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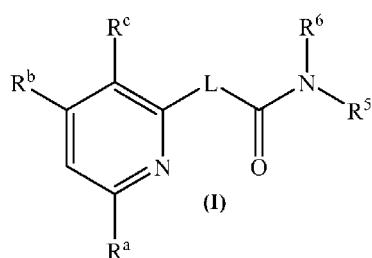
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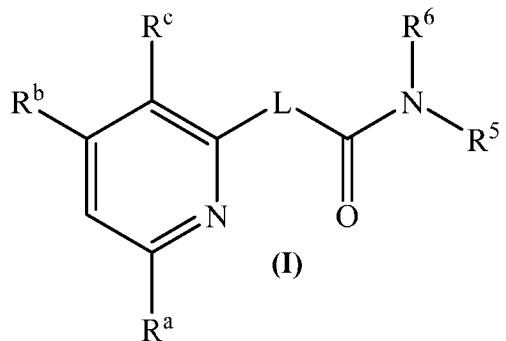
(57) Abstract: The present invention relates to compounds of formula (I), that possess DNA polymerase theta (POLQ) enzyme inhibitory activity, methods for their preparation, pharmaceutical compositions containing them, and their use in the treatment or prevention of diseases or disorders involving DNA polymerase theta (POLQ) enzyme.

POL THETA INHIBITORS

[01] This application claims the benefit of Indian Patent Application Nos. 202241005153, filed on January 31, 2022, 202241006844, filed on February 9, 2022, and 202241007579, filed on February 12, 2022, each of which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

[02] The present invention relates to compounds of formula (I) as DNA polymerase theta (POLQ) enzyme inhibitors.



[03] The present invention also relates to processes for the preparation of compounds of formula (I), pharmaceutical compositions comprising them, and their use in the treatment or prevention of diseases or disorders where there is an advantage in inhibiting DNA polymerase theta (POLQ) enzyme.

BACKGROUND OF THE INVENTION

[04] DNA polymerases act not only in genomic DNA replication but in various pathways of DNA repair and genome maintenance. In mammalian cells, there are ~15 known mammalian DNA polymerases (pol α s) that play a critical role in DNA replication (pol α , δ , ε), base excision repair (pol β), mitochondrial DNA replication and repair (pol γ and Primpol), non-homologous end-joining and immunological diversity (pol λ , μ , pol θ and terminal-deoxynucleotidyl transferase), and DNA damage tolerance by translesion synthesis (η , ι , κ , ζ , and Rev1). Some of these DNA polymerases have roles in more than one pathway of DNA processing. See, e.g.,

Hubscher *et al.*; *Ann. Rev. Biochem.*, 71, 133-163, 2002; Lange *et al.*; *Nature Reviews Cancer*, 11, 96–110, 2011; and Mathew *et al.*, *DNA Repair (Amst.)*, 12(1), 1-9, 2013. One of these is DNA polymerase theta (pol θ), also referred to as POLQ.

[05] The crystal structure of POLQ consists of three domains: an N-terminal helicase domain that is linked to a C-terminal polymerase domain by an unstructured central region. Seki independently isolated the first complete and functional POLQ cDNA, showing that it encodes a 2590 amino acid protein with both a DNA polymerase and helicase-like domain (*see* Seki *et al.*, *Nucleic Acids Res.*, 31, 6117-6126, 2003). Each domain fulfils specific functions that in combination contribute to the diverse functions of POLQ in DNA repair and damage tolerance pathways. *See* Black *et al.*, *Nat. Commun.*, 10, 2019; Schrempf *et al.*, *Trends in Cancer*, 7(2), 98-11, 2021. The helicase domain counteracts RPA and RAD51, thereby impeding repair by homologous recombination and promoting alt-NHEJ. In addition, helicase binding adjacent to the polymerase domain avoids an unproductive snap-back mechanism and therefore facilitates theta-mediated end joining (TMEJ) on long ssDNA substrates. Büttner *et al.*, *Nat. Struct. Mol. Biol.*, 14, 647-652, 2007. The central domain is vital for substrate selection as it autoinhibits POLQ activity on short ssDNA. The polymerase domain of POLQ is a ‘Swiss Army knife’ in DNA repair, In TMEJ, it can function as a terminal transferase or catalyse templated extension from an annealed sequence using both the same strand snapped back on itself (*in cis*) or the other strand (*in trans*). *See* Seki *et al.*, *The EMBO Journal*, 23, 4484-4494, 2004. In addition to double-strand break repair, the polymerase can function as a dRP-lyase in base excision repair and perform translesion synthesis opposite UV-induced DNA lesions.

[06] DNA damage repair processes are critical for genome maintenance and stability, among which, double-strand breaks (DSBs) are predominantly repaired by the nonhomologous end joining (NHEJ) pathway in the G1 phase of the cell cycle and by homologous recombination (HR) in S-G2 phases. A less addressed alternative end-joining (alt-EJ), also known as microhomology-mediated end-joining (MMEJ) pathway, is commonly considered as a “backup” DSB repair pathway when NHEJ or HR are compromised. Numerous genetic studies have highlighted the role of polymerase theta (encoded by POLQ) in stimulating MMEJ in higher organisms. *See* Chan *et al.*, *PLoS Genet.*, 6, e1001005, 2010; Roerink *et al.*, *Genome Research*,

24, 954-962, 2014; Ceccaldi *et al.*, *Nature*, 518, 258-62, 2015; and Mateos-Gomez *et al.*, *Nature*, 518, 254-57, 2015.

[07] Deficiency of homologous recombination (HR)-mediated DNA repair occurs mainly through genetic or epigenetic inactivation of the BRCA 1 and BRCA 2 (BRCA1/2) genes, and it plays a role in the initiation and progression of many tumor types (*See* Lord *et al.*, *Science*, 355, 1152-1158, 2017). HR deficiency also provides unique opportunities for targeted therapy, as exemplified by the extreme sensitivity of BRCA1/2-mutated tumors to PARPi (*See* Farmer *et al.*, *Nature*, 434, 917-921, 2005); and Bryant *et al.*, *Nature*, 434, 913-917, 2005). Poly(ADP-ribose)polymerase (PARP) inhibitors have been successfully used to treat BRCA-deficient breast and ovarian cancers (*See* Ivraghi *et al.*, *BMC Med.*, 13, 188, 2015). However, only a fraction of breast cancers are defective in BRCA1, BRCA2, or their functionally related HR pathway (“BRCAness”; up to 25%) (*See* Turner *et al.*, *Nat. Rev. Cancer*, 4, 814–819, 2004). Acquired resistance to PARP inhibitors also develops rapidly. It is highly desirable to develop alternative treatment strategies that will be effective for most breast cancers, including those with proficient HR activity.

[08] POLQ is overexpressed 5-fold or more in about 70% of breast cancer in both HR-proficient and deficient tumors, and overexpression is associated with poor prognosis. Its expression is particularly high in subtypes of breast and ovarian tumors with defects in HR, where it mediates backup DNA double-strand break (DSB) repair, compensating for the loss of HR (*See* Ceccaldi *et al.*, *Trends Cell Biol.*, 26, 52-64, 2016). As a result, inhibition of POLQ is synthetic and lethal with HR deficiency. POLQ inhibition in HR-deficient tumors induces cell death (*See* Ceccaldi *et al.*, *Nature*, 518, 258-262, 2015). In addition, POLQ depletion synergizes with PARPi in the killing of HR-deficient tumors (Mateos-Gomez *et al.*; *Nature*, 518, 254-257, 2015). Synthetic lethality between HR deficiency and POLQ inhibition hinges on several functions that POLQ exhibits in maintaining genomic stability and preventing tumorigenesis (*See* Wood *et al.*, *DNA Repair*, 44, 22-32, 2016). POLQ is also a crucial enzyme in the mutagenic microhomology-mediated end-joining (MMEJ) repair of DSBs), a pathway that plays a critical role in genomic stability (*See* Chan *et al.*, *PLoS Genet.*, 6, e1001005, 2010). Inhibiting PARP1, a key enzyme in MMEJ, prevents POLQ recruitment to sites of laser micro-irradiation. Because

POLQ depletion and PARPi have additive effects on HR-deficient cells, these data suggest that functions of POLQ outside PARP-mediated MMEJ are also key to the survival of HR-deficient cells.

[09] Recently, the antibiotic novobiocin has been identified to function as an inhibitor of POLQ helicase activity in an *in vitro* screen and as such being suppressive on HR-deficient cancer cell viability and tumor growth (*See* Jia Zhou et al., *Nature Cancer*, 2, 598-610, 2021).

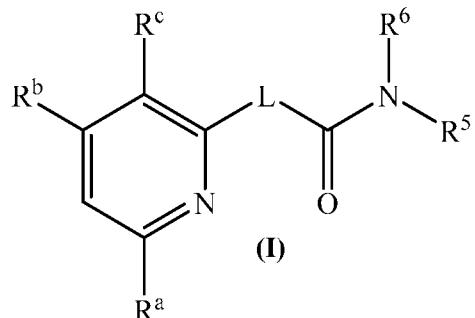
[10] Various publications disclose POLQ/POLQ inhibitors. *See*, e.g., International Publication Nos. WO 2020/160134, WO 2020/160213, WO 2020/243459, WO 2021/028643, WO 2021/028644, and WO 2021/123785.

[11] There is, however, a need for new and effective POL theta (θ) (POLQ) inhibitors that act as therapeutic agents for cancers, such as cancers containing DNA repair defects.

SUMMARY OF THE INVENTION

[12] The present invention relates to compounds of formula (I) as DNA polymerase theta (POLQ) enzyme inhibitors. The present invention also relates to processes for the preparation of compounds of formula (I), pharmaceutical compositions comprising them, and their use in the treatment or prevention of diseases or disorders where there is an advantage in inhibiting DNA polymerase theta (POLQ) enzyme.

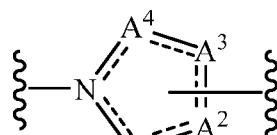
[13] Accordingly, in one aspect, the present invention relates to a compound of formula (I):



or a tautomer thereof, prodrug thereof, N-oxide thereof, stereoisomer thereof, pharmaceutically acceptable ester thereof, or pharmaceutically acceptable salt thereof,

wherein

R^a , R^b , and R^c are each independently selected from hydrogen, hydroxy, halo, cyano, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted heteroaryl;



L is (i) $-N(R^1)-C(R^2)(R^3)-$, or (ii) where the left squiggly line (~~~~) represents the point of attachment to the pyridyl group in formula (I) and the right squiggly line represents the point of attachment to the carbonyl group in formula (I);

R^1 , R^2 , and R^3 are each independently selected from hydrogen, hydroxy, halo, cyano, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted heteroaryl;

each dashed line (----) independently represents an optional bond such that at most two non-adjacent dashed lines represent a bond;

A^1 , A^2 , A^3 , and A^4 are each independently selected from CR^4 , CR^4R^{4a} , NR^4 , O , S , and $S(O)_2$, with the proviso that A^1 , A^2 , A^3 and A^4 cannot each be CR^4R^{4a} at the same time, NR^4 at the same time, O at the same time, S at the same time, or $S(O)_2$ at the same time;

each occurrence of R⁴ is independently selected from hydrogen, hydroxy, halo, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted heteroaryl;

each occurrence of R^{4a} independently is selected from hydrogen, hydroxy, halo, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted acyl, and substituted or unsubstituted alkyl;

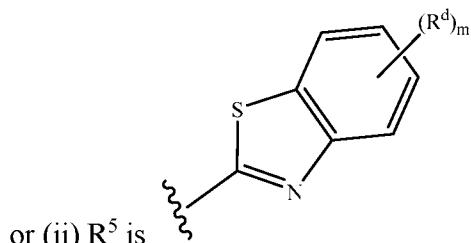
or R⁴ and R^{4a} together with the carbon atom to which they are bound may form a thiocarbonyl (-C(=S)-), carbonyl (-C(=O)-), imine (-C(=NH)-) group, or substituted or unsubstituted saturated or unsaturated 3-14 membered ring, which may optionally include one or more heteroatoms which may be the same or different and are independently selected from O, N, and S, and any ring carbon atom may optionally be substituted with oxo (=O), thio (=S), or imine (=NH);

R⁵ and R⁶ are each independently selected from hydrogen, hydroxy, halo, cyano, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted heteroaryl; or both R⁵ and R⁶ together with the nitrogen atom to which they are attached can form a substituted or unsubstituted heterocyclyl ring or substituted or unsubstituted heteroaryl;

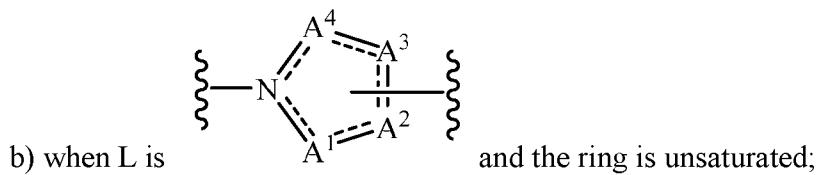
with the provisos that

a) when L is -N(R¹)-C(R²)(R³)-,

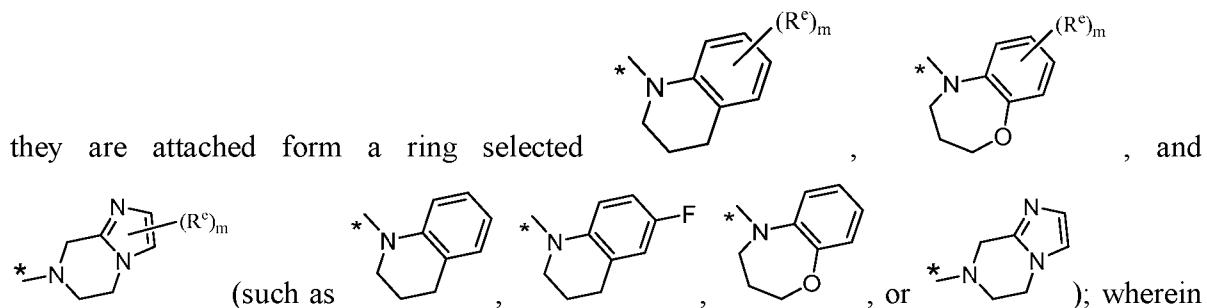
then (i) R⁵ and R⁶ together with the nitrogen atom to which they are attached form a substituted or unsubstituted heterocyclyl ring or substituted or unsubstituted heteroaryl;



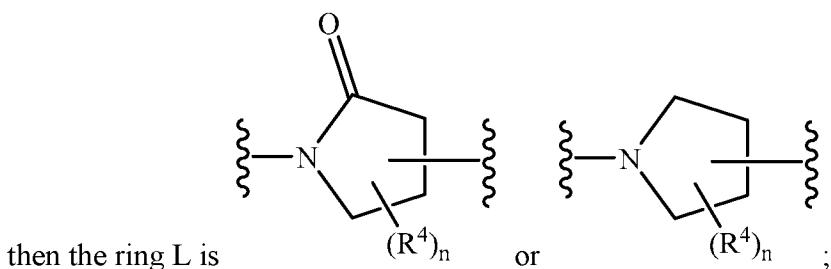
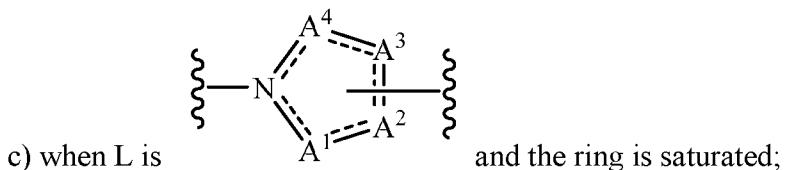
or (ii) R^5 is , and R^6 is selected from hydrogen, hydroxy, halo, cyano, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted heteroaryl; wherein each occurrence of R^d is independently selected from hydrogen, hydroxy, halo, cyano, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted amino, and substituted or unsubstituted alkyl; and m is 1, 2, or 3;



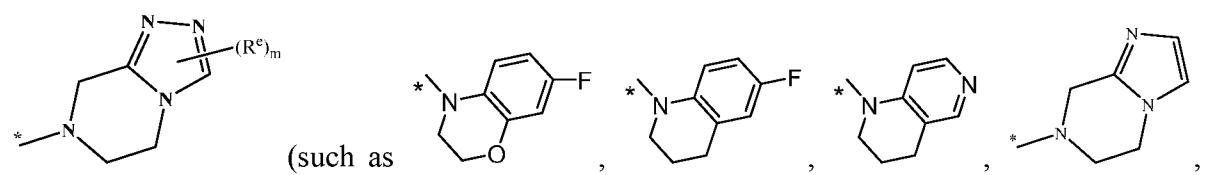
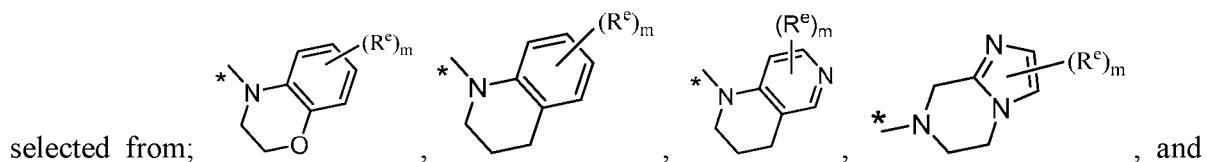
then R^5 and R^6 are each independently selected from hydrogen, hydroxy, halo, cyano, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted heteroaryl; or R^5 and R^6 together with the nitrogen atom to which



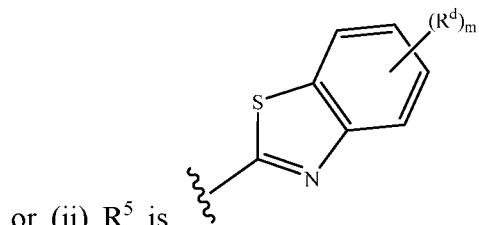
each occurrence of R^e is independently selected from hydrogen, hydroxy, halo, cyano, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted amino, and substituted or unsubstituted alkyl; and m is 0, 1, 2, or 3; and



(i) R^5 and R^6 together with the nitrogen atom to which they are attached form a ring



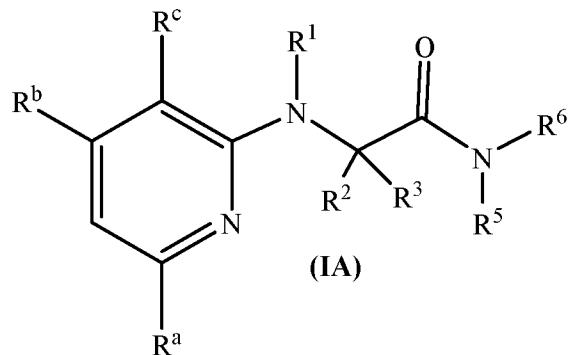
or); wherein each occurrence of R^e is independently selected from hydrogen, hydroxy, halo, cyano, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted amino, substituted or unsubstituted alkyl; and m is 0, 1, 2, or 3;



or (ii) R^5 is , and R^6 is selected from hydroxy, halo, cyano, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted heteroaryl; wherein each occurrence of R^d is independently selected from hydrogen, hydroxy, halo, cyano, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted amino, substituted or unsubstituted alkyl; and m is 0, 1, 2, or 3; and

the asterisk (*) represents the point of attachment of the ring to the main structure.

[14] In another aspect of the present invention, the compound of formula (I) is a compound of formula (IA):



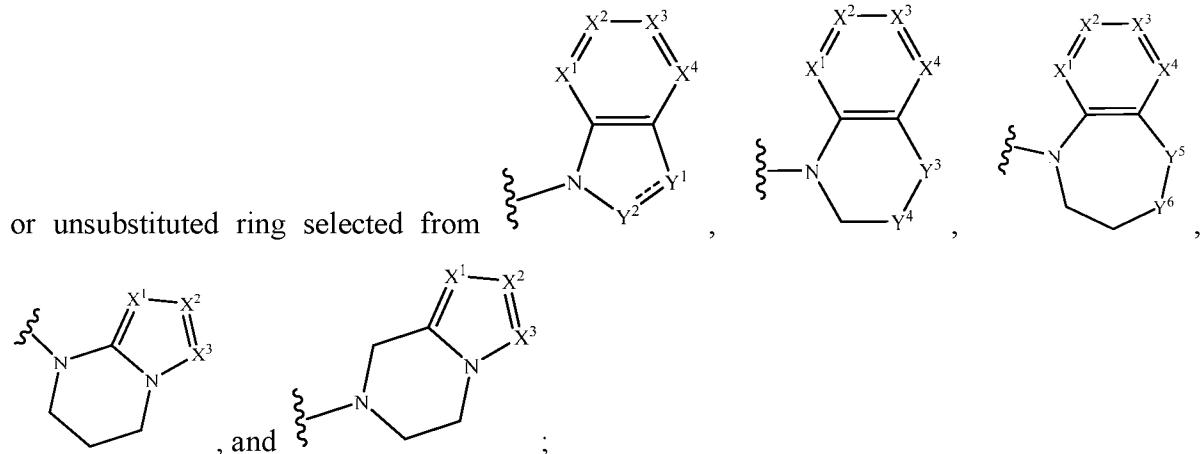
or a tautomer thereof, prodrug thereof, N-oxide thereof, stereoisomer thereof, pharmaceutically acceptable ester thereof, or pharmaceutically acceptable salt thereof,

wherein

R^a , R^b , and R^c are each independently selected from hydrogen, hydroxy, halo, cyano, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted heteroaryl;

R^1 , R^2 , and R^3 are each independently selected from hydrogen, hydroxy, halo, cyano, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted heteroaryl;

(i) R^5 and R^6 together with the nitrogen atom to which they are attached form a substituted



the squiggly line () represents the point of attachment to the rest of the compound of formula (IA);

the dashed line (----) represents an optional bond;

X^1 , X^2 , X^3 , and X^4 are, in each occurrence, independently selected from $-CR^7$ and N, with the proviso that, in the first three structures, at least one of X^1 , X^2 , X^3 , and X^4 is not N (i.e., in the first three structures, at least one of X^1 , X^2 , X^3 and X^4 is $-CR^7$);

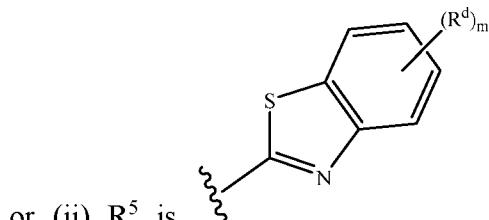
each occurrence of R^7 is independently selected from hydrogen, hydroxy, halo, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroaryl, and substituted or unsubstituted heteroarylalkyl;

or two R^7 groups present on adjacent carbon atoms, or any R^7 group along with an adjacent N ring atom, can be joined to form a substituted or unsubstituted saturated or unsaturated 3-14 membered ring, which may optionally include one or more heteroatoms, which may be the same or different, and are independently selected from O, N, and S, wherein any carbon atom in the ring may be substituted by oxo (=O), thio (=S), or imino (=NH);

Y^1 , Y^2 , Y^3 , Y^4 , Y^5 and Y^6 are each independently selected from CR^8R^{8a} , CR^8 , O, NR^{8a} , S, and $S(O)_2$, with the proviso that when the dashed line (-----) represents a bond (i.e., there is a double bond between Y^1 and Y^2), then each of Y^1 and Y^2 is CR^{8a} ,

each occurrence of R^8 and R^{8a} is independently selected from hydrogen, hydroxy, halo, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted amino, substituted or unsubstituted amide, substituted or unsubstituted aminoalkyl, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroaryl, and substituted or unsubstituted heteroarylalkyl;

or R⁸ and R^{8a}, together with the carbon atom to which they are bound, form a thiocarbonyl (-C(=S)-), carbonyl (-C(=O)-), imine (-C(=NH)-) group, or a substituted or unsubstituted saturated or unsaturated 3-14 membered ring, which may optionally include one or more heteroatoms, which may be the same or different, and are each selected from O, N, and S, wherein any carbon atom in the ring may be substituted by oxo (=O), thio (=S), or imino (=NH);



or (ii) R⁵ is , R⁶ is selected from hydroxy, halo, cyano, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted heteroaryl; each occurrence of R^d is independently selected from hydrogen, hydroxy, halo, cyano, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted amino, and substituted or unsubstituted alkyl; and m is 0, 1, 2, or 3.

[15] One embodiment is a compound of formula (I) or (IA), wherein R^a is hydrogen, haloalkyl, or alkyl.

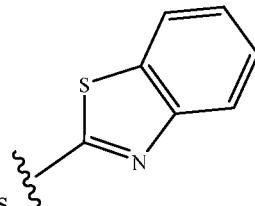
[16] One embodiment is a compound of formula (I) or (IA), wherein R^a is -CH₃, or -CF₃.

[17] One embodiment is a compound of formula (I) or (IA), wherein R^b is haloalkyl (e.g., -CF₃).

[18] One embodiment is a compound of formula (I) or (IA), wherein R^c is hydrogen, or cyano.

[19] One embodiment is a compound of formula (I) or (IA), wherein R¹ is hydrogen.

[20] One embodiment is a compound of formula (I) or (IA), wherein R² and R³ are both hydrogen.

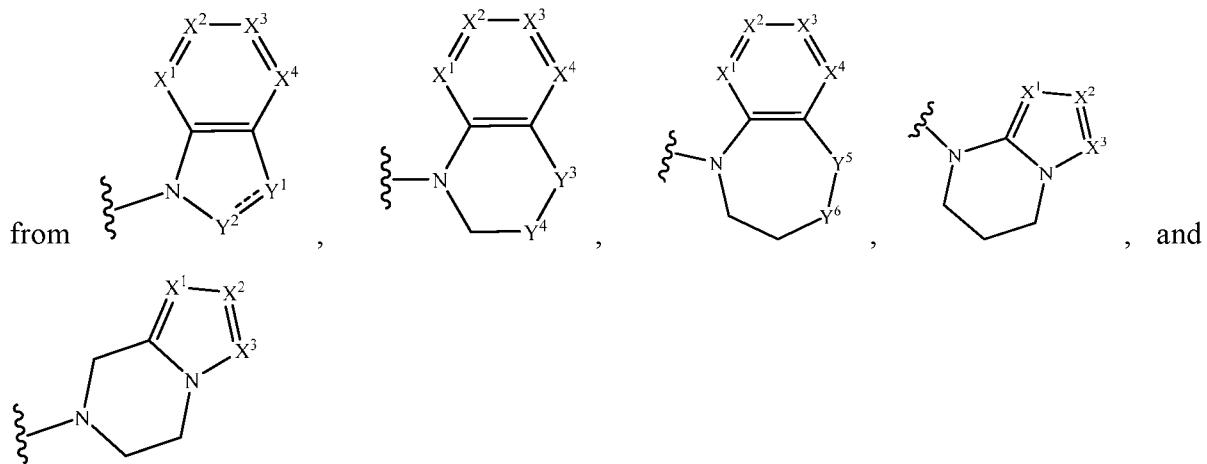


[21] One embodiment is a compound of formula (I) or (IA), wherein R⁵ is , and R⁶ is hydrogen or alkyl (e.g., -CH₃).

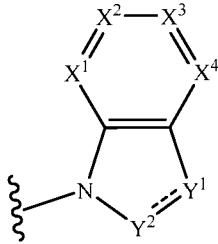
[22] One embodiment is a compound of formula (I) or (IA), wherein R⁵ and R⁶ together with the nitrogen atom to which they are attached form a substituted or unsubstituted heterocyclyl ring.

[23] Another embodiment is a compound of formula (I) or (IA), wherein R⁵ and R⁶ together with the nitrogen atom to which they are attached form a substituted or unsubstituted heteroaryl ring.

[24] One embodiment is a compound of formula (I) or (IA), wherein R⁵ and R⁶ together with the nitrogen atom to which they are attached form a substituted or unsubstituted ring selected

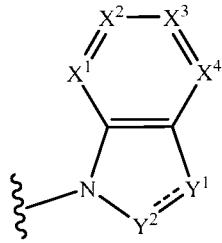


[25] One embodiment is a compound of formula (I) or (IA), wherein R⁵ and R⁶ together with



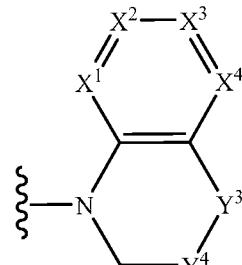
the nitrogen atom to which they are attached form the ring ; the dashed line (---) is a bond (i.e., there is a double bond between Y¹ and Y²); each of X¹, X², X³, and X⁴ is CR⁷; each occurrence of R⁷ is independently hydrogen or halogen; each of Y¹ and Y² is CR⁸; and each R⁸ is independently hydrogen or amido (e.g., -C(=O)NH₂).

[26] One embodiment is a compound of formula (I) or (IA), wherein R⁵ and R⁶ together with



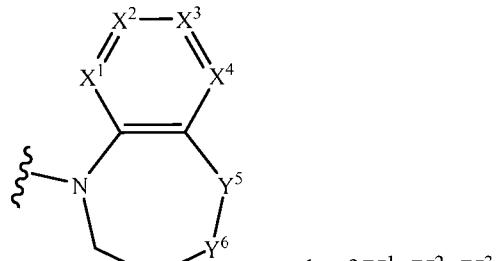
the nitrogen atom to which they are attached form a the ring ; the dashed line (----) is absent; each of X¹, X², X³, and X⁴ is CR⁷; each R⁷ is hydrogen; each of Y¹ and Y² is CR⁸R^{8a}; and each occurrence of R⁸ and R^{8a} is hydrogen.

[27] One embodiment is a compound of formula (I) or (IA), wherein R⁵ and R⁶ together with



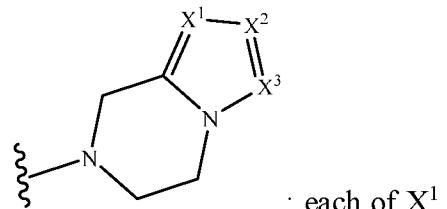
the nitrogen atom to which they are attached form the ring ; each of X¹, X², X⁴ is CR⁷; X³ is CR⁷ or N; each occurrence of R⁷ is independently hydrogen or halogen; Y³ and Y⁴ are each, independently, selected from CR⁸R^{8a}, O, NR^{8a}, and S(O)₂; and each occurrence of R⁸ and R^{8a} is hydrogen, or R⁸ and R^{8a}, together with the carbon atom to which they are attached, form a carbonyl (C=O) group.

[28] One embodiment is a compound of formula (I) or (IA), R⁵ and R⁶ together with the



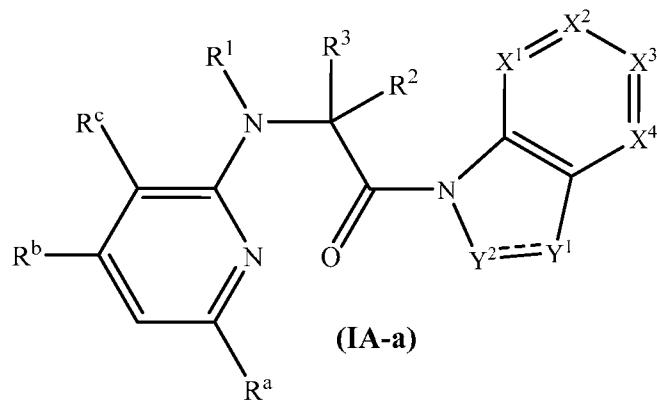
nitrogen atom to which they are attached form the ring ; each of X¹, X², X³, and X⁴ is CR⁷; each R⁷ is, independently, hydrogen or halogen; Y⁵ and Y⁶ are each, independently, selected from CR⁸R^{8a}, O, and NR^{8a}; each occurrence of R⁸ and R^{8a} is hydrogen, or R⁸ and R^{8a}, together with the carbon atom to which they are attached, form carbonyl (C=O) group.

[29] One embodiment is a compound of formula (I) or (IA), wherein R⁵ and R⁶ together with



the nitrogen atom to which they are attached form the ring ; each of X¹, X², and X³ is independently CR⁷ or N; and each occurrence of R⁷ is independently hydrogen, alkyl, or haloalkyl.

[30] In one embodiment of the present invention, the compound of formula (I) or (IA) is a compound of formula (IA-a):

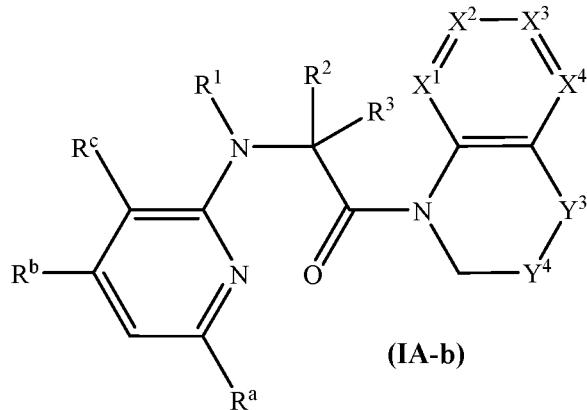


or a tautomer thereof, prodrug thereof, N-oxide thereof, stereoisomer thereof, pharmaceutically acceptable ester thereof, or pharmaceutically acceptable salt thereof,

wherein

the dashed line (-----), R^a, R^b, R^c, R¹, R², and R³ are as defined above for any embodiment of the compounds of formula (I) or (IA), and X¹, X², X³, X⁴, Y¹ and Y² are as defined above for any embodiment of the compounds of formula (IA).

[31] In one embodiment of the present invention, the compound of formula (I) or (IA) is a compound of formula (IA-b):

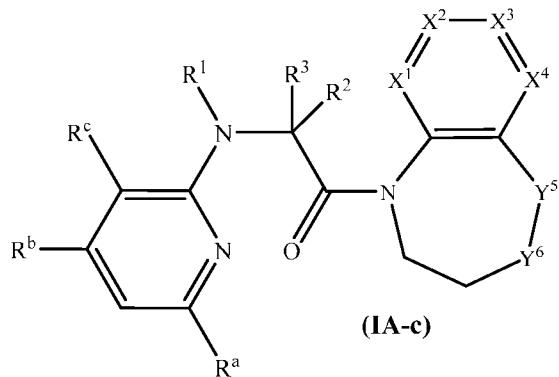


or a tautomer thereof, prodrug thereof, N-oxide thereof, stereoisomer thereof, pharmaceutically acceptable ester thereof, or pharmaceutically acceptable salt thereof,

wherein

R^a, R^b, R^c, R¹, R², and R³ are as defined above for any embodiment of the compounds of formula (I) or (IA), and X¹, X², X³, X⁴, Y³ and Y⁴ are as defined above for any embodiment of the compounds of formula (IA).

[32] In one embodiment of the present invention, the compound of formula (I) or (IA) is a compound of formula (IA-c):

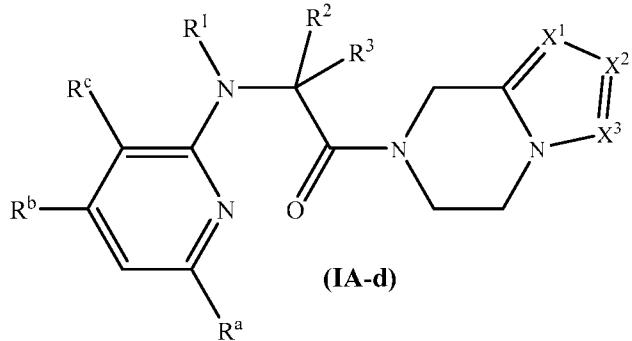


or a tautomer thereof, prodrug thereof, N-oxide thereof, stereoisomer thereof, pharmaceutically acceptable ester thereof, or pharmaceutically acceptable salt thereof,

wherein

R^a, R^b, R^c, R¹, R², and R³ are as defined above for any embodiment of the compounds of formula (I) or (IA), and X¹, X², X³, X⁴, Y⁵ and Y⁶ are as defined above for any embodiment of the compounds of formula (IA).

[33] In one embodiment of the present invention, the compound of formula (I) or (IA) is a compound of formula (IA-d):

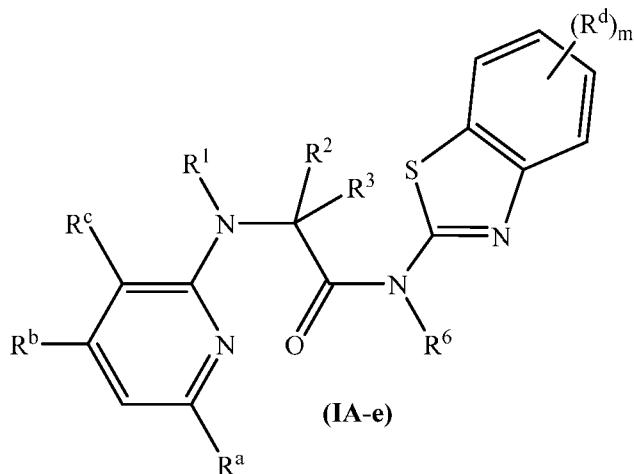


or a tautomer thereof, prodrug thereof, N-oxide thereof, stereoisomer thereof, pharmaceutically acceptable ester thereof, or pharmaceutically acceptable salt thereof,

wherein

R^a , R^b , R^c , R^1 , R^2 , and R^3 are as defined above for any embodiment of the compounds of formula (I) or (IA), and X^1 , X^2 and X^3 are as defined above for any embodiment of the compounds of formula (I).

[34] In one embodiment of the present invention, the compound of formula (I) or (IA) is a compound of formula (IA-e):

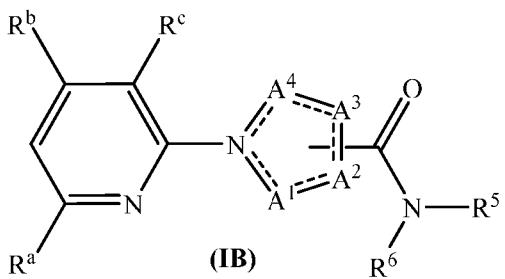


or a tautomer thereof, prodrug thereof, N-oxide thereof, stereoisomer thereof, pharmaceutically acceptable ester thereof, or pharmaceutically acceptable salt thereof,

wherein

R^a , R^b , R^c , R^1 , R^2 , R^3 , and R^6 are as defined above for any embodiment of the compounds of formula (I) or (IA), and R^d and m are as defined above for any embodiment of the compounds of formula (IA) or (IA).

[35] In another aspect of the present invention, the compound of formula (I) is a compound of formula (IB):



or a tautomer thereof, prodrug thereof, N-oxide thereof, stereoisomer thereof, pharmaceutically acceptable ester thereof, or pharmaceutically acceptable salt thereof,

wherein

R^a , R^b , and R^c are each independently selected from hydrogen, hydroxy, halo, cyano, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted heteroaryl;

each dashed line (----) independently represents an optional bond such that at most two non-adjacent dashed lines represent a bond;

A^1 , A^2 , A^3 , and A^4 are each independently selected from CR^4 , CR^4R^{4a} , NR^4 , O , S , and $S(O)_2$; with the proviso that A^1 , A^2 , A^3 and A^4 cannot each be CR^4R^{4a} at the same time, NR^3 at the same time, O at the same time, S at the same time, or $S(O)_2$ at the same time;

each occurrence of R^4 is independently selected from hydrogen, hydroxy, halo, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted heteroaryl;

each occurrence of R^{4a} independently is selected from hydrogen, hydroxy, halo, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted acyl, and substituted or unsubstituted alkyl;

or R⁴ and R^{4a} together with the carbon atom to which they are bound form a thiocarbonyl (-C(=S)-) group, carbonyl (-C(=O)-) group, imine (-C(=NH)-) group, or a substituted or unsubstituted saturated or unsaturated 3-14 membered ring, which may optionally include one or more heteroatoms which may be the same or different and are independently selected from O, N, or S, wherein any carbon atom in the ring may be substituted by oxo (=O), thio (=S), or imine (=NH); and

R⁵ and R⁶ are each independently selected from hydrogen, hydroxy, halo, cyano, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocycl; or both R⁵ and R⁶ together with the nitrogen atom to which they are attached can form a substituted or unsubstituted heterocycl ring or substituted or unsubstituted heteroaryl;

[36] One embodiment is a compound of formula (I) or (IB), wherein one dashed line (----) is a bond.

[37] One embodiment is a compound of formula (I) or (IB), wherein two dashed lines (----) are a bond and they are not adjacent to one another.

[38] One embodiment is a compound of formula (I) or (IB), wherein each dashed line (----) is not a bond (i.e., absent).

[39] One embodiment is a compound of formula (I) or (IB), wherein R^a is hydrogen, alkyl, or haloalkyl.

[40] One embodiment is a compound of formula (I) or (IB), wherein R^a is -CH₃, or -CF₃.

[41] One embodiment is a compound of formula (I) or (IB), wherein R^b is hydrogen or haloalkyl.

[42] One embodiment is a compound of formula (I) or (IB), wherein R^b is -CF₃.

[43] One embodiment is a compound of formula (I) or (IB), wherein R^c is cyano.

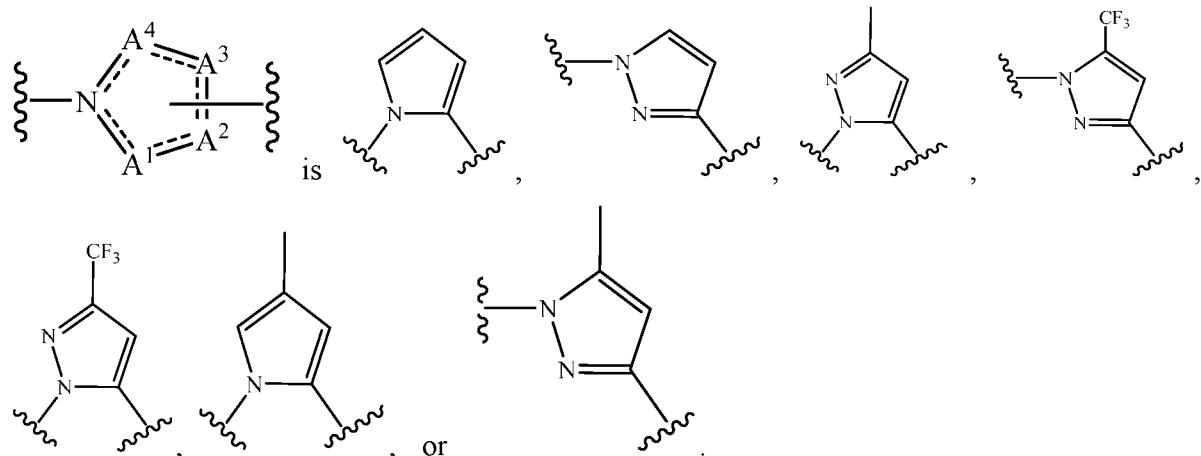
[44] One embodiment is a compound of formula (I) or (IB), wherein A¹, A², A³ and A⁴ are each -CR⁴; and each R⁴ is independently selected from hydrogen, substituted or unsubstituted alkyl (e.g., -CH₃), and substituted or unsubstituted haloalkyl (e.g., -CF₃).

[45] One embodiment is a compound of formula (I) or (IB), wherein A¹ and A² are each independently selected from -CR⁴ and -NR⁴; and A³ and A⁴ are each -CR⁴, wherein R⁴ at each occurrence is independently selected from hydrogen, substituted or unsubstituted alkyl, and substituted or unsubstituted haloalkyl.

[46] One embodiment is a compound of formula (I) or (IB), wherein A¹ is N and A², A³ and A⁴ are CH.

[47] One embodiment is a compound of formula (I) or (IB), wherein A¹, A², A³ and A⁴ are CH.

[48] One embodiment is a compound of formula (I) or (IB), wherein group



[49] One embodiment is a compound of formula (I) or (IB), wherein R⁵ is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl, and R⁶ is hydrogen or substituted or unsubstituted alkyl.

[50] One embodiment is a compound of formula (I) or (IB), wherein, R⁵ is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[51] One embodiment is a compound of formula (I) or (IB), wherein R⁵ is selected from 4-fluoro-3-methylphenyl, 3-methylphenyl, 4-fluorophenyl, 3,4-difluorophenyl, or substituted or unsubstituted heteroaryl (e.g., substituted or unsubstituted 4-pyridinyl or substituted or unsubstituted 4-pyridazinyl).

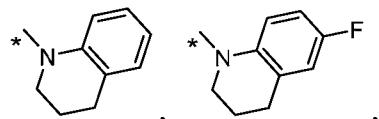
[52] One embodiment is a compound of formula (I) or (IB), wherein R⁶ is selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxyalkyl, substituted or unsubstituted hydroxyalkyl, and substituted or unsubstituted cycloalkylalkyl.

[53] One embodiment is a compound of formula (I) or (IB), wherein R⁶ is selected from hydrogen, -CH₃, -CH₂-CH₃, -CH(CH₃)CH₃, -CH₂-CH₂-OCH₃, -CH₂-CH₂OH, and -CH₂-cyclopropyl.

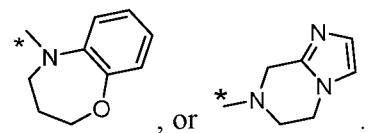
[54] One embodiment is a compound of formula (I) or (IB), wherein R⁵ and R⁶ together with the nitrogen atom to which they are attached form a substituted or unsubstituted heterocyclyl ring.

[55] One embodiment is a compound of formula (I) or (IB), wherein R⁵ and R⁶ together with the nitrogen atom to which they are attached form a substituted or unsubstituted heteroaryl.

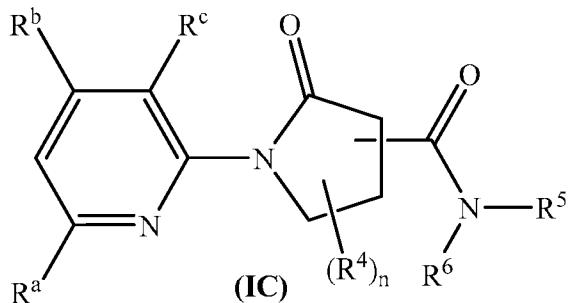
[56] One embodiment is a compound of formula (I) or (IB), wherein R⁵ and R⁶ together with



the nitrogen atom to which they are attached form the ring



[57] In another aspect of the present invention, the compound of formula (I) is a compound of formula (IC):



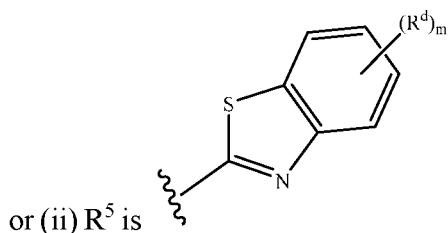
or a tautomer thereof, prodrug thereof, N-oxide thereof, stereoisomer thereof, pharmaceutically acceptable ester thereof, or pharmaceutically acceptable salt thereof,

wherein

R^a , R^b , and R^c are each independently selected from hydrogen, hydroxy, halo, cyano, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted heteroaryl;

each occurrence of R^4 is independently selected from hydrogen, hydroxy, halo, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, and substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted heteroaryl;

(i) R^5 and R^6 together with the nitrogen atom to which they are attached form a substituted or unsubstituted heterocyclyl ring or substituted or unsubstituted heteroaryl;



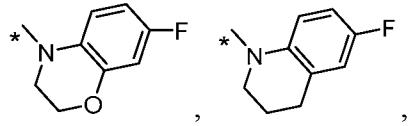
or (ii) R^5 is , R^6 is selected from hydroxy, halo, cyano, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted heteroaryl; and each occurrence of R^d is independently selected from hydrogen, hydroxy, halo, cyano, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted amino, and substituted or unsubstituted alkyl;

m is 0, 1, 2, or 3; and

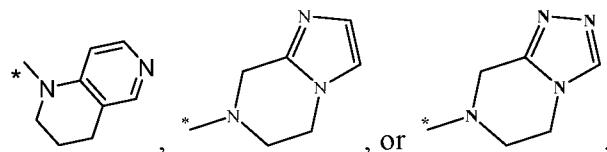
n is 0, 1, or 2.

- [58] One embodiment is a compound of formula (I) or (IC), wherein R^a is haloalkyl, or alkyl.
- [59] One embodiment is a compound of formula (I) or (IC), wherein R^a is -CH₃, or -CF₃.
- [60] One embodiment is a compound of formula (I) or (IC), wherein R^b is haloalkyl (e.g., -CF₃).
- [61] One embodiment is a compound of formula (I) or (IC), wherein R^c is hydrogen.
- [62] One embodiment is a compound of formula (I) or (IC), wherein R^4 is hydroxy and 'n' is 0 or 2.
- [63] One embodiment is a compound of formula (I) or (IC), wherein R^5 and R^6 together with the nitrogen atom to which they are attached form a substituted or unsubstituted heterocyclyl ring.
- [64] One embodiment is a compound of formula (I) or (IC), wherein R^5 and R^6 together with the nitrogen atom to which they are attached form a substituted or unsubstituted heteroaryl ring.

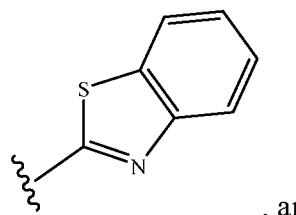
[65] One embodiment is a compound of formula (I) or (IC), wherein R⁵ and R⁶ together with



the nitrogen atom to which they are attached form the ring



[66] One embodiment is a compound of formula (I) or (IC), wherein R⁵ is



, and R⁶ is hydrogen or alkyl (e.g., -CH₃).

[67] Representative compounds of formulas (I), (IA), (IB), and (IC) of the present invention include those recited below. The present invention should not be construed to be limited to the compounds recited below:

2-((2-(3,4-dihydroquinolin-1(2H)-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-(indolin-1-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-(1H-indol-1-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-oxo-2-(3-oxo-3,4-dihydroquinoxalin-1(2H)-yl)ethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-(5-fluoro-1H-indol-1-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-oxo-2-(2,3,4,5-tetrahydro-1H-benzo[b]azepin-1-yl)ethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-oxo-2-(5-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-1-yl)ethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-oxo-2-(4-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-1-yl)ethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile ,

2-((2-(6-fluoro-3,4-dihydroquinolin-1(2H)-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-(7-fluoro-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-(2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-(3,4-dihydrobenzo[b][1,4]oxazepin-5(2H)-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-(2,3-dihydrobenzo[e][1,4]oxazepin-1(5H)-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

1-((3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)glycyl)-1H-indole-3-carboxamide,

2-((2-(5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-(5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-(8-fluoro-3,4-dihydrobenzo[b][1,4]oxazepin-5(2H)-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-(7-fluoro-3,4-dihydrobenzo[b][1,4]oxazepin-5(2H)-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-(9-fluoro-3,4-dihydrobenzo[b][1,4]oxazepin-5(2H)-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-(3,4-dihydro-1,6-naphthyridin-1(2H)-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-(3-hydroxy-3,4-dihydrobenzo[b][1,4]oxazepin-5(2H)-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-(1,1-dioxido-2,3-dihydro-4H-benzo[b][1,4]thiazin-4-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-(3,4-dihydro-1,5-naphthyridin-1(2H)-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-(7,8-difluoro-3,4-dihydrobenzo[b][1,4]oxazepin-5(2H)-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-(7-fluoro-5-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-1-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-(7-fluoro-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)-2-oxoethyl)amino)-6-methyl-4-(trifluoromethyl)nicotinonitrile,

2-((2-(7-fluoro-2,3-dihydrobenzo[e][1,4]oxazepin-1(5H)-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-(8-fluoro-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-(7-methoxy-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

1-(7-fluoro-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)-2-((6-methyl-4-(trifluoromethyl)pyridin-2-yl)amino)ethan-1-one,

2-((4,6-bis(trifluoromethyl)pyridin-2-yl)amino)-1-(7-fluoro-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)ethan-1-one,

2-((2-(5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl)-2-oxoethyl)amino)-6-methyl-4-(trifluoromethyl)nicotinonitrile,

2-((2-(3-methyl-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-(5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)-2-oxoethyl)amino)-6-methyl-4-(trifluoromethyl)nicotinonitrile,

6-methyl-2-((2-oxo-2-(3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)ethyl)amino)-4-(trifluoromethyl)nicotinonitrile,

6-methyl-2-((2-(3-methyl-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)-2-oxoethyl)amino)-4-(trifluoromethyl)nicotinonitrile,

2-((2-oxo-2-(3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)ethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((4,6-bis(trifluoromethyl)pyridin-2-yl)amino)-1-(5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)ethan-1-one,

2-((2-(5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((4,6-bis(trifluoromethyl)pyridin-2-yl)amino)-1-(5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)ethan-1-one,

2-((2-(6,7-dihydropyrazolo[1,5-a]pyrimidin-4(5H)-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-(2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-1-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-(6-chloro-7-fluoro-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-(6-chloro-7-fluoro-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)-2-oxoethyl)amino)-6-methyl-4-(trifluoromethyl)nicotinonitrile,

2-((2-(8-chloro-7-fluoro-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-(8-chloro-7-fluoro-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)-2-oxoethyl)amino)-6-methyl-4-(trifluoromethyl)nicotinonitrile,

1-(3-cyanopyridin-2-yl)-N-ethyl-N-(4-fluoro-3-methylphenyl)-1H-pyrrole-2-carboxamide,

1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-ethyl-N-(4-fluoro-3-methylphenyl)-1H-pyrrole-2-carboxamide,

1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-(4-fluorophenyl)-N-methyl-1H-pyrrole-2-carboxamide,

1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-ethyl-N-(4-fluorophenyl)-1H-pyrrole-2-carboxamide,

1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-(4-fluorophenyl)-N-methyl-1H-pyrazole-3-carboxamide,

1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-(4-fluorophenyl)-N,3-dimethyl-1H-pyrazole-5-carboxamide,

1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-(4-fluorophenyl)-1H-pyrrole-2-carboxamide,

1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-(3,4-difluorophenyl)-N-ethyl-1H-pyrrole-2-carboxamide,

1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-ethyl-N-(pyridin-4-yl)-1H-pyrrole-2-carboxamide,

1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-ethyl-N-(pyridazin-4-yl)-1H-pyrrole-2-carboxamide,

1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-(4-fluorophenyl)-N-(2-methoxyethyl)-1H-pyrrole-2-carboxamide,

1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-(4-fluorophenyl)-N-(2-hydroxyethyl)-1H-pyrrole-2-carboxamide,

1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-(cyclopropylmethyl)-N-(4-fluorophenyl)-1H-pyrrole-2-carboxamide,

1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-(4-fluorophenyl)-N-methyl-5-(trifluoromethyl)-1H-pyrazole-3-carboxamide,

1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-(4-fluorophenyl)-N-methyl-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide,

1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-ethyl-N-(4-fluorophenyl)-4-methyl-1H-pyrrole-2-carboxamide,

1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-ethyl-N-(4-fluorophenyl)-3-methyl-1H-pyrazole-5-carboxamide,

1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-ethyl-N-(4-fluorophenyl)-5-methyl-1H-pyrazole-3-carboxamide,

1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-(4-fluorophenyl)-N,5-dimethyl-1H-pyrazole-3-carboxamide,

1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N,3-dimethyl-N-(m-tolyl)-1H-pyrazole-5-carboxamide,

N-(3-chloro-4-fluorophenyl)-1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N,3-dimethyl-1H-pyrazole-5-carboxamide,

1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-methyl-N-(m-tolyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide,

1-(3-cyano-6-methyl-4-(trifluoromethyl)pyridin-2-yl)-N,3-dimethyl-N-(m-tolyl)-1H-pyrazole-5-carboxamide,

2-(2-(1,2,3,4-tetrahydroquinoline-1-carbonyl)-1H-pyrrol-1-yl)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-(2-(6-fluoro-1,2,3,4-tetrahydroquinoline-1-carbonyl)-1H-pyrrol-1-yl)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-(2-(2,3,4,5-tetrahydrobenzo[b][1,4]oxazepine-5-carbonyl)-1H-pyrrol-1-yl)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-(3-methyl-5-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-7-carbonyl)-1H-pyrazol-1-yl)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-(3-methyl-5-(5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine-7-carbonyl)-1H-pyrazol-1-yl)-4,6-bis(trifluoromethyl)nicotinonitrile,

(S)-1-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)-5-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-7-carbonyl)pyrrolidin-2-one,

(S)-1-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)-5-(5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine-7-carbonyl)pyrrolidin-2-one,

(S)-1-(4,6-bis(trifluoromethyl)pyridin-2-yl)-5-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-7-carbonyl)pyrrolidin-2-one,

(S)-1-(4,6-bis(trifluoromethyl)pyridin-2-yl)-5-(5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine-7-carbonyl)pyrrolidin-2-one,

(S)-1-(4,6-bis(trifluoromethyl)pyridin-2-yl)-5-(7-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazine-4-carbonyl)pyrrolidin-2-one,

(S)-5-(7-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazine-4-carbonyl)-1-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)pyrrolidin-2-one,

(S)-1-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)-5-(1,2,3,4-tetrahydro-1,6-naphthyridine-1-carbonyl)pyrrolidin-2-one,

N-(benzo[d]thiazol-2-yl)-2-((3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)amino)-N-methylacetamide,

N-(benzo[d]thiazol-2-yl)-2-((3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)amino)acetamide,

N-(benzo[d]thiazol-2-yl)-2-((3-cyano-6-methyl-4-(trifluoromethyl)pyridin-2-yl)amino)acetamide,

N-(benzo[d]thiazol-2-yl)-2-((3-cyano-6-methyl-4-(trifluoromethyl)pyridin-2-yl)amino)-N-methylacetamide,

(S)-N-(benzo[d]thiazol-2-yl)-1-(3-cyano-6-methyl-4-(trifluoromethyl)pyridin-2-yl)pyrrolidine-2-carboxamide,

(S)-N-(benzo[d]thiazol-2-yl)-1-(3-cyano-6-methyl-4-(trifluoromethyl)pyridin-2-yl)-N-methylpyrrolidine-2-carboxamide,

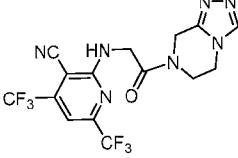
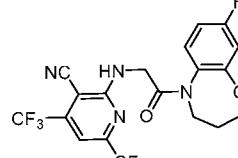
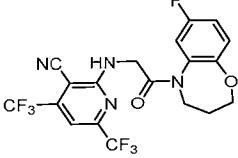
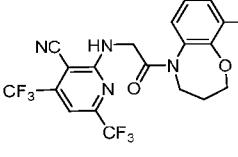
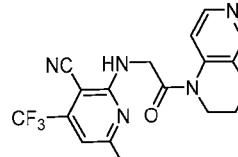
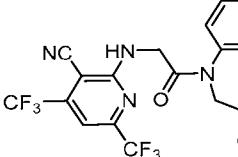
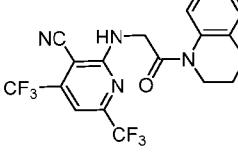
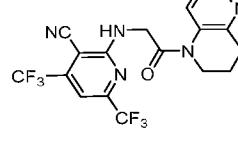
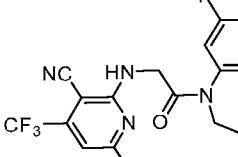
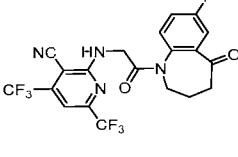
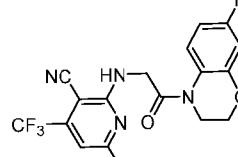
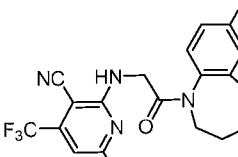
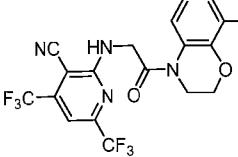
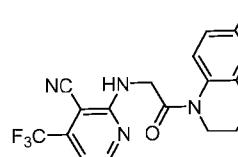
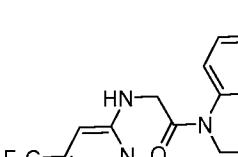
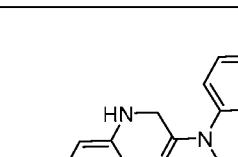
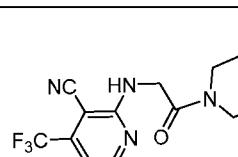
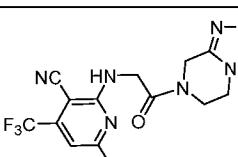
(3S,4S,5S)-5-(7-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazine-4-carbonyl)-3,4-dihydroxy-1-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)pyrrolidin-2-one,

or a tautomer thereof, prodrug thereof, N-oxide thereof, stereoisomer thereof, pharmaceutically acceptable ester thereof or pharmaceutically acceptable salt thereof.

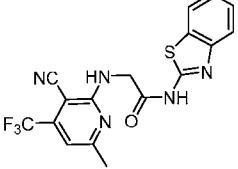
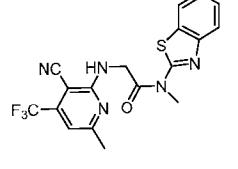
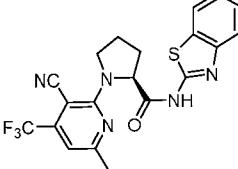
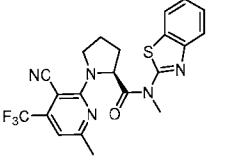
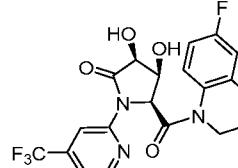
[68] Representative structures of formulas **(I)**, **(IA)**, **(IB)**, and **(IC)** are depicted in Table 1 below. The present invention includes the compounds in Table 1 and tautomers thereof, prodrugs thereof, N-oxides thereof, stereoisomers thereof, pharmaceutically acceptable esters thereof and pharmaceutically acceptable salts thereof.

TABLE-1

Ex. No.	Structure	Ex. No.	Structure	Ex. No.	Structure
1		2		3	
4		5		6	
7		8		9	
10		11		12	
13		14		15	

16		17		18	
19		20		21	
22		23		24	
25		26		27	
28		29		30	
31		32		33	

67		68		69	
70		71		72	
73		74		75	
76		77		78	
79		80		81	
82		83		84	

85		86		87	
88		89			

[69] Another aspect of the present invention is a pharmaceutical composition comprising a compound of the present invention (e.g., a compound of formula (I), (IA), (IB), or (IC), or a pharmaceutically acceptable thereof) and at least one pharmaceutically acceptable excipient.

[70] Another aspect is a method for the treatment of a polymerase theta (POL(θ)) associated disease, disorder, or condition comprising administering to a subject in need thereof an effective amount of the compound of the present invention. The method may include the step of administering simultaneously or sequentially to the subject at least one other anti-cancer agent, anti-inflammatory agent, immunomodulatory agent, steroid, non-steroidal anti-inflammatory agent, or any combination of any of the foregoing. The polymerase theta (POL(θ)) associated disease, disorder or condition may be an immune mediated disease, a disease or disorder involving inflammation, cancer or other proliferative disease. The method may include inhibiting DNA repair by inhibiting overexpression of POL(θ) in a cancer cell, such as a HR deficient cancer cell, or HR proficient cancer cell. The POL(θ) associated disease, disorder or condition may be homologous recombination (HR) deficient cancer or HR proficient cancer. In yet another embodiment, the POL(θ) associated disease, disorder or condition is a cancer characterized by a reduction or absence of BRCA or any HRR (homologous recombination repair) gene expression, the absence of the BRAC or any HRR gene, or reduced function of BRCA or HRR protein.

[71] In one embodiment, the polymerase theta (POL(θ)) associated disease, disorder or condition is selected from inflammation, glomerulonephritis, uveitis, hepatic diseases or disorders, renal diseases or disorders, rheumatoid arthritis, inflammatory bowel disease, vasculitis, dermatitis, osteoarthritis, inflammatory muscle disease, scleroderma, osteoporosis, eczema, allogeneic or xenogeneic transplantation, graft rejection, graft-versus-host disease, lupus erythematosus, pulmonary fibrosis, dermatomyositis, thyroiditis, myasthenia gravis, autoimmune hemolytic anemia, cystic fibrosis, chronic relapsing hepatitis, primary biliary cirrhosis, hepatitis, atopic dermatitis, asthma, Sjogren's syndrome, organ transplant rejection, multiple sclerosis, Guillain-Barre, autoimmune uveitis, autoimmune hemolytic anemia, pernicious anemia, autoimmune thrombocytopenia, temporal arteritis, antiphospholipid syndrome, vasculitides, Wegener's granulomatosis, Behcet's disease, psoriasis, dermatitis herpetiformis, pemphigus vulgaris, vitiligo, Crohn's disease, colitis, ulcerative colitis, primary biliary cirrhosis, autoimmune hepatitis, Type 1 or immune-mediated diabetes mellitus, Grave's disease, Hashimoto's thyroiditis, autoimmune oophoritis and orchitis, autoimmune disorder of the adrenal gland, systemic lupus erythematosus, polymyositis, dermatomyositis, ankylosing spondylitis, transplant rejection, skin graft rejection, arthritis, bone diseases associated with increased bone resorption, ileitis, Barrett's syndrome, sympathetic ophthalmitis, endophthalmitis, uremic complications, nephrosis, sclerodermatitis, psoriasis, chronic demyelinating diseases of the nervous system, AIDS-related neurodegeneration, Alzheimer's disease, infectious meningitis, encephalomyelitis, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis viral or autoimmune encephalitis, autoimmune disorders, immune-complex vasculitis, systemic lupus and erythematoses, systemic lupus erythematosus (SLE), metabolic disorders, and cancer.

[72] In another embodiment, the polymerase theta (POL(θ)) associated disease, disorder or condition is selected from hematopoietic tumors of lymphoid lineage, leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma and Burkett's lymphoma, hematopoietic tumors of myeloid lineage, acute myelogenous leukemias, chronic myelogenous leukemias, myelodysplastic syndrome, promyelocytic leukemia, carcinoma of the bladder,

carcinoma of the breast, carcinoma of the colon, carcinoma of the kidney, carcinoma of the liver, carcinoma of the lung, small cell lung cancer, esophageal cancer, gall bladder cancer, ovarian cancer, pancreatic cancer, stomach cancer, cervical cancer, thyroid cancer, prostate cancer, skin cancer, squamous cell carcinoma, tumors of mesenchymal origin, fibrosarcoma, rhabdomyosarcoma, tumors of the central and peripheral nervous system, astrocytoma, neuroblastoma, glioma, schwannoma, melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderma pigmentosum, keratoctanthoma, thyroid follicular cancer and Kaposi's sarcoma. In yet another embodiment, the polymerase theta (POL(θ)) associated disease, disorder or condition is carcinoma of the breast or ovarian cancer, cancer of the central nervous system, endometrium cancer, kidney cancer, large intestine cancer, lung cancer, oesophagus cancer, pancreatic cancer, prostate cancer, stomach cancer, head and neck cancer (upper aerodigestive cancer), urinary tract cancer, or colon cancer.

[73] Another aspect of the present invention is a method for treating, preventing, and/or ameliorating a disease characterized by overexpression of POL Theta (POL(θ)) in a patient (e.g., a patient in need thereof) comprising administering to the patient a therapeutically effective amount of at least one compound of the present invention (e.g., a compound of formula (I), (IA), (IB), or (IC), or a pharmaceutically acceptable salt thereof), or a pharmaceutical composition comprising at least one compound the present invention (e.g., a compound of formula (I), (IA), (IB), or (IC), or a pharmaceutically acceptable thereof) and at least one pharmaceutically acceptable excipient.

[74] In one embodiment of any of the methods described herein, the disease characterized by overexpression of POL(θ) is cancer.

[75] Another aspect of the present invention is a method for treating, preventing, and/or ameliorating a homologous recombinant (HR) deficient cancer in a patient (e.g., a patient in need thereof) comprising administering to the patient a therapeutically effective amount of at least one compound of the present invention (e.g., a compound of formula (I), (IA), (IB), or (IC), or a pharmaceutically acceptable salt thereof), or a pharmaceutical composition comprising at least one compound of the present invention (e.g., a compound of formula (I), (IA), (IB), or (IC), or

a pharmaceutically acceptable salt thereof) and at least one pharmaceutically acceptable excipient.

[76] Another aspect of the present invention is a method for inhibiting DNA repair by overexpression of POL(θ) in a cancer cell, comprising contacting the cell with an effective amount of a compound of the present invention (e.g., a compound of formula (I), (IA), (IB), or (IC) or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition comprising at least one compound of the present invention (e.g., a compound of formula (I), (IA), (IB), or (IC), or a pharmaceutically acceptable salt thereof) and at least one pharmaceutically acceptable excipient.

[77] In certain embodiments, the present invention provides a method for inhibiting DNA repair by over expression of POL(θ) in a cancer cell, wherein the cell is HR deficient.

[78] In certain embodiments, the HR-deficient cancer is breast cancer or ovarian cancer,

[79] In certain embodiments, the present invention provides a method for preventing, and/or ameliorating a cancer in a patient (e.g., a patient in need thereof) comprising administering to the patient a therapeutically effective amount of at least one compound of the present invention (e.g., a compound of formula (I), (IA), (IB), or (IC), or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition comprising at least one compound of the present invention (e.g., a compound of formula (I), (IA), (IB), or (IC), or a pharmaceutically acceptable salt thereof) and at least one pharmaceutically acceptable excipient, wherein the cancer is characterized by a reduction or absence of BRCA gene expression, the absence of the BRCA gene, or reduced function of BRCA protein.

[80] In certain embodiments, the present invention provides a method for treating, preventing, and/or ameliorating a cancer resistant to POL(θ) inhibitor therapy in a patient (e.g., a patient in need thereof) comprising administering to the patient a therapeutically effective amount of at least one compound of the present invention (e.g., a compound of formula (I), (IA), (IB), or (IC), or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition comprising at least one compound of the present invention (e.g., a compound of formula (I), (IA), (IB), or (IC),

or a pharmaceutically acceptable salt thereof) and at least one pharmaceutically acceptable excipient.

[81] In certain embodiments, the cancer resistant to POL(θ) inhibitor therapy includes, but is not limited to, breast cancer, ovarian cancer, lung cancer, bladder cancer, liver cancer, head and/or neck cancer, pancreatic cancer, gastrointestinal cancer, or colorectal cancer.

[82] In certain embodiments, the compounds described herein are useful in the treatment of a variety of cancers, including, but not limited to: (i) carcinoma, including that of the bladder, breast, colon, kidney, liver, lung, including small cell lung cancer and carcinoma of the esophagus, gall bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin, including squamous cell carcinoma; (ii) hematopoietic tumors of lymphoid lineage, including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma and Burkett's lymphoma; (iii) hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia; (iv) tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma; (v) tumors of the central and peripheral nervous system, including astrocytoma, neuroblastoma, glioma and schwannomas; and (vi) other tumors, including melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratoctanthoma, thyroid follicular cancer and Kaposi's sarcoma.

[83] In further aspect, the present invention is directed to the use of a compound or composition of the present invention according to any of the embodiments described herein in combination with one or more active therapeutic agents, chemotherapeutic agents, or other prophylactic or therapeutic modalities (such as radiation), for example, for the treatment or prevention of diseases or disorders where there is an advantage in inhibiting DNA polymerase theta (POLQ) enzyme.

[84] Yet another embodiment is a method of inhibiting a catalytic activity of a polymerase theta (POL(θ)) enzyme present in a cell comprising contacting the cell with an effective amount of a compound of the present invention. In one embodiment, the inhibition takes place in a

subject suffering from a disease or disorder which is cancer, a bone disorder, an inflammatory disease, an immune disease, a nervous system disease, or a metabolic disease.

DETAILED DESCRIPTION OF THE INVENTION

[85] As used herein the following definitions shall apply unless otherwise indicated. Further many of the groups defined herein can be optionally substituted. The listing of substituents in the definition is exemplary and is not to be construed to limit the substituents defined elsewhere in the specification.

[86] The terms "hydroxy" and "hydroxyl" are used interchangeably and refer to "-OH"

[87] The terms "halo", "halide", or, alternatively, "halogen" mean fluoro, chloro, bromo or iodo.

[88] The terms "haloalkyl," and "haloalkoxy" include alkyl, and alkoxy structures that are substituted with one or more halo groups or with combinations thereof. For example, the terms "fluoroalkyl" and "fluoroalkoxy" include haloalkyl and haloalkoxy groups, respectively, in which the halo group is fluorine.

[89] The term "alkyl", unless otherwise specified, refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to eight carbon atoms, and which is attached to the rest of the molecule by a single bond, e.g., methyl, ethyl, n-propyl, 1-methylethyl (isopropyl), n-butyl, n-pentyl, and 1,1-dimethylethyl (t-butyl).

[90] The term "alkoxy" unless otherwise specified, denotes an alkyl, cycloalkyl, or cycloalkylalkyl group as defined above attached via an oxygen linkage to the rest of the molecule. Examples include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, and cyclohexyloxy. In appropriate circumstances, the term "alkoxy" refers to a group as mentioned above which is bivalent.

[91] The term "hydroxyalkyl" or "hydroxylalkyl" means alkyl substituted with one or more hydroxyl groups, wherein the alkyl groups are as defined above. Examples of "hydroxyalkyl"

groups include, but are not limited to, hydroxymethyl, hydroxyethyl, and hydroxypropyl, propan-2-ol.

[92] The term "acyl" refers to a group defined as -(C=O)R, where R is a substituted or unsubstituted alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl group.

[93] The term "aminoalkyl" means an alkyl group substituted with one or more amine group(s), wherein the alkyl group is as defined above. Examples of "aminoalkyl" groups include, but are not limited to, aminomethyl and aminoethyl, 2-aminopropyl.

[94] The term "cycloalkyl" unless otherwise specified, denotes a non-aromatic mono or multicyclic ring system of about 3 to 12 carbon atoms such as, e.g., cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. Examples of multicyclic cycloalkyl groups include, e.g., perhydronaphthyl, adamantyl and norbornyl groups, bridged cyclic groups, and spirocyclic groups, e.g., spiro (4,4) non-2-yl. The term "C₃₋₆ cycloalkyl" refers to a cycloalkyl group as defined above having 3 to 6 carbon atoms.

[95] The term "cycloalkylalkyl", unless otherwise specified, refers to a cyclic ring-containing radical containing in the range of about 3 to about 8 carbon atoms directly attached to an alkyl group which is then attached to the main structure at any carbon from the alkyl group, Non limiting examples include cyclopropylmethyl, cyclobutylethyl, and cyclopentylethyl.

[96] The term "aryl", unless otherwise specified, refers to an aromatic radical having in the range of 6 up to 20 carbon atoms, such as, e.g., phenyl, naphthyl, tetrahydronaphthyl, indanyl, and biphenyl.

[97] The term "arylalkyl", unless otherwise specified, refers to an aryl group as defined above directly bonded to an alkyl group as defined above, e.g., -CH₂C₆H₅ and -C₂H₅C₆H₅.

[98] The term "heterocyclyl", unless otherwise specified, refers to a non-aromatic heterocyclic ring radical as defined below. The heterocyclyl ring radical may be attached to the main structure at any heteroatom or carbon atom. The term "heterocyclic ring", unless otherwise specified, refers to a non-aromatic 3-to-15-member ring radical which consists of carbon atoms and at least

one heteroatom selected from nitrogen, phosphorus, oxygen and sulfur. The heterocyclic ring radical may be a mono-, bi-, tri- or tetracyclic ring system, which may include fused, bridged or spiro ring systems, and the nitrogen, phosphorus, carbon, oxygen or sulfur atoms in the heterocyclic ring radical may be optionally oxidized to various oxidation states. In addition, the nitrogen atom may be optionally quaternized.

[99] The term “heterocyclalkyl”, unless otherwise specified, refers to a heterocyclic ring radical as defined above directly bonded to an alkyl group. The heterocyclalkyl radical may be attached to the main structure at any carbon atom in the alkyl group. Examples of heterocycloalkyl radicals include, but are not limited to, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, and 1,1-dioxo-thiomorpholinyl.

[100] The term “heteroaryl”, unless otherwise specified, refers to an optionally substituted 5-to-14-member aromatic ring having one or more heteroatoms selected from N, O, and S as ring atoms. The heteroaryl may be a mono-, bi- or tricyclic ring system. Examples of such “heterocyclic ring” or “heteroaryl” radicals include, but are not limited to, oxazolyl, thiazolyl, imidazolyl, pyrrolyl, furanyl, pyridinyl, pyrimidinyl, pyrazinyl, benzofuranyl, indolyl, benzothiazolyl, benzoxazolyl, carbazolyl, quinolyl, isoquinolyl, azetidinyl, acridinyl, benzodioxolyl, benzodioxanyl, benzofuranyl, carbazolyl, cinnolinyl, dioxolanyl, indolizinyl, naphthyridinyl, perhydroazepinyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, quinazolinyl, quinoxalinyl, tetrazoyl, tetrahydroisoquinolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, azepinyl, 4-piperidonyl, pyrrolidinyl, pyridazinyl, oxazolinyl, oxazolidinyl, triazolyl, indanyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolinyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, isoindolyl, indolinyl, isoindolinyl, octahydroindolyl, octahydroisoindolyl, decahydroisoquinolyl, benzimidazolyl, thiadiazolyl, benzopyranyl, tetrahydrofuryl, tetrahydropyranyl, thienyl, benzothienyl, thiamorpholinyl, thiamorpholinyl sulfoxide,

thiamorpholinyl sulfone, dioxaphospholanyl, oxadiazolyl, chromanyl, and isochromanyl. The heteroaryl ring radical may be attached to the main structure at any heteroatom or carbon atom. The term “substituted heteroaryl” also includes ring systems substituted with one or more oxide (=O) substituents, such as pyridinyl N-oxides.

[101] The term “heteroarylalkyl”, unless otherwise specified, refers to a heteroaryl ring radical as defined above directly bonded to an alkyl group. The heteroarylalkyl radical may be attached to the main structure at any carbon atom from alkyl group.

[102] The term “cyclic ring” refers to a cyclic ring containing 3 to 10 carbon atoms.

[103] The term “substituted” unless otherwise specified, refers to substitution with any one or any combination of the following substituents which may be the same or different and are independently selected from hydrogen, hydroxy, halogen, carboxyl, cyano, nitro, oxo (=O), thio (=S), substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic ring, substituted heterocyclalkyl ring, substituted or unsubstituted guanidine, -COOR^t, -C(O)R^v, -C(S)R^v, -C(O)NR^tR^u, -C(O)ONR^tR^u, -NR^tR^u, -NR^tCONR^uR^v, -N(R^t)SOR^u, -N(R^t)SO₂R^u, -(=N-N(R^t)R^u), -NR^tC(O)OR^u, -NR^tR^u, -NR^tC(O)R^u-, -NR^tC(S)R^u-NR^tC(S)NR^tR^u, -SONR^tR^u-, -SO₂NR^tR^u-, -OR^t, -OC(O)NR^uR^v, -OC(O)OR^u-, -OC(O)R^t, -OC(O)NR^tR^u, -R^tNR^uC(O)R^v, -R^tOR^u, -R^tC(O)OR^u, -R^tC(O)NR^uR^v, -R^tC(O)R^u, -R^tOC(O)R^u, -SR^t, -SOR^t, -SO₂R^t, and -ONO₂, wherein R^t, R^u and R^v in each of the above groups can independently be hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted amino, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted

or unsubstituted heterocyclic ring, or substituted heterocyclalkyl ring, or any two of R^t, R^u and R^v may be joined to form a substituted or unsubstituted saturated or unsaturated 3-10 membered ring, which may optionally include heteroatoms which may be the same or different and are selected from O, NR^t (e.g., R^t can be hydrogen or C₁₋₆ alkyl) or S. Substitution or the combinations of substituents envisioned by this invention are preferably those that result in the formation of a stable or chemically feasible compound.

[104] The term stable as used herein refers to the compounds or the structure that are not substantially altered when subjected to conditions to allow for their production, detection and preferably their recovery, purification, and incorporation into a pharmaceutical composition. The substituents in the aforementioned "substituted" groups cannot be further substituted.

[105] Certain of the compounds described herein contain one or more asymmetric centers and can thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that can be defined, in terms of absolute stereochemistry, as (R)- or (S)-. The present chemical entities, pharmaceutical compositions and methods are meant to include all such possible isomers, including racemic mixtures, optically pure forms and intermediate mixtures. Non-limiting examples of intermediate mixtures include a mixture of isomers in a ratio of 10:90, 13:87, 17:83, 20:80, or 22:78. Optically active (R)- and (S)- isomers can be prepared using chiral synthons or chiral reagents or resolved using conventional techniques. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers.

[106] The terms "tautomer" and "tautomers" refer to compounds which are characterized by relatively easy interconversion of isomeric forms in equilibrium. These isomers are intended to be covered by this invention. "Tautomers" are structurally distinct isomers that interconvert by tautomerization. "Tautomerization" is a form of isomerization and includes prototropic or proton-shift tautomerization, which is considered a subset of acid-base chemistry. "Prototropic tautomerization" or "proton-shift tautomerization" involves the migration of a proton accompanied by changes in bond order, often the interchange of a single bond with an adjacent double bond. Where tautomerization is possible (e.g., in solution), a chemical equilibrium of

tautomers can be reached. An example of tautomerization is keto-enol tautomerization. A specific example of keto-enol tautomerization is the interconversion of pentane-2,4-dione and 4-hydroxypent-3-en-2-one tautomers. Another example of tautomerization is phenol-keto tautomerization. A specific example of phenol-keto tautomerization is the interconversion of pyridin-4-ol and pyridin-4(1H)-one tautomers.

[107] The term "prodrug" refers to a compound, which is an inactive precursor of a compound, converted into its active form in the body by normal metabolic processes. Prodrug design is discussed generally in Hardma, *et al.*, (Eds.), Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, 9th Ed., pp. 11-16 (1996). A thorough discussion is provided in Higuchi *et al.*, *Prodrugs as Novel Delivery Systems*, Vol. 14, ASCD Symposium Series, and in Roche (Ed.), *Bioreversible Carriers in Drug Design*, American Pharmaceutical Association and Pergamon Press (1987). To illustrate, prodrugs can be converted into a pharmacologically active form through hydrolysis of, for example, an ester or amide linkage, thereby introducing or exposing a functional group on the resultant product. The prodrugs can be designed to react with an endogenous compound to form a water-soluble conjugate that further enhances the pharmacological properties of the compound, for example, increased circulatory half-life. Alternatively, prodrugs can be designed to undergo covalent modification on a functional group with, for example, glucuronic acid, sulfate, glutathione, amino acids, or acetate. The resulting conjugate can be inactivated and excreted in the urine or rendered more potent than the parent compound. High molecular weight conjugates also can be excreted into the bile, subjected to enzymatic cleavage, and released back into circulation, thereby effectively increasing the biological half-life of the originally administered compound.

[108] The term "ester" refers to a compound, which is formed by reaction between an acid and an alcohol with elimination of water. An ester can be represented by the general formula RCOOR' where R and R' can be any groups.

[109] These prodrugs and esters are intended to be covered within the scope of this invention.

[110] Additionally, the present invention also includes compounds which differ only in the presence of one or more isotopically enriched atoms for example replacement of hydrogen with deuterium or tritium, or the replacement of a carbon by ¹³C- or ¹⁴C-enriched carbon.

[111] The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of atoms that constitute such compounds. For example, the compounds may be radiolabelled with radioactive isotopes, such as for example tritium (³H), iodine-125 (¹²⁵I) or carbon-14 (¹⁴C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are encompassed within the scope of the present invention.

[112] Non-limiting pharmaceutically acceptable salts forming part of this invention include, but are not limited to, salts derived from inorganic bases such as Li, Na, K, Ca, Mg, Fe, Cu, Zn, and Mn; salts of organic bases such as N,N'-diacetylenediamine, glucamine, triethylamine, choline, hydroxide, dicyclohexylamine, metformin, benzylamine, trialkylamine, and thiamine; chiral bases such as alkylphenylamine, glycinol, and phenyl glycinol; salts of natural amino acids such as glycine, alanine, valine, leucine, isoleucine, norleucine, tyrosine, cystine, cysteine, methionine, proline, hydroxy proline, histidine, ornithine, lysine, arginine, and serine; quaternary ammonium salts of the compounds of invention with alkyl halides, alkyl sulphates such as MeI and (Me)₂SO₄; non-natural amino acids such as D-isomers or substituted amino acids; guanidine; and substituted guanidine wherein the substituents are selected from nitro, amino, alkyl, alkenyl, alkynyl, ammonium or substituted ammonium salts and aluminum salts. Salts may include acid addition salts where appropriate which are sulphates, nitrates, phosphates, perchlorates, borates, hydrohalides (e.g., hydrochlorides), acetates, tartrates, maleates, citrates, fumarates, succinates, palmoates, methanesulphonates, benzoates, salicylates, benzenesulfonates, ascorbates, glycerophosphates, and ketoglutarates.

[113] The term “HR” (“homologous recombination”) refers to the cellular process of genetic recombination in which nucleotide sequences are exchanged between two similar or identical DNA.

[114] The term “homologous recombination (HR) deficient cancer” refers to a cancer that is characterized by a reduction or absence of a functional HR repair pathway. HR deficiency may

arise from absence of one or more HR-associated genes or presence of one or more mutations in one or more HR-associated genes. Examples of HR-associated genes include, e.g., BRCA1, BRCA2, RAD54, RAD51B, CtlP (Choline Transporter-Like Protein), PALB2 (Partner and Localizer of BRCA2), XRCC2 (X-ray repair complementing defective repair in Chinese hamster cells 2), RECQL4 (RecQ Protein-like 4), BLM (Bloom syndrome, RecQ helicase-like), WRN (Werner syndrome, one or more HR-associated genes), Nbs 1 (Nibrin), and genes coding Fanconi anemia (FA) proteins or FA like genes e.g., FANCA, FANCB, FANCC, FANCD1 (BRCA2), FANCD2, FANCE, FANCF, FANCG, FANCI, FANJ (BRIP1), FANCL, FANCM, FANCN (RALB2), FANCP (SLX4), FANCS (BRCA1), RAD51C and XPF.

[115] When ranges are used herein for physical properties, such as molecular weight, or chemical properties, such as chemical formulae, all combinations and sub-combinations of ranges and specific embodiments therein are intended to be included.

[116] The term "about" when referring to a number or a numerical range means that the number or numerical range referred to is an approximation within experimental variability (or within statistical experimental error), and thus the number or numerical range may vary from, for example, between 1% and 15% of the stated number or numerical range.

[117] The term "comprising" (and related terms such as "comprise," "comprises," "having" or "including") includes those embodiments, for example, an embodiment of any composition of matter, composition, method, or process, or the like, that "consist of" or "consist essentially of" the described features.

[118] The term "co-administration," "administered in combination with," and their grammatical equivalents, as used herein, encompasses administration of two or more agents to an animal so that both agents and/or their metabolites are present in the animal at the same time. Co-administration includes simultaneous administration in separate compositions, administration at different times in separate compositions, or administration in a composition in which both agents are present.

[119] The term "effective amount" or "therapeutically effective amount" refers to that amount of a compound described herein that is sufficient to show the intended application including, but not limited to, disease treatment, as defined below. The therapeutically effective amount may vary depending upon the intended application (*in vitro* or *in vivo*), or the subject and disease condition being treated, e.g., the weight and age of the subject, the severity of the disease condition, the manner of administration and the like, which can readily be determined by one of ordinary skill in the art. The term also applies to a dose that will induce a particular response in target cells, e.g., reduction of platelet adhesion and/or cell migration. The specific dose will vary depending on the compounds chosen, the dosing regimen to be followed, whether it is administered in combination with other compounds, timing of administration, the tissue to which it is administered, and the physical delivery system in which it is carried. In one embodiment, the amount of compound of the present invention administered ranges from about 0.1 mg to about 5 g, such as from about 1 mg to about 2 g, from about 100 mg to about 1.5 g, from about 200 mg to about 1.5 g, from about 400 mg to about 1.5 g, or from about 400 mg to about 1 g.

[120] As used herein, "treatment," "treating," or "ameliorating" are used interchangeably. These terms refer to an approach for obtaining beneficial or desired results including but not limited to therapeutic benefit and/or a prophylactic benefit. By therapeutic benefit is meant eradication or amelioration of the underlying disorder being treated. Also, a therapeutic benefit is achieved with the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the patient, notwithstanding that the patient may still be afflicted with the underlying disorder. For prophylactic benefit, the compositions may be administered to a patient at risk of developing a particular disease, or to a patient reporting one or more of the physiological symptoms of a disease, even though a diagnosis of this disease may not have been made.

[121] The term "therapeutic effect," as used herein, encompasses a therapeutic benefit and/or a prophylactic benefit as described above. A prophylactic effect includes delaying or eliminating the appearance of a disease or condition, delaying or eliminating the onset of symptoms of a disease or condition, slowing, halting, or reversing the progression of a disease or condition, or any combination thereof.

[122] The term "subject" or "patient" refers to an animal, such as a mammal, for example a human. The methods and uses described herein can be useful in both human therapeutics and veterinary applications (e.g., dogs, cats, cows, sheep, pigs, horses, goats, chickens, turkeys, ducks, and geese).

[123] In some embodiments, the patient is a mammal, and in some embodiments, the patient is a human.

[124] "Radiation therapy" as used herein means exposing a patient, using routine methods and compositions known to the practitioner, to radiation emitters such as alpha-particle emitting radionuclides (e.g., actinium and thorium radionuclides), low linear energy transfer (LET) radiation emitters (i.e., beta emitters), conversion electron emitters (e.g., strontium-89 and samarium-153-EDTMP), or high-energy radiation, including without limitation x-rays, gamma rays, and neutrons.

[125] The term "pharmaceutically acceptable excipient" includes, but is not limited to, solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, diluents, fillers, salts, disintegrants, binders, lubricants, glidants, wetting agents, controlled release matrices, colorants/flavorings, carriers, buffers, stabilizers, solubilizers, and any combination of any of the foregoing. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions of the invention is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

[126] The methods and uses of the present invention may be applied to cell populations *in vivo* or *ex vivo*. "*In vivo*" means within a living individual, as within an animal or human or in a subject's body. In this context, the methods of the invention may be used therapeutically or prophylactically in an individual. "*Ex vivo*" or "*in vitro*" means outside of a living individual. Examples of *ex vivo* cell populations include *in vitro* cell cultures and biological samples including but not limited to fluid or tissue samples obtained from individuals. Such samples may be obtained by methods known in the art. Exemplary biological fluid samples include blood, cerebrospinal fluid, urine, and saliva. Exemplary tissue samples include tumors and biopsies

thereof. In this context, the invention may be used for a variety of purposes, including therapeutic and experimental purposes. For example, the invention may be used ex vivo or in vitro to determine the optimal schedule and/or dosing of administration of a POL((θ) inhibitor for a given indication, cell type, individual, and other parameters. Information gleaned from such use may be used for experimental or diagnostic purposes or in the clinic to set protocols for in vivo treatment.

Pharmaceutical Compositions

[127] The present invention further provides a pharmaceutical composition comprising one or more compounds of the present invention (e.g., a compound of formula **(I)**, **(IA)**, **(IB)**, or **(IC)**, or a pharmaceutically acceptable salt thereof). The pharmaceutical compositions described herein may include one or more additional active ingredients as described herein. In one embodiment, the pharmaceutical composition includes one or more additional therapeutic agents, such as an anti-cancer agent, anti-inflammatory agent, immunomodulatory agent, steroid, non-steroidal anti-inflammatory agent, or any combination of any of the foregoing. The pharmaceutical composition may be administered for any of the disorders described herein.

[128] The pharmaceutical compositions described herein are typically formulated to provide a therapeutically effective amount of a compound of the present invention as the active ingredient. Where desired, the pharmaceutical compositions contain a compound of the present invention as the active ingredient and one or more pharmaceutically acceptable carriers or excipients, such as inert solid diluents and fillers, diluents, including sterile aqueous solution and various organic solvents, permeation enhancers, solubilizers and adjuvants.

[129] The pharmaceutical compositions can be administered alone or in combination with one or more other active agents, which are also typically administered in the form of pharmaceutical compositions. Where desired, the subject compounds and other active agent(s) may be mixed into a preparation or both components may be formulated into separate preparations to use them in combination separately or at the same time.

[130] The methods and uses described herein include administration of a compound of the present invention by itself, or in combination as described herein, and in each case optionally including one or more suitable diluents, fillers, salts, disintegrants, binders, lubricants, glidants, wetting agents, controlled release matrices, colorants/flavorings, carriers, excipients, buffers, stabilizers, solubilizers, and any combination thereof.

[131] Preparations of various pharmaceutical compositions are well known in the art., *see, e.g.*, Anderson, Philip O.; Knoben, James E.; Troutman, William G, Eds., *Handbook of Clinical Drug Data*, Tenth Edition, McGraw-Hill, 2002; Pratt and Taylor, Eds., *Principles of Drug Action*, Third Edition, Churchill Livingston, New York, 1990; Katzung, Ed., *Basic and Clinical Pharmacology*, Ninth Edition, McGraw Hill, 2003; Goodman and Gilman, Eds., *The Pharmacological Basis of Therapeutics*, Tenth Edition, McGraw Hill, 2001; Remingtons *Pharmaceutical Sciences*, 20th Ed., Lippincott Williams & Wilkins., 2000; Martindale, *The Extra Pharmacopoeia*, Thirty-Second Edition (The Pharmaceutical Press, London, 1999), all of which are incorporated by reference herein in their entirety.

[132] The compounds and pharmaceutical compositions of the present invention can be administered by any route that enables delivery of the compound(s) to their intended site of action, such as, for example, oral routes, intraduodenal routes, parenteral injection (including intravenous, intraarterial, subcutaneous, intramuscular, intravascular, intraperitoneal or infusion), topical administration (e.g. transdermal application), rectal administration, via local delivery by catheter or stent or through inhalation. The compounds and pharmaceutical compositions of the present invention can also be administered intraadiposally or intrathecally.

[133] The compounds and pharmaceutical compositions described herein can be administered in solid, semi-solid, liquid or gaseous form, or may be in dried powder, such as lyophilized form. The pharmaceutical compositions can be packaged in forms convenient for delivery, including, for example, solid dosage forms such as capsules, sachets, cachets, gelatins, papers, tablets, capsules, suppositories, pellets, pills, troches, and lozenges. The type of packaging will generally depend on the desired route of administration. Implantable sustained release formulations are also contemplated, as are transdermal formulations.

Methods of Treatment

[134] The present invention also provides methods of using the compounds and pharmaceutical compositions according to any of the embodiments described herein to treat disease conditions, including, but not limited to, diseases associated with overexpression of POL(θ) and/or due to an excess of POL(θ).

[135] The present invention also provides a method for treating, preventing, and/or ameliorating a disease characterized by overexpression of POL(θ) in a patient (e.g., a patient in need thereof) comprising administering to the patient a therapeutically effective amount of compound or composition according to any of the embodiments described herein.

[136] The present invention also provides the use of a compound or composition according to any of the embodiments described herein in a method for treating, preventing, and/or ameliorating a homologous recombinant (HR) deficient cancer.

[137] The present invention also provides the use of a compound or composition according to any of the embodiments described herein in a method for inhibiting DNA repair by overexpression of POL(θ) in a cancer cell, comprising contacting the cell with an effective amount of a compound or composition according to any of the embodiments described herein.

[138] The present invention also provides the use of a compound or composition according to any of the embodiments described herein in a method for inhibiting DNA repair by overexpression of POL(θ) in a cancer cell.

[139] The present invention also provides the use of a compound or composition according to any of the embodiments described herein in a method for inhibiting DNA repair by overexpression of POL(θ) in a HR deficient cancer cell.

[140] The present invention also provides the use of a compound or composition according to any of the embodiments described herein in a method for inhibiting DNA repair by overexpression of POL(θ) in a HR deficient cancer cell; wherein the HR-deficient cancer is breast cancer or ovarian cancer,

[141] The present invention also provides the use of a compound or composition according to any of the embodiments described herein in a method for preventing and/or ameliorating a cancer in a patient, wherein the cancer is characterized by a reduction or absence of BRCA gene expression, the absence of the BRAC gene, or reduced function of BRCA protein.

[142] The present invention also provides the use of a compound or composition according to any of the embodiments described herein in a method for preventing and/or ameliorating a cancer in a patient resistant to POL(θ) inhibitor therapy.

[143] The present invention also provides the use of a compound or composition according to any of the embodiments described herein in a method for preventing and/or ameliorating a cancer in a patient resistant to POL(θ) inhibitor therapy; wherein the cancer is breast cancer, ovarian cancer, lung cancer, bladder cancer, liver cancer, head and neck cancer, pancreatic cancer, gastrointestinal cancer, and colorectal cancer.

[144] The treatment methods provided herein comprise administering to the subject a therapeutically effective amount of a compound of the invention. In one aspect, the present invention provides a method of treating an inflammation disorder, including autoimmune diseases, e.g., in a mammal. The method comprises administering to the mammal a therapeutically effective amount of a compound or composition according to any of the embodiments described herein.

[145] It will be appreciated that the treatment methods of the invention are useful in the fields of human medicine and veterinary medicine. Thus, the individual to be treated may be a mammal, preferably human, or another animal. For veterinary purposes, individuals include but are not limited to farm animals including cows, sheep, pigs, horses, and goats; companion animals such as dogs and cats; exotic and/or zoo animals; laboratory animals including mice, rats, rabbits, guinea pigs, and hamsters; and poultry such as chickens, turkeys, ducks, and geese.

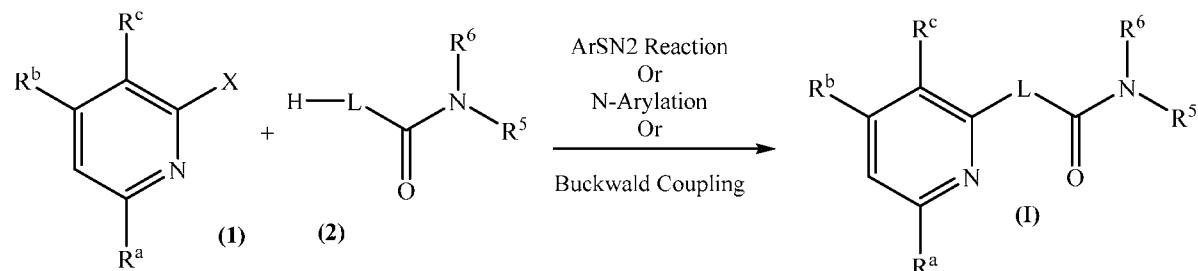
[146] The present invention also provides methods of using the compounds or pharmaceutical compositions of the present invention to treat disease conditions, including, but not limited to, diseases associated with overexpression of POL(θ) and/or due to an excess of POL(θ).

[147] The invention further provides methods of inhibiting POL(θ) expression by contacting a POL(θ) with an amount of a compound of the invention sufficient to inhibit the activity of the POL(θ) enzyme.

[148] In another aspect, the present invention also contemplates the use of POL(θ) inhibitors of compounds of formula (I), or a pharmaceutically acceptable salt, or a pharmaceutical composition thereof in combination with one or more active therapeutic agents, chemotherapeutic agents, or other prophylactic or therapeutic modalities (such as radiation).

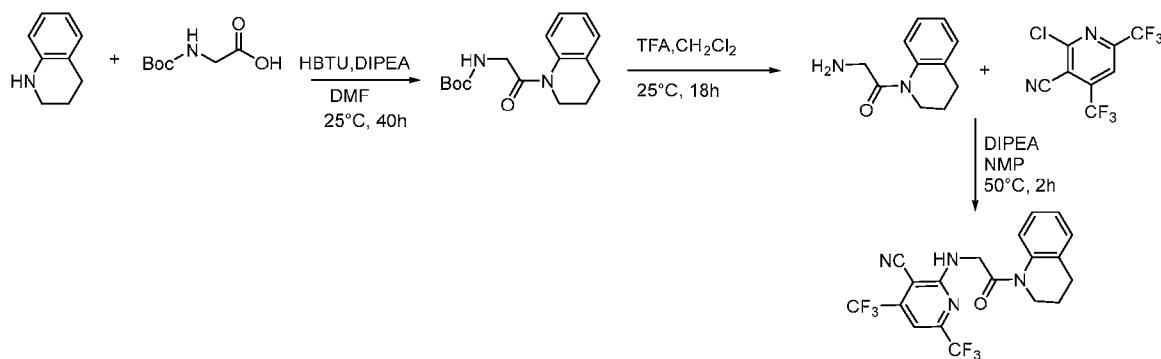
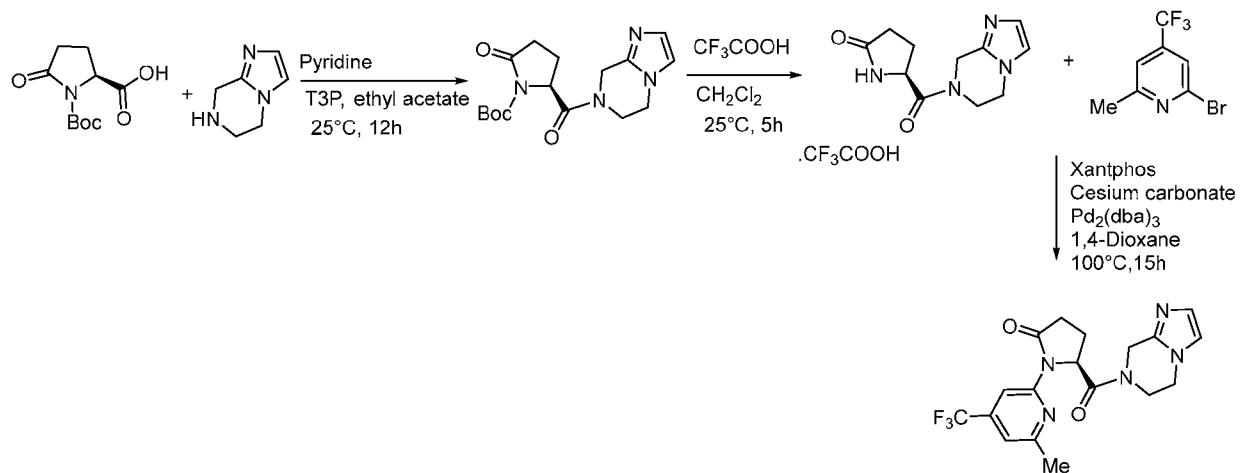
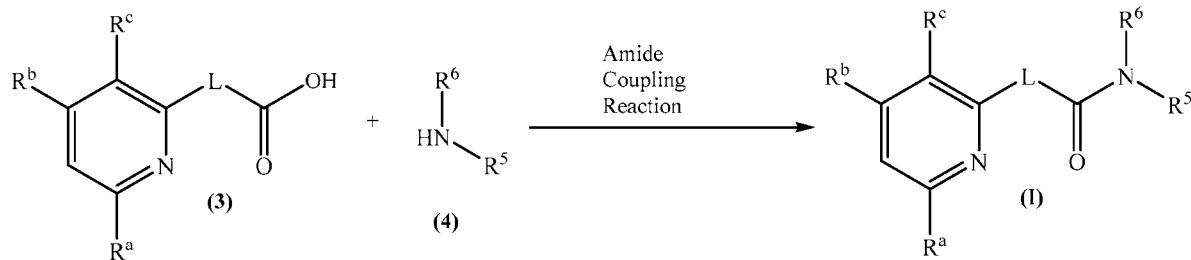
[149] The following general methodology described in the schemes below provides the manner and process of making and using the compounds of the present invention and are illustrative rather than limiting. Further modification of the provided methodology may also be devised to achieve and serve the purpose of the invention. Accordingly, there may be other embodiments which fall within the spirit and scope of the invention as defined by this specification.

General Scheme 1



[150] A compound of formula (I) may be synthesized by an ArSN2 reaction, N-arylation or a Buchwald coupling reaction of a compound of formula (1) with a compound of formula (2), where X is halogen or other leaving group, in a suitable solvent, such as DMF, 1,4-dioxane, THF, DMSO, n-BuOH, i-prOH, toluene or N-methylpyrrolidone, in the presence of a suitable base, such as potassium carbonate, cesium carbonate, sodium tert-butoxide or DIPEA and a suitable palladium catalyst, such as Pd(Ph₃P)₄ or Pd₂dba₃. This scheme is illustrated below as Illustrations 1 and 2.

Illustration 1

**Illustration 2****General Scheme 2**

[151] A compound of formula (I) may be synthesized by an amide coupling reaction of a compound of formula (3) with a compound of formula (4), using a coupling agent such as, e.g., HATU (1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide

hexafluorophosphate), HBTU (3-[bis(dimethylamino)methyl]imidoyl)-3H-benzotriazol-1-oxide hexafluorophosphate), T₃P (propylphosphonic anhydride) (PPAA), or EDC-HCl (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride). This scheme is illustrated below as Illustrations 3-6.

Illustration 3

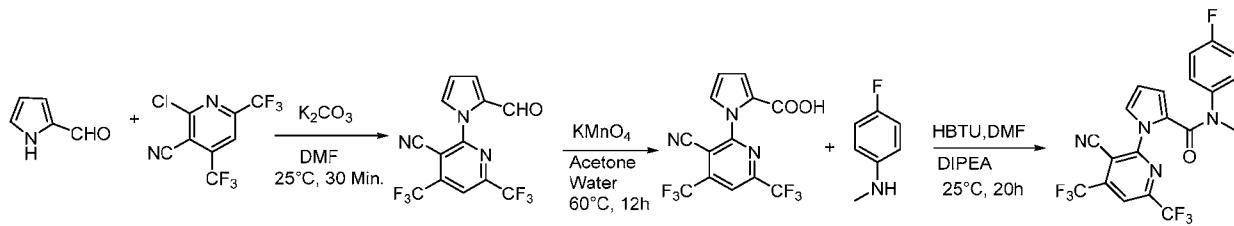


Illustration 4

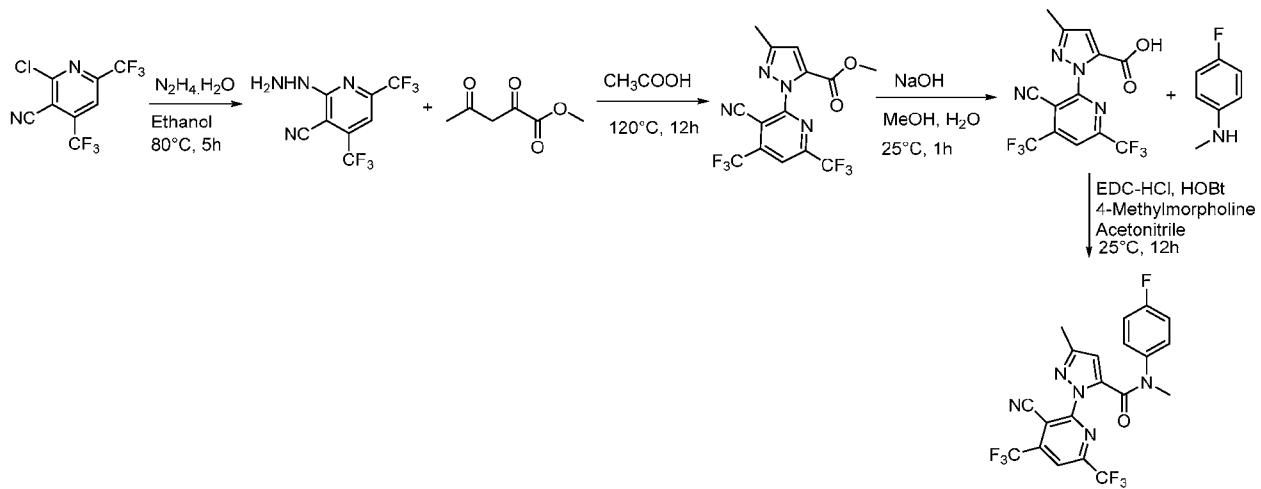


Illustration 5

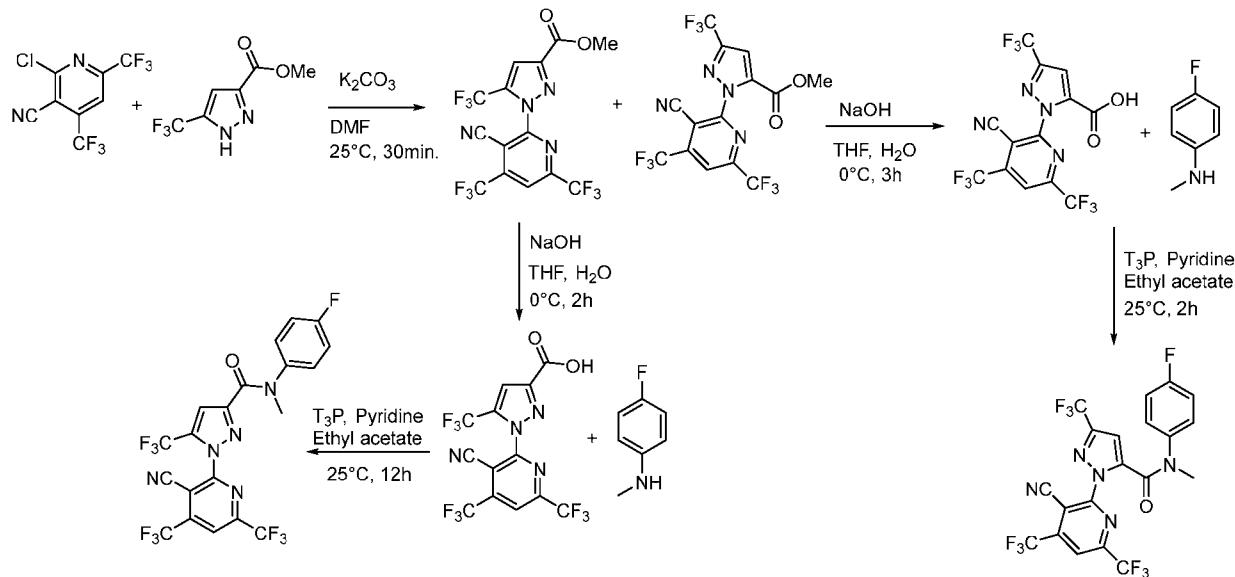
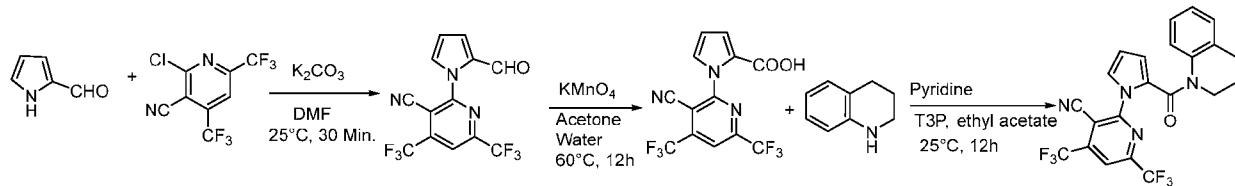


Illustration 6

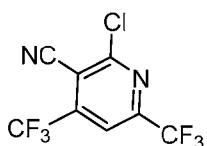


[152] General Procedure-1 for Amide Formation: To an amine (1 eq.), N-Boc glycine or acid (1.0 to 1.5 eq.) and a suitable coupling agent, such as HATU, HBTU, EDC-HCl or T₃P (1.5 to 2.5 eq.) in a suitable solvent, such as DMF, THF, ethyl acetate or dichloromethane, a suitable base, such as N,N-diisopropylethylamine, triethylamine, 4-methylmorpholine or pyridine (3 - 4 eq.) was added and stirred at room temperature for 2 to 48 hours. The reaction mixture was then diluted with water and extracted with a suitable solvent, such as ethyl acetate, dichloromethane or a mixture of methanol and dichloromethane. The organic layer was washed with saturated sodium bicarbonate solution, water, brine solution, dried using anhydrous Na₂SO₄ and distilled under vacuum using a rotavapor to obtain a crude product. The crude product was purified by combi-flash using a suitable mixture of ethyl acetate and petroleum ether or a mixture of methanol and dichloromethane.

[153] General Procedure-2 for Boc-Cleavage: To a Boc-protected amide (1 eq.) in a suitable solvent, such as dichloromethane, ethanol or 1,4-dioxane cooled to 0°C, trifluoroacetic acid or HCl (1 to 10 eq.) was added and stirred at room temperature for 2 to 24 hours. The reaction mixture was either concentrated to obtain a TFA salt or basified with 10% sodium bicarbonate solution and the aqueous layer was extracted with a suitable solvent, such as dichloromethane or a mixture of methanol and dichloromethane. The organic layer was dried using anhydrous Na₂SO₄ and distilled under vacuum using a rotavapor to obtain a crude product. The crude product was used without purification for next step or was purified by combi-flash using a suitable mixture of ethyl acetate and petroleum ether or a mixture of methanol and dichloromethane.

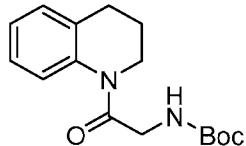
[154] General Procedure-3 for ArSN₂ Reaction or N-Arylation: To an amine (1 eq.) and chloro compound (1 eq.) in a suitable solvent, such as DMF, THF, N-methylpyrrolidone, a suitable base, such as N,N-diisopropylethylamine, triethylamine, 4-methylmorpholine or pyridine (1 - 3 eq.) was added and stirred at 25-60° C for 1 to 12 hours. The reaction mixture was then diluted with water and extracted with a suitable solvent, such as ethyl acetate, dichloromethane or a mixture of methanol and dichloromethane. The organic layer was washed with saturated sodium bicarbonate solution, water, brine solution, dried using anhydrous Na₂SO₄ and distilled under vacuum using a rotavapor to obtain a crude product. The crude product was purified by combi-flash using a suitable mixture of ethyl acetate and petroleum ether or a mixture of methanol and dichloromethane. N-Arylation reactions may also be performed by Buckwald reaction in a suitable solvent, such as DMF, 1,4-dioxane, THF, DMSO, n-BuOH, i-prOH, toluene or N-methylpyrrolidone, with a suitable base, such as potassium carbonate, caesium carbonate, sodium tert-butoxide or DIPEA and a suitable palladium catalyst, such as Pd(Ph₃P)₄ or Pd₂dba₃.

Intermediate 1: N-isopropyl-3-methylaniline



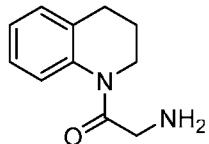
[155] To Cyanoacetamide (20 g, 238 mmol), 1,1,1,5,5-hexafluoroacetylacetone (49.5 g, 238 mmol) and sulfolane (114 g, 951 mmol) were added and the reaction mixture heated to 150°C for 16 h. After 18h, reaction mixture was cooled to room temperature, diluted with ethyl acetate (500 ml) and washed with sodium chloride solution (3 x 200 ml). Organic layer was dried on anhydrous Na₂SO₄ and evaporated to obtain a crude. The Crude compound (60 g) was cooled to 0°, POCl₃ (142 ml, 1.52 mol) was added followed by triethylamine (81.6 ml, 586 mmol). The reaction mixture heated to 125°C for 15 h. After 15h, reaction mixture was cooled to room temperature, quenched with ice cold water and extracted with dichloromethane (3 x 300 ml). The organic layer was washed with sodium chloride solution (2 x 300 ml), dried over anhydrous sodium sulphate and evaporated to obtain a crude. The crude product was purified by column chromatography using 60-120 mesh silica gel and using ethyl acetate and petroleum ether (5:95) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as a yellow liquid (16.5 g). Yield: 26%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 8.63 (s, 1H).

Intermediate 2: tert-butyl (2-(3,4-dihydroquinolin-1(2H)-yl)-2-oxoethyl)carbamate



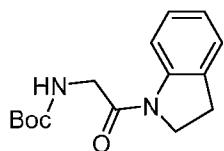
[156] Following the general procedure 1, the titled compound was synthesized from 1,2,3,4-Tetrahydroquinoline (2.50 g, 18.8 mmol mmol), DMF (12 ml), N-Boc-glycine (4.93 g, 28.2 mmol), HBTU (10.9 g, 28.2 mmol) and N-diisopropylethylamine (7.28 g, 56.3 mmol). Purification: Not done. Appearance: Brown solid (4.75 g). Yield: 87%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 7.52 (s, 1H), 7.19-7.15 (m, 2H), 7.11 (t, J 7.6, 1H), 6.88 (t, J 5.6, 1H), 3.90 (d, J 5.6, 2H), 3.68 (t, J 6.4, 2H), 2.71 (t, J 6.8, 2H), 1.89 (m, 2H), 1.37 (s, 9H). MS (m/z): 191.10 ([M-Boc]⁺).

Intermediate 3: 2-amino-1-(3,4-dihydroquinolin-1(2H)-yl)ethan-1-one



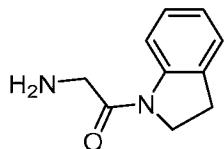
[157] Following the general procedure 2, the titled compound was synthesized from Intermediate 2 (2.00 g, 6.89 mmol mmol), dichloromethane (20 ml) and trifluoroacetic acid (15.7 g, 138 mmol). Purification: Not done. Appearance: Brown liquid (1.25 g). Yield: 95%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 7.51 (s, 1H), 7.18-7.05 (m, 3H), 3.66 (t, J 6.4, 2H), 3.46 (s, 2H), 2.71 (t, J 6.8, 2H), 1.87 (m, 4H). MS (m/z): 191.10 ([M+H]⁺).

Intermediate 4: tert-butyl (2-(indolin-1-yl)-2-oxoethyl)carbamate



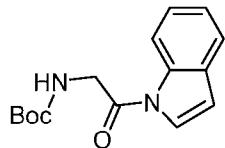
[158] Following the general procedure 1, the titled compound was synthesized from Indoline (1.00 g, 8.39 mmol mmol), DMF (10 ml), N-Boc-glycine (1.61 g, 9.23 mmol), HBTU (4.77 g, 12.59 mmol) and N-diisopropylethylamine (3.25 g, 25.17 mmol). Purification: Not done. Appearance: Off-white solid (1.80 g). Yield: 78%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 8.04 (d, J 8.0, 1H), 7.25 (d, J 7.2, 1H), 7.17 (t, J 7.6, 1H), 7.01-6.94 (m, 2H), 4.09 (t, J 8.8, 2H), 3.87 (d, J 5.6, 2H), 3.17 (t, J 8.4, 2H), 1.40 (s, 9H). MS (m/z): 177.10 ([M-Boc]⁺).

Intermediate 5: 2-amino-1-(indolin-1-yl)ethan-1-one



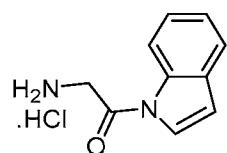
[159] Following the general procedure 2, the titled compound was synthesized from Intermediate 4 (1.80 g, 6.51 mmol mmol), dichloromethane (18 ml) and trifluoroacetic acid (0.743 g, 6.51 mmol). Purification: Not done. Appearance: Off-white solid (0.60 g). Yield: 50%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 8.09 (d, J 7.6, 1H), 7.24 (d, J 7.2, 1H), 7.17 (t, J 7.6, 1H), 7.00 (dt, J 7.2, 0.8, 1H), 4.03 (t, J 8.4, 2H), 3.44 (s, 2H), 3.15 (t, J 8.4, 2H), 2.14 (s, 2H). MS (m/z): 177.11 ([M+H]⁺).

Intermediate 6: tert-butyl (2-(1H-indol-1-yl)-2-oxoethyl)carbamate



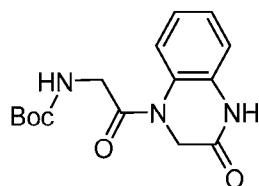
[160] Following the general procedure 1, the titled compound was synthesized from Indole (3.00 g, 25.61 mmol), DMF (10 ml), N-Boc-glycine (4.93 g, 28.17 mmol), HBTU (14.57 g, 38.41 mmol) and N-diisopropylethylamine (9.93 g, 76.82 mmol). Purification: Combi-Flash. Eluent: Ethyl acetate and petroleum ether (15:85) as eluent. Appearance: Off-white solid (1.70 g). Yield: 27%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 8.34 (d, J 8.0, 1H), 7.94 (d, J 3.6, 1H), 7.64 (d, J 7.2, 1H), 7.36-7.25 (m, 3H), 6.78 (d, J 3.6, 1H), 4.44 (d, J 6.0, 2H), 1.42 (s, 9H). 175.05 ([M-Boc]⁺).

Intermediate 7: 2-amino-1-(1H-indol-1-yl)ethan-1-one hydrochloride



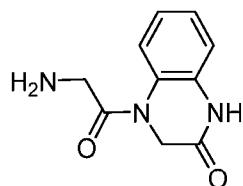
[161] To Intermediate 6 (1.00 g, 3.64 mmol), ethanol (20 ml) and HCl (1.66 ml, 18.23 mmol) were added and heated to 70°C. After 2h cooled to 0°C, filtered the solid and washed with ethanol (5 ml). The solid was dried under vacuum to afford the titled compound as an off-white solid (0.60 g). Yield: 80%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 8.55 (s, 3H), 8.35 (d, J 8.0, 1H), 7.87 (d, J 4.0, 1H), 7.67 (d, J 7.6, 1H), 7.41-7.31 (m, 2H), 6.86 (d, J 3.6, 1H), 4.58 (s, 2H). MS (m/z): 175.01 ([M+H]⁺).

Intermediate 8: tert-butyl (2-oxo-2-(3-oxo-3,4-dihydroquinoxalin-1(2H)-yl)ethyl)carbamate



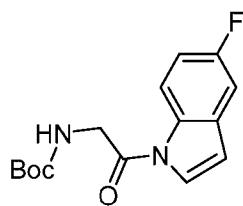
[162] Following the general procedure 1, the titled compound was synthesized from 3,4-dihydroquinoxalin-2(1H)-one (1.00 g, 6.74 mmol), DMF (10 ml), N-Boc-glycine (1.18 g, 6.74 mmol), HBTU (2.56 g, 6.74 mmol) and N-diisopropylethylamine (0.873 g, 6.74 mmol). Purification: Combi-Flash. Eluent: Ethyl acetate and petroleum ether (33:67) as eluent. Appearance: Pale-yellow solid (0.400 g). Yield: 20%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 12.40 (s, 1H), 7.57 (m, 1H), 7.23 (t, J 7.6, 1H), 7.06-6.99 (m, 3H), 3.92 (d, J 5.6, 2H), 2.69 (s, 2H), 1.37 (s, 9H). MS (m/z): 206.11 ([M-Boc]⁺).

Intermediate 9: 4-glycyl-3,4-dihydroquinoxalin-2(1H)-one



[163] To Intermediate 8 (400 mg, 1.31 mmol), ethanol (10 ml) and HCl (0.16 ml, 6.55 mmol) were added and heated to 70°C. After 3h, the solvent was evaporated, and pH adjusted to 7-8 by aqueous sodium bicarbonate solution. The aqueous solution was concentrated and stirred with 30% methanol in dichloromethane (50 ml) for 30 min. Filtered the solid and the filtrate was concentrated to afford the titled compound as a yellow gummy solid (0.100 g). Yield: 37%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 7.48 (m, 1H), 7.19 (m, 1H), 7.05 (m, 2H), 4.32 (s, 2H), 4.10 (s, 1H), 3.45 (s, 2H), 3.16 (s, 2H). MS (m/z): 206.09 ([M+H]⁺).

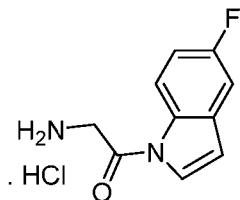
Intermediate 10: tert-butyl (2-(5-fluoro-1H-indol-1-yl)-2-oxoethyl)carbamate



[164] Following the general procedure 1, the titled compound was synthesized from 5-fluoroindole (2.00 g, 14.80 mmol), DMF (10 ml), N-Boc-glycine (2.85 g, 16.28 mmol), HBTU (8.42 g, 22.20 mmol) and N-diisopropylethylamine (5.74 g, 44.40 mmol). Purification: Combi-Flash. Eluent: Ethyl acetate and petroleum ether (15:85) as eluent. Appearance: Off-

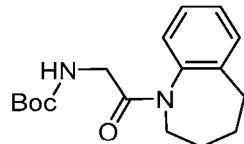
white solid (1.60 g). Yield: 41%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 8.34 (dd, J 9.2,4.8, 1H), 8.02 (d, J 4.0, 1H), 7.46 (dd, J 9.2,2.4, 1H), 7.35 (t, J 6.0, 1H), 7.20 (dt, J 9.2,2.4, 1H), 6.77 (d, J 3.6, 1H), 4.47 (d, J 6.0, 2H), 1.41 (s, 9H). MS (m/z): 193.10 ([M-Boc]⁺).

Intermediate 11: 2-amino-1-(5-fluoro-1H-indol-1-yl)ethan-1-one hydrochloride



[165] To Intermediate 10 (1.50 g, 5.13 mmol), ethanol (30 ml) and HCl (2.33 ml, 25.66 mmol) were added and heated to 70°C. After 2h cooled to 0°C, filtered the solid and washed with ethanol (5 ml). The solid was dried under vacuum to afford the titled compound as an off-white solid (1.10 g). Yield: 94%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 8.66 (s, 3H), 8.35 (dd, J 9.2,4.8, 1H), 7.97 (d, J 3.6, 1H), 7.50 (dd, J 9.2,2.8, 1H), 7.27 (dt, J 9.2,2.4, 1H), 6.85 (d, J 3.6, 1H), 4.58 (s, 2H). MS (m/z): 193.04 ([M+H]⁺).

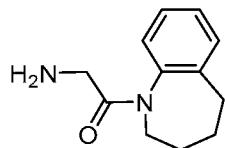
Intermediate 12: tert-butyl (2-oxo-2-(2,3,4,5-tetrahydro-1H-benzo[b]azepin-1-yl)ethyl)carbamate



[166] To 2,3,4,5-tetrahydro-1H-benzo[b]azepine (1.00 g, 6.79 mmol) in Dichloromethane (20 ml), N-Boc-glycine (1.30 g, 7.47 mmol) and triethylamine (2.74 g, 27.17 mmol) were added and cooled to 0°C. Propyl phosphonic anhydride (5.40 g, 16.98 mmol) was added and stirred at 25°C for 21h. After 21h, the reaction mixture was diluted with water (25 ml). The organic layer was dried with anhydrous sodium sulphate and distilled out to obtain the crude. Crude was purified by combi-flash using ethyl acetate and petroleum ether (20:80) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as a colourless liquid (1.50 g). Yield: 70%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 7.35-7.26 (m, 4H), 6.74 (t, J 5.6, 1H),

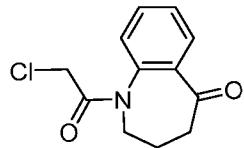
4.48 (d, J 13.2, 1H), 3.64 (dd, J 16.8, 6.0, 1H), 3.07 (dd, J 16.8, 5.6, 1H), 2.73-2.67 (m, 2H), 2.53 (m, 1H), 1.94 (m, 1H), 1.75 (m, 2H), 1.35 (s, 9H), 1.30 (m, 1H). MS (m/z): 205.08 [M-Boc]⁺.

Intermediate 13: 2-amino-1-(2,3,4,5-tetrahydro-1H-benzo[b]azepin-1-yl)ethan-1-one

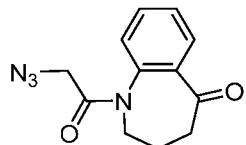


[167] To Intermediate 12 (1.00 g, 3.29 mmol), ethanol (10 ml) and HCl (1.49 ml, 16.43 mmol) were added and heated to 70°C. After 2h, the cooled to room temperature and pH adjusted to 7-8 by aqueous sodium bicarbonate solution. The aqueous solution was extracted with 20% methanol in dichloromethane (3 x 30 ml). The organic layer was concentrated to afford the titled compound as a colourless gummy solid (0.500 g). Yield: 75%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 7.33 (m, 1H), 7.27-7.25 (m, 3H), 4.53 (m, 1H), 3.23 (d, J 16.8, 1H), 2.70-2.52 (m, 4H), 1.93 (m, 1H), 1.77-1.69 (m, 2H), 1.52 (s, 2H), 1.32-1.21 (m, 1H). MS (m/z): 205.13 ([M+H]⁺).

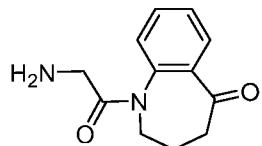
Intermediate 14: 1-(2-chloroacetyl)-1,2,3,4-tetrahydro-5H-benzo[b]azepin-5-one



[168] To 1,2,3,4-tetrahydro-5H-benzo[b]azepin-5-one (1.50 g, 9.30 mmol) in Dichloromethane (5 ml), triethylamine (1.88 g, 18.61 mmol) was added and cooled to 0°C. Chloroacetyl chloride (1.56 g, 13.96 mmol) was added and stirred at 25°C for 4h. After 4h, the reaction mixture was quenched with saturated sodium bicarbonate solution (20 ml) and extracted with dichloromethane (3 x 30 ml). The organic layer was dried with anhydrous sodium sulphate and distilled out to obtain the crude. Crude was purified by combi-flash using ethyl acetate and petroleum ether (20:80) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as a pale brown solid (1.50 g). Yield: 67%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 7.79 (d, J 7.2, 1H), 7.70 (t, J 7.2, 1H), 7.57 (m, 2H), 4.56 (br s, 1H), 4.17-4.02 (m, 2H), 3.09 (br s, 1H), 2.67 (m, 2H), 2.07 (br s, 1H), 1.68 (br s, 1H).

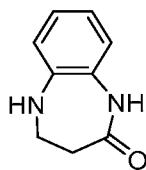
Intermediate 15: 1-(2-azidoacetyl)-1,2,3,4-tetrahydro-5H-benzo[b]azepin-5-one

[169] To intermediate 14 (1.10 g, 4.62 mmol) in DMSO (15 ml), sodium azide (451 mg, 6.94 mmol) was added and stirred at 25°C for 12h. After 12h, the reaction mixture was diluted with dichloromethane (25 ml). The organic layer was washed with water (3 x 25 ml), dried with anhydrous sodium sulphate and distilled out to obtain the titled compound as a dark brown solid (0.70 g). Yield: 66%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 7.79 (d, J 7.6, 1H), 7.68 (t, J 7.2, 1H), 7.53 (m, 2H), 4.59 (d, J 14.4, 1H), 4.11 (br s, 1H), 3.69 (d, J 9.6, 1H), 3.08 (br s, 1H), 2.61 (m, 2H), 2.13 (br s, 1H), 1.67 (br s, 1H). MS (m/z): 245.00 ([M+H]⁺).

Intermediate 16: 1-glycyl-1,2,3,4-tetrahydro-5H-benzo[b]azepin-5-one

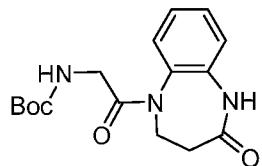
[170] To intermediate 15 (0.50 g, 2.05 mmol) in methanol (25 ml), 5% Pd/C (50% wet, 300 mg) was added and stirred at 25°C under 30 psi H₂ pressure for 2h. After 2h, the reaction mixture was filtered through cealite bed and washed with methanol (5 ml). The solvent was distilled out to obtain the crude. Crude was purified by combi-flash using methanol and dichloromethane (7:93) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as a pale brown solid titled compound as a colourless liquid (0.36 g). Yield: 80%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 7.76 (dd, J 8.0, 1.6, 1H), 7.67 (m, 1H), 7.50 (m, 2H), 4.61 (br s, 1H), 3.13 (br s, 1H), 3.03 (s, 1H), 2.58-2.54 (m, 3H), 2.11 (br s, 1H), 1.72 (m, 3H). MS (m/z): 219.23 ([M+H]⁺).

Intermediate 17: 1,3,4,5-tetrahydro-2H-benzo[b][1,4]diazepin-2-one



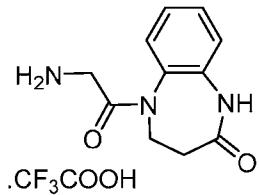
[171] To 1,2-diaminobenzene (5.00 g, 46 mmol) in xylene (100 ml), acrylamide (3.30 g, 46 mmol) and Imidazole hydrochloride (4.80 g, 46 mmol) were added and heated to 140° for 16h. After 16h, the reaction mixture was cooled to room temperature, diluted with water (250 ml) and extracted with ethyl acetate (3 x 300 ml). The organic layer was dried with anhydrous sodium sulphate and distilled out to obtain the crude. Crude was purified column chromatography using 60-120 mesh silica gel, using ethyl acetate and petroleum ether (50:50) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as a brown solid (2.0 g). Yield: 13%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 9.39 (s, 1H), 6.87-6.79 (m, 2H), 6.74 (dd, J 7.6,1.2, 1H), 6.29 (dt, J 7.6,1.2, 1H), 5.67 (s, 1H), 3.45-3.41(m, 2H), 2.51-2.46 (m, 2H). MS (m/z): 163.07 [M+H]⁺.

Intermediate 18: tert-butyl (2-oxo-2-(4-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-1-yl)ethyl)carbamate



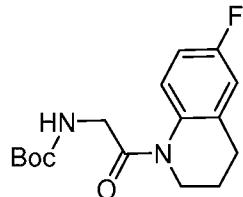
[172] Following the general procedure 1, the titled compound was synthesized from intermediate 17 (1.50 g, 9.25 mmol), Dichloromethane (15 ml), N-Boc-glycine (1.78 g, 10.17 mmol), triethylamine (3.74 g, 36.99 mmol) and T₃P (Propyl phosphonic anhydride) (7.35 g, 23.12 mmol). Purification: Combi-Flash. Eluent: Ethyl acetate and petroleum ether (50:50) as eluent. Appearance: Pale-brown solid (1.30 g). Yield: 44%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 9.80 (s, 1H), 7.44 (m, 2H), 7.26-7.16 (m, 2H), 6.81 (dt, J 5.6,1.6, 1H), 4.74 (dt, J 12.8,5.2, 1H), 3.65 (dd, J 17.2,6.4, 1H), 3.46 (dd, J 12.8,7.6, 1H), 2.92 (dd, J 16.8,5.6, 1H), 2.56 (m, 1H), 2.33 (m, 1H), 1.34 (s, 9H). MS (m/z): 220.15 [M-Boc]⁺.

Intermediate 19: 5-glycyl-1,3,4,5-tetrahydro-2H-benzo[b][1,4]diazepin-2-one triflate salt



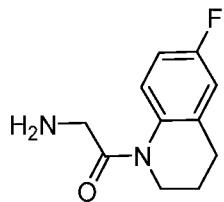
[173] Following the general procedure 2, the titled compound was synthesized from Intermediate 18 (0.80 g, 2.51 mmol), dichloromethane (30 ml) and trifluoroacetic acid (2.86 g, 25.1 mmol). Purification: Not done. Appearance: Brown solid (0.60 g). Yield: 70%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 9.86 (s, 1H), 7.99 (s, 3H), 7.49-7.44 (m, 2H), 7.28-7.20 (m, 2H), 4.77 (dt, J 13.2,5.2, 1H), 3.72 (d, J 12.4, 1H), 3.57 (dd, J 6.8,4.8, 1H), 2.87 (d, J 12.4, 1H), 2.66 (dt, J 13.6,6.8, 1H), 2.36 (m, 1H). MS (m/z): 220.14 ([M+H]⁺).

Intermediate 20: **tert-butyl (2-(6-fluoro-3,4-dihydroquinolin-1(2H)-yl)-2-oxoethyl)carbamate**



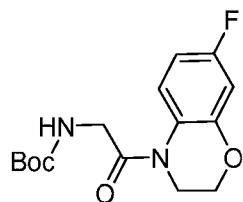
[174] Following the general procedure 1, the titled compound was synthesized from 6-fluoro-1,2,3,4-tetrahydroquinoline (500 mg, 3.31 mmol), DMF (10 ml), N-Boc-glycine (724 mg, 4.17 mmol), HBTU (1.25 g, 3.31 mmol) and N-Diisopropylethylamine (427 mg, 3.31 mmol). Purification: Combi-Flash. Eluent: Ethyl acetate and petroleum ether (30:70) as eluent. Appearance: Pale-brown solid (0.50 g). Yield: 50%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 7.58 (s, 1H), 7.06 (m, 2H), 6.89 (t, J 5.6, 1H), 3.89 (d, J 5.2, 2H), 3.66 (t, J 6.4, 2H), 2.73 (t, J 6.8, 2H), 1.89 (m, 2H), 1.37 (s, 9H). MS (m/z): 209.17 [M-Boc]⁺.

Intermediate 21: 2-amino-1-(6-fluoro-3,4-dihydroquinolin-1(2H)-yl)ethan-1-one



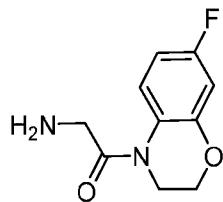
[175] Following the general procedure 2, the titled compound was synthesized from Intermediate 20 (0.50 g, 1.62 mmol), dichloromethane (5 ml) and trifluoroacetic acid (1.85 g, 16.2 mmol). Purification: Not done. Appearance: Pale-yellow solid (0.30 g). Yield: 88%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 7.58 (s, 1H), 7.05-6.96 (m, 2H), 3.64 (t, J 6.0, 2H), 3.44 (s, 2H), 2.72 (t, J 6.4, 2H), 1.88-1.79 (m, 4H). MS (m/z): 209.18 ([M+H]⁺).

Intermediate 22: **tert-butyl (2-(7-fluoro-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)-2-oxoethyl)carbamate**



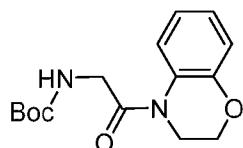
[176] Following the general procedure 1, the titled compound was synthesized from 7-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazine (0.50 g, 3.26 mmol), Dichloromethane (10 ml), N-Boc-glycine (629 mg, 3.59 mmol), triethylamine (1.32 g, 13.1 mmol) and T₃P (Propyl phosphonic anhydride) (2.60 g, 8.16 mmol). Purification: Not done. Appearance: Colourless liquid (1.00 g). Yield: 98%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 7.89 (s, 1H), 6.98 (t, J 6.0, 1H), 6.80 (m, 2H), 4.27 (d, J 4.0, 2H), 3.99 (d, J 6.0, 2H), 3.85 (t, J 4.8, 2H), 1.38 (s, 9H). MS (m/z): 211.14 [M-Boc]⁺.

Intermediate 23: **2-amino-1-(7-fluoro-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)ethan-1-one**



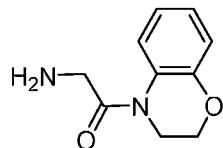
[177] Following the general procedure 2, the titled compound was synthesized from Intermediate 22 (1.00 g, 3.22 mmol), dichloromethane (9 ml) and trifluoroacetic acid (3.67 g, 32.22 mmol). Purification: Not done. Appearance: Pale-brown solid (0.40 g). Yield: 59%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 7.95 (s, 1H), 6.79-6.70 (m, 2H), 4.28 (t, J 4.4, 2H), 3.81 (t, J, 4.4, 2H), 3.52 (s, 2H), 1.69 (s, 2H). MS (m/z): 211.13 ([M+H]⁺).

Intermediate 24: tert-butyl (2-(2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)-2-oxoethyl)carbamate



[178] Following the general procedure 1, the titled compound was synthesized from 3,4-dihydro-2H-benzo[b][1,4]oxazine (1.00 g, 7.40 mmol), dichloromethane (10 ml), N-Boc-glycine (1.42 g, 8.10 mmol), triethylamine (3.0 g, 30 mmol) and T₃P (Propyl phosphonic anhydride) (5.90 g, 18 mmol). Purification: Not done. Appearance: Yellow liquid (1.60 g). Yield: 74%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 7.79 (s, 1H), 7.06 (t, J 7.6, 1H), 6.97 (t, J 5.6, 1H), 6.92 (m, 2H), 4.25 (t, J 5.2, 2H), 4.00 (d, J 6.0, 2H), 3.85 (t, J 4.8, 2H), 1.38 (s, 9H). MS (m/z): 193.11 [M-Boc]⁺.

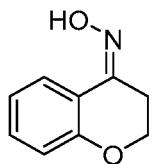
Intermediate 25: 2-amino-1-(2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)ethan-1-one



[179] Following the general procedure 2, the titled compound was synthesized from Intermediate 24 (1.60 g, 5.47 mmol), dichloromethane (10 ml) and trifluoroacetic acid (5.36 g,

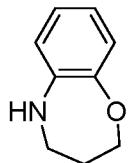
54.7 mmol). Purification: Not done. Appearance: Brown liquid (0.60 g). Yield: 60%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 7.82 (s, 1H), 7.05 (t, J 6.8, 1H), 6.92 (m, 2H), 4.25 (t, J 4.4, 2H), 3.82 (t, J 4.4, 2H), 3.56 (s, 2H), 3.26 (m, 2H). MS (m/z): 193.11 ([M+H]⁺).

Intermediate 26: Chroman-4-one oxime



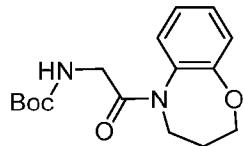
[180] To chroman-4-one (5.0 g, 34 mmol) in pyridine (25 ml), hydroxylamine hydrochloride (2.4 g, 34 mmol) was added at 25°C. After 1h, the reaction mixture was diluted with water (50 ml) and extracted with ethyl acetate (2 x 100 ml). The organic layer was washed with brine solution (3 x 30 ml), dried with anhydrous sodium sulphate and distilled out to obtain the titled compound as an off-white solid (3.5 g). Yield: 64%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 11.22 (s, 1H), 7.79 (dd, J 7.6, 1.6, 1H), 7.27 (m, 1H), 6.96-6.87 (m, 2H), 4.19 (t, J 6.0, 2H), 2.84 (t, J 6.4, 2H). MS (m/z): 164.10 [M+H]⁺.

Intermediate 27: 2,3,4,5-tetrahydrobenzo[b][1,4]oxazepine



[181] To intermediate 26 (2.50 g, 15 mmol) in dichloromethane (25 ml) cooled to 0°C, DIBAL-H (1M in toluene, 45 ml, 46 mmol) was added at 0°C. After 16h at room temperature, the reaction mixture was diluted with ethyl acetate (100 ml) and filtered through celite bed and washed with ethyl acetate (50 ml). The organic layer was washed with brine solution (50 ml), dried with anhydrous sodium sulphate and distilled out to obtain the titled compound as a red colour liquid (1.0 g). Yield: 44%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 6.80-6.74 (m, 3H), 6.62 (m, 1H), 5.33 (s, 1H), 3.97 (m, 2H), 3.08 (dt, J 5.6, 3.2, 2H), 1.87 (m, 2H). MS (m/z): 150.10 [M+H]⁺.

Intermediate 28: tert-butyl (2-(3,4-dihydrobenzo[b][1,4]oxazepin-5(2H)-yl)-2-oxoethyl)carbamate



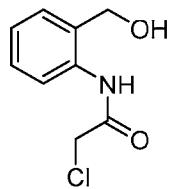
[182] Following the general procedure 1, the titled compound was synthesized from intermediate 27 (1.00 g, 6.70 mmol), dichloromethane (10 ml), N-Boc-glycine (1.30 g, 7.4 mmol), triethylamine (2.70 g, 27 mmol) and T₃P (Propyl phosphonic anhydride) (5.72 g, 18 mmol). Purification: Not done. Appearance: Colourless liquid (1.20 g). Yield: 58%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 7.38-7.29 (m, 2H), 7.15 (m, 2H), 6.78 (t, J 6.0, 1H), 4.57 (m, 1H), 4.37 (m, 1H), 3.77 (m, 2H), 3.08 (d, J 12.8, 1H), 2.81 (t, J 10.8, 1H), 1.43 (m, 2H), 1.36 (s, 9H). MS (m/z): 207.12 [M-Boc]⁺.

Intermediate 29: 2-amino-1-(3,4-dihydrobenzo[b][1,4]oxazepin-5(2H)-yl)ethan-1-one



[183] Following the general procedure 2, the titled compound was synthesized from Intermediate 28 (1.20 g, 3.92 mmol), dichloromethane (10 ml) and trifluoroacetic acid (3.84 g, 39.2 mmol). Purification: Not done. Appearance: Brown liquid (0.35 g). Yield: 43%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 7.39-7.25 (m, 2H), 7.13 (m, 2H), 4.60 (d, J 10.0, 1H), 4.37 (t, J 7.2, 1H), 3.66 (m, 1H), 3.31 (m, 1H), 2.76 (m, 2H), 1.99 (m, 2H), 1.85-1.77 (m, 2H). MS (m/z): 207.14 ([M+H]⁺).

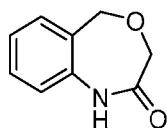
Intermediate 30: 2-chloro-N-(2-(hydroxymethyl)phenyl)acetamide



[184] To 2-aminobenzyl alcohol (5.0 g, 40.60 mmol) in THF (70 ml), triethylamine (4.10 g, 40.60 mmol) was added and cooled to 0°C. Chloroacetyl chloride (4.58 g, 40.60 mmol) was

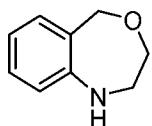
added at 0°C and stirred at 25°C for 12h. After 12h, diluted with water (50 ml) and extracted with ethyl acetate (3 x 30 ml). The organic layer was dried with anhydrous sodium sulphate and distilled out to obtain the crude. Crude was purified by combi-flash using ethyl acetate and petroleum ether (19:81) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as an off-white solid (5.0 g). Yield: 50%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 9.81 (s, 1H), 7.61 (d, J 8.0, 1H), 7.41 (dd, J 7.6,1.2, 1H), 7.28 (dt, J 7.6,1.6, 1H), 7.19 (dt, J 7.6,1.2, 1H), 5.44 (t, J 5.6, 1H), 4.52 (d, J 5.2, 2H), 4.33 (s, 2H). MS (m/z): 222.10 ([M+Na⁺]).

Intermediate 31: 1,5-dihydrobenzo[e][1,4]oxazepin-2(3H)-one



[185] To intermediate 30 (3.0 g, 15.03 mmol) in ethanol (20 ml) cooled to 0°C, 21% sodium ethoxide solution in ethanol (6.6 ml, 30.06 mmol) was added and heated to 90°C. After 24h, the reaction mixture was cooled to 0°C, diluted with water (15 ml) and extracted with ethyl acetate (3 x 50 ml). The organic layer was dried with anhydrous sodium sulphate and distilled out to obtain the crude. Crude was purified by combi-flash using ethyl acetate and petroleum ether (20:80) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as a pale-brown solid (1.0 g). Yield: 40%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 10.18 (s, 1H), 7.25 (dt, J 8.0,1.6, 1H), 7.17-7.11 (m, 2H), 7.00 (dt, J 7.2,1.2, 1H), 4.69 (s, 2H), 4.29 (s, 2H). MS (m/z): 164.12 ([M+H⁺]).

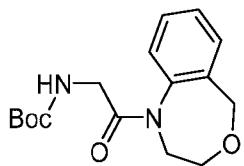
Intermediate 32: 1,2,3,5-tetrahydrobenzo[e][1,4]oxazepine



[186] To intermediate 31 (1.0 g, 6.13 mmol) in THF (50 ml) cooled to 0°C, Lithium aluminium hydride (233 mg, 6.13 mmol) was added and then heated to 80°C. After 4h, the reaction mixture was cooled to 0°C, 0.6 ml water was added slowly followed by 15% NaOH solution (0.6 ml) and

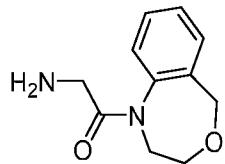
water (2 ml), diluted with water (15 ml) and extracted with ethyl acetate (3 x 50 ml). The reaction mixture was filtered through cealite bed and washed with ethyl acetate (100 ml). The filtrate was distilled out to obtain the crude. Crude was purified by combi-flash using ethyl acetate and petroleum ether (10:90) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as an off-white solid (0.70 g). Yield: 76%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 7.09-7.03 (m, 2H), 6.88 (dd, J 8.0,1.2, 1H), 6.72 (dt, J 7.2,1.2, 1H), 5.66 (s, 1H), 4.44 (s, 2H), 3.68 (m, 2H), 3.00 (m, 2H). MS (m/z): 150.04 ([M+H⁺]).

Intermediate 33: tert-butyl (2-(2,3-dihydrobenzo[e][1,4]oxazepin-1(5H)-yl)-2-oxoethyl)carbamate



[187] Following the general procedure 1, the titled compound was synthesized from intermediate 32 (500 mg, 3.35 mmol), ethyl acetate (10 ml), N-Boc-glycine (646 mg, 3.39 mmol), pyridine (1.06 g, 13.4 mmol) and T₃P (Propyl phosphonic anhydride) (2.67 g, 8.38 mmol). Purification: Combi-Flash. Eluent: Ethyl acetate and petroleum ether (30:70) as eluent. Appearance: Off-white gummy solid (0.70 g). Yield: 68%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 7.46-7.32 (m, 4H), 6.85 (t, J 5.6, 1H), 4.64 (d, J 13.2, 1H), 4.54 (m, 2H), 3.96 (d, J 12.4, 1H), 3.77 (dd, J 16.8,6.0, 1H), 3.62 (t, J 11.2, 1H), 3.24 (dd, J 16.8,6.0, 1H), 2.82 (t, J 12.0, 1H), 1.35 (s, 9H). MS (m/z): 207.13 [M-Boc]⁺.

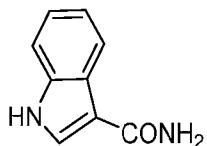
Intermediate 34: 2-amino-1-(2,3-dihydrobenzo[e][1,4]oxazepin-1(5H)-yl)ethan-1-one



[188] Following the general procedure 2, the titled compound was synthesized from Intermediate 33 (700 mg, 2.28 mmol), dichloromethane (7 ml) and trifluoroacetic acid 2.61 g, 22.8 mmol). Purification: Not done. Appearance: Pale-yellow gummy liquid (0.30 g). Yield:

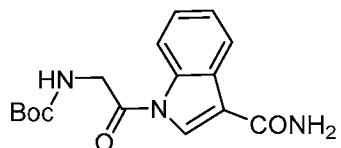
63%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 7.44-7.29 (m, 4H), 4.62-4.46 (m, 3H), 3.96 (d, J 12.0, 1H), 3.64 (t, J 11.6, 1H), 3.39 (d, J 16.8, 1H), 2.81 (m, 2H), 1.82 (s, 2H). MS (m/z): 207.14 ([M+H]⁺).

Intermediate 35: 1H-indole-3-carboxamide



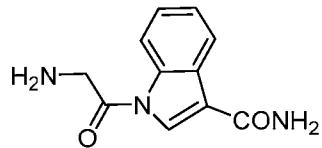
[189] To 3-cyanoindole (2.0 g, 14.0 mmol) in ethanol (10 ml), 30% H₂O₂ solution (11 ml) and 40% NaOH solution (5 ml) were added and stirred at 25°C for 2h. After 2h, the reaction mass diluted with water (20 ml). The aqueous layer was extracted with 10% methanol in dichloromethane (2 x 25 ml), dried with anhydrous sodium sulphate and the solvent was distilled out to obtain the titled compound as a brown solid (1.0 g). Yield: 40%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 11.49 (s, 1H), 8.14 (m, 1H), 8.00 (s, 1H), 7.41 (m, 1H), 7.30 (s, 1H), 7.15-7.05 (m, 2H), 6.80 (s, 1H). MS (m/z): 161.09 ([M+H]⁺).

Intermediate 36: tert-butyl (2-(3-carbamoyl-1H-indol-1-yl)-2-oxoethyl)carbamate



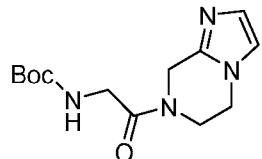
[190] Following the general procedure 1, the titled compound was synthesized from intermediate 35 (500 mg, 3.12 mmol), DMF (10 ml), N-Boc-glycine (602 mg, 3.43 mmol), HBTU (1.77 g, 4.68 mmol) and N-Diisopropylethylamine (1.21 g, 9.36 mmol). Purification: Combi-Flash. Eluent: Ethyl acetate and petroleum ether (70:30) as eluent. Appearance: Off-white solid (0.60 g). Yield: 60%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 8.61 (s, 1H), 8.33 (d, J 7.6, 1H), 8.21 (m, 1H), 7.67 (s, 1H), 7.40-7.24 (m, 4H), 4.48 (d, J 6.0, 2H), 1.42 (s, 9H). MS (m/z): 218.19 [M-Boc]⁺.

Intermediate 37: 1-glycyl-1H-indole-3-carboxamide



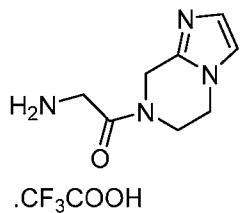
[191] Following the general procedure 2, the titled compound was synthesized from Intermediate 36(600 mg, 2.0 mmol), dichloromethane (10 ml) and trifluoroacetic acid (2.0 g, 20.0 mmol). Purification: Not done. Appearance: Off-white solid (0.30 g). Yield: 70%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 8.54 (s, 3H), 8.34 (d, J 8.0, 1H), 8.24 (m, 1H), 7.76 (s, 1H), 7.46-7.33 (m, 3H), 4.58 (s, 2H). MS (m/z): 218.13 [M+H]⁺.

Intermediate 38: tert-butyl (2-(5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl)-2-oxoethyl)carbamate



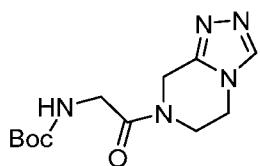
[192] Following the general procedure 1, the titled compound was synthesized from 5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine (1.0 g, 8.12 mmol), ethyl acetate (20 ml), N-Boc-glycine (1.56 g, 8.93 mmol), pyridine (2.57 g, 32.48 mmol) and T₃P (Propyl phosphonic anhydride) (6.45 g, 20.3 mmol). Purification: Combi-Flash. Eluent: Methanol and dichloromethane (4:96) as eluent. Appearance: Colourless gummy solid (1.40 g). Yield: 61%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 7.11 (d, J 1.2, 1H), 6.89 (m, 2H), 4.69 (s, 1H), 4.60 (s, 1H), 4.04-3.86 (m, 6H), 1.38 (s, 9H). MS (m/z): 281.12 [M+H]⁺.

Intermediate 39: 2-amino-1-(5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl)ethan-1-one trifluoroacetic acid salt



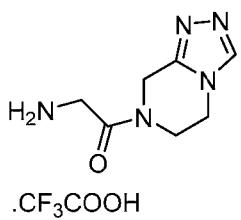
[193] Following the general procedure 2, the titled compound was synthesized from Intermediate 38 (700 mg, 2.5 mmol), dichloromethane (10 ml) and trifluoroacetic acid (2.85 g, 25.0 mmol). Purification: Not done. Appearance: Pale-brown gummy solid (1.10 g). Yield: >100% (crude). ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 8.21 (s, 2H), 7.69 (m, 2H), 4.96 (s, 2H), 4.28 (t, J 5.2, 1H), 4.14 (t, J 5.2, 1H), 4.03-3.91 (m, 4H). MS (m/z): 181.14 [M+H]⁺.

Intermediate 40: tert-butyl (2-(5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)-2-oxoethyl)carbamate



[194] Following the general procedure 1, the titled compound was synthesized from 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine (500 mg, 4.03 mmol), ethyl acetate (10 ml), N-Boc-glycine (776 mg, 4.43 mmol), pyridine (1.27 g, 16.1 mmol) and T₃P (Propyl phosphonic anhydride) (3.20 g, 10.1 mmol). Purification: Combi-Flash. Eluent: Methanol and dichloromethane (15:85) as eluent. Appearance: Off-white gummy solid (0.50 g). Yield: 40%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 8.48 (s, 1H), 6.90 (t, J 6.0, 1H), 4.86 (s, 1H), 4.76 (s, 1H), 4.12-3.85 (m, 6H), 1.38 (s, 9H). MS (m/z): 282.12 [M+H]⁺.

Intermediate 41: 2-amino-1-(5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)ethan-1-one trifluoroacetic acid salt



[195] Following the general procedure 2, the titled compound was synthesized from Intermediate 40 (500 mg, 1.78 mmol), dichloromethane (5 ml) and trifluoroacetic acid (2.03 g, 17.8 mmol). Purification: Not done. Appearance: off-white gummy solid (0.80 g). Yield:

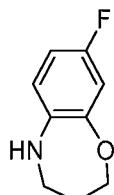
>100% (crude). ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 8.72 (d, J 2.8, 1H), 8.14 (s, 2H), 4.89 (t, J 5.6, 2H), 4.22 (t, J 4.8, 1H), 4.10-3.94 (m, 4H), 3.86 (t, J 5.2, 1H). MS (m/z): 182.17 [M+H]⁺.

Intermediate 42: 7-fluorochroman-4-one oxime



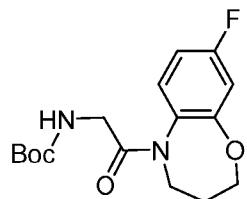
[196] To 7-Fluorochroman-4-one (2.0 g, 12 mmol) in pyridine (25 ml), hydroxylamine hydrochloride (1.7 g, 24 mmol) was added at 25°C. After 1h, the reaction mixture was diluted with water (50 ml) and extracted with ethyl acetate (2 x 100 ml). The organic layer was washed with brine solution (3 x 30 ml), dried with anhydrous sodium sulphate and distilled out to obtain the titled compound as an off-white solid (1.50 g). Yield: 69%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 11.23 (s, 1H), 7.82 (dd, J 8.8, 6.8, 1H), 6.83-6.76 (m, 2H), 4.22 (t, J 6.0, 2H), 2.84 (t, J 6.0, 2H). MS (m/z): 182.12 [M+H]⁺.

Intermediate 43: 8-Fluoro-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepine



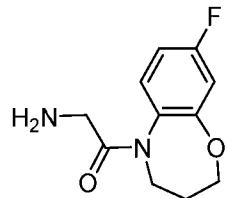
[197] To intermediate 42 (1.50 g, 8.30 mmol) in dichloromethane (30 ml) cooled to 0°C, DIBAL-H (1M in toluene, 50 ml, 50 mmol) was added at 0°C. After 2h at room temperature, the reaction mixture was cooled to 0°C, sodium fluoride (9.70 g, 232 mmol) and water (5 ml) were added slowly and stirred for 30 min. The reaction mixture was diluted with ethyl acetate (100 ml) and filtered through cealite bed and washed with ethyl acetate (50 ml). The organic layer was washed with brine solution (50 ml), dried with anhydrous sodium sulphate, distilled out the solvent and the residue were washed with pentane to obtain the titled compound as an off-white solid (0.520 g). Yield: 44%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 6.81-6.77 (m, 1H), 6.67-6.61 (m, 2H), 5.31 (s, 1H), 3.99 (m, 2H), 3.04 (m, 2H), 1.87 (m, 2H). MS (m/z): 168.08 [M+H]⁺.

Intermediate 44: tert-butyl (2-(8-fluoro-3,4-dihydrobenzo[b][1,4]oxazepin-5(2H)-yl)-2-oxoethyl)carbamate



[198] Following the general procedure 1, the titled compound was synthesized from intermediate 43 (0.50 g, 3.0 mmol), ethyl acetate (10 ml), N-Boc-glycine (0.58 g, 3.3 mmol), pyridine (0.95 g, 12 mmol) and T₃P (Propyl phosphonic anhydride) (2.40 g, 7.5 mmol). Purification: Combi-Flash. Eluent: Ethyl acetate and petroleum ether (20:80) as eluent. Appearance: Brown liquid (0.60 g). Yield: 60%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 7.45-7.40 (m, 1H), 7.02-6.95 (m, 2H), 6.81 (t, J 5.6, 1H), 4.54 (d, J 13.2, 1H), 4.41 (d, J 12.0, 1H), 3.80-3.64 (m, 2H), 3.14 (dd, J 17.2, 6.0, 1H), 2.83 (t, J 12.0, 1H), 2.02 (m, 1H), 1.82 (m, 1H), 1.35 (s, 9H). MS (m/z): 225.17 [M-Boc]⁺.

Intermediate 45: 2-amino-1-(8-fluoro-3,4-dihydrobenzo[b][1,4]oxazepin-5(2H)-yl)ethan-1-one



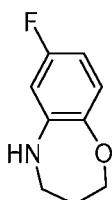
[199] Following the general procedure 2, the titled compound was synthesized from Intermediate 44 (0.45 g, 1.39 mmol), dichloromethane (10 ml) and trifluoroacetic acid (1.58 g, 13.9 mmol). Purification: Not done. Appearance: Off-white solid (0.30 g). Yield: 96%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 7.96 (s, 2H), 7.54 (dd, J 8.4, 6.0, 1H), 7.09-7.07 (m, 2H), 4.58 (d, J 13.2, 1H), 4.44 (d, J 12.4, 1H), 3.83 (t, J 10.8, 2H), 3.17 (m, 1H), 2.93 (t, J 11.2, 1H), 2.08 (m, 1H), 1.89 (m, 1H). MS (m/z): 225.15 ([M+H]⁺).

Intermediate 46: 6-fluorochroman-4-one oxime



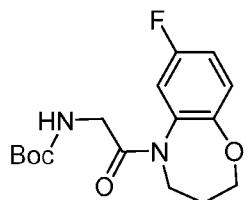
[200] To 6-Fluorochroman-4-one (2.0 g, 12 mmol) in pyridine (25 ml), hydroxylamine hydrochloride (1.7 g, 24 mmol) was added at 25°C. After 1h, the reaction mixture was diluted with water (50 ml) and extracted with ethyl acetate (2 x 100 ml). The organic layer was washed with brine solution (3 x 30 ml), dried with anhydrous sodium sulphate and distilled out to obtain the titled compound as an off-white solid (1.50 g). Yield: 69%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 11.43 (s, 1H), 7.46 (dd, J 9.6, 3.2, 1H), 7.14-7.09 (m, 1H), 6.95 (dd, J 8.8, 4.8, 1H), 4.18 (t, J 6.0, 2H), 2.82 (t, J 6.0, 2H). MS (m/z): 182.11 [M+H]⁺.

Intermediate 47: 7-Fluoro-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepine



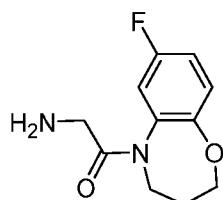
[201] To intermediate 46 (1.50 g, 8.28 mmol) in dichloromethane (30 ml) cooled to 0°C, DIBAL-H (1M in Toluene, 55 ml, 55 mmol) was added at 0°C. After 2h at room temperature, the reaction mixture was cooled to 0°C, sodium fluoride (9.73 g, 232 mmol) and water (5 ml) were added slowly and stirred for 30 min. The reaction mixture was diluted with ethyl acetate (100 ml) and filtered through cealite bed and washed with ethyl acetate (50 ml). The organic layer was washed with brine solution (50 ml), dried with anhydrous sodium sulphate, distilled out the solvent and the residue were washed with pentane to obtain the titled compound as an off-white solid (0.68 g). Yield: 49%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 6.79 (dd, J 8.4, 5.6, 1H), 6.59 (dd, J 10.8, 2.8, 1H), 6.38 (m, 1H), 5.62 (s, 1H), 3.96 (m, 2H), 3.12-3.08 (m, 2H), 1.88 (quintet, J 5.6, 2H). MS (m/z): 168.08 [M+H]⁺.

Intermediate 48: tert-butyl (2-(7-fluoro-3,4-dihydrobenzo[b][1,4]oxazepin-5(2H)-yl)-2-oxoethyl)carbamate

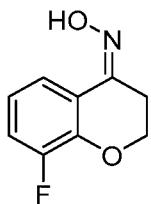


[202] Following the general procedure 1, the titled compound was synthesized from intermediate 47(0.50 g, 3.0 mmol), ethyl acetate (10 ml), N-Boc-glycine (0.58 g, 3.3 mmol), pyridine (0.95 g, 12 mmol) and T₃P (Propyl phosphonic anhydride) (2.4 g, 7.5 mmol). Purification: Combi-Flash. Eluent: Ethyl acetate and petroleum ether (20:80) as eluent. Appearance: Brown liquid (0.40 g). Yield: 40%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 7.40 (m, 1H), 7.17-7.10 (m, 2H), 6.83 (t, J 5.2, 1H), 4.54 (br s, 1H), 4.35 (br s, 1H), 3.79-3.67 (m, 2H), 3.17 (m, 1H), 2.80 (m, 1H), 1.98 (m, 1H), 1.81 (d, J 11.6, 1H), 1.35 (s, 9H). MS (m/z): 225.15 [M-Boc]⁺.

Intermediate 49: 2-amino-1-(7-fluoro-3,4-dihydrobenzo[b][1,4]oxazepin-5(2H)-yl)ethan-1-one

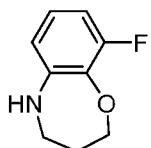


Intermediate 50: 8-fluorochroman-4-one oxime



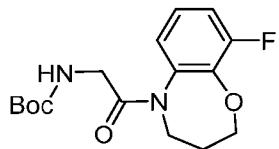
[204] To 8-Fluorochroman-4-one (1.0 g, 6 mmol) in pyridine (12.5 ml), hydroxylamine hydrochloride (418 mg, 6 mmol) was added at 25°C. After 2h, the reaction mixture was diluted with water (50 ml) and extracted with ethyl acetate (2 x 100 ml). The organic layer was washed with brine solution (3 x 30 ml), dried with anhydrous sodium sulphate and distilled out to obtain the crude. Crude was purified by combi-flash using ethyl acetate and petroleum ether (8.5:91.5) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as an off-white solid (0.92 g). Yield: 84%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 11.42 (s, 1H), 7.60 (td, J 8.0,1.2, 1H), 7.29 (m, 1H), 6.94 (dt, J 8.0,5.2, 1H), 4.28 (t, J 6.0, 2H), 2.88(t, J 6.0, 2H). MS (m/z): 182.15 [M+H]⁺.

Intermediate 51: 9-Fluoro-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepine



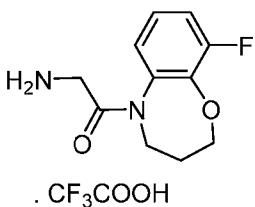
[205] To intermediate 50(900 mg, 4.96 mmol) in dichloromethane (60 ml) cooled to 0°C, DIBAL-H (1M in toluene, 29.8 ml, 29.8 mmol) was added at 0°C. After 2h at room temperature, the reaction mixture was cooled to 0°C, sodium fluoride (5.84 g, 139 mmol) and water (5 ml) were added slowly and stirred for 30 min. The reaction mixture was diluted with ethyl acetate (100 ml) and filtered through cealite bed and washed with ethyl acetate (50 ml). The organic layer was washed with brine solution (50 ml), dried with anhydrous sodium sulphate, distilled out to obtain the crude. Crude was purified by combi-flash using ethyl acetate and petroleum ether (12:88) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as an off-white solid (0.60 g). Yield: 70%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 6.75 (dt, J 8.4,6.0, 1H), 6.60 (td, J 8.4,1.6, 1H), 6.53 (m, 1H), 5.64 (s, 1H), 4.03 (m, 2H), 3.12 (m, 2H), 1.91 (quintet, J 5.6, 2H). MS (m/z): 168.10 [M+H]⁺.

Intermediate 52: tert-butyl (2-(9-fluoro-3,4-dihydrobenzo[b][1,4]oxazepin-5(2H)-yl)-2-oxoethyl)carbamate



[206] Following the general procedure 1, the titled compound was synthesized from intermediate 51(0.50 g, 3.0 mmol), ethyl acetate (10 ml), N-Boc-glycine (0.58 g, 3.3 mmol), pyridine (0.95 g, 12 mmol) and T₃P (Propyl phosphonic anhydride) (2.40 g, 7.5 mmol). Purification: Combi-Flash. Eluent: Ethyl acetate and petroleum ether (30:70) as eluent. Appearance: colourless semi solid (0.60 g). Yield: 62%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 7.31-7.23 (m, 2H), 7.15-7.09 (m, 1H), 6.82 (t, J 5.6, 1H), 4.58-4.45 (m, 2H), 3.77 (m, 2H), 3.16 (d, J 13.6, 1H), 2.82 (m, 1H), 2.02-1.80 (m, 2H), 1.35 (s, 9H). MS (m/z): 225.14 [M-Boc]⁺.

Intermediate 53: 2-amino-1-(9-fluoro-3,4-dihydrobenzo[b][1,4]oxazepin-5(2H)-yl)ethan-1-one trifluoroacetic acid salt



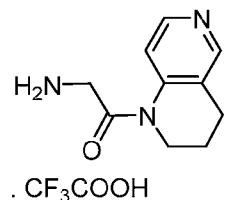
[207] Following the general procedure 2, the titled compound was synthesized from intermediate 52 (0.60 g, 1.85 mmol), dichloromethane (6 ml) and trifluoroacetic acid (2.11 g, 18.5 mmol). Purification: Not done. Appearance: Off-white solid (0.45 g). Yield: 71%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 8.03 (s, 2H), 7.37-7.30 (m, 2H), 7.19 (m, 1H), 4.61-4.48 (m, 2H), 3.89-3.71 (m, 2H), 3.24 (d, J 15.6, 1H), 2.93 (t, J 10.4, 1H), 2.06-1.90 (m, 2H). MS (m/z): 225.12 ([M+H]⁺).

Intermediate 54: tert-butyl (2-(3,4-dihydro-1,6-naphthyridin-1(2H)-yl)-2-oxoethyl)carbamate



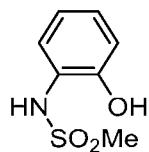
[208] Following the general procedure 1, the titled compound was synthesized from 1,2,3,4-Tetrahydro-1,6-naphthyridine (0.50 g, 3.73 mmol), acetonitrile (15 ml), N-Boc-glycine (0.718 g, 4.10 mmol), EDC-HCl (0.857 g, 4.47 mmol), HOBr (0.742 g, 4.84 mmol) and 4-Methylmorpholine (0.942 g, 9.32 mmol). Purification: Combi-Flash. Eluent: Methanol and dichloromethane (4:96) as eluent. Appearance: Pale-brown solid (0.12 g). Yield: 11%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 8.31 (s, 1H), 8.27 (d, J 5.6, 1H), 7.89 (d, J 5.6, 1H), 7.00 (t, J 5.6, 1H), 4.01 (d, J 6.0, 2H), 3.74 (t, J 6.0, 2H), 2.74 (t, J 6.4, 2H), 1.92 (m, 2H), 1.39 (s, 9H). MS (m/z): 292.21 ([M+H]⁺).

Intermediate 55: 2-amino-1-(3,4-dihydro-1,6-naphthyridin-1(2H)-yl)ethan-1-one trifluoroacetic acid salt



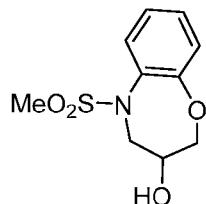
[209] Following the general procedure 2, the titled compound was synthesized from Intermediate 54 (100 mg, 0.343 mmol), dichloromethane (6 ml) and trifluoroacetic acid (391 mg, 3.43 mmol). Purification: Not done. Appearance: Pale-brown solid (0.10 g). Yield: 95%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 8.64 (s, 1H), 8.57 (d, J 6.0, 1H), 8.42 (d, J 5.6, 1H), 8.31 (s, 2H), 4.23 (s, 2H), 3.84 (t, J 5.6, 2H), 2.86 (t, J 5.6, 2H), 1.99 (t, J 5.6, 2H). MS (m/z): 192.14 ([M+H]⁺).

Intermediate 56: N-(2-hydroxyphenyl)methanesulfonamide



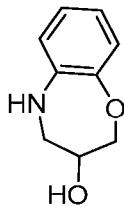
[210] 2-aminophenol (10 g, 91.6 mmol) and Pyridine (21.7 g, 275 mmol) were dissolved in dichloromethane (85 ml) and cooled to 0°C. Methane sulfonyl chloride (10.5 g, 91.63 mmol) was added at 0°C and stirred at 25°C for 1h. After h, the reaction mass was distilled out, diluted with ethyl acetate (150 ml) and pH adjusted to 1 with 2M HCl. The organic layer was washed with water (50 ml), brine solution (2 x 50 ml) distilled out to obtain crude. Crude was stirred with Di isopropyl ether (50 ml) for 30 min., filtered and dried under vacuum to obtain the titled compound as a brown solid (10.5 g). Yield: 61%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 9.78 (s, 1H), 8.72 (s, 1H), 7.19 (dd, J 8.0,1.6, 1H), 7.06 (m, 1H), 6.89 (dd, J 8.0,1.2, 1H), 6.79 (dt, J 7.6,1.6, 1H), 2.93 (s, 3H). MS (m/z): 186.19 ([M-H]⁺).

Intermediate 57: 5-(methylsulfonyl)-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-ol



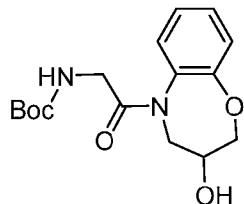
[211] Intermediate 56 (5 g, 26.7 mmol) was dissolved in ethanol (43 ml) and cooled to 0°C. sodium ethoxide solution (21% in ethanol, 10.45 ml, 30.7 mmol) was added at 0°C and stirred at 25°C for 30 min. The reaction mass was distilled out and co-distilled with THF (11 ml). To the residue, DMF (40 ml) and epichlorohydrin (2.47 g, 26.7mmol) were added and heated to 90°C. After 12h, the reaction mass was cooled to 25°C, diluted with water (100 ml) and extracted with ethyl acetate (4 x 50 ml). The organic layer was washed with water (2 x 50 ml), brine solution (2 x 50 ml) distilled out to obtain crude. Crude was purified by combi-flash using ethyl acetate and petroleum ether (36:64) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as a brown gummy liquid (5.0 g). Yield: 77%. MS (m/z): 243.99 ([M]⁺).

Intermediate 58: 2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-ol



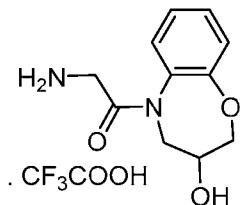
[212] Intermediate 57 (5 g, 20.5 mmol) was dissolved in toluene (100 ml) and cooled to 0°C. bis(2-methoxyethoxy) aluminium (III) sodium hydride solution (60% in toluene, 20 ml, 61.6 mmol) was added at 0°C and heated to 85°C. After 24h, the reaction mass was cooled to 0°C, quenched with saturated sodium bicarbonate solution and extracted with ethyl acetate (3 x 50 ml). The organic layer was distilled out to obtain crude. Crude was purified by combi-flash using ethyl acetate and petroleum ether (20:80) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as a pale-brown solid (0.45 g). Yield: 13%. MS (m/z): ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 6.75-6.67 (m, 3H), 6.57-6.53 (m, 1H), 5.32 (d, J 2.4, 1H), 4.96 (d, J 5.2, 1H), 4.20 (dd, J 12.0, 4.0, 1H), 3.89-3.77 (m, 2H), 3.29 (m, 1H), 3.04-2.98 (m, 1H). MS (m/z): 166.10 ([M+H]⁺).

Intermediate 59: tert-butyl (2-(3-hydroxy-3,4-dihydrobenzo[b][1,4]oxazepin-5(2H)-yl)-2-oxoethyl)carbamate



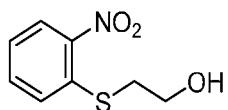
[213] Following the general procedure 1, the titled compound was synthesized from intermediate 58 (0.40 g, 2.42 mmol), DMF (4 ml), N-Boc-glycine (0.424 g, 2.42 mmol), HATU (1.01 g, 2.66 mmol) and Pyridine (0.211 g, 2.66 mmol). Purification: Combi-Flash. Eluent: Ethyl acetate and petroleum ether (40:60) as eluent. Appearance: Pale brown liquid (0.120 g). Yield: 15%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 7.39 (d, J 7.2, 1H), 7.33 (t, J 7.2, 1H), 7.14 (m, 2H), 6.81 (s, 1H), 5.36 (s, 1H), 4.62 (d, J 10.0, 1H), 4.34 (d, J 10.4, 1H), 3.85-3.62 (m, 3H), 3.40 (m, 1H), 3.14 (d, J 12.8, 1H), 1.37 (s, 9H). MS (m/z): 223.16 [M-Boc]⁺.

Intermediate 60: 2-amino-1-(3-hydroxy-3,4-dihydrobenzo[b][1,4]oxazepin-5(2H)-yl)ethan-1-one trifluoroacetic acid salt



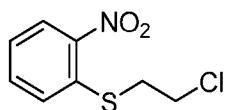
[214] Following the general procedure 2, the titled compound was synthesized from Intermediate 59(120 mg, 0.372 mmol), dichloromethane (6 ml) and trifluoroacetic acid (424 mg, 3.72 mmol). Purification: Not done. Appearance: Pale-brown solid (0.12 g). Yield: 95%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 8.10 (m, 3H), 7.46-7.10 (m, 3H), 4.65-3.61 (m, 5H), 3.44-3.16 (m, 2H), 2.93 (m, 1H). MS (m/z): 223.15 ([M+H]⁺).

Intermediate 61: N-(2-hydroxyphenyl)methanesulfonamide



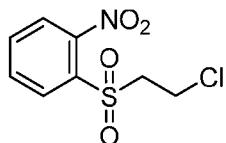
[215] To a solution of 1-fluoro-2-nitrobenzene (10 g, 71 mmol), potassium carbonate (20 g, 142 mmol) in DMF (400 ml), 2-mercaptoethanol (5.5 g, 71 mmol) was added at 25°C and heated to 110°C. After 12h, the reaction mass was cooled to room temperature, diluted with water (500ml) and the aqueous layer was extracted with ethyl acetate (3 x 250 ml). The organic layer was washed with water (2 x 250 ml), brine solution (2 x 250 ml) and the solvents distilled out to obtain the titled compound as a brown gummy solid (8.0 g). Yield: 60%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 8.18 (m, 1H), 7.74-7.66 (m, 2H), 7.42 (m, 1H), 3.68-3.53 (m, 2H), 3.17 (t, J 6.4, 1H), 2.88-2.72 (m, 2H). MS (m/z): 198.46 ([M-H]⁺).

Intermediate 62: (2-chloroethyl)(2-nitrophenyl)sulfane



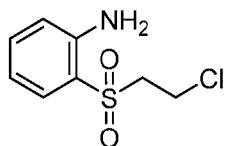
[216] To intermediate 61 (8.0 g, 46.11 mmol) in toluene (50 ml), thionyl chloride (14.33 g, 120.5 mmol) was added below 50°C and heated to 100°C. After 12h, the reaction mass was cooled to room temperature and the solvents distilled out to obtain crude. Crude was purified by combi-flash using ethyl acetate and petroleum ether (5:95) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as a dark yellow liquid (5.0 g). Yield: 60%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 8.20 (dd, J 8.0, 1.6, 1H), 7.76-7.69 (m, 2H), 7.45-7.41 (m, 1H), 3.86 (t, J 7.2, 2H), 3.52 (t, J 7.2, 2H). MS (m/z): 218.20 ([M+H]⁺).

Intermediate 63: 1-((2-chloroethyl)sulfonyl)-2-nitrobenzene



[217] To intermediate 62 (5.0 g, 23 mmol) in acetic acid (50 ml), 30% hydrogen peroxide solution (15 ml, 138 mmol) was added below 50°C and heated to 100°C. After 12h, the reaction mass was cooled to room temperature, quenched with ice cooled water, extracted with dichloromethane (3 x 100 ml) and the solvents distilled out to obtain crude. Crude was purified by combi-flash using ethyl acetate and petroleum ether (20:80) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as a pale-yellow solid (3.0 g). Yield: 50%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 8.17 (dd, J 7.6, 1.6, 1H), 8.14 (dd, J 8.0, 1.6, 1H), 8.05-7.95 (m, 2H), 4.15 (t, J 6.4, 2H), 4.00 (t, J 6.4, 2H).

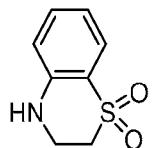
Intermediate 64: 2-((2-chloroethyl)sulfonyl)aniline



[218] To intermediate 63 (3.0 g, 12 mmol) in ethanol (13.5 ml), water (1.5 ml), Iron (2.68 g, 48 mmol) and con. HCl (1.62 ml) were added and heated to 80°C. After 8h, the reaction mass was filtered through cealite, washed with ethanol (30 ml) and concentrated. To the residue, water (50 ml) was added, extracted with ethyl acetate (3 x 50 ml) and the solvents distilled out to obtain crude. Crude was purified by combi-flash using ethyl acetate and petroleum ether (20:80) as

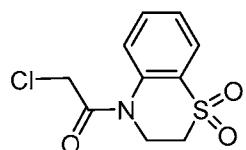
eluent. Combined pure fractions from column were evaporated to obtain the titled compound as a pale-yellow solid (1.5 g). Yield: 57%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 7.51 (dd, J 8.4,1.6, 1H), 7.39 (m, 1H), 6.89 (dd, J 8.4,0.8, 1H), 6.72 (m, 1H), 6.09 (s, 2H), 3.81 (m, 2H), 3.71 (m, 2H). MS (m/z): 220.16 ([M+H]⁺).

Intermediate 65: 3,4-dihydro-2H-benzo[b][1,4]thiazine 1,1-dioxide



[219] To intermediate 64 (1.50 g, 6.82 mmol) in DMF (5 ml), potassium carbonate (2.64 g, 19.1 mmol) was added and heated to 100°C. After 12h, the reaction mass was cooled to room temperature, quenched with water (50 ml), extracted with ethyl acetate (3 x 30 ml). The organic layer was washed with water (3 x 30 ml), brine solution (3 x 30 ml) and the solvents distilled out to obtain crude. Crude was purified by combi-flash using ethyl acetate and petroleum ether (40:60) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as an off-white solid (0.90 g). Yield: 71%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 7.49 (dd, J 7.6,1.2, 1H), 7.28 (m, 1H), 7.01 (s, 1H), 6.75 (dd, J 8.4,0.8, 1H), 6.67 (m, 1H), 3.73 (m, 2H), 3.37 (m, 2H). MS (m/z): 184.15 ([M+H]⁺).

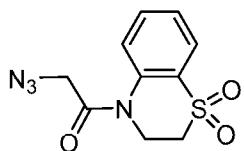
Intermediate 66: 2-chloro-1-(1,1-dioxido-2,3-dihydro-4H-benzo[b][1,4]thiazin-4-yl)ethan-1-one



[220] To intermediate 65 (0.45 g, 2.46 mmol) in dichloromethane (5 ml), triethylamine (497 mg, 4.91 mmol) was added and cooled to 0°C. Chloroacetyl chloride (832 mg, 7.37 mmol) was added at 0°C and stirred at 25°C for 4h. After 4h, quenched with sodium bicarbonate solution (20 ml) and extracted with dichloromethane (3 x 30 ml). The organic layer was dried with anhydrous sodium sulphate and distilled out to obtain the crude. Crude was purified by combi-

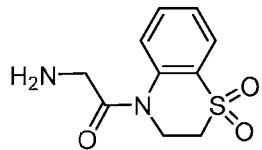
flash using ethyl acetate and petroleum ether (40:60) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as a pale brown liquid (0.50 g). Yield: 80%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 7.87 (dd, J 7.6,1.2, 1H), 7.74 (dd, J 8.4,0.8, 1H), 7.68 (dt, J 7.2,1.2, 1H), 7.52 (dt, J 7.6,0.8, 1H), 4.63 (s, 2H), 4.31 (m, 2H), 3.87 (t, J 6.0, 2H). MS (m/z): 260.07 ([M+H]⁺).

Intermediate 67: 2-azido-1-(1,1-dioxido-2,3-dihydro-4H-benzo[b][1,4]thiazin-4-yl)ethan-1-one



[221] To intermediate 66 (0.50 g, 1.93 mmol) in DMSO (30 ml), sodium azide (0.188 g, 2.9 mmol) was added and stirred at 25°C for 12h. After 12h, the reaction mixture was diluted with water (200 ml) and extracted with dichloromethane (2 x 100 ml). The organic layer was washed with brine solution (3 x 150 ml), dried with anhydrous sodium sulphate and distilled out to obtain crude. Crude was purified by combi-flash using ethyl acetate and petroleum ether (40:60) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as an off-white (0.40 g). Yield: 78%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 7.87 (dd, J 8.0,1.6, 1H), 7.75 (d, J 8.0, 1H), 7.68 (dt, J 7.2,1.6, 1H), 7.51 (dt, J 8.0,1.2, 1H), 4.34 (s, 2H), 4.25 (t, J 6.0, 2H), 3.89 (t, J 6.0, 2H). MS (m/z): 289.21 ([M+Na]⁺).

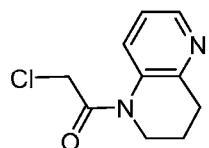
Intermediate 68: 2-amino-1-(1,1-dioxido-2,3-dihydro-4H-benzo[b][1,4]thiazin-4-yl)ethan-1-one



[222] To intermediate 67 (0.40 g, 1.5 mmol) in methanol (14 ml), 5% Pd/C (50% wet, 300mg) was added and stirred at 25°C under hydrogen pressure (30 psi) for 2h. After 2h, filtered through cealite bed, washed with methanol (5 ml) and distilled out to obtain the crude. Crude was

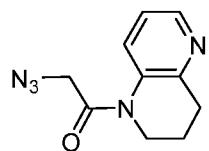
purified by combi-flash using methanol and dichloromethane (25:75) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as a colourless gummy solid (0.13 g). Yield: 36%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 7.85 (dd, J 8.0,1.6, 1H), 7.72 (dd, J 8.4,0.8, 1H), 7.66 (m, 1H), 7.48 (m, 1H), 4.27 (m, 2H), 3.82 (m, 2H), 3.51 (s, 2H), 3.38 (s, 2H). MS (m/z): 241.18 ([M+H]⁺).

Intermediate 69: 2-chloro-1-(3,4-dihydro-1,5-naphthyridin-1(2H)-yl)ethan-1-one



[223] To 1,2,3,4-tetrahydro-1,5-naphthyridine (0.65 g, 4.84 mmol) in dichloromethane (5 ml), triethylamine (1.96 g, 19.4 mmol) was added and cooled to 0°C. Chloroacetyl chloride (1.64 g, 14.5 mmol) was added at 0°C and stirred at 25°C for 4h. After 4h, quenched with sodium bicarbonate solution (20 ml) and extracted with dichloromethane (3 x 30 ml). The organic layer was dried with anhydrous sodium sulphate and distilled out to obtain the crude. Crude was purified by combi-flash using ethyl acetate and petroleum ether (50:50) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as a brown liquid (0.65 g). Yield: 63%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 8.26 (dd, J 4.8,1.2, 1H), 8.06 (s, 1H), 7.23 (dd, J 8.4,4.8, 1H), 4.61 (s, 2H), 3.75 (m, 2H), 2.90 (t, J 6.8, 2H), 2.02 (m, 2H). MS (m/z): 211.20 ([M+H]⁺).

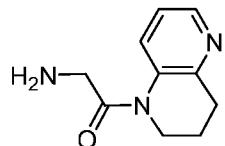
Intermediate 70: 2-azido-1-(3,4-dihydro-1,5-naphthyridin-1(2H)-yl)ethan-1-one



[224] To intermediate 69 (0.65 g, 3.10 mmol) in DMSO (30 ml), sodium azide (0.302 g, 4.65 mmol) was added and stirred at 25°C for 12h. After 12h, the reaction mixture was diluted with water (50 ml) and extracted with dichloromethane (2 x 40 ml). The organic layer was washed with brine solution (3 x 50 ml), dried with anhydrous sodium sulphate and distilled out to obtain crude. Crude was purified by combi-flash using ethyl acetate and petroleum ether (40:60) as

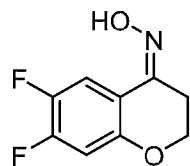
eluent. Combined pure fractions from column were evaporated to obtain the titled compound as a pale-yellow liquid (0.45 g). Yield: 67%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 8.25 (dd, J 4.4,1.2, 1H), 8.11 (s, 1H), 7.23 (dd, J 8.0,4.4, 1H), 4.34 (s, 2H), 3.66 (t, J 6.0, 2H), 2.88 (t, J 6.8, 2H), 2.00 (m, 2H). MS (m/z): 218.18 ([M+H]⁺).

Intermediate 71: 2-amino-1-(3,4-dihydro-1,5-naphthyridin-1(2H)-yl)ethan-1-one

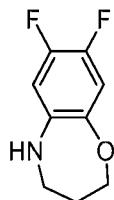


[225] To intermediate 70 (0.45 g, 2.07 mmol) in methanol (14 ml), 5% Pd/C (50% wet, 220 mg) was added and stirred at 25°C under hydrogen pressure (30 psi) for 3h. After 3h, filtered through ceelite bed, washed with methanol (5 ml) and distilled out to obtain the crude. Crude was purified by combi-flash using methanol and dichloromethane (10:90) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as a pale-yellow gummy solid (0.25 g). Yield: 63%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 8.22 (dd, J 4.8,1.6, 1H), 8.09 (d, J 6.8, 1H), 7.20 (dd, J 8.0,4.4, 1H), 3.69 (t, J 6.0, 2H), 3.50 (s, 2H), 2.87 (t, J 6.8, 2H), 1.97 (m, 2H), 1.70 (s, 2H). MS (m/z): 192.17 ([M+H]⁺).

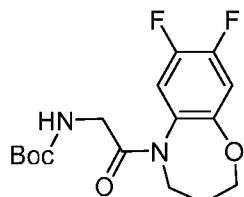
Intermediate 72: 6,7-difluorochroman-4-one oxime



[226] To 6,7-Difluorochroman-4-one (2.5 g, 14 mmol) in pyridine (25 ml), hydroxylamine hydrochloride (1.9 g, 27 mmol) was added at 25°C. After 16h, the reaction mixture was diluted with water (50 ml) and extracted with ethyl acetate (2 x 100 ml). The organic layer was washed with brine solution (3 x 30 ml), dried with anhydrous sodium sulphate, the solvents were distilled out and washed with pentane to obtain the titled compound as an off-white solid (1.50 g). Yield: 55%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 11.42 (s, 1H), 7.66 (dd, J 11.6,9.2, 1H), 7.09 (dd, J 11.6,7.2, 1H), 4.22 (t, J 6.0, 2H), 2.83 (t, J 6.0, 2H). MS (m/z): 200.22 [M+H]⁺.

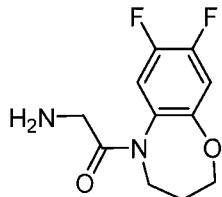
Intermediate 73: 7,8-difluoro-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepine

[227] To intermediate 72 (1.50 g, 7.53 mmol) in dichloromethane (30 ml) cooled to 0°C, DIBAL-H (1M in toluene, 50 ml, 50 mmol) was added at 0°C. After 2h at room temperature, the reaction mixture was cooled to 0°C, sodium fluoride (8.86 g, 211 mmol) and water (5 ml) were added slowly and stirred for 30 min. The reaction mixture was diluted with ethyl acetate (100 ml) and filtered through cealite bed and washed with ethyl acetate (50 ml). The organic layer was washed with brine solution (50 ml), dried with anhydrous sodium sulphate, distilled out the solvent and the residue were washed with pentane to obtain the titled compound as an off-white solid (0.60 g). Yield: 43%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 6.90 (dd, J 11.6, 8.0, 1H), 6.82 (dd, J 12.8, 8.4, 1H), 5.51 (s, 1H), 3.97 (m, 2H), 3.07 (m, 2H), 1.87 (quintet, J 5.6, 2H). MS (m/z): 186.11 [M+H]⁺.

Intermediate 74: tert-butyl (2-(7,8-difluoro-3,4-dihydrobenzo[b][1,4]oxazepin-5(2H)-yl)-2-oxoethyl)carbamate

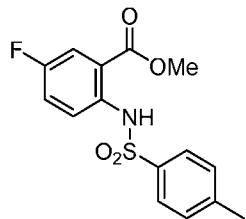
[228] Following the general procedure 1, the titled compound was synthesized from intermediate 73 (0.50 g, 2.7 mmol), ethyl acetate (10 ml), N-Boc-glycine (0.52 g, 3.0 mmol), pyridine (0.85 g, 11 mmol) and T₃P (Propyl phosphonic anhydride) (2.1 g, 6.8 mmol). Purification: Combi-Flash. Eluent: Ethyl acetate and petroleum ether (20:80) as eluent. Appearance: Brown solid (0.60 g). Yield: 60%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 7.69 (dd, J 10.8, 8.8, 1H), 7.31 (dd, J 11.6, 8.0, 1H), 6.85 (m, 1H), 4.53-4.37 (m, 2H), 3.77 (m, 2H), 3.23 (m, 1H), 2.83 (t, J 10.8, 1H), 1.99-1.77 (m, 2H), 1.35 (s, 9H). MS (m/z): 243.15 [M-Boc]⁺.

Intermediate 75: 2-amino-1-(7,8-difluoro-3,4-dihydrobenzo[b][1,4]oxazepin-5(2H)-yl)ethan-1-one



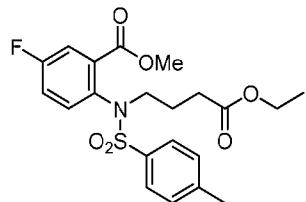
[229] Following the general procedure 2, the titled compound was synthesized from Intermediate 74 (0.60 g, 1.75 mmol), dichloromethane (10 ml) and trifluoroacetic acid (2.00 g, 17.5 mmol). Purification: Combi-Flash. Eluent: Methanol and dichloromethane (3:97) as eluent. Appearance: Brown solid (0.30 g). Yield: 70%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 8.02 (s, 2H), 7.78 (dd, J 11.2, 8.8, 1H), 7.39 (dd, J 11.6, 8.8, 1H), 4.54 (d, J 13.6, 1H), 4.41 (d, J 12.0, 1H), 3.97 (m, 1H), 3.79 (m, 1H), 3.25 (m, 1H), 2.94 (t, J 12.0, 1H), 2.03 (m, 1H), 1.86 (m, 1H). MS (m/z): 243.14 ([M+H]⁺).

Intermediate 76: methyl 5-fluoro-2-((4-methylphenyl)sulfonamido)benzoate



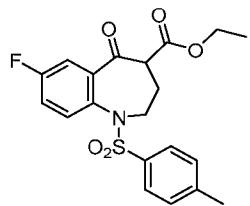
[230] Methyl 2-amino-5fluorobenzoate (5.0 g, 30 mmol) and triethylamine (3.0 g, 30 mmol) were dissolved in toluene (20 ml) and cooled to 0°C. 4-Methylbenzene sulfonyl chloride (5.0 g, 26 mmol) was added at 0°C and heated to 65°C. After 5h, the reaction mass cooled to room temperature, filtered and washed with hot toluene (10 ml). The filtrate was concentrated under vacuum using rotavapor. To the crude, isopropanol (5 ml) was added, heated to 55°C and stirred at room temperature for 2h. The solid precipitated was filtered and dried under vacuum to obtain the titled compound as an off-white solid (4.0 g). Yield: 42%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 10.07 (s, 1H), 7.61-7.54 (m, 3H), 7.49-7.41 (m, 2H), 7.36 (d, J 8.8, 2H), 3.77 (s, 3H), 2.34 (s, 3H). MS (m/z): 323.99 ([M+H]⁺).

Intermediate 77: methyl 2-((N-(4-ethoxy-4-oxobutyl)-4-methylphenyl)sulfonamido)-5-fluorobenzoate



[231] To Intermediate 76 (4.0 g, 12 mmol) in DMSO (20 ml), sodium carbonate (4.0, 38 mmol) was added and heated to 65°C. Ethyl 4-bromobutanoate (3.1 g, 15 mmol) was added at 65°C and stirred at 115°C for 6h. The reaction mass was cooled to 60-65°C, water (50 ml) and toluene (30 ml) were added and stirred at room temperature for 30 min. The aqueous layer was extracted with toluene (3 x 50 ml), the combined organic layer was washed with brine solution and distilled under vacuum using rotavapor. To the residue, methanol (10 ml) was added and heated to reflux for 15 min. After 1h at room temperature, the solid precipitated was filtered, washed with methanol, and dried under vacuum at 50°C to obtain the titled compound as a brown solid (4.0 g). Yield: 74%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 7.59 (dd, J 8.8,3.2, 1H), 7.43-7.38 (m, 5H), 7.00 (d, J 8.8,5.2, 1H), 4.06 (m, 2H), 3.75 (s, 3H), 3.17 (m, 1H), 3.46 (m, 1H), 2.39 (m, 5H), 1.68 (m, 2H), 1.16 (t, J 7.2, 3H). MS (m/z): 438.09 ([M+H]⁺).

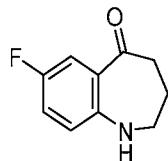
Intermediate 78: ethyl 7-fluoro-5-oxo-1-tosyl-2,3,4,5-tetrahydro-1H-benzo[b]azepine-4-carboxylate



[232] To Potassium tert-butoxide (1.60g, 14 mmol) in THF (20 ml) cooled to 0°C, intermediate 77 (4.0 g, 9.1 mmol) in THF (10 ml) was added slowly over 5 min. and stirred at 0-5°C for 3h. The reaction mass was quenched with acetic acid (0.79 ml) and allowed to reach room temperature, water (50 ml) and toluene (30 ml) were added and stirred for 15 min. The aqueous layer was extracted with toluene (3 x 50 ml), the combined organic layer was washed with brine

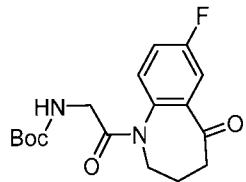
solution and distilled under vacuum using rotavapor. To the residue, isopropanol (10 ml) was added and heated to reflux for 15 min. After 1h at room temperature, cyclohexane (10 ml) was added, the solid precipitated was filtered, washed with isopropanol: cyclohexane (1:1) and dried under vacuum at 50°C to obtain the titled compound as an off-white solid (2.0 g). Yield: 54%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 7.52-7.31 (m, 7H), 4.19 (q, J 7.2, 2H), 3.99 (t, J 6.4, 2H), 3.69 (s, 1H), 2.36 (s, 3H), 2.21 (m, 2H), 1.27 (t, J 7.2, 3H). MS (m/z): 428.05 ([M+Na]⁺).

Intermediate 79: 7-fluoro-1,2,3,4-tetrahydro-5H-benzo[b]azepin-5-one



[233] To intermediate 78 (2.0 g, 4.9 mmol), sulphuric acid (15 g, 150 mmol) and water (2 ml) were added and heated to 100°C for 2h. The reaction mass was cooled to 0°C, quenched with ice cold water, basified with 20% NaOH solution to pH 9 and extracted with ethyl acetate (3 x 100 ml). The combined organic layer was washed with brine solution and distilled under vacuum using rotavapor to obtain crude. Crude was purified by combi-flash using ethyl acetate and petroleum ether (40:60) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as a brown liquid (0.60 g). Yield: 70%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 7.19-7.11 (m, 2H), 6.95 (dd, J 8.8, 4.4, 1H), 6.78 (m, 1H), 3.07 (m, 2H), 2.67 (t, J 7.2, 2H), 2.10 (m, 2H). MS (m/z): 180.05 ([M+H]⁺).

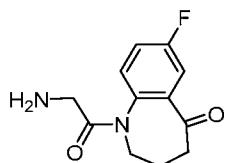
Intermediate 80: tert-butyl (2-(7-fluoro-5-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-1-yl)-2-oxoethyl)carbamate



[234] Following the general procedure 1, the titled compound was synthesized from intermediate 79 (0.50 g, 2.8 mmol), ethyl acetate (10 ml), N-Boc-glycine (0.54 g, 3.1 mmol),

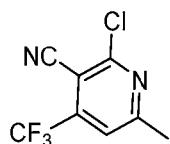
pyridine (0.88 g, 11 mmol) and T₃P (Propyl phosphonic anhydride) (2.2 g, 7.0 mmol). Purification: Combi-Flash. Eluent: Ethyl acetate and petroleum ether (20:80) as eluent. Appearance: Brown liquid (0.60 g). Yield: 60%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 7.60-7.47 (m, 3H), 6.91 (t, J 5.6, 1H), 4.57 (br s, 1H), 3.65 (d, J 12.8, 1H), 3.28 (m, 1H), 3.02 (br s, 1H), 2.16 (m, 2H), 2.10 (m, 1H), 1.68 (br s, 1H), 1.33 (s, 9H). MS (m/z): 237.17 [M-Boc]⁺.

Intermediate 81: 7-fluoro-1-glycyl-1,2,3,4-tetrahydro-5H-benzo[b]azepin-5-one



[235] Following the general procedure 2, the titled compound was synthesized from Intermediate 80(0.60 g, 1.78 mmol), dichloromethane (10 ml) and trifluoroacetic acid (2.03 g, 17.8 mmol). Purification: Combi-Flash. Eluent: Methanol and dichloromethane (2:98) as eluent. Appearance: Brown solid (0.30 g). Yield: 71%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 7.96 (s, 2H), 7.68-7.51 (m, 2H), 7.26-7.12 (m, 1H), 4.63 (m, 1H), 3.81 (m, 1H), 3.23-3.12 (m, 2H), 2.72-2.54 (m, 2H), 2.14 (m, 1H), 1.71 (m, 1H). MS (m/z): 237.24 ([M+H]⁺).

Intermediate 82: 2-chloro-6-methyl-4-(trifluoromethyl)nicotinonitrile



[236] To cyanoacetamide (3.0 g, 35.6 mmol), 1,1,1,trifluoropentan-2,4-dione (5.0 g, 32.4 mmol) in ethanol (40 ml), diethylamine (1.68 g, 23 mmol) was added and the reaction mixture heated to 70°C for 12 h. After 16h, the reaction mixture was cooled to room temperature, filtered and was washed with ethanol (20 ml) to obtain a crude. The Crude compound (6 g) was added slowly to POCl₃ (80 ml, 0.86 mol) and heated to 110°C for 12 h. After 12h, the reaction mixture was distilled out under vacuum using rotavapor to obtain crude. The crude product was purified by combi-Flash using ethyl acetate and petroleum ether (5:95) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as a yellow liquid (5.0 g). Yield

76%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 8.06 (s, 1H), 2.68 (s, 3H). MS (m/z): 221.10 ([M+H]⁺).

Intermediate 83: 2-chloro-N-(4-fluoro-2-(hydroxymethyl)phenyl)acetamide



[237] To 2-amino-5-fluorobenzyl alcohol (3.0 g, 21 mmol) in THF (30 ml), triethylamine (2.20 g, 21 mmol) was added and cooled to 0°C. Chloroacetyl chloride (2.40 g, 21 mmol) was added at 0°C and stirred at 25°C for 16h. After 16h, diluted with water (50 ml) and extracted with ethyl acetate (3 x 30 ml). The organic layer was dried with anhydrous sodium sulphate and distilled out to obtain the crude. Crude was purified by combi-flash using ethyl acetate and petroleum ether (19:81) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as an off-white solid (2.5 g). Yield: 54%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 9.75 (s, 1H), 7.49 (dd, J 8.8,5.2, 1H), 7.24 (dd, J 9.6,3.2, 1H), 7.11 (dt, J 8.4,3.2, 1H), 5.48 (t, J 5.6, 1H), 4.48 (d, J 5.2, 2H), 4.33 (s, 2H). MS (m/z): 216.12 ([M-H]⁺).

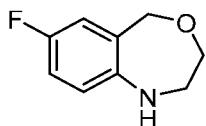
Intermediate 84: 7-fluoro-1,5-dihydrobenzo[e][1,4]oxazepin-2(3H)-one



[238] To intermediate 83 (2.5 g, 11 mmol) in ethanol (20 ml) cooled to 0°C, 21% sodium ethoxide solution in ethanol (7.5 ml, 23 mmol) was added and heated to 90°C. After 24h, the reaction mixture was cooled to 0°C, diluted with water (15 ml) and extracted with ethyl acetate (3 x 50 ml). The organic layer was dried with anhydrous sodium sulphate and distilled out to obtain the crude. Crude was purified by combi-flash using ethyl acetate and petroleum ether (20:80) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as a pale-brown solid (1.0 g). Yield: 40%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz):

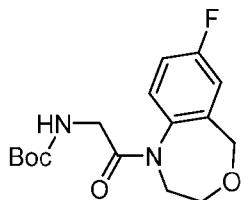
6.92 (dd, J 10.0,3.2, 1H), 6.79 (dt, J 8.8,3.2, 1H), 6.60 (dd, J 8.8,4.8, 1H), 5.13 (t, J 5.6, 1H), 4.75 (s, 2H), 4.35 (d, J 4.8, 2H). MS (m/z): 180.37 ([M-H⁺]).

Intermediate 85: 7-fluoro-1,2,3,5-tetrahydrobenzo[e][1,4]oxazepine



[239] To intermediate 84 (1.0 g, 5.5 mmol) in THF (20 ml) cooled to 0°C, Lithium aluminium hydride (520 mg, 14 mmol) was added and then heated to 80°C. After 4h, the reaction mixture was cooled to 0°C, 0.6 ml water was added slowly followed by 15% NaOH solution (0.6 ml) and water (2 ml), diluted with water (15 ml) and extracted with ethyl acetate (3 x 50 ml). The reaction mixture was filtered through cealite bed and washed with ethyl acetate (100 ml). The filtrate was distilled out to obtain the crude. Crude was purified by combi-flash using ethyl acetate and petroleum ether (10:90) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as a brown liquid (0.60 g). Yield: 76%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 7.00 (dd, J 10.8,2.4, 1H), 6.92-6.87(m, 2H), 5.64 (s, 1H), 4.42 (s, 2H), 3.68 (m, 2H), 2.97 (m,2H). MS (m/z): 168.06 ([M+H⁺]).

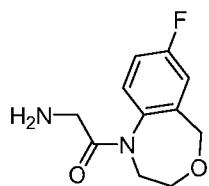
Intermediate 86: tert-butyl (2-(7-fluoro-2,3-dihydrobenzo[e][1,4]oxazepin-1(5H)-yl)-2-oxoethyl)carbamate



[240] Following the general procedure 1, the titled compound was synthesized from intermediate 85 (500 mg, 3.0 mmol), ethyl acetate (10 ml), N-Boc-glycine (520 mg, 3.0 mmol), pyridine (0.95 g, 12.0 mmol) and T₃P (Propyl phosphonic anhydride) (2.40 g, 7.5 mmol). Purification: Combi-Flash. Eluent: Ethyl acetate and petroleum ether (20:80) as eluent. Appearance: Brown liquid (0.60 g). Yield: 60%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 7.52 (dd, J 8.4,5.2, 1H), 7.38 (dd, J 8.8,2.8, 1H), 7.24 (m, 1H), 6.90 (t, J 6.0, 1H), 4.64 (d, J 13.2, 1H),

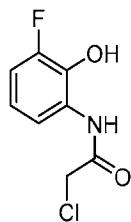
4.52 (m, 2H), 3.96 (d, J 12.4, 1H), 3.77 (dd, J 16.8,6.0, 1H), 3.62 (t, J 11.6, 1H), 3.27 (dd, J 16.8,6.0, 1H), 2.81 (t, J 11.6, 1H), 1.35 (s, 9H). MS (m/z):225.14 [M-Boc]⁺.

Intermediate 87: 2-amino-1-(7-fluoro-2,3-dihydrobenzo[e][1,4]oxazepin-1(5H)-yl)ethan-1-one



[241] Following the general procedure 2, the titled compound was synthesized from Intermediate 86(500 mg, 1.50 mmol), dichloromethane (10 ml) and trifluoroacetic acid (1.80 g, 15 mmol). Purification: Combi-Flash. Eluent: Methanol and dichloromethane (2:98) as eluent. Appearance: Brown liquid (0.30 g). Yield: 90%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 8.05 (s, 2H), 7.60 (dd, J 8.8,5.2, 1H), 7.43 (dd, J 8.8,2.8, 1H), 7.33 (m, 1H), 4.67 (d, J 13.6, 1H), 4.54 (m, 2H), 4.02 (d, J 12.4, 1H), 3.90 (m, 1H), 3.65 (m, 1H), 3.30 (m, 1H), 2.93 (m, 1H). MS (m/z): 225.12 ([M+H]⁺).

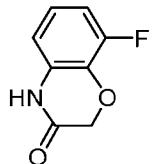
Intermediate 88: 2-chloro-N-(3-fluoro-2-hydroxyphenyl)acetamide



[242] To 2-amino-6-fluorophenol (1.0 g, 7.86 mmol) in 4-methyl-2-pentanone (8.4 ml), sodium bicarbonate (1.60 g, 19.12 mmol), water (8.4 ml) was added and cooled to 0°C. Chloroacetyl chloride (1.06 g, 9.44 mmol) was added at 0°C and stirred at 110°C for 16h. After 16h, diluted with water (50 ml) and extracted with ethyl acetate (3 x 30 ml). The organic layer was dried with anhydrous sodium sulphate and distilled out to obtain the crude. Crude was purified by combi-flash using ethyl acetate and petroleum ether (12.5:87.5) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as a pale-brown solid (0.700 g). Yield:

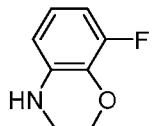
30%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 10.04 (s, 1H), 9.65 (s, 1H), 7.67 (d, J 8.0, 1H), 6.99 (m, 1H), 6.83 (m, 1H), 4.39 (s, 2H). MS (m/z): 204.11 ([M+H]⁺).

Intermediate 89: 8-fluoro-2H-benzo[b][1,4]oxazin-3(4H)-one



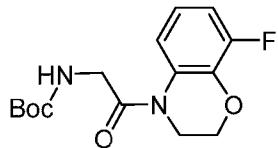
[243] To intermediate 88 (700 mg, 3.44 mmol) in DMF (3 ml), potassium carbonate (475 mg, 3.44 mmol) was added at 25°C. After 4h, the reaction mixture was diluted with water (30 ml), the solid precipitated was filtered, washed with water (20 ml) and dried under vacuum to obtain the titled compound as a pale-brown solid (0.40 g). Yield: 69%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 10.88 (s, 1H), 6.95 (m, 2H), 6.73 (m, 1H), 4.65 (s, 2H). MS (m/z): 166.08 ([M-H]⁺).

Intermediate 90: 8-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazine



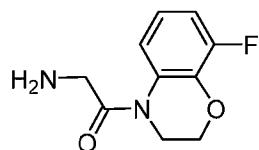
[244] To intermediate 89 (800 mg, 4.79 mmol) in THF (20 ml) cooled to 0°C, Lithium aluminium hydride (454 mg, 12 mmol) was added and then stirred at 25°C. After 2h, the reaction mixture was cooled to 0°C, 0.6 ml water was added slowly followed by 15% NaOH solution (0.6 ml) and water (2 ml). diluted with water (15 ml) and extracted with ethyl acetate (3 x 50 ml). The reaction mixture was filtered through cealite bed and washed with ethyl acetate (100 ml). The filtrate was distilled out to obtain the crude. Crude was purified by combi-flash using ethyl acetate and petroleum ether (15:85) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as a pale-yellow liquid (0.60 g). Yield: 81%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 6.62 (m, 1H), 6.37-6.31 (m, 2H), 6.04 (s, 1H), 4.19 (dt, J 3.6, 1.6, 2H), 3.30 (m, 2H). MS (m/z): 154.07 ([M+H]⁺).

Intermediate 91: tert-butyl (2-(8-fluoro-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)-2-oxoethyl)carbamate



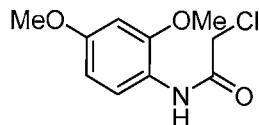
[245] Following the general procedure 1, the titled compound was synthesized from intermediate 90 (600 mg, 3.92 mmol), dichloromethane (10 ml), N-Boc-glycine (755 mg, 4.31 mmol), triethylamine (1.59 g, 15.7 mmol) and T₃P (Propyl phosphonic anhydride) (3.12 g, 9.79 mmol). Purification: Combi-Flash. Eluent: Ethyl acetate and petroleum ether (15:85) as eluent. Appearance: Pale-yellow liquid (0.80 g). Yield: 70%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 7.67 (s, 1H), 7.03-6.97 (m, 2H), 6.88 (m, 1H), 4.32 (t, J 4.4, 2H), 4.01 (d, J 6.0, 2H), 3.89 (t, J 4.4, 2H), 1.38 (s, 9H). MS (m/z): 211.10 [M-Boc]⁺.

Intermediate 92: 2-amino-1-(8-fluoro-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)ethan-1-one



[246] Following the general procedure 2, the titled compound was synthesized from Intermediate 91 (800 mg, 2.58 mmol), dichloromethane (9 ml) and trifluoroacetic acid (2.94 g, 2.58 mmol). Purification: Not done. Appearance: Pale-brown liquid (0.70 g). Yield: 83%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 8.18 (s, 3H), 7.08 (t, J 8.8, 1H), 6.94 (dt, J 8.4, 6.0, 1H), 4.38 (t, J 4.4, 2H), 4.13 (s, 2H), 3.89 (br s, 2H), MS (m/z): 211.06 ([M+H]⁺).

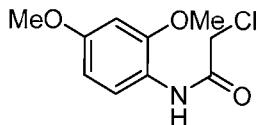
Intermediate 93: 2-chloro-N-(2,4-dimethoxyphenyl)acetamide



[247] To 2,4-dimethoxyaniline (10.0 g, 65 mmol) in dichloromethane (100 ml), triethylamine (13 g, 130 mmol) was added and cooled to 0°C. Chloroacetyl chloride (8.8 g, 78 mmol) was added at 0°C and stirred at 25°C for 3h. After 3h, diluted with water (50 ml) and extracted with

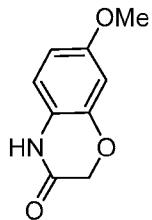
dichloromethane (3×30 ml). The organic layer was dried with anhydrous sodium sulphate and distilled out to obtain the crude. Crude was purified by combi-flash using ethyl acetate and petroleum ether (15:85) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as a brown solid (10.0 g). Yield: 67%. $^1\text{H-NMR}$ (δ ppm, DMSO-D₆, 400 MHz): 9.35 (s, 1H), 7.75 (d, J 8.4, 1H), 6.63 (d, J 2.4, 1H), 6.51 (dd, J 8.8, 2.8, 1H), 4.31 (s, 2H), 3.82 (s, 3H), 3.75 (s, 3H). MS (m/z): 230.11 ($[M+\text{H}]^+$).

Intermediate 94: 2-chloro-N-(2-hydroxy-4-methoxyphenyl)acetamide



[248] To intermediate 93 (4.0 g, 17.42 mmol) in dichloromethane (40 ml) cooled to 0°C, AlCl₃ (9.28 g, 69.7 mmol) was added at 0°C and stirred at 0°C for 3h. After 12h at room temperature, the reaction mixture was quenched with ice-water (200 ml) and extracted with ethyl acetate (3×50 ml). The organic layer was dried with anhydrous sodium sulphate and distilled out to obtain the crude. Crude was purified by combi-flash using ethyl acetate and petroleum ether (20:80) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as a pale-brown solid (2.0 g). Yield: 53%. $^1\text{H-NMR}$ (δ ppm, DMSO-D₆, 400 MHz): 9.90 (s, 1H), 9.32 (s, 1H), 7.65 (d, J 8.8, 1H), 6.45 (d, J 2.4, 1H), 6.38 (dd, J 8.8, 2.8, 1H), 4.32 (s, 2H), 3.68 (s, 3H). MS (m/z): 216.16 ($[M+\text{H}]^+$).

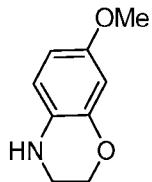
Intermediate 95: 7-methoxy-2H-benzo[b][1,4]oxazin-3(4H)-one



[249] To intermediate 94 (2.0 g, 9.27 mmol) in acetone (50 ml), potassium carbonate (1.28 g, 9.27 mmol) was added and heated to 60°C. After 4h, the reaction mixture was concentrated, dissolved in ethyl acetate (100 ml) and washed with brine solution (3×30 ml). The organic layer was dried with anhydrous sodium sulphate and distilled out to obtain the crude. Crude was

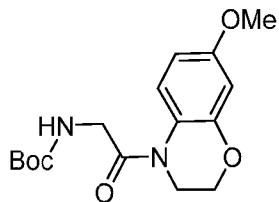
purified by combi-flash using ethyl acetate and petroleum ether (40:60) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as a pale-brown solid (1.3 g). Yield: 78%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 10.51 (s, 1H), 6.80 (d, J 8.4, 1H), 6.56-6.52 (m, 2H), 4.51 (s, 2H), 3.68 (s, 3H). MS (m/z): 180.12 ([M+H]⁺).

Intermediate 96: 7-methoxy-3,4-dihydro-2H-benzo[b][1,4]oxazine



[250] Intermediate 95 (1.30 g, 7.3 mmol) in THF (20 ml) was added to 0°C cooled suspension of Lithium aluminium hydride (0.69 g, 18 mmol) in THF (15 ml) and then stirred at 25°C. After 3h, the reaction mixture was cooled to 0°C, quenched with 5% NaOH solution (7 ml). The reaction mixture was filtered through cealite bed and washed with ethyl acetate (100 ml). The filtrate was distilled out to obtain the crude. Crude was purified by combi-flash using ethyl acetate and petroleum ether (25:75) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as a brown (0.80 g). Yield: 67%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 6.49 (td, J 8.8, 1.2, 1H), 6.30 (dd, J 9.2, 2.8, 1H), 6.27 (s, 1H), 5.23 (s, 1H), 4.09 (t, J 4.0, 2H), 3.60 (s, 3H), 3.20-3.17 (m, 2H). MS (m/z): 166.10 ([M+H]⁺).

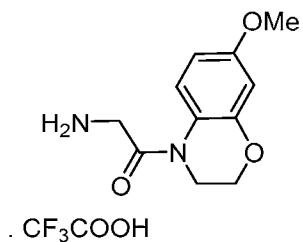
Intermediate 97: tert-butyl (2-(7-methoxy-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)-2-oxoethyl)carbamate



[251] Following the general procedure 1, the titled compound was synthesized from intermediate 96 (800 mg, 4.84 mmol), dichloromethane (10 ml), N-Boc-glycine (933 mg, 5.33 mmol), triethylamine (1.96 g, 19.4 mmol) and T₃P (Propyl phosphonic anhydride) (3.85 g, 12.1 mmol). Purification: Combi-Flash. Eluent: Ethyl acetate and petroleum ether (20:80) as eluent.

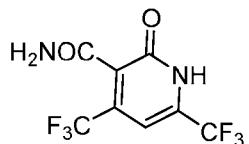
Appearance: Brown gummy liquid (1.10 g). Yield: 70%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 7.87 (s, 1H), 6.93 (t, J 5.6, 1H), 6.49 (d, J 2.8, 1H), 6.46 (s, 1H), 4.23 (t, J 4.0, 2H), 3.97 (d, J 6.0, 2H), 3.81 (t, J 4.4, 2H), 3.70 (s, 3H), 1.38 (s, 9H). MS (m/z): 223.19 [M-Boc+H]⁺.

Intermediate 98: 2-amino-1-(7-methoxy-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)ethan-1-one trifluoroacetic acid salt



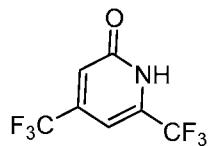
[252] Following the general procedure 2, the titled compound was synthesized from Intermediate 97 (1.10 g, 3.42 mmol), dichloromethane 11 ml) and trifluoroacetic acid (3.89 g, 34.12 mmol). Purification: Not done. Appearance: Pale-brown solid (0.90 g). Yield: 78%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 8.14 (br s, 3H), 8.03 (d, J 7.6, 0.7H), 7.28 (br s, 0.3H), 6.54-6.49 (m, 2H), 4.28 (br s, 2H), 4.08 (br s, 2H), 3.89 (s, 0.6H), 3.77 (s, 1.4H), 3.71 (s, 3H). MS (m/z): 223.12 [M-TFA+H]⁺.

Intermediate 99: 2-oxo-4,6-bis(trifluoromethyl)-1,2-dihydropyridine-3-carboxamide



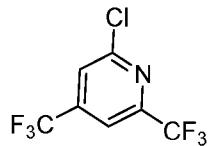
[253] To malonamide (4.9 g, 48 mmol), 1,1,1,5,5,5-hexafluoroacetylacetone (10 g, 48 mmol) and sulfolane (10 mmol) were added and the reaction mixture heated to 80°C for 2h followed by at 170°C for 3.5h. After 3.5h, reaction mixture was cooled to room temperature, diluted with water, the solid precipitated was filtered, washed with water (20 ml), dried at 80°C for 2h under vacuum to obtain the titled compound as a off-white solid (9.8 g). Yield: 74%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 13.01 (s, 1H), 7.98 (s, 1H), 7.81 (s, 1H), 7.61 (s, 1H). MS (m/z): 275.14 [M+H]⁺.

Intermediate 100: 4,6-bis(trifluoromethyl)pyridin-2(1H)-one



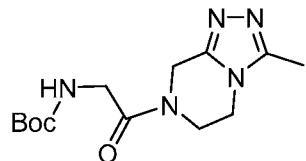
[254] To intermediate 99 (9.5 g, 35 mmol), sulphuric acid (21 ml) and water (13 ml) were added and heated to 170°C for 16h. After 16h, reaction mixture was cooled to room temperature, poured into ice-cold water (800 ml) and stirred for 20 min. The solid precipitated was filtered, dried under vacuum, dissolved in dichloromethane and concentrated under reduced pressure to obtain the titled compound as a off-white solid (5.8 g). Yield: 72%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 10.90 (s, 1H), 7.27 (s, 1H), 7.22 (s, 1H). MS (m/z): 230.08 [M-H]⁺.

Intermediate 101: 2-chloro-4,6-bis(trifluoromethyl)pyridine



[255] To intermediate 100 (5.5 g, 24 mmol) cooled to 0°C, POCl₃ (5.5 ml, 59 mol) was added followed by triethylamine (3.3 ml, 24 mmol). The reaction mixture was heated to 125°C for 15 h. After 15h, reaction mixture was cooled to room temperature, quenched with ice cold water and extracted with diethyl ether (2 x 30 ml). The organic layer was evaporated to obtain a crude. Crude was purified by combi-flash using hexane as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as a brown liquid (0.450 g). Yield: 7%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 6.97 (s, 1H), 6.74 (s, 1H).

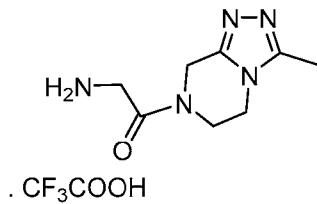
Intermediate 102: tert-butyl (2-(3-methyl-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)-2-oxoethyl)carbamate



[256] Following the general procedure 1, the titled compound was synthesized from 3-methyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine (500 mg, 3.62 mmol), ethyl acetate (5 ml),

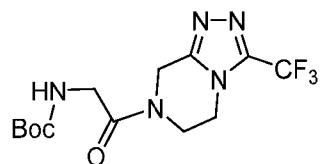
DMF (5 ml), N-Boc-glycine (697 mg, 3.98 mmol), pyridine (1.14 g, 14.5 mmol) and T₃P (Propyl phosphonic anhydride) (2.88 g, 9.05 mmol). Purification: Combi-Flash. Eluent: Methanol and dichloromethane (15:85) as eluent. Appearance: Off-white gummy solid (0.55 g). Yield: 51%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 6.91 (t, J 6.0, 1H), 4.80 (s, 0.8H), 4.71 (s, 1.2H), 3.96-3.87 9 (m, 6H), 2.29 (s, 3H), 1.38 (s, 9H). MS (m/z): 296.13 [M+H]⁺.

Intermediate 103: 2-amino-1-(3-methyl-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)ethan-1-onetrifluoroacetic acid salt



[257] Following the general procedure 2, the titled compound was synthesized from Intermediate 102 (500 mg, 1.61 mmol), dichloromethane (5 ml) and trifluoroacetic acid (1.93 g, 16.9 mmol). Purification: Not done. Appearance: Off-white gummy solid (0.650 g). Yield: >100%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 8.12 (s, 1H), 7.88 (br s, 3H), 4.89 (d, J 4.4, 2H), 4.01-3.88 (m, 6H), 2.45 (s, 3H). MS (m/z): 196.19 [M-TFA+H]⁺.

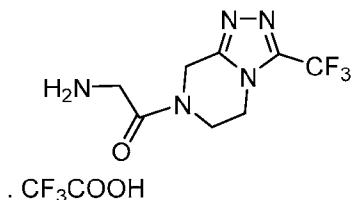
Intermediate 104: tert-butyl (2-oxo-2-(3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)ethyl)carbamate



[258] Following the general procedure 1, the titled compound was synthesized from 3-(trifluoromethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine (1.0 g, 5.20 mmol), ethyl acetate (10 ml), N-Boc-glycine (1.0 g, 5.72 mmol), pyridine (1.65 g, 20.8 mmol) and T₃P (Propyl phosphonic anhydride) (4.14 g, 13.01 mmol). Purification: Combi-Flash. Eluent: Methanol and dichloromethane (3.5:96.5) as eluent. Appearance: Off-white solid (1.45 g). Yield: 80%. ¹H-

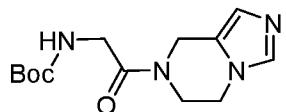
NMR (δ ppm, DMSO-D₆, 400 MHz): 6.91 (s, 1H), 4.96 (s, 0.8H), 4.87 (s, 1.2H), 4.24 (s, 1H), 4.10 (s, 1H), 3.95-3.91 (m, 4H), 1.38 (s, 9H). MS (m/z): 250.27 [M-Boc+H]⁺.

Intermediate 105: 2-amino-1-(3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)ethan-1-one trifluoroacetic acid salt



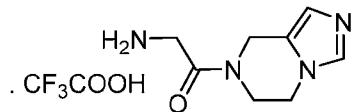
[259] Following the general procedure 2, the titled compound was synthesized from Intermediate 104 (700 mg, 2.0 mmol), dichloromethane (10 ml) and trifluoroacetic acid (2.28 g, 20.0 mmol). Purification: Not done. Appearance: Off-white gummy solid (0.72 g). Yield: 100%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 8.12 (s, 3H), 4.95 (s, 2H), 4.30 (t, J 5.6, 1H), 4.17 (t, J 5.2, 1H), 4.05-3.99 (m, 3H), 3.93 (t, J 5.6, 1H). MS (m/z): 250.17 [M-TFA+H]⁺.

Intermediate 106: tert-butyl (2-(5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)-2-oxoethyl)carbamate



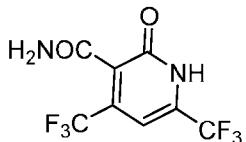
[260] Following the general procedure 1, the titled compound was synthesized from 5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine (950 mg, 7.71 mmol), ethyl acetate (20 ml), N-Boc-glycine (1.49 g, 8.48 mmol), pyridine (2.44 g, 30.9 mmol) and T₃P (Propyl phosphonic anhydride) (6.14 g, 19.30 mmol). Purification: Combi-Flash. Eluent: Methanol and dichloromethane (4:96) as eluent. Appearance: Colourless gummy solid (1.35 g). Yield: 62%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 7.59 (s, 1H), 6.84 (t, J 4.8, 1H), 6.74 (s, 1H), 4.71 (s, 0.8H), 4.63 (s, 1.2H), 4.10 (t, J 5.2, 1.2H), 4.02 (t, J 5.2, 0.8H), 3.88-3.84 (m, 2H), 3.80 (t, J 5.2, 2H), 1.38 (s, 9H). MS (m/z): 281.19 [M+H]⁺.

Intermediate 107: 2-amino-1-(5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)ethan-1-one trifluoroacetic acid salt



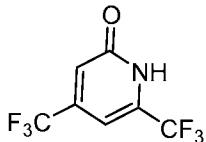
[261] Following the general procedure 2, the titled compound was synthesized from Intermediate 106 (350 mg, 1.25 mmol), dichloromethane (3.5 ml) and trifluoroacetic acid (1.42 g, 12.5 mmol). Purification: Not done. Appearance: Off-white gummy solid (0.80 g). Yield: >100% (crude). $^1\text{H-NMR}$ (δ ppm, DMSO- D_6 , 400 MHz): 9.10 (s, 1H), 8.19 (s, 3H), 7.56 (s, 1H), 4.81 (s, 2H), 4.38 (t, J 5.2, 1.3H), 4.28 (t, J 5.2, 0.7H), 4.04-3.95 (m, 2.7H), 3.89 (t, J 5.2, 1.3H). MS (m/z): 181.17 [$M-\text{TFA}+\text{H}]^+$).

Intermediate 108: 2-oxo-4,6-bis(trifluoromethyl)-1,2-dihydropyridine-3-carboxamide



[262] To malonamide (4.9 g, 48 mmol), 1,1,1,5,5,5-hexafluoroacetylacetone (10 g, 48 mmol) and sulfolane (10 mmol) were added and the reaction mixture heated to 80°C for 2h followed by at 170°C for 3.5h. After 3.5h, reaction mixture was cooled to room temperature, diluted with water, the solid precipitated was filtered, washed with water (20 ml), dried at 80°C for 2h under vacuum to obtain the titled compound as a off-white solid (9.8 g). Yield: 74%. $^1\text{H-NMR}$ (δ ppm, DMSO- D_6 , 400 MHz): 13.01 (s, 1H), 7.98 (s, 1H), 7.81 (s, 1H), 7.61 (s, 1H). MS (m/z): 275.14 [$M+\text{H}]^+$).

Intermediate 109: 4,6-bis(trifluoromethyl)pyridin-2(1H)-one



[263] To intermediate 108 (9.5 g, 35 mmol), sulphuric acid (21 ml) and water (13 ml) were added and heated to 170°C for 16h. After 16h, reaction mixture was cooled to room temperature, poured into ice-cold water (800 ml) and stirred for 20 min. The solid precipitated was filtered, dried under vacuum, dissolved in dichloromethane and concentrated under reduced pressure to

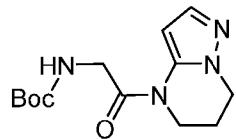
obtain the titled compound as a off-white solid (5.8 g). Yield: 72%. $^1\text{H-NMR}$ (δ ppm, DMSO-D₆, 400 MHz): 10.90 (s, 1H), 7.27 (s, 1H), 7.22 (s, 1H). MS (m/z): 230.08 [M-H]⁺.

Intermediate 110: 2-Bromo-4,6-bis(trifluoromethyl)pyridine



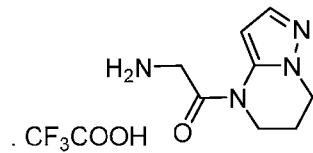
[264] To intermediate 109 (2.0 g, 8.65 mmol) cooled to 0°C, POBr₃ (6.20 g, 21.6 mmol) was added followed by triethylamine (0.876 g, 8.65 mmol). The reaction mixture was heated to 130°C for 3.5 h. After 3.5h, reaction mixture was cooled to room temperature, quenched with ice cold water (150 ml) and extracted with diethyl ether (3 x 100 ml). The organic layer was evaporated to obtain the titled compound as a brown liquid (1.70 g). Yield: 67%. $^1\text{H-NMR}$ (δ ppm, DMSO-D₆, 400 MHz): 7.93 (s, 1H), 7.85 (s, 1H).

Intermediate 111: tert-butyl (2-(6,7-dihydropyrazolo[1,5-a]pyrimidin-4(5H)-yl)-2-oxoethyl)carbamate



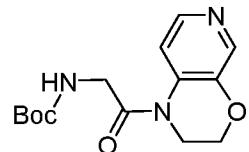
[265] Following the general procedure 1, the titled compound was synthesized from 4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine (950 mg, 7.71 mmol), ethyl acetate (20 ml), N-Boc-glycine (1.49 g, 8.48 mmol), pyridine (2.44 g, 30.9 mmol) and T₃P (Propyl phosphonic anhydride) (6.14 g, 19.30 mmol). Purification: Combi-Flash. Eluent: Methanol and dichloromethane (3.5:96.5) as eluent. Appearance: Colourless gummy solid (1.0 g). Yield: 46%. $^1\text{H-NMR}$ (δ ppm, DMSO-D₆, 400 MHz): 7.32 (s, 1H), 6.98 (t, J 5.6, 1H), 6.54 (s, 1H), 4.12 (t, J 6.0, 2H), 4.01 (d, J 6.0, 2H), 3.85 (t, J 6.0, 2H), 2.12-2.08 (m, 2H), 1.39 (s, 9H). MS (m/z): 281.22 [M+H]⁺.

Intermediate 112: 2-amino-1-(6,7-dihydropyrazolo[1,5-a]pyrimidin-4(5H)-yl)ethan-1-one trifluoroacetic acid salt



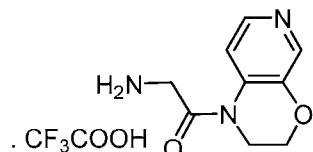
[266] Following the general procedure 2, the titled compound was synthesized from Intermediate 111 (460 mg, 1.60 mmol), dichloromethane (5 ml) and trifluoroacetic acid (2.8 g, 25 mmol). Purification: Not done. Appearance: Off-white gummy solid (0.480 g). Yield: >100% (crude). ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 8.20 (s, 3H), 7.37 (s, 1H), 6.62 (s, 1H), 4.16-4.07 (m, 4H), 3.83 (t, J 5.2, 2H), 2.19-2.11 (m, 2H). MS (m/z): 181.14 [M-TFA+H]⁺.

Intermediate 113: tert-butyl (2-(2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-1-yl)-2-oxoethyl)carbamate



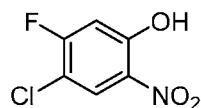
[267] Following the general procedure 1, the titled compound was synthesized from 2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazine (500 mg, 7.71 mmol), acetonitrile 15 ml), N-Boc-glycine (643 mg, 3.67 mmol), EDC.HCl (845 mg, 4.41 mmol) HOEt (731 mg, 4.77 mmol) and 4-methylmorpholine (929 mg, 9.18 mmol). Purification: Combi-Flash. Eluent: Methanol and dichloromethane (2.7:97.3) as eluent. Appearance: Off-white solid (200 mg). Yield: 18%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 8.18 (s, 1H), 8.12 (d, J 5.6, 1H), 8.04 (d, J 5.2, 1H), 7.06 (t, J 6.0, 1H), 4.30 (t, J 4.8, 2H), 4.05 (d, J 6.0, 2H), 3.92 (t, J 4.4, 2H), 1.39 (s, 9H). MS (m/z): 294.16 [M+H]⁺.

Intermediate 114: 2-amino-1-(2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-1-yl)ethan-1-one trifluoroacetic acid salt



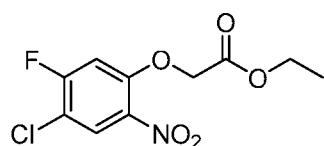
[268] Following the general procedure 2, the titled compound was synthesized from Intermediate 113 (200 mg, 0.68 mmol), dichloromethane (2 ml) and trifluoroacetic acid (777 mg, 6.82 mmol). Purification: Not done. Appearance: Yellow gummy solid (0.300 g). Yield: >100% (crude). ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 8.42 (s, 1H), 8.37 (d, J 5.6, 1H), 8.28 (s, 3H), 8.23 (d, J 6.0, 1H), 4.40 (t, J 4.8, 2H), 4.21 (d, J 4.4, 2H), 3.95 (t, J 4.8, 2H). MS (m/z): 194.14 [M-TFA+H]⁺.

Intermediate 115: 4-chloro-5-fluoro-2-nitrophenol



[269] To 4-chloro-3-fluorophenol (4.93 g, 33.69 mmol) in dichloromethane (99 ml) was cooled to 0°C, sulphuric acid (3.30 g, 33.69 mmol) was added and followed by nitric acid (3.60 g, 757.1 mmol) at -5°C. After 1h, quenched into chilled water (50 ml) and extracted with dichloromethane (3 x 100 ml). The organic layer was washed with sodium bicarbonate solution (100 ml), brine solution (100 ml), dried with anhydrous sodium sulphate and distilled out to obtain the crude. Crude was purified by combi-flash using ethyl acetate and petroleum ether (5.95) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as a yellow solid (3.50 g). Yield: 55%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 11.79 (s, 1H), 8.22 (d, J 7.6, 1H), 7.13 (d, J 10.8, 1H). MS (m/z): 190.11 ([M-H]⁺).

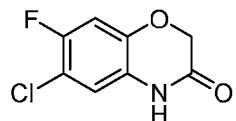
Intermediate 116: ethyl 2-(4-chloro-5-fluoro-2-nitrophenoxy)acetate



[270] To intermediate 115 (3.50 g, 18.3 mmol) in acetone (44 ml), potassium carbonate (2.53 g, 18.3 mmol) was added at 25°C. Ethyl bromoacetate (3.05 g, 18.3 mmol) was added and heated to 70°C. After 15h, the reaction mixture was concentrated, diluted with dichloromethane (100 ml), washed with 10% sodium bicarbonate solution (100 ml), brine solution (100 ml), dried with anhydrous sodium sulphate and distilled out to obtain the crude. Crude was purified by combi-

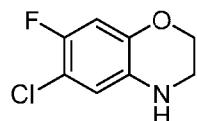
flash using ethyl acetate and petroleum ether (5:95) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as a pale-green solid (4.20 g). Yield: 83%.
¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 8.07 (d, J 7.6, 1H), 6.82 (d, J 9.6, 1H). 4.76 (s, 2H), 4.31 (q, J 7.2, 2H), 1.32 (t, J 7.1, 3H). MS (m/z): 278.18 ([M+H⁺]).

Intermediate 117: 6-chloro-7-fluoro-2H-benzo[b][1,4]oxazin-3(4H)-one))



[271] To intermediate 116 (4.20 g, 15.13 mmol) in methanol (30 ml) and water (30 ml), iron (5.06 g, 90.77 mmol) and ammonium chloride (8.09 g, 151.3 mmol) were added and heated to 80°C. After 24h, the reaction mixture was hot filtered and washed with 10% dichloromethane in methanol (150 ml), concentrated under reduced pressure. To the residue water (50 ml) was added, extracted with ethyl acetate (2 x 100 ml), washed with brine solution (100 ml), dried with anhydrous sodium sulphate and distilled out to obtain the titled compound as a pale-brown solid (2.0 g). Yield: 66%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 10.80 (s, 1H), 7.16 (d, J 10.0, 1H), 6.98 (d, J 7.6, 1H). 4.62 (s, 2H). MS (m/z): 200.15 ([M-H⁺]).

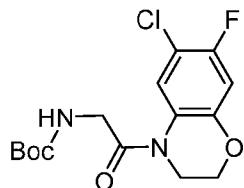
Intermediate 118: 6-chloro-7-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazine



[272] To intermediate 117 (1.90 g, 9.43 mmol) in dichloromethane (90 ml) cooled to 0°C. DIBAL-H (1M in toluene, 23.6 ml, 23.6 mmol) was added at 0°C. After 24h at room temperature, the reaction mixture was cooled to 0°C, sodium fluoride (11.1 g, 264 mmol) and water (5 ml) were added slowly and stirred for 30 min. The reaction mixture was diluted with ethyl acetate (100 ml) and filtered through celite bed and washed with ethyl acetate (50 ml). The organic layer was washed with brine solution (50 ml), dried with anhydrous sodium sulphate, concentrated under reduced pressure to obtain the crude. Crude was purified by combi-flash using ethyl acetate and petroleum ether (12:88) as eluent. Combined pure fractions from column

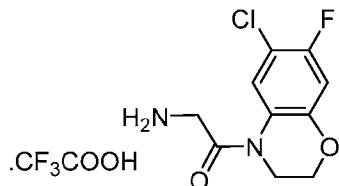
were evaporated to obtain the titled compound as a pale-brown solid (1.20 g). Yield: 68%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 6.75 (d, J 10.4, 1H), 6.65 (d, J 7.6, 1H), 5.89 (s, 1H), 4.13 (t, J 2.4, 2H), 3.25-3.23 (m, 2H). MS (m/z): 188.12 ([M+H]⁺).

Intermediate 119: tert-butyl (2-(6-chloro-7-fluoro-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)-2-oxoethyl)carbamate



[273] Following the general procedure 1, the titled compound was synthesized from intermediate 118 (1.0 g, 5.33 mmol), dichloromethane (20 ml), N-Boc-glycine (1.02 g, 5.86 mmol), triethylamine (21.15 g, 21.32 mmol) and T₃P (Propyl phosphonic anhydride) (4.24 g, 13.33 mmol). Purification: Combi-Flash. Eluent: Ethyl acetate and petroleum ether (25:75) as eluent. Appearance: Pale-brown solid (0.70 g). Yield: 38%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 8.18 (s, 1H), 7.06 (d, J 10.4, 1H), 7.01 (t, J 6.0, 1H), 4.30 (t, J 4.4, 2H), 4.20 (d, J 8.4, 2H), 3.86 (t, J 4.4, 2H), 1.39 (s, 9H). MS (m/z): 245.10 [M-Boc+H]⁺.

Intermediate 120: 2-amino-1-(6-chloro-7-fluoro-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)ethan-1-one trifluoroacetic acid salt



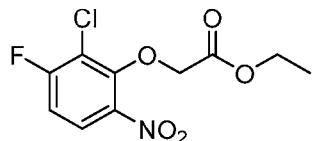
[274] Following the general procedure 2, the titled compound was synthesized from Intermediate 119 (700 mg, 2.33 mmol), dichloromethane (7 ml) and trifluoroacetic acid (1.99 g, 20.3 mmol). Purification: Not done. Appearance: Pale-brown liquid (0.640 g). Yield: 92%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 8.31 (s, 1H), 8.17 (s, 3H), 7.14 (t, J 10.4, 1H), 4.34 (br s, 2H), 4.14 (s, 2H), 3.84 (br s, 2H). MS (m/z): 245.19 ([M-TFA+H]⁺).

Intermediate 121: 2-chloro-3-fluoro-6-nitrophenol



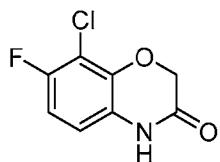
[275] To 2-chloro-1,3-difluoro-4-nitrobenzene (20.0 g, 103.3 mmol) in DMSO (20 ml), KOH (5.79 g, 103.3 mmol) in water (64 ml) was added and stirred at room temperature. After 12h, the reaction mixture was filtered and washed with water (50 ml). The aqueous layer was washed with petroleum ether (2 x 50 ml), the pH adjusted to 3-4 using 2N HCl at 0°C. The solid precipitated was filtered, washed with water (50 ml), dissolved in dichloromethane ((100 ml) and concentrated under reduced pressure to obtain the titled compound as a yellow solid (6.0 g). Yield: 30%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 11.52 (s, 1H), 8.07 (dd, J 9.6,6.0, 1H), 7.13 (dd, J 9.2,8.0, 1H). MS (m/z): 190.06 ([M-H]⁺).

Intermediate 122: ethyl 2-(2-chloro-3-fluoro-6-nitrophenoxy)acetate



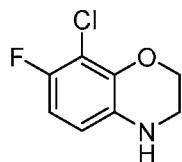
[276] To intermediate 121 (5.0 g, 26.1 mmol) in acetone (44 ml), potassium carbonate (3.61 g, 26.1 mmol) was added at 25°C. Ethyl bromoacetate (4.36 g, 26.1 mmol) was added and heated to 70°C. After 15h, the reaction mixture was concentrated, diluted with dichloromethane (100 ml), washed with 10% sodium bicarbonate solution (100 ml), brine solution (100 ml), dried with anhydrous sodium sulphate and distilled out to obtain the crude. Crude was purified by combi-flash using ethyl acetate and petroleum ether (8:92) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as a yellow solid (2.800 g). Yield: 38%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 7.88 (dd, J 9.2,5.6, 1H), 7.13 (dd, J 9.2,7.2, 1H), 4.81 (s, 2H), 4.32 (q, J 7.2, 2H), 1.33 (t, J 7.2, 3H). MS (m/z): 278.17 ([M+H]⁺).

Intermediate 123: 8-chloro-7-fluoro-2H-benzo[b][1,4]oxazin-3(4H)-one



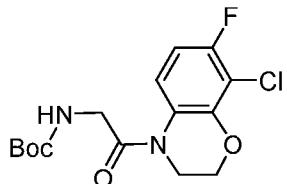
[277] To intermediate 122 (2.80 g, 10.09 mmol) in methanol (30 ml) and water (30 ml), iron (3.38 g, 60.51 mmol) and ammonium chloride (5.39 g, 100.9 mmol) were added and heated to 80°C. After 24h, the reaction mixture was hot filtered and washed with 10% dichloromethane in methanol (150 ml), concentrated under reduced pressure. To the residue water (50 ml) was added, extracted with ethyl acetate (2 x 100 ml), washed with brine solution (100 ml), dried with anhydrous sodium sulphate and distilled out to obtain the titled compound as a brown solid (1.8 g). Yield: 88%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 10.87 (s, 1H), 7.03 (t, J 8.8, 1H), 6.86 (dt, J 8.8, 5.2, 1H). 4.72 (s, 2H). MS (m/z): 200.18 ([M-H⁺]).

Intermediate 124: 8-chloro-7-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazine



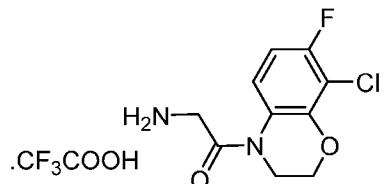
[278] To intermediate 123 (1.80 g, 8.93 mmol) in dichloromethane (85 ml) cooled to 0°C. DIBAL-H (1M in toluene, 22.3 ml, 22.3 mmol) was added at 0°C. After 48h at room temperature, the reaction mixture was cooled to 0°C, sodium fluoride (10.5 g, 250 mmol) and water (5 ml) were added slowly and stirred for 30 min. The reaction mixture was diluted with ethyl acetate (100 ml) and filtered through cealite bed and washed with ethyl acetate (50 ml). The organic layer was washed with brine solution (50 ml), dried with anhydrous sodium sulphate, concentrated under reduced pressure to obtain the crude. Crude was purified by combi-flash using ethyl acetate and petroleum ether (12:88) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as a pale-brown solid (1.10 g). Yield: 66%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 6.72 (t, J 4.0, 1H), 6.54 (dd, J 9.2, 5.6, 1H), 5.91 (s, 1H), 4.23 (t, J 4.0, 2H), 3.27-3.24 (m, 2H). MS (m/z): 188.14 ([M+H⁺]).

Intermediate 125: tert-butyl (2-(8-chloro-7-fluoro-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)-2-oxoethyl)carbamate



[279] Following the general procedure 1, the titled compound was synthesized from intermediate 124 (1.0 g, 5.33 mmol), dichloromethane (20 ml), N-Boc-glycine (1.02 g, 5.86 mmol), triethylamine (21.15 g, 21.32 mmol) and T₃P (Propyl phosphonic anhydride) (4.24 g, 13.33 mmol). Purification: Combi-Flash. Eluent: Ethyl acetate and petroleum ether (21:79) as eluent. Appearance: Off-white solid (0.75 g). Yield: 41%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 7.82 (s, 1H), 7.02-6.92 (m, 2H), 4.40 (t, J 4.4, 2H), 4.00 (d, J 6.0, 2H), 3.89 (t, J 4.4, 2H), 1.38 (s, 9H). MS (m/z): 345.82 [M+H]⁺.

Intermediate 126: 2-amino-1-(8-chloro-7-fluoro-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)ethan-1-one trifluoroacetic acid salt



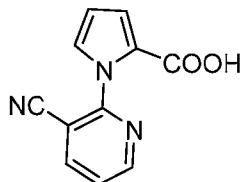
[280] Following the general procedure 2, the titled compound was synthesized from Intermediate 125 (700 mg, 2.33 mmol), dichloromethane (7 ml) and trifluoroacetic acid (1.99 g, 20.3 mmol). Purification: Not done. Appearance: Pale-brown liquid (0.640 g). Yield: 92%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 8.31(s, 1H), 8.17 (s, 3H), 7.14 (t, J 10.4, 1H), 4.34 (br s, 2H), 4.14 (s, 2H), 3.84 (br s, 2H). MS (m/z): 245.19 ([M-TFA+H]⁺).

Intermediate 127: 2-(2-formyl-1H-pyrrol-1-yl)nicotinonitrile



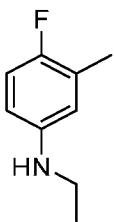
[281] To 1H-pyrrole-2-carboxaldehyde (0.500 g, 5.26 mmol) in DMF (2 ml), potassium carbonate (0.727 g, 5.26 mmol) and 2-chloro-3-cyanopyridine (1.46 g, 10.5 mmol) were added under nitrogen atmosphere and heated the reaction mixture to 70°C for 12 h. After 12h, reaction mixture cooled to room temperature, water (10 ml) was added to the reaction mixture and extracted with ethyl acetate (3 x 50 ml). Organic layer dried on anhydrous Na₂SO₄ and evaporated to obtain a crude. Crude was purified by combi-flash using ethyl acetate and petroleum ether (25:75) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as a pale brown solid (0.55 g). Yield: 53%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 9.59 (s, 1H), 8.83 (dd, J 4.8,2.0, 1H), 8.57 (dd, J 7.6,1.6, 1H), 7.71 (dd, J 7.6,4.8, 1H), 7.69 (m, 1H), 7.37 (dd, J 4.0,1.6, 1H), 6.57 (dd, J 7.6,2.8, 1H). MS (m/z): 198.04 ([M+H]⁺).

Intermediate 128: 1-(3-cyanopyridin-2-yl)-1H-pyrrole-2-carboxylic acid



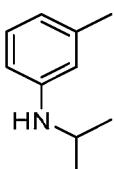
[282] To Intermediate 127 (0.500 g, 2.54 mmol) in acetone (4 ml), potassium permanganate (0.401 g, 2.54 mmol) in water (7.4 ml) was added and heated the reaction mixture to 60°C for 12 h. After 12h, reaction mixture cooled to room temperature, filtered through celite bed and washed with water (5 ml). Filtrate was washed with dichloromethane (20 ml) and pH adjusted to 3 with 2N HCl. The solid precipitated was filtered, washed with water (1 ml) and dried under vacuum to afford the titled compound as a pale brown solid (0.250g). Yield: 46%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 12.56 (s, 1H), 8.81 (dd, J 5.2,2.0, 1H), 8.53 (dd, J 7.6,1.6, 1H), 7.72 (dd, J 7.6,4.8, 1H), 7.40 (dd, J 2.8,2.0, 1H), 7.05 (dd, J 3.6,2.4, 1H), 6.41 (dd, J 3.2,2.8, 1H). MS (m/z): 214.05 ([M+H]⁺).

Intermediate 129: N-ethyl-4-fluoro-3-methylaniline

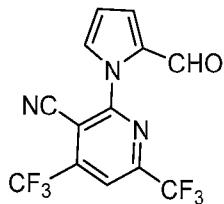


[283] To 4-fluoro-3-methylaniline (3.0 g, 24 mmol) in DMF (15 ml), cesium hydroxide monohydrate (4.83 g, 28.8 mmol) was added followed by 2-iodoethane (7.48 g, 47.9 mmol) and the reaction mixture stirred at 25°C for 18 h. After 18h, reaction mixture was diluted with water (25 ml) and extracted with ethyl acetate (3 x 25 ml). Organic layer was washed with water (2 x 25 ml), dried on anhydrous Na₂SO₄ and evaporated to obtain a crude. Crude was purified by combi-flash using ethyl acetate and petroleum ether (1:99) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as a pale-yellow liquid (1.40 g). Yield: 38%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 6.84 (t, J 9.60, 1H), 6.39 (d, J 7.6,0, 1H), 6.34 (t, J 4.4, 1H), 5.29 (s, 1H), 2.99 (m, 2H), 2.11(s, 3H), 1.14 (t, J 6.8, 3H). MS (m/z): 154.03 ([M+H]⁺).

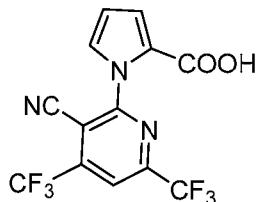
Intermediate 130: N-isopropyl-3-methylaniline



[284] To m-toluidine (2.5 g, 23 mmol) in DMF (2.5 ml), cesium hydroxide monohydrate (3.90 g, 23) was added followed by 2-iodopropane (4.0 g, 23 mmol) and the reaction mixture stirred at 25°C for 18 h. After 18h, reaction mixture was diluted with water (25 ml) and extracted with ethyl acetate (3 x 25 ml). Organic layer was washed with water (2 x 25 ml), dried on anhydrous Na₂SO₄ and evaporated to obtain a crude. Crude was purified by combi-flash using ethyl acetate and petroleum ether (1:99) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as a pale-yellow liquid (2.20 g). Yield: 63%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 6.93 (t, J 8.0, 1H), 6.34-6.28 (m, 3H), 5.18 (d, J 7.6,0, 1H), 3.54 (m, 1H), 2.16 (s, 3H), 1.14 (dt, J 6.4, 6H). MS (m/z): 150.00 ([M+H]⁺).

Intermediate 131: 2-(2-formyl-1H-pyrrol-1-yl)-4,6-bis(trifluoromethyl)nicotinonitrile

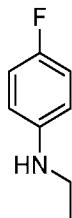
[285] To 1H-pyrrole-2-carboxaldehyde (1.00 g, 10.52 mmol) in DMF (10 ml), potassium carbonate (2.90 g, 21.03 mmol) was added and stirred at 25°C for 30 min. Intermediate 1 (3.17 g, 11.57 mmol) was added and stirred at 25°C for 30 min. The reaction mixture was diluted with water (100 ml) and extracted with ethyl acetate (3 x 150 ml). The Organic layer was washed with water (2 x 150ml), saturated sodium bicarbonate solution (50 ml), brine solution (2 x 150 ml), dried on anhydrous Na₂SO₄ and evaporated to obtain a crude. Crude was purified by combi-flash using ethyl acetate and petroleum ether (4:94) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as an off-white solid (1.70 g). Yield: 49%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 9.63 (s, 1H), 8.75 (s, 1H), 7.70 (d, J 0.8, 1H), 7.48 (dd, J 4.0, 1.6, 1H), 6.67 (t, J 3.2, 1H). MS (m/z): 334.20 ([M+H]⁺).

Intermediate 132: 1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-1H-pyrrole-2-carboxylic acid

[286] To intermediate 131 (1.70 g, 5.10 mmol) in acetone (32 ml), potassium permanganate (2.42 g, 15.3 mmol) in water (21.4 ml) was added and heated the reaction mixture to 60°C for 12 h. After 12h, reaction mixture cooled to room temperature, filtered through ceelite bed and washed with water (20 ml). Filtrate pH was adjusted to 10-12 by 2N NaOH solution, washed with dichloromethane (50 ml) and pH adjusted to 3 with 2N HCl. The solid precipitated was

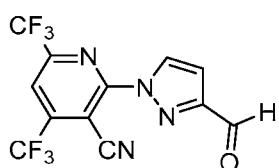
filtered, washed with water (2 ml) and dried under vacuum to afford the titled compound as a brown solid (0.550g). Yield: 30%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 12.95 (s, 1H), 8.71 (s, 1H), 7.49 (dd, J 2.8,2.0, 1H), 7.15 (dd, J 3.6,1.6, 1H), 6.51 (t, J 7.3,6, 1H).

Intermediate 133: N-ethyl-4-fluoroaniline



[287] To 4-fluoroaniline (2.0 g, 218mmol) in DMF (15 ml), cesium hydroxide monohydrate (3.63 g, 21.6 mmol) was added followed by 2-iodoethane (5.61 g, 36 mmol) and the reaction mixture stirred at 25°C for 18 h. After 18h, reaction mixture was diluted with water (25 ml) and extracted with ethyl acetate (3 x 25 ml). Organic layer was washed with water (2 x 25 ml), dried on anhydrous Na₂SO₄ and evaporated to obtain a crude. Crude was purified by combi-flash using ethyl acetate and petroleum ether (1:99) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as a pale-yellow liquid (1.30 g). Yield: 51%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 6.92 (t, J 8.8, 2H), 6.53 (dd, J 8.4,4.0, 2H), 5.14 (s, 1H), 3.00 (m, 2H), 1.15 (t, J 7.2, 3H). MS (m/z): 139.99 ([M+H]⁺).

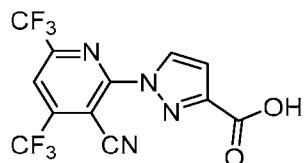
Intermediate 134: 2-(3-formyl-1H-pyrazol-1-yl)-4,6-bis(trifluoromethyl)nicotinonitrile



[288] To 1H-pyrazole-3-carboxaldehyde (1.50 g, 15.6 mmol) in DMF (15 ml), potassium carbonate (4.31 g, 31.22 mmol) was added and stirred at 25°C for 30 min. Intermediate 1 (4.71 g, 17.2 mmol) was added and stirred for 30 min. The reaction mixture was diluted with water (100 ml) and extracted with ethyl acetate (3 x 150 ml). The Organic layer was washed with water (2 x 150ml), saturated sodium bicarbonate solution (50 ml), brine solution (2 x 150 ml), dried on anhydrous Na₂SO₄ and evaporated to obtain a crude. Crude was purified by combi-flash using

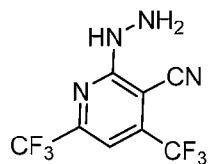
ethyl acetate and petroleum ether (6.6:93.4) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as a yellow solid (1.20 g). Yield: 23%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 10.08 (s, 1H), 8.79 (dd, 3.2, 1H), 8.61 (s, 1H), 7.18 (d, J 3.2, 1H). MS (m/z): 335.32 ([M+H]⁺).

Intermediate 135: 1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-1H-pyrazole-3-carboxylic acid



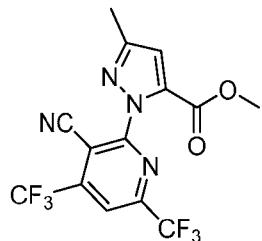
[289] To intermediate 134 (0.50 g, 1.50 mmol) in DMF (8 ml), Oxone (2.00 g, 3.25 mmol) was added and heated the reaction mixture to 25°C for 1.5 h. After 1.5h, reaction mixture was quenched with water (75 ml) and stirred for 1h. The solid precipitated was filtered, washed with water (50 ml), dissolved in ethyl acetate (50 ml) and dried concentrated to afford the titled compound as an off-white solid (0.425 g). Yield: 80%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 13.43 (s, 1H), 8.69 (d, J 3.2, 1H), 8.56 (s, 1H), 7.09 (d, J 2.8, 1H). MS (m/z): 331.11 ([M+H]⁺).

Intermediate 136: 2-hydrazinyl-4,6-bis(trifluoromethyl)nicotinonitrile



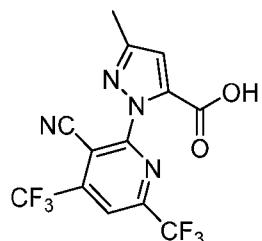
[290] To intermediate 1 (5.0 g, 18.2 mmol) in ethanol (50 ml), hydrazine hydrate (0.816 g, 16.3 mmol) was added and heated the reaction mixture to 80°C for 5 h. After 5h, reaction mixture was quenched with water (75 ml) and extracted with ethyl acetate (2 x 50 ml), dried on anhydrous Na₂SO₄ and evaporated to obtain a crude. Crude was purified by combi-flash using ethyl acetate and petroleum ether (17:83) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as a dark yellow solid (1.80 g). Yield: 37%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 13.39 (s, 1H), 7.73 (s, 1H), 5.35 (s, 2H). MS (m/z): 271.22 ([M+H]⁺).

Intermediate 137: 2-methyl 1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-3-methyl-1H-pyrazole-5-carboxylate



[291] To Intermediate 136 (0.500 g, 1.85 mmol), methyl 2,4-dioxopentanoate (0.267 g, 1.85 mmol) and acetic acid (7.5 ml) were added and heated the reaction mixture to 120°C for 12 h. After 12h, reaction mixture was concentrated, quenched with saturated sodium bicarbonate solution (75 ml) and extracted with ethyl acetate (3 x 50 ml), dried on anhydrous Na₂SO₄ and evaporated to obtain a crude. Crude was purified by combi-flash using ethyl acetate and petroleum ether (17:83) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as a pale-yellow solid (0.10 g). Yield: 14%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 8.40 (s, 1H), 8.17 (s, 1H), 4.02 (s, 3H), 3.08 (s, 3H). MS (m/z): 379.28 ([M+H]⁺).

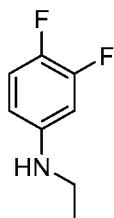
Intermediate 138: 1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-3-methyl-1H-pyrazole-5-carboxylic acid



[292] To Intermediate 137 (80 mg, 0.21 mmol), methanol (4 ml) was added and cooled to 0°C. 2N NaOH solution (2 ml) was added stirred the reaction mixture at 25°C for 1 h. After 1h, reaction mixture was concentrated, water ((10 ml) was added and pH adjusted to 3 using 2N HCl. Solid precipitated was filtered, washed with water (10 ml) and dried under vacuum to obtain the

titled compound as a yellow solid (50 mg). Yield: 65%. $^1\text{H-NMR}$ (δ ppm, DMSO-D₆, 400 MHz): 14.09 (s, 1H), 8.36 (s, 1H), 8.15 (s, 1H), 3.06 (s, 1H). MS (m/z): 365.28 ([M+H]⁺).

Intermediate 139: N-ethyl-3,4-difluoroaniline



[293] To 3,4-difluoroaniline (2.0 g, 15.49 mmol) in DMF (15 ml), cesium hydroxide monohydrate (3.12 g, 18.59 mmol) was added followed by 2-iodoethane (4.83 g, 30.98 mmol) and the reaction mixture stirred at 25°C for 18 h. After 18h, reaction mixture was diluted with water (25 ml) and extracted with ethyl acetate (3 x 25 ml). Organic layer was washed with water (2 x 25 ml), brine solution (3 x 25 ml), dried on anhydrous Na₂SO₄ and evaporated to obtain a crude. Crude was purified by combi-flash using ethyl acetate and petroleum ether (0.1:99.9) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as a pale-yellow liquid (1.30 g). Yield: 53%. $^1\text{H-NMR}$ (δ ppm, DMSO-D₆, 400 MHz): 7.11 (m, 1H), 6.49 (m, 1H), 6.32 (m, 1H), 5.73 (t, J 4.8, 1H), 3.00 (m, 2H), 1.15 (t, J 7.2, 3H). MS (m/z): 158.07 ([M+H]⁺).

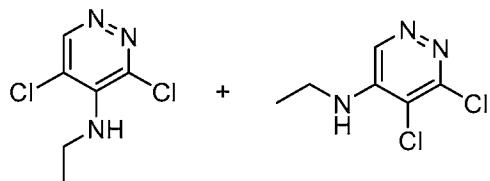
Intermediate 140: N-ethylpyridin-4-amine



[294] To 4-pyridylamine (5.0 g, 53.12 mmol) in THF (40 ml) cooled to 0°C, BuLi (3.40 g, 53.12 mmol; 21.25 ml (2.5 M in THF)) was added and stirred for 30 min. Ethyl iodide (9.94 g, 63.75 mmol) was added to the reaction mixture to 25°C and stirred for 2h. After 2h, reaction mixture was quenched with saturated ammonium chloride solution (50 ml) and extracted 5% MeOH in dichloromethane (3 x 50 ml). Organic layer was dried on anhydrous Na₂SO₄ and

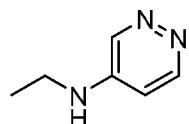
evaporated to obtain a crude. Crude was purified by combi-flash using methanol and dichloromethane (5:95) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as a pale-brown solid (1.30 g). Yield: 20%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 8.03 (dd, J 5.2, 1.6, 2H), 6.92 (m, 1H), 6.53 (d, J 4.8, 1.6, 2H), 3.14 (m, 2H), 1.16 (t, J 7.2, 3H). MS (m/z): 123.08 ([M+H]⁺).

Intermediate 141: 3,5-dichloro-N-ethylpyridazin-4-amine and 5,6-dichloro-N-ethylpyridazin-4-amine



[295] To 3,4,5-trichloropyridazine (5.0 g, 27.26 mmol) in butyl acetate (25 ml), ethylamine (70% in water, 5.26 ml, 81.78 mmol) was added and the reaction mixture heated to 45°C for 3 h. After 3h, reaction mixture was evaporated to obtain a crude. Crude product was stirred with Diisopropyl ether (10 ml), filtered, washed with diisopropyl ether (5 ml) and to obtain the mixture of titled compounds as a pale-yellow liquid (3.5 g). Yield: 67%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 8.76 (s, 1H), 8.69 (s, 1H), 7.19 (t, J 5.2, 1H), 6.79 (t, J 5.2, 1H), 3.70 (m, 2H), 3.63 (m, 2H), 1.91 (t, J 6.8, 3H, 1.86 (t, J 6.8, 3H). MS (m/z): 192.13 ([M]⁺).

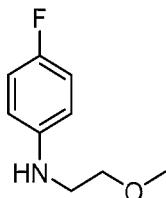
Intermediate 142: N-ethylpyridazin-4-amine



[296] To intermediate 141 (1.0 g, 5.206 mmol) in ethanol (5 ml), Pd/C (5%, 50% wet, 60mg) was added and stirred in an autoclave at 40°C for 12 h under hydrogen pressure (0.2bar). After 12h, reaction mixture was cooled to room temperature, filter through celite and washed with ethanol (25 ml). The filtrate was stirred with solid potassium carbonate (2g), filtered and evaporated to obtain a crude. Crude was purified by combi-flash using methanol and dichloromethane (3:97) as eluent. Combined pure fractions from column were evaporated to

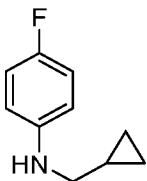
obtain the titled compound as a pale-brown solid (0.32 g). Yield: 50%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 8.54 (dd, J 3.2, 0.8, 1H), 8.48 (d, J 6.0, 1H), 6.87 (br s, 1H), 6.55 (dd, J 6.0, 3.2, 1H), 3.14 (m, 2H), 1.17 (t, J 7.2, 3H). MS (m/z): 124.04 ([M+H]⁺).

Intermediate 143: 4-fluoro-N-(2-methoxyethyl)aniline



[297] To 4-fluoroaniline (2.0 g, 18.0 mmol) in DMF (20 ml), sodium carbonate (3.82 g, 36.0 mmol) was added followed by 1-bromo-2-methoxyethane (2.50 g, 18.0 mmol) and the reaction mixture heated to 80°C and stirred for 18 h. After 18h, reaction mixture cooled to room temperature, diluted with water (100 ml) and extracted with ethyl acetate (3 x 50 ml). Organic layer was washed with water (2 x 150 ml), dried on anhydrous Na₂SO₄ and evaporated to obtain a crude. Crude was purified by combi-flash using ethyl acetate and petroleum ether (8.1:91.9) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as a yellow liquid (2.10 g). Yield: 69%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 6.91-6.87 (m, 2H), 6.59-6.54 (m, 2H), 5.46 (t, J 5.6, 1H), 3.45 (m, 2H), 3.27 (s, 3H), 3.15 (q, J 5.6, 2H).

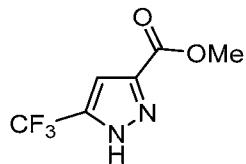
Intermediate 144: N-(cyclopropylmethyl)-4-fluoroaniline



[298] To 4-Fluoroaniline (1.0 g, 9.0 mmol) and cyclopropane carboxylic acid (1.51 g, 27.1 mmol) in acetonitrile (35 ml), borane-ammonia complex (556 mg, 18.0 mmol) was added followed by methane sulfonic acid (1.730 g, 18.0 mmol) and the reaction mixture heated to 60°C and stirred for 18 h. After 18h, reaction mixture cooled to room temperature and evaporated to obtain a crude. Crude was purified by combi-flash using ethyl acetate and petroleum ether (10.5:89.5) as eluent. Combined pure fractions from column were evaporated to obtain the titled

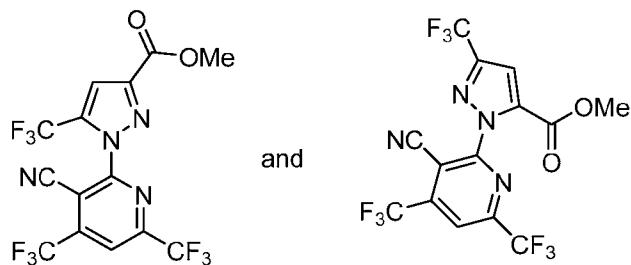
compound as a yellow liquid (250 mg). Yield: 17%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 6.90-6.86 (m, 2H), 6.57-6.53 (m, 2H), 5.52 (t, J 5.6, 1H), 2.84 (t, J 6.4, 2H), 1.03-0.97 (m, 1H), 0.47-0.43 (m, 2H), 0.21-0.17 (m, 2H). MS (m/z): 166.11 ([M+H]⁺).

Intermediate 145: methyl 5-(trifluoromethyl)-1H-pyrazole-3-carboxylate



[299] To 2,2,2-Trifluoroethylamine hydrochloride (5.0 g, 36.9 mmol), sodium nitrite (2.55 g, 36.9 mmol), Toluene (60 ml) and water (3 ml) were added and stirred at 0°C for 30 min. Methyl propiolate (1.09 g, 12.9 mmol) was added and warmed to room temperature. After 1h, reaction mixture was quenched with water (25 ml) and extracted with ethyl acetate 30 ml). The organic layer was distilled out completely to obtain a crude. Crude product was stirred with Petroleum ether (25 ml), filtered and washed with petroleum ether (10 ml) to obtain the titled compound as an off-white solid (2.4g). Yield: 34%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 14.88 (s, 1H), 7.31 (s, 1H), 3.88 (s, 3H). MS (m/z): 195.11 ([M+H]⁺).

Intermediate 146: methyl 1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-5-(trifluoromethyl)-1H-pyrazole-3-carboxylate (147a) and methyl 1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxylate (147b)



146a

146b

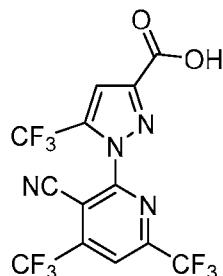
[300] To intermediate 145 (1.50 g, 7.72 mmol) in DMF (35 ml), potassium carbonate (2.13 g, 14.46 mmol) was added and stirred at 25°C for 30 min. Intermediate 131 (2.33 g, 8.5 mmol) was added and stirred for 30 min. The reaction mixture was diluted with water (100 ml) and extracted

with ethyl acetate (3×150 ml). The Organic layer was washed with water (2×150 ml), brine solution (2×150 ml), dried on anhydrous Na_2SO_4 and evaporated to obtain a crude mixture of 21a and 21b. Crude was purified by combi-flash using ethyl acetate and petroleum ether (4.6:95.4) as eluent. Compound 23a was eluting fast and 23b was eluting later. Combined pure fractions from column were evaporated to obtain the titled compounds as a pale-brown solid (21a: 1.50 g and 21b: 0.90 g). Yield: 72%.

146a: $^1\text{H-NMR}$ (δ ppm, CDCl_3 , 400 MHz): 8.19 (s, 1H), 7.33 (s, 1H), 3.89 (s, 3H). MS (m/z): 431.45 ($[M-\text{H}]^+$).

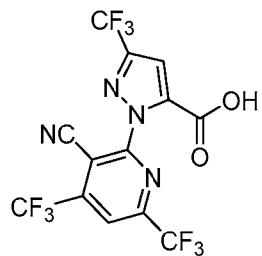
146b: $^1\text{H-NMR}$ (δ ppm, CDCl_3 , 400 MHz): 8.17 (s, 1H), 7.50 (s, 1H), 4.02 (s, 3H). MS (m/z): 433.43 ($[M+\text{H}]^+$).

Intermediate 147: 1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-5-(trifluoromethyl)-1H-pyrazole-3-carboxylic acid



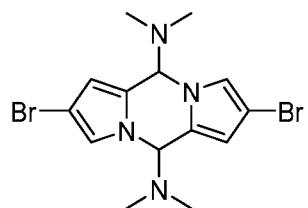
[301] To Intermediate 146a (500 mg, 1.16 mmol) in THF (20 ml) cooled to 0°C, NaOH (0.80 mg, 19.9 mmol) in water (10 ml) was added and stirred the reaction mixture at 0°C for 3 h. After 3h, reaction mixture was quenched with ice cold water and pH adjusted to 3 using 2N HCl . The aqueous solution was extracted with dichloromethane (3×20 ml) and distilled out completely to obtain the crude. The crude product was washed with petroleum ether to obtain the titled compound as an Off-white solid (250 mg). Yield: 51%. $^1\text{H-NMR}$ (δ ppm, DMSO-D_6 , 400 MHz): 8.89 (s, 1H), 7.81 (s, 1H). MS (m/z): 419.21 ($[M+\text{H}]^+$).

Intermediate 148: 1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxylic acid



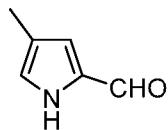
[302] To Intermediate 146b (200 mg, 0.46 mmol) in THF (8 ml) cooled to 0°C, NaOH (0.31 g, 7.87 mmol) in water (4 ml) was added and stirred the reaction mixture at 0°C for 2 h. After 2h, reaction mixture was quenched with ice cold water and pH adjusted to 3 using 2N HCl. The aqueous solution was extracted with dichloromethane (3 x 20 ml) and distilled out completely and stirred with petroleum ether (2 ml) and filtered to obtain the titled compound as an off-white solid (90 mg). Yield:47%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 13.89 (s, 1H), 8.76 (s, 1H), 7.82 (s, 1H). MS (m/z): 441.34 ([M+Na]⁺).

Intermediate 149: 2,7-dibromo-N5,N5,N10,N10-tetramethyl-5H,10H-dipyrrolo[1,2-a:1',2'-d]pyrazine-5,10-diamine



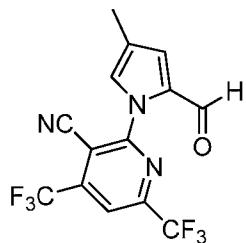
[303] To 4-bromo-pyrrole-2-carboxaldehyde (5.0 g, 28.7 mmol), dimethylamine in 40% water (25 ml, 0.36 mol) was added and stirred the reaction mixture at 25°C for 4h. After 4h, reaction mixture was quenched with water (25 ml). The solid formed was filtered, washed with 1N NaOH solution (25 ml), ethyl acetate (5 ml) and dried under vacuum for 12h. The solid was stirred with diethyl ether (10 ml) for 30 min., filtered, washed with diethyl ether (5 ml) and dried under vacuum to obtain the titled compound as an off-white solid (3.50 g). Yield:30%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 7.07 (d, J 1.6, 2H), 6.20 (d, J 1.2, 2H), 5.79 (s, 2H), 2.13 (s, 12H).

Intermediate 150: 4-methyl-1H-pyrrole-2-carbaldehyde



[304] To intermediate 149 (1.50 g, 3.73 mmol) in THF (100 ml) cooled to -78°C, tert-BuLi (1.5 M in pentane, 9.95 ml, 14.92 mmol) was added and stirred the reaction mixture at -78°C for 30 min. Methyl iodide (2.11 g, 14.92 mmol) was added at -78°C, stirred at -78°C for 30 min., -50°C for 1h and then at 25°C for 30 min. The reaction mixture was quenched with water (25 ml) and sodium bicarbonate solution (50 ml). The reaction mixture was heated to 90°C. After 15h, cooled to room temperature and extracted with ethyl acetate (3 x 50 ml). The organic layer was distilled under vacuum using rotavapor to obtain the crude. Crude was purified by combi-flash using ethyl acetate and petroleum ether 15:85) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as a pale brown gummy solid (50 mg). Yield: 61%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 11.78 (s, 1H), 9.37 (d, J 1.2, 1H), 7.21 (m, 1H), 6.78 (t, 1.6, 1H), 2.05 (s, 3H). MS (m/z): 110.01 ([M+H]⁺).

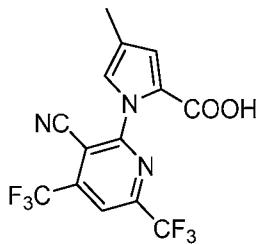
Intermediate 151: **2-(2-formyl-4-methyl-1H-pyrrol-1-yl)-4,6-bis(trifluoromethyl)nicotinonitrile**



[305] To intermediate 150 (0.50 g, 4.58 mmol) in DMF (35 ml), potassium carbonate (1.27 g, 9.16 mmol) was added and stirred at 25°C for 30 min. Intermediate 1 (1.38 g, 5.04 mmol) was added and stirred for 30 min. The reaction mixture was diluted with water (10 ml) and extracted with ethyl acetate (3 x 15 ml). The Organic layer was washed with water (2 x 15 ml), brine solution (2 x 15 ml), dried on anhydrous Na₂SO₄ and evaporated to obtain a crude. Crude was purified by combi-flash using ethyl acetate and petroleum ether (4:94) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as a pale-brown solid (0.50

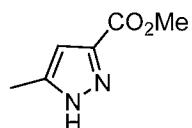
g). Yield: 30%. $^1\text{H-NMR}$ (δ ppm, DMSO-D₆, 400 MHz): 9.56 (s, 1H), 8.70 (s, 1H), 7.49 (s, 1H), 7.31 (s, 1H), 2.17 (s, 3H). MS (m/z): 348.25 ($[M+\text{H}]^+$).

Intermediate 152: 1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-4-methyl-1H-pyrrole-2-carboxylic acid



[306] To Intermediate 151 (0.50 g, 1.44 mmol) in acetone (18 ml), potassium permanganate (0.455 g, 2.88 mmol) in water (13 ml) was added and heated the reaction mixture to 25°C for 4 h. After 12h, reaction mixture cooled to room temperature, filtered through cealite bed and washed with water (20 ml). Filtrate pH was adjusted 3 with 2N HCl and extracted with ethyl acetate (3 x 50 ml). The Organic layer was dried on anhydrous Na₂SO₄ and evaporated to obtain a crude. Crude was purified by combi-flash using ethyl acetate and petroleum ether (15:85) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as a pale-brown solid (0.150 g). Yield: 28%. $^1\text{H-NMR}$ (δ ppm, DMSO-D₆, 400 MHz): 12.85 (s, 1H), 8.66 (s, 1H), 7.25 (s, 1H), 6.99 (d, J 1.2, 1H), 2.12 (s, 3H). MS (m/z): 364.19 ($[M+\text{H}]^+$).

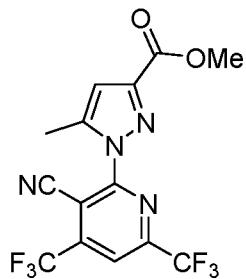
Intermediate 153: methyl 5-methyl-1H-pyrazole-3-carboxylate



[307] To methyl 2,4-dioxopentanoate (5.0 g, 34.6 mmol) in methanol (65 ml) cooled to 0°C, hydrazine hydrate (80%) was added and stirred for 30 min. After 30 min. at room temperature, the solvent was distilled out under vacuum using rotavapor. The residue was dissolved in ethyl acetate (50 ml), washed with water (2 x 20 ml), dried over anhydrous sodium sulphate and concentrated under reduced pressure using rotavapor. The crude obtained was stirred with petroleum ether (20 ml), filtered and washed with petroleum ether (10 ml) to obtain the titled

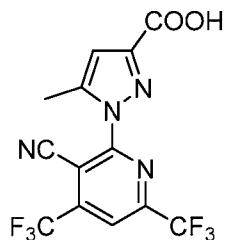
compound as an off-white solid (3.0 g). Yield: 61%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 13.71 (s, 1H), 6.47 (s, 1H), 3.76 (s, 3H), 2.25 (s, 3H). MS (m/z): 140.96 ([M+H]⁺).

Intermediate 154: methyl 1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-5-methyl-1H-pyrazole-3-carboxylate



[308] To intermediate 153 (1.0 g, 7.14 mmol) in DMF (10 ml), potassium carbonate (1.97 g, 14.27 mmol) was added and stirred at 25°C for 30 min. Intermediate 1 (2.33 g, 8.5 mmol) was added and stirred for 30 min. The reaction mixture was diluted with water (30 ml) and extracted with ethyl acetate (3 x 50 ml). The Organic layer was washed with water (2 x 50ml), brine solution (2 x 50 ml), dried on anhydrous Na₂SO₄ and evaporated to obtain a crude. Crude was purified by combi-flash using ethyl acetate and petroleum ether (10:90) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as an off-white solid (1.70 g). Yield: 63%. ¹H-NMR (δ ppm, CDCl₃, 400 MHz): 8.03 (s, 1H), 6.85 (s, 1H), 3.79 (s, 3H), 2.61 (s, 3H). MS (m/z): 379.11 ([M+H]⁺).

Intermediate 155: 1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-5-methyl-1H-pyrazole-3-carboxylic acid



[309] To Intermediate 154 (1.0 g, 2.64 mmol) in THF (40 ml) cooled to 0°C, NaOH (1.80 g, 44.95 mmol) in water (20 ml) was added stirred the reaction mixture at 0°C for 3 h. After 3h,

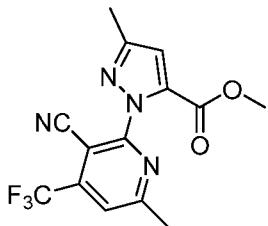
reaction mixture was quenched with ice cold water (10 ml), the pH adjusted to 3 using 2N HCl, extracted with dichloromethane (3 x 30 ml). The organic layer was washed with water (2 x 20 ml), distilled under vacuum using rotavapor to obtain the crude. The crude compound was washed with diethyl ether (5 ml) to obtain the titled compound as an off-white solid (0.60 g). Yield: 62%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 13.26 (s, 1H), 8.65 (s, 1H), 6.88 (s, 1H), 2.53 (s, 3H). MS (m/z): 365.07 ([M+H]⁺).

Intermediate 156: 2-hydrazinyl-6-methyl-4-(trifluoromethyl)nicotinonitrile



[310] To Intermediate 82 (5.0 g, 22.7 mmol) in ethanol (50 ml), hydrazine hydrate (1.02 g, 20.3 mmol) was added and heated the reaction mixture to 100°C for 72 h. After 72h, reaction mixture was quenched with water (75 ml) and the solid precipitated was filtered and washed with water (100 ml).to obtain a crude. Crude was purified by combi-flash using ethyl acetate and petroleum ether (37:63) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as a yellow solid (1.30 g). Yield: 27%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 12.60 (s, 1H), 7.26 (s, 1H), 4.96 (s, 2H), 2.60 (s, 3H). MS (m/z): 217.20 ([M+H]⁺).

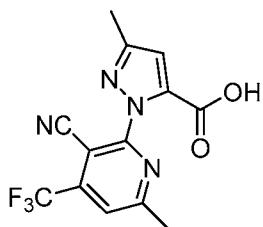
Intermediate 157: methyl 1-(3-cyano-6-methyl-4-(trifluoromethyl)pyridin-2-yl)-3-methyl-1H-pyrazole-5-carboxylate



[311] To Intermediate 156 (1.30 g, 6.01 mmol), methyl 2,4-dioxopentanoate (0.867 g, 6.01 mmol) and acetic acid (20 ml) were added and heated the reaction mixture to 120°C for 12 h. After 12h, reaction mixture was concentrated, quenched with saturated sodium bicarbonate solution (75 ml) and extracted with ethyl acetate (3 x 100 ml), dried on anhydrous Na₂SO₄ and

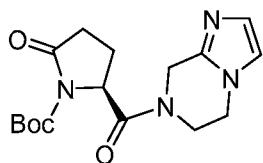
evaporated to obtain a crude. Crude was purified by combi-flash using ethyl acetate and petroleum ether (37:63) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as a pale-yellow solid (0.155 g). Yield: 8%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 8.19 (s, 1H), 7.74 (s, 1H), 3.99 (s, 3H), 3.01 (s, 3H), 2.81 (s, 3H). MS (m/z): 325.34 ([M+H]⁺).

Intermediate 158: 1-(3-cyano-6-methyl-4-(trifluoromethyl)pyridin-2-yl)-3-methyl-1H-pyrazole-5-carboxylic acid



[312] To Intermediate 157 (155 mg, 0.47 mmol), THF (13 ml) was added and cooled to 0°C. NaOH (329 mg, 8.22 mmol) in water (12 ml) was added stirred the reaction mixture at 0°C for 2 h. After 2h, reaction mixture was quenched with water ((5 ml) was added and pH adjusted to 3 using 2N HCl. The aqueous layer was extracted with dichloromethane (3 x 20 ml). The organic layer was washed with water (20 ml) and concentrated under vacuum to obtain the titled compound as a yellow solid (110 mg). Yield: 74%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 13.88 (s, 1H), 8.15 (s, 1H), 7.71 (s, 1H), 3.00 (s, 3H), 2.81 (s, 3H). MS (m/z): 311.24 ([M+H]⁺).

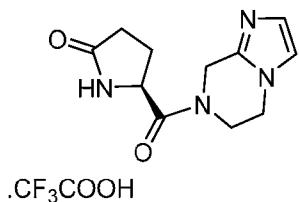
Intermediate 159: tert-butyl (S)-2-oxo-5-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-7-carbonyl)pyrrolidine-1-carboxylate



[313] Following the general procedure 1, the titled compound was synthesized from (R)-1-(tert-butoxycarbonyl)-5-oxopyrrolidine-2-carboxylic acid (500 mg, 2.18 mmol), ethyl acetate (5 ml), 5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine (269 mg, 2.18 mmol), pyridine (1.73 g, 21.8 mmol) and Propyl phosphonic acid anhydride (T3P) (3.47 g, 10.9 mmol; 6.94 ml (50% solution in ethyl

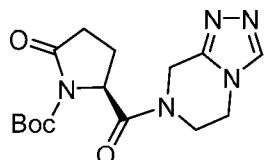
acetate). Purification: Combi-Flash. Eluent: methanol and dichloromethane (10:90) as eluent. Appearance: Off-white solid (320 mg). Yield: 43%. MS (m/z): 335.18 ($[M+H]^+$).

Intermediate 160: (S)-5-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-7-carbonyl)pyrrolidin-2-one trifluoroacetic acid salt



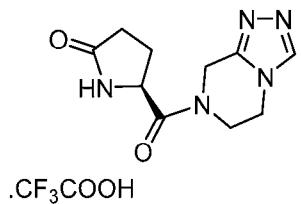
[314] Following the general procedure 2, the titled compound was synthesized from Intermediate 159 (310 mg, 0.927 mmol), dichloromethane (5 ml) and trifluoroacetic acid (1.06 g, 9.27 mmol). Purification: Not done. Appearance: Brown gummy liquid (0.60 g). Yield: >100%. MS (m/z): 235.28 ($[M-TFA+H]^+$).

Intermediate 161: tert-butyl (S)-2-oxo-5-(5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine-7-carbonyl)pyrrolidine-1-carboxylate



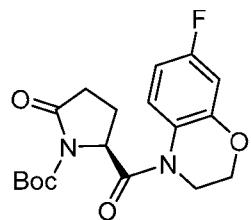
[315] Following the general procedure 1, the titled compound was synthesized from (R)-1-(tert-butoxycarbonyl)-5-oxopyrrolidine-2-carboxylic acid (500 mg, 2.18 mmol), ethyl acetate (5 ml), DMF (1 ml), 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine (271 mg, 2.18 mmol), pyridine (690 mg, 8.72 mmol) and Propyl phosphonic acid anhydride (T3P) (1.74 g, 5.45 mmol; 7.12 ml (50% solution in ethyl acetate). Purification: Combi-Flash. Eluent: methanol and dichloromethane (11.6:88.4) as eluent. Appearance: Off-white solid (150 mg). Yield: 20%. MS (m/z): 336.17 ($[M+H]^+$).

Intermediate 162: (S)-5-(5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine-7-carbonyl)pyrrolidin-2-one trifluoroacetic acid salt



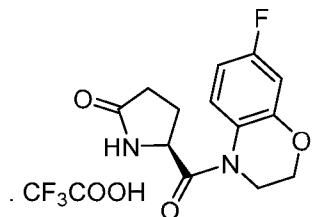
[316] Following the general procedure 2, the titled compound was synthesized from Intermediate 161 (150 mg, 0.467 mmol), dichloromethane (2.5 ml) and trifluoroacetic acid (532 mg g, 4.67 mmol). Purification: Not done. Appearance: Brown gummy liquid (0.30 g). Yield: >100%. MS (m/z): 236.33 ([M-TFA+H]⁺).

Intermediate 163: tert-butyl (S)-2-(7-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazine-4-carbonyl)-5-oxopyrrolidine-1-carboxylate



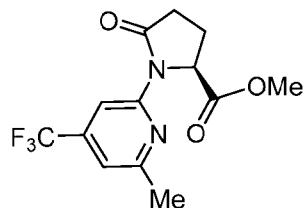
[317] Following the general procedure 1, the titled compound was synthesized from (R)-1-(tert-butoxycarbonyl)-5-oxopyrrolidine-2-carboxylic acid (1.49 g, 6.53 mmol), ethyl acetate (18 ml), 7-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazine (1.00 g, 6.53 mmol), pyridine (2.06 g, 26.12 mmol) and Propyl phosphonic acid anhydride (T3P) (5.19 g, 16.32 mmol; 10.4 ml (50% solution in ethyl acetate). Purification: Combi-Flash. Eluent: ethyl acetate and petroleum ether (40:60) as eluent. Appearance: Off-white solid (1.00 g). Yield: 42%. MS (m/z): 265.25 ([M-Boc+H]⁺).

Intermediate 164: (S)-5-(7-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazine-4-carbonyl)pyrrolidin-2-one trifluoroacetic acid salt



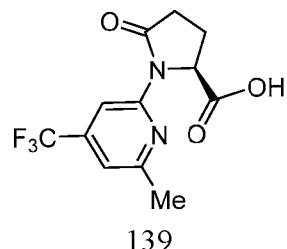
[318] Following the general procedure 2, the titled compound was synthesized from Intermediate 163 (850 mg, 2.33 mmol), dichloromethane (8.5 ml) and trifluoroacetic acid (2.66 g, 23.3 mmol). Purification: Not done. Appearance: Brown gummy liquid (0.900 g). Yield: >100%. MS (m/z): 265.25 ($[M-TFA+H]^+$).

Intermediate 165: methyl (S)-1-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)-5-oxopyrrolidine-2-carboxylate



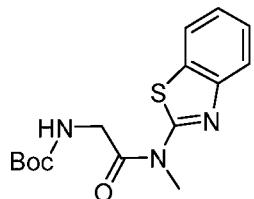
[319] To methyl (S)-5-oxopyrrolidine-2-carboxylate (0.50 g, 3.49 mmol) in 1,4-dioxane (20 ml), 2-bromo-6-methyl-4-(trifluoromethyl)pyridine (1.26 g, 5.24 mmol), xantphos (412 mg, 0.713 mmol), cesium carbonate (2.28 g, 6.69 mmol) was added and degassed with nitrogen for 30 min. Pd₂(dba)₃ (320 mg, 0.349 mmol) was added again degassed with nitrogen for 20 min. The reaction mixture was stirred at 100°C. After 30 min., the reaction mixture cooled to room temperature, filtered through cealite bed and washed with ethyl acetate (50 ml). The filtrate was washed with water (50 ml), brine solution (50 ml), dried with anhydrous sodium sulphate and evaporated to obtain crude. Crude product was purified by combi-flash using ethyl acetate: petroleum ether (16:84) as eluent to obtain the titled compound as a yellow liquid (400 mg). Yield: 57 %. ¹H-NMR (δ ppm, DMSO-*d*₆, 400 MHz): 8.34 (t, J 0.8, 1H), 7.42 (s, 1H), 5.02 (dd, J 9.6, 3.6, 1H), 3.68 (s, 3H), 2.69-2.63 (m, 2H), 2.49-2.41 (m, 1H), 2.47 (s, 3H), 2.09-2.01 (m, 1H). MS (m/z): 303.28 ($[M+H]^+$).

Intermediate 166: (S)-1-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)-5-oxopyrrolidine-2-carboxylic acid



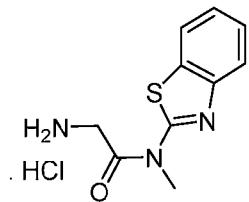
[320] To Intermediate 165 (300 mg, 0.993 mmol), THF (7 ml) was added and cooled to 0°C. LiOH (71.3 mg, 2.98 mmol) in water (1.7 ml) was added stirred the reaction mixture at 25°C for 16 h. After 16h, water ((5 ml) was added, reaction mixture was concentrated, and pH adjusted to 5 using 2N HCl. The aqueous layer was extracted with 10% methanol in dichloromethane (3 x 30 ml), washed with brine solution (20 ml), dried with anhydrous sodium sulphate and concentrated under reduced pressure. The residue was triturated with petroleum ether (5 ml), filtered the solid precipitated and dried under vacuum to obtain the titled compound as a yellow solid (50 mg). Yield: 17%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 12.89 (s, 1H), 8.04 (s, 1H), 7.41 (s, 1H), 4.98 (dd, J 9.6,3.2, 1H), 3.68 (s, 3H), 2.72-2.57 (m, 2H), 2.49 (s, 3H), 2.48-2.40 (m, 1H), 2.09-2.01 (m, 1H). MS (m/z): 289.31 ([M+H]⁺).

Intermediate 167: tert-butyl (2-(benzo[d]thiazol-2-yl(methyl)amino)-2-oxoethyl)carbamate



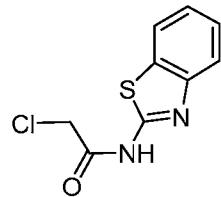
[321] Following the general procedure 1, the titled compound was synthesized from N-methylbenzo[d]thiazol-2-amine (1.00 g, 6.08 mmol), ethyl acetate (20 ml), N-Boc-glycine (1.06 g, 6.08 mmol), pyridine 1.93 g, 24.36 mmol and Propyl phosphonic acid anhydride (T3P) (4.84 g, 15.22 mmol; 9.7 ml (50% solution in ethyl acetate). Purification: Combi-Flash. Eluent: ethyl acetate and petroleum ether (25:75) as eluent. Appearance: Off-white solid (1.20 g). Yield: 61%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 7.98 (d, J 7.6, 1H), 7.82 (d, J 7.6, 1H), 7.47 (dt, J 7.2,1.2, 1H), 7.34 (dt, J 8.0,1.2, 1H), 7.21 (t, J 6.0, 1H), 4.23 (d, J 6.0, 2H), 3.73 (s, 3H), 1.42 (s, 9H). MS (m/z): 322.03 ([M+Boc+H]⁺).

Intermediate 168: 2-amino-N-(benzo[d]thiazol-2-yl)-N-methylacetamide hydrochloride



[322] To Intermediate 167 (500 mg, 1.56 mmol), ethanol (10 ml) and HCl (1.13 g, 31.1 mmol) were added and heated to 70°C. After 1h cooled to 0°C, filtered the solid and washed with ethanol (5 ml). The solid was dried under vacuum to afford the titled compound as an off-white solid (0.24 g). Yield: 60%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 8.57 (s, 3H), 8.04-8.02 (m, 1H), 7.87-7.84 (m, 1H), 7.50 (dt, J 7.2,1.2, 1H), 7.39 (dt, J 7.2,1.2, 1H), 4.34 (s, 2H), 3.74 (s, 3H). MS (m/z): 222.09 ([M-HCl+H]⁺).

Intermediate 169: N-(benzo[d]thiazol-2-yl)-2-chloroacetamide



[323] To benzo[d]thiazol-2-amine (3.0 g, 19.97 mmol) in Dichloromethane (80 ml), triethylamine (4.04 g, 39.95 mmol) was added and cooled to 0°C. Chloroacetyl chloride (2.70 g, 23.97 mmol) was added and stirred at 25°C for 3h. After 3h, the reaction mixture was quenched with saturated sodium bicarbonate solution (20 ml) and extracted with dichloromethane (3 x 30 ml). The organic layer was dried with anhydrous sodium sulphate and distilled out to obtain the crude. Crude was purified by combi-flash using ethyl acetate and petroleum ether (20:80) as eluent. Combined pure fractions from column were evaporated to obtain the titled compound as a pale brown solid (2.40 g). Yield: 53%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 12.71 (s, 1H), 8.01 (d, J 7.6, 1H), 7.78 (d, J 8.0, 1H), 7.47 (dt, J 8.0,1.2, 1H), 7.35 (dt, J 8.0,0.8, 1H), 4.46 (s, 2H).

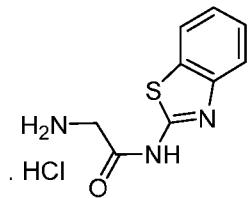
MS (m/z): 227.18 ([M+H]⁺).

Intermediate 170: 2-azido-N-(benzo[d]thiazol-2-yl)acetamide



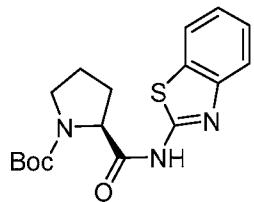
[324] To intermediate 169 (1.00 g, 4.00 mmol) in DMSO (10 ml), sodium azide (400 mg, 7.0 mmol) was added and stirred at 25°C for 4h. After 4h, the reaction mixture was diluted with water (50 ml), the precipitate formed was filtered and dried under vacuum to obtain the titled compound as a pale brown solid (0.90 g). Yield: 90%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 12.56 (s, 1H), 8.01 (d, J 8.0, 1H), 7.77 (d, J 8.0, 1H), 7.47 (dt, J 8.0, 1.2, 1H), 7.34 (dt, J 8.0, 0.8, 1H), 4.29 (s, 2H). MS (m/z): 234.13 ([M+H]⁺).

Intermediate 171: 2-amino-N-(benzo[d]thiazol-2-yl)acetamide hydrochloride



[325] To intermediate 170 (800 mg, 3.43 mmol) in THF (10.6 ml), triphenylphosphine (1.80 g, 6.86 mmol) was added and stirred at room temperature for 2h. water (1.6 ml mmol) was added and stirred at 75°C for 4h. After 3h, the reaction mixture was diluted with water (50 ml) and extracted with ethyl acetate (3 x 50 ml). The organic layer was dried with anhydrous sodium sulphate and distilled out to obtain the crude. To the crude, ethanol (5 ml) and HCl (0.8 ml) were added, stirred at 0°C for 30 min. The precipitate formed was filtered, washed with ethanol (5 ml) and dried under vacuum to obtain the titled compound as a pale brown solid (600 mg). Yield: 70%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 8.54 (s, 3H), 8.03 (d, J 7.6, 1H), 7.79 (d, J 8.0, 1H), 7.48 (dt, J 7.6, 1.6, 1H), 7.36 (dt, J 8.0, 1.2, 1H), 3.99 (q, J 6.0, 2H). MS (m/z): 208.17 ([M-HCl+H]⁺).

Intermediate 172: tert-butyl (S)-2-(benzo[d]thiazol-2-ylcarbamoyl)pyrrolidine-1-carboxylate



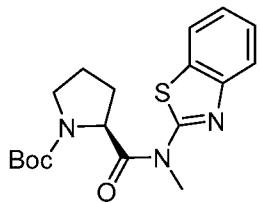
[326] Following the general procedure 1, the titled compound was synthesized from tert-butoxycarbonyl-L-proline (1.58 g, 7.32 mmol), ethyl acetate (10 ml), benzo[d]thiazol-2-amine (1.00 g, 6.66 mmol), pyridine (2.11 g, 26.6 mmol) and Propyl phosphonic acid anhydride (T3P) (4.24 g, 13.3 mmol; 8.5 ml (50% solution in ethyl acetate). Purification: Combi-Flash. Eluent: ethyl acetate and petroleum ether (21:79) as eluent. Appearance: Off-white solid (0.85 g). Yield: 37%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 12.54 (s, 1H), 8.03 (d, J 7.6, 1H), 7.75 (d, J 8.0, 1H), 7.46 (dt, J 8.4, 1.2, 1H), 7.33 (d, J 8.0, 1H), 4.40 (dd, J 8.0, 4.8, 1H), 3.47-3.31 (m, 2H), 2.27-2.23 (m, 1H), 1.94-1.81 (m, 3H), 1.40 (s, 3H), 1.23 (s, 6H). MS (m/z): 348.03 ([M+H]⁺).

Intermediate 173: (S)-N-(benzo[d]thiazol-2-yl)pyrrolidine-2-carboxamide hydrochloride



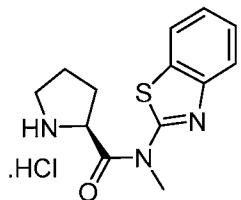
[327] To Intermediate 172 (630 mg, 1.80 mmol), ethanol (10 ml) and HCl (66 mg, 1.80 mmol) were added and heated to 80°C. After 1h cooled to 0°C, filtered the solid and washed with ethanol (5 ml). The solid was dried under vacuum to afford the titled compound as an off-white solid (0.41 g). Yield: 80%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 13.04 (s, 1H), 9.99 (s, 1H), 8.93 (s, 1H), 8.04 (d, J 8.0, 1H), 7.81 (d, J 8.0, 1H), 7.49 (dt, J 7.2, 1.2, 1H), 7.37 (dt, J 8.0, 0.8, 1H), 4.55 (t, J 7.6, 1H), 3.32-3.27 (m, 2H), 2.46-2.40 (m, 1H), 2.07-1.93 (m, 3H), MS (m/z): 248.17 ([M-HCl+H]⁺).

Intermediate 174: tert-butyl (S)-2-(benzo[d]thiazol-2-yl(methyl)carbamoyl)pyrrolidine-1-carboxylate



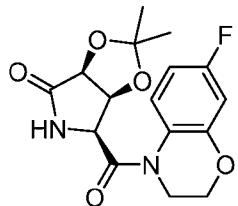
[328] Following the general procedure 1, the titled compound was synthesized from tert-butoxycarbonyl-L-proline (1.44 g, 6.70 mmol), ethyl acetate (10 ml), N-methylbenzo[d]thiazol-2-amine (1.00 g, 6.09 mmol), pyridine (1.93 g, 24.4 mmol) and Propyl phosphonic acid anhydride (T3P) (3.87 g, 12.2 mmol; 7.7 ml (50% solution in ethyl acetate). Purification: Combi-Flash. Eluent: ethyl acetate and petroleum ether (23:77) as eluent. Appearance: Off-white solid (1.50 g). Yield: 68%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 8.00 (t, J 8.0, 1H), 7.83 (d, J 8.0, 1H), 7.47 (d, J 8.0, 1H), 7.35 (t, J 7.6, 1H), 4.95 (dd, J 7.6, 4.4, 1H), 3.80 (s, 3H), 3.50-3.36 (m, 2H), 2.41-2.30 (m, 1H), 2.01-1.85 (m, 3H), 1.40 (s, 3H), 1.23 (s, 6H). MS (m/z): 361.96 ([M+H]⁺).

Intermediate 175: ((S)-N-(benzo[d]thiazol-2-yl)-N-methylpyrrolidine-2-carboxamide hydrochloride



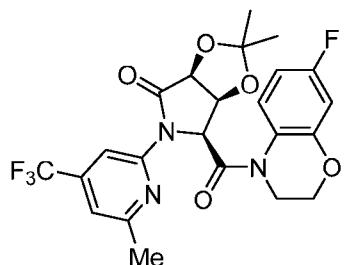
[329] To Intermediate 174 (600 mg, 1.70 mmol), 2M HCl in Dioxan (6.6 ml) was added and stirred at room temperature. After 1h, diluted with diethyl ether (20 ml), filtered the solid and washed with diethyl ether (50 ml). The solid was dried under vacuum to afford the titled compound as an off-white solid (0.45 g). Yield: 91%. ¹H-NMR (δ ppm, DMSO-D₆, 400 MHz): 10.38 (s, 1H), 8.96-8.92 (m, 1H), 8.04 (d, J 8.0, 1H), 7.88 (d, J 8.0, 1H), 7.51 (dt, J 7.6, 1.2, 1H), 7.40 (dt, J 8.0, 1.2, 1H), 5.08-4.98 (m, 1H), 3.77 (s, 3H), 3.33-3.25 (m, 2H), 2.53-2.50 (m, 1H), 2.10-1.93 (m, 3H), MS (m/z): 262.17 ([M-HCl+H]⁺).

Intermediate 176: (3aS,6S,6aS)-6-(7-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazine-4-carbonyl)-2,2-dimethyltetrahydro-4H-[1,3]dioxolo[4,5-c]pyrrol-4-one



[330] Following the general procedure 1, the titled compound was synthesized from (3aS,4S,6aS)-2,2-dimethyl-6-oxotetrahydro-4H-[1,3]dioxolo[4,5-c]pyrrole-4-carboxylic acid (300 mg, 1.49 mmol), ethyl acetate (5 ml), 7-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazine (251 mg, 1.64 mmol), pyridine (472 mg, 5.96 mmol) and Propyl phosphonic acid anhydride (T3P) (2.37 g, 7.44 mmol; 14.9 ml (50% solution in ethyl acetate)). Purification: Combi-Flash. Eluent: methanol and dichloromethane (2.2:97.8) as eluent. Appearance: Off-white solid (250 mg). Yield: 49%. MS (m/z): 337.16 ($[M+H]^+$).

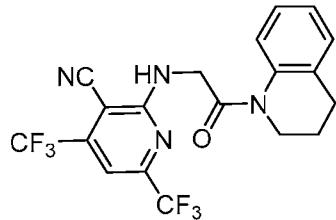
Intermediate 177: (3aS,6S,6aS)-6-(7-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazine-4-carbonyl)-2,2-dimethyl-5-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)tetrahydro-4H-[1,3]dioxolo[4,5-c]pyrrol-4-one



[331] To Intermediate 176 (0.250, 0.74 mmol) in 1,4-dioxane (15 ml), intermediate 110 (271mg, 1.13 mmol), xantphos (87.7 mg, 0.152 mmol), cesium carbonate (727 mg, 2.23 mmol) was added and degassed with nitrogen for 30 min. Pd₂(dba)₃ (68.1mg, 0.743 mmol) was added again degassed with nitrogen for 20 min. The reaction mixture was stirred at 100°C. After 1.5h, reaction mixture was filtered through cealite bed, washed with ethyl acetate (50 ml and evaporated to obtain crude. Crude product was purified by combi-flash using ethyl acetate: petroleum ether (19:81) as eluent to obtain the titled compound as a pale-yellow solid (120 mg). Yield: 32%. MS (m/z): 496.25 ($[M+H]^+$).

Example 1

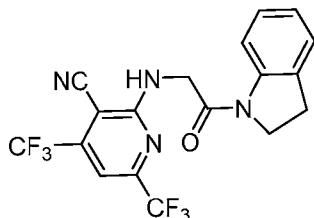
2-((2-(3,4-dihydroquinolin-1(2H)-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile



[332] To Intermediate 3 (200 mg, 1.10 mmol) in N-Methylpyrrolidone (5 ml), intermediate 1 (290 mg, 1.10 mmol) and N-diisopropylethylamine (270 mg, 2.10 mmol) were added and heated to 50°C. After 2h, the reaction mixture was cooled to room temperature, quenched with water (50 ml) and extracted with ethyl acetate (3 x 25 ml). The organic layer was washed with water (3 x 100 ml), dried with anhydrous sodium sulphate and distilled out to obtain crude. Crude was purified by combi-flash using ethyl acetate and petroleum ether (15:85) as eluent. Pure fractions from column were combined and distilled to obtain the titled compound as an off-white solid. Yield: 280 mg. % Yield: 62. M.P.: 174-177°C. ¹H-NMR (δ ppm, DMSO-*d*₆, 400 MHz): 8.42 (t, J 5.2, 1H), 7.49 (d, J 7.6, 1H), 7.44 (s, 1H), 7.22-7.10 (m, 3H), 4.35 (d, J 5.2, 2H), 3.72 (t, J 6.4, 2H), 2.73 (t, J 6.4, 2H), 1.92-1.85 (m, 2H). MS (m/z): 429.19 ([M+H]⁺).

Example 2

2-((2-(indolin-1-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile

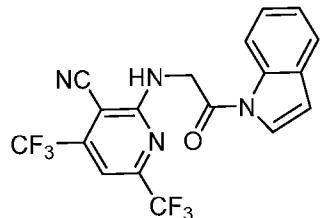


[333] Following the general procedure 3, the titled compound was synthesized from intermediate 5 (200 mg, 1.13 mmol), N-Methylpyrrolidone (5 ml), intermediate 1 (312 mg, 1.13 mmol) and N-diisopropylethylamine (147 mg, 1.13 mmol). Purification: Combi-Flash. Eluent: Ethyl acetate and petroleum ether (20:80) as eluent. Appearance: Off-white solid. Yield: 230 mg. % Yield: 49. M.P.: 234-238°C. ¹H-NMR (δ ppm, DMSO-*d*₆, 400 MHz): 8.35 (t, J 4.8, 1H), 8.00

(d, J 8.0, 1H), 7.47 (s, 1H), 7.28 (d, J 7.2, 1H), 7.16 (t, J 7.6, 1H), 7.01 (dd, J 7.2, 6.4, 1H), 4.35 (d, J 5.2, 2H), 4.21 (t, J 8.4, 2H), 3.23 (t, J 8.0, 2H). MS (m/z): 415.30 ($[M+H]^+$).

Example 3

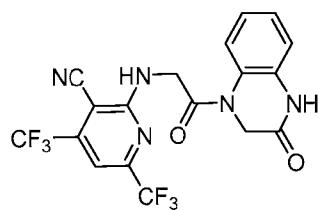
2-((2-(1H-indol-1-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile



[334] Following the general procedure 3, the titled compound was synthesized from Intermediate 7 (300 mg, 1.42 mmol), N-Methylpyrrolidone (5 ml), intermediate 1 (391 mg, 1.42 mmol) and N-diisopropylethylamine (184 mg, 1.42 mmol). Purification: Combi-Flash. Eluent: Ethyl acetate and petroleum ether (10:90) as eluent. Appearance: off-white solid. Yield: 250 mg. % Yield: 49. M.P.: 195-198°C. $^1\text{H-NMR}$ (δ ppm, DMSO- d_6 , 400 MHz): 8.72 (t, J 5.6, 1H), 8.28 (dd, J 8.8, 1.2, 1H), 8.09 (d, J 3.6, 1H), 7.66-7.64 (m, 1H), 7.50 (s, 1H), 7.34-7.26 (m, 2H), 6.88 (dd, J 3.6, 0.4, 1H), 4.93 (t, J 5.6, 2H). MS (m/z): 413.08 ($[M+H]^+$).

Example 4

2-((2-oxo-2-(3-oxo-3,4-dihydroquinoxalin-1(2H)-yl)ethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile

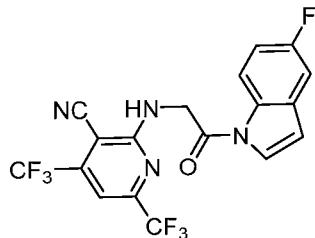


[335] Following the general procedure 3, the titled compound was synthesized from Intermediate 9 (100 mg, 0.487 mmol), N-Methylpyrrolidone (5 ml), intermediate 1 (147 mg, 0.536 mmol) and N-diisopropylethylamine (189 mg, 1.46 mmol). Purification: Ethyl acetate and petroleum ether (35:65) as eluent. Appearance: Off-white solid. Yield: 70 mg. % Yield: 32. M.P.: 224-227°C. $^1\text{H-NMR}$ (δ ppm, DMSO- d_6 , 400 MHz): 10.70 (s, 1H), 8.52 (s, 1H), 7.56 (d, J

8.0, 1H), 7.42 (s, 1H), 7.23 (t, J 6.8, 1H), 7.06-7.02 (m, 2H), 4.38-4.32 (m, 4H). MS (m/z): 444.14 ([M+H]⁺).

Example 5

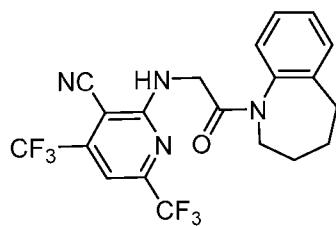
2-((2-(5-fluoro-1H-indol-1-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile



[336] Following the general procedure 3, the titled compound was synthesized from intermediate 11 (170 mg, 0.885 mmol), N-Methylpyrrolidone (3 ml), intermediate 1 (243 mg, 0.885 mmol) and N-diisopropylethylamine (343 mg, 2.65 mmol). Purification: Combi-Flash. Eluent: Ethyl acetate and petroleum ether (32:68) as eluent. Appearance: Off-white solid. Yield: 80 mg. % Yield: 21. M.P.: 206-208°C. ¹H-NMR (δ ppm, DMSO-*d*₆, 400 MHz): 8.74 (t, J 5.6, 1H), 8.28 (dd, J 8.8, 4.8, 1H), 8.19 (d, J 4.0, 1H), 7.50 (s, 1H), 7.48 (dd, J 9.2, 2.8, 1H), 7.19 (dt, J 9.2, 2.8, 1H), 6.83 (d, J 3.6, 1H), 4.93 (d, J 5.6, 2H). MS (m/z): 431.19 ([M+H]⁺).

Example 6

2-((2-oxo-2-(2,3,4,5-tetrahydro-1H-benzo[b]azepin-1-yl)ethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile

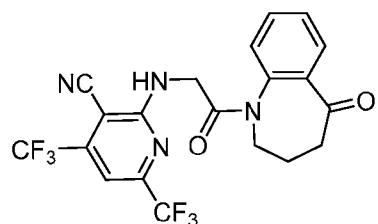


[337] Following the general procedure 3, the titled compound was synthesized from Intermediate 13 (200 mg, 0.979 mmol), N-Methylpyrrolidone (5 ml), intermediate 1 (296 mg, 1.08 mmol) and N-diisopropylethylamine (380 mg, 2.94 mmol). Purification: Combi-Flash. Eluent: Ethyl acetate and petroleum ether (25:75) as eluent. Appearance: Off-white solid. Yield:

110 mg. % Yield: 25. M.P.: 125-128°C. ¹H-NMR (δ ppm, DMSO-*d*₆, 400 MHz): 8.25 (t, J 5.6, 1H), 7.43 (s, 1H), 7.37-7.29 (m, 4H), 4.49 (d, J 13.2, 1H), 4.08 (dd, J 16.8, 6.0, 1H), 3.62 (dd, J 16.4, 6.0, 1H), 2.91 (t, J 13.2, 1H), 2.77 (dd, J 12.8, 5.2, 1H), 2.59-2.54 (m, 1H), 1.96-1.89 (m, 1H), 1.76-1.68 (m, 2H), 1.36-1.23 (m, 1H). MS (m/z): 443.28 ([M+H]⁺).

Example 7

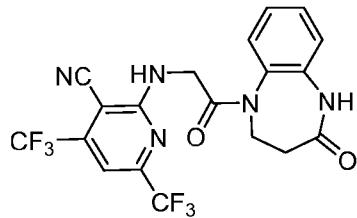
2-((2-oxo-2-(5-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-1-yl)ethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile



[338] Following the general procedure 3, the titled compound was synthesized from intermediate 16 (200 mg, 0.916 mmol), N-Methylpyrrolidone (5 ml), intermediate 1 (277 mg, 1.01 mmol) and N-diisopropylethylamine (355 mg, 2.75 mmol). Purification: Combi-Flash. Appearance: Ethyl acetate and petroleum ether (27:73) as eluent. Appearance: Off-white solid. Yield: 80 mg. % Yield: 19. M.P.: 145-148°C. ¹H-NMR (δ ppm, CDCl₃, 400 MHz): 7.95 (dd, J 7.6, 1.6, 1H), 7.70 (dt, J 7.6, 1.6, 1H), 7.58 (t, J 7.2, 1H), 7.38 (d, J 7.6, 1H), 7.18 (s, 1H), 6.54 (t, J 5.6, 1H), 4.81 (d, J 5.6, 1H), 4.35 (d, J 14.8, 1H), 3.74 (d, J 15.6, 1H), 3.22-3.12 (m, 1H), 2.84 (t, J 14.8, 1H), 2.60 (t, J 13.6, 1H), 2.23 (d, J 3.6, 1H), 1.86-1.72 (m, 1H). MS (m/z): 457.26 ([M+H]⁺).

Example 8

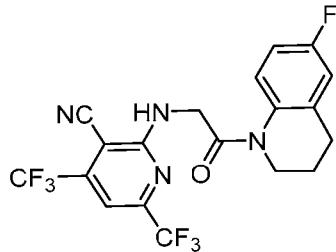
2-((2-oxo-2-(4-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-1-yl)ethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile



[339] Following the general procedure 3, the titled compound was synthesized from intermediate 19 (400 mg, 1.20 mmol), N-Methylpyrrolidone (5 ml), intermediate 1 (362 mg, 1.32 mmol) and N-diisopropylethylamine (465 mg, 3.60 mmol). Purification: Combi-Flash. Eluent: Ethyl acetate and petroleum ether (15:85) as eluent. Appearance: Off-white solid. Yield: 50 mg. % Yield: 8. M.P.: 241-244°C. ¹H-NMR (δ ppm, DMSO-*d*₆, 400 MHz): 9.80 (s, 1H), 8.22 (t, *J* 5.6, 1H), 7.46-7.41 (m, 3H), 7.28-7.20 (m, 2H), 4.67 (dt, *J* 12.8, 5.2, 1H), 4.19 (dd, *J* 16.4, 5.6, 1H), 3.50-3.39 (m, 2H), 2.61 (m, 1H), 2.30 (m, 1H). MS (m/z): 458.32 ([M+H]⁺).

Example 9

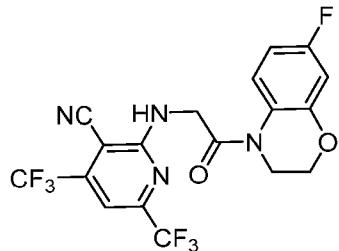
2-((2-(6-fluoro-3,4-dihydroquinolin-1(2H)-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile



[340] Following the general procedure 3, the titled compound was synthesized from Intermediate 21 (200 mg, 0.960 mmol), N-Methylpyrrolidone (4 ml), intermediate 1 (290 mg, 1.06 mmol) and N-diisopropylethylamine (372 mg, 2.88 mmol). Purification: Combi-Flash. Eluent: Ethyl acetate and petroleum ether (20:80) as eluent. Appearance: Off-white solid. Yield: 200 mg. % Yield: 46. M.P.: 209-212°C. ¹H-NMR (δ ppm, DMSO-*d*₆, 400 MHz): 8.41 (s, 1H), 7.58-7.49 (s, 1H), 7.10 (d, *J* 8.8, 1H), 7.03 (dt, *J* 8.8, 2.8, 1H), 4.34 (d, *J* 4.0, 2H), 3.71 (t, *J* 6.4, 2H), 2.74 (t, *J* 6.8, 2H), 1.91-1.85 (m, 2H). MS (m/z): 447.25 ([M+H]⁺).

Example 10

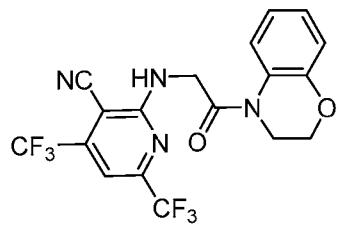
2-((2-(7-fluoro-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile



[341] Following the general procedure 3, the titled compound was synthesized from intermediate 23 (170 mg, 0.809 mmol), N-Methylpyrrolidone (4 ml), intermediate 1 (244 mg, 0.890 mmol) and N-diisopropylethylamine (314 mg, 2.43 mmol). Purification: Combi-Flash. Eluent: Ethyl acetate and petroleum ether (20:80) as eluent. Appearance: Off-white solid. Yield: 150 mg. % Yield: 41. M.P.: 198-201°C. $^1\text{H-NMR}$ (δ ppm, DMSO- d_6 , 400 MHz): 8.46 (s, 1H), 7.73 (s, 1H), 7.46 (s, 1H), 6.83 (dd, J 9.6, 2.4, 1H), 6.76 (dt, J 8.4, 2.4, 1H), 4.45 (d, J 5.6, 2H), 4.28 (br s, 2H), 3.91 (br s, 2H). MS (m/z): 449.18 ($[M+\text{H}]^+$).

Example 11

2-((2-(2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile

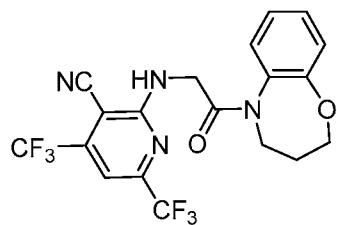


[342] Following the general procedure 3, the titled compound was synthesized from intermediate 25 (200 mg, 1.04 mmol), N-Methylpyrrolidone (4 ml), intermediate 1 (314 mg, 1.14 mmol) and N-diisopropylethylamine (403 mg, 3.12 mmol). Purification: Combi-Flash. Eluent: Ethyl acetate and petroleum ether (10:90) as eluent. Appearance: Off-white solid. Yield: 50 mg. % Yield: 11. M.P.: 146-149°C. $^1\text{H-NMR}$ (δ ppm, DMSO- d_6 , 400 MHz): 8.45 (s, 1H), 7.68 (s,

1H), 7.46 (s, 1H), 7.09 (t, J 7.2, 1H), 6.93-6.86 (m, 2H), 4.47 (d, J 5.6, 2H), 4.27 (t, J 4.4, 2H), 3.91 (t, J 4.4, 2H). MS (m/z): 431.19 ([M+H]⁺).

Example 12

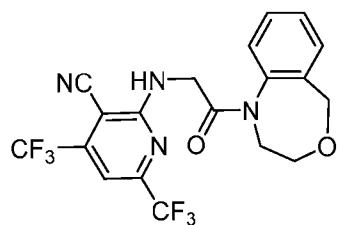
2-((2-(3,4-dihydrobenzo[b][1,4]oxazepin-5(2H)-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile



[343] Following the general procedure 3, the titled compound was synthesized from intermediate 29 (300 mg, 1.45 mmol), N-Methylpyrrolidone (4 ml), intermediate 1 (439 mg, 1.60 mmol) and N-diisopropylethylamine (564 mg, 4.36 mmol). Purification: Combi-Flash. Eluent: Ethyl acetate and petroleum ether (10:90) as eluent. Appearance: Off-white solid. Yield: 260 mg. % Yield: 42. M.P.: 124-128°C. ¹H-NMR (δ ppm, DMSO-*d*₆, 400 MHz): 8.24 (t, J 5.2, 1H), 7.44-7.41 (m, 2H), 7.35 (dt, J 7.6, 1.6, 1H), 7.18-7.14 (m, 2H), 4.58 (d, J 12.8, 1H), 4.39 (d, J 11.6, 1H), 4.23 (dd, J 16.8, 4.4, 1H), 3.75-3.58 (m, 2H), 2.86 (t, J 12.4, 1H), 1.97 (br s, 1H), 1.81 (d, J 14.4, 1H). MS (m/z): 445.21 ([M+H]⁺).

Example 13

2-((2-(2,3-dihydrobenzo[e][1,4]oxazepin-1(5H)-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile

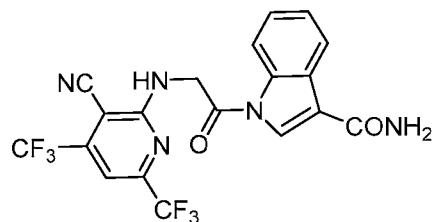


[344] Following the general procedure 3, the titled compound was synthesized from intermediate 34 (200 mg, 0.971 mmol), N-Methylpyrrolidone (4 ml), intermediate 1 (293 mg,

1.07 mmol) and N-diisopropylethylamine (376 mg, 2.91 mmol). Purification: Combi-Flash. Eluent: Ethyl acetate and petroleum ether (20:80) as eluent. Appearance: Off-white solid. Yield: 220 mg. % Yield: 51. M.P.: 152-154°C. $^1\text{H-NMR}$ (δ ppm, DMSO-*d*₆, 400 MHz): 8.34 (t, J 5.2, 1H), 7.52-7.34 (m, 5H), 4.66 (d, J 13.2, 1H), 4.61 (t, J 13.2, 1H), 4.53 (d, J 14.4, 1H), 4.23 (dd, J 16.8, 5.6, 1H), 3.97 (d, J 10.8, 1H), 3.77 (dd, J 16.4, 5.6, 1H), 3.60 (t, J 11.6, 1H), 2.87 (t, J 12.0, 1H). MS (m/z): 445.28 ([M+H]⁺).

Example 14

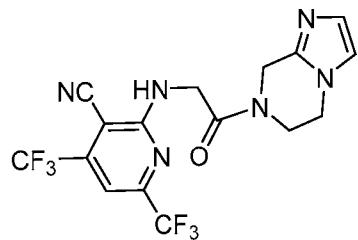
1-((3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)glycyl)-1H-indole-3-carboxamide



[345] Following the general procedure 3, the titled compound was synthesized from intermediate 37 (300 mg, 1.38 mmol), N-Methylpyrrolidone (4 ml), intermediate 1 (417 mg, 1.52 mmol) and N-diisopropylethylamine (536 mg, 4.14 mmol). Purification: Combi-Flash. Eluent: Ethyl acetate and petroleum ether (15:85) as eluent. Appearance: Off-white solid. Yield: 100 mg. % Yield: 16. M.P.: 167-169°C. $^1\text{H-NMR}$ (δ ppm, DMSO-*d*₆, 400 MHz): 8.73 (s, 2H), 8.27-8.21 (m, 2H), 7.73 (s, 1H), 7.53 (s, 1H), 7.38-7.29 (m, 3H), 4.95 (d, J 4.4, 2H). MS (m/z): 456.39 ([M+H]⁺).

Example 15

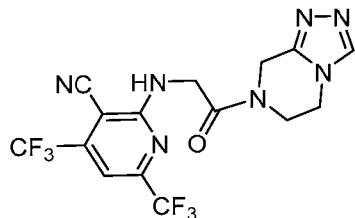
2-((2-(5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile



[346] Following the general procedure 3, the titled compound was synthesized from Intermediate 39 (200 mg, 0.680 mmol), N-Methylpyrrolidone (4 ml), intermediate 1 (205 mg, 0.748 mmol) and N-diisopropylethylamine (351 mg, 2.72 mmol). Purification: Combi-Flash. Eluent: Methanol and dichloromethane (3:97) as eluent. Appearance: Off-white solid. Yield: 100 mg. % Yield: 40. M.P.: 164-166°C. ¹H-NMR (δ ppm, DMSO-*d*₆, 400 MHz): 8.24 (t, J 4.8, 1H), 7.45 (s, 1H), 7.13 (s, 1H), 6.92 (d, J, 16.4, 1H), 4.82 (s, 0.8H), 4.64 (s, 1.2H), 4.41-4.38 (m 2H), 4.11-4.05 (m, 1.2H), 3.97-3.89 (m, 2.8H). MS (m/z): 419.42 ([M+H]⁺).

Example 16

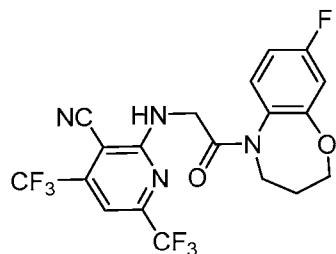
2-((2-(5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile



[347] Following the general procedure 3, the titled compound was synthesized from intermediate 41 (400 mg, 1.35 mmol), N-Methylpyrrolidone (5 ml), intermediate 1 (409 mg, 1.49 mmol) and N-diisopropylethylamine (700 mg, 5.42 mmol). Purification: Combi-Flash. Eluent: Methanol and dichloromethane (7:93) as eluent. Appearance: Off-white solid. Yield: 80 mg. % Yield: 14. M.P.: 202-204°C. ¹H-NMR (δ ppm, DMSO-*d*₆, 400 MHz): 8.52 (s, , 1H), 8.27 (s, 1H), 7.43 (s, 1H), 5.00 (s, 0.8H), 4.79 (s, 1.2H), 4.39 (d, J, 9.2, 2H), 4.19-4.12 (m, 1.2H), 4.05-3.95 (m, 2H), 3.92-3.869 (m, 0.8H). MS (m/z): 420.44 ([M+H]⁺).

Example 17

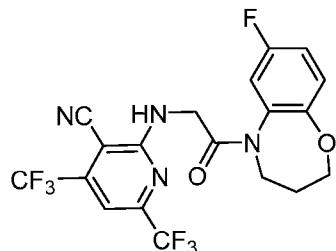
2-((2-(8-fluoro-3,4-dihydrobenzo[b][1,4]oxazepin-5(2H)-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile



[348] Following the general procedure 3, the titled compound was synthesized from Intermediate 45 (300 mg, 1.30 mmol), N-Methylpyrrolidone (4 ml), intermediate 1 (400 mg, 1.58 mmol) and N-diisopropylethylamine (520 mg, 4.0 mmol). Purification: Combi-Flash. Eluent: Ethyl acetate and petroleum ether (15:85) as eluent. Appearance: Off-white solid. Yield: 300 mg. % Yield: 49. M.P.: 138-141°C. $^1\text{H-NMR}$ (δ ppm, $\text{DMSO}-d_6$, 400 MHz): 8.27 (t, J 5.6, 1H), 7.49-7.44 (m, 2H), 7.04-7.6.99 (m, 2H), 4.55-4.37 (m, 2H), 4.19 (dd, J 16.8, 5.6, 1H), 3.82 (t, J 9.6, 1H), 3.69 (dd, J 16.8, 5.2, 1H), 2.87 (t, J 10.8, 1H), 2.04-1.97 (m, 1H), 1.85-1.75 (m, 1H). MS (m/z): 463.26 ($[M+\text{H}]^+$).

Example 18

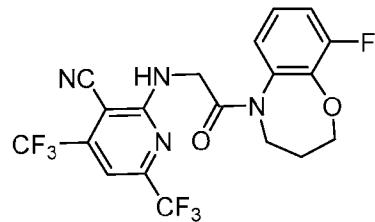
2-((2-(7-fluoro-3,4-dihydrobenzo[b][1,4]oxazepin-5(2H)-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile



[349] Following the general procedure 3, the titled compound was synthesized from intermediate 49 (300 mg, 1.30 mmol), N-Methylpyrrolidone (4 ml), intermediate 1 (400 mg, 1.58 mmol) and N-diisopropylethylamine (520 mg, 4.0 mmol). Purification: Combi-Flash. Eluent: Ethyl acetate and petroleum ether (16:84) as eluent. Appearance: Off-white solid. Yield: 310 mg. % Yield: 50. M.P.: 120-123°C. $^1\text{H-NMR}$ (δ ppm, $\text{DMSO}-d_6$, 400 MHz): 8.28 (t, J 5.2, 1H), 7.44 (s, 1H), 7.40 (d, J 8.4, 1H), 7.21-7.18 (m, 2H), 4.58-4.49 (m, 1H), 4.33-4.23 (m, 2H), 3.78-3.60 (m, 2H), 2.88-2.78 (m, 1H), 1.96-1.79 (m, 2H). MS (m/z): 463.24 ($[M+\text{H}]^+$).

Example 19

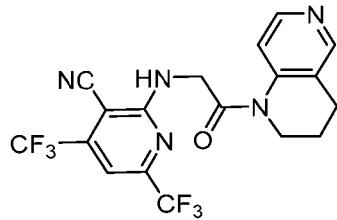
2-((2-(9-fluoro-3,4-dihydrobenzo[b][1,4]oxazepin-5(2H)-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile



[350] Following the general procedure 3, the titled compound was synthesized from intermediate 53 (300 mg, 0.88 mmol), N-Methylpyrrolidone (4 ml), intermediate 1 (268 mg, 0.976 mmol) and N-diisopropylethylamine (459 mg, 3.55 mmol). Purification: Combi-Flash. Eluent: Ethyl acetate and petroleum ether (25:75) as eluent. Appearance: Off-white solid. Yield: 230 mg. % Yield: 56. M.P.: 108-112°C. $^1\text{H-NMR}$ (δ ppm, DMSO- d_6 , 400 MHz): 8.26 (t, J 5.2, 1H), 7.44 (s, 1H), 7.33-7.13 (m, 3H), 4.59-4.44 (m, 2H), 4.24 (d, J 14.8, 1H), 3.79-3.67 (m, 2H), 2.91-2.81 (m, 1H), 1.99-1.83 (m, 2H). MS (m/z): 463.25 ($[M+\text{H}]^+$).

Example 20

2-((2-(3,4-dihydro-1,6-naphthyridin-1(2H)-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile

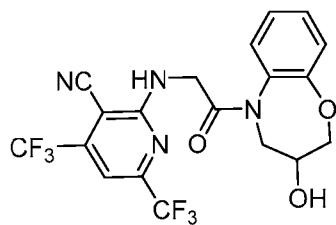


[351] Following the general procedure 3, the titled compound was synthesized from intermediate 55 (30 mg, 0.32 mmol), N-Methylpyrrolidone (4 ml), intermediate 1 (99 mg, 0.36 mmol) and N-diisopropylethylamine (169 mg, 1.31 mmol). Purification: Combi-Flash. Eluent: Methanol and dichloromethane (2:98) as eluent. Appearance: Off-white solid. Yield: 45 mg. % Yield: 32. M.P.: 216-218°C. $^1\text{H-NMR}$ (δ ppm, DMSO- d_6 , 400 MHz): 8.49 (t, J 5.6, 1H), 8.35 (s,

1H), 8.26 (d, J 5.6, 1H), 7.74 (d, J 5.6, 1H), 7.47 (s, 1H), 4.47 (d, J 5.6, 2H), 3.81 (t, J 6.0, 2H), 2.77 (t, J 6.4, 2H), 1.96-1.90 (m, 2H). MS (m/z): 430.42 ($[M+H]^+$).

Example 21

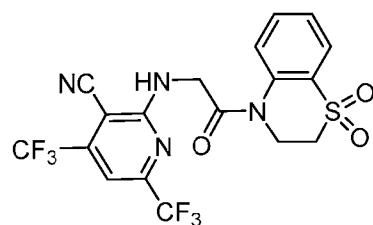
2-((2-(3-hydroxy-3,4-dihydrobenzo[b][1,4]oxazepin-5(2H)-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile



[352] Following the general procedure 3, the titled compound was synthesized from intermediate 60 (120 mg, 0.357 mmol), N-Methylpyrrolidone (4 ml), intermediate 1 (108 mg, 0.393 mmol) and N-diisopropylethylamine (184 mg, 1.43 mmol). Purification: Combi-Flash. Eluent: Ethyl acetate and petroleum ether (25:75) as eluent. Appearance: Off-white solid. Yield: 40 mg. % Yield: 24. M.P.: 106-108°C. $^1\text{H-NMR}$ (δ ppm, DMSO- d_6 , 400 MHz): 8.27 (s, 1H), 7.44-6.98 (m, 5H), 5.38 (d, J 4.0, 1H), 4.63 (d, J 10.4, 1H), 4.33-4.22 (m, 2H), 3.88-3.80 (m, 1H), 3.67-3.62 (m, 1H), 3.43 (t, J 8.8, 1H), 2.63-2.57 (m, 1H). MS (m/z): 461.32 ($[M+H]^+$).

Example 22

2-((2-(1,1-dioxido-2,3-dihydro-4H-benzo[b][1,4]thiazin-4-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile

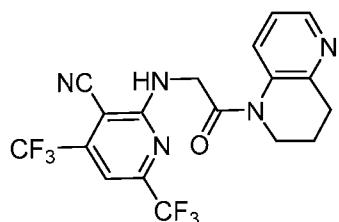


[353] Following the general procedure 3, the titled compound was synthesized from Intermediate 68 (120 mg, 0.499 mmol), N-Methylpyrrolidone (4 ml), intermediate 1 (151 mg, 0.549 mmol) and N-diisopropylethylamine (194 mg, 1.50 mmol). Purification: Combi-Flash.

Eluent: Ethyl acetate and petroleum ether (30:70) as eluent. Appearance: Pale-brown solid. Yield: 100 mg. % Yield: 41. M.P.: 102-104°C. ¹H-NMR (δ ppm, DMSO-*d*₆, 400 MHz): 8.39 (t, J 5.2, 1H), 7.88 (dd, J 8.0, 1.2, 1H), 7.71-6.63 (m, 2H), 7.51-7.47 (m, 2H), 4.47 (d, J 5.2, 2H), 4.36 (t, J 6.0, 2H), 3.78 (t, J 6.0, 2H). MS (m/z): 479.16 ([M+H]⁺).

Example 23

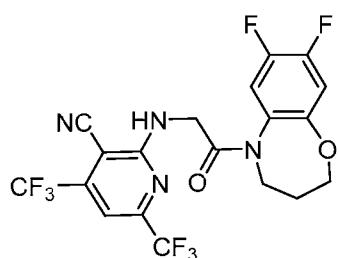
2-((2-(3,4-dihydro-1,5-naphthyridin-1(2H)-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile



[354] Following the general procedure 3, the titled compound was synthesized from Intermediate 71 (220 mg, 1.15 mmol), N-Methylpyrrolidone (4 ml), intermediate 1 (347 mg, 1.27 mmol) and N-diisopropylethylamine (446 mg, 3.45 mmol). Purification: Combi-Flash. Eluent: Methanol and dichloromethane (2:98) as eluent. Appearance: Off-white solid. Yield: 300 mg. % Yield: 60. M.P.: 127-130°C. ¹H-NMR (δ ppm, DMSO-*d*₆, 400 MHz): 8.46 (t, J 4.8, 1H), 8.25 (dd, J 4.4, 0.8, 1H), 7.95 (d, J 8.0, 1H), 7.46 (s, 1H), 7.21 (dd, J 8.0, 4.4, 1H), 4.14 (d, J 5.2, 2H), 3.79 (t, J 5.6, 2H), 2.90 (t, J 6.8, 2H), 2.02-1.96 (m, 2H). MS (m/z): 430.40 ([M+H]⁺).

Example 24

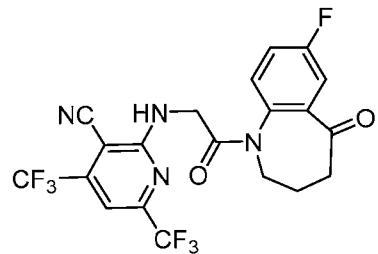
2-((2-(7,8-difluoro-3,4-dihydrobenzo[b][1,4]oxazepin-5(2H)-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile



[355] Following the general procedure 3, the titled compound was synthesized from intermediate 75 (300 mg, 1.20 mmol), N-Methylpyrrolidone (4 ml), intermediate 1 (370 mg, 1.40 mmol) and N-diisopropylethylamine (480 mg, 3.70 mmol). Purification: Combi-Flash. Eluent: Ethyl acetate and petroleum ether (25:75) as eluent. Appearance: Off-white solid. Yield: 350 mg. % Yield: 59. M.P.: 130-133°C. ¹H-NMR (δ ppm, DMSO-*d*₆, 400 MHz): 8.31 (t, J 5.2, 1H), 7.69 (dd, J 10.8, 8.8, 1H), 7.44 (s, 1H), 7.31 (dd, J 11.6, 8.0, 1H), 4.54-4.47 4.35 (d, J 12.4, 1H), 4.22-4.12 (m, 1H), 3.84-3.76 (m, 2H), 2.85 (t, J 10.8, 1H), 1.98-1.88 (m, 1H), 1.82-1.72 (m, 1H). MS (m/z): 481.23 ([M+H]⁺).

Example 25

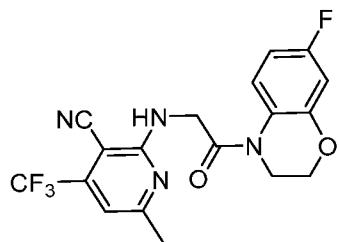
2-((2-(7-fluoro-5-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-1-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile



[356] Following the general procedure 3, the titled compound was synthesized from Intermediate 81 (300 mg, 1.30 mmol), N-Methylpyrrolidone (4 ml), intermediate 1 (380 mg, 1.40 mmol) and N-diisopropylethylamine (490 mg, 3.8 mmol). Purification: Combi-Flash. Eluent: Ethyl acetate and petroleum ether (25:75) as eluent. Appearance: Off-white solid. Yield: 200 mg. % Yield: 33. M.P.: 165-169°C. ¹H-NMR (δ ppm, DMSO-*d*₆, 400 MHz): 8.25 (t, J 5.2, 1H), 7.63-7.44 (m, 4H), 4.53 (m, 1H), 4.14-4.10 (m, 1H), 3.79-3.75 (m, 1H), 3.11-3.01 (m, 1H), 2.68-2.49 (m, 2H), 2.08 (m, 1H), 1.71-1.60 (m, 1H). MS (m/z): 475.25 ([M+H]⁺).

Example 26

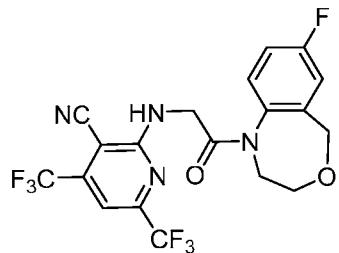
2-((2-(7-fluoro-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)-2-oxoethyl)amino)-6-methyl-4-(trifluoromethyl)nicotinonitrile



[357] Following the general procedure 3, the titled compound was synthesized from Intermediate 23 (180 mg, 0.856 mmol), N-Methylpyrrolidone (5 ml), intermediate 82 (208 mg, 0.942 mmol) and N-diisopropylethylamine (332 mg, 2.57 mmol). Purification: Combi-Flash. Eluent: Ethyl acetate and petroleum ether (25:75) as eluent. Appearance: Pale brown solid. Yield: 70 mg. % Yield: 21. M.P.: 214-216°C. ¹H-NMR (δ ppm, DMSO-*d*₆, 400 MHz): 7.76 (s, 2H), 7.00 (s, 1H), 6.84 (dd, J 10.0, 2.8, 1H), 6.78 (m, 1H), 4.47 (d, J 5.2, 2H), 4.30 (br s, 2H), 3.90 (br s, 2H), 2.39 (s, 3H). MS (m/z): 395.12 ([M+H]⁺).

Example 27

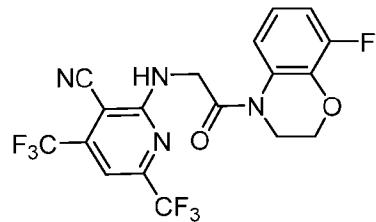
2-((2-(7-fluoro-2,3-dihydrobenzo[e][1,4]oxazepin-1(5H)-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile



[358] Following the general procedure 3, the titled compound was synthesized from Intermediate 87 (300 mg, 1.30 mmol), N-Methylpyrrolidone (4 ml), intermediate 1 (400 mg, 1.50 mmol) and N-diisopropylethylamine (502 mg, 4.00 mmol). Purification: Combi-Flash. Eluent: Ethyl acetate and petroleum ether (25:75) as eluent. Appearance: Off-white solid. Yield: 50 mg. % Yield: 8. M.P.: 147-150°C. ¹H-NMR (δ ppm, DMSO-*d*₆, 400 MHz): 8.35 (s, 1H), 7.59 (dd, J 8.4, 5.2, 1H), 7.45 (s, 1H), 7.43 (dd, J 8.8, 2.8, 1H), 7.27 (dt, J 8.4, 2.8, 1H), 4.69 (d, J 13.2, 1H), 4.56-4.47 (m, 2H), 4.19 (d, J 16.8, 1H), 3.98 (d, J 12.0, 1H), 3.79 (d, J 16.4, 1H), 3.06 (t, J 11.6, 1H), 2.86-2.80 (m, 1H). MS (m/z): 463.24 ([M+H]⁺).

Example 28

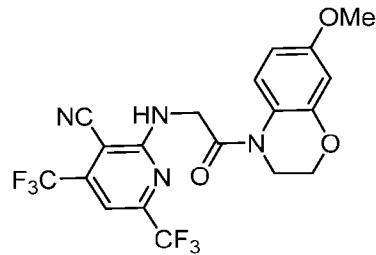
2-((2-(8-fluoro-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile



[359] Following the general procedure 3, the titled compound was synthesized from Intermediate 92 (350 mg, 1.08 mmol), N-Methylpyrrolidone (5 ml), intermediate 1 (326 mg, 1.19 mmol) and N-diisopropylethylamine (698 mg, 5.4 mmol). Purification: Combi-Flash. Eluent: Ethyl acetate and petroleum ether (18:82) as eluent. Appearance: Off-white solid. Yield: 280 mg. % Yield: 57. M.P.: 145-152°C. ¹H-NMR (δ ppm, DMSO-*d*₆, 400 MHz): 8.49 (s, 1H), 7.55 (s, 1H), 7.47 (s, 1H), 7.07 (t, J 8.8, 1H), 6.88 (dt, J 8.4, 5.6, 1H), 4.48 (d, J 5.6, 2H), 4.34 (t, J 4.8, 2H), 3.97 (t, J 4.4, 2H). MS (m/z): 449.12 ([M+H]⁺).

Example 29

2-((2-(7-methoxy-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile

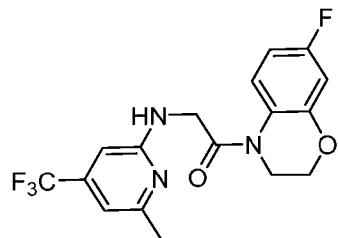


[360] Following the general procedure 3, the titled compound was synthesized from Intermediate 98 (350 mg, 1.04 mmol), N-Methylpyrrolidone (5 ml), intermediate 1 (314 mg, 1.14 mmol) and N-diisopropylethylamine (673 mg, 5.20 mmol). Purification: Combi-Flash. Eluent: Ethyl acetate and petroleum ether (18:82) as eluent. Appearance: Pale-yellow solid.

Yield: 280 mg. % Yield: 58. M.P.: 198-200°C. $^1\text{H-NMR}$ (δ ppm, DMSO- d_6 , 400 MHz): 8.43 (s, 1H), 7.75 (s, 1H), 7.45 (s, 1H), 6.49 (s, 1H), 6.47 (s, 1H), 4.43 (d, J 5.6, 2H), 4.24 (br s, 2H), 3.86 br s, 2H), 3.71 (s, 3H). MS (m/z): 461.23 ($[M+\text{H}]^+$).

Example 30

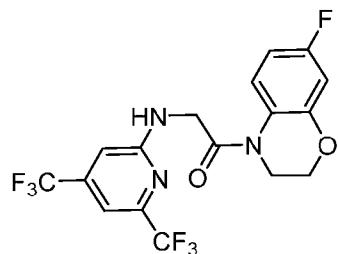
1-(7-fluoro-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)-2-((6-methyl-4-(trifluoromethyl)pyridin-2-yl)amino)ethan-1-one



[361] To Intermediate 23 (0.30 g, 0.97 mmol) in 1,4-dioxane (5 ml), 2-chloro-6-methyl-4-(trifluoromethyl)pyridine (210 mg, 1.07 mmol), BINAP (54.7 mg, 0.087 mmol), cesium carbonate (477 mg, 1.46 mmol) was added and degassed with nitrogen for 30 min. Palladium acetate (11mg, 0.048 mmol) was added again degassed with nitrogen for 20 min. The reaction mixture was stirred at 80°C. After 1h, reaction mixture diluted with water (10 ml) and extracted with ethyl acetate (3 x 30 ml). The organic layer was evaporated to obtain crude. Crude product was purified by combi-flash using ethyl acetate and petroleum ether (20:80) as eluent to obtain the titled compound as an off-white solid (80 mg). Yield: 22 %. M.P.: 101-104°C. $^1\text{H-NMR}$ (δ ppm, DMSO- d_6 , 400 MHz): 7.81 (d, J 2.8, 1H), 7.29 (s, 1H), 6.82-6.72 (m, 3H), 6.63 (s, 1H), 4.32-4.20 (m, 4H), 3.89 (s, 2H), 2.29 (s, 3H). MS (m/z): 370.21 ($[M+\text{H}]^+$).

Example 31

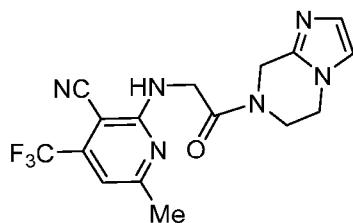
2-((4,6-bis(trifluoromethyl)pyridin-2-yl)amino)-1-(7-fluoro-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)ethan-1-one



[362] To Intermediate 23 (0.20 g, 0.65 mmol) in 1,4-dioxane (10 ml), intermediate 101 (179 mg, 0.71 mmol), BINAP (36.5 mg, 0.058 mmol), cesium carbonate (530 mg, 1.63 mmol) was added and degassed with nitrogen for 30 min. Palladium acetate (7.3 mg, 0.032 mmol) was added again degassed with nitrogen for 20 min. The reaction mixture was stirred at 80°C. After 2h, reaction mixture diluted with water (10 ml) and extracted with ethyl acetate (3 x 30 ml). The organic layer was evaporated to obtain crude. Crude product was purified by combi-flash using ethyl acetate and petroleum ether (20:80) as eluent to obtain the titled compound as an off-white solid (30 mg). Yield: 7 %. M.P.: 104-108°C. ¹H-NMR (δ ppm, DMSO-*d*₆, 400 MHz): 8.00 (s, 1H), 7.79 (d, J 7.6, 1H), 7.88 (s, 1H), 7.18 (s, 1H), 6.82-6.73 (m, 2H), 4.42 (d, J 6.0, 2H), 4.29 (s, 2H), 3.89 (d, J 4.0, 2H). MS (m/z): 422.61 ([M+H]⁺).

Example 32

2-((2-(5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl)-2-oxoethyl)amino)-6-methyl-4-(trifluoromethyl)nicotinonitrile

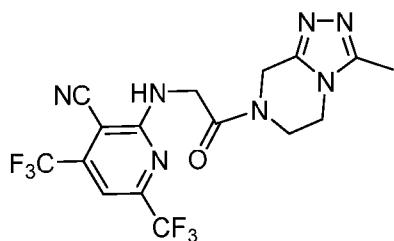


[363] Following the general procedure 3, the titled compound was synthesized from Intermediate 39 (400 mg, 1.36 mmol), N-Methylpyrrolidone (8 ml), intermediate 82 (330 mg, 1.50 mmol) and N-diisopropylethylamine (703 mg, 5.44 mmol). Purification: Combi-Flash. Eluent: methanol and dichloromethane (4:96) as eluent. Appearance: Off-white solid. Yield: 100 mg. % Yield: 20. M.P.: 164-166°C. ¹H-NMR (δ ppm, DMSO-*d*₆, 400 MHz): 7.55 (s, 0.4H),

7.50 (s, 0.6H), 7.14 (s, 1H), 7.00 (s, 1H), 6.92 (s, 0.4H), 6.88 (s, 0.6H), 4.83 (s, 0.8H), 4.65 (s, 1.2H), 4.39 (d, J 4.8, 1.2H), 4.33 (d, J 4.2, 0.8H), 4.12-3.91 (m, 4H), 2.37 (s, 1.8H), 2.35 (s, 1.2H). MS (m/z): 365.42 ([M+H]⁺).

Example 33

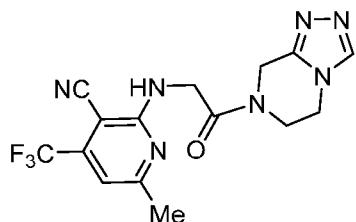
2-((2-(3-methyl-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile



[364] Following the general procedure 3, the titled compound was synthesized from Intermediate 103 (500 mg, 1.62 mmol), N-Methylpyrrolidone (5 ml), intermediate 1 (488 mg, 1.78 mmol) and N-diisopropylethylamine (836 mg, 6.47 mmol). Purification: Combi-Flash. Eluent: methanol and dichloromethane (7:93) as eluent. Appearance: Off-white solid. Yield: 250 mg. % Yield: 35. M.P.: 254-256°C. ¹H-NMR (δ ppm, DMSO-*d*₆, 400 MHz): 8.29 (s, 1H), 7.44 (s, 1H), 4.94 (s, 0.8H), 4.74 (s, 1.2H), 4.39 (s, 1.2H), 4.36 (s, 0.8H), 4.01 (s, 2.5H), 3.88 (d, J 5.6, 1.5H), 2.31 (s, 3H). MS (m/z): 434.49 ([M+H]⁺).

Example 34

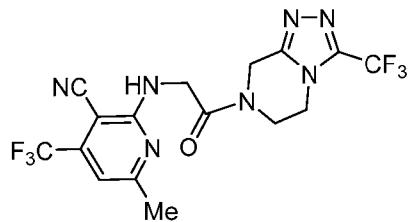
2-((2-(5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)-2-oxoethyl)amino)-6-methyl-4-(trifluoromethyl)nicotinonitrile



Following the general procedure 3, the titled compound was synthesized from Intermediate 41 (480 mg, 1.63 mmol), N-Methylpyrrolidone (5 ml), intermediate 82 (395 mg, 1.79 mmol) and N-diisopropylethylamine (841 mg, 6.50 mmol). Purification: Combi-Flash. Eluent: methanol and dichloromethane (7:93) as eluent. Appearance: Off-white solid. Yield: 50 mg. % Yield: 8. M.P.: 186-188°C. $^1\text{H-NMR}$ (δ ppm, DMSO- d_6 , 400 MHz): 8.52 (s, 1H), 7.57 (s, 0.4H), 7.52 (s, 0.6H), 7.00 (s, 1H), 5.00 (s, 0.8H), 4.81 (s, 1.2H), 4.38-3.90 (m, 6H), 2.36 (s, 1.8H), 2.34 (s, 1.2H). MS (m/z): 366.39 ($[M+\text{H}]^+$).

Example 35

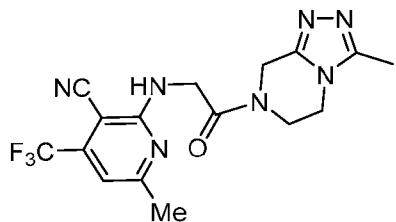
6-methyl-2-((2-oxo-2-(3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)ethyl)amino)-4-(trifluoromethyl)nicotinonitrile



[365] Following the general procedure 3, the titled compound was synthesized from Intermediate 105 (580 mg, 1.60 mmol), N-Methylpyrrolidone (8 ml), intermediate 82 (387 mg, 1.76 mmol) and N-diisopropylethylamine (826 mg, 6.39 mmol). Purification: Combi-Flash. Eluent: methanol and dichloromethane (5.5:94.5) as eluent. Appearance: Off-white solid. Yield: 80 mg. % Yield: 12. M.P.: 165-167°C. $^1\text{H-NMR}$ (δ ppm, DMSO- d_6 , 400 MHz): 7.58 (s, 0.4H), 7.51 (s, 0.6H), 7.00 (s, 1H), 5.11 (s, 0.8H), 4.92 (s, 1.2H), 4.39-3.98 (m, 6H), 2.36 (s, 3H). MS (m/z): 434.41 ($[M+\text{H}]^+$).

Example 36

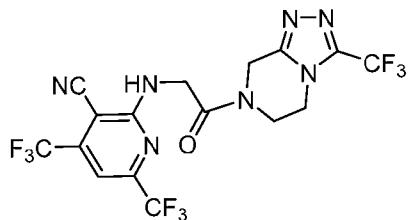
6-methyl-2-((2-(3-methyl-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)-2-oxoethyl)amino)-4-(trifluoromethyl)nicotinonitrile



[366] Following the general procedure 3, the titled compound was synthesized from Intermediate 103 (500 mg, 1.62 mmol), N-Methylpyrrolidone (5 ml), intermediate 82 (392 mg, 1.78 mmol) and N-diisopropylethylamine (836 mg, 6.47 mmol). Purification: Combi-Flash. Eluent: methanol and dichloromethane (6.6:93.4) as eluent. Appearance: Pale-brown solid. Yield: 40 mg. % Yield: 6. M.P.: 267-269°C. ¹H-NMR (δ ppm, DMSO-*d*₆, 400 MHz): 7.57 (s, 0.4H), 7.53 (s, 0.6H), 7.00 (s, 1H), 4.94 (s, 0.8H), 4.76 (s, 1.2H), 4.39 (d, J 5.2, 1.2H), 4.34 (d, J 4.8, 0.8H), 4.02-3.89 (m, 4H), 2.36 (s, 3H), 2.34 (s, 3H). MS (m/z): 380.48 ([M+H]⁺).

Example 37

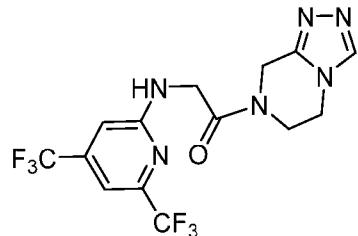
2-((2-oxo-2-(3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)ethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile



[367] Following the general procedure 3, the titled compound was synthesized from Intermediate 105 (700 mg, 2.02 mmol), N-Methylpyrrolidone (8 ml), intermediate 1 (611 mg, 2.22 mmol) and N-diisopropylethylamine (1.31 g, 10.1 mmol). Purification: Combi-Flash. Eluent: methanol and dichloromethane (2.9:97.1) as eluent. Appearance: Off-white solid. Yield: 400 mg. % Yield: 40. M.P.: 210-212°C. ¹H-NMR (δ ppm, DMSO-*d*₆, 400 MHz): 8.37 (t, J 4.8, 1H), 7.43 (s, 1H), 5.11 (s, 0.7H), 4.91 (s, 1.3H), 4.40 (d, J 5.2, 1.3H), 4.36 (d, J 4.0, 0.7H), 4.28 (d, J 4.8, 1.3H), 4.09 (s, 2H), 3.97 (s, 0.7H). MS (m/z): 488.35 ([M+H]⁺).

Example 38

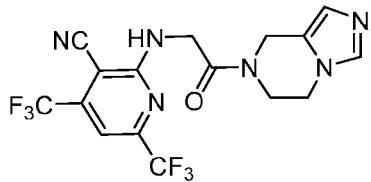
2-((4,6-bis(trifluoromethyl)pyridin-2-yl)amino)-1-(5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)ethan-1-one



[368] Following the general procedure 3, the titled compound was synthesized from Intermediate 41 (380 mg, 1.37 mmol), N-Methylpyrrolidone (4 ml), intermediate 101 (442 mg, 1.50 mmol) and N-diisopropylethylamine (883 mg, 6.83 mmol). Purification: Combi-Flash. Eluent: methanol and dichloromethane (7.5:95.5) as eluent. Appearance: Off-white solid. Yield: 30 mg. % Yield: 6. M.P.: 156-158°C. ¹H-NMR (δ ppm, DMSO-*d*₆, 400 MHz): 8.51 (s, 1H), 7.87 (br s, 1H), 7.31 (s, 1H), 7.17 (s, 1H), 4.96 (s, 0.7H), 4.80 (s, 1.3H), 4.35 (d, J 4.8, 2H), 4.19 (br s, 1.3H), 4.03 (br s, 0.7H), 3.95-3.86 (m, 2H). MS (m/z): 395.38 ([M+H]⁺).

Example 39

2-((2-(5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile



[369] Following the general procedure 3, the titled compound was synthesized from Intermediate 107 (350 mg, 1.19 mmol), N-Methylpyrrolidone (5 ml), intermediate 1 (359 mg, 1.31 mmol) and N-diisopropylethylamine (769 mg, 5.95 mmol). Purification: Combi-Flash. Eluent: methanol and dichloromethane (3.5:96.5) as eluent. Appearance: Off-white solid. Yield: 180 mg. % Yield: 36. M.P.: 212-214°C. ¹H-NMR (δ ppm, DMSO-*d*₆, 400 MHz): 8.21 (s, 1H), 7.62 (s, 1H), 7.45 (s, 1H), 6.78 (s, 0.4H), 6.74 (s, 0.6H), 4.83 (s, 0.8H), 4.66 (s, 1.2H), 4.38-

4.30 (m, 2H), 4.15 (s, 1.2H), 4.02 (s, 0.8H), 3.90 (br s, 1.2H), 3.82 (br s, 0.8H). MS (m/z): 419.40 ($[M+H]^+$).

Example 40

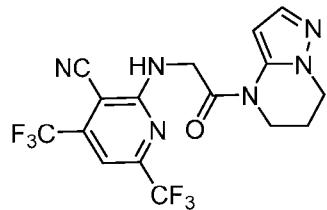
2-((4,6-bis(trifluoromethyl)pyridin-2-yl)amino)-1-(5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)ethan-1-one



[370] Following the general procedure 3, the titled compound was synthesized from Intermediate 107 (500 mg, 1.70 mmol), N-Methylpyrrolidone (5 ml), intermediate 110 (550 mg, 1.87 mmol) and N-diisopropylethylamine (1.10 g, 8.50 mmol). Purification: Combi-Flash. Eluent: methanol and dichloromethane (3.9:96.1) as eluent. Appearance: Off-white solid. Yield: 90 mg. % Yield: 13. M.P.: 148-150°C. $^1\text{H-NMR}$ (δ ppm, DMSO-*d*₆, 400 MHz): 7.84 (s, 1H), 7.61 (s, 1H), 7.33 (s, 1H), 7.17 (s, 1H), 6.78 (s, 0.4H), 6.75 (s, 0.6H), 4.81 (s, 0.8H), 4.67 (s, 1.2H), 4.33-4.25 (m, 2H), 4.18 (t, J 5.2, 1.2H), 4.03 (t, J 5.2, 0.8H), 3.87-3.83 (m, 2H). MS (m/z): 394.38 ($[M+H]^+$).

Example 41

2-((2-(6,7-dihydropyrazolo[1,5-a]pyrimidin-4(5H)-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile

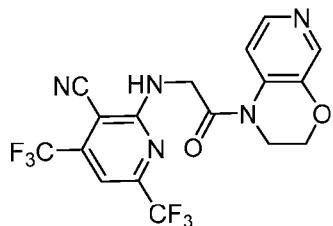


[371] Following the general procedure 3, the titled compound was synthesized from Intermediate 112 (480 mg, 1.70 mmol), N-Methylpyrrolidone (5 ml), intermediate 1 (520 mg, 1.90 mmol) and N-diisopropylethylamine (1.10 g, 8.50 mmol). Purification: Combi-Flash.

Eluent: methanol and dichloromethane (1.5:98.5) as eluent. Appearance: Off-white solid. Yield: 200 mg. % Yield: 28. M.P.: 188-190°C. ¹H-NMR (δ ppm, DMSO-*d*₆, 400 MHz): 8.34 (s, 1H), 7.48 (s, 1H), 7.33 (s, 1H), 6.49 (s, 1H), 4.49 (d, J 5.6, 2H), 4.16 (t, J 6.0, 2H), 3.93 (br s, 2H), 2.15 (br s, 2H). MS (m/z): 419.43 ([M+H]⁺).

Example 42

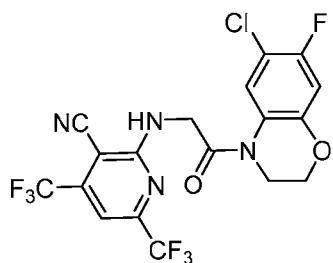
2-((2-(2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-1-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile



[372] Following the general procedure 3, the titled compound was synthesized from Intermediate 114 (195 mg, 0.67 mmol), N-Methylpyrrolidone (3.8 ml), intermediate 1 (203 mg, 0.74 mmol) and N-diisopropylethylamine (434 mg, 3.36 mmol). Purification: Combi-Flash. Eluent: methanol and dichloromethane (2.2:97.8) as eluent. Appearance: Off-white solid. Yield: 120 mg. % Yield: 41. M.P.: 221-223°C. ¹H-NMR (δ ppm, DMSO-*d*₆, 400 MHz): 8.51 (t, J 4.8, 1H), 8.21 (s, 1H), 8.03 (d, J 5.6, 1H), 7.96 (d, J 5.2, 1H), 7.48 (s, 1H), 4.51 (d, J 5.2, 2H), 4.34 (t, J 4.8, 2H), 4.01 (t, J 4.8, 2H). MS (m/z): 432.36 ([M+H]⁺).

Example 43

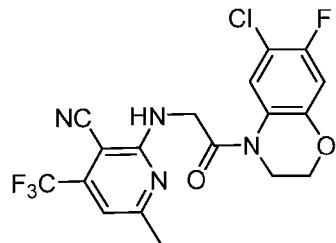
2-((2-(6-chloro-7-fluoro-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile



[373] Following the general procedure 3, the titled compound was synthesized from Intermediate 120 (320 mg, 0.93 mmol), N-Methylpyrrolidone (4 ml), intermediate 1 (283 mg, 1.03 mmol) and N-diisopropylethylamine (363 mg, 2.81 mmol). Purification: Combi-Flash. Eluent: ethyl acetate and Petroleum ether (16:94) as eluent. Appearance: Off-white solid. Yield: 200 mg. % Yield: 44. M.P.: 190-192°C. ¹H-NMR (δ ppm, DMSO-*d*₆, 400 MHz): 8.50 (s, 1H), 8.02 (s, 1H), 7.48 (s, 1H), 7.09 (d, J 10.4, 1H), 4.47 (d, J 5.2, 2H), 4.31 (br s, 2H), 3.93 (br s, 2H). MS (m/z): 483.21 ([M+H]⁺).

Example 44

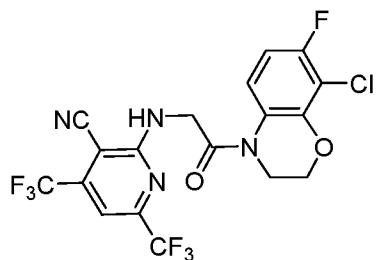
2-((2-(6-chloro-7-fluoro-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)-2-oxoethyl)amino)-6-methyl-4-(trifluoromethyl)nicotinonitrile



[374] Following the general procedure 3, the titled compound was synthesized from Intermediate 120 (400 mg, 1.17 mmol), N-Methylpyrrolidone (4 ml), intermediate 82 (284 mg, 1.29 mmol) and N-diisopropylethylamine (454 mg, 3.51 mmol) under microwave irradiation (microwave power = 150W, temperature = 100 °C) for 1h. Purification: Combi-Flash. Eluent: ethyl acetate and Petroleum ether (21:79) as eluent. Appearance: Off-white solid. Yield: 30 mg. % Yield: 7. M.P.: 216-219°C. ¹H-NMR (δ ppm, DMSO-*d*₆, 400 MHz): 8.10 (d, J 2.0, 1H), 7.78 (s, 1H), 7.10 (d, J 10.4, 1H), 7.02 (s, 1H), 4.45 (d, J 5.2, 2H), 4.33 (t, J 4.0, 2H), 3.94 (t, J 4.0, 2H), 2.40 (s, 3H). MS (m/z): 429.06 ([M+H]⁺).

Example 45

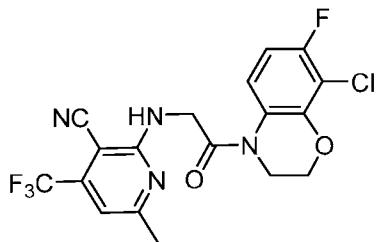
2-((2-(8-chloro-7-fluoro-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile



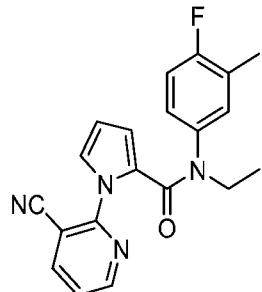
[375] Following the general procedure 3, the titled compound was synthesized from Intermediate 126 (250 mg, 0.73 mmol), N-Methylpyrrolidone (2.5 ml), intermediate 1 (221 mg, 0.80 mmol) and N-diisopropylethylamine (284 mg, 2.20 mmol). Purification: Combi-Flash. Eluent: ethyl acetate and Petroleum ether (16:94) as eluent. Appearance: Off-white solid. Yield: 150 mg. % Yield: 42. M.P.: 199-201°C. $^1\text{H-NMR}$ (δ ppm, $\text{DMSO-}d_6$, 400 MHz): 8.49 (s, 1H), 7.72 (s, 1H), 7.46 (s, 1H), 6.99 (t, J 8.8, 1H), 4.46 (d, J 5.6, 2H), 4.41 (br s, 2H), 3.95 (br s, 2H). MS (m/z): 483.03 ($[M+\text{H}]^+$).

Example 46

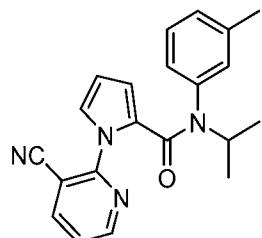
2-((2-(8-chloro-7-fluoro-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)-2-oxoethyl)amino)-6-methyl-4-(trifluoromethyl)nicotinonitrile



[376] Following the general procedure 3, the titled compound was synthesized from Intermediate 126 (400 mg, 1.17 mmol), N-Methylpyrrolidone (4 ml), intermediate 82 (284 mg, 1.29 mmol) and N-diisopropylethylamine (454 mg, 3.51 mmol) under microwave irradiation (microwave power = 150W, temperature = 100 °C) for 1h. Purification: Combi-Flash. Eluent: ethyl acetate and Petroleum ether (21:79) as eluent. Appearance: Off-white solid. Yield: 40 mg. % Yield: 8. M.P.: 242-244°C. $^1\text{H-NMR}$ (δ ppm, $\text{DMSO-}d_6$, 400 MHz): 7.82-7.70 (m, 2H), 7.01 (s, 1H), 6.98 (t, J 8.8, 1H), 4.45-4.38 (m, 4H), 3.95 (t, J 4.0, 2H), 2.38 (s, 3H). MS (m/z): 429.23 ($[M+\text{H}]^+$).

Example 47**1-(3-cyanopyridin-2-yl)-N-ethyl-N-(4-fluoro-3-methylphenyl)-1H-pyrrole-2-carboxamide**

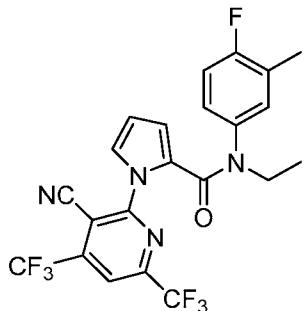
[377] To Intermediate 129 (163 mg, 1.06 mmol) in ethyl acetate (2 ml), intermediate 128 (250 mg, 1.17 mmol) and pyridine (336 mg, 4.25 mmol) were added and cooled to 0°C. Propylphosphonic acid anhydride (T3P) (0.677 g, 2.18 mmol; 1.35 ml (50% solution in ethyl acetate) was added and stirred for 30 min. After stirring at room temperature for 8h, the reaction mixture was cooled to 0°C and diluted with water (10 ml). The organic layer was washed with saturated sodium bicarbonate solution (2 x 10ml), dried with anhydrous sodium sulphate and distilled out to obtain crude. Crude was purified by combi-flash using ethyl acetate and petroleum ether (40:60) as eluent. Pure fractions from column were combined and distilled to obtain the titled compound as an off-white solid. Yield: 150 mg. % Yield: 40%. M.P.: 119-123°C. ¹H-NMR (δ ppm, DMSO-*d*₆, 400 MHz): 8.78 (dd, J 4.8, 1.6, 1H), 8.49 (dd, J 7.6, 1.6, 1H), 7.64 (dd, J 8.0, 4.8, 1H), 7.24-7.20 (m, 2H), 7.14-7.10 (m, 2H), 6.15 (t, J 7.2, 1H), 5.78(s, 1H), 3.70 (q, J 6.8, 2H), 2.19 (s, 3H), 1.04 (t, J 6.8, 3H). MS (m/z): 349.00 ([M+H]⁺).

Example 48**1-(3-cyanopyridin-2-yl)-N-isopropyl-N-(m-tolyl)-1H-pyrrole-2-carboxamide**

Following the general procedure 1, the titled compound was synthesized from intermediate 130 (200 mg, 1.34 mmol), ethyl acetate (2 ml), intermediate 128 (314 mg, 1.47 mmol), pyridine (424 mg, 5.36 mmol) and Propyl phosphonic acid anhydride (T3P) (0.853 g, 2.68 mmol; 1.70 ml (50% solution in ethyl acetate). Purification: Combi-Flash. Eluent: Ethyl acetate and petroleum ether (40:60) as eluent. Appearance: Pale-brown solid. Yield: 14 mg. % Yield: 3%. M.P.: 108-110°C. Crude was purified by combi-flash using ethyl acetate and petroleum ether (40:60) as eluent. Pure fractions from column were combined and distilled to obtain the titled compound as a pale-brown solid. Yield: 14 mg. % Yield: 3%. M.P.: 108-110°C. ¹H-NMR (δ ppm, DMSO-*d*₆, 400 MHz): 8.78 (d, J 3.6 Hz, 1H), 8.49 (d, J 7.2, 1H), 7.64 (dd, J 7.2, 4.8, 1H), 7.31 (t, J 7.6, 1H), 7.22-7.12 (m, 4H), 6.05 (s, 1H), 5.55 (s, 1H), 4.75 (quintet, J 6.4, 1H), 2.31 (s, 3H), 1.05 (d, J 6.8, 6H). MS (m/z): 345.01 ([M+H]⁺).

Example 49

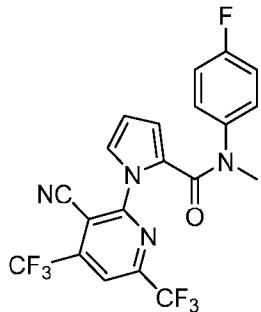
1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-ethyl-N-(4-fluoro-3-methylphenyl)-1H-pyrrole-2-carboxamide



[378] Following the general procedure 1, the titled compound was synthesized from intermediate 132 (100 mg, 0.286 mmol), DMF (2 ml), intermediate 129 (49 mg, 0.313 mmol), HBTU (109 mg, 0.286 mmol) and N-diisopropylethylamine (37 mg, 0.286 mmol). Purification: Combi-Flash. Eluent: Ethyl acetate and petroleum ether (4:94) as eluent. Appearance: Off-white solid. Yield: 25 mg. % Yield: 18%. M.P.: 112-115°C. ¹H-NMR (δ ppm, DMSO-*d*₆, 400 MHz): 8.61 (s, 1H), 7.39 (s, 1H), 7.27 (d, J 5.2, 1H), 7.20-7.14 (m, 2H), 6.25 (t, J 3.2, 1H), 5.82 (s, 1H), 3.69 (q, J 6.4, 2H), 2.20 (s, 3H), 1.00 (t, J 6.8, 3H). MS (m/z): 485.13 ([M+H]⁺).

Example 50

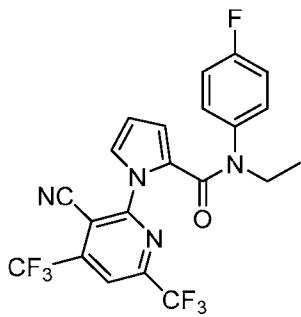
1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-(4-fluorophenyl)-N-methyl-1H-pyrrole-2-carboxamide



[379] Following the general procedure 1, the titled compound was synthesized from intermediate 132 (300 mg, 0.859 mmol), DMF (4 ml), 4-fluoro-N-methylaniline (108 mg, 0.859 mmol), HBTU (391 mg, 1.03 mmol) and N-diisopropylethylamine (333 mg, 2.58 mmol). Purification: Combi-Flash. Eluent: Methanol and dichloromethane (5:95) as eluent. Appearance: off-white solid. Yield: 40 mg. % Yield: 10%. M.P.: 108-110°C. ¹H-NMR (δ ppm, DMSO-*d*₆, 400 MHz): 8.61 (s, 1H), 7.41 (dd, J 2.8, 1.2, 1H), 7.31-7.20 (m, 4H), 6.28 (t, J 3.2, 1H), 5.92 (s, 1H), 3.22 (s, 3H). MS (m/z): 457.12 ([M+H]⁺).

Example 51

1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-ethyl-N-(4-fluorophenyl)-1H-pyrrole-2-carboxamide

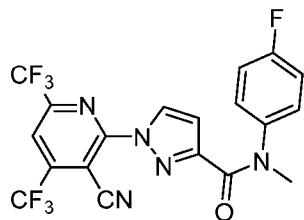


[380] Following the general procedure 1, the titled compound was synthesized from intermediate 132 (250 mg, 0.716 mmol), dichloromethane (4 ml), intermediate 133 (110 mg, 0.788 mmol), triethylamine (290 mg, 2.86 mmol) and Propyl phosphonic acid anhydride (T3P)

(0.228 g, 0.716 mmol; 0.45 ml (50% solution in ethyl acetate). Purification: Combi-Flash. Eluent: ethyl acetate and petroleum ether (5:95) as eluent. Appearance: Brown solid. Yield: 60 mg. % Yield: 18. M.P.: 128-131°C. $^1\text{H-NMR}$ (δ ppm, DMSO-*d*₆, 400 MHz): 8.62 (s, 1H), 7.40-7.35 (m, 3H), 7.30-7.25 (m, 2H), 6.24 (t, J 3.6, 1H), 5.74 (s, 1H), 3.69 (q, J 7.2, 2H), 1.01 (t, J 7.2, 3H). MS (m/z): 471.10 ([$M+\text{H}]^+$).

Example 52

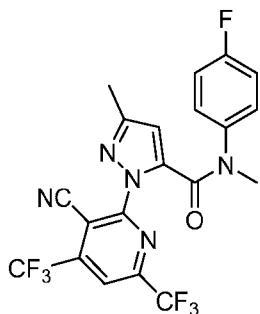
1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-(4-fluorophenyl)-N-methyl-1H-pyrazole-3-carboxamide



[381] Following the general procedure 1, the titled compound was synthesized from intermediate 135 (150 mg, 0.43 mmol), ethyl acetate (5 ml), 4-fluoro-N-methylaniline (54 mg, 0.43 mmol), pyridine (140 mg, 1.70 mmol) and Propyl phosphonic acid anhydride (T3P) (0.550 g, 0.86 mmol; 1.10 ml (50% solution in ethyl acetate). Purification: Combi-Flash. Eluent: ethyl acetate and petroleum ether (23:77) as eluent. Appearance: Off-white solid. Yield: 100 mg. % Yield: 51. M.P.: 123-125°C. $^1\text{H-NMR}$ (δ ppm, DMSO-*d*₆, 400 MHz): 8.52 (s, 1H), 8.46 (s, 1H), 7.36 (s, 2H), 7.16 (s, 2H), 6.56 (br s, 1H), 3.43 (s, 3H). MS (m/z): 458.22 ([$M+\text{H}]^+$).

Example 53

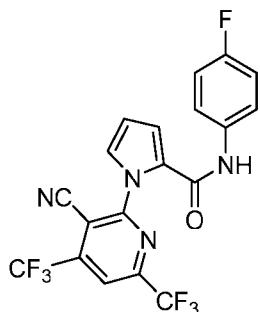
1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-(4-fluorophenyl)-N,3-dimethyl-1H-pyrazole-5-carboxamide



[382] Following the general procedure 1, the titled compound was synthesized from intermediate 138 (100 mg, 0.275 mmol), acetonitrile (5 ml), 4-fluoro-N-methylaniline (52 mg, 0.41 mmol), EDC-HCl (63.2 mg, 0.329 mmol), HOBr (54.7 mg, 0.357) and 4-methylmorpholine (69.4 mg, 0.686 mmol). Purification: Combi-Flash. Eluent: ethyl acetate and petroleum ether (40:60) as eluent. Appearance: Yellow solid. Yield: 60 mg. % Yield: 46. M.P.: 196-198°C. ¹H-NMR (δ ppm, DMSO-*d*₆, 400 MHz): 8.07 (s, 1H), 8.02 (s, 1H), 7.31 (br s, 2H), 7.01 (br s, 2H), 3.49 (s, 3H), 3.00 (s, 3H). MS (m/z): 472.44 ([M+H]⁺).

Example 54

1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-(4-fluorophenyl)-1H-pyrrole-2-carboxamide

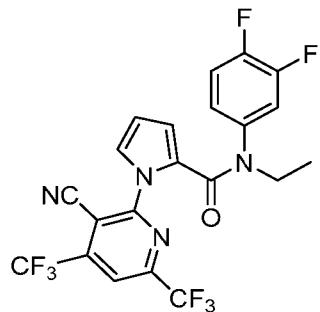


[383] Following the general procedure 1, the titled compound was synthesized from intermediate 132 (500 mg, 1.43 mmol), acetonitrile (15 ml), 4-fluoroaniline (239 mg, 2.15 mmol), EDC-HCl (329 mg, 1.72 mmol), HOBr (285 mg, 1.86 mmol) and 4-methylmorpholine (362 mg, 3.58 mmol). Purification: Combi-Flash. Eluent: ethyl acetate and petroleum ether (10:90) as eluent. Appearance: Off-white solid. Yield: 400 mg. % Yield: 63. M.P.: 148-150°C.

¹H-NMR (δ ppm, DMSO-*d*₆, 400 MHz): 10.32 (s, 1H), 8.67 (s, 1H), 8.02 (s, 1H), 7.59-7.56 (m, 2H), 7.48 (dd, J 2.8, 1.6, 1H), 7.38 (dd, J 4.0, 1.6, 1H), 7.16-7.12 (m, 2H), 6.55 (t, J 3.2, 1H). MS (m/z): 443.06 ([M+H]⁺).

Example 55

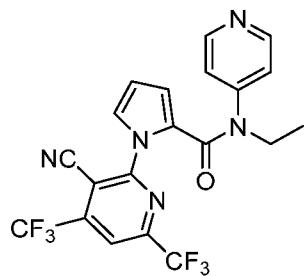
1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-(3,4-difluorophenyl)-N-ethyl-1H-pyrrole-2-carboxamide



[384] Following the general procedure 1, the titled compound was synthesized from intermediate 132 (250 mg, 0.716 mmol), ethyl acetate (3 ml), intermediate 139 (113 mg, 0.716 mmol), pyridine (227 mg, 2.86 mmol) and Propylphosphonic acid anhydride (T3P) (456 mg, 1.43 mmol; 0.912 ml (50% solution in ethyl acetate). Purification: Combi-Flash. Eluent: ethyl acetate and petroleum ether (6.5:93.5) as eluent. Appearance: Off-white solid. Yield: 180 mg. % Yield: 51. M.P.: 127-130°C. ¹H-NMR (δ ppm, DMSO-*d*₆, 400 MHz): 8.62 (s, 1H), 7.54-7.44 (m, 3H), 7.21-7.18 (m, 1H), 6.28 (t, J 3.6, 1H), 5.95 (d, J 2.4, 1H), 3.75 (q, J 7.2, 2H), 1.01 (t, J 7.2, 3H). MS (m/z): 489.08 ([M+H]⁺).

Example 56

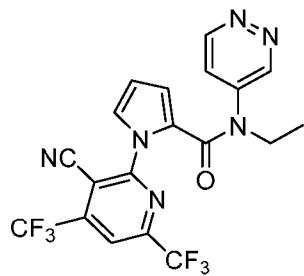
1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-ethyl-N-(pyridin-4-yl)-1H-pyrrole-2-carboxamide



[385] Following the general procedure 1, the titled compound was synthesized from intermediate 132 (100 mg, 0.286 mmol), DMF (2 ml), intermediate 140 (35 mg, 0.286 mmol), HATU (163 mg, 0.432 mmol) and N-diisopropylethylamine (111 mg, 0.859 mmol). Purification: Combi-Flash. Eluent: ethyl acetate and petroleum ether (28:72) as eluent. Appearance: Pale brown solid. Yield: 40 mg. % Yield: 31. M.P.: 152-155°C. ¹H-NMR (δ ppm, DMSO-*d*₆, 400 MHz): 8.63 (s, 1H), 8.55 (dd, J 4.8, 1.6, 2H), 7.53 (dd, J 2.8, 1.6, 1H), 7.34 (dd, J 4.8, 1.6, 2H), 6.29 (t, J 3.6, 1H), 6.19 (dd, J 3.6, 1.2, 1H), 3.82 (q, J 7.2, 2H), 1.01 (t, J 7.2, 3H). MS (m/z): 454.30 ([M+H]⁺).

Example 57

1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-ethyl-N-(pyridazin-4-yl)-1H-pyrrole-2-carboxamide

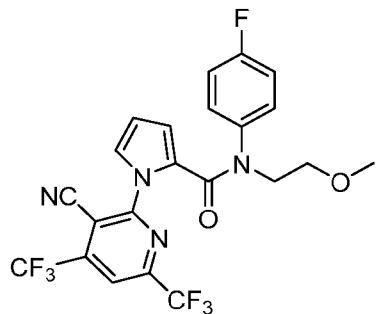


[386] Following the general procedure 1, the titled compound was synthesized from intermediate 132 (100 mg, 0.286 mmol), DMF (2 ml), intermediate 142 (35 mg, 0.286 mmol), HATU (163 mg, 0.432 mmol) and N-diisopropylethylamine (111 mg, 0.859 mmol). Purification: Combi-Flash. Eluent: ethyl acetate and petroleum ether (45:55) as eluent. Appearance: Off-white solid. Yield: 60 mg. % Yield: 46. M.P.: 138-140°C. ¹H-NMR (δ ppm, DMSO-*d*₆, 400 MHz):

9.23 (d, J 5.2, 1H), 9.20 (s, 1H), 8.67 (s, 1H), 7.72 (d, J 2.8, 1H), 7.64 (s, 1H), 6.33 (s, 1H), 6.23 (s, 1H), 3.91 (q, J 6.8, 2H), 1.04 (t, J 6.8, 3H). MS (m/z): 455.29 ($[M+H]^+$).

Example 58

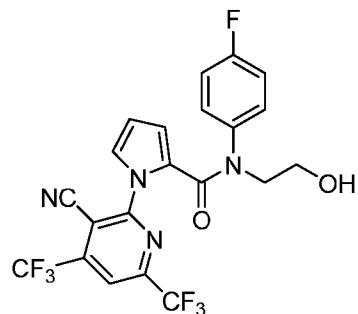
1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-(4-fluorophenyl)-N-(2-methoxyethyl)-1H-pyrrole-2-carboxamide



Following the general procedure 1, the titled compound was synthesized from intermediate 132 (500 mg, 1.40 mmol), ethyl acetate (10 ml), intermediate 143 (240 mg, 1.40 mmol), pyridine (450 mg, 5.70 mmol) and Propylphosphonic acid anhydride (T3P) (910 mg, 2.90 mmol; 1.84 ml (50% solution in ethyl acetate). Purification: Combi-Flash. Eluent: ethyl acetate and petroleum ether (8:92) as eluent. Appearance: Yellow solid. Yield: 320 mg. % Yield: 43. M.P.: 85-87°C. $^1\text{H-NMR}$ (δ ppm, DMSO-*d*₆, 400 MHz): 8.62 (s, 1H), 7.40-7.37 (m, 3H), 7.29-7.24 (m, 2H), 6.24 (t, J 3.2, 1H), 5.70 (s, 1H), 3.81 (t, J 5.6, 2H), 3.41 (t, J 5.6, 2H), 3.15 (s, 3H). MS (m/z): 501.15 ($[M+H]^+$).

Example 59

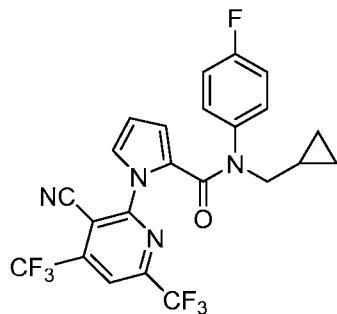
1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-(4-fluorophenyl)-N-(2-hydroxyethyl)-1H-pyrrole-2-carboxamide



[387] To Example 58 (160 mg, 0.32 mmol) in dichloromethane (5 ml) cooled to 0°C, BCl₃ (1M in dichloromethane, 4.80 ml, 4.80 mmol) and stirred for 3h. After stirring at room temperature for 2h, the reaction mixture was quenched with 1M HCl solution (50 ml) and extracted with dichloromethane (2 x 30 ml). The organic layer was washed with saturated sodium bicarbonate solution (2 x 30 ml), dried with anhydrous sodium sulphate and distilled out to obtain crude. Crude was purified by combi-flash using ethyl acetate and petroleum ether (38.5:61.5) as eluent. Pure fractions from column were combined and distilled to obtain the titled compound as a pale-yellow solid. Yield: 50 mg. % Yield: 32. M.P.: 111-114°C. ¹H-NMR (δ ppm, DMSO-*d*₆, 400 MHz): 8.62 (s, 1H), 7.40-7.37 (m, 3H), 7.27 (m, 2H), 6.24 (s, 1H), 5.75 (s, 1H), 4.74 (t, J 4.4, 1H), 3.68 (m, 2H), 3.48-3.44 (m, 2H). MS (m/z): 487.16 ([M+H]⁺).

Example 60

1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-(cyclopropylmethyl)-N-(4-fluorophenyl)-1H-pyrrole-2-carboxamide

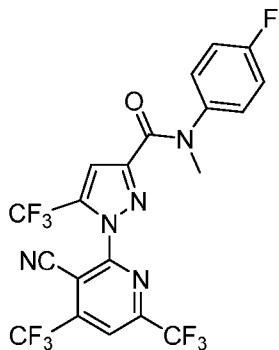


[388] Following the general procedure 1, the titled compound was synthesized from intermediate 132 (250 mg, 0.716 mmol), ethyl acetate (3 ml), intermediate 144 (118 mg, 0.716

mmol), pyridine (227 mg, 2.86 mmol) and Propylphosphonic acid anhydride (T3P) (456 mg, 1.43 mmol; 0.92 ml (50% solution in ethyl acetate). Purification: Combi-Flash. Eluent: ethyl acetate and petroleum ether (6:94) as eluent. Appearance: Pale-yellow solid. Yield: 22 mg. % Yield: 6. M.P.: 134-138°C. $^1\text{H-NMR}$ (δ ppm, DMSO- d_6 , 400 MHz): 8.62 (s, 1H), 7.45-7.38 (m, 3H), 7.30-7.26 (m, 2H), 6.24 (t, J 3.2, 1H), 5.70 (s, 1H), 3.56 (t, J 7.2, 2H), 0. 0.88-0.82 (m, 1H), 0.37-0.36 (m, 2H), 0.05-0.01 (m, 2H). MS (m/z): 497.31 ($[M+\text{H}]^+$).

Example 61

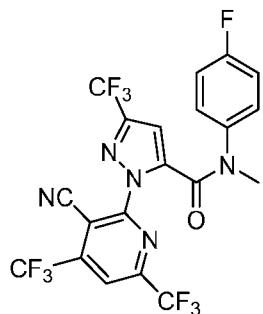
1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-(4-fluorophenyl)-N-methyl-5-(trifluoromethyl)-1H-pyrazole-3-carboxamide



[389] Following the general procedure 1, the titled compound was synthesized from intermediate 147 (100 mg, 0.239 mmol), ethyl acetate (2 ml), 4-fluoro-N-methylaniline (32.9 mg, 0.263 mmol), pyridine (75.7 mg, 0.957 mmol) and Propylphosphonic acid anhydride (T3P) (190 mg, 0.598 mmol; 0.38 ml (50% solution in ethyl acetate). Purification: Combi-Flash. Eluent: ethyl acetate and petroleum ether (30:70) as eluent. Appearance: Off-white solid. Yield: 40 mg. % Yield: 32. M.P.: 118-120°C. $^1\text{H-NMR}$ (δ ppm, DMSO- d_6 , 400 MHz): 8.74 (s, 1H), 7.18-7.07 (m, 5H), 3.27 (s, 3H). MS (m/z): 526.30 ($[M+\text{H}]^+$).

Example 62

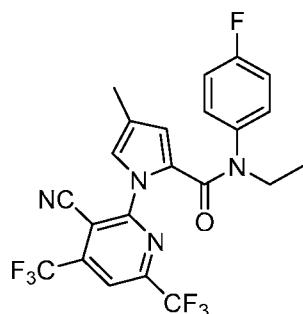
1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-(4-fluorophenyl)-N-methyl-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide



[390] Following the general procedure 1, the titled compound was synthesized from intermediate 148 (90 mg, 0.22 mmol), ethyl acetate (2 ml), 4-fluoro-N-methylaniline (30 mg, 0.24 mmol), pyridine (68 mg, 0.86 mmol) and Propyl phosphonic acid anhydride (T3P) (170 mg, 0.54 mmol; 0.34 ml (50% solution in ethyl acetate). Purification: Combi-Flash. Eluent: ethyl acetate and petroleum ether (10:90) as eluent. Appearance: Off-white solid. Yield: 80 mg. % Yield: 71. M.P.: 144-146°C. ^1H -NMR (δ ppm, CDCl_3 , 400 MHz): 8.05 (s, 1H), 7.26-6.99 (m, 5H), 3.47 (s, 3H). MS (m/z): 526.29 ($[M+\text{H}]^+$).

Example 63

1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-ethyl-N-(4-fluorophenyl)-4-methyl-1H-pyrrole-2-carboxamide

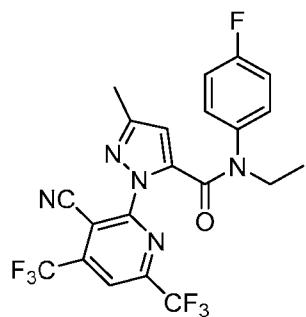


[391] Following the general procedure 1, the titled compound was synthesized from intermediate 152 (140 mg, 0.385 mmol), ethyl acetate (2 ml), intermediate 133 (65 mg, 0.46 mmol), pyridine (122 mg, 1.54 mmol) and Propyl phosphonic acid anhydride (T3P) (307 mg, 0.964 mmol; 0.62 ml (50% solution in ethyl acetate). Purification: Combi-Flash. Eluent: ethyl acetate and petroleum ether (10:90) as eluent. Appearance: Pale-brown solid. Yield: 110 mg.

% Yield: 58. M.P.: 123-126°C. $^1\text{H-NMR}$ (δ ppm, DMSO-*d*₆, 400 MHz): 8.56 (s, 1H), 7.37-7.25 (m, 4H), 7.17 (s, 1H), 5.63 (s, 1H), 3.68 (q, J 7.2, 2H), 1.90 (s, 3H), 1.00 (t, J 7.2, 3H). MS (m/z): 485.15 ([$M+\text{H}]^+$).

Example 64

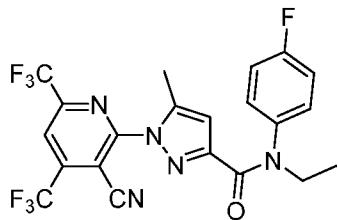
1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-ethyl-N-(4-fluorophenyl)-3-methyl-1H-pyrazole-5-carboxamide



[392] Following the general procedure 1, the titled compound was synthesized from intermediate 138 (100 mg, 0.275 mmol), ethyl acetate (2 ml), intermediate 133 (42 mg, 0.30 mmol), pyridine (87 mg, 1.10 mmol) and Propyl phosphonic acid anhydride (T3P) (218 mg, 0.68 mmol; 0.44 ml (50% solution in ethyl acetate). Purification: Combi-Flash. Eluent: ethyl acetate and petroleum ether (22:78) as eluent. Appearance: Yellow solid. Yield: 90 mg. % Yield: 68. M.P.: 178-180°C. $^1\text{H-NMR}$ (δ ppm, CDCl₃, 400 MHz): 7.78 (s, 1H), 7.72 (s, 1H), 7.13-7.12 (m, 2H), 6.90 (t, J 8.0, 2H), 4.05 (q, J 6.8, 2H), 3.05 (s, 3H), 1.31 (t, J 7.2, 3H). MS (m/z): 486.36 ([$M+\text{H}]^+$).

Example 65

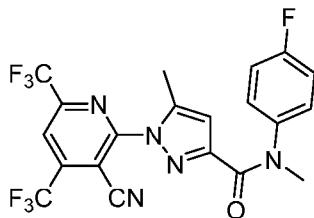
1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-ethyl-N-(4-fluorophenyl)-5-methyl-1H-pyrazole-3-carboxamide



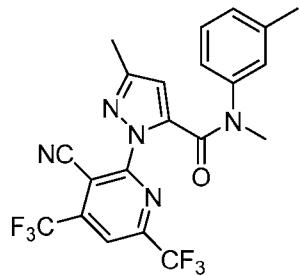
[393] Following the general procedure 1, the titled compound was synthesized from intermediate 155 (120 mg, 0.329 mmol), ethyl acetate (2 ml), intermediate 133 (50.4 mg, 0.362 mmol), pyridine (104 mg, 1.32 mmol) and Propyl phosphonic acid anhydride (T₃P) (262 mg, 0.824 mmol; 0.52 ml (50% solution in ethyl acetate). Purification: Combi-Flash. Eluent: ethyl acetate and petroleum ether (15:85) as eluent. Appearance: Off-white solid. Yield: 100 mg. % Yield: 62. M.P.: 115-118°C. ¹H-NMR (δ ppm, CDCl₃, 400 MHz): 7.91 (s, 1H), 7.21 (m, 2H), 6.99 (m, 2H), 6.34 (s, 1H), 3.93 (q, J 7.2, 2H), 2.50 (s, 3H), 1.25 (t, J 7.2, 3H). MS (m/z): 486.27 ([M+H]⁺).

Example 66

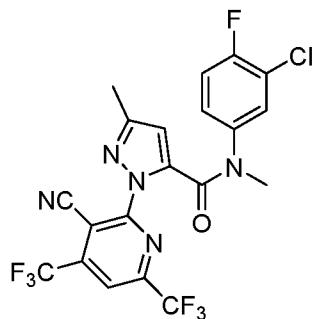
1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-(4-fluorophenyl)-N,5-dimethyl-1H-pyrazole-3-carboxamide



[394] Following the general procedure 1, the titled compound was synthesized from intermediate 155 (120 mg, 0.329 mmol), ethyl acetate (2 ml), 4-fluoro-N-methylaniline (45.4 mg, 0.362 mmol), pyridine (104 mg, 1.32 mmol) and Propyl phosphonic acid anhydride (T₃P) (262 mg, 0.824 mmol; 0.52 ml (50% solution in ethyl acetate). Purification: Combi-Flash. Eluent: ethyl acetate and petroleum ether (20:80) as eluent. Appearance: Off-white solid. Yield: 100 mg. % Yield: 64. M.P.: 118-120°C. ¹H-NMR (δ ppm, CDCl₃, 400 MHz): 7.93 (s, 1H), 7.25-7.20 (m, 2H), 6.99 (m, 2H), 6.36 (s, 1H), 3.46 (s, 3H), 2.53 (s, 3H). MS (m/z): 472.24 ([M+H]⁺).

Example 67**1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N,3-dimethyl-N-(m-tolyl)-1H-pyrazole-5-carboxamide**

[395] Following the general procedure 1, the titled compound was synthesized from intermediate 138 (100 mg, 0.275 mmol), ethyl acetate (2 ml), N,3-dimethylaniline (33.3 mg, 0.275 mmol), pyridine (87 mg, 1.10 mmol) and Propyl phosphonic acid anhydride (T3P) (218 mg, 0.68 mmol; 0.44 ml (50% solution in ethyl acetate). Purification: Combi-Flash. Eluent: ethyl acetate and petroleum ether (25:75) as eluent. Appearance: Yellow solid. Yield: 70 mg. % Yield: 54. M.P.: 172-174°C. $^1\text{H-NMR}$ (δ ppm, DMSO-*d*₆, 400 MHz): 8.06 (s, 1H), 8.03 (s, 1H), 7.19 (s, 1H), 7.09-6.81 (m, 3H), 3.48 (s, 3H), 2.99 (s, 3H), 2.18 (s, 3H). MS (m/z): 468.38 ([*M*+H]⁺).

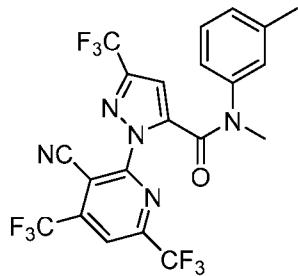
Example 68**N-(3-chloro-4-fluorophenyl)-1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N,3-dimethyl-1H-pyrazole-5-carboxamide**

[396] Following the general procedure 1, the titled compound was synthesized from intermediate 138 (100 mg, 0.275 mmol), ethyl acetate (2 ml), 3-chloro-4-fluoro-N-methylaniline

(43.8 mg, 0.275 mmol), pyridine (87 mg, 1.10 mmol) and Propyl phosphonic acid anhydride (T3P) (218 mg, 0.68 mmol; 0.44 ml (50% solution in ethyl acetate). Purification: Combi-Flash. Eluent: ethyl acetate and petroleum ether (25:75) as eluent. Appearance: Yellow solid. Yield: 50 mg. % Yield: 36. M.P.: 184-186°C. $^1\text{H-NMR}$ (δ ppm, $\text{DMSO-}d_6$, 400 MHz): 8.12 (s, 1H), 8.03 (s, 1H), 7.77 (dd, J 7.2, 1.6, 1H), 7.22-7.12 (br s, 2H), 3.49 (s, 3H), 3.02 (s, 3H). MS (m/z): 506.55 ($[M+\text{H}]^+$).

Example 69

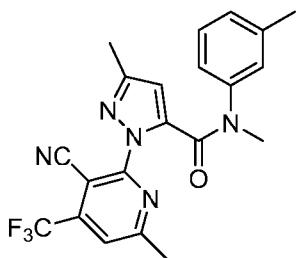
1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-methyl-N-(m-tolyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide



[397] Following the general procedure 1, the titled compound was synthesized from intermediate 148 (200 mg, 0.47 mmol), ethyl acetate (2 ml), N,3-dimethylaniline (69 mg, 0.57 mmol), pyridine (151 mg, 1.91 mmol) and Propyl phosphonic acid anhydride (T3P) (608 mg, 1.91 mmol; 1.22 ml (50% solution in ethyl acetate). Purification: Combi-Flash. Eluent: ethyl acetate and petroleum ether (10:90) as eluent. Appearance: Off-white solid. Yield: 130 mg. % Yield: 52. M.P.: 112-114°C. $^1\text{H-NMR}$ (δ ppm, $\text{DMSO-}d_6$, 400 MHz): 8.67 (s, 1H), 7.27-7.08 (m, 5H), 3.44 (s, 3H), 2.26 (s, 3H). MS (m/z): 522.45 ($[M+\text{H}]^+$).

Example 70

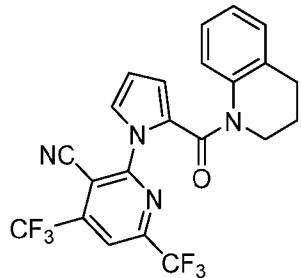
1-(3-cyano-6-methyl-4-(trifluoromethyl)pyridin-2-yl)-N,3-dimethyl-N-(m-tolyl)-1H-pyrazole-5-carboxamide



[398] Following the general procedure 1, the titled compound was synthesized from intermediate 158 (100 mg, 0.32 mmol), ethyl acetate (2 ml), N,3-dimethylaniline (39.1 mg, 0.32 mmol), pyridine (102 mg, 1.29 mmol) and Propyl phosphonic acid anhydride (T3P) (256 mg, 0.80 mmol; 0.52 ml (50% solution in ethyl acetate). Purification: Combi-Flash. Eluent: ethyl acetate and petroleum ether (50:50) as eluent. Appearance: Off-white solid. Yield: 70 mg. % Yield: 53. M.P.: 162-165°C. $^1\text{H-NMR}$ (δ ppm, DMSO- d_6 , 400 MHz): 7.82 (s, 1H), 7.59 (s, 1H), 7.16 (s, 1H), 7.07-6.81 (m, 3H), 3.46 (s, 3H), 2.92 (s, 3H), 2.75 (s, 3H). MS (m/z): 414.45 ($[M+\text{H}]^+$).

Example 71

2-(2-(1,2,3,4-tetrahydroquinoline-1-carbonyl)-1H-pyrrol-1-yl)-4,6-bis(trifluoromethyl)nicotinonitrile

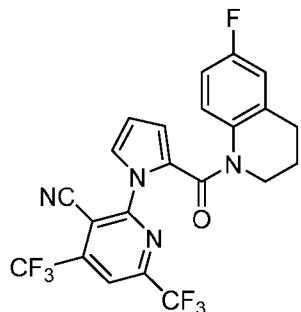


[399] Following the general procedure 1, the titled compound was synthesized from intermediate 132 (500 mg, 1.43 mmol), ethyl acetate (5 ml), 1,2,3,4-tetrahydroquinoline (191 mg, 1.43 mmol), pyridine (453 mg, 5.73 mmol) and Propyl phosphonic acid anhydride (T3P) (911 mg, 2.86 mmol; 1.82 ml (50% solution in ethyl acetate). Purification: Combi-Flash. Eluent: ethyl acetate and petroleum ether (7.5:92.5) as eluent. Appearance: Yellow solid. Yield: 200 mg. % Yield: 30. M.P.: 82-84°C. $^1\text{H-NMR}$ (δ ppm, DMSO- d_6 , 400 MHz): 8.60 (s, 1H), 7.51 (dd, J

3.2,1.6, 1H), 7.13 (dd, J 7.2,4.0, 2H), 7.05-7.00 (m, 2H), 6.56 (d, J 2.4, 1H), 6.42 (t, J 3.2, 1H), 3.81 (t, J 6.4, 2H), 2.59 (t, J 7.2, 2H), 1.89-1.85 (m, 2H). MS (m/z): 465.17 ($[M+H]^+$).

Example 72

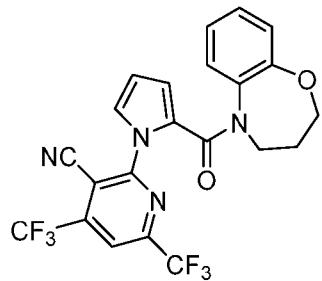
2-(2-(6-fluoro-1,2,3,4-tetrahydroquinoline-1-carbonyl)-1H-pyrrol-1-yl)-4,6-bis(trifluoromethyl)nicotinonitrile



[400] Following the general procedure 1, the titled compound was synthesized from intermediate 132 (254 mg, 0.728 mmol), DMF (2 ml), 6-fluoro-1,2,3,4-tetrahydroquinoline (100 mg, 0.661 mmol), HBTU (376 mg, 0.992 mmol) and N-diisopropylethylamine (256 mg, 1.98 mmol). Purification: Combi-Flash. Eluent: ethyl acetate and petroleum ether (7:93) as eluent. Appearance: Yellow solid. Yield: 20 mg. % Yield: 6. M.P.: 74-76°C. $^1\text{H-NMR}$ (δ ppm, DMSO- d_6 , 400 MHz): 8.60 (s, 1H), 7.53 (dd, J 2.8,1.6, 1H), 7.19 (dd, J 8.8,5.2, 1H), 7.03 (dd, J 9.2,3.2, 1H), 6.91 (dd, J 8.8,2.8, 1H), 6.58 (d, J 2.4, 1H), 6.42 (t, J 3.2, 1H), 3.82 (t, J 6.4, 2H), 2.62 (t, J 6.4, 2H), 1.90-1.84 (m, 2H). MS (m/z): 483.13 ($[M+H]^+$).

Example 73

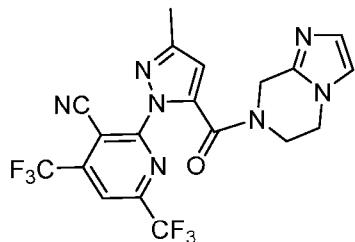
2-(2-(2,3,4,5-tetrahydrobenzo[b][1,4]oxazepine-5-carbonyl)-1H-pyrrol-1-yl)-4,6-bis(trifluoromethyl)nicotinonitrile



[401] Following the general procedure 1, the titled compound was synthesized from intermediate 132 (250 mg, 0.716 mmol), ethyl acetate (2.5 ml), intermediate 27 (107 mg, 0.716 mmol), pyridine (227 mg, 2.86 mmol) and Propylphosphonic acid anhydride (T3P) (456 mg, 1.43 mmol; 0.92 ml (50% solution in ethyl acetate). Purification: Combi-Flash. Eluent: ethyl acetate and petroleum ether (14:86) as eluent. Appearance: Yellow solid. Yield: 50 mg. % Yield: 14. M.P.: 78-81°C. ¹H-NMR (δ ppm, DMSO-*d*₆, 400 MHz): 8.62 (s, 1H), 7.36 (s, 1H), 7.29 (dt, J 8.0, 1.6, 1H), 7.18 (dd, J 8.0, 1.6, 1H), 7.09 (dd, J 8.0, 1.2, 1H), 7.04 (dt, J 7.6, 1.2, 1H), 6.24 (t, J 3.2, 1H), 5.77 (br s, 1H), 4.62 (br s, 1H), 4.30 (br s, 1H), 3.76 (br s, 1H), 2.85 (br s, 1H), 1.87-1.83 (m, 2H). MS (m/z): 481.19 ([M+H]⁺).

Example 74

2-(3-methyl-5-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-7-carbonyl)-1H-pyrazol-1-yl)-4,6-bis(trifluoromethyl)nicotinonitrile

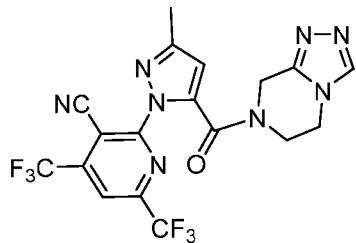


[402] Following the general procedure 1, the titled compound was synthesized from intermediate 138 (100 mg, 0.275 mmol), ethyl acetate (2.0 ml), 5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine (33.8 mg, 0.275 mmol), pyridine (86.9 mg, 1.10 mmol) and Propylphosphonic acid anhydride (T3P) (218 mg, 0.686 mmol; 0.43 ml (50% solution in ethyl acetate)). Purification: Combi-Flash. Eluent: methanol and dichloromethane (4:96) as eluent. Appearance: Yellow solid.

Yield: 70 mg. % Yield: 61. M.P.: 264-266°C. $^1\text{H-NMR}$ (δ ppm, $\text{DMSO-}d_6$, 400 MHz): 8.16-8.11 (m, 2H), 7.22 (d, J 1.2, 0.6H), 7.14 (d, J 1.2, 0.4H), 6.95 (d, J 1.2, 0.6H), 6.85 (d, J 0.8, 0.4H), 5.02 (s, 0.8H), 4.92 (s, 1.2H), 4.22-4.14 (m, 4H), 3.06 (s, 1.9H), 3.03 (s, 1.1H). MS (m/z): 470.46 ($[M+\text{H}]^+$).

Example 75

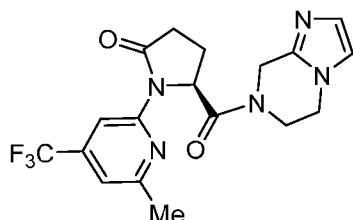
2-(3-methyl-5-(5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine-7-carbonyl)-1H-pyrazol-1-yl)-4,6-bis(trifluoromethyl)nicotinonitrile



[403] Following the general procedure 1, the titled compound was synthesized from intermediate 138 (100 mg, 0.275 mmol), ethyl acetate (2.0 ml), 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine (34.1 mg, 0.275 mmol), pyridine (86.9 mg, 1.10 mmol) and Propylphosphonic acid anhydride (T3P) (218 mg, 0.686 mmol; 0.43 ml (50% solution in ethyl acetate). Purification: Combi-Flash. Eluent: methanol and dichloromethane (6:94) as eluent. Appearance: Yellow solid. Yield: 80 mg. % Yield: 62. M.P.: >300°C. $^1\text{H-NMR}$ (δ ppm, $\text{DMSO-}d_6$, 400 MHz): 8.60 (s, 0.6H), 8.51 (s, 0.4H), 8.17-8.12 (m, 2H), 5.21 (s, 0.8H), 5.09 (s, 1.2H), 4.25-4.18 (m, 4H), 3.06 (s, 1.8H), 3.04 (s, 1.2H). MS (m/z): 471.56 ($[M+\text{H}]^+$).

Example 76

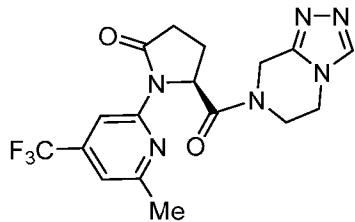
(S)-1-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)-5-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-7-carbonyl)pyrrolidin-2-one



[404] To Intermediate 160 (0.30 g, 0.90 mmol) in 1,4-dioxane (15 ml), 2-bromo-6-methyl-4-(trifluoromethyl)pyridine (330 mg, 1.38 mmol), xantphos (107 mg, 0.185 mmol), cesium carbonate (885 mg, 2.72 mmol) was added and degassed with nitrogen for 30 min. Pd₂(dba)₃ (82.9 mg, 0.09 mmol) was added again degassed with nitrogen for 20 min. The reaction mixture was stirred at 100°C. After 1h, reaction mixture diluted with water (30 ml) and extracted with 10% methanol in dichloromethane (3 x 30 ml). The organic layer was evaporated to obtain crude. Crude product was purified by combi-flash using methanol: dichloromethane (4:96) as eluent to obtain the titled compound as an off-white solid (80 mg). Yield: 22 %. M.P.: 162-164°C. ¹H-NMR (δ ppm, DMSO-*d*₆, 400 MHz): 8.41 (d, J 10.4, 1H), 7.32 (s, 1H), 7.18 (d, J 11.6, 1H), 6.94 (s, 0.5H), 6.89 (s, 0.5H), 5.67 (t, J 9.2, 1H), 5.21 (d, J 16.4, 0.5H), 4.92 (d, J 16.0, 0.5H), 4.84 (d, J 16.4, 0.5H), 4.47 (d, J 16.4, 0.5H), 4.27-4.19 (m, 1.5H), 4.10-3.90 (m, 1.5H), 3.90-3.80 (m, 0.5H), 3.76-3.60 (m, 0.5H), 2.72-2.41 (m, 3H), 2.21 (s, 1.5H), 2.09 (s, 1.5H), 2.03-1.92 (m, 1H). MS (m/z): 394.45 ([M+H]⁺).

Example 77

(S)-1-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)-5-(5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine-7-carbonyl)pyrrolidin-2-one

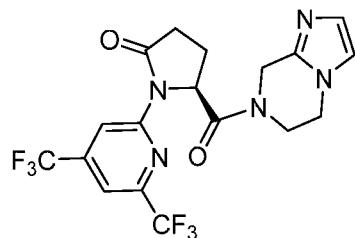


[405] To Intermediate 162 (0.150 g, 0.451 mmol) in 1,4-dioxane (7.5 ml), 2-bromo-6-methyl-4-(trifluoromethyl)pyridine (163 mg, 0.677 mmol), xantphos (53.3 mg, 0.092 mmol), cesium carbonate (441 mg, 1.35 mmol) was added and degassed with nitrogen for 30 min. Pd₂(dba)₃ (41.39 mg, 0.045 mmol) was added again degassed with nitrogen for 20 min. The reaction mixture was stirred at 100°C. After 1h, reaction mixture was filtered through celite bed and washed with 10% methanol in dichloromethane (50 ml). The filtrate was washed with water (50 ml), brine solution (50ml) and evaporated to obtain crude. Crude product was purified by combi-flash using methanol: dichloromethane (4:96) as eluent to obtain the titled compound as

an off-white solid (15 mg). Yield: 8 %. M.P.: 147-150°C. $^1\text{H-NMR}$ (δ ppm, DMSO-*d*₆, 400 MHz): 8.57 (s, 0.6H), 8.54 (s, 0.4H), 8.41 (s, 0.6H), 8.39 (s, 0.4H), 7.33 (s, 1H), 5.68-5.63 (m, 1H), 5.40 (d, J 16.4, 0.4H), 5.08 (d, J 16.8, 0.4H), 4.99 (d, J 16.8, 0.6H), 4.64 (d, J 16.8, 0.6H), 4.29-4.22 (m, 1.5H), 4.17-4.03 (m, 1.5H), 3.97-3.91 (m, 0.5H), 3.78-3.72 (m, 0.5H), 2.71-2.57 (m, 2H), 2.45-2.37 (m, 1H), 2.20 (s, 1.5H), 2.08 (s, 1.5H), 2.06-1.90 (m, 1H). MS (m/z): 395.48 ([*M*+H]⁺).

Example 78

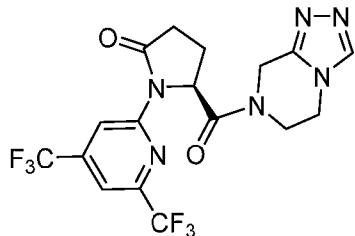
(S)-1-(4,6-bis(trifluoromethyl)pyridin-2-yl)-5-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-7-carbonyl)pyrrolidin-2-one



[406] To Intermediate 160 (0.290 g, 0.875 mmol) in 1,4-dioxane (10 ml), intermediate 110 (386 mg, 1.31 mmol), xantphos (103 mg, 0.179 mmol), cesium carbonate (856 mg, 2.63 mmol) was added and degassed with nitrogen for 30 min. Pd₂(dba)₃ (80.2 mg, 0.087 mmol) was added again degassed with nitrogen for 20 min. The reaction mixture was stirred at 100°C. After 1h, reaction mixture was filtered through cealite bed and washed with 10% methanol in dichloromethane (50 ml). The filterate was washed with water (50 ml), brine solution (50ml) and evaporated to obtain crude. Crude product was purified by combi-flash using methanol: dichloromethane (6:94) as eluent to obtain the titled compound as an off-white solid (110 mg). Yield: 28 %. M.P.: 97-100°C. $^1\text{H-NMR}$ (δ ppm, DMSO-*d*₆, 400 MHz): 8.86 (d, J 8.4, 1H), 8.00 (d, J 8.4, 1H), 7.16 (s, 1H), 6.94 (s, 0.4H), 6.89 (s, 0.6H), 5.70-5.63 (m, 1H), 5.05-4.95 (m, 1H), 4.76 (d, J 16.8, 0.6H), 4.47 (d, J 16.4, 0.6H), 4.20-4.08 (m, 2.8H), 3.87 (s, 2H), 2.74-2.68 (m, 2H), 2.10-1.95 (m, 1H). MS (m/z): 448.41 ([*M*+H]⁺).

Example 79

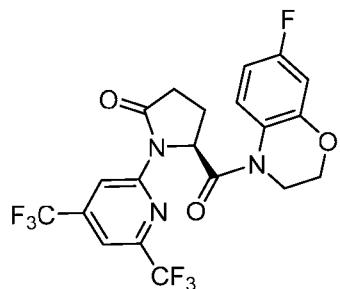
(S)-1-(4,6-bis(trifluoromethyl)pyridin-2-yl)-5-(5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine-7-carbonyl)pyrrolidin-2-one



[407] To Intermediate 162 (0.390 g, 1.17 mmol) in 1,4-dioxane (10 ml), intermediate 110 (518 mg, 1.76 mmol), xantphos (139 mg, 0.239 mmol), cesium carbonate (1.15 g, 3.52 mmol) was added and degassed with nitrogen for 30 min. Pd₂(dba)₃ (107 mg, 0.117 mmol) was added again degassed with nitrogen for 20 min. The reaction mixture was stirred at 100°C. After 1h, reaction mixture was filtered through cealite bed and washed with 10% methanol in dichloromethane (50 ml). The filterate was washed with water (50 ml), brine solution (50ml) and evaporated to obtain crude. Crude product was purified by combi-flash using methanol: dichloromethane (8:92) as eluent to obtain the titled compound as an off-white solid (70 mg). Yield: 13%. M.P.: 103-106°C. ¹H-NMR (δ ppm, DMSO-*d*₆, 400 MHz): 8.88 (s, 0.6H), 8.86 (s, 0.4H), 8.56 (s, 0.6H), 8.55 (s, 0.4H), 8.00 (s, 0.4H), 7.98 (s, 0.6H), 5.70-5.65 (m, 1H), 5.24 (d, J 16.4, 0.4H), 5.11 (d, J 16.4, 0.4H), 4.97 (d, J 16.8, 0.6H), 4.59 (d, J 16.8, 0.6H), 4.33-4.21 (m, 1H), 4.16-4.10 (m, 1H), 4.03-3.96 (m, 1H), 3.91-3.85 (m, 0.5H), 3.82-3.78 (m, 0.5H), 2.74-2.66 (m, 2H), 2.50-2.45 (m, 1H), 2.11-1.95 (m, 1H). MS (m/z): 449.48 ([M+H]⁺).

Example 80

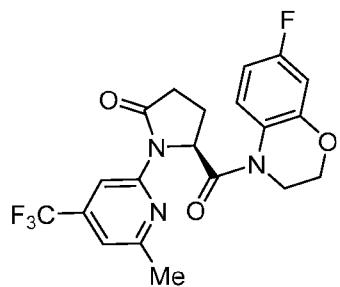
(S)-1-(4,6-bis(trifluoromethyl)pyridin-2-yl)-5-(7-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazine-4-carbonyl)pyrrolidin-2-one



[408] To Intermediate 164 (0.390 g, 1.08 mmol) in 1,4-dioxane (10 ml), intermediate 110 (476 mg, 1.62 mmol), BINAP (60.5 mg, 0.097 mmol), cesium carbonate (1.06 g, 3.24 mmol) was added and degassed with nitrogen for 15 min. Pd(OAc)₂ (12.1 mg, 0.054 mmol) was added again degassed with nitrogen for 15 min. The reaction mixture was stirred at 100°C. After 1h, reaction mixture was filtered through cealite bed and washed with ethyl acetate (100 ml). The filterate was washed with water (50 ml), brine solution (50ml) and evaporated to obtain crude. Crude product was purified by combi-flash using ethyl acetate: petroleum ether (30:70) as eluent to obtain the titled compound as a pale-brown solid (110 mg). Yield: 20 %. M.P.: 72-74°C. ¹H-NMR (δ ppm, DMSO-*d*₆, 400 MHz): 8.89 (s, 1H), 8.03 (s, 1H), 7.86-7.72 (t, J 7.2, 0.6H), 7.42-7.31(m, 0.4H), 6.93-6.74 (m, 1.4H), 6.69-6.62 (m, 0.6H), 5.70-5.61 (m, 1H), 4.40-4.25 (m, 1.6H), 4.33-4.22 (m, 0.4H), 4.16-4.02 (m, 1.6H), 3.52-3.44 (m, 0.4H), 2.75-2.67 (m, 2.6H), 2.32-2.17 (m, 1.4H). MS (m/z): 478.33 ([M+H]⁺).

Example 81

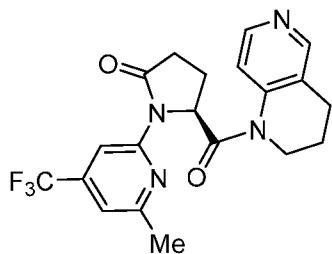
(S)-5-(7-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazine-4-carbonyl)-1-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)pyrrolidin-2-one



[409] To Intermediate 164 (0.490 g, 1.36 mmol) in 1,4-dioxane (10 ml), 2-bromo-6-methyl-4-(trifluoromethyl)pyridine (488 mg, 2.03 mmol), BINAP (76 mg, 0.122 mmol), cesium carbonate (1.33 g, 4.07 mmol) was added and degassed with nitrogen for 15 min. Pd(OAc)₂ (15.2 mg, 0.067 mmol) was added again degassed with nitrogen for 15 min. The reaction mixture was stirred at 100°C. After 1h, reaction mixture was filtered through cealite bed and washed with ethyl acetate (100 ml). The filterate was washed with water (50 ml), brine solution (50ml) and evaporated to obtain crude. Crude product was purified by combi-flash using ethyl acetate: petroleum ether (31:69) as eluent to obtain the titled compound as a pale-brown solid (110 mg). Yield: 19 %. M.P.: 138-140°C. ¹H-NMR (δ ppm, DMSO-*d*₆, 400 MHz): 8.41 (s, 1H), 7.83 (s, 0.4H), 7.38 (s, 0.6H), 7.36 (s, 1H), 6.96-6.79 (m, 1.6H), 6.69 (m, 0.4H), 5.69-5.56 (m, 0.4H), 5.58-5.49 (m, 0.6H), 4.49-4.39 (m, 2H), 4.22-4.12 (m, 0.5H), 4.09-3.99 (m, 1H), 2.78-2.70 (m, 1H), 2.67-2.60 (m, 1.5H), 2.49-2.31 (m, 4H), 2.29-2.27 (m, 0.6H), 2.12-2.08 (m, 0.4H). MS (m/z): 424.39 ([M+H]⁺).

Example 82

(S)-1-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)-5-(1,2,3,4-tetrahydro-1,6-naphthyridine-1-carbonyl)pyrrolidin-2-one

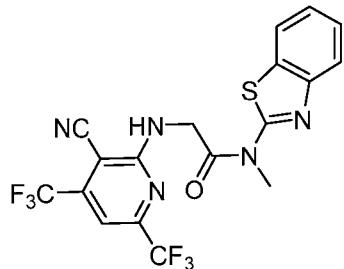


[410] Following the general procedure 1, the titled compound was synthesized from intermediate 166 (100 mg, 0.347 mmol), acetonitrile (3 ml), 1,2,3,4-tetrahydro-1,6-naphthyridine (51.2 mg, 0.382 mmol), EDC-HCl (79.8 mg, 0.416 mmol), HOEt (69.1 mg, 0.451 mmol) and 4-methylmorpholine (87.7 mg, 0.867 mmol). Purification: Combi-Flash. Eluent: methanol and dichloromethane (2.5:97.5) as eluent. Appearance: Off-white solid. Yield: 35 mg. % Yield: 25. M.P.: 162-164°C. ¹H-NMR (δ ppm, DMSO-*d*₆, 400 MHz): 8.43 (s, 1H), 8.39 (s, 1H), 8.28 (br s, 1H), 7.66 (br s, 1H), 7.38 (s, 1H), 5.65 (dd, J 9.6,2.4, 1H), 3.96-3.90 (m, 2H),

2.84 (t, J 6.4, 2H), 2.77-2.61 (m, 2H), 2.49-2.43 (m, 1H), 2.36 (s, 3H), 2.18-2.11 (m, 1H), 2.04-1.98 (m, 2H). MS (m/z): 405.25 ([M+H]⁺).

Example 83

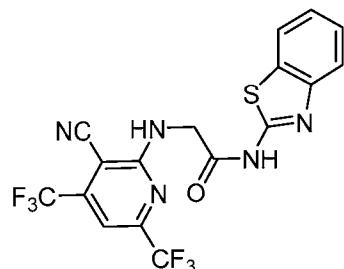
N-(benzo[d]thiazol-2-yl)-2-((3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)amino)-N-methylacetamide



[411] Following the general procedure 3, the titled compound was synthesized from Intermediate 168 (240 mg, 0.931 mmol), N-Methylpyrrolidone (5 ml), intermediate 1 (281 mg, 1.02 mmol) and N-diisopropylethylamine (602 mg, 4.66 mmol). Purification: Combi-Flash. Eluent: Ethyl acetate and petroleum ether (15:85) as eluent. Appearance: Off-white solid. Yield: 80 mg. % Yield: 19. M.P.: 225-228°C. ¹H-NMR (δ ppm, DMSO-*d*₆, 400 MHz): 8.63 (t, J 5.2, 1H), 7.96 (d, J 8.0, 1H), 7.84 (d, J 8.0, 1H), 7.50 (s, 1H), 7.48 (dt, J 7.2, 1.2, 1H), 7.35 (dt, J 8.0, 1.2, 1H), 4.68 (d, J 5.6, 2H), 3.85 (s, 3H). MS (m/z): 460.24 ([M+H]⁺).

Example 84

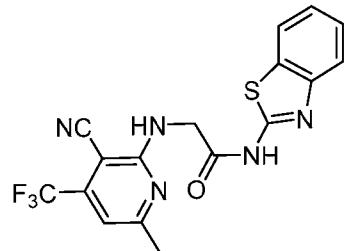
N-(benzo[d]thiazol-2-yl)-2-((3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)amino)acetamide



[412] Following the general procedure 3, the titled compound was synthesized from Intermediate 171 (300 mg, 1.23 mmol), N-Methylpyrrolidone (5 ml), intermediate 1 (400 mg, 1.45 mmol) and N-diisopropylethylamine (500 mg, 3.86 mmol). Purification: Combi-Flash. Eluent: Ethyl acetate and petroleum ether (15:85) as eluent. Appearance: Off-white solid. Yield: 80 mg. % Yield: 10. M.P.: 228-230°C. ¹H-NMR (δ ppm, DMSO-*d*₆, 400 MHz): 12.52 (s, 1H), 8.61 (t, J 5.6, 1H), 7.97 (d, J 7.6, 1H), 7.75 (d, J 7.6, 1H), 7.49 (s, 1H), 7.46 (dt, J 7.2, 1.2, 1H), 7.33 (dt, J 8.0, 0.8, 1H), 4.37 (d, J 5.6, 2H). MS (m/z): 446.32 ([M+H]⁺).

Example 85

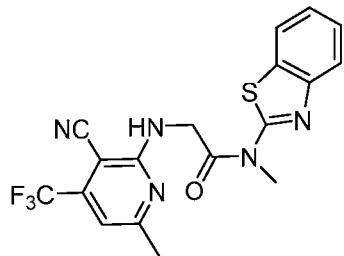
N-(benzo[d]thiazol-2-yl)-2-((3-cyano-6-methyl-4-(trifluoromethyl)pyridin-2-yl)amino)acetamide



[413] Following the general procedure 3, the titled compound was synthesized from Intermediate 171 (300 mg, 1.23 mmol), N-Methylpyrrolidone (5 ml), intermediate 82 (299 mg, 1.35 mmol) and N-diisopropylethylamine (477 mg, 3.67 mmol). Purification: Combi-Flash. Eluent: Ethyl acetate and petroleum ether (25:75) as eluent. Appearance: Off-white solid. Yield: 80 mg. % Yield: 17. M.P.: 240-244°C. ¹H-NMR (δ ppm, DMSO-*d*₆, 400 MHz): 12.50 (s, 1H), 7.98 (d, J 7.6, 1H), 7.91 (t, J 5.6, 1H), 7.75 (d, J 7.6, 1H), 7.46 (dt, J 7.6, 1.2, 1H), 7.32 (dt, J 8.0, 1.2, 1H), 7.03 (s, 1H), 4.36 (d, J 5.6, 2H), 2.38 (s, 3H). MS (m/z): 392.07 ([M+H]⁺).

Example 86

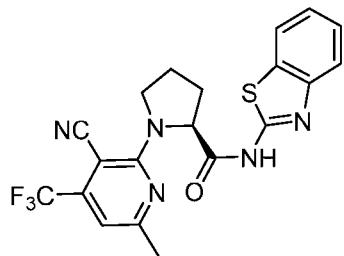
N-(benzo[d]thiazol-2-yl)-2-((3-cyano-6-methyl-4-(trifluoromethyl)pyridin-2-yl)amino)-N-methylacetamide



[414] Following the general procedure 3, the titled compound was synthesized from Intermediate 168 (300 mg, 1.16 mmol), N-Methylpyrrolidone (5 ml), intermediate 82 (282 mg, 1.28 mmol) and N-diisopropylethylamine (451 mg, 3.49 mmol). Purification: Combi-Flash. Eluent: Ethyl acetate and petroleum ether (50:50) as eluent. Appearance: Off-white solid. Yield: 180 mg. % Yield: 38. M.P.: 194-198°C. ¹H-NMR (δ ppm, DMSO-*d*₆, 400 MHz): 7.64 (s, 1H), 7.59 (dd, J 8.0,1.6, 1H), 7.42 (dt, J 7.6,1.6, 1H), 7.17 (s, 1H), 7.09-7.03 (m, 2H), 3.72 (s, 2H), 2.66 (s, 3H), 2.44 (s, 3H). MS (m/z): 406.38 ([M+H]⁺).

Example 87

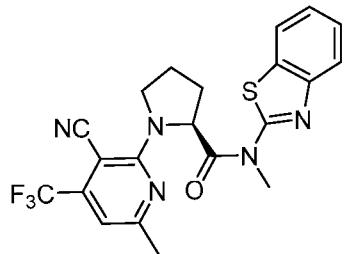
(S)-N-(benzo[d]thiazol-2-yl)-1-(3-cyano-6-methyl-4-(trifluoromethyl)pyridin-2-yl)pyrrolidine-2-carboxamide



[415] Following the general procedure 3, the titled compound was synthesized from Intermediate 173 (300 mg, 1.10 mmol), N-Methylpyrrolidone (5 ml), intermediate 82 (260 mg, 1.20 mmol) and N-diisopropylethylamine (410 mg, 3.20 mmol). Purification: Combi-Flash. Eluent: Ethyl acetate and petroleum ether (23:77) as eluent. Appearance: Off-white solid. Yield: 45 mg. % Yield: 10. M.P.: 122-124°C. ¹H-NMR (δ ppm, DMSO-*d*₆, 400 MHz): 12.60 (s, 1H), 7.97 (d, J 7.6, 1H), 7.75 (d, J 8.0, 1H), 7.45 (dt, J 8.0,0.8, 1H), 7.32 (dt, J 8.0,0.8, 1H), 7.05 (s, 1H), 4.87 (dd, J 7.6,2.0, 1H), 4.11-3.97 (m, 2H), 2.36-2.32 (m, 1H), 2.26 (s, 3H), 2.16-1.99 (m, 3H). MS (m/z): 432.09 ([M+H]⁺).

Example 88

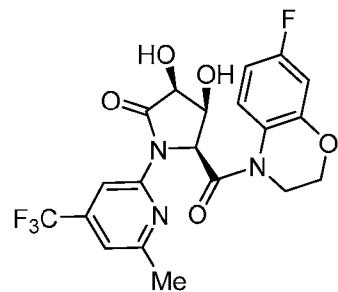
(S)-N-(benzo[d]thiazol-2-yl)-1-(3-cyano-6-methyl-4-(trifluoromethyl)pyridin-2-yl)-N-methylpyrrolidine-2-carboxamide



[416] Following the general procedure 3, the titled compound was synthesized from Intermediate 175 (410 mg, 1.40 mmol), N-Methylpyrrolidone (7 ml), intermediate 82 (330 mg, 1.50 mmol) and N-diisopropylethylamine (710 mg, 5.50 mmol). Purification: Combi-Flash. Eluent: Ethyl acetate and petroleum ether (38:62) as eluent. Appearance: Off-white solid. Yield: 150 mg. % Yield: 24. M.P.: 116-118°C. ¹H-NMR (δ ppm, DMSO-*d*₆, 400 MHz): 7.69 (s, 1H), 7.55 (dd, J 7.6, 1.2, 1H), 7.42 (dt, J 8.0, 1.6, 1H), 7.14 (dd, J 8.0, 1.2, 1H), 7.07 (dt, J 7.6, 1.6, 1H), 4.12 (dd, J 9.2, 7.2, 1H), 2.77 (s, 3H), 2.76-2.66 (m, 2H), 2.42 (s, 3H), 2.07-2.00 (m, 1H), 1.80-1.72 (m, 2H), 1.48-1.39 (m, 1H). MS (m/z): 446.43 ([M+H]⁺).

Example 89

(3S,4S,5S)-5-(7-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazine-4-carbonyl)-3,4-dihydroxy-1-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)pyrrolidin-2-one



[417] To intermediate 177 (120 mg, 0.24 mmol), 2M HCl in 1,4-dioxane (9.8 ml) was added and stirred at room temperature for 16h. After 16h, thereaction mass was concentrated, pH

adjusted to 7-8 with aqueous sodium bicarbonate solution and extracted with 10% methanol in dichloromethane (3 x 20 ml). The organic layer was distilled under vacuum to obtain a crude. Crude product was purified by combi-flash using methanol: dichloromethane (1.8:98.2) as eluent to obtain the titled compound as an off-white solid (50 mg). Yield: 45 %. M.P.: 138-140°C. ¹H-NMR (δ ppm, DMSO-*d*₆, 400 MHz): 8.31 (s, 1H), 7.68 (dd, J 8.8,6.8, 1H), 7.39 (s, 1H), 6.91-6.62 (m, 2H), 5.70-5.42 (m, 3H), 4.65-4.21 (m, 4H), 4.19-4.10 (m, 2H), 2.40 (s, 3H). MS (m/z): 456.25 ([M+H]⁺).

BIOLOGICAL DATA

Pol Theta Enzyme Assay

[418] Pol theta polymerase domain spanning 1819-2590 amino acids was used in the enzyme assay for screening Pol theta inhibitors. 20 μ L of a reaction mixture containing Pol theta enzyme (50 ng/well) was prepared in an assay buffer containing 20 mM TRIS (tris(hydroxymethyl)aminomethane), pH 7.8, 50 mM KCl, 10 mM MgCl₂, 1 mM DTT [dithiothreitol], 0.01% BSA [bis(trimethylsilyl)acetamide], and 0.01% Tween-20 and was incubated with a test compound for 30 minutes at room temperature. Reactions containing DMSO with enzyme (high control) and DMSO with assay buffer (low control) were set up in parallel. An equal volume (20 μ L) of dNTP [deoxyribonucleotide triphosphate] (50 μ M) substrate mix and primed molecular beacon (100 μ M) prepared in assay buffer was added to all the test wells. Primed molecular beacons were prepared by annealing template (5'-CCTTCCTCCGTGCTTG-TACCTTCCGTCA-GGAGGAAGG-3') containing 5'-TAMRA and 3'-BHQ and primer DNA (5'-GACGGGAAGG-3') in annealing buffer (10 mM Tris-HCl pH 8.0, 100 mM NaCl). The enzyme activity was measured by monitoring the fluorescence change at 535 nm (emission) and 485 nm (excitation) for 2 hours. High control with high fluorescence represents no inhibition of polymerase reaction and low control with low fluorescence represent 100% inhibition. Percent inhibition was calculated as follows:

$$100 - ((\text{Compound} - \text{Low control}) / (\text{High Control} - \text{Min}) * 100).$$

Pol Theta inhibitory activity for selected test compounds of the present invention is provided in Table 2 below.

TABLE 2

Compound	Percent Inhibition of PolQ Enzyme Activity	
	10 µM	1 µM
1	++	++
4	+	+
8	++	+
9	++	++
10	++	+
12	++	++
49	++	++
50	++	++
51	++	+
53	++	++
54	++	+
71	++	+

“+” represents 25 to 50 percent inhibition and “++” represents more than 50 percent inhibition up to 100 percent inhibition.

Cell Proliferation Assay

[419] UWB 1.289 cells or DLD-1 BRCA2(--) were plated at pre-determined density in a 96-well plate and incubated at 37° C and 5% CO₂ overnight. The cells were treated with the test compounds and the plates were incubated at 37° C and 5% CO₂ for 144 hours. After the desired incubation, MTT (4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide)) was added to the wells and MTT reaction was performed. Formazan crystals formed due to the MTT reaction were dissolved in DMSO and absorbance was read at A560 nM and A640 nM. GI₅₀ values were calculated using GraphPad Prism.

Results: GI₅₀ values determined for select compounds of the invention are presented in Table 3 below.

TABLE 3

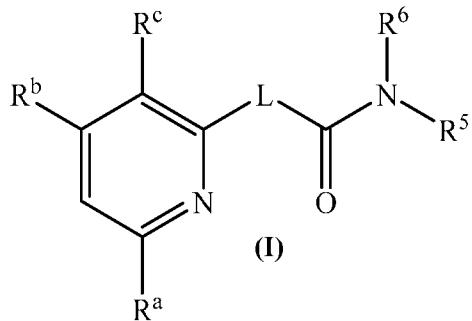
Test Compound	GI ₅₀ in UWB 1.289 Cells (μM)	GI ₅₀ in DLD-1 BRCA2(--) Cells (μM)
52	ND	5
53	10.3	ND
62	3.4	3.4
64	3.8	ND
80	8.68	7.3
69	ND	1.53
70	ND	9
1	3.26	ND
8	15.6	ND
10	3.5	3.2
12	9.3	ND
20	3.2	7.7
24	9.2	ND
26	5.05	1.1
28	1.1	1.1

31	4.59	ND
37	ND	8.5
42	8.5	ND
43	ND	3.5
44	ND	1.3
45	ND	0.88
46	ND	1.0
84	1.15	3.7
87	ND	8

ND: Not determined

WE CLAIM:

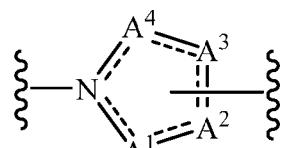
1. A compound of formula (I)



or a tautomer thereof, prodrug thereof, N-oxide thereof, stereoisomer thereof, pharmaceutically acceptable ester thereof, or pharmaceutically acceptable salt thereof,

wherein

R^a , R^b , and R^c are each independently selected from hydrogen, hydroxy, halo, cyano, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted heteroaryl;



L is (i) $-N(R^1)-C(R^2)(R^3)-$, or (ii) where the left squiggly line (~~~~) represents the point of attachment to the pyridyl group in formula (I) and the right squiggly line represents the point of attachment to the carbonyl group in formula (I);

R^1 , R^2 , and R^3 are each independently selected from hydrogen, hydroxy, halo, cyano, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted amino, substituted or unsubstituted

aminoalkyl, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted heteroaryl;

each dashed line (----) independently represents an optional bond such that at most two non-adjacent dashed lines represent a bond;

A^1 , A^2 , A^3 , and A^4 are each independently selected from CR^4 , CR^4R^{4a} , NR^4 , O, S, and $S(O)_2$; with the proviso that A^1 , A^2 , A^3 and A^4 cannot each be CR^4R^{4a} at the same time, NR^4 at the same time, O at the same time, S at the same time, or $S(O)_2$ at the same time;

each occurrence of R^4 is independently selected from hydrogen, hydroxy, halo, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, and substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted heteroaryl;

each occurrence of R^{4a} independently is selected from hydrogen, hydroxy, halo, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted acyl, and substituted or unsubstituted alkyl;

or R^4 and R^{4a} together with the carbon atom to which they are bound may form a thiocarbonyl (-C(=S)-), carbonyl (-C(=O)-), imine (-C(=NH)-) group, or substituted or unsubstituted saturated or unsaturated 3-14 membered ring, which may optionally include one or more heteroatoms which may be the same or different and are independently selected from O, N, and S, and any ring carbon atom may optionally be substituted with oxo (=O), thio (=S), or imine (=NH);

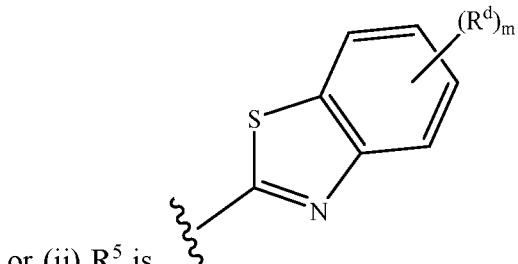
R^5 and R^6 are each independently selected from hydrogen, hydroxy, halo, cyano, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted amino, substituted or unsubstituted

aminoalkyl, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted heteroaryl; or both R⁵ and R⁶ together with the nitrogen atom to which they are attached form a substituted or unsubstituted heterocyclyl ring or substituted or unsubstituted heteroaryl;

with the provisos that

a) when L is -N(R¹)-C(R²)(R³)-,

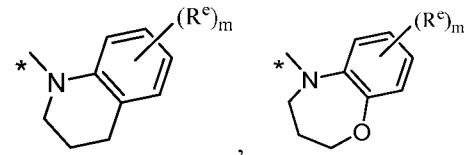
then (i) R⁵ and R⁶ together with the nitrogen atom to which they are attached form a substituted or unsubstituted heterocyclyl ring or substituted or unsubstituted heteroaryl;



or (ii) R⁵ is , and R⁶ is selected from hydrogen, hydroxy, halo, cyano, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted heteroaryl; wherein each occurrence of R^d is independently selected from hydrogen, hydroxy, halo, cyano, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted amino, and substituted or unsubstituted alkyl; and m is 1, 2, or 3;

b) when L is

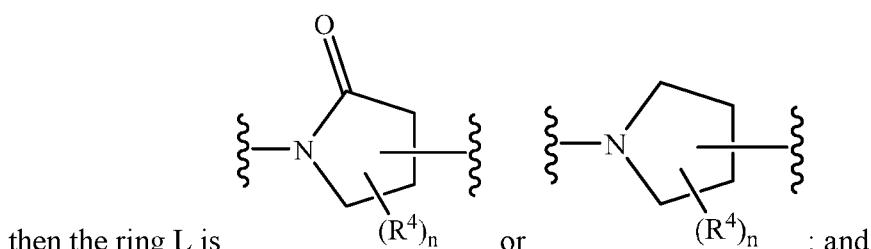
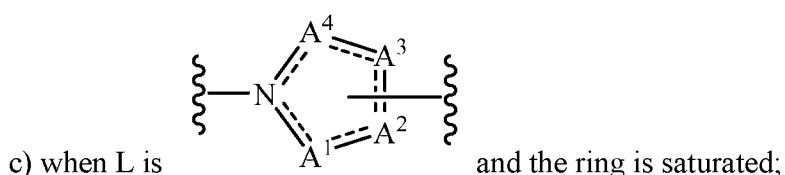
then R⁵ and R⁶ are each independently selected from hydrogen, hydroxy, halo, cyano, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocycll, and substituted or unsubstituted heteroaryl; or R⁵ and R⁶ together with the nitrogen atom to which they are attached form a ring selected from



atom to which they are attached form a ring selected from

, and

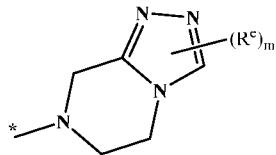
; wherein each occurrence of R^e is independently selected from hydrogen, hydroxy, halo, cyano, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted amino, and substituted or unsubstituted alkyl; and m is 0, 1, 2, or 3; and



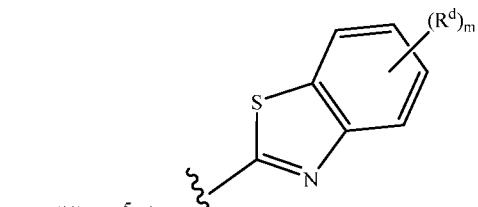
(i) R⁵ and R⁶ together with the nitrogen atom to which they are attached form a ring

selected from

, and



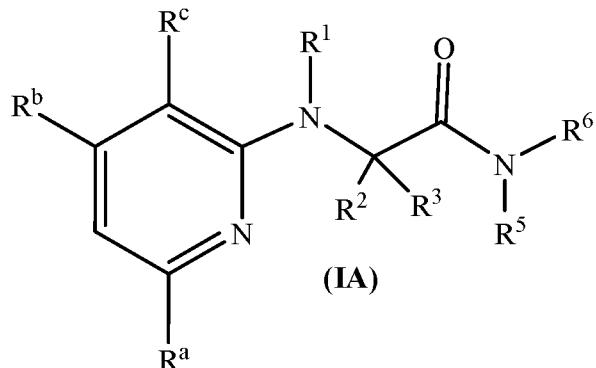
; wherein each occurrence of R^e is independently selected from hydrogen, hydroxy, halo, cyano, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted amino, and substituted or unsubstituted alkyl; and m is 0, 1, 2, or 3;



or (ii) R⁵ is  , and R⁶ is selected from hydroxy, halo, cyano, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclil, and substituted or unsubstituted heteroaryl; wherein each occurrence of R^d is independently selected from hydrogen, hydroxy, halo, cyano, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted amino, substituted or unsubstituted alkyl; and m is 0, 1, 2, or 3; and

the asterisk (*) represents the point of attachment of the ring to the main structure.

2. The compound of claim 1, having the formula (IA):



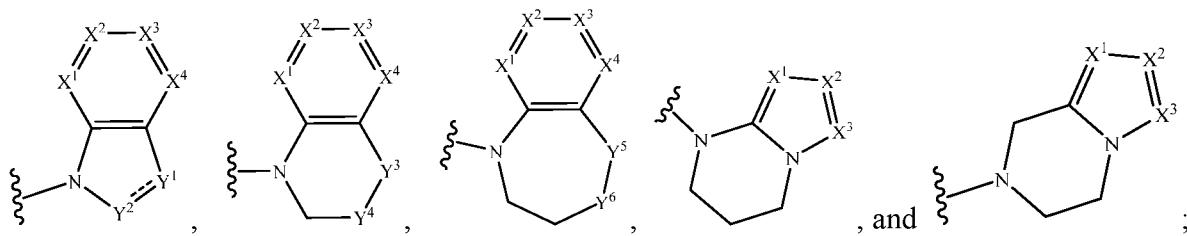
or a tautomer thereof, prodrug thereof, N-oxide thereof, stereoisomer thereof, pharmaceutically acceptable ester thereof, or pharmaceutically acceptable salt thereof,

wherein

R^a , R^b , and R^c are each independently selected from hydrogen, hydroxy, halo, cyano, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted heteroaryl;

R^1 , R^2 , and R^3 are each independently selected from hydrogen, hydroxy, halo, cyano, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted heteroaryl;

(i) R^5 and R^6 together with the nitrogen atom to which they are attached form a substituted or unsubstituted ring selected from



the squiggly line () represents the point of attachment to the rest of the compound of formula (IA);

the dashed line (-----) represents an optional bond;

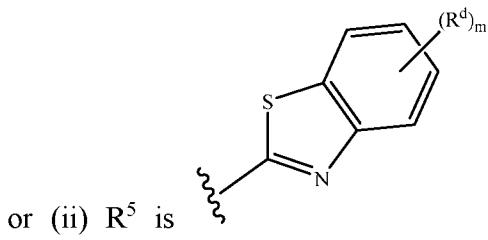
X^1 , X^2 , X^3 , and X^4 are, in each occurrence, independently selected from $-CR^7$ and N, with the proviso that, in the first three structures, at least one of X^1 , X^2 , X^3 , and X^4 is not N (i.e., in the first three structures, at least one of X^1 , X^2 , X^3 and X^4 is $-CR^7$);

each occurrence of R^7 is independently selected from hydrogen, hydroxy, halo, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroaryl, and substituted or unsubstituted heteroarylalkyl;

or two R^7 groups present on adjacent carbon atoms, or any R^7 group along with an adjacent N ring atom, can be joined to form a substituted or unsubstituted saturated or unsaturated 3-14 membered ring, which may optionally include one or more heteroatoms, which may be the same or different, and are independently selected from O, N, and S, wherein any carbon atom in the ring may be substituted by oxo (=O), thio (=S), and imino (=NH);

Y^1 , Y^2 , Y^3 , Y^4 , Y^5 and Y^6 are each independently selected from $CR^{8a}R^{8a}$, CR^8 , O, NR^{8a} , S, and $S(O)_2$, with the proviso that when the dashed line (-----) represents a bond, then each of Y^1 and Y^2 is CR^{8a} ;

each occurrence of R⁸ and R^{8a} is independently selected from hydrogen, hydroxy, halo, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted amino, substituted or unsubstituted amide, substituted or unsubstituted aminoalkyl, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroaryl, and substituted or unsubstituted heteroarylalkyl; or R⁸ and R^{8a}, together with the carbon atom to which they are bound, form a thiocarbonyl (-C(=S)-), carbonyl (-C(=O)-), imine (-C(=NH)-) group, or a substituted or unsubstituted saturated or unsaturated 3-14 membered ring, which may optionally include one or more heteroatoms, which may be the same or different, and are each selected from O, N, and S, wherein any carbon atom in the ring may be substituted by oxo (=O), thio (=S), and imino (=NH);

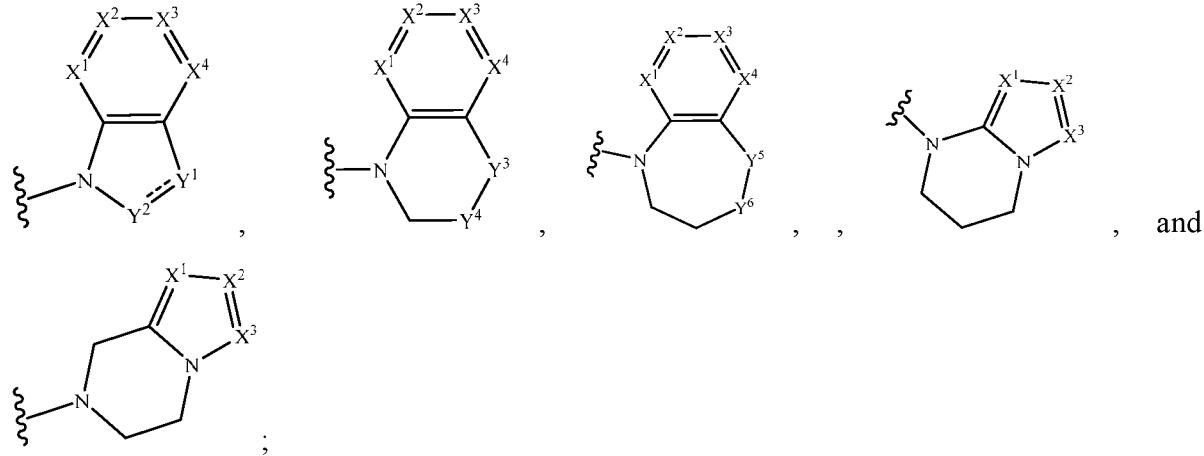


or (ii) R⁵ is , R⁶ is selected from hydroxy, halo, cyano, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted heteroaryl; each occurrence of R^d is independently selected from hydrogen, hydroxy, halo, cyano, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted amino, and substituted or unsubstituted alkyl; and m is 0,1,2, or 3.

3. The compound of any one of claims 1 to 2, wherein R^a is hydrogen, -CH₃, or -CF₃, R^b is -CF₃, and R^c is hydrogen or cyano.

4. The compound of any one of claims 1 to 3, wherein R¹, R², and R³ are each hydrogen.

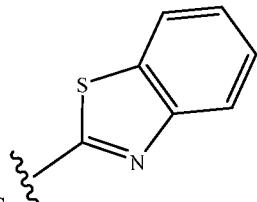
5. The compound of any one of claims 1 or 4, wherein R⁵ and R⁶ together with the nitrogen atom to which they are attached form a substituted or unsubstituted ring selected from



X¹, X², X³, and X⁴ are, in each occurrence, independently selected from -CR⁷ and N, with the proviso that, in the first structure, at least one of X¹, X², X³, and X⁴ is not N;

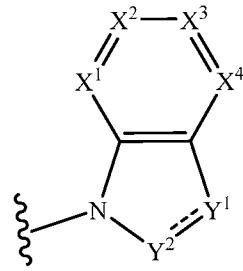
each occurrence of R⁷ is independently selected from hydrogen, hydroxy, halo, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroaryl, and substituted or unsubstituted heteroarylalkyl; and

or two R⁷ groups present on adjacent carbon atoms, or any R⁷ group along with an adjacent N ring atom, can be joined to form a substituted or unsubstituted saturated or unsaturated 3-14 membered ring, which may optionally include one or more heteroatoms, which may be the same or different, and are independently selected from O, N, and S, wherein any carbon atom in the ring may be substituted by oxo (=O), thio (=S), and imino (=NH).



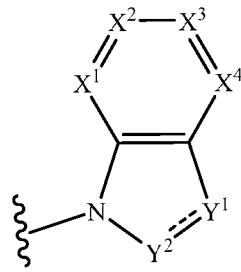
6. The compound of any one of claims 1 to 4, wherein R⁵ is and R⁶ is hydrogen or alkyl.

7. The compound of any one of claims 1 to 5, wherein R⁵ and R⁶ together with the nitrogen



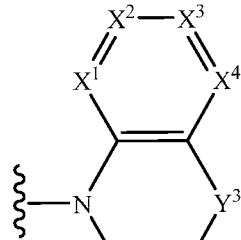
atom to which they are attached form the ring ; the dashed line (----) is a bond; each of X¹, X², X³, and X⁴ is CR⁷; each occurrence of R⁷ is independently hydrogen or halogen; each of Y¹ and Y² is CR⁸; and each R⁸ is independently hydrogen or amido.

8. The compound of any one of claims 1 to 5, wherein R⁵ and R⁶ together with the nitrogen



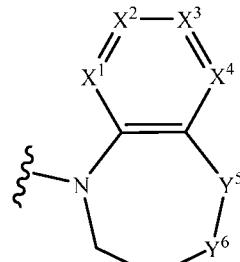
atom to which they are attached form the ring ; the dashed line (----) is absent; each of X¹, X², X³, and X⁴ is CR⁷; each R⁷ is hydrogen; each of Y¹ and Y² is CR⁸R^{8a}; and each occurrence of R⁸ and R^{8a} is hydrogen.

9. The compound of any one of claims 1 to 6, wherein R⁵ and R⁶ together with the nitrogen



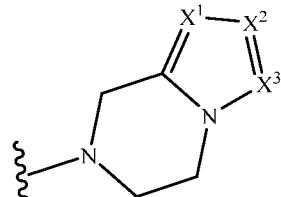
atom to which they are attached form the ring ; each of X¹, X², X⁴ is CR⁷, and X³ is independently CR⁷ or N; each occurrence of R⁷ is independently hydrogen or halogen; Y³ and Y⁴ are each, independently, selected from CR⁸R^{8a}, O, NR^{8a}, and S(O)₂; and each occurrence of R⁸ and R^{8a} is hydrogen, or R⁸ and R^{8a}, together with the carbon atom to which they are attached, form a carbonyl (C=O) group.

10. The compound of any one of claims 1 to 6, wherein R⁵ and R⁶ together with the nitrogen



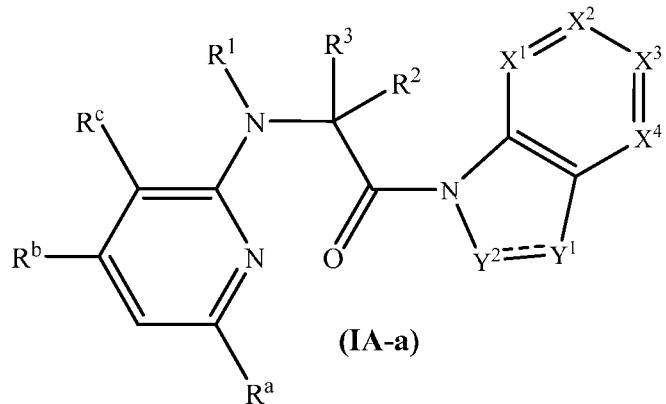
atom to which they are attached form the ring , each of X¹, X², X³, and X⁴ is CR⁷; each R⁷ is, independently, hydrogen or halogen; Y⁵ and Y⁶ are each, independently, selected from CR⁸R^{8a}, O, and NR^{8a}; each occurrence of R⁸ and R^{8a} is hydrogen, or R⁸ and R^{8a}, together with the carbon atom to which they are attached, form a carbonyl -(C=O) group.

11. The compound of any one of claims 1 to 6, wherein R⁵ and R⁶ together with the nitrogen



atom to which they are attached form the ring , each of X¹, X², and X³ is independently CR⁷ or N; and each occurrence of R⁷ is hydrogen, alkyl, or haloalkyl.

12. The compound of any one of claims 2-5, 7 and 8, wherein the compound is a compound of formula **(IA-a)**:

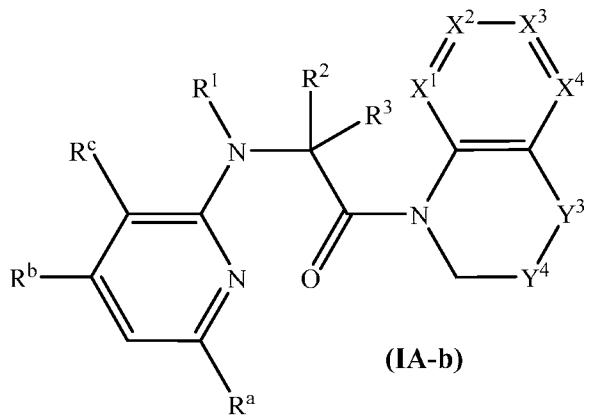


or a tautomer thereof, prodrug thereof, N-oxide thereof, stereoisomer thereof, pharmaceutically acceptable ester thereof, or pharmaceutically acceptable salt thereof,

wherein

the dashed line (-----), R^a, R^b, R^c, R¹, R², R³, X¹, X², X³, X⁴, Y¹ and Y² are as defined in any one of claims 2-11.

13. The compound of any one of claims 2-5 and 9, wherein the compound is a compound of formula **(IA-b)**:

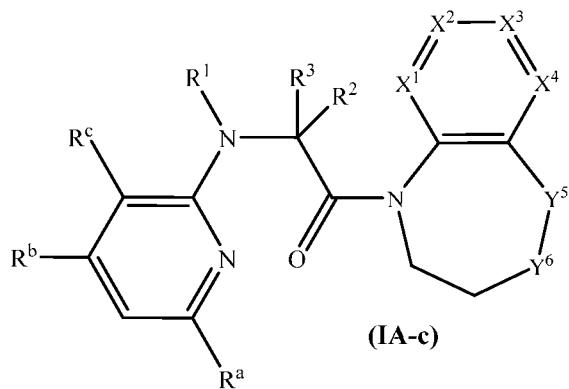


or a tautomer thereof, prodrug thereof, N-oxide thereof, stereoisomer thereof, pharmaceutically acceptable ester thereof, or pharmaceutically acceptable salt thereof,

wherein,

R^a , R^b , R^c , R^1 , R^2 , R^3 , X^1 , X^2 , X^3 , X^4 , Y^3 and Y^4 are as defined in any one of claims 2-5 and 9.

14. The compound of any one of claims 2-5 and 10, wherein the compound is a compound of formula **(IA-c)**:

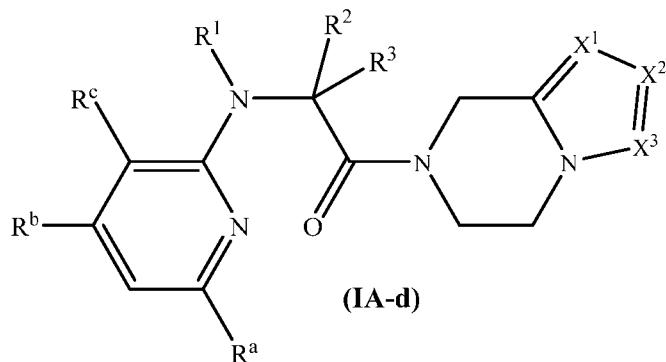


or a tautomer thereof, prodrug thereof, N-oxide thereof, stereoisomer thereof, pharmaceutically acceptable ester thereof, or pharmaceutically acceptable salt thereof,

wherein,

R^a , R^b , R^c , R^1 , R^2 , R^3 , X^1 , X^2 , X^3 , X^4 , Y^5 and Y^6 are as defined in any one of claims 2-5 and 10.

15. The compound of any one of claims 2-5 and 11, wherein the compound is a compound of formula **(IA-d)**:

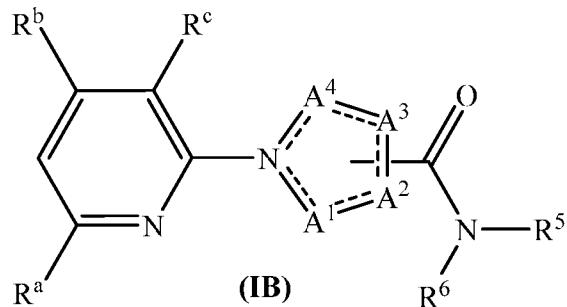


or a tautomer thereof, prodrug thereof, N-oxide thereof, stereoisomer thereof, pharmaceutically acceptable ester thereof, or pharmaceutically acceptable salt thereof,

wherein,

R^a , R^b , R^c , R^1 , R^2 , R^3 , X^1 , X^2 and X^3 are as defined in any one of claims 2-5 and 11.

16. The compound of claim 1, wherein the compound having a formula **(I)** is a compound having formula **(IB)**:



or a tautomer thereof, prodrug thereof, N-oxide thereof, stereoisomer thereof, pharmaceutically acceptable ester thereof, or pharmaceutically acceptable salt thereof,

wherein

R^a , R^b , and R^c are each independently selected from hydrogen, hydroxy, halo, cyano, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or

unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted heteroaryl;

each dashed line (----) independently represents an optional bond such that at most two non-adjacent dashed lines represent a bond;

A^1 , A^2 , A^3 , and A^4 are each independently selected from CR^4 , CR^4R^{4a} , NR^4 , O, S, and $S(O)_2$; with the proviso that A^1 , A^2 , A^3 and A^4 cannot each be CR^4R^{4a} at the same time, NR^3 at the same time, O at the same time, S at the same time, or $S(O)_2$ at the same time;

each occurrence of R^4 is independently selected from hydrogen, hydroxy, halo, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted heteroaryl;

each occurrence of R^{4a} independently is selected from hydrogen, hydroxy, halo, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted acyl, and substituted or unsubstituted alkyl;

or R^4 and R^{4a} together with the carbon atom to which they are bound may form a thiocarbonyl (-C(=S)-), carbonyl (-C(=O)-), imine (-C(=NH)-) group, or substituted or unsubstituted saturated or unsaturated 3-14 membered ring, which may optionally include one or more heteroatoms which may be the same or different and are independently selected from O, N, and S, and any ring carbon atom may optionally be substituted with oxo (=O), thio (=S), and imine (=NH); and

R^5 and R^6 are each independently selected from hydrogen, hydroxy, halo, cyano, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or

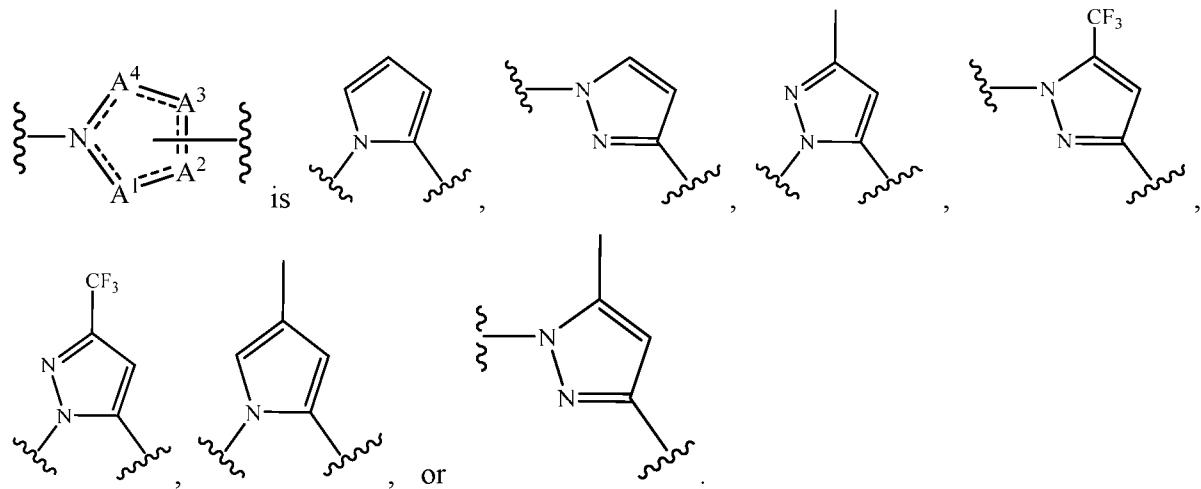
unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted heteroaryl; or both R⁵ and R⁶ together with the nitrogen atom to which they are attached form a substituted or unsubstituted heterocyclyl ring or substituted or unsubstituted heteroaryl.

17. The compound of any one of claims 1 and 16, wherein (i) one dashed line (----) is a bond, (ii) two dashed lines (----) are a bond, or (iii) each dashed line (----) is not a bond.

18. The compound of any one of claims 1 and 16 to 17, wherein R^a is hydrogen, -CH₃, or -CF₃, R^b is hydrogen or -CF₃, and R^c is cyano.

19. The compound of any of claims 1 and 16 to 18, wherein (i) A¹, A², A³ and A⁴ are each -CR⁴; and each R⁴ is independently selected from hydrogen, substituted or unsubstituted alkyl (-CH₃), and substituted or unsubstituted haloalkyl; (ii) A¹ and A² are each independently selected from -CR⁴ or -NR⁴; and A³ and A⁴ are each -CR⁴, wherein R⁴ at each occurrence is independently selected from hydrogen, substituted or unsubstituted alkyl, and substituted or unsubstituted haloalkyl; or (iii) A¹ is N and A², A³ and A⁴ are CH.

20. The compound of any one of the claims 1 and 16 to 19, wherein the group



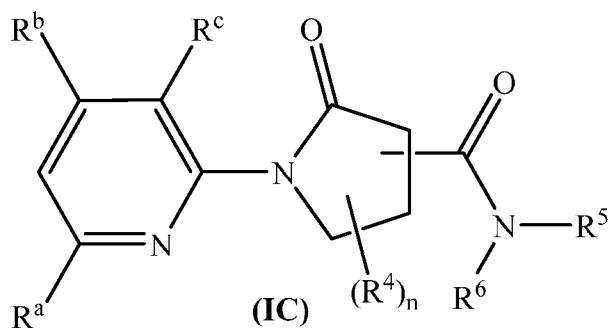
21. The compound of any one of claims 1 and 16 to 20, wherein R⁵ is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl, and R⁶ is hydrogen or substituted or unsubstituted alkyl.

22. The compound of any one of claims 1 and 16 to 21, wherein R⁵ is selected from 4-fluoro-3-methylphenyl, 3-methylphenyl, 4-fluorophenyl, 3,4-difluorophenyl, or substituted or unsubstituted heteroaryl and R⁶ is hydrogen, -CH₃, -CH₂-CH₃, -CH(CH₃)CH₃, -CH₂-CH₂-OCH₃, -CH₂-CH₂OH, or -CH₂-cyclopropyl.

23. The compound of any one of claims 1 and 16 to 22, wherein R⁵ and R⁶ together with the

nitrogen atom to which they are attached form the ring , or ; and the asterisk (*) represents the point of attachment of the ring to the main structure.

24. The compound of claim 1, wherein the compound having a formula (I) is a compound having formula (IC):



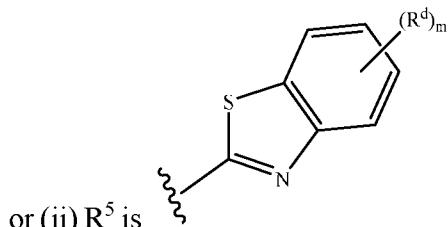
or a tautomer thereof, prodrug thereof, N-oxide thereof, stereoisomer thereof, pharmaceutically acceptable ester thereof, or pharmaceutically acceptable salt thereof,

wherein

R^a , R^b , and R^c are each independently selected from hydrogen, hydroxy, halo, cyano, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted heteroaryl;

each occurrence of R^4 is independently selected from hydrogen, hydroxy, halo, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, and substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted heteroaryl;

(i) R^5 and R^6 together with the nitrogen atom to which they are attached form a substituted or unsubstituted heterocyclyl ring or substituted or unsubstituted heteroaryl,



or (ii) R^5 is , R^6 is selected from hydroxy, halo, cyano, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocyclyl; each occurrence of R^d is independently selected from hydrogen, hydroxy, halo, cyano, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted amino, substituted or unsubstituted alkyl;

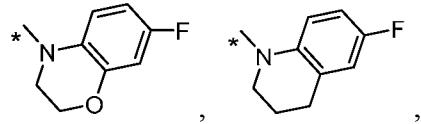
m is 0, 1, 2, or 3; and

n is 0, 1, or 2.

25. The compound of any one of claims 1 and 24, wherein R^a is $-CH_3$, or $-CF_3$, R^b is $-CF_3$, R^c is hydrogen, each occurrence of R^4 is hydrogen or hydroxy, and n is 1 or 2.

26. The compound of any one of claims 1 and 24 to 25, wherein R⁵ and R⁶ together with the

nitrogen atom to which they are attached form the ring



, or , and the asterisk (*) represents the point of attachment of the ring to the main structure.

27. The compound of any one of claims 1 and 24 to 26, wherein R⁵ is , and R⁶ is hydrogen or alkyl.

28. A compound selected from

2-((2-(3,4-dihydroquinolin-1(2H)-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-(indolin-1-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-(1H-indol-1-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-oxo-2-(3-oxo-3,4-dihydroquinoxalin-1(2H)-yl)ethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-(5-fluoro-1H-indol-1-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-oxo-2-(2,3,4,5-tetrahydro-1H-benzo[b]azepin-1-yl)ethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-oxo-2-(5-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-1-yl)ethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-oxo-2-(4-oxo-2,3,4,5-tetrahydro-1H-benzo[b]diazepin-1-yl)ethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-(6-fluoro-3,4-dihydroquinolin-1(2H)-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-(7-fluoro-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-(2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-(3,4-dihydrobenzo[b][1,4]oxazepin-5(2H)-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-(2,3-dihydrobenzo[e][1,4]oxazepin-1(5H)-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

1-((3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)glycyl)-1H-indole-3-carboxamide,

2-((2-(5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-(5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-(8-fluoro-3,4-dihydrobenzo[b][1,4]oxazepin-5(2H)-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-(7-fluoro-3,4-dihydrobenzo[b][1,4]oxazepin-5(2H)-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-(9-fluoro-3,4-dihydrobenzo[b][1,4]oxazepin-5(2H)-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-(3,4-dihydro-1,6-naphthyridin-1(2H)-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-(3-hydroxy-3,4-dihydrobenzo[b][1,4]oxazepin-5(2H)-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-(1,1-dioxido-2,3-dihydro-4H-benzo[b][1,4]thiazin-4-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-(3,4-dihydro-1,5-naphthyridin-1(2H)-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-(7,8-difluoro-3,4-dihydrobenzo[b][1,4]oxazepin-5(2H)-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-(7-fluoro-5-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-1-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-(7-fluoro-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)-2-oxoethyl)amino)-6-methyl-4-(trifluoromethyl)nicotinonitrile,

2-((2-(7-fluoro-2,3-dihydrobenzo[e][1,4]oxazepin-1(5H)-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-(8-fluoro-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-(7-methoxy-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

1-(7-fluoro-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)-2-((6-methyl-4-(trifluoromethyl)pyridin-2-yl)amino)ethan-1-one,

2-((4,6-bis(trifluoromethyl)pyridin-2-yl)amino)-1-(7-fluoro-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)ethan-1-one,

2-((2-(5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl)-2-oxoethyl)amino)-6-methyl-4-(trifluoromethyl)nicotinonitrile,

2-((2-(3-methyl-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-(5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)-2-oxoethyl)amino)-6-methyl-4-(trifluoromethyl)nicotinonitrile,

6-methyl-2-((2-oxo-2-(3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)ethyl)amino)-4-(trifluoromethyl)nicotinonitrile,

6-methyl-2-((2-(3-methyl-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)-2-oxoethyl)amino)-4-(trifluoromethyl)nicotinonitrile,

2-((2-oxo-2-(3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)ethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((4,6-bis(trifluoromethyl)pyridin-2-yl)amino)-1-(5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)ethan-1-one,

2-((2-(5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((4,6-bis(trifluoromethyl)pyridin-2-yl)amino)-1-(5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)ethan-1-one,

2-((2-(6,7-dihydropyrazolo[1,5-a]pyrimidin-4(5H)-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-(2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-1-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-(6-chloro-7-fluoro-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-(6-chloro-7-fluoro-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)-2-oxoethyl)amino)-6-methyl-4-(trifluoromethyl)nicotinonitrile,

2-((2-(8-chloro-7-fluoro-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)-2-oxoethyl)amino)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-((2-(8-chloro-7-fluoro-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)-2-oxoethyl)amino)-6-methyl-4-(trifluoromethyl)nicotinonitrile,

1-(3-cyanopyridin-2-yl)-N-ethyl-N-(4-fluoro-3-methylphenyl)-1H-pyrrole-2-carboxamide,

1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-ethyl-N-(4-fluoro-3-methylphenyl)-1H-pyrrole-2-carboxamide,

1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-(4-fluorophenyl)-N-methyl-1H-pyrrole-2-carboxamide,

1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-ethyl-N-(4-fluorophenyl)-1H-pyrrole-2-carboxamide,

1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-(4-fluorophenyl)-N-methyl-1H-pyrazole-3-carboxamide,

1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-(4-fluorophenyl)-N,3-dimethyl-1H-pyrazole-5-carboxamide,

1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-(4-fluorophenyl)-1H-pyrrole-2-carboxamide,

1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-(3,4-difluorophenyl)-N-ethyl-1H-pyrrole-2-carboxamide,

1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-ethyl-N-(pyridin-4-yl)-1H-pyrrole-2-carboxamide,

1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-ethyl-N-(pyridazin-4-yl)-1H-pyrrole-2-carboxamide,

1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-(4-fluorophenyl)-N-(2-methoxyethyl)-1H-pyrrole-2-carboxamide,

1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-(4-fluorophenyl)-N-(2-hydroxyethyl)-1H-pyrrole-2-carboxamide,

1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-(cyclopropylmethyl)-N-(4-fluorophenyl)-1H-pyrrole-2-carboxamide,

1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-(4-fluorophenyl)-N-methyl-5-(trifluoromethyl)-1H-pyrazole-3-carboxamide,

1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-(4-fluorophenyl)-N-methyl-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide,

1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-ethyl-N-(4-fluorophenyl)-4-methyl-1H-pyrrole-2-carboxamide,

1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-ethyl-N-(4-fluorophenyl)-3-methyl-1H-pyrazole-5-carboxamide,

1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-ethyl-N-(4-fluorophenyl)-5-methyl-1H-pyrazole-3-carboxamide,

1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-(4-fluorophenyl)-N,5-dimethyl-1H-pyrazole-3-carboxamide,

1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N,3-dimethyl-N-(m-tolyl)-1H-pyrazole-5-carboxamide,

N-(3-chloro-4-fluorophenyl)-1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N,3-dimethyl-1H-pyrazole-5-carboxamide,

1-(3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)-N-methyl-N-(m-tolyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide,

1-(3-cyano-6-methyl-4-(trifluoromethyl)pyridin-2-yl)-N,3-dimethyl-N-(m-tolyl)-1H-pyrazole-5-carboxamide,

2-(2-(1,2,3,4-tetrahydroquinoline-1-carbonyl)-1H-pyrrol-1-yl)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-(2-(6-fluoro-1,2,3,4-tetrahydroquinoline-1-carbonyl)-1H-pyrrol-1-yl)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-(2-(2,3,4,5-tetrahydrobenzo[b][1,4]oxazepine-5-carbonyl)-1H-pyrrol-1-yl)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-(3-methyl-5-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-7-carbonyl)-1H-pyrazol-1-yl)-4,6-bis(trifluoromethyl)nicotinonitrile,

2-(3-methyl-5-(5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine-7-carbonyl)-1H-pyrazol-1-yl)-4,6-bis(trifluoromethyl)nicotinonitrile,

(S)-1-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)-5-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-7-carbonyl)pyrrolidin-2-one,

(S)-1-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)-5-(5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine-7-carbonyl)pyrrolidin-2-one,

(S)-1-(4,6-bis(trifluoromethyl)pyridin-2-yl)-5-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-7-carbonyl)pyrrolidin-2-one,

(S)-1-(4,6-bis(trifluoromethyl)pyridin-2-yl)-5-(5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine-7-carbonyl)pyrrolidin-2-one,

(S)-1-(4,6-bis(trifluoromethyl)pyridin-2-yl)-5-(7-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazine-4-carbonyl)pyrrolidin-2-one,

(S)-5-(7-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazine-4-carbonyl)-1-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)pyrrolidin-2-one,

(S)-1-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)-5-(1,2,3,4-tetrahydro-1,6-naphthyridine-1-carbonyl)pyrrolidin-2-one,

N-(benzo[d]thiazol-2-yl)-2-((3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)amino)-N-methylacetamide,

N-(benzo[d]thiazol-2-yl)-2-((3-cyano-4,6-bis(trifluoromethyl)pyridin-2-yl)amino)acetamide,

N-(benzo[d]thiazol-2-yl)-2-((3-cyano-6-methyl-4-(trifluoromethyl)pyridin-2-yl)amino)acetamide,

N-(benzo[d]thiazol-2-yl)-2-((3-cyano-6-methyl-4-(trifluoromethyl)pyridin-2-yl)amino)-N-methylacetamide,

(S)-N-(benzo[d]thiazol-2-yl)-1-(3-cyano-6-methyl-4-(trifluoromethyl)pyridin-2-yl)pyrrolidine-2-carboxamide,

(S)-N-(benzo[d]thiazol-2-yl)-1-(3-cyano-6-methyl-4-(trifluoromethyl)pyridin-2-yl)-N-methylpyrrolidine-2-carboxamide,

(3S,4S,5S)-5-(7-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazine-4-carbonyl)-3,4-dihydroxy-1-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)pyrrolidin-2-one,

or a tautomer thereof, prodrug thereof, N-oxide thereof, stereoisomer thereof, pharmaceutically acceptable ester thereof or pharmaceutically acceptable salt thereof.

29. A pharmaceutical composition comprising a compound of any one of claims 1-28 and a pharmaceutically acceptable excipient.
30. The pharmaceutical composition of claim 29, further comprising one or more additional therapeutic agents.
31. The pharmaceutical composition of claim 30, wherein the one or more additional therapeutic agents is an anti-cancer agent, anti-inflammatory agent, immunomodulatory agent, steroid, non-steroidal anti-inflammatory agent, or any combination of any of the foregoing.
32. A method of inhibiting a catalytic activity of a polymerase theta (POL(θ)) enzyme present in a cell comprising contacting the cell with an effective amount of a compound of any one of claims 1-28.
33. The method of claim 32, wherein the inhibition takes place in a subject suffering from a disease or disorder which is cancer, a bone disorder, an inflammatory disease, an immune disease, a nervous system disease, or a metabolic disease.
34. Use of a compound of any one of claims 1-28 in the manufacture of a medicament for the treatment of a disease, disorder, or condition that would benefit from inhibiting catalytic activity of an enzyme.
35. The use of claim 34, wherein the enzyme is polymerase theta (POL(θ)).
36. A method for the treatment of a polymerase theta (POL(θ)) associated disease, disorder, or condition comprising administering to a subject in need thereof an effective amount of the compound of any one of claims 1-28.
37. The method of claim 36, further comprising the step of administering simultaneously or sequentially to the subject at least one other anti-cancer agent, anti-inflammatory agent, immunomodulatory agent, steroid, non-steroidal anti-inflammatory agent, or any combination of any of the foregoing.

38. The method of claim 36 or 37, wherein the polymerase theta (POL(θ)) associated disease, disorder or condition is an immune mediated disease, a disease or disorder involving inflammation, cancer or other proliferative disease.
39. The method of claim 36 or 37, wherein the polymerase theta (POL(θ)) associated disease, disorder or condition is selected from inflammation, glomerulonephritis, uveitis, hepatic diseases or disorders, renal diseases or disorders, rheumatoid arthritis, inflammatory bowel disease, vasculitis, dermatitis, osteoarthritis, inflammatory muscle disease, scleroderma, osteoporosis, eczema, allogeneic or xenogeneic transplantation, graft rejection, graft-versus-host disease, lupus erythematosus, pulmonary fibrosis, dermatomyositis, thyroiditis, myasthenia gravis, autoimmune hemolytic anemia, cystic fibrosis, chronic relapsing hepatitis, primary biliary cirrhosis, hepatitis, atopic dermatitis, asthma, Sjogren's syndrome, organ transplant rejection, multiple sclerosis, Guillain-Barre, autoimmune uveitis, autoimmune hemolytic anemia, pernicious anemia, autoimmune thrombocytopenia, temporal arteritis, antiphospholipid syndrome, vasculitides, Wegener's granulomatosis, Behcet's disease, psoriasis, dermatitis herpetiformis, pemphigus vulgaris, vitiligo, Crohn's disease, colitis, ulcerative colitis, primary biliary cirrhosis, autoimmune hepatitis, Type 1 or immune-mediated diabetes mellitus, Grave's disease, Hashimoto's thyroiditis, autoimmune oophoritis and orchitis, autoimmune disorder of the adrenal gland, systemic lupus erythematosus, polymyositis, dermatomyositis, ankylosing spondylitis, transplant rejection, skin graft rejection, arthritis, bone diseases associated with increased bone resorption, ileitis, Barrett's syndrome, sympathetic ophthalmitis, endophthalmitis, uremic complications, nephrosis, sclerodermatitis, psoriasis, chronic demyelinating diseases of the nervous system, AIDS-related neurodegeneration, Alzheimer's disease, infectious meningitis, encephalomyelitis, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis viral or autoimmune encephalitis, autoimmune disorders, immune-complex vasculitis, systemic lupus and erythematoses, systemic lupus erythematosus (SLE), metabolic disorders, and cancer.
40. The method of claim 36 or 37, wherein the polymerase theta (POL(θ)) associated disease, disorder or condition is selected from hematopoietic tumors of lymphoid lineage, leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma,

Hodgkin's lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma and Burkett's lymphoma, hematopoietic tumors of myeloid lineage, acute myelogenous leukemias, chronic myelogenous leukemias, myelodysplastic syndrome, promyelocytic leukemia, carcinoma of the bladder, carcinoma of the breast, carcinoma of the colon, carcinoma of the kidney, carcinoma of the liver, carcinoma of the lung, small cell lung cancer, esophageal cancer, gall bladder cancer, ovarian cancer, pancreatic cancer, stomach cancer, cervical cancer, thyroid cancer, prostate cancer, skin cancer, squamous cell carcinoma, tumors of mesenchymal origin, fibrosarcoma, rhabdomyosarcoma, tumors of the central and peripheral nervous system, astrocytoma, neuroblastoma, glioma, schwannoma, melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderma pigmentosum, keratoctanthoma, thyroid follicular cancer and Kaposi's sarcoma.

41. The method of claim 36 or 37, wherein the polymerase theta (POL(θ)) associated disease, disorder or condition is carcinoma of the breast or ovarian cancer, cancer of the central nervous system, endometrium cancer, kidney cancer, large intestine cancer, lung cancer, oesophagus cancer, pancreatic cancer, prostate cancer, stomach cancer, head and neck cancer (upper aerodigestive cancer), urinary tract cancer, or colon cancer.
42. The method of claim 36 or 37, wherein the method comprises inhibiting DNA repair by inhibiting overexpression of POL(θ) in a cancer cell.
43. The method of claim 36 or 37, wherein the method comprises inhibiting DNA repair by inhibiting overexpression of POL(θ) in a HR deficient cancer cell, or HR proficient cancer cell.
44. The method of claim 36 or 37, wherein the polymerase theta (POL(θ)) associated disease, disorder or condition is a homologous recombination (HR) deficient cancer or HR proficient cancer.
45. The method of claim 36 or 37, wherein the polymerase theta (POL(θ)) associated disease, disorder or condition is a cancer characterized by a reduction or absence of BRCA or any HRR (homologous recombination repair) gene expression, the absence of the BRAC or any HRR gene, or reduced function of BRCA or HRR protein.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2023/050798

A. CLASSIFICATION OF SUBJECT MATTER

INV.	C07D401/04	C07D401/12	C07D413/12	A61P29/00	C07D413/14
	C07D417/12	C07D417/14	C07D471/04	C07D487/04	C07D498/04
	A61P35/00	A61K31/4985	A61K31/4709	A61K31/538	

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 A61P

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)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CN 105 330 644 B (UNIV CHINA AGRICULTURAL) 19 December 2017 (2017-12-19) compounds I-08 and I-09 -----	1,17,19, 23
X	US 4 584 292 A (TOMIYAMA TSUYOSHI [JP]) 22 April 1986 (1986-04-22) compound 4 -----	1,2,4,5, 10,14
X	FR 2 315 270 A1 (KUBELA RUDOLF ET AL) 21 January 1977 (1977-01-21) compound 34 -----	1,2,4,5, 12
		-/-

X Further documents are listed in the continuation of Box C.

X 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	Date of mailing of the international search report
8 March 2023	16/03/2023
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Schuemacher, Anne

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2023/050798

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PRAMOD K. SRIVASTAVA ET AL: "Synthesis of some local anesthetics", JOURNAL OF MEDICINAL CHEMISTRY, vol. 13, no. 5, 1 September 1970 (1970-09-01), pages 977-979, XP055753997, US ISSN: 0022-2623, DOI: 10.1021/jm00299a045 table 1 -----	1, 2, 4, 6, 27
X	WO 2020/160134 A1 (IDEAYA BIOSCIENCES INC [US]) 6 August 2020 (2020-08-06) embodiment 10 on p. 34; claim 1 -----	1-15, 28-45
X	WO 2021/028643 A1 (ARTIOS PHARMA LTD [GB]) 18 February 2021 (2021-02-18) claim 1 -----	1, 16-22, 24-45
X, P	WO 2022/026548 A1 (IDEAYA BIOSCIENCES INC [US]) 3 February 2022 (2022-02-03) claim 1 -----	1-15, 29-45
X, P	WO 2022/026565 A9 (IDEAYA BIOSCIENCES INC [US]) 8 December 2022 (2022-12-08) claim 1 -----	1, 24-27, 29-45

INTERNATIONAL SEARCH REPORT

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: **1 (partially)**
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims;; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 1 (partially)

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty for the compounds of claim 1, wherein L is an unsaturated five-membered nitrogen-containing ring, wherein L is -N(R1)C(R2R3) and R5 and R6 form any kind of heterocycle with the nitrogen to which they are attached. So many documents were retrieved for such kind of compounds that it is impossible to determine which structural features of said compounds are to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, the search was performed taking into consideration the non-compliance in determining the extent of the search of claim 1.

The

search of claim 1 was restricted to the compounds of claim 1,
-except

when L is an unsaturated five-membered nitrogen-containing ring, then L has been limited to pyrrole and pyrazole ring (claim 20) and R5 and R6 are taken together to form a heterocycle as defined in claim 23 and;

-

when L is -N(R1)C(R2R3), then R5 is a benzothiazole ring (claim 6). Furthermore, the claims do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined because claim 1 refers to the term "prodrugs". "Prodrugs" is a functional definition which attempts to define a chemical compound in terms of a result to be achieved. The said term has neither been searched.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guidelines C-IV, 7.2), should the problems which led to the Article 17(2) PCT declaration be overcome.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2023/050798

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WO 2020160134	A1	06-08-2020	AU 2020215710 A1 19-08-2021 CA 3127490 A1 06-08-2020 EP 3917627 A1 08-12-2021 JP 2022519237 A 22-03-2022 US 2022098154 A1 31-03-2022 WO 2020160134 A1 06-08-2020		
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WO 2022026548	A1	03-02-2022	NONE		
WO 2022026565	A9	08-12-2022	NONE		