not methyl, trifluoromethyl, pyridinyl, or methoxy;

the compound of Formula (I) is not



if Q is CH₂ or CH₂CH₂ and m=1, then R⁷ is 6-fluoro;

if Q is CH₂ and m=2, then A is not cycloalkyl;

if Q is CH(CH₃) and m = 1, then R⁷ is not amido;

if the compound is of Formula (II), and Q is a bond, then A is not heterocyclyl; and

if Q is a bond and m is 2, then A is aryl or heteroaryl, and A is not substituted with sulfone,

alkylthio, difluoromethoxy, or 1,1-difluoroethyl.

45. The method of claim 44, wherein the cancer is selected from lymphoma, ovarian, uterine, glioma, lung, kidney, melanoma, head and neck carcinoma, pancreatic, stomach, breast, colon, bladder, esophageal, and liver cancer.

46. The method of claim 45, wherein the cancer is selected from Hodgkin's lymphoma, diffuse large B-cell lymphoma (DLBCL), melanoma, ovarian, pancreatic, lung carcinoma and colon carcinoma.

47. The method of any one of claims 44-46, further comprising conjointly administering one or more additional chemotherapeutic agents.

48. The method of claim 47, wherein the one or more additional chemotherapeutic agents are selected from 1-amino-4-phenylamino-9,10-dioxo-9,10-dihydroanthracene-2-sulfonate (acid blue 25), 1-amino-4-[4-hydroxyphenyl-amino]-9,10-dioxo-9,10-dihydroanthracene-2-sulfonate, 1-amino-4-[4-aminophenylamino]-9,10-dioxo-9,10-dihydroanthracene-2-sulfonate, 1-amino-4-[1-naphthylamino]-9,10-dioxo-9,10-dihydroanthracene-2-sulfonate, 1-amino-4-[4-fluoro-2-carboxyphenylamino]-9,10-dioxo-9,10-dihydroanthracene-2-sulfonate, 1-amino-4-[2-antracenylamino]-9,10-dioxo-9,10-dihydroanthracene-2-sulfonate, ABT-263, afatinib dimaleate, axitinib, aminoglutethimide, amsacrine, anastrozole, APCP, asparaginase, AZD5363, Bacillus Calmette-Guérin vaccine (bcg), bicalutamide, bleomycin, bortezomib, β -methylene-ADP (AOPCP), buserelin, busulfan, cabazitaxel, cabozantinib, camptothecin, capecitabine, carboplatin, carfilzomib, carmustine, ceritinib, chlorambucil, chloroquine, cisplatin, cladribine, clodronate, cobimetinib, colchicine, crizotinib, cyclophosphamide, cyproterone, cytarabine, dacarbazine, dactinomycin, daunorubicin, demethoxyviridin, dexamethasone, dichloroacetate, dienestrol, diethylstilbestrol, docetaxel, doxorubicin, epirubicin, eribulin, erlotinib, estradiol, estramustine, etoposide, everolimus, exemestane, filgrastim, fludarabine, fludrocortisone, fluorouracil, fluoxymesterone, flutamide, gefitinib, gemcitabine, genistein, goserelin, GSK1120212, hydroxyurea, idarubicin, ifosfamide, imatinib, interferon, irinotecan, ixabepilone, lenalidomide, letrozole, leucovorin, leuprolide, levamisole, lomustine, lonidamine, mechlorethamine, medroxyprogesterone, megestrol, melphalan, mercaptopurine, mesna, metformin, methotrexate, miltefosine, mitomycin, mitotane, mitoxantrone, MK-2206, mutamycin, N-(4-sulfamoylphenylcarbamothioyl) pivalamide, NF279, NF449, nilutamide, nocodazole, octreotide, olaparib, osimertinib, oxaliplatin, paclitaxel, palbociclib, pamidronate, pazopanib, pemexetred, pentostatin, perifosine, PF-04691502, plicamycin, pomalidomide, porfimer, PPADS, procarbazine, quercetin, raltitrexed, ramucirumab, reactive blue 2, rituximab, rolofylline, romidepsin, rucaparib, selumetinib, sirolimus, sodium 2,4-dinitrobenzenesulfonate, sorafenib, streptozocin, sunitinib, suramin, talazoparib, tamoxifen, temozolomide, temsirolimus, teniposide, testosterone, thalidomide, thioguanine, thiotepa, titanocene dichloride,

tonapofylline, topotecan, trametinib, trastuzumab, tretinoin, veliparib, vinblastine, vincristine, vindesine, vinorelbine, and vorinostat (SAHA).

49. The method of claim 46, wherein the one or more additional chemotherapeutic agents are selected from 1-amino-4-phenylamino-9,10-dioxo-9,10-dihydroanthracene-2-sulfonate (acid blue 25), 1-amino-4-[4-hydroxyphenyl-amino]-9,10-dioxo-9,10-dihydroanthracene-2-sulfonate, 1-amino-4-[4-aminophenylamino]-9,10-dioxo-9,10-dihydroanthracene-2-sulfonate, 1-amino-4-[1-naphthylamino]-9,10-dioxo-9,10-dihydroanthracene-2-sulfonate, 1-amino-4-[4-fluoro-2-carboxyphenylamino]-9,10-dioxo-9,10-dihydroanthracene-2-sulfonate, 1-amino-4-[2-antracenylamino]-9,10-dioxo-9,10-dihydroanthracene-2-sulfonate, APCP, β -methylene-ADP (AOPCP), capecitabine, cladribine, cytarabine, fludarabine, doxorubicin, gemcitabine, N-(4-sulfamoylphenylcarbamothioyl) pivalamide, NF279, NF449, PPADS, quercetin, reactive blue 2, rolofylline sodium 2,4-dinitrobenzenesulfonate, sumarin, and tonapofylline.

50. The method of claim 47, wherein the additional chemotherapeutic agent is an immuno-oncology agent.

51. The method of claim 50, wherein the chemotherapeutic agent is anti-PD-L1.

FIG. 1

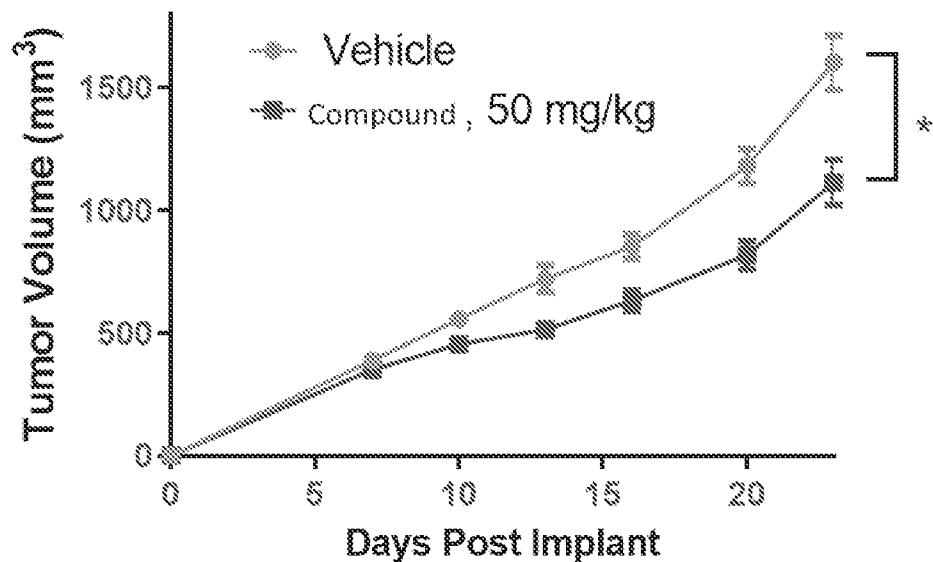


FIG. 2

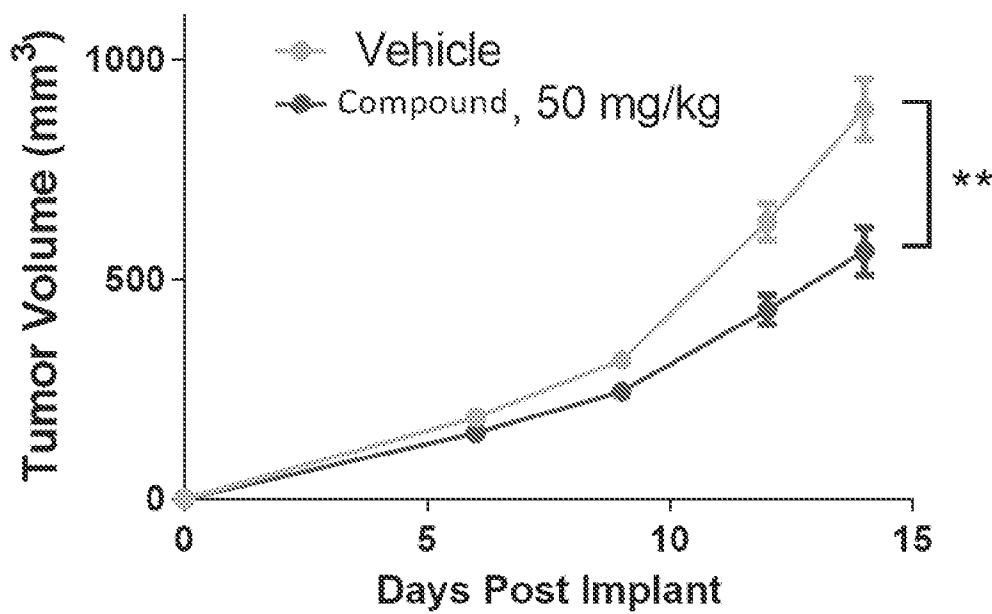


FIG. 3

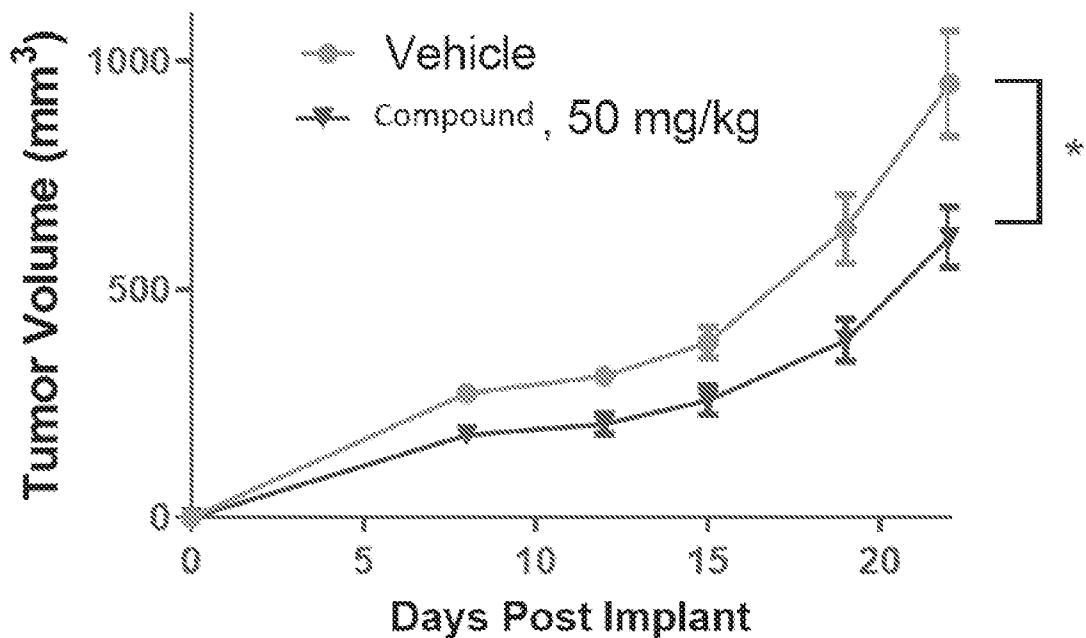


FIG. 4

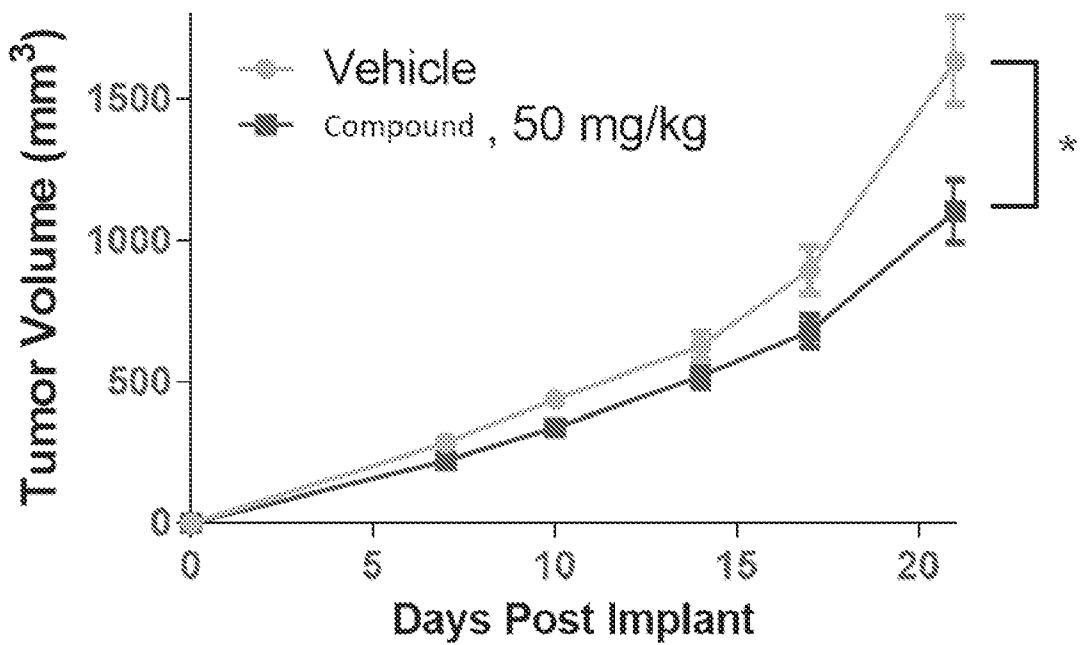


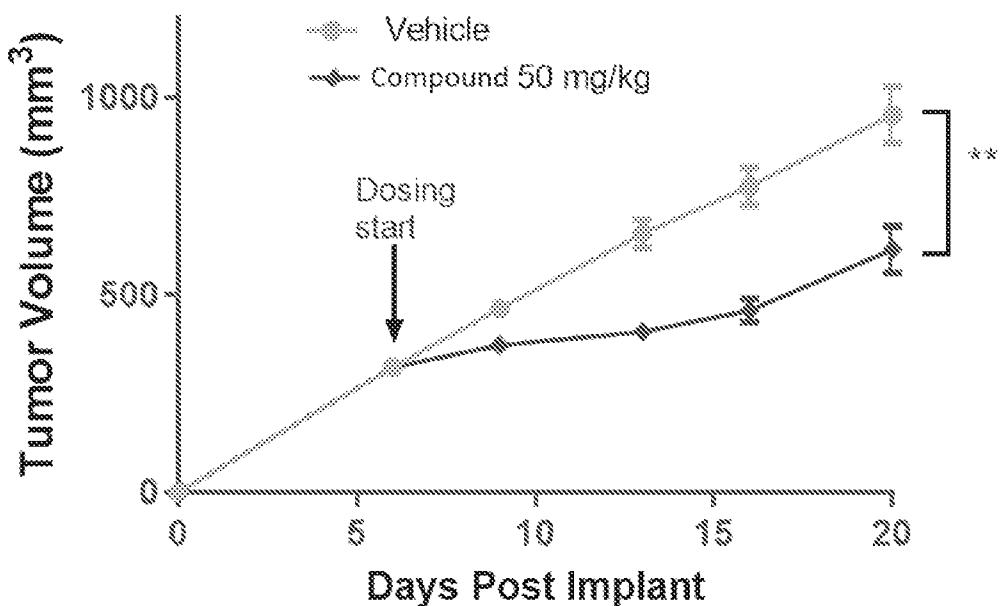
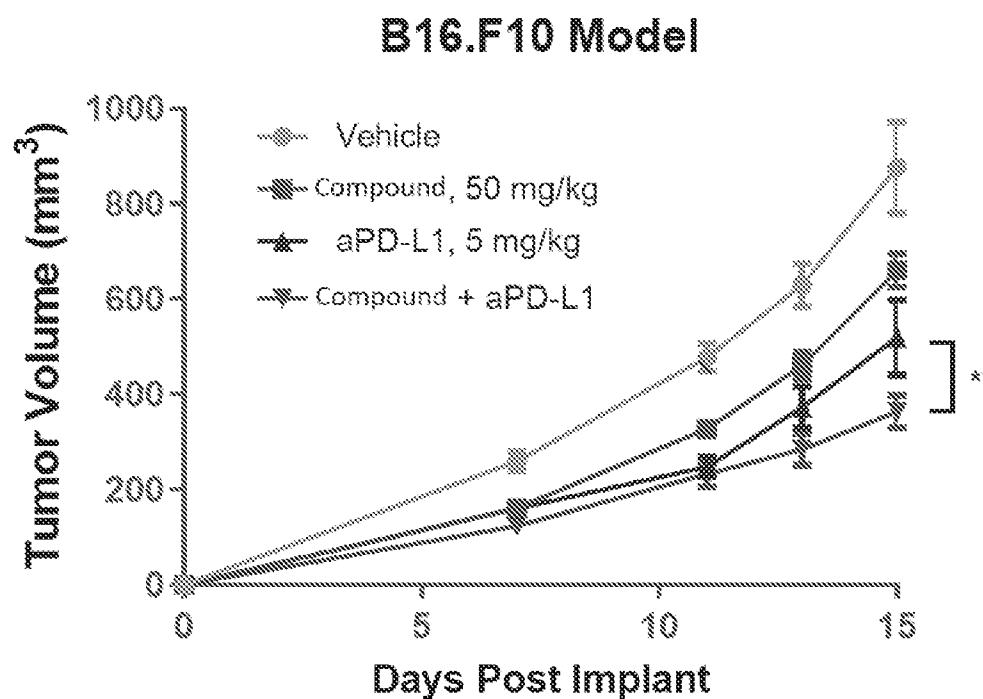
FIG. 5

FIG. 6

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2021/055504

A. CLASSIFICATION OF SUBJECT MATTER

C07D 239/80(2022.01)i; **A61P 35/00**(2022.01)i; **A61K 31/551**(2022.01)i; **A61K 31/517**(2022.01)i; **A61K 45/06**(2022.01)i;
C07D 495/04(2022.01)i; **C07D 401/04**(2022.01)i; **C07D 403/04**(2022.01)i; **C07D 403/10**(2022.01)i; **C07D 403/12**(2022.01)i;
C07D 405/10(2022.01)i; **C07D 405/12**(2022.01)i; **C07D 413/04**(2022.01)i; **C07D 413/10**(2022.01)i; **C07D 413/12**(2022.01)i;
C07D 243/04(2022.01)i
CPC:C07D 239/80; A61P 35/00; A61K 31/551; A61K 31/517; A61K 45/06; C07D 495/04; C07D 401/04; C07D 403/04;
C07D 403/10; C07D 403/12; C07D 405/10; C07D 405/12; C07D 413/04; C07D 413/10; C07D 413/12; C07D 243/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D 239/80; A61P 35/00; A61K 31/551; A61K 31/517; A61K 45/06; C07D 495/04; C07D 401/04; C07D 403/04; C07D 403/10; C07D 403/12; C07D 405/10; C07D 405/12; C07D 413/04; C07D 413/10; C07D 413/12; C07D 243/04
CPC:C07D 239/80; A61P 35/00; A61K 31/551; A61K 31/517; A61K 45/06; C07D 495/04; C07D 401/04; C07D 403/04;
C07D 403/10; C07D 403/12; C07D 405/10; C07D 405/12; C07D 413/04; C07D 413/10; C07D 413/12; C07D 243/04

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Databases consulted: PATENTSCOPE, Esp@cenet, Google Patents, CAPLUS, MARPAT, REGISTRY, Google Scholar Search
terms used: INTERLEUKIN 4 (IL4)-INDUCED GENE 1, IL4I1; 1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one; cancer; 3,
4-Dihydroquinazolin-2(1H)-one; 1,2,4,5-Tetrahydro-2-oxo-3H-1,3-benzodiazepin; *CANCER, *PROLIFER*, CARCINOMA,
*NEOPLAS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2011042145 A1 (SIENA BIOTECH SPA. [IT], et al - 14 April 2011) 14 April 2011 (2011-04-14) page 30, Formula Im, wherein R2=H and Y=OH; page 81, example 16; claims 5-6, 9, 10; claim 1, definition of R2	1,8,10,38,39,42-51
X	Specific nonpeptide inhibitors of puromycin-sensitive aminopeptidase with a 2, 4 (1H, 3H)- quinazolinedione skeleton. Chemical and pharmaceutical bulletin, 2003, 51.11: 1273-1282 KAKUTA, Hiroki, et al. (2003/11/15) abstract; page 1277, Table 2, compound 30	1-3,9,12,14,16-19,22- 24,28,29,35,38,42-51

Further documents are listed in the continuation of Box C.

See patent family annex.

- * Special categories of cited documents:
- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed
- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search 30 January 2022	Date of mailing of the international search report 30 January 2022
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Name and mailing address of the ISA/IL

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Email: **pctoffice@justice.gov.il**

Authorized officer

NAHAMANI Moshe

Telephone No.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2021/055504**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1847541 A1 (TAKEDA PHARMACEUTICAL. [JP]) 24 October 2007 (2007-10-24) page 98, example 36; paragraph 0095; claims 2-4, 16, 19-21	1,2,4-7,9-30,42-51
X	WO 2017167150 A1 (SUZHOU YUNXUAN PHARMACEUTICAL CO LTD. [CN]) 17 October 2022 (2022-10-17) claims 1-4, 11-13	1,9-26,31-34,38,42-51
X	Selenium-Catalyzed Carbonylative Synthesis of 3, 4-Dihydroquinazolin-2 (1 H)-one Derivatives with TFBen as the CO Source. ACS combinatorial science, 2019, 21.8: 573-577 [Publication Date:July 18, 2019] ZHOU, Rong; QI, Xinxin; WU, Xiao-Feng (2019/07/18) Table 2	1-3,9,10,12,14,16-26, 28,29,33-37,40-51

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2021/055504

Patent document cited in search report				Publication date (day/month/year)		Patent family member(s)		Publication date (day/month/year)	
WO	2011042145	A1	14 April 2011	WO	2011042145	A1		14 April 2011	
				AR	078549	A1		16 November 2011	
				EP	2485728	A1		15 August 2012	
				EP	2485728	B1		10 July 2013	
				TW	201118081	A		01 June 2011	
				US	2012196851	A1		02 August 2012	
				US	8865704	B2		21 October 2014	
EP	1847541	A1	24 October 2007	EP	1847541	A1		24 October 2007	
				EP	1847541	A4		30 December 2009	
				JP	WO2006083005	A1		26 June 2008	
				US	2009062258	A1		05 March 2009	
				WO	2006083005	A1		10 August 2006	
WO	2017167150	A1	17 October 2022	WO	2017167150	A1		05 October 2017	
				CN	105254613	A		20 January 2016	
				CN	106565673	A		19 April 2017	
				CN	106565673	B		06 December 2019	
				CN	107286135	A		24 October 2017	
				CN	107286135	B		04 August 2020	
				CN	107286136	A		24 October 2017	
				CN	107286136	B		04 August 2020	
				CN	107759584	A		06 March 2018	
				CN	107759584	B		01 June 2021	
				CN	111196803	A		26 May 2020	
				EP	3359154	A1		15 August 2018	
				EP	3359154	A4		15 May 2019	
				EP	3359154	B1		26 May 2021	
				JP	2018535949	A		06 December 2018	
				JP	6853819	B2		31 March 2021	
				KR	20180061363	A		07 June 2018	
				US	2018244651	A1		30 August 2018	
				US	10450300	B2		22 October 2019	
				US	2020048223	A1		13 February 2020	
				WO	2017062688	A1		13 April 2017	