Novel Compounds for Targeted Protein Degradation

FIELD

The present disclosure relates to a novel class of compounds that are useful in a targeted or selective degradation of a protein.

BACKGROUND

Targeted Protein Degradation (TPD) is a therapeutic modality, which relies on the use of synthetic molecules to repurpose intracellular protein degradation machinery to induce degradation of specific disease-causing proteins. TPD approaches offer a number of advantages over other drug modalities (e.g. small molecule inhibitors, antibodies & protein-based agents, antisense oligonucleotides and related knockdown approaches) including: potentiated pharmacology due to catalytic protein removal from within cells; ability to inhibit multiple functions of a specific drug target including e.g. scaffolding function through target knockdown; opportunity for systemic dosing with good biodistribution; potent *in vivo* efficacy due to catalytic potency and prolonged duration of action limited only by *de novo* protein resynthesis; and facile chemical synthesis and formulation using application of small molecule processes.

The majority of physiologic post-translational regulation of intracellular protein levels as well as removal of damaged, misfolded, or excess proteins is mediated by the ubiquitin-proteasome system (UPS). The UPS relies on a complex cascade of protein-protein interactions that enables the polypeptide ubiquitin to be covalently attached to the protein intended for removal. The ubiquitin on the protein then acting as a marker or tag to the proteasome which then degrades and removes the protein from the cell.

The UPS can be repurposed to degrade specific proteins using bifunctional chemical molecules, commonly referred to as bifunctional degraders, as therapeutic agents. These molecules act by inducing the proximity of desired substrates with UPS proteins to initiate a cascade of events which ultimately leads to degradation, and removal of the protein from the cell by the proteasome.

Proteolysis targeting chimeras (PROTACs) constitute one such class of bifunctional degraders, which induce proximity of target proteins to the UPS by recruitment of specific ubiquitin E3 ligases. PROTACs are composed of two ligands joined by a linker - one ligand to engage a desired target protein and another ligand to recruit a ubiquitin E3 ligase.

The ubiquitin E3 ligases used most frequently in PROTACs are von Hippel-Lindau (VHL) and Cereblon (CRBN). PROTACs recruiting VHL are typically based on hydroxyproline-containing ligands, whereas PROTACs recruiting CRBN are typically characterised by the presence of a glutarimide moiety, such as thalidomide, pomalidomide and lenalidomide or close analogues to act as the warhead. Other ligases including mdm2 and the IAP family have also shown utility in PROTAC design.

However, these approaches suffer from a range of limitations, which restrict their utility to treat a wide range of diseases. For example, limitations of current PROTAC approaches include: inability to efficiently degrade some targets; poor activity of PROTACs in many specific cells due to low and variable expression of E3 ligases and other proteins required for efficient degradation; chemical properties which

make it more difficult to prepare degraders with suitable drug-like properties including good drug metabolism & pharmacokinetic profiles; and high susceptibility to induced resistance mechanisms in tumours.

Because of these limitations, there remains a need to identify novel degrading mechanisms and warheads able to deliver new compounds, which show efficient degradation across a range of targets and cellular systems and/or with improved profiles suitable for drug development.

Further compounds which can be used for these purposes have been described in WO 2019/238886, WO 2019/238817, WO 2019/238816, and WO 2022/129925.

BRD9 is a protein encoded by the BRD9 gene on chromosome 5. BRD9 is a component of the BAF (BRG1- or BRM-associated factors) complex, a SWI/SNF ATPase chromatin remodeling complex, and belongs to family IV of the bromodomain- containing proteins (D. Hay et al., Med. Chem. Commun., 2015, 6, 1381-1386). SWI/SNF uses the energy of ATP hydrolysis to remodel chromatin and mobilize nucleosomes. SWI/SNF is implicated in activating transcription by remodelling nucleosomes, thereby permitting increased access of transcription factors for their binding sites. It is also required for transcriptional repression of some genes, and so controls transcription in various ways.

Recurrent inactivating mutations in certain subunits of SWI/SNF complex have been identified in different cancers. Despite its known roles in tumour suppression, the mammalian SWI/SNF complex has recently received attention as a potential target for therapeutic inhibition (L. J. Martin et al., J. Med. Chem., 2016, 59, 4462-4475).

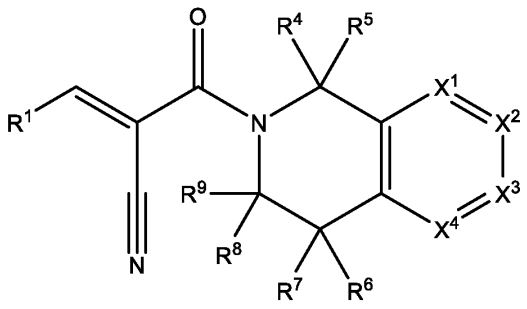
Studies have shown that BRD9 is preferentially used by cancers that harbour SMARCB1 abnormalities such as malignant rhabdoid tumors and several specific types of sarcoma (X. Zhu, Y. Liao and L. Tang, Onco Targets Ther., 2020, 13, 13191-13200). BRD9-containing complexes bind to both active promoters and enhancers, where they contribute to gene expression. Loss of BRD9 results in gene expression changes related to apoptosis regulation, translation, and development regulation. BRD9 is essential for the proliferation of SMARCB1-deficient cancer cell lines, suggesting it is a therapeutic target for these lethal cancers. (Xiaofeng Wang et. al., Nature Communications, 2019, 10 (1881)). Recent studies highlight a role of BRD9 in leukemia growth: BRD9 was shown to be required for the proliferation of acute myeloid leukemia (AML) cells (Nature Chemical Biology, 2016, 101038/nchembio.2115). In addition to the role of BRD9 as a functional dependency in certain cancers, BRD9 also plays a pivotal role in immune cells as a regulator of regulatory T cells (Tregs) via transcriptional control of Foxp3 target genes, “BioRxiv, 10.1101/2020.02.26.964981.

Because of BRD9’s role in cancer proliferation there has been interest in the development of BRD9 inhibitors for the treatment of cancers including those described in: WO 2014/114721, WO 2016/077375, WO 2016/077378, WO 2016/139361, WO 2019/152440, a paper by Martin L. J. et. al., (Journal of Medicinal Chemistry 2016, 59, 4462-4475) titled “Structure-Based Design of an in Vivo Active Selective BRD9 Inhibitor”; a paper by Theodoulou N. H. et. al., (Journal of Medicinal Chemistry 2015, 59, 1425-1439) titled “Discovery of I-BRD9, a selective Cell Active Chemical Probe for Bromodomain Containing Protein 9 Inhibition”; and a paper by Clack P. et. al., (Angewandte Chemie, 2015, 127, 6315-6319).

SUMMARY

The present disclosure is based on the identification of a novel class of compounds that are useful in a targeted and/or selective degradation of a desired protein, e.g. a "target protein". In particular, the present disclosure provides compounds which facilitate proteasomal degradation of selected target protein(s) using a novel class of warhead.

In one aspect, the present invention provides a compound comprising a moiety of formula (I)



(I)

wherein

R^1 is selected from C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_1-C_6 alkyl-(C_3-C_8cycloalkyl), 3-8 membered heterocycloalkyl, C_1-C_6 alkyl-(3-8 membered heterocycloalkyl), C_6-C_{10} aryl, C_1-C_6 alkyl-(C_6-C_{10} aryl), 5-10 membered heteroaryl, and C_1-C_6 alkyl-(5-10 membered heteroaryl), wherein each heterocycloalkyl and heteroaryl comprises one or more heteroatoms selected from the group consisting of N, S and O, and wherein the alkyl, cycloalkyl, alkyl(cycloalkyl), heterocycloalkyl, alkyl(heterocycloalkyl), aryl, alkyl(aryl), heteroaryl, and alkyl(heteroaryl) are each optionally substituted with one or more groups independently selected from halogen, OR^2, C_1-C_6 alkyl, and $N(R^3)_2$;

each R^2 is independently selected from H, C_1-C_6 alkyl and C_1-C_6 haloalkyl;

each R^3 is independently selected from H, C_1-C_6 alkyl and C_1-C_6 haloalkyl;

R^4, R^5, R^6, R^7, R^8, and R^9 are each independently selected from H and C_1-C_6 alkyl, wherein each alkyl is optionally substituted with one or more groups independently selected from halogen, OR^2, C_1-C_6 alkyl, CN, and $N(R^3)_2$;

X^1 is selected from N and CR^{10};

X^2 is selected from N and CR^{11};

X^3 is selected from N and CR^{12};

X^4 is selected from N and CR^{13};

R^{10}, R^{11}, R^{12}, and R^{13} are each independently selected from H, halogen, OR^2, C_1-C_6 alkyl, and $N(R^3)_2$ wherein each alkyl is optionally substituted with one or more groups independently selected from halogen, OR^2, and $N(R^3)_2$;

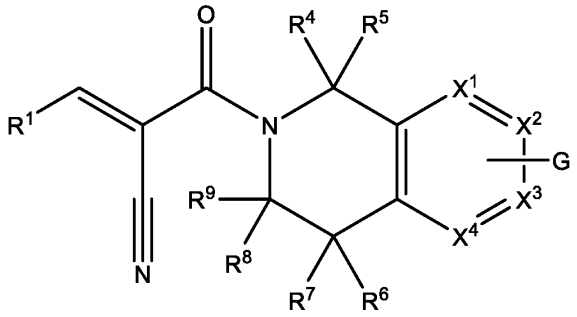
or a pharmaceutically acceptable salt thereof;

wherein:

- if X^1 is CR^{10}, X^2 is CR^{11}, X^3 is CR^{12} and X^4 is CR^{13}, then at least one of R^{10}, R^{11}, R^{12}, and R^{13} is not H; and

- no more than three of X^1, X^2, X^3 and X^4 are N.

In another aspect, the present invention provides a compound of formula (II)



(II)

wherein R^1, R^4, R^5, R^6, R^7, R^8, R^9, X^1, X^2, X^3, and X^4 are as defined for a compound of formula (I); and

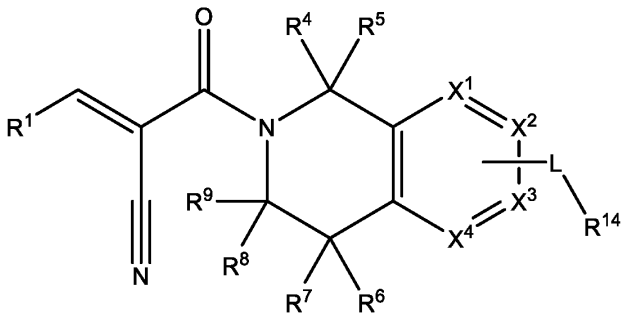
G is a moiety which enables the attachment of the compound to another chemical structure via formation of a new covalent bond;

or a pharmaceutically acceptable salt thereof;

wherein if X^1 is CR^{10}, X^2 is CR^{11}, X^3 is CR^{12} and X^4 is CR^{13}, then at least one of R^{10}, R^{11}, R^{12}, and R^{13} is not H; and

wherein no more than three of X^1, X^2, X^3 and X^4 are N.

In another aspect, the present invention provides a compound of formula (III)



(III)

wherein

R^1, R^4, R^5, R^6, R^7, R^8, R^9, X^1, X^2, X^3, and X^4 are as defined for a compound of formula (I);

L is a covalent bond or a linker; and

R^{14} is a ligand that binds to a protein;

or a pharmaceutically acceptable salt thereof;

wherein if X^1 is CR^{10}, X^2 is CR^{11}, X^3 is CR^{12} and X^4 is CR^{13}, then at least one of R^{10}, R^{11}, R^{12}, and R^{13} is not H; and

wherein no more than three of X^1, X^2, X^3 and X^4 are N.

In another aspect, the present invention provides a pharmaceutical composition comprising a compound of formula (III), together with a pharmaceutically acceptable carrier, optionally wherein the compound of formula (III) is present in the composition as a pharmaceutically acceptable salt, solvate or derivative.

In another aspect, the present invention provides a compound of formula (III), or a pharmaceutical composition comprising a compound of formula (III), for use in medicine.

The present invention also provides a method of selectively degrading and/or increasing proteolysis of a target protein (e.g. BRD9) in a cell or a subject in need thereof, the method comprising contacting and/or treating the cell with a compound of formula (III) or a pharmaceutical composition comprising a compound of formula (III).

In another aspect, the present invention provides a pharmaceutical composition comprising a compound comprising a moiety of formula (I), together with a pharmaceutically acceptable carrier, optionally wherein the compound comprising a moiety of formula (I) is present in the composition as a pharmaceutically acceptable salt, solvate or derivative.

In another aspect, the present invention provides a compound comprising a moiety of formula (I), or a pharmaceutical composition comprising a compound comprising a moiety of formula (I), for use in medicine.

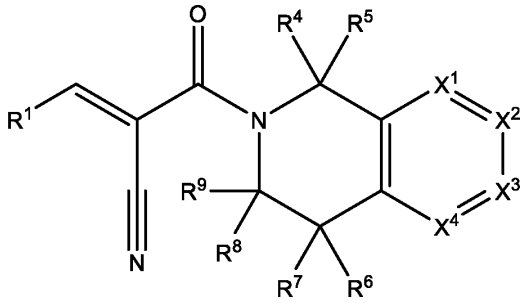
The present invention also provides a method of selectively degrading and/or increasing proteolysis of a target protein (e.g. BRD9) in a cell or a subject in need thereof, the method comprising contacting and/or treating the cell with a compound of formula (I) or a pharmaceutical composition comprising a compound comprising a moiety of formula (I).

The present invention also provides a method of making a compound of formula (I), (II) or (III).

The present invention also provides a compound library comprising a plurality of compounds of formula (I), (II) or (III).

DETAILED DESCRIPTION

In one aspect, the present invention provides a compound comprising a moiety of formula (I)



(I)

wherein

R^1 is selected from C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_1-C_6 alkyl-(C_3-C_8cycloalkyl), 3-8 membered heterocycloalkyl, C_1-C_6 alkyl-(3-8 membered heterocycloalkyl), C_6-C_{10} aryl, C_1-C_6 alkyl-(C_6-C_{10} aryl), 5-

10 membered heteroaryl, and C_1-C_6 alkyl-(5-10 membered heteroaryl), wherein each heterocycloalkyl and heteroaryl comprises one or more heteroatoms selected from the group consisting of N, S and O, and wherein the alkyl, cycloalkyl, alkyl(cycloalkyl), heterocycloalkyl, alkyl(heterocycloalkyl), aryl, alkyl(aryl), heteroaryl, and alkyl(heteroaryl) are each optionally substituted with one or more groups independently selected from halogen, OR^2, C_1-C_6 alkyl, and $N(R^3)_2$;

each R^2 is independently selected from H, C_1-C_6 alkyl and C_1-C_6 haloalkyl;

each R^3 is independently selected from H, C_1-C_6 alkyl and C_1-C_6 haloalkyl;

R^4, R^5, R^6, R^7, R^8, and R^9 are each independently selected from H and C_1-C_6 alkyl, wherein each alkyl is optionally substituted with one or more groups independently selected from halogen, OR^2, C_1-C_6 alkyl, CN, and $N(R^3)_2$;

X^1 is selected from N and CR^{10};

X^2 is selected from N and CR^{11};

X^3 is selected from N and CR^{12};

X^4 is selected from N and CR^{13};

R^{10}, R^{11}, R^{12}, and R^{13} are each independently selected from H, halogen, OR^2, C_1-C_6 alkyl, and $N(R^3)_2$ wherein each alkyl is optionally substituted with one or more groups independently selected from halogen, OR^2, and $N(R^3)_2$;

or a pharmaceutically acceptable salt thereof;

wherein:

- if X^1 is CR^{10}, X^2 is CR^{11}, X^3 is CR^{12} and X^4 is CR^{13}, then at least one of R^{10}, R^{11}, R^{12}, and R^{13} is not H; and
- wherein no more than three of X^1, X^2, X^3 and X^4 are N.

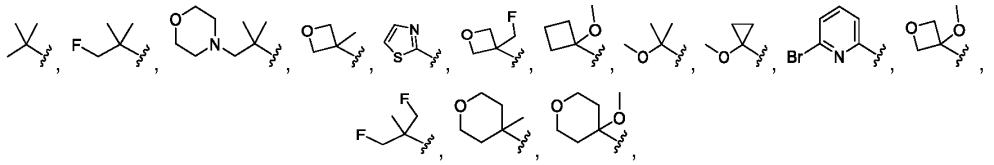
In embodiments, R^1 is selected from C_1-C_6 alkyl (e.g. methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, n-pentyl, 2-methylbutan-2-yl, 2,2-dimethylpropyl, 3-methylbutyl, 1-methylbutyl, 1-ethylpropyl, 1,2-dimethylpropyl, 2-methylbutyl, n-hexane, 2-methyl pentane, 3-methyl pentane, 2,2-dimethyl butane, 2,3-dimethyl butane, C_3-C_8 cycloalkyl, C_1-C_6 alkyl-(C_3-C_8cycloalkyl), 3-8 membered heterocycloalkyl, C_1-C_6 alkyl-(3-8 membered heterocycloalkyl), C_6-C_{10} aryl, C_1-C_6 alkyl-(C_6-C_{10} aryl), 5-10 membered heteroaryl, and C_1-C_6 alkyl-(5-10 membered heteroaryl), wherein each heterocycloalkyl and heteroaryl comprises one or more heteroatoms selected from the group consisting of N, S and O, and wherein the alkyl, cycloalkyl, alkyl(cycloalkyl), heterocycloalkyl, alkyl(heterocycloalkyl), aryl, alkyl(aryl), heteroaryl, and alkyl(heteroaryl) are each optionally substituted with one or more groups independently selected from halogen, OR^2, C_1-C_6 alkyl, and $N(R^3)_2$.

In embodiments, R^1 is selected from C_1-C_6 alkyl, 3-8 membered heterocycloalkyl, C_1-C_6alkyl(3-8 membered heterocycloalkyl), and 5-10 membered heteroaryl, wherein each heterocycloalkyl and heteroaryl comprises one or more heteroatoms selected from the group consisting of N, S and O, and wherein the alkyl, cycloalkyl, heterocycloalkyl, alkyl(heterocycloalkyl), and heteroaryl are each optionally substituted with one or more groups independently selected from halogen and C_1-C_6 alkyl.

In embodiments, R^1 is selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, 3-8 membered heterocycloalkyl, 3-8 membered heterocycloalkyl substituted with C_1-C_6 alkyl, C_1-C_6 alkyl(3-8 membered

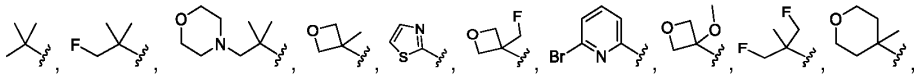
heterocycloalkyl), 5-10 membered heteroaryl, and 5-10 membered heteroaryl substituted with halogen, wherein each heterocycloalkyl and heteroaryl comprises one or more heteroatoms selected from the group consisting of N, S and O.

In embodiments, R^1 is selected from the following groups:



wherein the wavy line intersects the bond between R^1 and the rest of the compound.

In embodiments, R^1 is selected from the following groups:



wherein the wavy line intersects the bond between R^1 and the rest of the compound.

In embodiments, R^1 is selected from the following groups:



wherein the wavy line intersects the bond between R^1 and the rest of the compound.

In embodiments, R^4, R^5, R^6, R^7, R^8, and R^9 are each independently selected from H and C_1 to C_6 alkyl optionally substituted with one or more groups independently selected from halogen and CN (for example methyl substituted with CN).

In embodiments, R^4, R^5, R^6, R^7, R^8, and R^9 are each independently selected from H, C_1 to C_6 alkyl, and C_1 to C_6 haloalkyl.

In embodiments, R^4 and R^5 are each independently selected from H and C_1 to C_6 alkyl optionally substituted with one or more groups independently selected from halogen and CN (for example methyl substituted with CN).

In embodiments, R^4 and R^5 are each independently selected from H, C_1 to C_6 alkyl, and C_1 to C_6 haloalkyl.

In embodiments, R^4 and R^5 are each independently selected from H, C_1 to C_6 alkyl, and C_1 to C_6 fluoroalkyl.

In embodiments, R^4 and R^5 are each independently selected from H, and C_1 to C_6 alkyl.

In embodiments, R^4 and R^5 are each independently selected from H, methyl, and isopropyl.

In embodiments, R^4 and R^5 are each independently selected from H, and methyl.

In embodiments, R^4 and R^5 are both methyl.

In embodiments, R^4 is selected from H, and C_1 to C_6 alkyl optionally substituted with one or more groups independently selected from halogen and CN (for example methyl substituted with CN).

In embodiments, R^4 is selected from H, C_1 to C_6 alkyl, and C_1 to C_6 haloalkyl.

In embodiments, R^4 is selected from H, C_1 to C_6 alkyl, and C_1 to C_6 fluoroalkyl.

In embodiments, R^4 is selected from H, and C_1 to C_6 alkyl.

In embodiments, R^4 is selected from H, methyl, and isopropyl.

In embodiments, R^4 is selected from methyl and isopropyl.

In embodiments, R^4 is methyl.

In embodiments, R^4 is isopropyl.

In embodiments, R^5 is selected from H, and C_1 to C_6 alkyl optionally substituted with one or more groups independently selected from halogen and CN (for example methyl substituted with CN).

In embodiments, R^5 is selected from H, C_1 to C_6 alkyl, and C_1 to C_6 haloalkyl.

In embodiments, R^5 is selected from H, C_1 to C_6 alkyl, and C_1 to C_6 fluoroalkyl.

In embodiments, R^5 is selected from H and C_1 to C_6 alkyl.

In embodiments, R^5 is selected from H, methyl and isopropyl.

In embodiments, R^5 is H.

In embodiments, R^4 and R^5 are each independently selected from H, and C_1 to C_6 alkyl optionally substituted with one or more groups independently selected from halogen and CN (for example methyl substituted with CN); and

R^6, R^7, R^8, and R^9 are H.

In embodiments, R^4 and R^5 are each independently selected from H, C_1 to C_6 alkyl, and C_1 to C_6 haloalkyl; and

R^6, R^7, R^8, and R^9 are H.

In embodiments, R^4 and R^5 are each independently selected from H, C_1 to C_6 alkyl, and C_1 to C_6 fluoroalkyl; and

R^6, R^7, R^8, and R^9 are H.

In embodiments, R^4 and R^5 are each independently selected from H, and C_1 to C_6 alkyl; and

R^6, R^7, R^8, and R^9 are H.

In embodiments, R^4 and R^5 are each independently selected from H, methyl, and isopropyl; and

R^6, R^7, R^8, and R^9 are H.

In embodiments, R^4 and R^5 are each independently selected from H, and methyl; and

R^6, R^7, R^8, and R^9 are H.

In embodiments, R^4 and R^5 are both methyl; and

R^6, R^7, R^8, and R^9 are H.

In In embodiments, R^4 is selected from H, C_1 to C_6 alkyl, and C_1 to C_6 fluoroalkyl; and

R^5, R^6, R^7, R^8, and R^9 are H.

In embodiments, R^4 is selected from H, and C_1 to C_6 alkyl; and

R^5, R^6, R^7, R^8, and R^9 are H.

In embodiments, R^4 is selected from H, methyl, and isopropyl; and

R^5, R^6, R^7, R^8, and R^9 are H.

In embodiments, R^4 is selected from methyl and isopropyl; and

R^5, R^6, R^7, R^8, and R^9 are H.

In embodiments, R^4 is methyl; and

R^5, R^6, R^7, R^8, and R^9 are H.

In embodiments of the moiety of formula (I), at least one and no more than three (e.g. one) of X^1, X^2, X^3 and X^4 is N.

In embodiments of the moiety of formula (I), at least two and not more than three (e.g. two) of X^1, X^2, X^3 and X^4 are N.

In embodiments of the moiety of formula (I), three of X^1, X^2, X^3 and X^4 are N.

In embodiments of the moiety of formula (I), R^{10}, R^{11}, R^{12}, and R^{13} are each independently selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy.

In embodiments of the moiety of formula (I), R^{10}, R^{11}, R^{12}, and R^{13} are each independently selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy.

In embodiments of the moiety of formula (I), R^{10}, R^{11}, R^{12}, and R^{13} are each independently selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy.

In embodiments of the moiety of formula (I), no more than two of R^{10}, R^{11}, R^{12}, and R^{13} are H.

In embodiments of the moiety of formula (I), two of R^{10}, R^{11}, R^{12}, and R^{13} are H.

In embodiments of the moiety of formula (I), R^{10} and R^{11} are each independently selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy.

In embodiments of the moiety of formula (I), R^{10} and R^{11} are each independently selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein at least two of R^{10}, R^{11}, R^{12} and R^{13} are H.

In embodiments of the moiety of formula (I), R^{10} and R^{11} are each independently selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein at least one of R^{10}, R^{11}, R^{12} and R^{13} is H.

In embodiments of the moiety of formula (I), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy.

In embodiments of the moiety of formula (I), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least two of R^{10}, R^{11}, R^{12} and R^{13} are H.

In embodiments of the moiety of formula (I), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least one of R^{10}, R^{11}, R^{12} and R^{13} is H.

In embodiments of the moiety of formula (I), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy.

In embodiments of the moiety of formula (I), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least two of R^{10}, R^{11}, R^{12} and R^{13} are H.

In embodiments of the moiety of formula (I), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

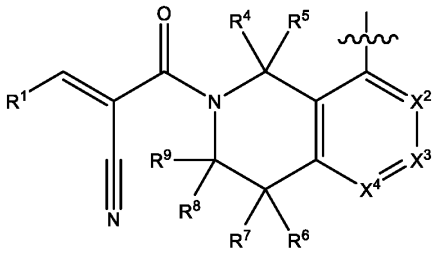
R^{13} is selected from H, fluorine, and methoxy;

wherein at least one of R^{10}, R^{11}, R^{12} and R^{13} is H.

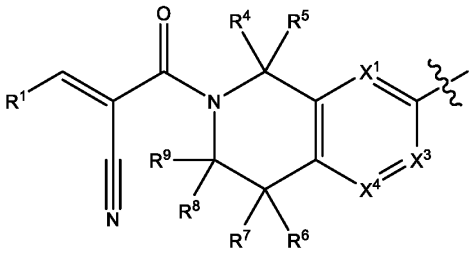
In embodiments of the moiety of formula (I), one of R^{10}, R^{11}, R^{12}, and R^{13} is replaced by a covalent bond to the rest of the compound.

In the compounds comprising a moiety of formula (I), the moiety of formula (I) may be covalently attached to the rest of the compound at any suitable position e.g. provided it has the correct valency and/or is chemically suitable. For example, R^{10}, R^{11}, R^{12}, or R^{13} may be replaced by a covalent bond to the rest of the compound (e.g. a ligand capable of binding to a selected target protein, optionally through a linker). For example, R^{11}, R^{12} or R^{13} may be replaced by a covalent bond to the rest of the compound. For example, R^{11} or R^{13} may be replaced by a covalent bond to the rest of the compound.

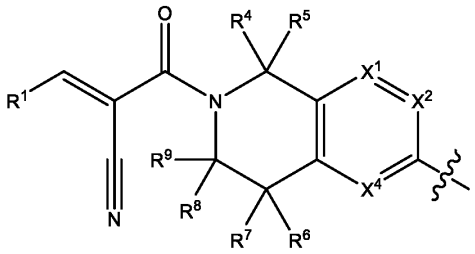
Formula (I) therefore encompasses the compounds of formula (IA), (IB), (IC) and (ID):



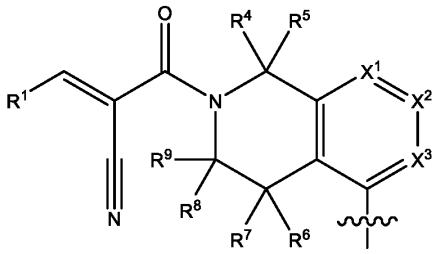
(IA)



(IB)



(IC)



(ID)

wherein in the compounds of formula (IA), (IB), (IC) and (ID), R^1, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, X^1, X^2, X^3, and X^4 are as defined for the moiety of formula (I), and the wavy line intersects the bond between the moiety of formula (I) and the rest of the compound. In the compound of formula (IA), when X^2 is CR^{11}, X^3 is CR^{12}, and X^4 is CR^{13}, then one of R^{11}, R^{12} and R^{13} is not H. In the compound of formula (IB), when X^1 is CR^{10}, X^3 is CR^{12}, and X^4 is CR^{13}, then one of R^{10}, R^{12} and R^{13} is not H. In the compound of formula (IC), when X^1 is CR^{10}, X^2 is CR^{11}, and X^4 is CR^{13}, then one of R^{10}, R^{11} and R^{14} is not H. In the compound of formula (ID), when X^1 is CR^{10}, X^2 is CR^{11}, and X^3 is CR^{12}, then one of R^{10}, R^{11} and R^{12} is not H.

In embodiments of the moiety of formula (I), R^{10} is replaced by a covalent bond to the rest of the compound;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy.

In embodiments of the moiety of formula (I), R^{10} is replaced by a covalent bond to the rest of the compound;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein at least two of R^{11}, R^{12} and R^{13} are H.

In embodiments of the moiety of formula (I), R^{10} is replaced by a covalent bond to the rest of the compound;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein two of R^{11}, R^{12} and R^{13} are H.

In embodiments of the moiety of formula (I), R^{10} is replaced by a covalent bond to the rest of the compound;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein at least one of R^{11}, R^{12} and R^{13} is H.

In embodiments of the moiety of formula (I), R^{10} is replaced by a covalent bond to the rest of the compound;

R^{11} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy.

In embodiments of the moiety of formula (I), R^{10} is replaced by a covalent bond to the rest of the compound;

R^{11} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least two of R^{11}, R^{12} and R^{13} are H.

In embodiments of the moiety of formula (I), R^{10} is replaced by a covalent bond to the rest of the compound;

R^{11} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein two of R^{11}, R^{12} and R^{13} are H.

In embodiments of the moiety of formula (I), R^{10} is replaced by a covalent bond to the rest of the compound;

R^{11} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least one of R^{11}, R^{12} and R^{13} is H.

In embodiments of the compound of formula (I), R^{10} is replaced by a covalent bond to the rest of the compound;

R^{11} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy.

In embodiments of the compound of formula (I), R^{10} is replaced by a covalent bond to the rest of the compound;

R^{11} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least two of R^{10}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (I), R^{10} is replaced by a covalent bond to the rest of the compound;

R^{11} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein two of R^{10}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (I), R^{10} is replaced by a covalent bond to the rest of the compound;

R^{11} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least one of R^{10}, R^{12} and R^{13} is H.

In embodiments of the moiety of formula (I), R^{10} and R^{11} are each independently selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{12} is replaced by a covalent bond to the rest of the compound; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy.

In embodiments of the moiety of formula (I), R^{10} and R^{11} are each independently selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{12} is replaced by a covalent bond to the rest of the compound; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein at least two of R^{10}, R^{11}, and R^{13} are H.

In embodiments of the moiety of formula (I), R^{10} and R^{11} are each independently selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{12} is replaced by a covalent bond to the rest of the compound; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein two of R^{10}, R^{11}, and R^{13} are H.

In embodiments of the moiety of formula (I), R^{10} and R^{11} are each independently selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{12} is replaced by a covalent bond to the rest of the compound; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein at least one of R^{10}, R^{11}, and R^{13} is H.

In embodiments of the moiety of formula (I), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{12} is replaced by a covalent bond to the rest of the compound; and

R^{13} is selected from H, fluorine, and methoxy.

In embodiments of the moiety of formula (I), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{12} is replaced by a covalent bond to the rest of the compound; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least two of R^{10}, R^{11}, and R^{13} are H.

In embodiments of the moiety of formula (I), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{12} is replaced by a covalent bond to the rest of the compound; and

R^{13} is selected from H, fluorine, and methoxy;

wherein two of R^{10}, R^{11}, and R^{13} are H.

In embodiments of the moiety of formula (I), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{12} is replaced by a covalent bond to the rest of the compound; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least one of R^{10}, R^{11}, and R^{13} is H.

In embodiments of the moiety of formula (I), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{12} is replaced by a covalent bond to the rest of the compound; and

R^{13} is selected from H, fluorine, and methoxy.

In embodiments of the moiety of formula (I), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{12} is replaced by a covalent bond to the rest of the compound; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least two of R^{10}, R^{11}, and R^{13} are H.

In embodiments of the moiety of formula (I), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{12} is replaced by a covalent bond to the rest of the compound; and

R^{13} is selected from H, fluorine, and methoxy;

wherein two of R^{10}, R^{11}, and R^{13} are H.

In embodiments of the moiety of formula (I), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{12} is replaced by a covalent bond to the rest of the compound; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least one of R^{10}, R^{11}, and R^{13} is H.

In embodiments of the moiety of formula (I), R^{10} and R^{11} are each independently selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is replaced by a covalent bond to the rest of the compound.

In embodiments of the moiety of formula (I), R^{10} and R^{11} are each independently selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is replaced by a covalent bond to the rest of the compound;

wherein at least two of R^{10}, R^{11}, and R^{12} are H.

In embodiments of the moiety of formula (I), R^{10} and R^{11} are each independently selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is replaced by a covalent bond to the rest of the compound;

wherein two of R^{10}, R^{11}, and R^{12} are H.

In embodiments of the moiety of formula (I), R^{10} and R^{11} are each independently selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is replaced by a covalent bond to the rest of the compound;

wherein at least one of R^{10}, R^{11}, and R^{12} is H.

In embodiments of the moiety of formula (I), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is replaced by a covalent bond to the rest of the compound.

In embodiments of the moiety of formula (I), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is replaced by a covalent bond to the rest of the compound;

wherein at least two of R^{10}, R^{11}, and R^{12} are H.

In embodiments of the moiety of formula (I), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is replaced by a covalent bond to the rest of the compound;

wherein two of R^{10}, R^{11}, and R^{12} are H.

In embodiments of the moiety of formula (I), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is replaced by a covalent bond to the rest of the compound;

wherein at least one of R^{10}, R^{11}, and R^{12} is H.

In embodiments of the moiety of formula (I), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is replaced by a covalent bond to the rest of the compound.

In embodiments of the moiety of formula (I), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is replaced by a covalent bond to the rest of the compound;

wherein at least two of R^{10}, R^{11}, and R^{12} are H.

In embodiments of the moiety of formula (I), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is replaced by a covalent bond to the rest of the compound;

wherein two of R^{10}, R^{11}, and R^{12} are H.

In embodiments of the moiety of formula (I), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is replaced by a covalent bond to the rest of the compound;

wherein at least one of R^{10}, R^{11}, and R^{12} is H.

In embodiments of the moiety of formula (I), R^{10} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy.

In embodiments of the moiety of formula (I), R^{10} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein at least two of R^{10}, R^{11}, R^{12} and R^{13} are H.

In embodiments of the moiety of formula (I), R^{10} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein two of R^{10}, R^{11}, R^{12} and R^{13} are H.

In embodiments of the moiety of formula (I), R^{10} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein at least one of R^{10}, R^{11}, R^{12} and R^{13} is H.

In embodiments of the moiety of formula (I), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy.

In embodiments of the moiety of formula (I), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least two of R^{10}, R^{11}, R^{12} and R^{13} are H.

In embodiments of the moiety of formula (I), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein two of R^{10}, R^{11}, R^{12} and R^{13} are H.

In embodiments of the moiety of formula (I), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least one of R^{10}, R^{11}, R^{12} and R^{13} is H.

In embodiments of the moiety of formula (I), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy.

In embodiments of the moiety of formula (I), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least two of R^{10}, R^{11}, R^{12} and R^{13} are H.

In embodiments of the moiety of formula (I), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein two of R^{10}, R^{11}, R^{12} and R^{13} are H.

In embodiments of the moiety of formula (I), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least one of R^{10}, R^{11}, R^{12} and R^{13} is H.

In embodiments of the moiety of formula (I), R^{10} is replaced by a covalent bond to the rest of the compound;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy.

In embodiments of the moiety of formula (I), R^{10} is replaced by a covalent bond to the rest of the compound;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein at least two of R^{11}, R^{12} and R^{13} are H.

In embodiments of the moiety of formula (I), R^{10} is replaced by a covalent bond to the rest of the compound;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein two of R^{11}, R^{12} and R^{13} are H.

In embodiments of the moiety of formula (I), R^{10} is replaced by a covalent bond to the rest of the compound;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein at least one of R^{11}, R^{12} and R^{13} is H.

In embodiments of the moiety of formula (I), R^{10} is replaced by a covalent bond to the rest of the compound;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy.

In embodiments of the moiety of formula (I), R^{10} is replaced by a covalent bond to the rest of the compound;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least two of R^{11}, R^{12} and R^{13} are H.

In embodiments of the moiety of formula (I), R^{10} is replaced by a covalent bond to the rest of the compound;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein two of R^{11}, R^{12} and R^{13} are H.

In embodiments of the moiety of formula (I), R^{10} is replaced by a covalent bond to the rest of the compound;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least one of R^{11}, R^{12} and R^{13} is H.

In embodiments of the moiety of formula (I), R^{10} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{11} is replaced by a covalent bond to the rest of the compound;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy.

In embodiments of the moiety of formula (I), R^{10} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{11} is replaced by a covalent bond to the rest of the compound;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein at least two of R^{10}, R^{12} and R^{13} are H.

In embodiments of the moiety of formula (I), R^{10} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{11} is replaced by a covalent bond to the rest of the compound;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein two of R^{10}, R^{12} and R^{13} are H.

In embodiments of the moiety of formula (I), R^{10} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{11} is replaced by a covalent bond to the rest of the compound;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein at least one of R^{10}, R^{12} and R^{13} is H.

In embodiments of the moiety of formula (I), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{11} is replaced by a covalent bond to the rest of the compound;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy.

In embodiments of the moiety of formula (I), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{11} is replaced by a covalent bond to the rest of the compound;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least two of R^{10}, R^{12} and R^{13} are H.

In embodiments of the moiety of formula (I), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{11} is replaced by a covalent bond to the rest of the compound;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein two of R^{10}, R^{12} and R^{13} are H.

In embodiments of the moiety of formula (I), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{11} is replaced by a covalent bond to the rest of the compound;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least one of R^{10}, R^{12} and R^{13} is H.

In embodiments of the moiety of formula (I), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{11} is replaced by a covalent bond to the rest of the compound;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy.

In embodiments of the moiety of formula (I), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{11} is replaced by a covalent bond to the rest of the compound;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least two of R^{10}, R^{12} and R^{13} are H.

In embodiments of the moiety of formula (I), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{11} is replaced by a covalent bond to the rest of the compound;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein two of R^{10}, R^{12} and R^{13} are H.

In embodiments of the moiety of formula (I), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{11} is replaced by a covalent bond to the rest of the compound;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least one of R^{10}, R^{12} and R^{13} is H.

In embodiments of the moiety of formula (I), R^{10} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R^{12} is replaced by a covalent bond to the rest of the compound; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy.

In embodiments of the moiety of formula (I), R^{10} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R^{12} is replaced by a covalent bond to the rest of the compound; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein at least two of R^{10}, R^{11}, and R^{13} are H.

In embodiments of the moiety of formula (I), R^{10} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R^{12} is replaced by a covalent bond to the rest of the compound; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein two of R^{10}, R^{11}, and R^{13} are H.

In embodiments of the moiety of formula (I), R^{10} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R^{12} is replaced by a covalent bond to the rest of the compound; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein at least one of R^{10}, R^{11}, and R^{13} is H.

In embodiments of the moiety of formula (I), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is replaced by a covalent bond to the rest of the compound; and

R^{13} is selected from H, fluorine, and methoxy.

In embodiments of the moiety of formula (I), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is replaced by a covalent bond to the rest of the compound; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least two of R^{10}, R^{11}, and R^{13} are H.

In embodiments of the moiety of formula (I), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is replaced by a covalent bond to the rest of the compound; and

R^{13} is selected from H, fluorine, and methoxy;

wherein two of R^{10}, R^{11}, and R^{13} are H.

In embodiments of the moiety of formula (I), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is replaced by a covalent bond to the rest of the compound; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least one of R^{10}, R^{11}, and R^{13} is H.

In embodiments of the moiety of formula (I), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is replaced by a covalent bond to the rest of the compound; and

R^{13} is selected from H, fluorine, and methoxy.

In embodiments of the moiety of formula (I), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is replaced by a covalent bond to the rest of the compound; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least two of R^{10}, R^{11}, and R^{13} are H.

In embodiments of the moiety of formula (I), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is replaced by a covalent bond to the rest of the compound; and

R^{13} is selected from H, fluorine, and methoxy;

wherein two of R^{10}, R^{11}, and R^{13} are H.

In embodiments of the moiety of formula (I), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is replaced by a covalent bond to the rest of the compound; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least one of R^{10}, R^{11}, and R^{13} is H.

In embodiments of the moiety of formula (I), R^{10} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is replaced by a covalent bond to the rest of the compound.

In embodiments of the moiety of formula (I), R^{10} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is replaced by a covalent bond to the rest of the compound;

wherein at least two of R^{10}, R^{11}, and R^{12} are H.

In embodiments of the moiety of formula (I), R^{10} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is replaced by a covalent bond to the rest of the compound;

wherein two of R^{10}, R^{11}, and R^{12} are H.

In embodiments of the moiety of formula (I), R^{10} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is replaced by a covalent bond to the rest of the compound;

wherein at least one of R^{10}, R^{11}, and R^{12} is H.

In embodiments of the moiety of formula (I), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is replaced by a covalent bond to the rest of the compound.

In embodiments of the moiety of formula (I), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is replaced by a covalent bond to the rest of the compound;

wherein at least two of R^{10}, R^{11}, and R^{12} are H.

In embodiments of the moiety of formula (I), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is replaced by a covalent bond to the rest of the compound;

wherein two of R^{10}, R^{11}, and R^{12} are H.

In embodiments of the moiety of formula (I), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is replaced by a covalent bond to the rest of the compound;

wherein at least one of R^{10}, R^{11}, and R^{12} is H.

In embodiments of the moiety of formula (I), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is replaced by a covalent bond to the rest of the compound.

In embodiments of the moiety of formula (I), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is replaced by a covalent bond to the rest of the compound;

wherein at least two of R^{10}, R^{11}, and R^{12} are H.

In embodiments of the moiety of formula (I), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is replaced by a covalent bond to the rest of the compound;

wherein two of R^{10}, R^{11}, and R^{12} are H.

In embodiments of the moiety of formula (I), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

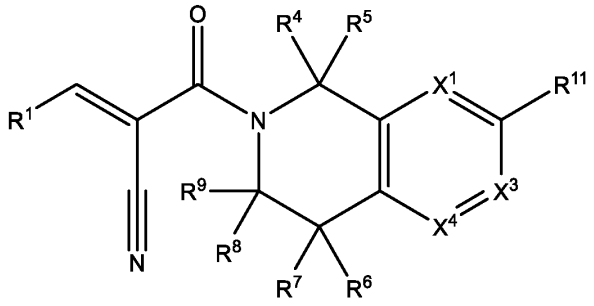
R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is replaced by a covalent bond to the rest of the compound;

wherein at least one of R^{10}, R^{11}, and R^{12} is H.

In an embodiment, the moiety of formula (I) is a moiety of formula (Ia)



(Ia)

wherein

X^1 is selected from N and CR^{10};

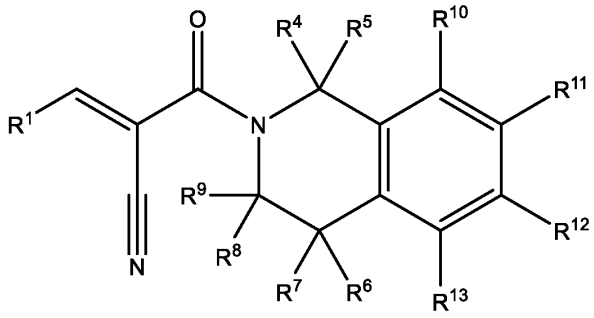
X^3 is selected from N and CR^{12};

X^4 is selected from N and CR^{13}; and

R^1, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, and R^{13} are as defined for the moiety of formula (I),

wherein if X^1 is CR^{10}, X^2 is CR^{11}, X^3 is CR^{12} and X^4 is CR^{13}, then at least one of R^{10}, R^{11}, R^{12}, and R^{13} is not H.

In an embodiment, the moiety of formula (I) is a moiety of formula (Ib)

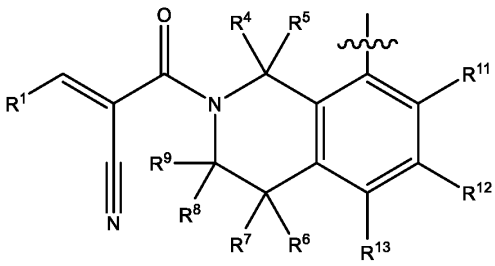


(Ib)

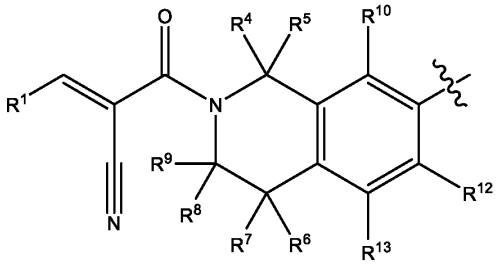
wherein

R^1, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, and R^{13} are as defined for the moiety of formula (I).

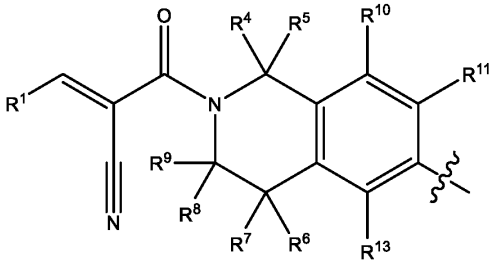
Formula (Ib) therefore embodies compounds of formula (Iba), (Ibb), (Ibc) and (Ibd):



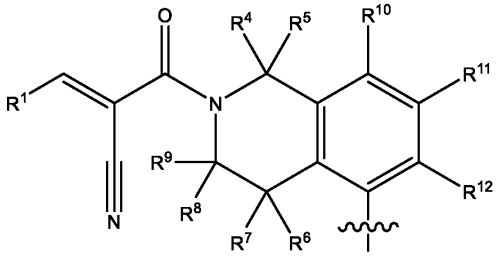
(IIba)



(IIbb)



(IIbc)

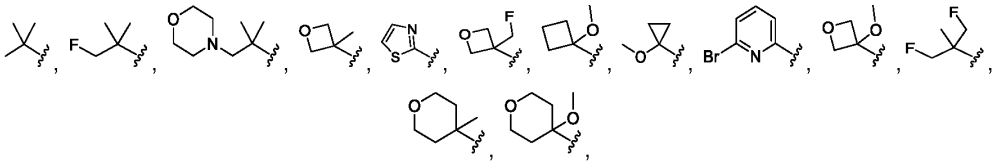


(IIbd)

wherein in the compounds of formula (Iba), (Ibb), (Ibc) and (Ibd), R^1, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, and R^{13} are as defined for the moiety of formula (I), and the wavy line intersects the bond between the moiety of formula (Ib) and the rest of the compound. In the compound of (Iba), (Ibb), (Ibc) or (Ibd), one of R^{10}, R^{11}, R^{12}, and R^{13} (as is applicable for the particular compound) is not H. That is to

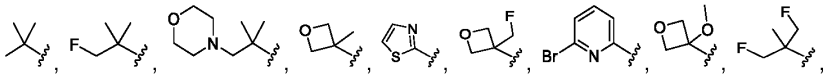
say, in compounds of formula (Iba), one of R^{11}, R^{12}, and R^{13} is not H; in compounds of formula (Ibb), one of R^{10}, R^{12}, and R^{13} is not H; in compounds of formula (Ibc), one of R^{10}, R^{11}, and R^{13} is not H; and in compounds of formula (Ibd), one of R^{10}, R^{11}, and R^{12} is not H. An alternative way to express this is that in the compounds of formula (Iba), (Ibb), (Ibc) and (Ibd) (and therefore in the compounds of formula (I) and formula (Ib)), no more than two of R^{10}, R^{11}, R^{12}, and R^{13} are H.

In embodiments, R^1 is selected from the following groups:



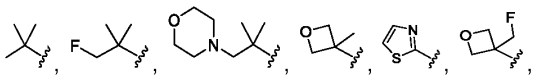
wherein the wavy line intersects the bond between R^1 and the rest of the compound.

In embodiments, R^1 is selected from the following groups:



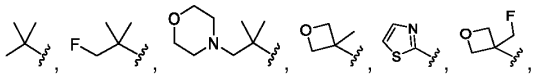
wherein the wavy line intersects the bond between R^1 and the rest of the compound.

In an embodiment of the moiety of formula (Ib), R^1 is selected from the following groups:



wherein the wavy line intersects the bond between R^1 and the rest of the compound.

In an embodiment of the moiety of formula (Ib), R^1 is selected from the following groups:



wherein the wavy line intersects the bond between R^1 and the rest of the compound;

R^4 is selected from H, methyl and isopropyl;

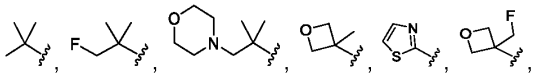
R^5, R^6, R^7, R^8, and R^9 are H;

R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy.

In an embodiment of the moiety of formula (Ib), R^1 is selected from the following groups:



wherein the wavy line intersects the bond between R^1 and the rest of the compound;

R^4 is selected from H, methyl and isopropyl;

R^5, R^6, R^7, R^8, and R^9 are H;

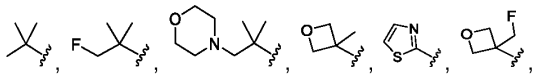
R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein one of R^{10}, R^{11}, R^{12}, and R^{13} is replaced by a covalent bond to the rest of the compound.

In an embodiment of the moiety of formula (Ib), R^1 is selected from the following groups:



wherein the wavy line intersects the bond between R^1 and the rest of the compound;

R^4 is selected from H, methyl and isopropyl;

R^5, R^6, R^7, R^8, and R^9 are H;

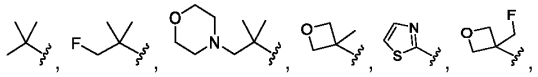
R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy.

In an embodiment of the moiety of formula (Ib), R^1 is selected from the following groups:



wherein the wavy line intersects the bond between R^1 and the rest of the compound;

R^4 is selected from H, methyl and isopropyl;

R^5, R^6, R^7, R^8, and R^9 are H;

R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

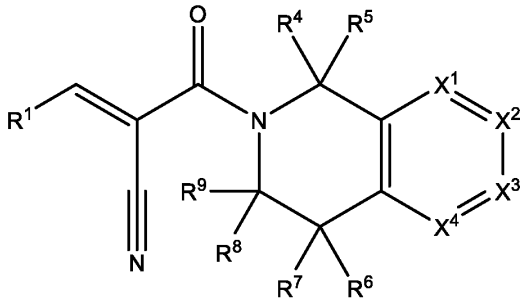
R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein one of R^{10}, R^{11}, R^{12}, and R^{13} is replaced by a covalent bond to the rest of the compound.

In an embodiment, the moiety of formula (I) is a moiety of formula (Ic)



(Ic)

wherein

X^1 is CR^{10} or N;

X^2 is CR^{11};

X^3 is CR^{12} or N; and

X^4 is CR^{13} or N;

R^{10}, R^{11}, R^{12}, and R^{13} are each H; and

R^1, R^4, R^5, R^6, R^7, R^8, and R^9 are as defined for the moiety of formula (I);

wherein at least one of X^1, X^2, X^3 and X^4 is N; and

no more than three of X^1, X^2, X^3 and X^4 are N.

In embodiments of the moiety of formula (Ic), one of X^1, X^2, X^3 and X^4 is N.

In embodiments of the moiety of formula (Ic), at least two and not more than three (e.g. two) of X^1, X^2, X^3 and X^4 are N.

In embodiments of the moiety of formula (Ic), three of X^1, X^2, X^3 and X^4 are N.

In embodiments of the moiety of formula (Ic), one of R^{10}, R^{11}, R^{12} and R^{13} is replaced by a covalent bond to the rest of the compound, and the others are as defined for the moiety of formula (I).

In embodiments of the moiety of formula (Ic), R^{11} is replaced by a covalent bond to the rest of the compound, and R^{10}, R^{12}, and R^{13} are as defined for the moiety of formula (I).

In embodiments of the moiety of formula (Ic), R^{10}, R^{11}, R^{12}, and R^{13} are H.

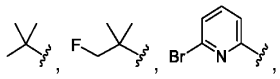
In embodiments of the moiety of formula (Ic), one of R^{10}, R^{11}, R^{12} and R^{13} is replaced by a covalent bond to the rest of the compound, and the others are H.

In embodiments of the moiety of formula (Ic), R^{11} is replaced by a covalent bond to the rest of the compound, and R^{10}, R^{12}, R^{13} are H.

In embodiments of the moiety of formula (Ic), R^1 is selected from C_1-C_6 alkyl and 5-10 membered heteroaryl comprising one or more heteroatoms selected from the group consisting of N, S and O, wherein the alkyl and heteroaryl are each optionally substituted with one or more groups independently selected from halogen and C_1-C_6 alkyl.

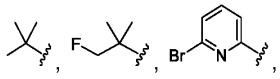
In embodiments of the moiety of formula (Ic), R^1 is selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, and 5-10 membered heteroaryl substituted with halogen.

In embodiments of the moiety of formula (Ic), R^1 is selected from the following groups:



wherein the wavy line intersects the bond between R^1 and the rest of the compound.

In embodiments of the moiety of formula (Ic), R^1 is selected from the following groups:

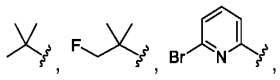


wherein the wavy line intersects the bond between R^1 and the rest of the compound;

R^4 is methyl; and

R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, and R^{13} are H.

In embodiments of the moiety of formula (Ic), R^1 is selected from the following groups:



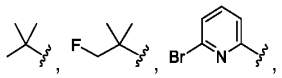
wherein the wavy line intersects the bond between R^1 and the rest of the compound;

R^4 is methyl;

R^5, R^6, R^7, R^8, and R^9 are H; and

one of R^{10}, R^{11}, R^{12}, and R^{13} is replaced by a covalent bond to the rest of the compound, and the others are H.

In embodiments of the moiety of formula (Ic), R^1 is selected from the following groups:



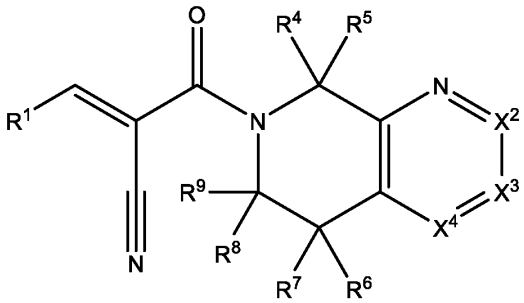
wherein the wavy line intersects the bond between R^1 and the rest of the compound;

R^4 is methyl;

R^5, R^6, R^7, R^8, R^9, R^{10}, R^{12}, and R^{13} are H; and

R^{11} is replaced by a covalent bond to the rest of the compound.

In an embodiment, the moiety of formula (I) is a moiety of formula (Id)



(Id)

wherein

X^2 is CR^{11};

X^3 is CR^{12};

X^4 is CR^{13}; and

R^1, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, and R^{13} are as defined for the moiety of formula (I).

In embodiments of the moiety of formula (Id), one of R^{11}, R^{12}, and R^{13} is replaced by a covalent bond to the rest of the compound, and the others are as defined for the moiety of formula (I).

In embodiments of the moiety of formula (Id), R^{11} is replaced by a covalent bond to the rest of the compound, and R^{10}, R^{12}, and R^{13} are as defined for the moiety of formula (I).

In embodiments of the moiety of formula (Id), R^{11}, R^{12}, and R^{13} are H.

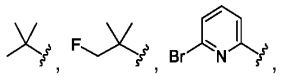
In embodiments of the moiety of formula (Id), one of R^{11}, R^{12}, and R^{13} is replaced by a covalent bond to the rest of the compound, and the others are H.

In embodiments of the moiety of formula (Id), R^{11} is replaced by a covalent bond to the rest of the compound, and R^{12} and R^{13} are H.

In embodiments of the moiety of formula (Id), R^1 is selected from C_1-C_6 alkyl and 5-10 membered heteroaryl comprising one or more heteroatoms selected from the group consisting of N, S and O, wherein the alkyl and heteroaryl are each optionally substituted with one or more groups independently selected from halogen and C_1-C_6 alkyl.

In embodiments of the moiety of formula (Id), R^1 is selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, and 5-10 membered heteroaryl substituted with halogen.

In embodiments of the moiety of formula (Id), R^1 is selected from the following groups:



wherein the wavy line intersects the bond between R^1 and the rest of the compound.

In embodiments of the moiety of formula (Id), R^1 is



wherein the wavy line intersects the bond between R^1 and the rest of the compound.

In embodiments of the moiety of formula (Id), R^1 is



wherein the wavy line intersects the bond between R^1 and the rest of the compound;

R^4 is methyl;

R^5, R^6, R^7, R^8, R^9, R^{11}, R^{12}, and R^{13} are H.

In embodiments of the moiety of formula (Id), R^1 is



wherein the wavy line intersects the bond between R^1 and the rest of the compound;

R^4 is methyl;

R^5, R^6, R^7, R^8, and R^9 are H; and

one of R^{11}, R^{12}, and R^{13} is replaced by a covalent bond to the rest of the compound, and the others are H.

In embodiments of the moiety of formula (Id), R^1 is



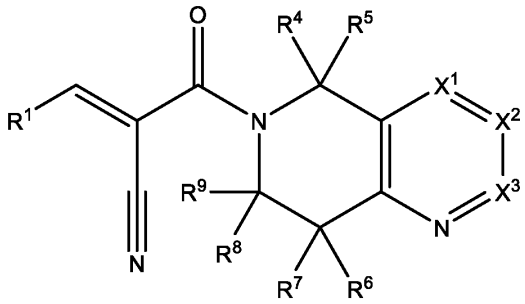
wherein the wavy line intersects the bond between R^1 and the rest of the compound;

R^4 is methyl;

R^5, R^6, R^7, R^8, R^9, R^{12}, and R^{13} are H; and

R^{11} is replaced by a covalent bond to the rest of the compound.

In an embodiment, the moiety of formula (I) is a moiety of formula (Ie)



(Ie)

wherein

X^1 is CR^{10};

X^2 is CR^{11};

X^3 is CR^{12}; and

R^1, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, and R^{13} are as defined for the moiety of formula (I).

In embodiments of the moiety of formula (Ie), one of R^{10}, R^{11}, and R^{12} is replaced by a covalent bond to the rest of the compound, and the others are as defined for the moiety of formula (I).

In embodiments of the moiety of formula (Ie), R^{11} is replaced by a covalent bond to the rest of the compound, and R^{10} and R^{12} are as defined for the moiety of formula (I).

In embodiments of the moiety of formula (Ie), R^{10}, R^{11}, and R^{12} are H.

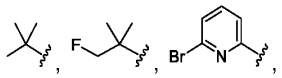
In embodiments of the moiety of formula (Ie), one of R^{10}, R^{11}, and R^{12} is replaced by a covalent bond to the rest of the compound, and the others are H.

In embodiments of the moiety of formula (Ie), R^{11} is replaced by a covalent bond to the rest of the compound, and R^{10} and R^{12} are H.

In embodiments of the moiety of formula (Ie), R^1 is selected from C_1-C_6 alkyl and 5-10 membered heteroaryl comprising one or more heteroatoms selected from the group consisting of N, S and O, wherein the alkyl and heteroaryl are each optionally substituted with one or more groups independently selected from halogen and C_1-C_6 alkyl.

In embodiments of the moiety of formula (Ie), R^1 is selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, and 5-10 membered heteroaryl substituted with halogen.

In embodiments of the moiety of formula (Ie), R^1 is selected from the following groups:



wherein the wavy line intersects the bond between R^1 and the rest of the compound.

In embodiments of the moiety of formula (Ie), R^1 is



wherein the wavy line intersects the bond between R^1 and the rest of the compound.

In embodiments of the moiety of formula (Ie), R^1 is



wherein the wavy line intersects the bond between R^1 and the rest of the compound;

R^4 is methyl;

R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are H.

In embodiments of the moiety of formula (Ie), R^1 is



wherein the wavy line intersects the bond between R^1 and the rest of the compound;

R^4 is methyl;

R^5, R^6, R^7, R^8, and R^9 are H; and

one of R^{10}, R^{11}, and R^{12} is replaced by a covalent bond to the rest of the compound, and the others are H.

In embodiments of the moiety of formula (Ie), R^1 is



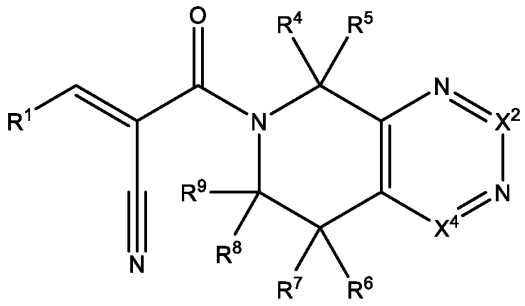
wherein the wavy line intersects the bond between R^1 and the rest of the compound;

R^4 is methyl;

R^5, R^6, R^7, R^8, R^9, R^{10}, and R^{12} are H;

R^{11} is replaced by a covalent bond to the rest of the compound.

In an embodiment, the moiety of formula (I) is a moiety of formula (If)



(If)

wherein

X^2 is CR^{11};

X^4 is CR^{13}; and

R^1, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, and R^{13} are as defined for the moiety of formula (I).

In embodiments of the moiety of formula (If), one of R^{11} and R^{13} is replaced by a covalent bond to the rest of the compound, and the other is as defined for the moiety of formula (I).

In embodiments of the moiety of formula (If), R^{11} is as defined for the moiety of formula (I), and R^{13} is replaced by a covalent bond to the rest of the compound.

In embodiments of the moiety of formula (If), R^{11} and R^{13} are H.

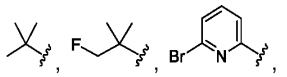
In embodiments of the moiety of formula (If), one of R^{11} and R^{13} is replaced by a covalent bond to the rest of the compound, and the other is H.

In embodiments of the moiety of formula (If), R^{11} is H and R^{13} is replaced by a covalent bond to the rest of the compound.

In embodiments of the moiety of formula (If), R^1 is selected from C_1-C_6 alkyl and 5-10 membered heteroaryl comprising one or more heteroatoms selected from the group consisting of N, S and O, wherein the alkyl and heteroaryl are each optionally substituted with one or more groups independently selected from halogen and C_1-C_6 alkyl.

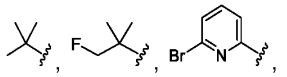
In embodiments of the moiety of formula (If), R^1 is selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, and 5-10 membered heteroaryl substituted with halogen.

In embodiments of the moiety of formula (If), R^1 is selected from the following groups:



wherein the wavy line intersects the bond between R^1 and the rest of the compound.

In embodiments of the moiety of formula (If), R^1 is selected from the following groups:

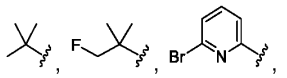


wherein the wavy line intersects the bond between R^1 and the rest of the compound;

R^4 is methyl; and

R^5, R^6, R^7, R^8, R^9, R^{11} and R^{13} are H.

In embodiments of the moiety of formula (If), R^1 is selected from the following groups:



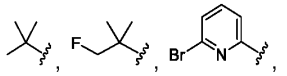
wherein the wavy line intersects the bond between R^1 and the rest of the compound;

R^4 is methyl;

R^5, R^6, R^7, R^8, and R^9 are H; and

one of R^{11} and R^{13} is replaced by a covalent bond to the rest of the compound, and the other is H.

In embodiments of the moiety of formula (If), R^1 is selected from the following groups:



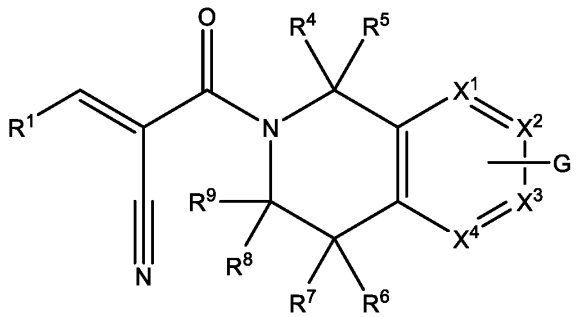
wherein the wavy line intersects the bond between R^1 and the rest of the compound;

R^4 is methyl;

R^5, R^6, R^7, R^8, R^9, and R^{11} are H; and

R^{13} is replaced by a covalent bond to the rest of the compound.

In one aspect, the present invention provides a compound of formula (II)



(II)

wherein

R^1, R^4, R^5, R^6, R^7, R^8, R^9 are as defined for the moiety of formula (I);

X^1 is selected from N and CR^{10};

X^2 is selected from N and CR^{11};

X^3 is selected from N and CR^{12};

X^4 is selected from N and CR^{13};

R^{10}, R^{11}, R^{12}, and R^{13} are each independently selected from H, halogen, OR^2, C_1-C_6 alkyl, and $N(R^3)_2$ wherein each alkyl is optionally substituted with one or more groups independently selected from halogen, OR^2, and $N(R^3)_2$;

each R^2 is independently selected from H, C_1-C_6 alkyl and C_1-C_6 haloalkyl;

each R^3 is independently selected from H, C_1-C_6 alkyl and C_1-C_6 haloalkyl; and

G is a moiety which enables the attachment of the compound to another chemical structure via formation of a new covalent bond;

or a pharmaceutically acceptable salt thereof;

wherein if X^1 is CR^{10}, X^2 is CR^{11}, X^3 is CR^{12} and X^4 is CR^{13}, then at least one of R^{10}, R^{11}, R^{12}, and R^{13} is not H; and

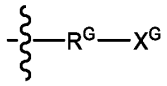
wherein no more than three of X^1, X^2, X^3 and X^4 are N.

In the compound of formula (II), G may be covalently attached to the aromatic moiety of the compound of formula (II) at any suitable position e.g. provided it has the correct valency and/or is chemically suitable. For example, R^{10}, R^{11}, R^{12}, or R^{13} may be replaced by G. For example, R^{11}, R^{12} or R^{13} may be replaced by G. For example, R^{11} or R^{13} may be replaced by G.

In embodiments of compounds of formula (II), G comprises a functional group that is able to facilitate the formation of a new covalent bond.

In embodiments of compounds of formula (II), G comprises a functional group that is able to facilitate the formation of an amide, ester, thioester, keto, urethane, amine, or ether linkage, or a carbon-carbon bond or carbon-nitrogen bond.

In embodiments of compounds of formula (II), G is



wherein R^G is absent, or is selected from C_1-C_6 alkylene or a 5- or 7-membered heterocycloalkylene comprising one or two N atoms, wherein the alkylene is optionally substituted with one or more groups independently selected from halogen, OR^2, C_1-C_6 alkyl, and $N(R^3)_2$, and wherein the heterocycloalkylene is optionally substituted by one or two C_3-C_4 spirocycloalkyl;

each R^2 is independently selected from H and C_1-C_6 alkyl;

each R^3 is independently selected from H and C_1-C_6 alkyl;

X^G is a group that is selected from $-CO_2H$, -(CO)-N-hydroxysuccinimide, -(CO)-pentafluorphenol esters, -CHO, $-COR^{G1}$, -OH, $-OR^{G1}$, $-NH_2$, $-NHR^{G2}$, halo, O-leaving group, alkynyl, azide, dienyl, aminoxy, tetrazinyl, (E)-cyclooctenyl, cyclooctynyl, norbornyl, boronic acid, boronate ester,

alkylboranes, an organometallic group, or C_1-C_6 alkyl optionally substituted by CO_2H, O-NH_2, or azide; or wherein X^G is a 5- or 7-membered heterocycloalkylene comprising one or two N atoms, optionally substituted by one or two C_3-C_4 spirocycloalkyl; and

R^{G1} and R^{G2} are each independently selected from C_1-C_6 alkyl; and

wherein wavy line intersects the bond between G and the rest of the compound.

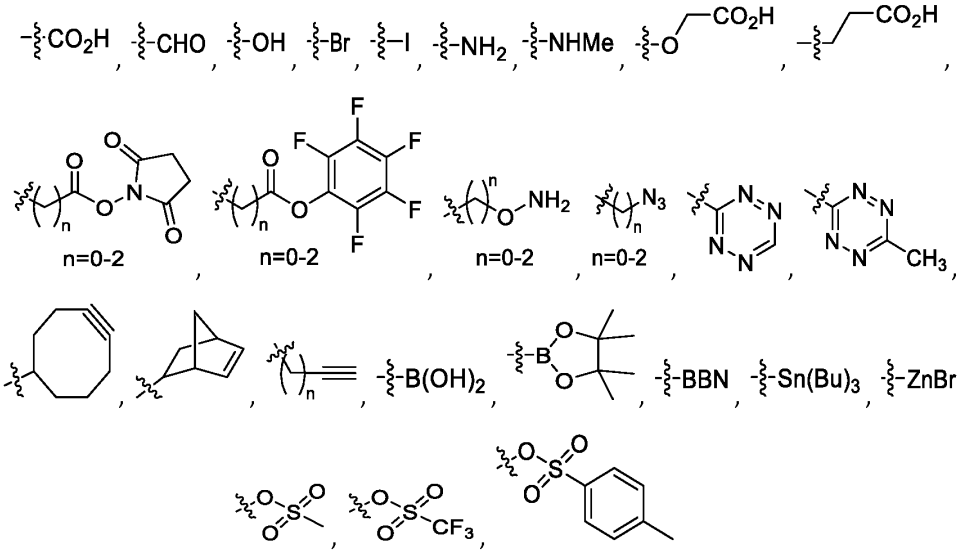
In embodiments of compounds of formula (II), R^G is absent or is C_1-C_6 alkylene.

In embodiments of compounds of formula (II), X^G is a group that is selected from -CO_2H, -(CO)-N-hydroxysuccinimide, -(CO)-pentafluorphenol esters, -CHO, -COR^{G1}, -OH, -OR^{G1}, -NH_2, -NHR^{G2}, -$N(R^{G1}R^{G2})$, halogen, -OTs (tosylate), OMs (mesylate), –OTf (triflate), alkynyl, azide, dienyl, aminoxy, tetrazinyl, (E)-cyclooctenyl, cyclooctynyl, norbornyl, boronic acid, boronate ester, alkylboranes, an organometallic group, or C_1-C_6 alkyl optionally substituted by CO_2H, O-NH_2, or azide.

In embodiments of compounds of formula (II), X^G is a group that is selected from -CO_2H, -(CO)-N-hydroxysuccinimide, -(CO)-pentafluorphenol esters, -CHO, -COR^{G1}, -OH, -OR^{G1}, -NH_2, -NHR^{G2}, -$N(R^{G1}R^{G2})$, halogen, -OTs (tosylate), OMs (mesylate), –OTf (triflate), alkynyl, azide, dienyl, aminoxy, tetrazinyl, (E)-cyclooctenyl, cyclooctynyl, norbornyl, boronic acid, boronate ester, alkylboranes, organotin, zinc, or C_1-C_6 alkyl optionally substituted by CO_2H, O-NH_2, or azide.

In embodiments of compounds of formula (II), X^G is a group that is selected from -CO_2H, -(CO)-N-hydroxysuccinimide, -(CO)-pentafluorphenol esters, -CHO, -COR^{G1}, -OH, -OR^{G1}, -NH_2, -NHR^{G2}, -$N(R^{G1}R^{G2})$, iodine, bromine, -OTs (tosylate), OMs (mesylate), –OTf (triflate), alkynyl, azide, dienyl, aminoxy, tetrazinyl, (E)-cyclooctenyl, cyclooctynyl, norbornyl, boronic acid, boronate ester, alkylboranes, organotin, zinc, or C_1-C_6 alkyl optionally substituted by CO_2H, O-NH_2, or azide.

In embodiments of compounds of formula (II), G is selected from:



wherein wavy line intersects the bond that forms the link with the aromatic moiety of the compound of formula (II).

In embodiments of the compound of formula (I), at least one and no more than three (e.g. one) of X^1, X^2, X^3 and X^4 is N.

In embodiments of the compound of formula (I), at least two and not more than three (e.g. two) of X^1, X^2, X^3 and X^4 are N.

In embodiments of the compound of formula (I), three of X^1, X^2, X^3 and X^4 are N.

In embodiments of the compound of formula (II), R^{10}, R^{11}, R^{12}, and R^{13} are each independently selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy.

In embodiments of the compound of formula (II), R^{10}, R^{11}, R^{12}, and R^{13} are each independently selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy.

In embodiments of the compound of formula (II), R^{10}, R^{11}, R^{12}, and R^{13} are each independently selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy.

In the compound of formula (II), no more than two of R^{10}, R^{11}, R^{12}, and R^{13} are H.

In embodiments of the compound of formula (II), two of R^{10}, R^{11}, R^{12}, and R^{13} are H.

In embodiments of the compound of formula (II), R^{10} and R^{11} are each independently selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy.

In embodiments of the compound of formula (II), R^{10} and R^{11} are each independently selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein at least two of R^{10}, R^{11}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (II), R^{10} and R^{11} are each independently selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein two of R^{10}, R^{11}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (II), R^{10} and R^{11} are each independently selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein at least one of R^{10}, R^{11}, R^{12} and R^{13} is H.

In embodiments of the compound of formula (II), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy.

In embodiments of the compound of formula (II), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least two of R^{10}, R^{11}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (II), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein two of R^{10}, R^{11}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (II), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least one of R^{10}, R^{11}, R^{12} and R^{13} is H.

In embodiments of the compound of formula (II), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy.

In embodiments of the compound of formula (II), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least two of R^{10}, R^{11}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (II), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein two of R^{10}, R^{11}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (II), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

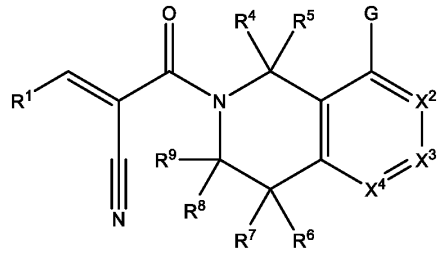
R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

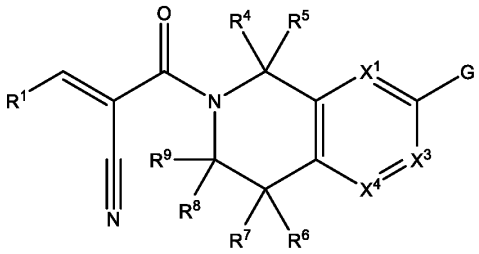
wherein at least one of R^{10}, R^{11}, R^{12} and R^{13} is H.

In embodiments of the compound of formula (II), one of R^{10}, R^{11}, R^{12}, and R^{13} is replaced by G.

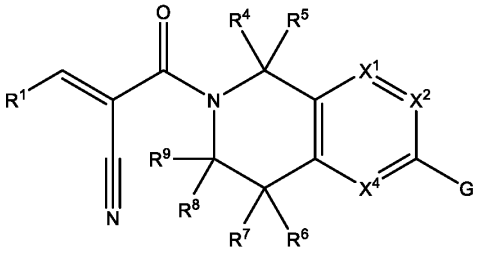
Formula (II) therefore encompasses the compounds of formula (IIA), (IIB), (IIC) and (IID):



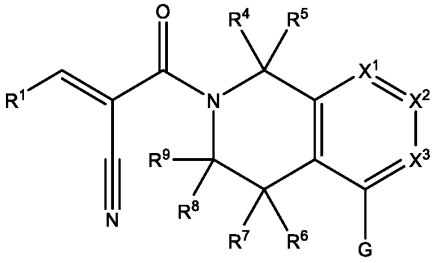
(IIA)



(IIB)



(IIC)



(IID)

wherein in the compounds of formula (IIA), (IIB), (IIC) and (IID), R^1, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, X^1, X^2, X^3, X^4, and G are as defined for the compound of formula (II). In the compound of formula (IIA), when X^2 is CR^{11}, X^3 is CR^{12}, and X^4 is CR^{13}, then one of R^{11}, R^{12} and R^{13} is not H. In the compound of formula (IIB), when X^1 is CR^{10}, X^3 is CR^{12}, and X^4 is CR^{13}, then one of R^{10}, R^{12} and R^{13} is not H. In the compound of formula (IIC), when X^1 is CR^{10}, X^2 is CR^{11}, and X^4 is CR^{13}, then one of R^{10}, R^{11} and R^{14} is not H. In the compound of formula (IID), when X^1 is CR^{10}, X^2 is CR^{11}, and X^3 is CR^{12}, then one of R^{10}, R^{11} and R^{12} is not H.

In embodiments of the compound of formula (II), R^{10} is replaced by G;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy.

In embodiments of the compound of formula (II), R^{10} is replaced by G;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein at least two of R^{11}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (II), R^{10} is replaced by G;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein two of R^{11}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (II), R^{10} is replaced by G;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein at least one of R^{11}, R^{12} and R^{13} is H.

In embodiments of the compound of formula (II), R^{10} is replaced by G;

R^{11} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy.

In embodiments of the compound of formula (II), R^{10} is replaced by G;

R^{11} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least two of R^{11}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (II), R^{10} is replaced by G;

R^{11} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein two of R^{11}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (II), R^{10} is replaced by G;

R^{11} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least one of R^{11}, R^{12} and R^{13} is H.

In embodiments of the compound of formula (III), R^{10} is replaced by G;

R^{11} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy.

In embodiments of the compound of formula (III), R^{10} is replaced by G;

R^{11} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least two of R^{10}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (III), R^{10} is replaced by G;

R^{11} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein two of R^{10}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (III), R^{10} is replaced by G;

R^{11} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least one of R^{10}, R^{12} and R^{13} is H.

In embodiments of the compound of formula (II), R^{10} and R^{11} are each independently selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{12} is replaced by G; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy.

In embodiments of the compound of formula (II), R^{10} and R^{11} are each independently selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{12} is replaced by G; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein at least two of R^{10}, R^{11}, and R^{13} are H.

In embodiments of the compound of formula (II), R^{10} and R^{11} are each independently selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{12} is replaced by G; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein two of R^{10}, R^{11}, and R^{13} are H.

In embodiments of the compound of formula (II), R^{10} and R^{11} are each independently selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{12} is replaced by G; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein at least one of R^{10}, R^{11}, and R^{13} is H.

In embodiments of the compound of formula (II), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{12} is replaced by G; and

R^{13} is selected from H, fluorine, and methoxy.

In embodiments of the compound of formula (II), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{12} is replaced by G; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least two of R^{10}, R^{11}, and R^{13} are H.

In embodiments of the compound of formula (II), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{12} is replaced by G; and

R^{13} is selected from H, fluorine, and methoxy;

wherein two of R^{10}, R^{11}, and R^{13} are H.

In embodiments of the compound of formula (II), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{12} is replaced by G; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least one of R^{10}, R^{11}, and R^{13} is H.

In embodiments of the compound of formula (II), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{12} is replaced by G; and

R^{13} is selected from H, fluorine, and methoxy.

In embodiments of the compound of formula (II), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{12} is replaced by G; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least two of R^{10}, R^{11}, and R^{13} are H.

In embodiments of the compound of formula (II), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{12} is replaced by G; and

R^{13} is selected from H, fluorine, and methoxy;

wherein two of R^{10}, R^{11}, and R^{13} are H.

In embodiments of the compound of formula (II), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{12} is replaced by G; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least one of R^{10}, R^{11}, and R^{13} is H.

In embodiments of the compound of formula (II), R^{10} and R^{11} are each independently selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is replaced by G.

In embodiments of the compound of formula (II), R^{10} and R^{11} are each independently selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is replaced by G;

wherein at least two of R^{10}, R^{11}, and R^{12} are H.

In embodiments of the compound of formula (II), R^{10} and R^{11} are each independently selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is replaced by G;

wherein two of R^{10}, R^{11}, and R^{12} are H.

In embodiments of the compound of formula (II), R^{10} and R^{11} are each independently selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is replaced by G;

wherein at least one of R^{10}, R^{11}, and R^{12} is H.

In embodiments of the compound of formula (II), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is replaced by G.

In embodiments of the compound of formula (II), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is replaced by G;

wherein at least two of R^{10}, R^{11}, and R^{12} are H.

In embodiments of the compound of formula (II), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is replaced by G;

wherein two of R^{10}, R^{11}, and R^{12} are H.

In embodiments of the compound of formula (II), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is replaced by G;

wherein at least one of R^{10}, R^{11}, and R^{12} is H.

In embodiments of the compound of formula (II), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is replaced by G.

In embodiments of the compound of formula (II), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is replaced by G;

wherein at least two of R^{10}, R^{11}, and R^{12} are H.

In embodiments of the compound of formula (II), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is replaced by G;

wherein two of R^{10}, R^{11}, and R^{12} are H.

In embodiments of the compound of formula (II), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is replaced by G;

wherein at least one of R^{10}, R^{11}, and R^{12} is H.

In embodiments of the compound of formula (II), R^{10} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy.

In embodiments of the compound of formula (II), R^{10} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein at least two of R^{10}, R^{11}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (II), R^{10} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein two of R^{10}, R^{11}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (II), R^{10} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein at least one of R^{10}, R^{11}, R^{12} and R^{13} is H.

In embodiments of the compound of formula (II), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy.

In embodiments of the compound of formula (II), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least two of R^{10}, R^{11}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (II), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein two of R^{10}, R^{11}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (II), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least one of R^{10}, R^{11}, R^{12} and R^{13} is H.

In embodiments of the compound of formula (II), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy.

In embodiments of the compound of formula (II), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least two of R^{10}, R^{11}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (II), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein two of R^{10}, R^{11}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (II), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least one of R^{10}, R^{11}, R^{12} and R^{13} is H.

In embodiments of the compound of formula (II), one of R^{10}, R^{11}, R^{12}, and R^{13} is replaced by G.

In embodiments of the compound of formula (II), R^{10} is replaced by G;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy.

In embodiments of the compound of formula (II), R^{10} is replaced by G;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein at least two of R^{11}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (II), R^{10} is replaced by G;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein two of R^{11}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (II), R^{10} is replaced by G;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein at least one of R^{11}, R^{12} and R^{13} is H.

In embodiments of the compound of formula (II), R^{10} is replaced by G;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy.

In embodiments of the compound of formula (II), R^{10} is replaced by G;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least two of R^{11}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (II), R^{10} is replaced by G;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein two of R^{11}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (II), R^{10} is replaced by G;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least one of R^{11}, R^{12} and R^{13} is H.

In embodiments of the compound of formula (II), R^{10} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{11} is replaced by G;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy.

In embodiments of the compound of formula (II), R^{10} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{11} is replaced by G;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein at least two of R^{10}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (II), R^{10} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{11} is replaced by G;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein two of R^{10}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (II), R^{10} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{11} is replaced by G;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein at least one of R^{10}, R^{12} and R^{13} is H.

In embodiments of the compound of formula (II), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{11} is replaced by G;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy.

In embodiments of the compound of formula (II), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{11} is replaced by G;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least two of R^{10}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (II), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{11} is replaced by G;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein two of R^{10}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (II), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{11} is replaced by G;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least one of R^{10}, R^{12} and R^{13} is H.

In embodiments of the compound of formula (II), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{11} is replaced by G;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy.

In embodiments of the compound of formula (II), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{11} is replaced by G;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least two of R^{10}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (II), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{11} is replaced by G;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein two of R^{10}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (II), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{11} is replaced by G;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least one of R^{10}, R^{12} and R^{13} is H.

In embodiments of the compound of formula (II), R^{10} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R^{12} is replaced by G; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy.

In embodiments of the compound of formula (II), R^{10} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R^{12} is replaced by G; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein at least two of R^{10}, R^{11}, and R^{13} are H.

In embodiments of the compound of formula (II), R^{10} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R^{12} is replaced by G; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein two of R^{10}, R^{11}, and R^{13} are H.

In embodiments of the compound of formula (II), R^{10} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R^{12} is replaced by G; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein at least one of R^{10}, R^{11}, and R^{13} is H.

In embodiments of the compound of formula (II), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is replaced by G; and

R^{13} is selected from H, fluorine, and methoxy.

In embodiments of the compound of formula (II), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is replaced by G; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least two of R^{10}, R^{11}, and R^{13} are H.

In embodiments of the compound of formula (II), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is replaced by G; and

R^{13} is selected from H, fluorine, and methoxy;

wherein two of R^{10}, R^{11}, and R^{13} are H.

In embodiments of the compound of formula (II), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is replaced by G; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least one of R^{10}, R^{11}, and R^{13} is H.

In embodiments of the compound of formula (II), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is replaced by G; and

R^{13} is selected from H, fluorine, and methoxy.

In embodiments of the compound of formula (II), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is replaced by G; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least two of R^{10}, R^{11}, and R^{13} are H.

In embodiments of the compound of formula (II), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is replaced by G; and

R^{13} is selected from H, fluorine, and methoxy;

wherein two of R^{10}, R^{11}, and R^{13} are H.

In embodiments of the compound of formula (II), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is replaced by G; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least one of R^{10}, R^{11}, and R^{13} is H.

In embodiments of the compound of formula (II), R^{10} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is replaced by G.

In embodiments of the compound of formula (II), R^{10} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is replaced by G;

wherein at least two of R^{10}, R^{11}, and R^{12} are H.

In embodiments of the compound of formula (II), R^{10} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is replaced by G;

wherein two of R^{10}, R^{11}, and R^{12} are H.

In embodiments of the compound of formula (II), R^{10} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is replaced by G;

wherein at least one of R^{10}, R^{11}, and R^{12} is H.

In embodiments of the compound of formula (II), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is replaced by G.

In embodiments of the compound of formula (II), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is replaced by G;

wherein at least two of R^{10}, R^{11}, and R^{12} are H.

In embodiments of the compound of formula (II), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is replaced by G;

wherein two of R^{10}, R^{11}, and R^{12} are H.

In embodiments of the compound of formula (II), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is replaced by G;

wherein at least one of R^{10}, R^{11}, and R^{12} is H.

In embodiments of the compound of formula (II), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is replaced by G.

In embodiments of the compound of formula (II), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is replaced by G;

wherein at least two of R^{10}, R^{11}, and R^{12} are H.

In embodiments of the compound of formula (II), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is replaced by G;

wherein two of R^{10}, R^{11}, and R^{12} are H.

In embodiments of the compound of formula (II), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

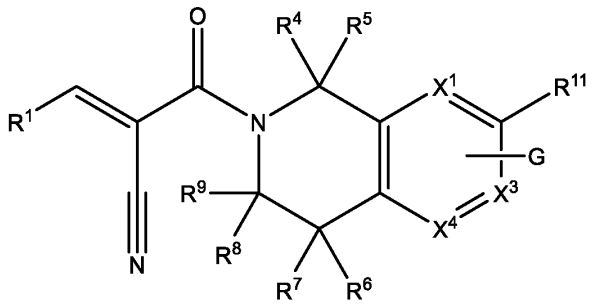
R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is replaced by G;

wherein at least one of R^{10}, R^{11}, and R^{12} is H.

In an embodiment, the compound of formula (II) is a compound of formula (IIa)



(IIa)

wherein

X^1 is selected from N and CR^{10};

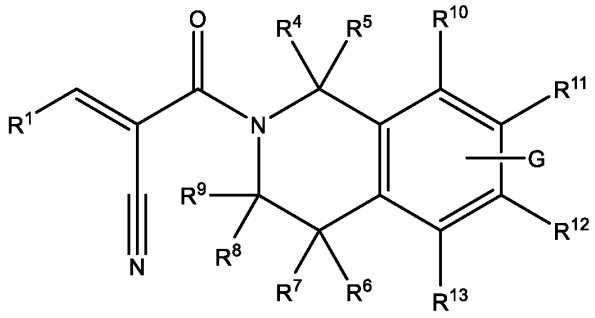
X^3 is selected from N and CR^{12};

X^4 is selected from N and CR^{13}; and

R^1, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, and G are as defined for the compound of formula (II),

wherein if X^1 is CR^{10}, X^2 is CR^{11}, X^3 is CR^{12} and X^4 is CR^{13}, then at least one of R^{10}, R^{11}, R^{12}, and R^{13} is not H.

In an embodiment, the compound of formula (II) is a compound of formula (IIb)

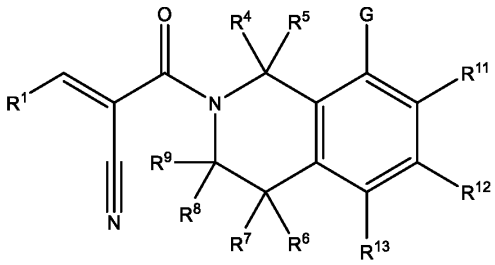


(IIb)

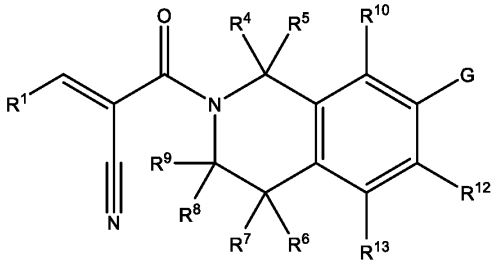
wherein

R^1, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, and G are as defined for the compound of formula (II).

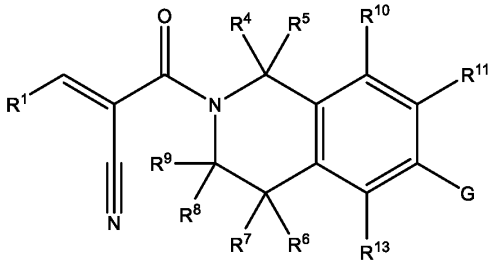
Therefore, Formula (IIb) embodies the compounds of formula (IIba), (IIbb), (IIbc) and (IIbd):



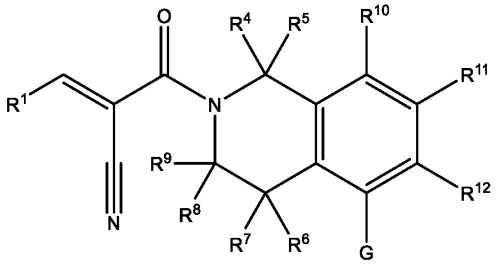
(IIba)



(IIbb)



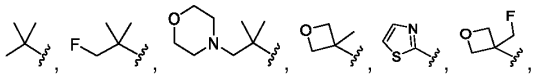
(IIbc)



(IIbd)

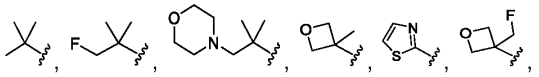
wherein in the compounds of formula (IIba), (IIbb), (IIbc) and (IIbd), R^1, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, and G are as defined for the compound of formula (II). In the compound of (IIba), (IIbb), (IIbc) or (IIbd), one of R^{10}, R^{11}, R^{12}, and R^{13} (as is applicable for the particular compound) is not H. That is to say, in compounds of formula (IIba), one of R^{11}, R^{12}, and R^{13} is not H; in compounds of formula (IIbb), one of R^{10}, R^{12}, and R^{13} is not H; in compounds of formula (IIbc), one of R^{10}, R^{11}, and R^{13} is not H; and in compounds of formula (IIbd), one of R^{10}, R^{11}, and R^{12} is not H. An alternative way to express this is that in the compounds of formula (IIba), (IIbb), (IIbc) and (IIbd) (and therefore in the compounds of formula (II) and formula (IIb)), no more than two of R^{10}, R^{11}, R^{12}, and R^{13} are H.

In an embodiment of the compound of formula (IIb), R^1 is selected from the following groups:



wherein the wavy line intersects the bond between R^1 and the rest of the compound.

In an embodiment of the compound of formula (IIb), R^1 is selected from the following groups:



wherein the wavy line intersects the bond between R^1 and the rest of the compound;

R^4 is selected from H, methyl and isopropyl;

R^5, R^6, R^7, R^8, and R^9 are H;

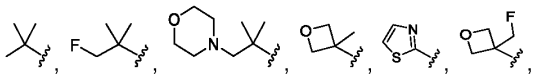
R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl;

R^{13} is selected from H, fluorine, and methoxy; and

G is as defined for compounds of formula (II).

In an embodiment of the compound of formula (IIb), R^1 is selected from the following groups:



wherein the wavy line intersects the bond between R^1 and the rest of the compound;

R^4 is selected from H, methyl and isopropyl;

R^5, R^6, R^7, R^8, and R^9 are H;

R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

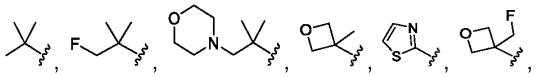
R^{12} is selected from H, fluorine, and methyl;

R^{13} is selected from H, fluorine, and methoxy; and

G is as defined for compounds of formula (II);

wherein one of R^{10}, R^{11}, R^{12}, and R^{13} is replaced by G.

In an embodiment of the compound of formula (IIb), R^1 is selected from the following groups:



wherein the wavy line intersects the bond between R^1 and the rest of the compound;

R^4 is selected from H, methyl and isopropyl;

R^5, R^6, R^7, R^8, and R^9 are H;

R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

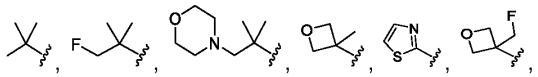
R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl;

R^{13} is selected from H, fluorine, and methoxy; and

G is as defined for compounds of formula (II).

In an embodiment of the compound of formula (IIb), R^1 is selected from the following groups:



wherein the wavy line intersects the bond between R^1 and the rest of the compound;

R^4 is selected from H, methyl and isopropyl;

R^5, R^6, R^7, R^8, and R^9 are H;

R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

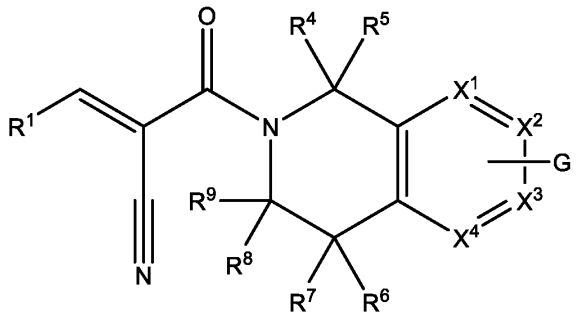
R^{12} is selected from H, fluorine, and methyl;

R^{13} is selected from H, fluorine, and methoxy; and

G is as defined for compounds of formula (II);

wherein one of R^{10}, R^{11}, R^{12}, and R^{13} is replaced by G.

In an embodiment, the compound of formula (II) is a compound of formula (IIc)



(IIc)

wherein

X^1 is CR^{10} or N;

X^2 is CR^{11};

X^3 is CR^{12} or N; and

X^4 is CR^{13} or N;

R^{10}, R^{11}, R^{12}, and R^{13} are each H; and

R^1, R^4, R^5, R^6, R^7, R^8, R^9, and G are as defined for the compound of formula (II);

wherein at least one of X^1, X^3 and X^4 is N; and

no more than three of X^1, X^2, X^3 and X^4 are N.

In embodiments of the compound of formula (IIc), one of X^1, X^2, X^3 and X^4 is N.

In embodiments of the compound of formula (IIc), at least two and not more than three (e.g. two) of X^1, X^2, X^3 and X^4 are N.

In embodiments of the compound of formula (IIc), three of X^1, X^2, X^3 and X^4 are N.

In embodiments of the compound of formula (IIc), one of R^{10}, R^{11}, R^{12} and R^{13} is replaced by G, and the others are as defined for the moiety of formula (I).

In embodiments of the compound of formula (IIc), R^{11} is replaced by G, and R^{10}, R^{12}, and R^{13} are as defined for the moiety of formula (I).

In embodiments of the compound of formula (IIc), R^{10}, R^{11}, R^{12}, and R^{13} are H.

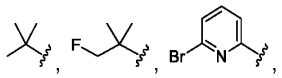
In embodiments of the compound of formula (IIc), one of R^{10}, R^{11}, R^{12} and R^{13} is replaced by G, and the others are H.

In embodiments of the compound of formula (IIc), R^{11} is replaced by G, and R^{10}, R^{12}, R^{13} are H.

In embodiments of the compound of formula (IIc), R^1 is selected from C_1-C_6 alkyl and 5-10 membered heteroaryl comprising one or more heteroatoms selected from the group consisting of N, S and O, wherein the alkyl and heteroaryl are each optionally substituted with one or more groups independently selected from halogen and C_1-C_6 alkyl.

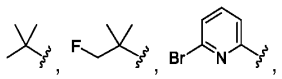
In embodiments of the compound of formula (IIc), R^1 is selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, and 5-10 membered heteroaryl substituted with halogen.

In embodiments of the compound of formula (IIc), R^1 is selected from the following groups:



wherein the wavy line intersects the bond between R^1 and the rest of the compound.

In embodiments of the compound of formula (IIc), R^1 is selected from the following groups:



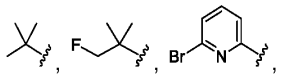
wherein the wavy line intersects the bond between R^1 and the rest of the compound;

R^4 is methyl;

R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, and R^{13} are H; and

G is as defined for compounds of formula (II).

In embodiments of the compound of formula (IIc), R^1 is selected from the following groups:



wherein the wavy line intersects the bond between R^1 and the rest of the compound;

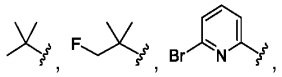
R^4 is methyl;

R^5, R^6, R^7, R^8, and R^9 are H;

G is as defined for compounds of formula (II); and

one of R^{10}, R^{11}, R^{12}, and R^{13} is replaced by G, and the others are H.

In embodiments of the compound of formula (IIc), R^1 is selected from the following groups:



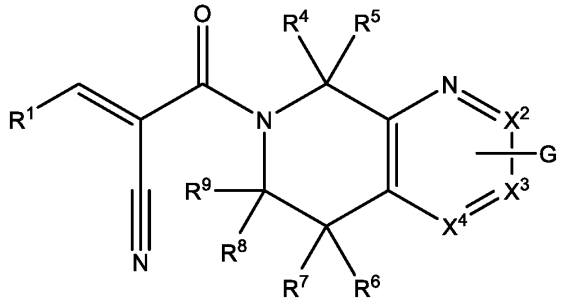
wherein the wavy line intersects the bond between R^1 and the rest of the compound;

R^4 is methyl;

R^5, R^6, R^7, R^8, R^9, R^{10}, R^{12}, and R^{13} are H; and

R^{11} is replaced by G.

In an embodiment, the moiety of formula (II) is a moiety of formula (IId)



(IId)

wherein

X^2 is CR^{11};

X^3 is CR^{12};

X^4 is CR^{13}; and

R^1, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, and G are as defined for the moiety of formula (II).

In embodiments of the compound of formula (IId), one of R^{11}, R^{12}, and R^{13} is replaced by G, and the others are as defined for the moiety of formula (II).

In embodiments of the compound of formula (IId), R^{11} is replaced by G, and R^{12} and R^{13} are as defined for the moiety of formula (II).

In embodiments of the compound of formula (IId), R^{11}, R^{12}, and R^{13} are H.

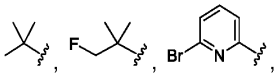
In embodiments of the compound of formula (IId), one of R^{11}, R^{12}, and R^{13} is replaced by G, and the others are H.

In embodiments of the compound of formula (IId), R^{11} is replaced by G, and R^{12} and R^{13} are H.

In embodiments of the compound of formula (Id), R^1 is selected from C_1-C_6 alkyl and 5-10 membered heteroaryl comprising one or more heteroatoms selected from the group consisting of N, S and O, wherein the alkyl and heteroaryl are each optionally substituted with one or more groups independently selected from halogen and C_1-C_6 alkyl.

In embodiments of the compound of formula (Id), R^1 is selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, and 5-10 membered heteroaryl substituted with halogen.

In embodiments of the compound of formula (Id), R^1 is selected from the following groups:



wherein the wavy line intersects the bond between R^1 and the rest of the compound.

In embodiments of the compound of formula (IId), R^1 is



wherein the wavy line intersects the bond between R^1 and the rest of the compound.

In embodiments of the compound of formula (IId), R^1 is



wherein the wavy line intersects the bond between R^1 and the rest of the compound;

R^4 is methyl;

R^5, R^6, R^7, R^8, R^9, R^{11}, R^{12}, and R^{13} are H; and

G is as defined for compounds of formula (II).

In embodiments of the compound of formula (IId), R^1 is



wherein the wavy line intersects the bond between R^1 and the rest of the compound;

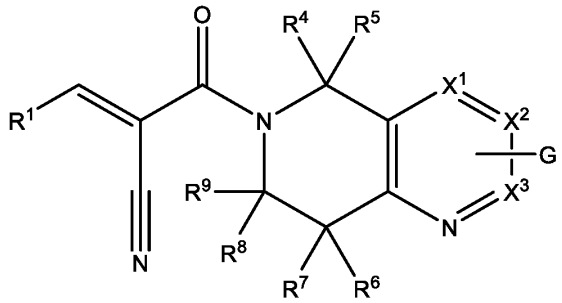
R^4 is methyl;

R^5, R^6, R^7, R^8, and R^9 are H;

G is as defined for compounds of formula (II); and

one of R^{11}, R^{12}, and R^{13} is replaced by G, and the others are H.

In an embodiment, the compound of formula (II) is a compound of formula (IIe)



(IIe)

wherein

X^1 is CR^{10};

X^2 is CR^{11};

X^3 is CR^{12}; and

R^1, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, and G are as defined for the moiety of formula (II).

In embodiments of the compound of formula (IIe), one of R^{10}, R^{11}, and R^{12} is replaced by G, and the others are as defined for the compound of formula (II).

In embodiments of the compound of formula (IIe), R^{11} is replaced by G, and R^{10} and R^{12} are as defined for the compound of formula (II).

In embodiments of the compound of formula (IIe), R^{10}, R^{11}, and R^{12} are H.

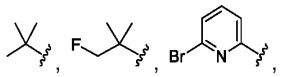
In embodiments of the compound of formula (IIe), one of R^{10}, R^{11}, and R^{12} is replaced by G, and the others are H.

In embodiments of the compound of formula (IIe), R^{11} is replaced by G, and R^{10} and R^{12} are H.

In embodiments of the compound of formula (IIe), R^1 is selected from C_1-C_6 alkyl and 5-10 membered heteroaryl comprising one or more heteroatoms selected from the group consisting of N, S and O, wherein the alkyl and heteroaryl are each optionally substituted with one or more groups independently selected from halogen and C_1-C_6 alkyl.

In embodiments of the compound of formula (IIe), R^1 is selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, and 5-10 membered heteroaryl substituted with halogen.

In embodiments of the compound of formula (IIe), R^1 is selected from the following groups:



wherein the wavy line intersects the bond between R^1 and the rest of the compound.

In embodiments of compounds of formula (IIe), R^1 is



wherein the wavy line intersects the bond between R^1 and the rest of the compound.

In embodiments of compounds of formula (IIe), R^1 is



wherein the wavy line intersects the bond between R^1 and the rest of the compound;

R^4 is methyl;

R^5, R^6, R^7, R^8, R^9,

R^{11}, R^{12}, and R^{13} are H; and

G is as defined for compounds of formula (II).

In embodiments of compounds of formula (IIe), R^1 is



wherein the wavy line intersects the bond between R^1 and the rest of the compound;

R^4 is methyl;

R^5, R^6, R^7, R^8, and R^9 are H;

G is as defined for compounds of formula (II); and

one of R^{11}, R^{12}, and R^{13} is replaced by G, and the others are H.

In embodiments of the moiety of formula (Ie), R^1 is



wherein the wavy line intersects the bond between R^1 and the rest of the compound;

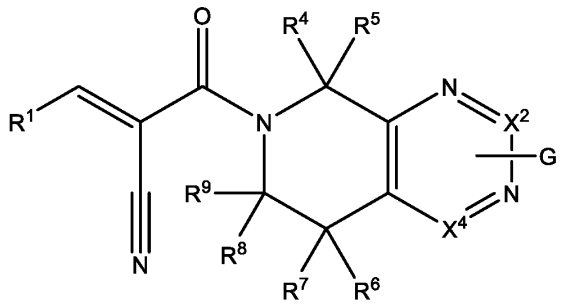
R^4 is methyl;

R^5, R^6, R^7, R^8, R^9, R^{10}, and R^{12} are H;

G is as defined for compounds of formula (II); and

R^{11} is replaced by G.

In an embodiment, the compound of formula (II) is a compound of formula (IIf)



(IIf)

wherein

X^2 is CR^{11};

X^4 is CR^{13}; and

R^1, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, and G are as defined for the moiety of formula (II).

In embodiments of the compound of formula (IIf), one of R^{11} and R^{13} is replaced by G, and the other is as defined for the moiety of formula (II).

In embodiments of the compound of formula (IIf), R^{11} is as defined for the moiety of formula (II), and R^{13} is replaced by G.

In embodiments of the compound of formula (IIf), R^{11} and R^{13} are H.

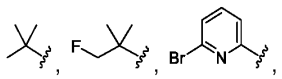
In embodiments of the compound of formula (IIf), one of R^{11} and R^{13} is replaced by G, and the other is H.

In embodiments of the compound of formula (IIf), R^{11} is H and R^{13} is replaced by G.

In embodiments of the compound of formula (IIf), R^1 is selected from C_1-C_6 alkyl and 5-10 membered heteroaryl comprising one or more heteroatoms selected from the group consisting of N, S and O, wherein the alkyl and heteroaryl are each optionally substituted with one or more groups independently selected from halogen and C_1-C_6 alkyl.

In embodiments of the compound of formula (IIf), R^1 is selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, and 5-10 membered heteroaryl substituted with halogen.

In embodiments of the compound of formula (IIf), R^1 is selected from the following groups:



wherein the wavy line intersects the bond between R^1 and the rest of the compound;

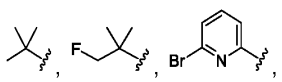
R^4 is methyl;

R^5, R^6, R^7, R^8, and R^9,

R^{11} and R^{13} are H; and

G is as defined for compounds of formula (II).

In embodiments of the compound of formula (IIf), R^1 is selected from the following groups:



wherein the wavy line intersects the bond between R^1 and the rest of the compound;

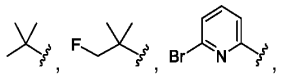
R^4 is methyl;

R^5, R^6, R^7, R^8, and R^9 are H;

G is as defined for compounds of formula (II); and

one of R^{11} and R^{13} is replaced by G, and the other is H.

In embodiments of the compound of formula (IIf), R^1 is selected from the following groups:



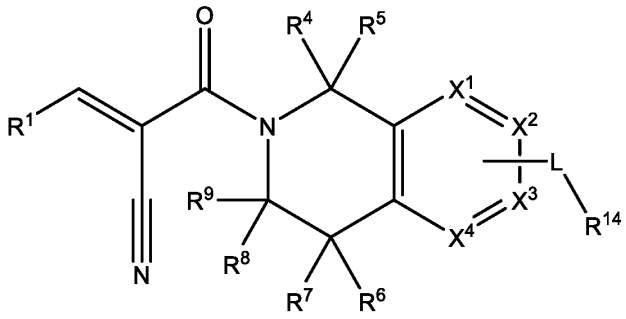
wherein the wavy line intersects the bond between R^1 and the rest of the compound;

R^4 is methyl;

R^5, R^6, R^7, R^8, R^9, and R^{11} are H; and

R^{13} is replaced by G.

In one aspect, the present invention provides a compound of formula (III) wherein a moiety -L-R^{14} is coupled to a moiety of formula (I) as described above. In embodiments, the compound of formula (III) is as shown below:



(III)

wherein

R^1, R^4, R^5, R^6, R^7, R^8, R^9 are as defined for the moiety of formula (I);

X^1 is selected from N and CR^{10};

X^2 is selected from N and CR^{11};

X^3 is selected from N and CR^{12};

X^4 is selected from N and CR^{13};

R^{10}, R^{11}, R^{12}, and R^{13} are each independently selected from H, halogen, OR^2, C_1-C_6 alkyl, and $N(R^3)_2$ wherein each alkyl is optionally substituted with one or more groups independently selected from halogen, OR^2, and $N(R^3)_2$;

each R^2 is independently selected from H, C_1-C_6 alkyl and C_1-C_6 haloalkyl;

each R^3 is independently selected from H, C_1-C_6 alkyl and C_1-C_6 haloalkyl;

L is a covalent bond or a linker; and

R^{14} is a ligand that binds to a protein;

or a pharmaceutically acceptable salt thereof;

wherein if X^1 is CR^{10}, X^2 is CR^{11}, X^3 is CR^{12} and X^4 is CR^{13}, then at least one of R^{10}, R^{11}, R^{12}, and R^{13} is not H; and

wherein no more than three of X^1, X^2, X^3 and X^4 are N.

In the compounds of formula (III), -L-R^{14} may be covalently attached to the aromatic moiety of the compound of formula (III) at any suitable position e.g. provided it has the correct valency and/or is chemically suitable. For example, R^{10}, R^{11}, R^{12}, or R^{13} may be replaced by -L-R^{14}. For example, R^{11}, R^{12} or R^{13} may be replaced by -L-R^{14}. For example, R^{11} or R^{13} may be replaced by -L-R^{14}. For example, R^{10}, R^{11}, or R^{12} may be replaced by -L-R^{14}.

As described herein, R^{14} is linked or coupled to the moiety of formula (I) via L. L may be a chemical linker (e.g. a chemical linker moiety) and, for example, may be a covalent linker, by which is meant that the linker is coupled to the moiety of formula (I) and/or R^{14} by a covalent bond.

L acts to tether R^{14} and the moiety of formula (I) to one another whilst also allowing both of these portions to bind to their respect targets and/or perform their intended function. In particular, L may act to tether R^{14} to the moiety of formula (I) whilst also mitigating the possibility of the moiety of formula (I) disrupting, interfering with and/or inhibiting the binding of R^{14} to the target protein. Additionally or alternatively, L may act to tether the moiety of formula (I) to R^{14} whilst also mitigating the possibility of R^{14} disrupting, interfering with and/or inhibiting the cellular interactions of the moiety of formula (I) (e.g. its function in modulating, facilitating and/or promoting the proteasomal degradation of the target protein).

In other words, L may function to facilitate targeted protein degradation by allowing each end of the compounds of formula (III) to be available for binding (or another type of cellular interaction) with various components of the cellular environment. For example, L may be configured to allow R^{14} to bind to the target protein without interference, disruption and/or inhibition from the moiety of formula (I). Additionally or alternatively, L may be configured to allow the moiety of formula (I) to interact with the various components in the cellular environment to modulate, facilitate and/or promote the proteasomal degradation of the target protein without interference, disruption and/or inhibition from R^{14}.

In many cases, a broad range of linkers will be tolerated. The selection of linker may depend upon the protein being targeted for degradation (the target protein) and/or the particular R^{14}.

L may be selected to provide a particular length and/or flexibility, e.g. such that R^{14} and the moiety of formula (I) are held within a particular distance and/or geometry. As will be appreciated by one of skill in the art, the length and/or flexibility of L may be varied dependent upon the structure and/or nature of R^{14}.

In some examples, R^{14} is connected directly to the moiety of formula (I) by a covalent bond i.e, L is a covalent bond. Such a direct connection is also encompassed within the term “linker” within the context of the present disclosure (and unless otherwise stated).

By way of example only, L may comprise any number of atoms between 1 and 200, between 1 and 100, between 1 and 50, between 1 and 30 or between 1 and 10. In some cases L may comprise any number of atoms in a single linear chain of between 1 and 200, between 1 and 100, between 1 and 50, between 1 and 30 or between 1 and 10. In some examples of the disclosure, L may comprise any

number of atoms in a single linear chain between 1 and 25, such as 3 and 25, or between 1 and 20, such as 3 and 20, or between 1 and 18, such as 3 and 18. In some examples of the disclosure, L may comprise 1 to 25 or 1 to 18 atoms in a single linear chain.

The degree of flexibility of L may depend upon the number of rotatable bonds present in L. A rotatable bond is defined as a single non-ring bond, bound to a nonterminal heavy atom (e.g. non-hydrogen atom). As described herein, an amide (C-N) bond is not considered rotatable because of the high rotational energy barrier. In some cases, L may comprise one or more moieties selected from rings, double bonds and amides to reduce the flexibility of L. In other cases, L may comprise a greater number and/or proportion of single bonds (e.g. may predominantly comprise single non-ring bonds) to increase the flexibility of L. It may also be appreciated that the length of L may affect the degree of flexibility. For example, a shorter L comprising fewer bonds may also reduce the flexibility of L.

In some examples, the number of rotatable bonds present in L may be any number between 1 and 20, between 1 and 15, between 1 and 10, or between 1 and 8. In some examples, the number of rotatable bonds present in L may be any number between 2 and 9, between 2 and 8, or between 3 and 6. In some examples, the number of rotatable bonds present in L may be 1 to 10, or 1 to 8.

In some examples, L may comprise any number of atoms in a single linear chain between 10 and 20; and/or the number of rotatable bonds present in L may be any number between 1 and 8.

The structure of L may be represented as follows:

$$(L_x)_q$$

wherein each L_x represents a subunit of L; and

q is an integer greater than or equal to 1.

For example, q may be any integer between 1 and 30, between 1 and 20 or between 1 and 5.

By way of example, in the case where q is 1, L comprises only one L_x subunit and may be represented as L_1. In the case where q is 2, L comprises two L_x subunits that are covalently linked to one another and which may be represented as L_1- L_2. In another example, where q is 3, L comprises three L_x subunits that are covalently linked to one another and may be represented as L_1-L_2-L_3. For even higher integer values of q, L may comprise the following subunits L_1, L_2, L_3, L_4 ….up to L_q.

Each of L_x may be independently selected from $CR^{L1}R^{L2}$, O, C=O, S, S=O, SO_2, NR^{L3}, $SONR^{L4}$, $SONR^{L5}C=O$, $CONR^{L6}$, $NR^{L7}CO$, $C(R^{L8})=C(R^{L9})$, C≡C, C_6-C_{10}aryl, 5-10 membered heteroaryl, C_3-C_8cycloalkyl, 3-8 membered heterocycloalkyl, wherein each heterocycloalkyl and heteroaryl comprises one or more heteroatoms selected from the group consisting of N, S and O, and wherein the aryl, heteroaryl, cycloalklyl, and heterocycloalkyl are each optionally substituted with one or more groups independently selected from halogen, OR^{15}, C_1-C_6 alkyl, and $N(R^{16})_2$;

wherein each R^{15} may be independently selected from H and C_1-C_6 alkyl; and

each R^{16} may be independently selected from H and C_1-C_6 alkyl.

Each of R^{L1}, R^{L2}, R^{L3}, R^{L4}, R^{L5}, R^{L6}, R^{L7}, R^{L8}, and R^{L9} may be independently selected from H, halogen, C_1-C_6 alkyl, C_1-C_6, haloalkyl, OH, C_1-C_6 alkoxy, NH_2, $NH(C_1$-C_6 alkyl), NO_2, CN, $CONH_2$, $CONH(C_1$-C_6 alkyl), $CON(C_1$-C_6 alkyl)$_2$, $SO_2(C_1$-C_6 alkyl), $CO_2(C_1$-C_6 alkyl), and $CO(C_1$-C_6 alkyl). In

some examples, each of R^{L1}, R^{L2}, R^{L3}, R^{L4}, R^{L5}, R^{L6}, R^{L7}, R^{L8} and R^{L9} may be independently selected from H-C_1 to C_6 alkyl.

The terminal L_x subunits may link or couple L moiety to R^{14} and the moiety of formula (I). For example, if the terminal L_x subunits are designated as L_1 and L_q, L_1 may link L to R^{14} and L_q may link L to the the moiety of formula (I). In those cases where q is 1, the one L_x subunit (e.g. L_1) provides the link between R^{14} and the moiety of formula (I).

R^{14} and the moiety of formula (I) may be covalently linked to L through any group which is appropriate and stable to the chemistry of L. By way of example only, L may be covalently bonded to R^{14} via a carbon-carbon bond, keto, amino, amide, ester or ether linkage. Similarly, L may be covalently bonded to the moiety of formula (I) via a carbon-carbon bond, carbon-nitrogen bond, keto, amino, amide, ester or ether linkage.

In some cases, each terminal L_x subunit (e.g. L_1 and L_q) is independently selected from O, C=O, $CR^{L1}R^{L2}$, NR^{L3}, $CONR^{L6}$, $NR^{L7}CO$, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl and substituted heterocycloalkyl groups.

In some examples, at least one of L_x comprises a ring structure and is, for example, selected from a heterocycloalkyl, heteroaryl, cycloalkyl or aryl group.

In alternative examples, L may be, or may comprise an alkyl linker comprising, a repeating subunit of -CH_2-; where the number of repeats is from 1 to 50, for example, 1-50, 1-40, 1-30, 1-20, 1-19, 1-18, 1-17, 1-16, 1-15, 1-14, 1-13, 1-12, 1-11, 1-10, 1-9. 1-8, 1-7, 1-6, 1-5, 1-4, 1-3 and 1-2.

In other examples, L may be, or may comprise a polyalkylene glycol. By way of example only, L may be, or may comprise a polyethylene glycol (PEG) comprising repeating subunits of ethylene glycol (C_2H_4O), for example, having from about 1-50 ethylene glycol subunits, for example where the number of repeats is from 1 to 100, for example, 1-50, 1-40, 1-30, 1-20, 1-19 1-18, 1-17, 1-16, 1-15, 1-14, 1-13, 1-12 or 1-5 repeats.

In some of the examples described herein, the structure of L may be, or may comprise, a structure represented as shown in formula (L1a):

$$L^{1A}\text{-}L^{2A}\text{-}L^{3A}$$

(L1a)

wherein L^{1A} is absent or is selected from C_1-C_6 alkylene (e.g. ethylene), C_1-C_6 alkoxy (e.g. -$O(CH_2)$-, -$O(CH_2)_2$-, -$O(CH_2)_5$-, -CH_2OCH_2-) and C_1-C_6 alkylamino (e.g. -$NR^{L2A}(CH_2)$-, -$R^{L2A}(CH_2)_2$-, -$R^{L2A}(CH_2)_5$-, -$CH_2R^{L2A}CH_2$-);

L^{2A} is -$NR^{L2A}C$=O- or -C=ONR^{L2A}-; and

L^{3A} is selected from C_1-C_3 alkylene (e.g. ethylene), C_1-C_6 alkoxy (e.g. -$(CH_2)O$-, -$(CH_2)_2O$-, -$(CH_2)_5O$-, -CH_2OCH_2-) and C_1-C_6 alkylamino (e.g. -$(CH_2)NR^{L2A}$-, -$(CH_2)_2NR^{L2A}$-, -$(CH_2)_5NR^{L2A}$-, -$CH_2NR^{L2A}CH_2$-);

wherein R^{L2A} is H or C_1-C_6 alkyl (e.g. C_1-C_3 alkyl).

In further examples, the structure of L may be, or may comprise, a structure represented as shown in formula (L1b):

$$L^{1B}\text{-}L^{2B}\text{-}L^{3B}\text{-}L^{4B}\text{-}L^{5B}$$

(L1b)

wherein L^{1B} is absent or is selected from C_1-C_3 alkylene (e.g. ethylene), C_1-C_6 alkoxy (e.g. -$O(CH_2)$-, -$O(CH_2)_2$-, -$O(CH_2)_5$-, -CH_2OCH_2-) and C_1-C_6 alkylamino (e.g. -$NR^{L2A}(CH_2)$-, -$NR^{L2A}(CH_2)_2$-, -$R^{L2A}(CH_2)_5$-, -$CH_2R^{L2A}CH_2$-);

L^{2B} is -$NR^{L2A}C$=O- or -C=ONR^{L2A}-;

L^{3B} is selected from C_1-C_{15} alkylene, and -$[(CH_2)_2O]_{1\text{-}6}(CH_2)_2$-;

L^{4B} is -$NR^{L2A}C$=O- or -C=ONR^{L2A}- wherein R^{L2A} is H or C_1-C_6 alkyl (e.g. C_1-C_3 alkyl);

L^{5B} is selected from C_1-C_3 alkylene (e.g. ethylene), C_1-C_6 alkoxy (e.g. -$(CH_2)O$-, -$(CH_2)_2O$-, -$(CH_2)_5O$-, -CH_2OCH_2-) and C_1-C_6 alkylamino (e.g. -$(CH_2)NR^{L2A}$-, -$NR^{L2A}(CH_2)_2$-, -$(CH_2)_5NR^{L2A}$-, -$CH_2NR^{L2A}CH_2$-);

wherein R^{L2A} is H or C_1-C_6 alkyl (e.g. C_1-C_3 alkyl).

In some of the examples described herein, the structure of L may be, or may comprise, a structure represented as shown in formula (L1c):

$$L^{1C}\text{-}L^{2C}\text{-}L^{3C}\text{-}L^{4C}$$

(L1c)

wherein L^{1C} is a4- to 7-membered monocyclic N-heterocycloalkyl, a 7- to 12-membered bicyclic N-heterocycloalkyl, or a 8- to 18-membered tricyclic N-heterocycloalkyl, wherein the monocyclic, bicyclic, and tricyclic N-heterocycloalkyl each optionally containing one or two additional ring heteroatoms selected from N, O and S, and are each optionally substituted with one or more groups independently selected from halogen, OR^{15}, C_1-C_6 alkyl, and $N(R^{16})_2$;

L^{2C} is absent or is selected from C_1-C_3 alkylene (e.g. ethylene), C_1-C_6 alkoxy (e.g. -$(CH_2)O$-, -$(CH_2)_2O$-, -$(CH_2)_5O$-, -CH_2OCH_2-) and C_1-C_6 alkylamino (e.g. -$(CH_2)NR^{L2A}$-, -$(CH_2)_2NR^{L2A}$-, -$(CH_2)_5NR^{L2A}$-, -$CH_2NR^{L2A}CH_2$-);

L^{3C} is -$R^{L2B}C$=O- or –(C=O)R^{L2B}-; and

L^{4C} is selected from C_1-C_3 alkylene (e.g. ethylene), C_1-C_6 alkoxy (e.g. -$(CH_2)O$-, -$(CH_2)_2O$-, -$(CH_2)_5O$-, -CH_2OCH_2-) and C_1-C_6 alkylamino (e.g. -$(CH_2)NR^{L2A}$-, -$(CH_2)_2NR^{L2A}$-, -$(CH_2)_5NR^{L2A}$-, -$CH_2NR^{L2A}CH_2$-);

each R^{15} is independently selected from H and C_1-C_6 alkyl;

each R^{16} is independently selected from H and C_1-C_6 alkyl;

R^{L2A} is H or C_1-C_6 alkyl (e.g. C_1-C_3 alkyl); and

R^{L2B} is NR^{L2A}; or an N-linked 4- to 7-membered monocyclic N-heterocycloalkyl, a 7- to 12-membered bicyclic N-heterocycloalkyl, or an 8- to 18-membered tricyclic N-heterocycloalkyl, wherein the monocyclic, bicyclic, and tricyclic N-heterocycloalkyl each optionally containing one or two additional ring heteroatoms selected from N, O and S, and are each optionally substituted with one or more groups independently selected from halogen, OR^{17}, C_1-C_6 alkyl, and $N(R^{18})_2$.

In examples of L represented by the Formula L1c, L^{1C} and L^{2C} may be both absent. In such examples, R^{L2B} in L^{3C} is an N-linked 4- to 7-membered monocyclic N-heterocycloalkyl, optionally containing one or two additional ring heteroatoms selected from N, O and S, and optionally substituted

with one or more groups independently selected from halogen, OR^{15}, C_1-C_6 alkyl, and $N(R^{16})_2$, and L^{3C} is the terminal subunit of the linker attached, suitably covalently attached, to R^{14} via R^{L2B}.

In some of the examples described herein, the structure of L may be, or may comprise, a structure represented as shown in formula (L1d):

$$L^{1D}\text{-}L^{2D}\text{-}L^{3D}$$

(L1d)

wherein L^{1D} is absent or is selected from C_1-C_3 alkylene, CO, C_1-C_3 alkylene(N(C_1-C_3 alkyl);

L^{2D} is NR^{L2A} or a 4- to 7-membered monocyclic N-heterocycloalkyl, a 7- to 12-membered bicyclic N-heterocycloalkyl, or an 8- to 18-membered tricyclic N-heterocycloalkyl, wherein the monocyclic, bicyclic, and tricyclic N-heterocycloalkyl each optionally contain one or two additional ring heteroatoms selected from N, O and S, and are each optionally substituted with one or more groups independently selected from halogen, OR^{15}, C_1-C_6 alkyl, and $N(R^{16})_2$;

each R^{19} is independently selected from H and C_1-C_6 alkyl;

each R^{20} is independently selected from H and C_1-C_6 alkyl; and

R^{L2A} is H or C_1-C_6 alkyl (e.g. C_1-C_3 alkyl); and

L^{3D} is absent or is selected from C_1-C_3 alkylene, -O-, -N(C_1-C_3 alkyl)-, and CO.

In further examples, the structure of the linker (L) may be, or may comprise, a structure represented as shown in formula (L1e):

$$L^{1E}\text{-}L^{2E}\text{-}L^{3E}$$

(L1e)

wherein L^{1E} is C_1-C_3 alkylene (e.g. methylene) or CO;

L^{2E} is a 4- to 7-membered monocyclic N-heterocycloalkyl, or a 7- to 12-membered bicyclic N-heterocycloalkyl, wherein the monocyclic, and bicyclic N-heterocycloalkyl each optionally contain one or two additional ring heteroatoms selected from N, O and S, and are each optionally substituted with one or more groups independently selected from halogen, OR^{15}, C_1-C_6 alkyl, and $N(R^{16})_2$;

each R^{15} is independently selected from H and C_1-C_6 alkyl;

each R^{16} is independently selected from H and C_1-C_6 alkyl; and

L^{3E} is selected from C_1-C_3 alkylene (e.g. methylene).

In some examples, L^{1A}, L^{1B}, L^{1C}, L^{1D}, or L^{1E} is the terminal subunit of the linker structure attached (i.e. covalently bonded) to the moiety of formula (I) and L^{3A}, L^{5B}, L^{4C}, L^{3D}, L^{3E} is the terminal subunit of the linker structure attached (i.e. covalently bonded) to R^{14}.

Where any of L^{1A}, L^{1B} or L^{1D} are absent, L^{2A}, L^{2B} or L^{2D} is directly attached (i.e. covalently bonded) to the moiety of formula (I). Where L^{3D} is absent, L^{2D} is directly attached (i.e. covalently bonded) to R^{14}.

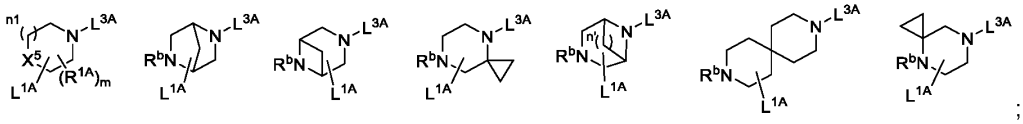
As stated above, a number of linker portions, such as L^{1C}, L^{2D}, L^{2E} examples of R^{L2B} and, may be bicyclic or tricyclic, and unless otherwise stated, these moieties may comprise rings that are joined by a bond, rings that are fused, a bridged ring and/or rings that are joined at a spiro centre.

When any one of L^{1C}, L^{2D}, L^{2E} examples of R^{L2B} is bicyclic, it may be a bridged bicyclic ring (i.e. it may comprise two rings that share three or more atoms) or it may be a spirocyclic bicyclic ring (i.e. it may comprise two rings that share one atom, e.g. the two rings may be joined at a spiro centre).

When any one of L^{1C}, L^{2D}, L^{2E} examples of R^{L2B} is a bridged bicyclic ring, it may be a 7- to 12-membered bridged bicyclic N-heterocycloalkyl optionally containing one or two additional ring heteroatoms selected from N, O and S, and optionally substituted with one or more groups independently selected from halogen, OR^{15}, C_1-C_6 alkyl, and $N(R^{16})_2$. In some examples, L^{1C}, L^{2D}, L^{2E}, and examples of R^{L2B} may be a 7- or 8-membered bridged bicyclic N-heterocycloalkyl optionally containing one or two additional ring heteroatoms selected from N, O and S. In some examples, L^{1C}, L^{2D}, L^{2E}, and examples of R^{L2B} may be a 7- or 8-membered bridged bicyclic N-heterocycloalkyl optionally containing one additional ring atom selected from N.

When any one of L^{1C}, L^{2D}, L^{2E}, and examples of R^{L2B} is a spirocyclic bicyclic ring, it may be a 7- to 12-membered spirocyclic bicyclic N-heterocycloalkyl optionally containing one or two additional ring heteroatoms selected from N, O and S, and optionally substituted with one or more groups independently selected from halogen, OR^{15}, C_1-C_6 alkyl, and $N(R^{16})_2$. In some examples, L^{1C}, L^{2D}, L^{2E}, and examples of R^{L2B} may be a 7- to 12-membered spirocyclic bicyclic N-heterocycloalkyl optionally containing one or two additional ring heteroatoms selected from N, O and S. In some cases, L^{1C}, L^{2D}, L^{2E}, and examples of R^{L2B} may be bicyclic and comprises a first 5- to 7-membered ring and a second 3- to 7-membered ring. For example, L^{1C}, L^{2D}, L^{2E}, and examples of R^{L2B} may be a spirocyclic bicyclic N-heterocycloalkyl comprising a first 5- or 6-membered ring and a second 3- to 6-membered ring, and optionally containing one or two additional ring heteroatoms selected from N, O and S. In some examples, L^{1C}, L^{2D}, L^{2E}, and examples of R^{L2B} may be a spirocyclic bicyclic N-heterocycloalkyl comprising a first 5- or 6-membered ring and a second 3- to 6-membered ring, and optionally containing one additional ring heteroatoms selected from N.

In some examples, the structure of L^{1C}, L^{2D}, L^{2E}, and examples of R^{L2B} may be any one selected from:



;

wherein L^{1A} and L^{3A} are as defined above;

X^5 is $C(R^b)_2$, NR^b or O;

R^b is H or optionally substituted $C_{1\text{-}3}$alkyl;

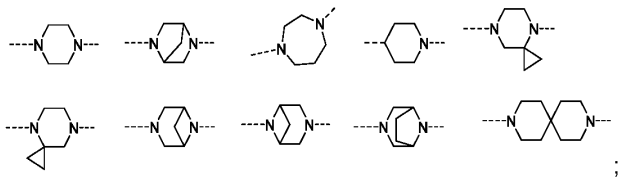
n1 is 0, 1, 2 or 3;

n' is 1 or 2;

m is 0, 1 or 2

The dotted line on the structures above indicates that the linker may be joined to the structure shown at any position indicated (provided that it has the correct valency and/or is chemically suitable).

In some examples L^{1C}, L^{2D}, L^{2E}, and examples of R^{L2B} is any one selected from:



;

The dotted line on the structures above indicates that the linker may be joined to the structure shown at any position indicated (provided that it has the correct valency and/or is chemically suitable).

As stated above, L^{1D} is absent or is selected from C_1-C_3 alkylene, –O-, -N(C_1-C_3 alkyl)-, and CO. In some examples, L^{3D} is selected from C_1-C_3 alkylene (e.g. methylene).

In some of the examples described herein, L may be, or may comprise, a structure represented as shown in formula (L1f):

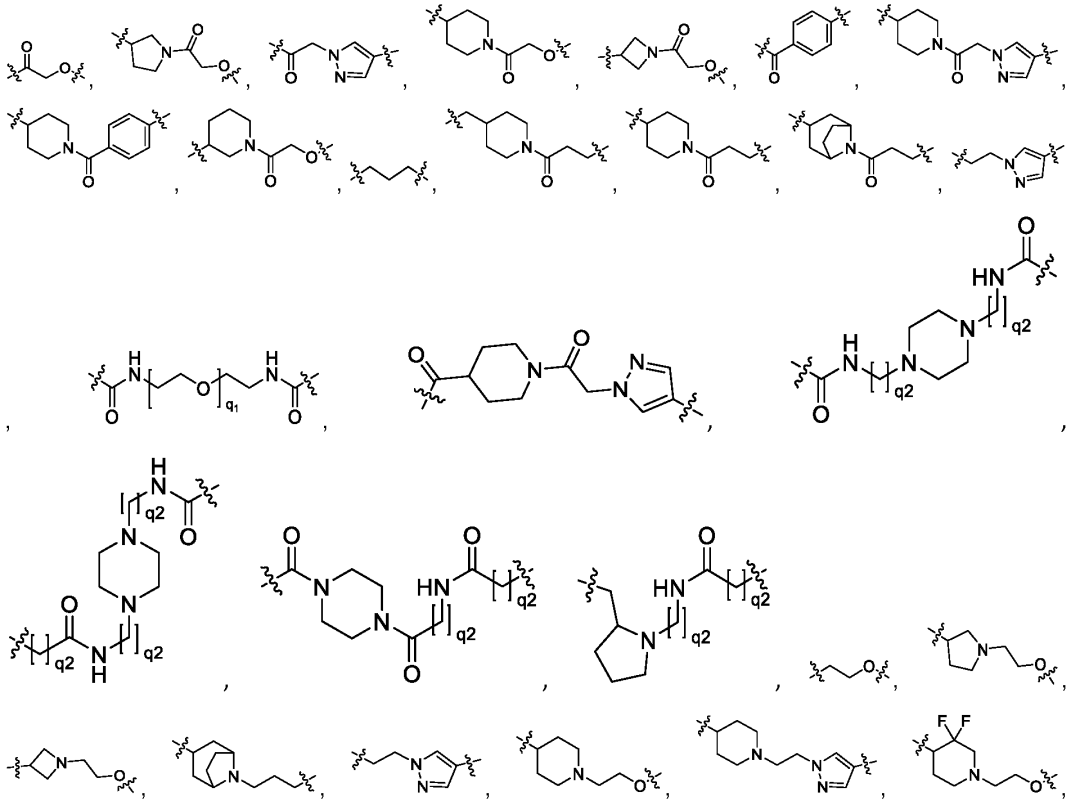
L^{1F}

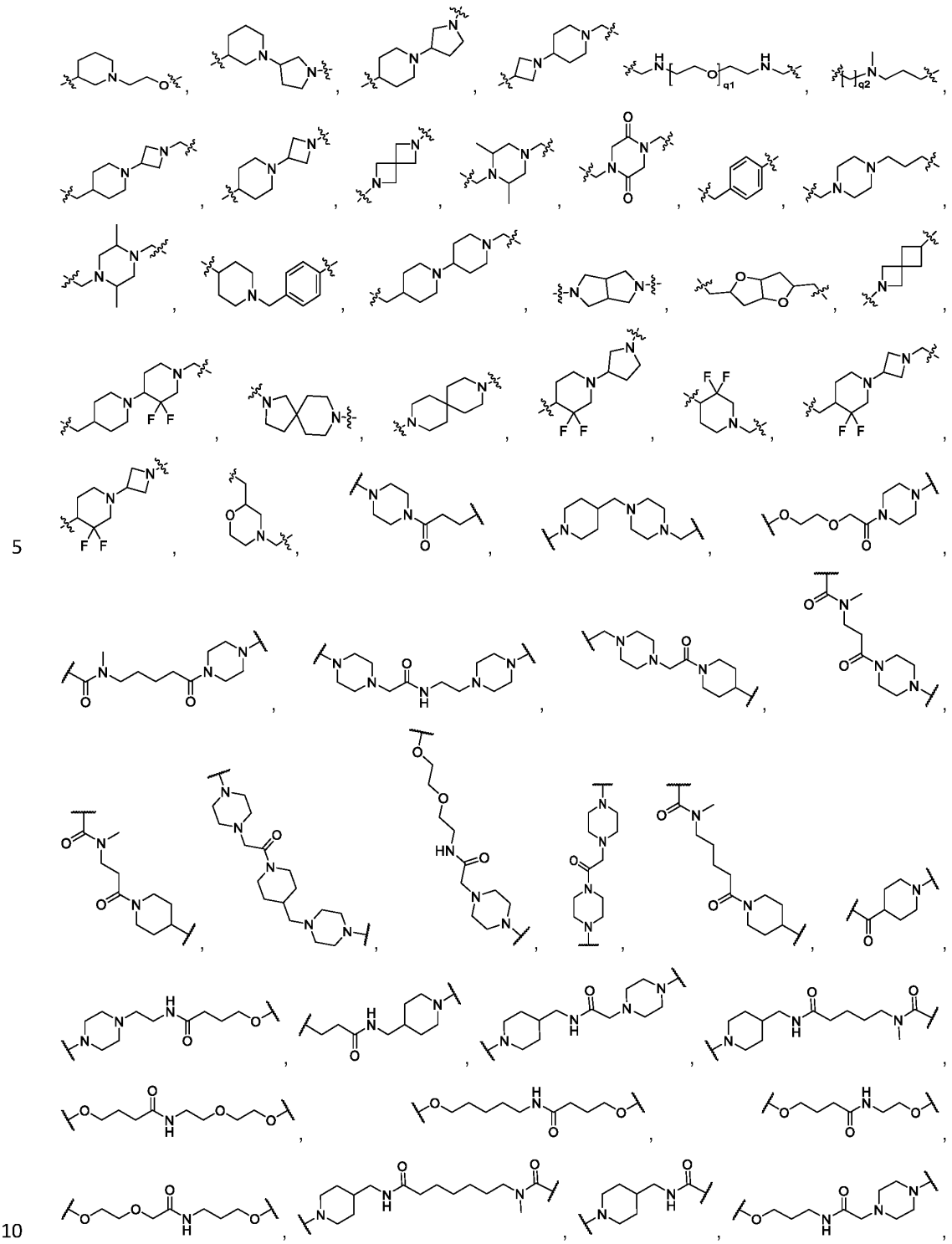
(L1f)

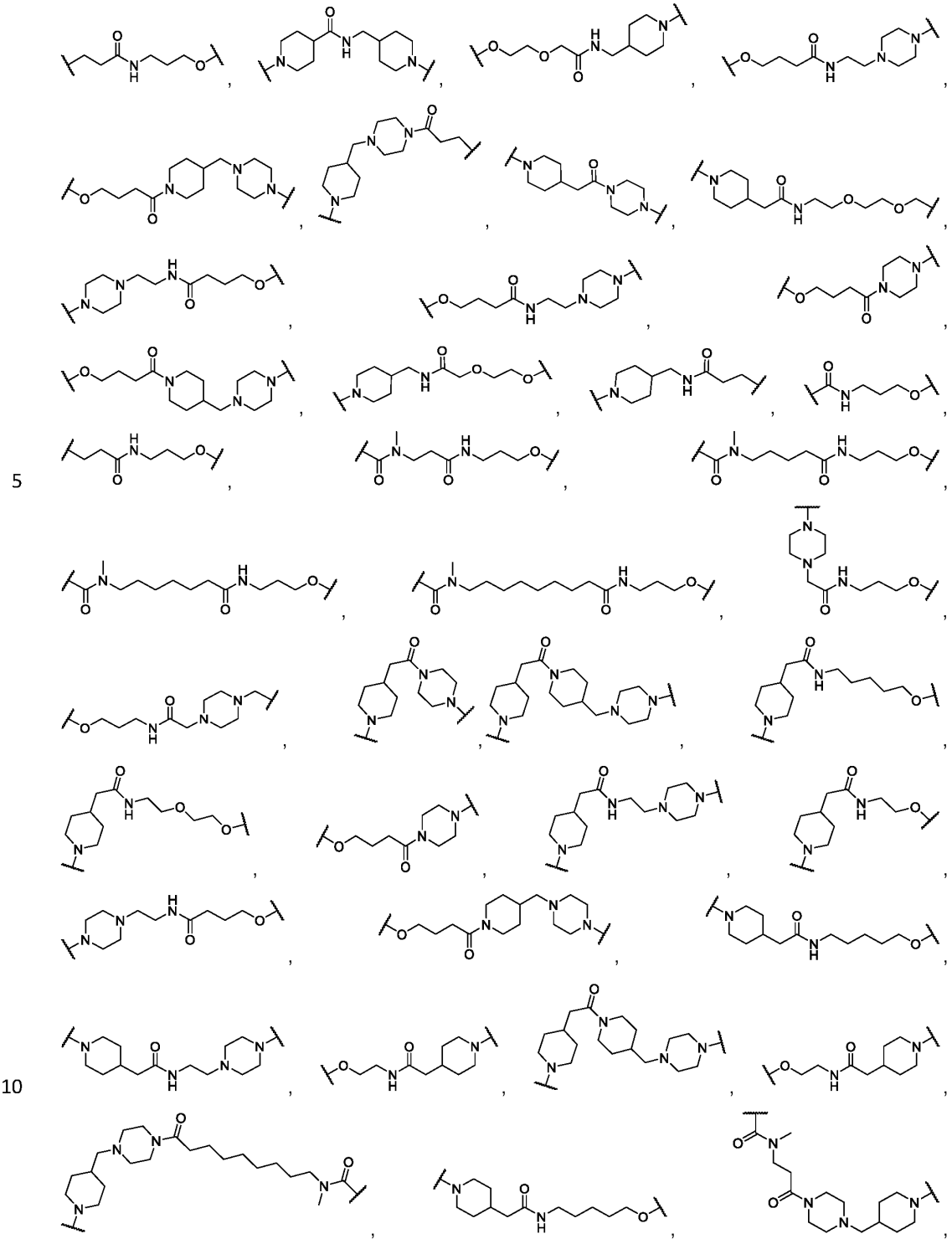
wherein L^{1F} is selected from C_1-C_3 alkylene, CO, and C_1-C_3 alkylene(NR^{L1C}); wherein R^{L1C} is H or C_1-C_3 alkyl.

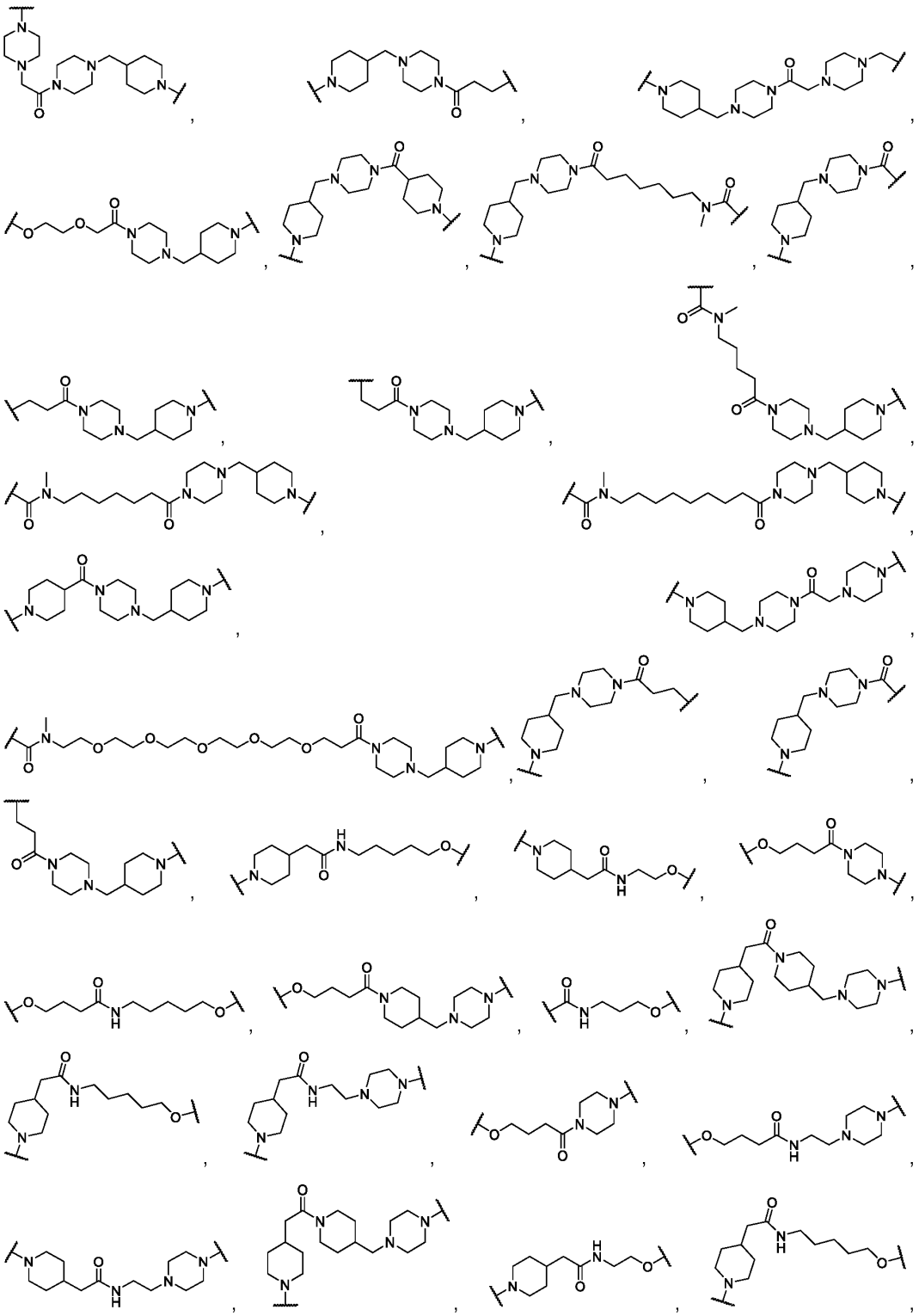
In some examples, L^{1F} is selected from C_1-C_3 alkylene (such as methylene).

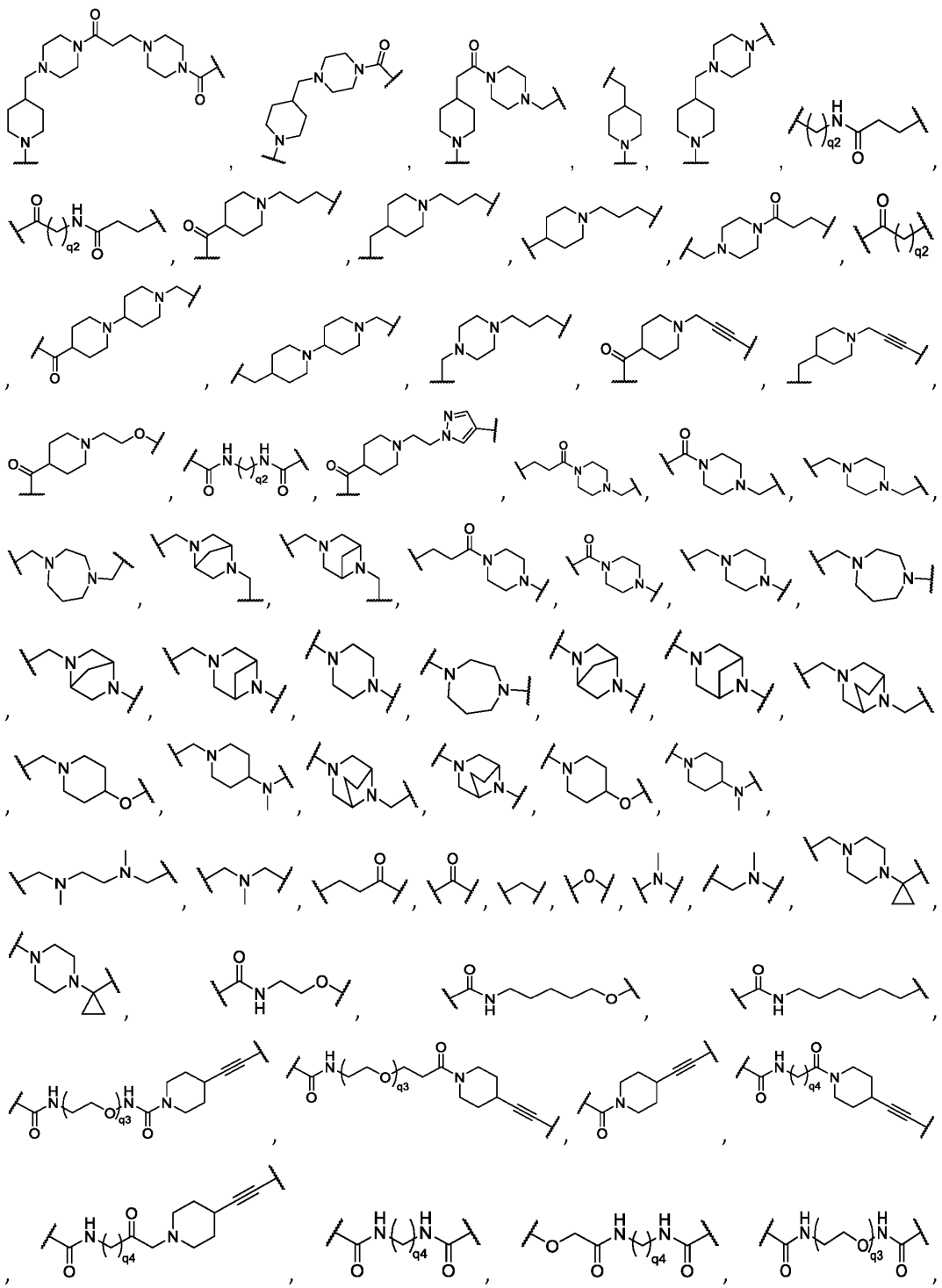
In any of the examples described herein, the linker is or comprises one or more of:

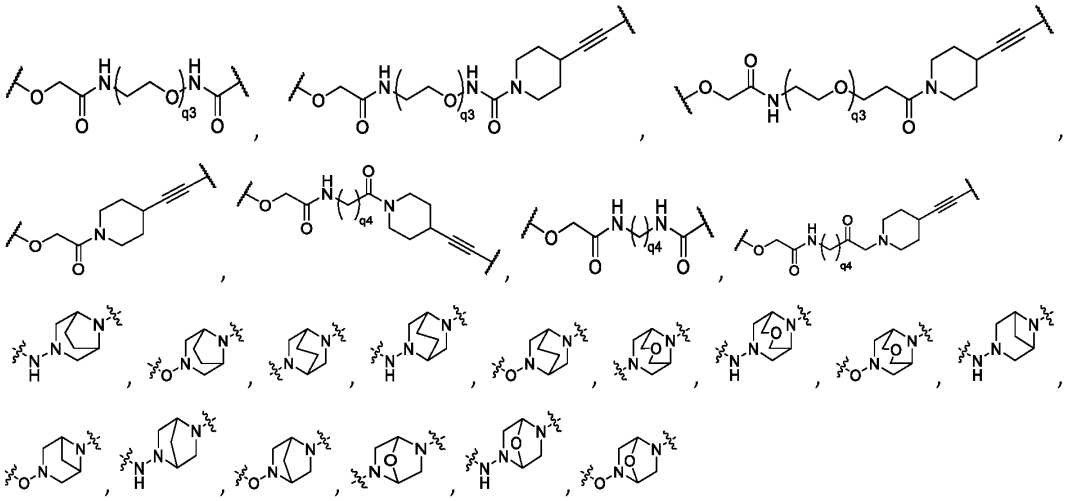












wherein:

q1 is any integer between 1 and 20, or between 1 and 10 (e.g. between 1 and 5);

q2 is any integer between 1 and 20, or between 1 and 10 (e.g. 3, 4, 5, 6 or 10);

q3 is 1 to 8, such as 1 to 5; and

q4 is 1 to 12, such as 1 to 10.

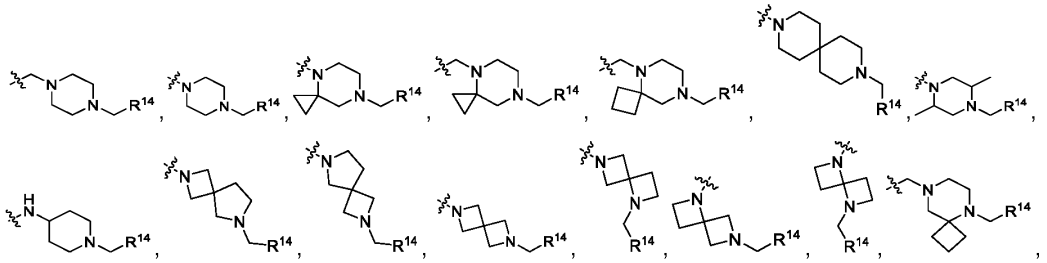
In some cases, the structures shown above represent the entirety of L. In other examples, L may comprise a plurality of the structures shown above.

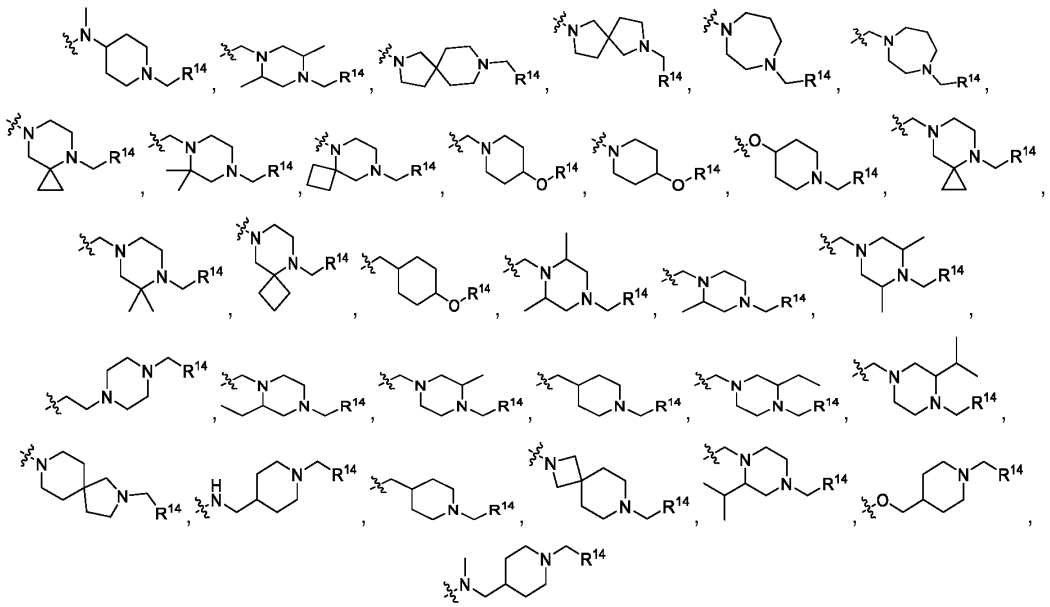
In these structures, the wavy lines are shown over the bond(s) that forms the link with R^{14} and the moiety of formula (I).

In some examples, the bond(s) that forms the link with R^{14} and/or the moiety of formula (I) is (are) attached to a ring structure. On many of the structures described herein, this bond is shown as being attached at a particular position on the ring structure. However, the disclosure also encompasses joining or coupling to the R^{14} and the moiety of formula (I) at any chemically suitable position on these ring structures.

The present disclosure encompasses the use of any of the linkers disclosed herein in combination with any of the Z moieties and TBL moieties described herein.

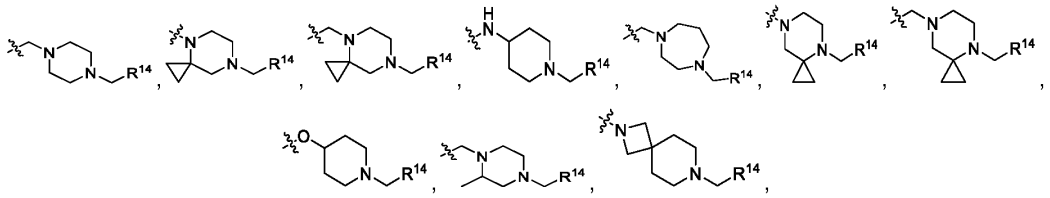
In some examples, the -L-R^{14} moiety comprises a structure selected from:





wherein the wavy line intersects the bond between L and the rest of the compound.

In some examples, the -L-R^{14} moiety comprises a structure selected from:



wherein the wavy line intersects the bond between L and the moiety of formula (I).

R^{14} is a ligand or moiety that binds to a protein (a "target protein"). A target protein may be any polypeptide or protein that the skilled practitioner wishes to selectively degrade in a cell or a mammal, e.g., a human or animal subject. In other words, a target protein may be a protein or polypeptide that is selected by the skilled practitioner for increased proteolysis in a cell. The term "selected target protein" may be any polypeptide or protein which has been selected to be targeted for protein degradation and/or increased proteolysis.

In some examples of the present disclosure, the term "target protein" does not include androgen receptor. As used herein, "androgen receptor" means a protein with the UniProtKB designation of P10275 (ANDR_HUMAN).

In some examples of the present disclosure, the term "target protein" does not include estrogen receptor. As used herein, "estrogen receptor" means a protein with the UniProtKB designation of P03372 (ESR1_HUMAN).

In other words, in some examples, the compounds of formula (III) of the present invention may not be intended for use or may not be suitable for use in the targeted degradation of a target protein selected from an: (i) estrogen receptor; and (ii) androgen receptor.

According to the disclosure, degradation of a target protein may occur when the target protein is subjected to and/or contacted with a compound of formula (III) as described herein, e.g. when the target protein is subjected to and/or contacted with any one of the compounds of formula (III) in a cell.

Selective degradation and/or increased proteolysis of the target protein will reduce levels of the target protein and so can reduce the effects of the target protein in the cell. The control of specific protein levels afforded by the compounds of formula (III) described herein may provide treatment of a disease state or condition, which is modulated through or by the target protein by lowering the level of that protein in the cells of a subject.

Target proteins that may be subject to increased proteolysis and/or selective degradation when contacted to the compounds of formula (III) of this disclosure (and the associated methods of using such compounds) include any proteins and polypeptides. Target proteins include proteins and polypeptides having a biological function or activity such as structural, regulatory, hormonal, enzymatic, genetic, immunological, contractile, storage, transportation, and signal transduction functions and activities.

By way of example, target proteins may include structural proteins, receptors, enzymes, cell surface proteins, proteins pertinent to the integrated function of a cell, including proteins involved in catalytic activity, epigenetic regulation, aromatase activity, motor activity, helicase activity, metabolic processes (anabolism and catabolism), antioxidant activity, proteolysis, biosynthesis, proteins with kinase activity, oxidoreductase activity, transferase activity, hydrolase activity, lyase activity, isomerase activity, ligase activity, enzyme regulator activity, signal transducer activity, structural molecule activity, binding activity (protein, lipid carbohydrate), receptor activity, cell motility, membrane fusion, cell communication, regulation of biological processes, development, cell differentiation, response to stimulus, behavioural proteins, cell adhesion proteins, proteins involved in cell death, proteins involved in transport (including protein transporter activity, nuclear transport, ion transporter activity, channel transporter activity, carrier activity, permease activity, secretion activity, electron transporter activity, pathogenesis, chaperone regulator activity, nucleic acid binding activity, transcription regulator activity, extracellular organization and biogenesis activity, and translation regulator activity.

Target proteins may include proteins from eukaryotes and prokaryotes, including humans, other animals, including domesticated animals, microbes, viruses, fungi and parasites, among numerous other targets for drug therapy.

In some examples, target proteins may include, but are not limited to: (i) kinases (such as serine/threonine kinases and receptor tyrosine kinases); (ii) bromodomain-containing proteins (such as BET family proteins); (iii) epigenetic proteins (including histone or DNA methyl transferases, acetyl transferases, deacetylases and demethylases); (iv) transcription factors (including STAT3 and myc); (v) GTPases (including KRAS (including KRAS G12D), NRAS, and HRAS); (vi) phosphatases; (vii) ubiquitin E3 ligases and deubiquitinase enzymes; (viii) nuclear hormone receptors (including, for example, thyroid hormone receptor, androgen receptor (AR) and estrogen receptor (ER), but as stated above, in some examples, the target protein does not include androgen receptor and estrogen receptor); (ix) aggregation-prone proteins (including Beta-amyloid, tau, Htt, alpha-synuclein and polyQ-expanded

proteins); (x) apoptotic & anti-apoptotic factors (including Bcl2, Bcl-xl and Mcl-1); and (xi) polymerases (including PARP & POLQ) among numerous others.

A target protein may also be selected from targets for human therapeutic drugs. These include proteins which may be used to restore function in numerous diseases, e.g. polygenic diseases, including for example, target proteins selected from B7.1 and B7, TNFR1, TNFR2, NADPH oxidase, Bcll/Bax and other partners in the apoptosis pathway, C5a receptor, HMG-CoA reductase, PDE V phosphodiesterase type, PDE IV phosphodiesterase type 4, PDE I, PDEII, PDEIII, squalene cyclase inhibitor, CXCR1, CXCR2, nitric oxide (NO) synthase, cyclo-oxygenase 1, cyclo-oxygenase 2, 5HT receptors, dopamine receptors, G Proteins, i.e., Gq, histamine receptors, 5-lipoxygenase, tryptase serine protease, thymidylate synthase, purine nucleoside phosphorylase, GAPDH trypanosomal, glycogen phosphorylase, Carbonic anhydrase, chemokine receptors, JAK STAT, RXR and similar, HIV 1 protease, HIV 1 integrase, influenza, neuraminidase, hepatitis B reverse transcriptase, sodium channel, multi drug resistance (MDR), protein P-glycoprotein (and MRP), serine/threonine kinases, tyrosine kinases, CD23,CD124, tyrosine kinase p56 lck, CD4, CD5, IL-2 receptor, IL-1 receptor, TNF-alphaR, ICAM1, Cat+ channels, VCAM, VLA-4 integrin, selectins, CD40/CD40L, neurokinins and receptors, inosine monophosphate dehydrogenase, p38 MAP Kinase, Ras/Raf/MEK/ERK pathway, interleukin-1 converting enzyme, caspase, HCV, NS3 protease, HCV NS3 RNA helicase, glycinamide ribonucleotide formyl transferase, rhinovirus 3C protease, herpes simplex virus-1 (HSV-I), protease, cytomegalovirus (CMV) protease, poly (ADP-ribose) polymerase, cyclin dependent kinases, vascular endothelial growth factor, oxytocin receptor, microsomal transfer protein inhibitor, bile acid transport inhibitor, 5 alpha reductase inhibitors, angiotensin 11, glycine receptor, noradrenaline reuptake receptor, endothelin receptors, neuropeptide Y and receptor, adenosine receptors, adenosine kinase and AMP deaminase, purinergic receptors (P2Y1, P2Y2, P2Y4,P2Y6, P2X1-7), farnesyltransferases, geranylgeranyl transferase, TrkA a receptor for NGF, beta-amyloid, tyrosine kinase Flk-IIKDR, vitronectin receptor, integrin receptor, Her-21 neu, telomerase inhibition, cytosolic phospholipaseA2 and EGF receptor tyrosine kinase. Additional protein targets include, for example, ecdysone 20-monooxygenase, ion channel of the GABA gated chloride channel, acetylcholinesterase, voltage-sensitive sodium channel protein, calcium release channel, and chloride channels. Still further target proteins include Acetyl-CoA carboxylase, adenylosuccinate synthetase, SMARCA2; SMARCA4 protoporphyrinogen oxidase, and enolpyruvylshikimate-phosphate synthase.

Target proteins may also be haloalkane dehalogenase enzymes. By way of example, compounds of formula (III) according to the disclosure which contain chloroalkane peptide binding moieties (C1-C12 often about C2-C10 alkyl halo groups) may be used to inhibit and/or degrade haloalkane dehalogenase enzymes which are used in fusion proteins or related diagnostic proteins as described in PCT/US2012/063401 filed December 6, 2011 and published as WO 2012/078559 on June 14, 2012, the contents of which is incorporated by reference herein.

R^{14} is a ligand or moiety which binds to a protein, i.e. a target protein, e.g. a selected target protein (i.e. R^{14} is a target protein binding ligand). By way of example, R^{14} may be any moiety, which selectively and/or specifically binds a target protein. R^{14} may be a ligand or moiety which binds to the

target protein with sufficient binding affinity such that the target protein is more susceptible to degradation or proteolysis than if unbound by the compound of formula (III).

R^{14} may bind to a target protein with a binding affinity of less than or equal to about 10 μM, less than or equal to about 1 μM, less than or equal to about 0.5 μM, or less than or equal to about 0.1 μM.

In some examples, the R^{14} may bind to the target protein with a binding affinity of about 0.01 nM to about 10 μM, such as about 0.01 nM to about 8 μM, about 0.01 nM to about 5 μM, about 0.01 nM to about 3 μM.

For the avoidance of doubt, binding affinity is a measure of the propensity of an object comprising two components bound together to separate (dissociate) into the two components. As used herein, the binding affinity is the measure of the propensity of the complex formed when the R^{14} binds to the target protein to dissociate into separate components, i.e. the propensity of R^{14} to dissociate from the target protein.

The binding between the target protein and R^{14} may comprise one or more binding interactions, such as one or more of the group consisting of hydrogen bonding, dipole-dipole bonding, ion-dipole bonding, ion-induced dipole bonding, ionic bonding and covalent bonding. For example, the binding between the target protein and R^{14} may comprise a salt bridge (a combination of hydrogen and ionic bonding).

As stated above, in some examples, R^{14} may not be a target protein binding ligand selected from: (i) an estrogen receptor binding ligand; and (ii) an androgen receptor binding ligand. In particular, in some examples, the R^{14} of the present disclosure is: (i) not a ligand that specifically binds to an estrogen receptor; and (ii) not a ligand that specifically binds to an androgen receptor.

In some examples, the R^{14} does not bind to an estrogen receptor with a binding affinity of less than or equal to about 10 μM, or less than or equal to about 1 μM.

In other words, in some examples, R^{14} does not bind to an estrogen receptor with sufficient binding affinity such that the estrogen receptor is selectively degraded. In particular, if the compounds of formula (III) as described herein were to be contacted with an estrogen receptor, the observed DC_{50} values (for degradation of the estrogen receptor) would be greater than about 10000 nM, or greater than about 1000 nM.

In some examples, R^{14} does not bind to an androgen receptor with a binding affinity of less than or equal to about 10 μM, or less than or equal to about 1 μM.

Additionally, in some examples, R^{14} does not bind to an androgen receptor with sufficient binding affinity such that the androgen receptor is selectively degraded. In particular, if the compound of formula (III) as described herein were to be contacted with an androgen receptor, the observed DC_{50} values (for degradation of the androgen receptor) would be greater than about 10000 nM, or greater than about 1000 nM.

R^{14} may comprise or be derived from a small molecule (or analogue or fragment thereof) already known to act as a modulator, promoter and/or inhibitor of protein function (e.g. any small molecule known to bind to the target protein). By way of example, the R^{14} may comprise or be derived from a small molecule that is known to inhibit activity of a given target protein.

Non-limiting examples of small molecules that can be comprised in R^{14} described herein include: (i) binders to kinases (including serine/threonine kinases e.g. RAF, receptor tyrosine kinases and other classes), (ii) compounds binding to bromodomain-containing proteins (including BET family and others), (iii) epigenetic modulator compounds (including binders to histone or DNA methyl transferases, acetyl transferases, deacetylases & demethylases and others e.g. histone deacetylase (HDAC), lysine acetyl transferases such as P300 (EP300; adenoviral E1A binding protein of 300 kDa) and CBP (CREBBP; cyclic-AMP response element binding protein)), (iv) binders to transcription factors including STAT3, myc and others, (v) binders to GTPases (including KRAS (including KRAS G12D), NRAS, HRAS and others), (vi) binders of phosphatases, (vii) binders of ubiquitin E3 ligases (e.g. MDM2) and deubiquitinase enzymes; (viii) binders of nuclear hormone receptors (including, for example, thyroid receptor, androgen receptor (AR) and estrogen receptor (ER), although in some examples, as stated above, the target binding ligands do not comprise binders to androgen receptor and estrogen receptor); (ix) binders to aggregation-prone proteins (including Beta-amyloid, tau, Htt, alpha-synuclein and polyQ-expanded proteins); (x) binders to apoptotic & anti-apoptotic factors (including Bcl2, Bcl-xl and Mcl-1), and (xi) binders to polymerases (including PARP & POLQ) among numerous others.

For example, R^{14} described herein may be selected from: (i) binders to kinases (including serine/threonine kinases e.g. RAF, receptor tyrosine kinases and other classes); (ii) compounds binding to bromodomain-containing proteins (including BET family and others); (iii) epigenetic modulator compounds (including binders to histone or DNA methyl transferases, acetyl transferases, deacetylases & demethylases and others e.g. histone deacetylase (HDAC), lysine acetyl transferases such as P300 (EP300; adenoviral E1A binding protein of 300 kDa) and CBP (CREBBP; cyclic-AMP response element binding protein)); (iv) binders to transcription factors including STAT3, myc and others; (v) binders of phosphatases; (vi) binders of ubiquitin E3 ligases (e.g. MDM2) and/or deubiquitinase enzymes; (vii) binders of nuclear hormone receptors (including, for example, thyroid receptor, androgen receptor (AR) and estrogen receptor (ER), although in some examples, as stated above, the target binding ligands do not comprise binders to androgen receptor and estrogen receptor); (viii) binders to aggregation-prone proteins (including Beta-amyloid, tau, Htt, alpha-synuclein and polyQ-expanded proteins); (ix) binders to apoptotic & anti-apoptotic factors (including Bcl2, Bcl-xl and Mcl-1), and (x) binders to polymerases (including PARP & POLQ).

Other non-limiting examples of small molecules that can be comprised in R^{14} include: (i) Hsp90 inhibitors, (ii) human lysine methyltransferase inhibitors, (iii) angiogenesis inhibitors, (iv) compounds targeting the aryl hydrocarbon receptor (AHR), (v) compounds targeting FKBP, (vi) compounds targeting HIV protease, (vii) compounds targeting HIV integrase, (viii) compounds targeting HCV protease, (ix) compounds targeting acyl-protein thioesterase-1 and -2 (APT1 and APT2) among numerous others.

In an embodiment, R^{14} refers to a ligand or moiety, which binds BRD9, SMARCA2, SMARCA4, and/or KRAS (including KRAS G12D) e.g. specifically binds BRD9, SMARCA2, SMARCA4, or KRAS (including KRAS G12D), i.e. R^{14} is a BRD9, SMARCA2, SMARCA4, and/or KRAS (including KRAS G12D) binder. R^{14} of a compound of formula (III) according to this embodiment may bind to the BRD9, SMARCA2, SMARCA4, and/or KRAS (including KRAS G12D) target protein with sufficient binding

affinity such that the BRD9, SMARCA2, SMARCA4, and/or KRAS (including KRAS G12D) target protein is more susceptible to degradation or proteolysis than if unbound by the compound of formula (III).

In an embodiment, R^{14} refers to a ligand or moiety, which binds SMARCA2 e.g. specifically binds SMARCA2, i.e. R^{14} is a SMARCA2 binder. R^{14} of a compound of formula (III) according to this embodiment may bind to the SMARCA2 target protein with sufficient binding affinity such that the SMARCA2 target protein is more susceptible to degradation or proteolysis than if unbound by the compound of formula (III).

In an embodiment, R^{14} refers to a ligand or moiety, which binds SMARCA4 e.g. specifically binds SMARCA4, i.e. R^{14} is a SMARCA4 binder. R^{14} of a compound of formula (III) according to this embodiment may bind to the SMARCA4 target protein with sufficient binding affinity such that the SMARCA4 target protein is more susceptible to degradation or proteolysis than if unbound by the compound of formula (III).

In an embodiment, R^{14} refers to a ligand or moiety, which binds SMARCA2 and SMARCA4 i.e. R^{14} is a SMARCA2 and SMARCA4 binder. R^{14} of a compound of formula (III) according to this embodiment may bind to the SMARCA2 and SMARCA4 target proteins with sufficient binding affinity such that the SMARCA2 and SMARCA4 target proteins are more susceptible to degradation or proteolysis than if unbound by the compound of formula (III).

In an embodiment, R^{14} refers to a ligand or moiety, which binds KRAS (including KRAS G12D) e.g. specifically binds KRAS (including KRAS G12D), i.e. R^{14} is a KRAS (including KRAS G12D) binder. R^{14} of a compound of formula (III) according to this embodiment may bind to the KRAS (including KRAS G12D) target protein with sufficient binding affinity such that the KRAS (including KRAS G12D) target protein is more susceptible to degradation or proteolysis than if unbound by the compound of formula (III).

In an embodiment, R^{14} refers to a ligand or moiety, which binds BRD9, e.g. specifically binds BRD9, i.e. R^{14} is a BRD9 binder. R^{14} of a compound of formula (III) according to this embodiment may bind to the BRD9 target protein with sufficient binding affinity such that the BRD9 target protein is more susceptible to degradation or proteolysis than if unbound by the compound of formula (III).

R^{14} may comprise or be derived from a small molecule (or analogue or fragment thereof) already known to act as a modulator, promoter and/or inhibitor of BRD9 protein function. By way of example, R^{14} may comprise or be derived from a small molecule that is known to inhibit activity of BRD9 target protein.

By way of example, R^{14} of the compounds of formula (III) of this embodiment may bind to BRD9 with sufficient binding affinity such that BRD9 is selectively degraded. In particular, if the compounds of formula (III) of this embodiment were to be contacted with BRD9, the observed DC_{50} values (for degradation of BRD9) may be less than or equal to about 15 μM, less than or equal to about 10 μM, less than or equal to 1000 nM, less than or equal to 500 nM, less than or equal to 100 nM, or less than or equal to 25 nM, less than or equal to 10 nM, less than or equal to 5 nM, less than or equal to 1.25 nM, less than or equal to 1 nM, or less than or equal to 0.5 nM.

By way of further example, R^{14} of the compounds of formula (III) of this embodiment may may bind to BRD9 with a dissociation constant of less than or equal to about 10 μM, less than or equal to about 5 μM, or less than or equal to about 3 μM. In some examples, R^{14} of the compounds of formula (III) of this embodiment may bind to BRD9 with a dissociation constant of less than or equal to 1000 nM, less than or equal to 500 nM, less than or equal to 100 nM, less than or equal to 50 nM, or less than or equal to 20 nM. In some examples, the R^{14} of the compounds of formula (III) of this embodiment may bind to BRD9 with a dissociation constant of about 0.001 nM to about 10 μM, such as about 0.001 nM to about 8 μM, about 0.001 nM to about 5 μM, about 0.001 nM to about 3 μM or about 0.001 nM to about 2.7 μM. In some examples, the R^{14} of the compounds of formula (III) of this embodiment may bind to BRD9 with a dissociation constant of about 0.01 nM to about 10 μM, such as about 0.01 nM to about 8 μM, about 0.01 nM to about 5 μM, about 0.01 nM to about 3 μM or about 0.01 nM to about 2.7 μM.

In some examples, R^{14} of the compounds of formula (III) of this embodiment may bind to BRD9 with a dissociation constant of about 0.1 nM to about 10 μM, such as about 0.1 nM to about 8 μM, about 0.1 nM to about 5 μM, about 0.1 nM to about 3 μM or about 0.1 nM to about 2.7 μM. In some examples, R^{14} of the compounds of formula (III) of this embodiment may bind to BRD9 with a dissociation constant of about 1 nM to about 10 μM, such as about 1 nM to about 8 μM, about 1 nM to about 5 μM, about 1 nM to about 3 μM or about 1 nM to about 2.7 μM.

For the avoidance of doubt, the dissociation constant is a measure of the propensity of an object comprising two components bound together to separate (dissociate) into the two components. As used herein, the dissociation constant is the measure of the propensity of the complex formed when R^{14} binds to the target protein to dissociate into separate components, i.e. the propensity of R^{14} to dissociate from the target protein.

The binding between the BRD9 protein and R^{14} may comprise one or more binding interactions, such as one or more of the group consisting of hydrogen bonding, dipole-dipole bonding, ion-dipole bonding, ion-induced dipole bonding, ionic bonding and covalent bonding. For example, the binding between the BRD9 protein and R^{14} may comprise a salt bridge (a combination of hydrogen and ionic bonding).

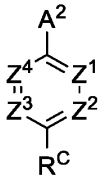
In some examples, the compounds of formula (III) of this embodiment may be selective degraders of BRD9 proteins, for example the compounds of formula (III) may selectively degrade BRD9 over other proteins, such as other BRD proteins (e.g. BRD7 or BRD4). In more specific examples, the compounds of formula (III) of this embodiment may be selective degraders of certain types of BRD9 protein. By way of example, the compounds of formula (III) of this embodiment may have a greater binding affinity for certain BRD9 mutants than for other types of protein, such as other types of BRD9 protein (e.g. wild type BRD9).

Representative examples of BRD9 targeting agents have been developed over the years, including those described in: WO 2014/114721, WO 2016/077375, WO 2016/077378, WO 2016/139361, WO 2019/152440, a paper by Martin L. J. et. Al., (Journal of Medicinal Chemistry 2016, 59, 4462-4475) titled “Structure-Based Design of an in Vivo Active Selective BRD9 Inhibitor”; a paper by Theodoulou N. H. et. Al., (Journal of Medicinal Chemistry 2015, 59, 1425-1439) titled “Discovery of

I-BRD9, a selective Cell Active Chemical Probe for Bromodomain Containing Protein 9 Inhibition"; and a paper by Clack P. et. Al., (Angewandte Chemie, 2015, 127, 6315-6319).

Such BRD9 binding molecules (as referenced in the paragraph above) can be incorporated into the compound (III) of this embodiment as R^{14}.

In some examples, R^{14} is of formula 1a:



1a,

wherein:

Z^1 is N or CR^A;

Z^2 is N or CR^B;

Z^3 is N or CR^D;

Z^4 is N or CR^E;

wherein no more than 3 of Z^1, Z^2, Z^3 and Z^4 are N;

R^A and R^E are each independently selected from the group consisting of -H, -O-C_{1-3}alkyl and –C_{1-3}alkyl;

R^B and R^D are each independently selected from the group consisting of -O-C_{1-3}alkyl, -H, -OH, halogen, -NH_2, -C_{1-3}alkyl, -O-C_{1-3}haloalkyl, -C_{1-3}alkyl-O-C_{1-3}alkyl, 4-7 membered heterocycloalkyl, -C_{1-3}alkyl-SO_2-C_{1-3}alkyl, -C_{1-3}alkyl-NH_2, -C_{1-3}alkyl-N(-C_{1-3}alkyl)$_2$, -N(C_{1-3}alkyl)$_2$, -NH-R^F, for example wherein the heterocycloalkyl comprises one or more heteroatoms selected from the group consisting of N, S and O;

R^F is selected from -SO_2-C_{1-3}alkyl and –C_{1-3}alkyl, wherein the –C_{1-3}alkyl is optionally substituted with a 5 to 6 membered heteroaryl;

alternatively, R^A and R^B taken together form a benzene ring;

alternatively, R^C and Z^2 or R^C and Z^3 taken together (e.g. R^C and R^B or R^C and R^D taken together with the carbon atoms to which they are joined) form a 5-7 membered heterocycloalkyl optionally substituted with –C_{1-3}alkyl, for example wherein the heterocycloalkyl comprises one or more heteroatoms selected from the group consisting of N, S and O;

R^C is selected from the group consisting of -H, -Y-R^G, -NH_2, -C_{1-3}alkyl and 4-7 membered heterocycloalkyl, for example wherein the heterocycloalkyl comprises one or more heteroatoms selected from the group consisting of N, S and O;

Y is absent or is selected from the group consisting of -CR^HR^I-, -SO_2- and -CO-;

R^H and R^I are each independently selected from -H or –C_{1-3}alkyl; or R^H and R^I taken together form a –C_{3-4}cycloalkyl,

R^G is selected from the group consisting of -NH_2, -OH, -C_{1-3}alkyl, -N(R^JR^K), -O-R^L, aryl, 5-6 membered heteroaryl, wherein the aryl and heteroaryl are optionally and independently substituted with one or more halogen, optionally substituted 4- to 7- membered monocyclic heterocycloalkyl, and

optionally substituted 7- to 12-membered bicyclic heterocycloalkyl, which monocylic or bicyclic heterocycloalkyl are optionally substituted with any suitable substituent, such as one or more groups independently selected from halogen, -OH, -NH_2, -C_{1-3}alkyl, -NHC_{1-3}alkyl, -$N(C_{1-3}alkyl)_2$, -O-C_{1-3}alkyl and -CH_2-R^{M1};

R^{M1} is selected from 5-10 membered mono- or bicyclic aryl or heteroaryl, which is optionally substituted with -NH_2, -OH, halogen, -CN, C_{1-3}alkyl, -O-C_{1-3}alkyl;

R^J is -H or –C_{1-3}alkyl;

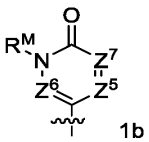
R^K is selected from the group consisting of –C_{1-3}alkyl, -C_{2-3}alkyl-$N(C_{1-3}alkyl)_2$, -C_{2-3}alkyl-NHC_{1-3}alkyl, optionally substituted 4- to 7- membered monocyclic heterocycloalkyl, and optionally substituted 7- to 12-membered bicyclic heterocycloalkyl, which monocyclic or bicyclic heterocycloalkyl are optionally substituted with any suitable substituent, such as –C_{1-3}alkyl (e.g. wherein R^K is selected from the group consisting of C_{1-3} alkyl, C_{2-3}alkyl-$N(C_{1-3}alkyl)_2$, C_{2-3}alkyl-NHC_{1-3}alkyl, 4- to 7- membered monocyclic heterocycloalkyl, and 7- to 12-membered bicyclic heterocycloalkyl, wherein each monocyclic or bicyclic heterocycloalkyl comprises one or more heteroatoms selected from the group consisting of N, S and O, and is optionally substituted with C_{1-3}alkyl);

R^L is –C_{1-3}alkyl or a 4-7 membered heterocycloalkyl, which heterocycloalkyl is optionally substituted with C_{1-3}alkyl;

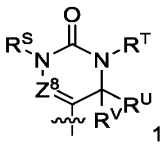
wherein when R^C is Y-R^G, R^B and R^D are each independently selected from -H, -OH, halogen, -NH_2, -CN, -C_{1-3}alkyl, -C_{1-3}haloalkyl, -O-C_{1-3}alkyl, -O-C_{1-3}haloalkyl and –C_{1-3}alkyl-O-C_{1-3}alkyl; wherein at least one of the substituents R^A to R^E is not hydrogen;

and

A^2 is selected from formulae 1b or 1c:



1b



1c ,

wherein the wavy lines intersect the bond between A^2 and the carbon atom positioned *ortho to* R^A and R^E;

R^M is selected from the group consisting of optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl, optionally substituted C_{1-6}heteroalkyl, optionally substituted C_{3-10}cycloalkyl, C_{2-6}alkynyl and H, for example wherein the heteroalkyl comprises one or more heteroatoms selected from the group consisting of N, S and O, and wherein the alkyl, alkenyl, heteroalkyl and cycloalkyl are each optionally substituted with C_1-C_3 alkyl;

Z^5 is N or CR^O;

Z^6 is N or CR^P;

Z^7 is N or CR^N;

wherein only one of Z^5, Z^6 and Z^7 is N;

Z^8 is CR^W or N;

R^N is selected from the group consisting of halogen, optionally substituted -C_{1-6}alkyl, -H, C(O)C_{1-5}alkyl, -NH_2, optionally substituted amino, –OH, cyano, optionally substituted C_{1-6}heteroalkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted C_{2-9}heterocycloalkyl, optionally substituted C_{6-10}aryl, optionally substituted C_{2-9}heteroaryl, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-6}heteroalkenyl and thiol (e.g. halogen, -C_{1-6}alkyl, -H, C(O)C_{1-5}alkyl, -NH_2, -OH, cyano, C_{1-6}heteroalkyl, C_{3-10} cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{2-9}heteroaryl, C_{2-6}alkenyl, C_{2-6}heteroalkenyl and thiol, wherein each heteroalkyl and heteroalkenyl comprises one or more heteroatoms selected from the group consisting of N, S and O, each heterocycloalkyl and heteroaryl comprises one or more heteroatoms selected from the group consisting of N, S and O, and the alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkenyl and heteroalkenyl are each optionally substituted with C_1-C_3 alkyl);

R^O is selected from the group consisting of H, halogen, cyano, optionally substituted C_{1-6}alkyl, optionally substituted C_{1-6}heteroalkyl, optionally substituted C_{3-10}cycloalkyl, optionally substituted C_{2-9}heterocycloalkyl, optionally substituted C_{6-10}aryl, optionally substituted C_{2-9}heteroaryl, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-6}heteroalkenyl, hydroxy, thiol and optionally substituted amino (e.g. H, halogen, cyano, C_{1-6}alkyl, C_{1-6}heteroalkyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{2-9}heteroaryl, C_{2-6}alkenyl, C_{2-6}heteroalkenyl, hydroxy, and thiol, wherein each heteroalkyl and heteroalkenyl comprises one or more heteroatoms selected from the group consisting of N, S and O, each heterocycloalkyl and heteroaryl comprises one or more heteroatoms selected from the group consisting of N, S and O, and the alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkenyl and heteroalkenyl are each optionally substituted with C_1-C_3 alkyl);

R^P is selected from the group consisting of H, halogen, optionally substituted C_{1-6}alkyl, optionally substituted C_{1-6}heteroalkyl, optionally substituted C_{3-10}cycloalkyl and optionally substituted C_{6-10}aryl (wherein R^P is selected from the group consisting of H, halogen, C_{1-6} alkyl, C_{1-6} heteroalkyl comprising one or more heteroatoms selected from the group consisting of N, S and O, C_{3-10} cycloalkyl and C_{6-10} aryl, wherein the alkyl, heteroalkyl, cycloalkyl, and aryl are each optionally substituted with C_1-C_3 alkyl);

alternatively, R^N and Z^5 taken together, combine to form an optionally substituted C_{6-10}arene or optionally substituted C_{2-9}heteroarene; optionally wherein R^N and R^O taken together with the carbon atoms to which they are joined, combine to form an optionally substituted C_{6-10}arene or optionally substituted C_{2-9}heteroarene (e.g. wherein R^N and Z^5 taken together combine to form a C_{6-10}arene or C_{2-9}heteroarene, wherein the heteroarene comprises one or more heteroatoms selected from the group consisting of N, S and O, and the arene or heteroarene are each optionally substituted with C_1-C_3 alkyl; optionally wherein R^N and R^O taken together with the carbon atoms to which they are joined, combine to form a C_{6-10}arene or C_{2-9}heteroarene, wherein the heteroarene comprises one or more heteroatoms selected from the group consisting of N, S and O, and the arene or heteroarene are each optionally substituted with C_1-C_3 alkyl);

R^S is selected from the group consisting of H, optionally substituted C_{1-6}alkyl, optionally substituted C_{1-6}heteroalkyl and optionally substituted C_{3-10}cycloalkyl;

R^T is selected from the group consisting of H, optionally substituted C_{1-6}alkyl, optionally substituted C_{1-6}heteroalkyl, optionally substituted C_{3-10}cycloalkyl, optionally substituted C_{2-9}heterocycloalkyl, optionally substituted C_{6-10}aryl, optionally substituted C_{2-9}heteroaryl, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-6}heteroalkenyl, optionally substituted sulfone and optionally substituted sulfonamide, or R^T and R^U together with the atoms to which each is attached, form an optionally substituted C_{2-9}heterocycloalkyl;

R^U and R^V are each independently selected from the group consisting of H, halogen, hydroxyl, optionally substituted C_{1-6}alkyl, optionally substituted C_{1-6}heteroalkyl, optionally substituted C_{3-10}cycloalkyl, optionally substituted C_{2-9}heterocycloalkyl, optionally substituted C_{6-10}aryl, optionally substituted C_{2-9}heteroaryl, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-6}heteroalkenyl, thiol, optionally substituted sulfone and optionally substituted amino;

alternatively, R^T and R^U together with the atoms to which each is attached, form an optionally substituted C_{2-9}heterocycloalkyl;

R^W is selected from the group consisting of H, halogen, optionally substituted C_{1-6}alkyl, optionally substituted C_{1-6}heteroalkyl, optionally substituted C_{3-10}cycloalkyl, optionally substituted C_{2-9}heterocycloalkyl, optionally substituted C_{6-10}aryl and optionally substituted C_{2-9}heteroaryl;

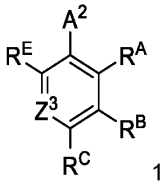
and

wherein R^{14} is attached to the linker at any suitable position.

In some examples of formula 1a above, the R^C group may be H and the linker may be attached at this position. In other words, the linker (L) may replace the R^C group. Such examples may be designated as formula 1a''.

In some embodiments, no more than 1 of Z^1, Z^2, Z^3 and Z^4 of formula 1a is N. Sometimes, Z^1 is CR^A, Z^2 is CR^B, Z^3 is N or CR^D and Z^4 is CR^E, i.e. only Z^3 may be N.

In embodiments, R^{14} may be of formula 1a':

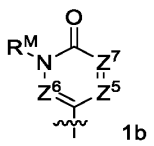


1a',

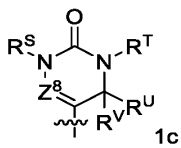
wherein:

R^A, R^B, R^C, R^E, Z^3 and A^2 are as defined above and herein.

A^2 is selected from formulae 1b or 1c:



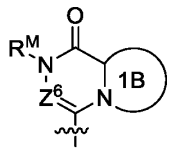
1b



1c,

wherein the wavy lines intersect the bond between A^2 and the carbon atom positioned *ortho to* R^A and R^E, and Z^5, Z^6, Z^7, Z^8, R^M, R^S, R^T, R^U and R^V are as defined above and herein.

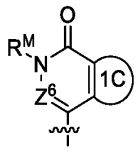
Z^7 is N or CR^N and Z^5 is N or CR^O. In some examples, R^N (with the carbon to which it is bonded) and Z^5 taken together, may combine to form an optionally substituted C_{6-10}arene or optionally substituted C_{2-9}heteroarene. For the avoidance of doubt, where Z^5 is N and R^N (with the carbon to which it is bonded) and Z^5 taken together combine to form an optionally substituted C_{6-10}arene or optionally substituted C_{2-9}heteroarene, R^N (with the carbon to which it is bonded) and Z^5 taken together combine to form an optionally substituted N-C_{2-4}heteroarene. For example, where Z^5 is N, R^N and N may combine to form an optionally substituted N-C_{2-4}heteroaryl, as shown below:



,

wherein the wavy lines intersect the bond between A^2 and the carbon atom positioned *ortho to* R^A and R^E, Z^6 and R^M are as defined above, and where 1B is an optionally substituted N-C_{2-4}heteroarene, such as an optionally substituted 5 membered heteroarene e.g. any one selected from the optionally substituted group consisting of pyrrole, imidazole, pyrazole and triazole (including 1,2,3 and 1,2,4-triazoles).

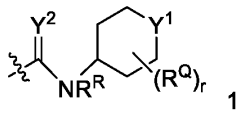
In some examples, where Z^5 is CR^O and Z^7 is CR^N, R^N and R^O taken together with the carbons to which they are bonded, may combine to form an optionally substituted C_{6-10}arene or optionally substituted C_{2-9}heteroarene, as shown below:



,

wherein the wavy lines intersect the bond between A^2 and the carbon atom positioned *ortho to* R^A and R^E, Z^6 and R^M are as defined above, and where, as stated above, ring 1C is an optionally substituted C_{6-10}arene or optionally substituted C_{2-9}heteroarene. For example, ring 1C may be an optionally substituted benzene or 5-6 membered heteroarene, such as any one selected from the optionally substituted group consisting of benzene, pyridine, pyrrole, imidazole, pyrimidine, thiophene and pyrazole.

In some embodiments, R^N (taken with the carbon atoms to which it is joined) and Z^5 taken together may form a benzene ring or a 5-6 membered heteroarene ring (e.g. ring 1C may be a benzene ring or a 5-6 membered heteroarene), each of which rings can be optionally and independently substituted with one or more groups selected from halogen, -OH, -NH_2, -NH-C_{1-3}alkyl and –C_{1-5}alkyl, C_{1-5}haloalkyl, C_{1-5}alkoxy, C_{1-4}haloalkoxy, 1d, C_{3-5}azacycloalkyl, C_{2-5}alkenyl, C_{2-5}alkynyl, C_{3-5}cycloalkyl, wherein the –C_{1-5}alkyl group can be optionally substituted with 5-6 membered heteroaryl or phenyl; wherein 1d is:



1d ,

wherein

Y^2 is NR^R or O;

Y^1 is $S(O)_a$ or NR^R;

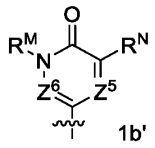
each R^R is independently H or C_{1-4}alkyl;

each R^Q is independently selected from the group consisting of C_{1-4}alkyl, C_{1-4}haloalkyl, halogen and $–C(O)C_{1-3}$alkyl;

a is 0 to 2; and

r is 0 to 3.

In some embodiments, Z^7 is CR^N, i.e. A^2 is selected from formula 1b':



1b' ,

wherein the wavy line intersects the bond between A^2 and the carbon atom positioned *ortho* to R^A and R^E, and Z^5, Z^6, R^M and R^N are as defined above and herein.

As stated previously, R^M may be selected from the group consisting of optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl, optionally substituted C_{1-6}heteroalkyl, optionally substituted C_{3-10}cycloalkyl, C_{2-6}alkynyl and H. In some embodiments, R^M may be selected from the group consisting of optionally substituted C_{1-6}alkyl, optionally substituted C_{3-6}cycloalkyl and H. For example, R^M may be selected from the group consisting of C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6}haloalkyl and H. In some embodiments, R^M is selected from the group consisting of $–C_{1-5}$alkyl, -cyclopropyl, $-C_{1-4}$haloalkyl and H, such as C_{1-5}alkyl. In some embodiments, R^M is C_{1-3}alkyl.

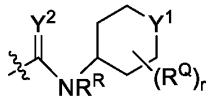
As stated previously, R^N may be selected from the group consisting of halogen, optionally substituted $-C_{1-6}$alkyl, -H, $C(O)C_{1-5}$alkyl, $-NH_2$, optionally substituted amino, –OH, cyano, optionally substituted C_{1-6}heteroalkyl, optionally substituted C_{3-10} cycloalkyl, optionally substituted C_{2-9}heterocycloalkyl, optionally substituted C_{6-10}aryl, optionally substituted C_{2-9}heteroaryl, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-6}heteroalkenyl and thiol. In some embodiments, R^N may be selected from the group consisting of halogen, optionally substituted C_{1-6}alkyl, H, $C(O)C_{1-5}$alkyl, $-NH_2$, $-NHC_{1-3}$alkyl and –OH. In some embodiments, R^N is selected from the group consisting of halogen, $-C_{1-5}$alkyl, $-C_{1-3}$haloalkyl, -H, $C(O)C_{1-5}$alkyl, $-NH_2$, $-NHC_{1-3}$alkyl and –OH. For example, R^N may be C_{1-5}alkyl or halogen.

As described above, Z^5 is N or CR^O, where R^O is selected from the group consisting of H, halogen, cyano, optionally substituted C_{1-6}alkyl, optionally substituted C_{1-6}heteroalkyl, optionally substituted C_{3-10}cycloalkyl, optionally substituted $C_{2–9}$heterocycloalkyl, optionally substituted C_{6-10}aryl, optionally substituted C_{2-9}heteroaryl, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-}

$_{6}$heteroalkenyl, hydroxy, thiol and optionally substituted amino. For example, R^O may be H or optionally substituted C_{1-6}alkyl, such as C_{1-3}alkyl. In some embodiments, R^O may be H or –C_{1-3}alkyl.

In some embodiments, R^N is -C_{1-5}alkyl or halogen, or R^N and Z^5 taken together form an optionally substituted 5-6 membered heteroarene or benzene ring. In some embodiments, the optionally substituted 5-6 membered heteroarene ring may comprise one or more heteroatoms selected from the group consisting of N, S and O, such as N and S, i.e. the optionally substituted 5-6 membered heteroarene ring may be an N- or S-heteroarene. In some embodiments, the optionally substituted 5-6 membered heteroarene ring is any one selected from the optionally substituted group consisting of pyridine, pyrrole, imidazole, pyrimidine, thiophene and pyrazole.

For the avoidance of doubt, the optional substituents may be one or more groups selected from halogen, -OH, -NH_2, -NH-C_{1-3}alkyl and –C_{1-5}alkyl, C_{1-5}haloalkyl, C_{1-5}alkoxy, C_{1-4}haloalkoxy, 1d, C_{3-5}azacycloalkyl, C_{2-5}alkenyl, C_{2-5}alkynyl, C_{3-5}cycloalkyl, wherein the –C_{1-5}alkyl group can be optionally substituted with 5-6 membered heteroaryl or phenyl; wherein 1d is:



1d ,

wherein

Y^2 is NR^R or O;

Y^1 is $S(O)_a$ or NR^R;

each R^R is independently H or C_{1-4}alkyl;

each R^Q is independently selected from the group consisting of C_{1-4}alkyl, C_{1-4}haloalkyl, halogen and –$C(O)C_{1-3}$alkyl;

a is 0 to 2; and

r is 0 to 3.

For example, the optional substituents may be independently selected from the group consisting of halogen, -OH, -NH_2, -NH-C_{1-3}alkyl –C_{1-5}alkyl, C_{1-5}haloalkyl, C_{1-5}alkoxy and C_{1-4}haloalkoxy. In some cases, the optional substituents may be independently selected from C_1-C_4alkyl, allyl, crotyl, C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-5}haloalkyl, C_{3-5}cycloalkyl, C_1-C_4alkoxy, and halo. In some embodiments, where R^N and Z^5 taken together combine to form an optionally substituted C_{6-10}aryl or optionally substituted C_{2-9}heteroaryl, the C_{6-10}aryl or C_{2-9}heteroaryl is not substituted.

As described above, Z^6 is N or CR^P, where R^P is selected from the group consisting of H, halogen, optionally substituted C_{1-6}alkyl, optionally substituted C_{1-6}heteroalkyl, optionally substituted C_{3-10}cycloalkyl and optionally substituted C_{6-10}aryl. For example, R^P may be H or optionally substituted C_{1-6}alkyl, such as H or C_{1-6}alkyl. In some embodiments, R^P is H or –C_{1-3}alkyl, i.e. Z^6 is N, CH or C–C_{1-3}alkyl. For example, Z^6 may be CH or C–C_{1-3}alkyl.

In some particular embodiments, A^2 is selected from formula 1b', wherein formula 1b' is:



1b',

wherein the wavy line intersects the bond between A^2 and the carbon atom positioned *ortho to* R^A and R^E;

R^M is selected from the group consisting of $-C_{1-5}$alkyl, -cyclopropyl, $-C_{1-4}$haloalkyl and H;

R^N is selected from the group consisting of halogen, $-C_{1-5}$alkyl, $-C_{1-3}$haloalkyl, -H, $C(O)C_{1-5}$alkyl, $-NH_2$, $-NHC_{1-3}$alkyl and –OH;

Z^5 is N or CR^O

Z^6 is N or CR^P wherein only one of Z^5 and Z^6 may be N;

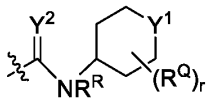
R^O is H or $-C_{1-3}$alkyl;

R^P is H or $-C_{1-3}$alkyl;

wherein only one of R^O and R^P may be $-C_{1-3}$alkyl;

alternatively, R^N and Z^5 taken together form a benzene ring or a 5-6 membered heteroarene ring, each of which rings can be optionally and independently substituted with one or more groups selected from halogen, -OH, $-NH_2$, -NH-C_{1-3}alkyl and $-C_{1-5}$alkyl, C_{1-5}haloalkyl, C_{1-5}alkoxy, C_{1-4}haloalkoxy, 1d, C_{3-5}azacycloalkyl, C_{2-5}alkenyl, C_{2-5}alkynyl, C_{3-5}cycloalkyl, wherein the $-C_{1-5}$alkyl group can be optionally substituted with 5-6 membered heteroaryl or phenyl;

wherein 1d is:



1d,

wherein

Y^2 is NR^R or O;

Y^1 is $S(O)_a$ or NR^R;

each R^R is independently H or C_{1-4}alkyl;

each R^Q is independently selected from the group consisting of C_{1-4}alkyl, C_{1-4}haloalkyl, halogen and $-C(O)C_{1-3}$alkyl;

a is 0 to 2; and

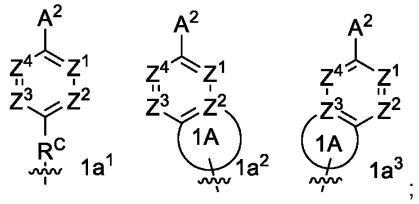
r is 0 to 3.

As described above, R^{14} is attached to the linker at any suitable position (provided it has the correct valency and/or is chemically suitable). For example, the linker may be attached to R^{14} by way of a covalent bond between an atom on the linker and an atom forming part of R^C, R^A, R^B, R^D or R^E. Alternatively, the linker may be attached directly to the ring to which R^C, R^A, R^B, R^D and/or R^E are bound, i.e. the linker may replace R^C, R^A, R^B, R^D or R^E. In some embodiments, the linker is attached to R^{14} by way of a covalent bond between an atom on the linker and an atom forming part of R^C or by way of a

covalent bond between an atom on the linker and the atom to which R^C would otherwise be bound, i.e. the linker replaces R^C.

Alternatively, where R^C and Z^2 or R^C and Z^3 taken together (e.g. R^C and R^B or R^C and R^D taken together with the carbon atoms to which they are joined) form a 5-7 membered heterocycloalkyl optionally substituted with $–C_{1-3}$alkyl, the linker may be attached to R^{14} by way of a covalent bond between an atom on the linker and an atom forming part of the 5-7 membered heterocycloalkyl.

In some embodiments, R^{14} is of formula $1a^1$, $1a^2$, $1a^3$:



;

wherein the wavy line intersects the bond between R^{14} and the linker;

A^2, Z^1, Z^2, Z^3 and Z^4 are as defined above and herein;

R^C is absent or is as defined above and herein;

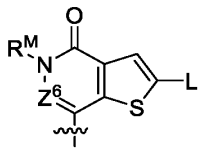
and ring 1A is a 5-7 membered heterocycloalkane optionally substituted with $–C_{1-3}$alkyl.

Ring 1A may comprise one or two heteroatoms independently selected from the list consisting of N, S and O. For example, ring 1A may be selected from the list consisting of pyrrolidine, piperidine, piperazine, morpholine, oxolane, oxane, tetrahydrothiophene and thiane. In some cases, ring 1A may be an N-heterocycloalkane such as pyrrolidine, piperidine or piperazine. In particular examples, ring 1A is pyrrolidine.

For the avoidance of doubt, where the linker is attached to R^{14} by way of a covalent bond between an atom on the linker and an atom forming part of a feature on R^{14} (such as R^C), the linker replaces a chemical group or an atom of the feature with a valency of 1 (such as a hydrogen atom) in order for valencies to be satisfied. For example, where the feature on R^{14} binder is dimethylamido (-$C(O)N(CH_3)_2$) or dimethylaminomethylene (-$CH_2N(CH_3)_2$), the linker may replace a methyl group or a hydrogen atom on the feature.

As another alternative, the linker may be attached to R^{144} by way of a covalent bond between an atom on the linker and an atom forming part of A^2, for example an atom forming part of R^M, R^N, R^O, R^P, R^S, R^T, R^U, R^V, or R^W or the linker may replace R^M, R^N, R^O, R^P, R^S, R^T, R^U, R^V, or R^W. Alternatively, where R^N and Z^5 taken together combine to form an optionally substituted C_{6-10}arene or optionally substituted $C_{2–9}$heteroarene; optionally wherein R^N and R^O taken together with the carbon atoms to which they are joined, combine to form an optionally substituted C_{6-10}arene or optionally substituted $C_{2–9}$heteroarene, the linker may be attached to R^{14} by way of a covalent bond between an atom on the linker and an atom forming part of the optionally substituted C_{6-10}arene or optionally substituted $C_{2–9}$heteroarene.

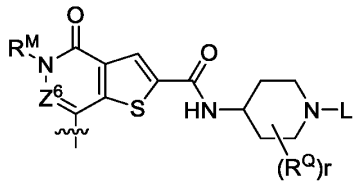
In one exemplary R^{14}, where R^N and Z^5 taken together combine to form an optionally substituted thiophene, the linker may be attached to R^{14} as shown in the structure below:



;

wherein the wavy line intersects the bond between A^2 and the carbon atom positioned *ortho to* R^A and R^E; and R^M and Z^6 are as defined above and herein.

The linker may be attached to an atom forming part of a substituent bonded to the same positions indicated above. For example, the linker may be attached to an atom forming part of substituent 1d bonded to the same positions indicated above. This is exemplified in the structure below, where R^N and Z^5 taken together combine to form an optionally substituted thiophene; the wavy line intersects the bond between A^2 and the carbon atom positioned *ortho to* R^A and R^E; and Y^2 is O, Y^1 is N, R^R is H, and R^Q and r are as defined above:



.

As described above, Z^1, Z^2, Z^3, Z^4 and R^C of R^{14} are defined as follows:

Z^1 is N or CR^A;

Z^2 is N or CR^B;

Z^3 is N or CR^D;

Z^4 is N or CR^E;

wherein no more than 3 of Z^1, Z^2, Z^3 and Z^4 are N;

R^A and R^E are each independently selected from the group consisting of -H, -O-C_{1-3}alkyl and –C_{1-3}alkyl;

R^B and R^D are each independently selected from the group consisting of -O-C_{1-3}alkyl, -H, -OH, halogen, -NH_2, -C_{1-3}alkyl, -O-C_{1-3}haloalkyl, -C_{1-3}alkyl-O-C_{1-3}alkyl, 4-7 membered heterocycloalkyl, -C_{1-3}alkyl-SO_2-C_{1-3}alkyl, -C_{1-3}alkyl-NH_2, -C_{1-3}alkyl-N(-C_{1-3}alkyl)$_2$, -N(C_{1-3}alkyl)$_2$, -NH-R^F;

R^F is selected from -SO_2-C_{1-3}alkyl and –C_{1-3}alkyl, wherein the –C_{1-3}alkyl is optionally substituted with a 5 to 6 membered heteroaryl;

alternatively, R^A and R^B taken together form a benzene ring; alternatively, R^C and Z^2 or R^C and Z^3 taken together (e.g. R^C and R^B or R^C and R^D taken together with the carbon atoms to which they are joined) form a 5-7 membered heterocycloalkyl optionally substituted with –C_{1-3}alkyl;

R^C is selected from the group consisting of -H, -Y-R^G, -NH_2, -C_{1-3}alkyl and 4-7 membered heterocycloalkyl;

Y is absent or is selected from the group consisting of -CR^HR^I-, -SO_2- and -CO-;

R^H and R^I are each independently selected from -H or –C_{1-3}alkyl; or R^H and R^I taken together form a –C_{3-4}cycloalkyl,

R^G is selected from the group consisting of -NH_2, -OH, -C_{1-3}alkyl, -N(R^JR^K), -O-R^L, aryl, 5-6 membered heteroaryl, wherein the aryl and heteroaryl are optionally and independently substituted with one or more halogen, optionally substituted 4- to 7- membered monocyclic heterocycloalkyl, and optionally substituted 7- to 12- membered bicyclic heterocycloalkyl, which monocyclic or bicyclic heterocycloalkyl are optionally substituted with any suitable substituent, such as one or more groups independently selected from halogen, -OH, -NH_2, -C_{1-3}alkyl, -NHC_{1-3}alkyl, -N(C_{1-3}alkyl)$_2$, -O-C_{1-3}alkyl and -CH_2-R^{M1};

R^{M1} is selected from 5-10 membered mono- or bicyclic aryl or heteroaryl, which is optionally substituted with -NH_2, -OH, halogen, -CN, C_{1-3}alkyl, -O-C_{1-3}alkyl;

R^J is -H or –C_{1-3}alkyl;

R^K is selected from the group consisting of –C_{1-3}alkyl, -C_{2-3}alkyl-N(C_{1-3}alkyl)$_2$, -C_{2-3}alkyl-NHC_{1-3}alkyl, optionally substituted 4- to 7-membered monocyclic heterocycloalkyl, and optionally substituted 7- to 12-membered bicyclic heterocycloalkyl, which monocyclic or bicyclic heterocycloalkyl are optionally substituted with any suitable substituent, such as –C_{1-3}alkyl;

R^L is –C_{1-3}alkyl or a 4-7 membered heterocycloalkyl, which heterocycloalkyl is optionally substituted with C_{1-3}alkyl;

wherein when R^C is Y-R^G, R^B and R^D are each independently selected from -H, -OH, halogen, -NH_2, -CN, -C_{1-3}alkyl, -C_{1-3}haloalkyl, -O-C_{1-3}alkyl, -O-C_{1-3}haloalkyl and –C_{1-3}alkyl-O-C_{1-3}alkyl; wherein at least one of the substituents R^A to R^E is not hydrogen.

In alternative examples of the above, the list of groups for R^G and R^K may be replaced as follows:

R^G may be selected from the group consisting of -NH_2, -OH, -C_{1-3}alkyl, -N(R^JR^K), -O-R^L, aryl, 5-6 membered heteroaryl, wherein the aryl and heteroaryl are optionally and independently substituted with one or more halogen, 4-7 membered heterocycloalkyl, which heterocycloalkyl is optionally substituted with one or more groups independently selected from halogen, -OH, -NH_2, -C_{1-3}alkyl, -NHC_{1-3}alkyl, -N(C_{1-3}alkyl)$_2$, -O-C_{1-3}alkyl and -CH_2-R^{M1};

R^K may be selected from the group consisting of –C_{1-3}alkyl, -C_{2-3}alkyl-N(C_{1-3}alkyl)$_2$, -C_{2-3}alkyl-NHC_{1-3}alkyl and 4-7 membered heterocycloalkyl, which heterocycloalkyl is optionally substituted with –C_{1-3}alkyl; and

wherein R^J, R^L, R^{M1} are as defined above.

In some examples of R^{14} described herein (and unless otherwise stated):

(i) R^A, R^B, R^D and R^E are independently selected from the group consisting of -O-C_{1-3}alkyl, -H, halogen, -O-C_{1-3}haloalkyl, -OH, -NH_2, -C_{1-3}alkyl, -C_{1-3}alkyl-NH_2, -C_{1-3}alkyl-N(-C_{1-3}alkyl)$_2$ and -N(C_{1-3}alkyl)$_2$; or

(ii) R^A, R^D and R^E are independently selected from the group consisting of -O-C_{1-3}alkyl, -H, halogen, -O-C_{1-3}haloalkyl, -OH, -NH_2, -C_{1-3}alkyl, -C_{1-3}alkyl-NH_2, -C_{1-3}alkyl-N(-C_{1-3}alkyl)$_2$ and -N(C_{1-3}alkyl)$_2$ and R^B and R^C taken together form a 5-7 membered heterocycloalkyl optionally substituted with –C_{1-3}alkyl.

In such embodiments, the 5-7 membered heterocycloalkyl may be as defined above for ring 1A.

In some embodiments, R^A, R^B, R^D and R^E are independently selected from the group consisting of -O-C_{1-3}alkyl, -H, halogen, -O-C_{1-3}haloalkyl, -OH, -NH_2, -C_{1-3}alkyl, -C_{1-3}alkyl-NH_2, -C_{1-3}alkyl-N(-C_{1-3}alkyl)$_2$ and -N(C_{1-3}alkyl)$_2$. For example, R^A, R^B, R^D and R^E may be independently selected from the group consisting of -O-C_{1-3}alkyl, -H, halogen and -O-C_{1-3}haloalkyl.

In some cases, at least one of R^A, R^B, R^D and R^E may be –H. For example, at least one of R^A and R^B may be –H. In particular embodiments, at least two of R^A, R^B, R^D and R^E are –H.

In some embodiments, at least one of R^A, R^B, R^D and R^E is selected from the group consisting of -O-C_{1-3}alkyl, halogen and -O-C_{1-3}haloalkyl. Sometimes, R^B and R^E are selected from the group consisting of -O-C_{1-3}alkyl, halogen and -O-C_{1-3}haloalkyl.

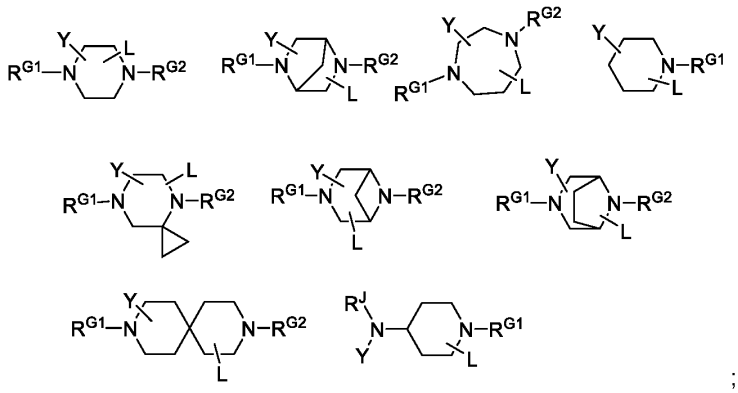
In some embodiments, R^C is –H or -Y-R^G. Y may be -CR^HR^I- or -CO-, wherein R^H and R^I are as defined above. Each of R^H and R^I may be -H; or R^H and R^I taken together may form a –C_{3-4}cycloalkyl.

R^G may be as defined above, or may be selected from the group consisting of -NH_2, -OH, -C_{1-3}alkyl -N(R^JR^K), -O-R^L and optionally substituted 4- to 7- membered monocyclic heterocycloalkyl, and optionally substituted 7- to 12-membered bicyclic heterocycloalkyl, where R^J, R^K and R^L and the optional substituents of the 4- to 7- membered monocyclic heterocycloalkyl and 7- to 12-membered bicyclic heterocycloalkyl are as defined above. R^J may be -H or –C_{1-3}alkyl and R^K may be selected from –C_{1-3}alkyl, optionally substituted 4- to 7- membered monocyclic heterocycloalkyl, and optionally substituted 7- to 12-membered bicyclic heterocycloalkyl. R^L may be –C_{1-3}alkyl.

Where R^G or R^K is an optionally substituted 4- to 7-membered monocyclic heterocycloalkyl, the optionally substituted 4- to 7- membered monocyclic heterocycloalkyl may be a 5- to 7-membered monocyclic heterocycloalkyl comprising between one and three ring heteroatoms selected from N, O and S. In some examples, the optionally substituted 4- to 7- membered monocyclic heterocycloalkyl may be a 5- to 7- membered monocyclic heterocycloalkyl comprising one or two ring heteroatoms selected from N. In some examples, the optionally substituted 4- to 7- membered monocyclic heterocycloalkyl may be piperazinyl, piperidinyl or diazepanyl (each of which may optionally comprise between one and three substituents as described herein).

Where R^G or R^K is an optionally substituted 7- to 12-membered bicyclic heterocycloalkyl, the optionally substituted 7- to 12-membered bicyclic heterocycloalkyl may be a bridged bicyclic ring or a spirocyclic bicyclic ring (i.e it may comprise two rings joined at a spiro centre). By way of example only, the optionally substituted 7- to 12-membered bicyclic heterocycloalkyl may be a bridged piperazinyl or bridged piperidinyl. In other examples, the optionally substituted 7- to 12-membered bicyclic heterocycloalkyl may be an optionally substituted spirocyclic bicyclic heterocycloalkyl comprising between one and three ring heteroatoms selected from N, O and S (e.g. between one and two ring heteroatoms selected from N). In some examples, the optionally substituted 7- to 12-membered bicyclic heterocycloalkyl may be spirocyclic and comprise a first 5- or 6-membered ring and a second 3- to 6-membered ring.

In some examples, R^C may be any one selected from:



;

wherein Y is CR^HR^I (e.g. CH_2);

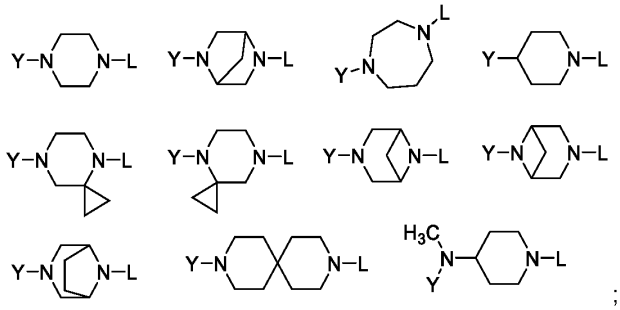
R^{G1} and R^{G2} are each independently selected from H and C_1-C_3 alkyl;

R^J is as defined above and herein; and

L shows the point of attachment of the linker.

In the structures shown above, both the Y and L groups may be attached to the heterocyclic ring(s) by way of a covalent bond between an atom on the Y and L group respectively and an atom on the heterocyclic ring. These groups may be bonded at any chemically suitable position provided valencies are satisfied (e.g. by replacing a H atom).

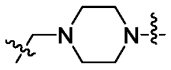
By way of further example only, R^C may be any one selected from:



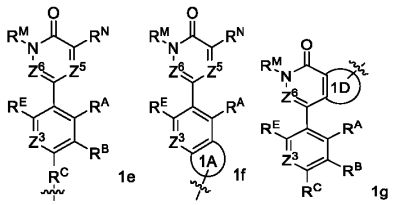
;

wherein Y is CR^HR^I (e.g. CH_2); and

L shows the point of attachment of the linker.

In particular embodiments, R^C is any one selected from the group consisting of  , $-CH_2N(C_{1\text{-}3}alkyl)_2$, $-C(O)N(C_{1\text{-}3}alkyl)_2$, $-C(CH_2CH_2)N(C_{1\text{-}3}alkyl)_2$, and CH_2OCH_3, wherein the wavy lines intersect the bond between R^C and the rest of R^{14} and the bond between R^C and the linker.

In some embodiments, R^{14} is a moiety of formula 1e, 1f or 1g:



1e 1f 1g

wherein the wavy line intersects the bond between R^{14} and the linker;

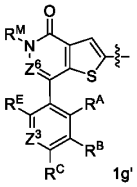
R^A, R^B, R^E, R^M, R^N, Z^3, Z^5 and Z^6 are as defined above;

R^C is absent, or is as defined for R^C above and herein;

ring 1A is a 5-7 membered heterocycloalkane (e.g. comprising one or two heteroatoms selected from the list consisting of N, S and O) optionally substituted with $-C_{1-3}$alkyl; and

ring 1D is an optionally substituted C_{6-10}arene or optionally substituted C_{2-9}heteroarene (e.g. a C_{6-10}aryl or C_{2-9}heteroaryl comprising one or more heteroatoms selected from the group consisting of N, S and O, each of which are optionally substituted with C_{1-3}alkyl).

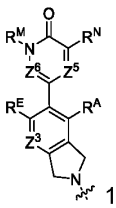
In some embodiments, ring 1D is optionally substituted benzene or an optionally substituted 5-6 membered heteroarene. The 5-6 membered heteroarene may comprise one or more heteroatoms selected from the group consisting of S, N and O, such as S. In some cases, ring 1D may be a 5-6 membered N-heteroarene or S-heteroarene, for example any one selected from the group consisting of thiophene, pyrazole, imidazole, pyrrole, pyrimidine and pyridine. In particular examples, ring 1D is thiophene fused to the rest of R^{14} at the 2' and 3' positions and, in even more particular examples, bonded to the linker by way of a covalent bond between an atom on the linker and the carbon atom at the 5' position of the thiophene. In such particular examples, R^{14} may be of formula 1g':



1g',

wherein the wavy line intersects the bond between R^{14} and the linker; and wherein R^A, R^B, R^C, R^E, R^M, Z^3, and Z^6 are as defined above.

In some embodiments, ring 1A is pyrrolidine. In particular examples, ring 1A is pyrrolidine fused to the rest of R^{14} at the 3' and 4' positions and, in even more particular embodiments, bonded to the linker by way of a covalent bond between an atom on the linker and the nitrogen atom of the pyrrolidine. In such particular embodiments, R^{14} may be of formula 1f':

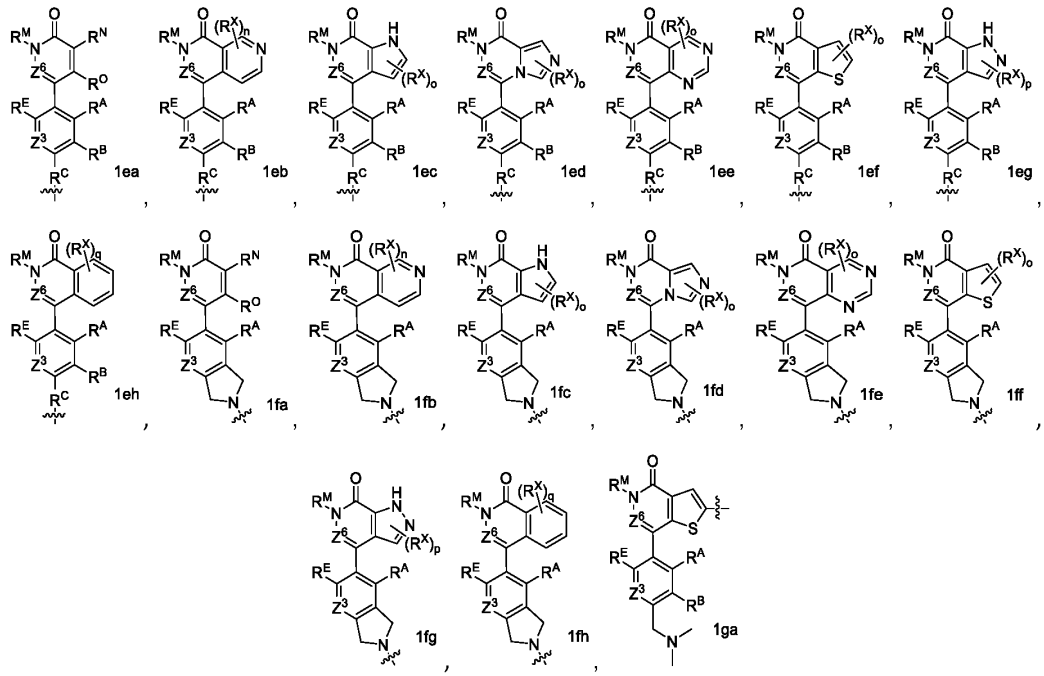


1f',

wherein the wavy line intersects the bond between R^{14} and the linker; and wherein R^A, R^E, R^M, R^N, Z^3, Z^5 and Z^6 are as defined above and herein.

In some embodiments, R^{14} is of formula 1e, 1f' or 1g'.

In particular embodiments, R^{14} is any one of formulae 1ea to 1eh, 1fa to 1fh and 1ga:



wherein the wavy line intersects the bond between R^{14} and the linker;

R^A, R^B, R^E, R^M, Z^3 and Z^6 are as defined above and herein;

R^C is absent, or is as defined above and herein;

R^N is as defined above and herein, for example is selected from the group consisting of halogen, -C_{1-5}alkyl, -C_{1-3}haloalkyl, -H, C(O)C_{1-5}alkyl, -NH_2, -NHC_{1-3}alkyl and –OH;

R^O is as defined above and herein, for example is -H or –C_{1-3}alkyl;

each R^X is as defined for the optional substituents of the optionally substituted C_{6-10}aryl or optionally substituted C_{2-9}heteroaryl formed from R^N and Z^5 (taken together), for example each R^X may be independently selected from the group consisting of halogen, -OH, -NH_2, -NH-C_{1-3}alkyl –C_{1-5}alkyl, C_{1-5}haloalkyl, C_{1-5}alkoxy and C_{1-4}haloalkoxy;

n is 0 to 3 (such as 0);

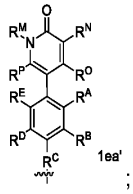
o is 0 to 2 (such as 0);

p is 0 or 1 (such as 0); and

q is 0 to 4 (such as 0).

Each of n, o, p and q may be 0.

In some embodiments, R^{14} is according to formula 1ea':



;

wherein the wavy line intersects the bond between R^{14} and L;

R^A and R^E are as defined above and herein, for example are each independently selected from H and -O-C_{1-3}alkyl;

R^B and R^D are as defined above and herein, for example are each independently selected from -O-C_{1-3}alkyl, -H, - halo, -C_{1-3}alkyl, and -O-C_{1-3}haloalkyl;

R^C is absent, or is –Y-R^G;

Y is selected from the group consisting of -CR^HR^I-, and -CO-;

R^H and R^I are each independently selected from -H or –C_{1-3}alkyl; or R^H and R^I taken together form a –C_{3-4}cycloalkyl;

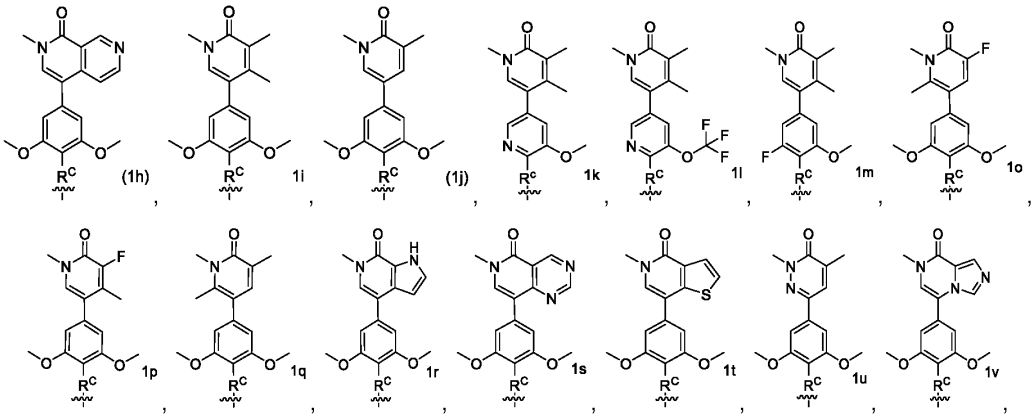
R^G is selected from the group consisting of –N(R^JR^K) (e.g. -N(C_{1-3}alkyl)-, -N(C_{1-3}alkyl)(optionally substituted 4- to 7-membered monocyclic heterocycloalkylene), or -N(C_{1-3}alkyl)(optionally substituted 7- to 12-membered bicyclic heterocycloalkylene)); -O-; optionally substituted 4- to 7- membered monocyclic heterocycloalkylene; and optionally substituted 7- to 12-membered bicyclic heterocycloalkylene (e.g. cycloalkaneocycloalkene comprises one or more heteroatoms selected from the group consisting of N, S and O, and is optionally substituted with C_1-C_3 alkyl);

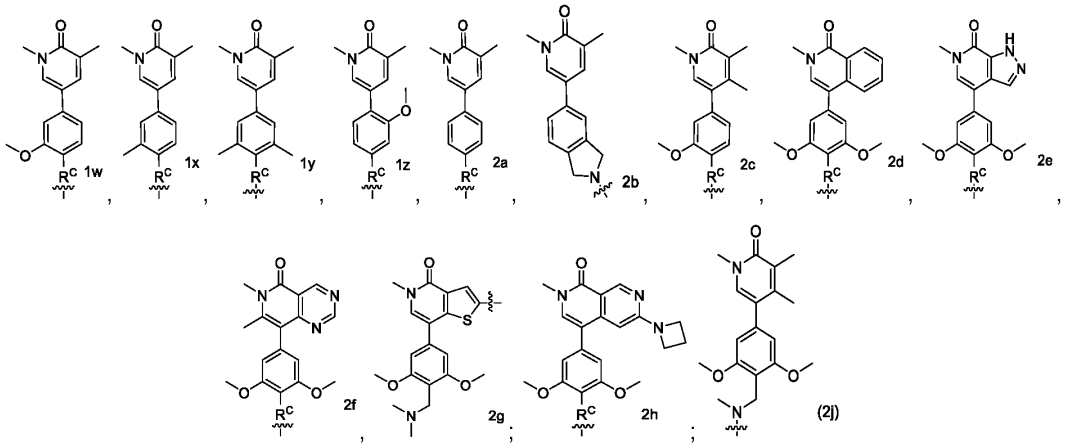
R^J and R^K are as defined above and herein;

R^M is as defined above and herein, for example is C_{1-3}alkyl; and

R^N, R^O and R^P are each as defined above and herein, for example are each independently selected from the group consisting of halo, -C_{1-3}alkyl, and -C_{1-3}haloalkyl.

In even more particular embodiments, R^{14} is any one of formulae (1h) to (1m), (1o) to (1z) or 2a to 2j:





wherein R^C is absent, or is –Y-R^G;

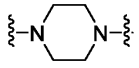
Y is selected from the group consisting of -CR^HR^I-, and -CO-;

R^H and R^I are each -H; or R^H and R^I taken together form a –C_{3-4}cycloalkyl;

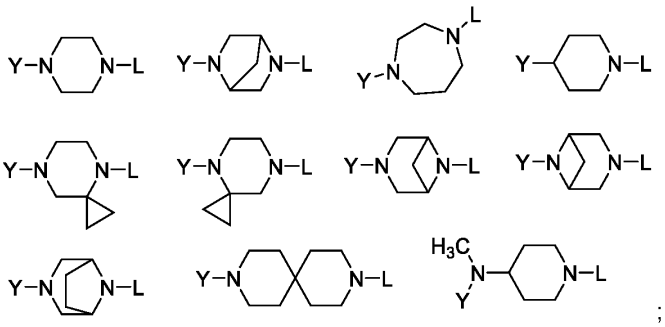
R^G is selected from the group consisting of –$N(R^JR^K)$ (e.g. -$N(C_{1-3}alkyl)$-, $N(C_{1-3}alkyl)$(optionally substituted 4- to 7-membered monocyclic heterocycloalkylene), or -$N(C_{1-3}alkyl)$(optionally substituted 7- to 12-membered bicyclic heterocycloalkylene)); -O-; optionally substituted 4- to 7- membered monocyclic heterocycloalkylene containing one or two N ring atoms; and optionally substituted 7- to 12-membered bicyclic heterocycloalkylene containing one or two N ring atoms (e.g. wherein R^{G3} is selected from the group consisting of $N(R^JR^K)$, $N(C_{1-3}alkyl)$(4- to 7-membered monocyclic heterocycloalkylene), or $N(C_{1-3}alkyl)$(7- to 12-membered bicyclic heterocycloalkylene)); -O-; 4- to 7-membered monocyclic heterocycloalkylene; and 7- to 12-membered bicyclic heterocycloalkylene, wherein each monocyclic or bicyclic heterocycloalkyl comprises one or more heteroatoms selected from the group consisting of N, S and O, and is optionally substituted with C_{1-3} alkyl);

R^J and R^K are as defined above and herein;

wherein the wavy line intersects the bond between R^{14} and the linker.

In particular examples of any of the above formulae (e.g. any one of formulae 1e, 1g, 1g', 1ea to 1eh, 1ea', 1h to 1z, 2a to 2g, 2h and 2j and unless otherwise stated), R^G is -$N(C_{1-3}alkyl)$-, -O- or  .

In some examples of any of the above formulae (e.g. any one of formulae 1e, 1g, 1g', 1ea to 1eh, 1ea', 1h to 1z, 2a to 2g, 2h and 2j and unless otherwise stated), R^C may be any one selected from:



;

wherein Y is CR^HR^I (e.g. CH_2) or –CO-;

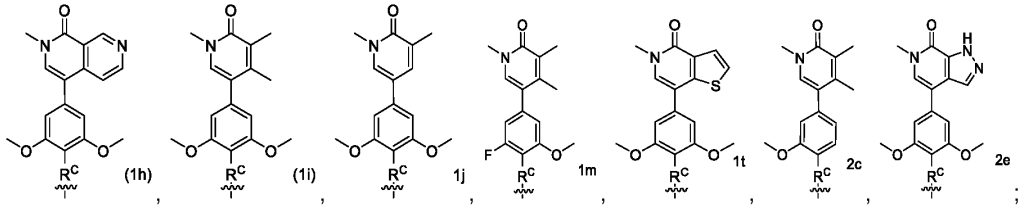
R^H and R^I are as defined above and herein; and

L shows the point of attachment of the linker.

In particular, in each of the structures shown above, Y may be CH_2.

In some examples of any of the above formula (e.g. any one of formulae 1e, 1g, 1g', 1ea to 1eh, 1ea', 1h to 1z, 2a to 2g, 2h and 2j, and unless otherwise stated), R^C may be absent and the linker may be attached (i.e. covalently bonded) to the parent structure at this position. Such examples may be designated with "and so be referred to as formulae 1e'', 1g'', 1g''', 1ea'' to 1eh'', 1ea'', 1h'' to 1z'', 2a'' to 2g'', and 2h" respectively herein.

In some embodiments, R^{14} is any one of formulae 1h, 1i, 1j, 1m, 1t, 2c or 2e:



;

wherein R^C is absent, or is –Y-R^G;

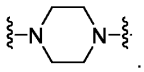
Y is selected from the group consisting of -CR^HR^I-, and -CO-;

R^H and R^I are each -H; or R^H and R^I taken together form a –C_{3-4}cycloalkyl;

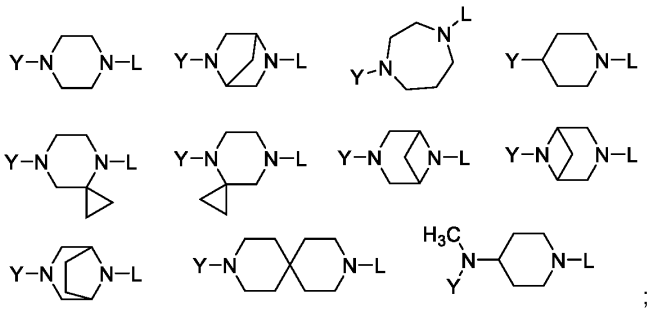
R^G is selected from the group consisting of –$N(R^JR^K)$ (e.g. -N(C_{1-3}alkyl)-, N(C_{1-3}alkyl)(optionally substituted 4- to 7-membered monocyclic heterocycloalkylene), or -N(C_{1-3}alkyl)(optionally substituted 7- to 12-membered bicyclic heterocycloalkylene)); -O-; optionally substituted 4- to 7- membered monocyclic heterocycloalkylene containing one or two N ring atoms; and optionally substituted 7- to 12-membered bicyclic heterocycloalkylene containing one or two N ring atoms;

R^J and R^K are as defined above and herein;

wherein the wavy line intersects the bond between R^{14} and the linker.

In particular examples of any of the above formulae, R^G is -N(C_{1-3}alkyl)-, -O- or  .

In some examples of any of the above formulae, R^C may be any one selected from:



;

wherein Y is CR^HR^I (e.g. CH_2) or –CO-;

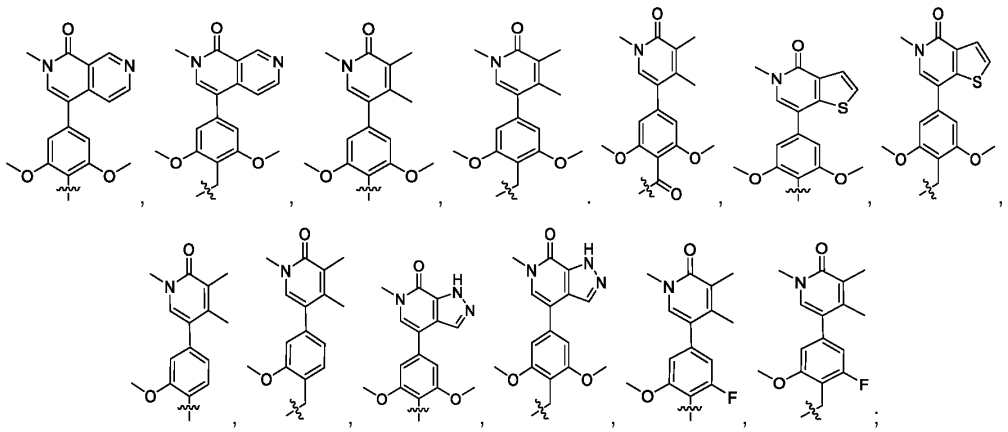
R^H and R^I are as defined above and herein; and

L shows the point of attachment of the linker.

In particular, in each of the structures shown above, Y may be CH_2.

In some examples of any of the above formula, R^C may be absent and the linker may be attached (i.e. covalently bonded) to the parent structure at this position. Such examples may be designated with ” and so be referred to as formulae 1h’’, 1i’’, 1j’’, 1m’’, 1t’’, 2c’’ or 2e’’ respectively herein.

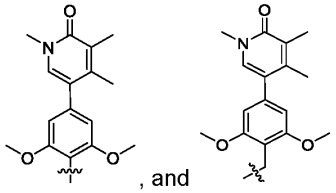
In some embodiments, R^{14} is selected from the following:



;

wherein the wavy line intersects the bond between R^{14} and the linker.

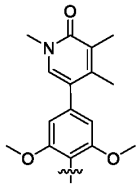
In some embodiments, R^{14} is a moiety of formula (1ia) or (1ib):



(1ia) (1ib);

wherein the wavy line intersects the bond between R^{14} and the linker.

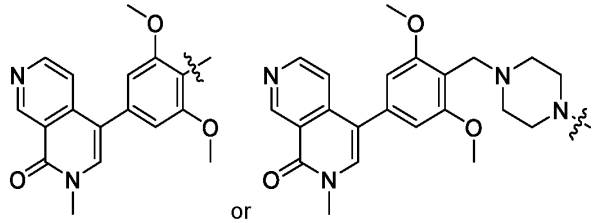
In some embodiments, R^{14} is a moiety of formula (1ia):



(1ia),

wherein the wavy line intersects the bond between R^{14} and the linker.

In some cases, R^{14} may not be:



or ,

wherein the wavy line intersects the bond between R^{14} and the linker.

In embodiments of the compound of formula (III), at least one and no more than three (e.g. one) of X^1, X^2, X^3 and X^4 is N.

In embodiments of the compound of formula (III), at least two and not more than three (e.g. two) of X^1, X^2, X^3 and X^4 are N.

In embodiments of the compound of formula (III), three of X^1, X^2, X^3 and X^4 are N.

In embodiments of the compound of formula (III), R^{10}, R^{11}, R^{12}, and R^{13} are each independently selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy.

In embodiments of the compound of formula (III), R^{10}, R^{11}, R^{12}, and R^{13} are each independently selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy.

In the compounds of formula (III), no more than two of R^{10}, R^{11}, R^{12}, and R^{13} are H.

In embodiments of the compound of formula (III), two of R^{10}, R^{11}, R^{12}, and R^{13} are H.

In embodiments of the compound of formula (III), R^{10}, R^{11}, R^{12}, and R^{13} are each independently selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy.

In embodiments of the compound of formula (III), R^{10} and R^{11} are each independently selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy.

In embodiments of the compound of formula (III), R^{10} and R^{11} are each independently selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein at least two of R^{10}, R^{11}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (III), R^{10} and R^{11} are each independently selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein two of R^{10}, R^{11}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (III), R^{10} and R^{11} are each independently selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein at least one of R^{10}, R^{11}, R^{12} and R^{13} is H.

In embodiments of the compound of formula (III), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy.

In embodiments of the compound of formula (III), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least two of R^{10}, R^{11}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (III), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein two of R^{10}, R^{11}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (III), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least one of R^{10}, R^{11}, R^{12} and R^{13} is H.

In embodiments of the compound of formula (III), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy.

In embodiments of the compound of formula (III), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least two of R^{10}, R^{11}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (III), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein two of R^{10}, R^{11}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (III), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

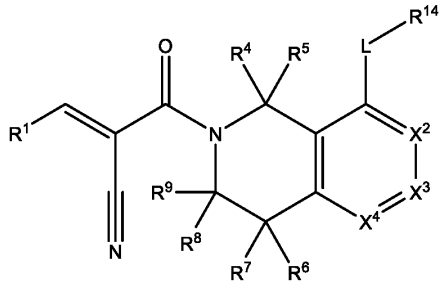
R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

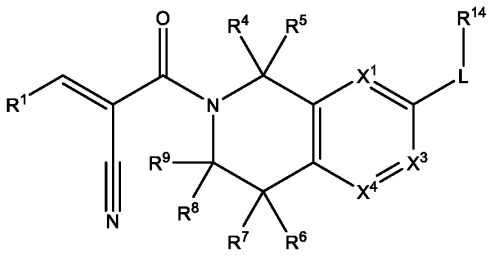
wherein at least one of R^{10}, R^{11}, R^{12} and R^{13} is H.

In embodiments of the compound of formula (III), one of R^{10}, R^{11}, R^{12}, and R^{13} is replaced by -L-R^{14}.

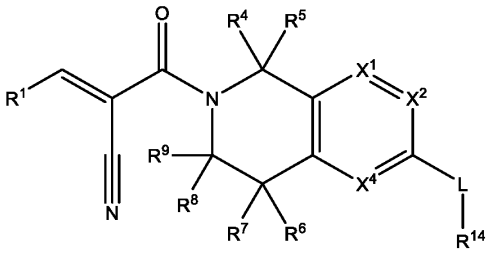
Formula (III) therefore encompasses the compounds of formula (IIIA), (IIIB), (IIIC) and (IIID):



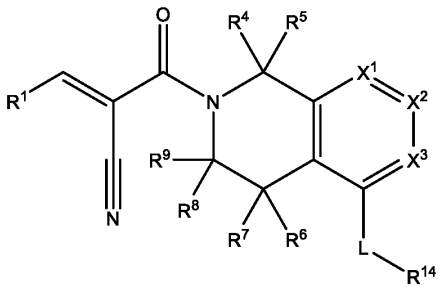
(IIIA)



(IIIB)



(IIIC)



(IIID)

wherein in the compounds of formula (IIIA), (IIIB), (IIIC) and (IIID), R^1, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, X^1, X^2, X^3, X^4, and L are as defined for the compound of formula (III). In the compound of formula (IIIA), when X^2 is CR^{11}, X^3 is CR^{12}, and X^4 is CR^{13}, then one of R^{11}, R^{12} and R^{13} is not H. In the compound of formula (IIIB), when X^1 is CR^{10}, X^3 is CR^{12}, and X^4 is CR^{13}, then one of R^{10}, R^{12} and R^{13} is not H. In the compound of formula (IIIC), when X^1 is CR^{10}, X^2 is CR^{11}, and X^4 is CR^{13}, then one of R^{10}, R^{11} and R^{14} is not H. In the compound of formula (IIID), when X^1 is CR^{10}, X^2 is CR^{11}, and X^3 is CR^{12}, then one of R^{10}, R^{11} and R^{12} is not H.

In embodiments of the compound of formula (III), R^{10} is replaced by -L-R^{14};

R^{11} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy.

In embodiments of the compound of formula (III), R^{10} is replaced by -L-R^{14};

R^{11} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein at least two of R^{11}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (III), R^{10} is replaced by -L-R^{14};

R^{11} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein two of R^{11}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (III), R^{10} is replaced by -L-R^{14};

R^{11} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein at least one of R^{11}, R^{12} and R^{13} is H.

In embodiments of the compound of formula (III), R^{10} is replaced by -L-R^{14};

R^{11} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy.

In embodiments of the compound of formula (III), R^{10} is replaced by -L-R^{14};

R^{11} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least two of R^{11}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (III), R^{10} is replaced by -L-R^{14};

R^{11} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein two of R^{11}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (III), R^{10} is replaced by -L-R^{14};

R^{11} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least one of R^{11}, R^{12} and R^{13} is H.

In embodiments of the compound of formula (III), R^{10} is replaced by -L-R^{14};

R^{11} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy.

In embodiments of the compound of formula (III), R^{10} is replaced by -L-R^{14};

R^{11} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least two of R^{10}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (III), R^{10} is replaced by -L-R^{14};

R^{11} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein two of R^{10}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (III), R^{10} is replaced by -L-R^{14};

R^{11} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least one of R^{10}, R^{12} and R^{13} is H.

In embodiments of the compound of formula (III), R^{10} and R^{11} are each independently selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{12} is replaced by -L-R^{14}; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy.

In embodiments of the compound of formula (III), R^{10} and R^{11} are each independently selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{12} is replaced by -L-R^{14}; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein at least two of R^{10}, R^{11}, and R^{13} are H.

In embodiments of the compound of formula (III), R^{10} and R^{11} are each independently selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{12} is replaced by -L-R^{14}; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein two of R^{10}, R^{11}, and R^{13} are H.

In embodiments of the compound of formula (III), R^{10} and R^{11} are each independently selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{12} is replaced by -L-R^{14}; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein at least one of R^{10}, R^{11}, and R^{13} is H.

In embodiments of the compound of formula (III), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{12} is replaced by -L-R^{14}; and

R^{13} is selected from H, fluorine, and methoxy.

In embodiments of the compound of formula (III), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{12} is replaced by -L-R^{14}; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least two of R^{10}, R^{11}, and R^{13} are H.

In embodiments of the compound of formula (III), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{12} is replaced by -L-R^{14}; and

R^{13} is selected from H, fluorine, and methoxy;

wherein two of R^{10}, R^{11}, and R^{13} are H.

In embodiments of the compound of formula (III), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{12} is replaced by -L-R^{14}; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least one of R^{10}, R^{11}, and R^{13} is H.

In embodiments of the compound of formula (III), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{12} is replaced by -L-R^{14}; and

R^{13} is selected from H, fluorine, and methoxy.

In embodiments of the compound of formula (III), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{12} is replaced by -L-R^{14}; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least two of R^{10}, R^{11}, and R^{13} are H.

In embodiments of the compound of formula (III), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{12} is replaced by -L-R^{14}; and

R^{13} is selected from H, fluorine, and methoxy;

wherein two of R^{10}, R^{11}, and R^{13} are H.

In embodiments of the compound of formula (III), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{12} is replaced by -L-R^{14}; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least one of R^{10}, R^{11}, and R^{13} is H.

In embodiments of the compound of formula (III), R^{10} and R^{11} are each independently selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is replaced by -L-R^{14}.

In embodiments of the compound of formula (III), R^{10} and R^{11} are each independently selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is replaced by -L-R^{14};

wherein at least two of R^{10}, R^{11}, and R^{12} are H.

In embodiments of the compound of formula (III), R^{10} and R^{11} are each independently selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is replaced by -L-R^{14};

wherein two of R^{10}, R^{11}, and R^{12} are H.

In embodiments of the compound of formula (III), R^{10} and R^{11} are each independently selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is replaced by -L-R^{14};

wherein at least one of R^{10}, R^{11}, and R^{12} is H.

In embodiments of the compound of formula (III), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is replaced by -L-R^{14}.

In embodiments of the compound of formula (III), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is replaced by -L-R^{14};

wherein at least two of R^{10}, R^{11}, and R^{12} are H.

In embodiments of the compound of formula (III), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is replaced by -L-R^{14};

wherein two of R^{10}, R^{11}, and R^{12} are H.

In embodiments of the compound of formula (III), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is replaced by -L-R^{14};

wherein at least one of R^{10}, R^{11}, and R^{12} is H.

In embodiments of the compounds of formula (III), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is replaced by -L-R^{14}.

In embodiments of the compounds of formula (III), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is replaced by -L-R^{14};

wherein at least two of R^{10}, R^{11}, and R^{12} are H.

In embodiments of the compounds of formula (III), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is replaced by -L-R^{14};

wherein two of R^{10}, R^{11}, and R^{12} are H.

In embodiments of the compounds of formula (III), R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is replaced by -L-R^{14};

wherein at least one of R^{10}, R^{11}, and R^{12} is H.

In embodiments of the compound of formula (III), R^{10} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy.

In embodiments of the compound of formula (III), R^{10} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein at least two of R^{10}, R^{11}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (III), R^{10} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein two of R^{10}, R^{11}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (III), R^{10} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein at least one of R^{10}, R^{11}, R^{12} and R^{13} is H.

In embodiments of the compound of formula (III), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy.

In embodiments of the compound of formula (III), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least two of R^{10}, R^{11}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (III), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein two of R^{10}, R^{11}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (III), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least one of R^{10}, R^{11}, R^{12} and R^{13} is H.

In embodiments of the compound of formula (III), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy.

In embodiments of the compound of formula (III), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least two of R^{10}, R^{11}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (III), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein two of R^{10}, R^{11}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (III), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least one of R^{10}, R^{11}, R^{12} and R^{13} is H.

In embodiments of the compound of formula (III), one of R^{10}, R^{11}, R^{12}, and R^{13} is replaced by -L-R^{14}.

In embodiments of the compound of formula (III), R^{10} is replaced by -L-R^{14};

R^{11} is selected from H, halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy.

In embodiments of the compound of formula (III), R^{10} is replaced by -L-R^{14};

R^{11} is selected from H, halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein at least two of R^{11}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (III), R^{10} is replaced by -L-R^{14};

R^{11} is selected from H, halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein two of R^{11}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (III), R^{10} is replaced by -L-R^{14};

R^{11} is selected from H, halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein at least one of R^{11}, R^{12} and R^{13} is H.

In embodiments of the compound of formula (III), R^{10} is replaced by -L-R^{14};

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy.

In embodiments of the compound of formula (III), R^{10} is replaced by -L-R^{14};

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least two of R^{11}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (III), R^{10} is replaced by -L-R^{14};

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein two of R^{11}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (III), R^{10} is replaced by -L-R^{14};

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least one of R^{11}, R^{12} and R^{13} is H.

In embodiments of the compound of formula (III), R^{10} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{11} is replaced by -L-R^{14};

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy.

In embodiments of the compound of formula (III), R^{10} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{11} is replaced by -L-R^{14};

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein at least two of R^{10}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (III), R^{10} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{11} is replaced by -L-R^{14};

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein two of R^{10}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (III), R^{10} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{11} is replaced by -L-R^{14};

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein at least one of R^{10}, R^{12} and R^{13} is H.

In embodiments of the compound of formula (III), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{11} is replaced by -L-R^{14};

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy.

In embodiments of the compound of formula (III), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{11} is replaced by -L-R^{14};

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least two of R^{10}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (III), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{11} is replaced by -L-R^{14};

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein two of R^{10}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (III), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{11} is replaced by -L-R^{14};

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least one of R^{10}, R^{12} and R^{13} is H.

In embodiments of the compound of formula (III), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{11} is replaced by -L-R^{14};

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy.

In embodiments of the compound of formula (III), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{11} is replaced by -L-R^{14};

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least two of R^{10}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (III), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{11} is replaced by -L-R^{14};

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein two of R^{10}, R^{12} and R^{13} are H.

In embodiments of the compound of formula (III), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{11} is replaced by -L-R^{14};

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least one of R^{10}, R^{12} and R^{13} is H.

In embodiments of the compound of formula (III), R^{10} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R^{12} is replaced by -L-R^{14}; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy.

In embodiments of the compound of formula (III), R^{10} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R^{12} is replaced by -L-R^{14}; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein at least two of R^{10}, R^{11}, and R^{13} are H.

In embodiments of the compound of formula (III), R^{10} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R^{12} is replaced by -L-R^{14}; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein two of R^{10}, R^{11}, and R^{13} are H.

In embodiments of the compound of formula (III), R^{10} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R^{12} is replaced by -L-R^{14}; and

R^{13} is selected from H, halogen, and C_1-C_6 alkoxy;

wherein at least one of R^{10}, R^{11}, and R^{13} is H.

In embodiments of the compound of formula (III), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is replaced by -L-R^{14}; and

R^{13} is selected from H, fluorine, and methoxy.

In embodiments of the compound of formula (III), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is replaced by -L-R^{14}; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least two of R^{10}, R^{11}, and R^{13} are H.

In embodiments of the compound of formula (III), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is replaced by -L-R^{14}; and

R^{13} is selected from H, fluorine, and methoxy;

wherein two of R^{10}, R^{11}, and R^{13} are H.

In embodiments of the compound of formula (III), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is replaced by -L-R^{14}; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least one of R^{10}, R^{11}, and R^{13} is H.

In embodiments of the compound of formula (III), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is replaced by -L-R^{14}; and

R^{13} is selected from H, fluorine, and methoxy.

In embodiments of the compound of formula (III), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is replaced by -L-R^{14}; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least two of R^{10}, R^{11}, and R^{13} are H.

In embodiments of the compound of formula (III), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is replaced by -L-R^{14}; and

R^{13} is selected from H, fluorine, and methoxy;

wherein two of R^{10}, R^{11}, and R^{13} are H.

In embodiments of the compound of formula (III), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is replaced by -L-R^{14}; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least one of R^{10}, R^{11}, and R^{13} is H.

In embodiments of the compound of formula (III), R^{10} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is replaced by -L-R^{14}.

In embodiments of the compound of formula (III), R^{10} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is replaced by -L-R^{14};

wherein at least two of R^{10}, R^{11}, and R^{12} are H.

In embodiments of the compound of formula (III), R^{10} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is replaced by -L-R^{14};

wherein two of R^{10}, R^{11}, and R^{12} are H.

In embodiments of the compound of formula (III), R^{10} is selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkoxy;

R^{11} is selected from H, halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R^{12} is selected from H, halogen, and C_1-C_6 alkyl; and

R^{13} is replaced by -L-R^{14};

wherein at least one of R^{10}, R^{11}, and R^{12} is H.

In embodiments of the compound of formula (III), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is replaced by -L-R^{14}.

In embodiments of the compound of formula (III), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is replaced by -L-R^{14};

wherein at least two of R^{10}, R^{11}, and R^{12} are H.

In embodiments of the compound of formula (III), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is replaced by -L-R^{14};

wherein two of R^{10}, R^{11}, and R^{12} are H.

In embodiments of the compound of formula (III), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, fluoromethoxy, difluoromethoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is replaced by -L-R^{14};

wherein at least one of R^{10}, R^{11}, and R^{12} is H.

In embodiments of the compounds of formula (III), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is replaced by -L-R^{14}.

In embodiments of the compounds of formula (III), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is replaced by -L-R^{14};

wherein at least two of R^{10}, R^{11}, and R^{12} are H.

In embodiments of the compounds of formula (III), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is replaced by -L-R^{14};

wherein two of R^{10}, R^{11}, and R^{12} are H.

In embodiments of the compounds of formula (III), R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

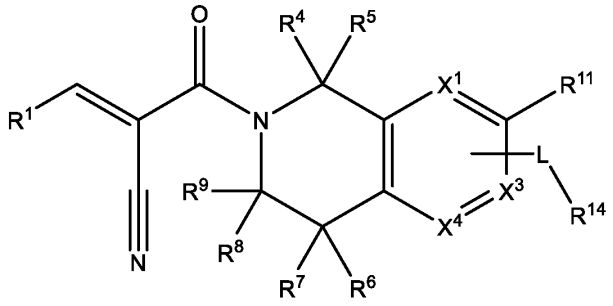
R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is replaced by -L-R^{14};

wherein at least one of R^{10}, R^{11}, and R^{12} is H.

In an embodiment, the compound of formula (III) is a compound of formula (IIIa)



(IIIa)

wherein

X^1 is selected from N and CR^{10};

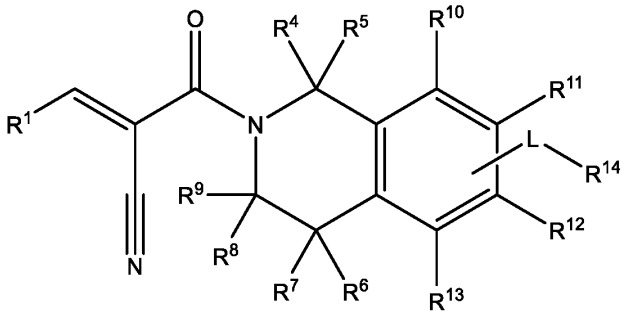
X^3 is selected from N and CR^{12};

X^4 is selected from N and CR^{13}; and

R^1, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14} and L are as defined for the compound of formula (III),

wherein if X^1 is CR^{10}, X^2 is CR^{11}, X^3 is CR^{12} and X^4 is CR^{13}, then at least one of R^{10}, R^{11}, R^{12}, and R^{13} is not H.

In an embodiment, the compound of formula (III) is a compound of formula (IIIb)

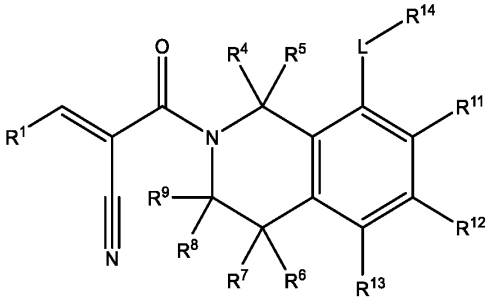


(IIIb)

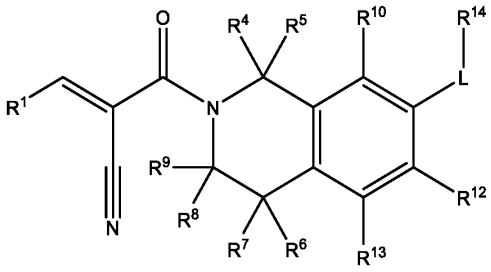
wherein

R^1, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14} and L are as defined for the compound of formula (III).

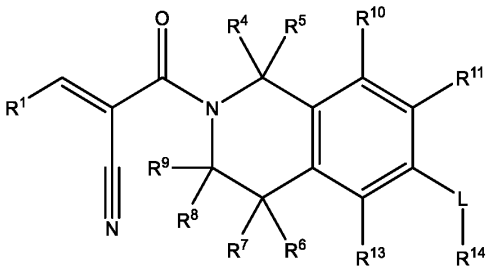
Formula (IIIb) therefore embodies the compounds of formula (IIIba), (IIIbb), (IIIbc) and (IIIbd):



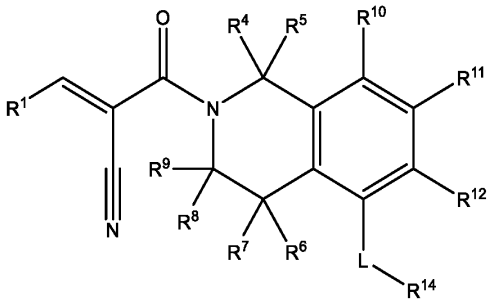
(IIIba)



(IIIbb)



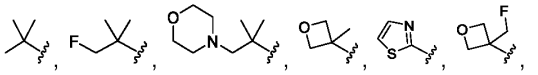
(IIIbc)



(IIIbd)

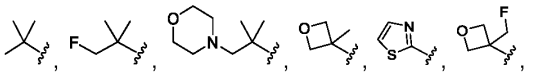
wherein in the compounds of formula (IIIba), (IIIbb), (IIIbc) and (IIIbd), R^1, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, and L are as defined for the compound of formula (III). In the compound of (IIIba), (IIIbb), (IIIbc) or (IIIbd), one of R^{10}, R^{11}, R^{12}, and R^{13} (as is applicable for the particular compound) is not H. That is to say, in compounds of formula (IIIba), one of R^{11}, R^{12}, and R^{13} is not H; in compounds of formula (IIIbb), one of R^{10}, R^{12}, and R^{13} is not H; in compounds of formula (IIIbc), one of R^{10}, R^{11}, and R^{13} is not H; and in compounds of formula (IIIbd), one of R^{10}, R^{11}, and R^{12} is not H. An alternative way to express this is that in the compounds of formula (IIIba), (IIIbb), (IIIbc) and (IIIbd) (and therefore in the compounds of formula (III) and formula (IIIb)), no more than two of R^{10}, R^{11}, R^{12}, and R^{13} are H.

In an embodiment of the moiety of formula (IIIb), R^1 is selected from the following groups:



wherein the wavy line intersects the bond between R^1 and the rest of the compound.

In an embodiment of the compound of formula (IIIb), R^1 is selected from the following groups:



wherein the wavy line intersects the bond between R^1 and the rest of the compound;

R^4 is selected from H, methyl and isopropyl;

R^5, R^6, R^7, R^8, and R^9 are H;

R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, and methoxy;

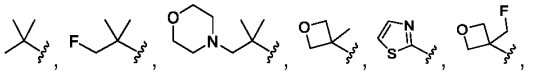
R^{12} is selected from H, fluorine, and methyl;

R^{13} is selected from H, fluorine, and methoxy;

and

R^{14} and L are as defined for compounds of formula (III).

In an embodiment of the compound of formula (IIIb), R^1 is selected from the following groups:



wherein the wavy line intersects the bond between R^1 and the rest of the compound;

R^4 is selected from H, methyl and isopropyl;

R^5, R^6, R^7, R^8, and R^9 are H;

R^{10} and R^{11} are each independently selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

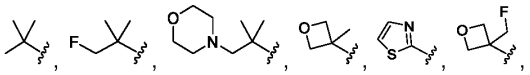
R^{12} is selected from H, fluorine, and methyl;

R^{13} is selected from H, fluorine, and methoxy; and

R^{14} and L are as defined for compounds of formula (III);

wherein one of R^{10}, R^{11}, R^{12}, and R^{13} is replaced by -L-R^{14}.

In an embodiment of the compound of formula (IIIb), R^1 is selected from the following groups:



wherein the wavy line intersects the bond between R^1 and the rest of the compound;

R^4 is selected from H, methyl and isopropyl;

R^5, R^6, R^7, R^8, and R^9 are H;

R^{10} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

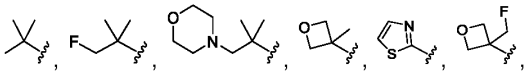
R^{12} is selected from H, fluorine, and methyl;

R^{13} is selected from H, fluorine, and methoxy;

and

R^{14} and L are as defined for compounds of formula (III).

In an embodiment of the compound of formula (IIIb), R^1 is selected from the following groups:



wherein the wavy line intersects the bond between R^1 and the rest of the compound;

R^4 is selected from H, methyl and isopropyl;

R^5, R^6, R^7, R^8, and R^9 are H;

R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

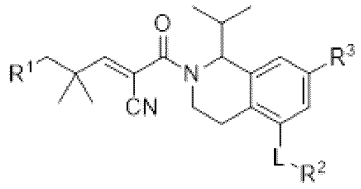
R^{12} is selected from H, fluorine, and methyl;

R^{13} is selected from H, fluorine, and methoxy; and

R^{14} and L are as defined for compounds of formula (III);

wherein one of R^{10}, R^{11}, R^{12}, and R^{13} is replaced by -L-R^{14}.

In embodiments, the compound of formula (III) or formula (IIIb) is not a compound of formula (IIIbe):



(IIIbe)

or a pharmaceutically acceptable salt, solvate or derivative thereof, wherein

L is a covalent bond or linker;

R^1 is selected from H, F, C_1-C_4 alkyl and C_1-C_4 alkoxy;

R^2 is a BRD9 binder;

R^3 is selected from halogen, OR^4, C_1-C_6 alkyl, and $N(R^5)_2$ wherein each alkyl is optionally substituted with one or more groups independently selected from halogen, OR^4, and $N(R^5)_2$;

each R^4 is independently selected from H, C_1-C_6 alkyl and C_1-C_6 haloalkyl; and

each R^5 is independently selected from H, C_1-C_6 alkyl and C_1-C_6 haloalkyl.

In an embodiment, the compound comprising a moiety of formula (I), the compound comprising a moiety of formula (Ib), the compound of formula (III) or the compound of formula (IIIb) is not selected from the compounds in Table A (i.e. the compound comprising a moiety of formula (I), the compound comprising a moiety of formula (Ib), the compound of formula (III) or the compound of formula (IIIb) is not any of compounds 1A, 2A, 3A, 4A, 5A, 6A, 7A, 8A, 9A, 10A, 11A, 12A, 13A or 14A shown in Table A).

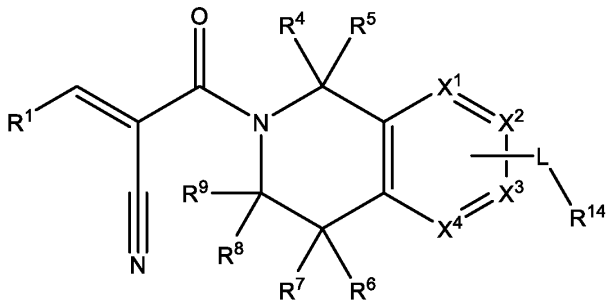
Table A

Compound	Compound name
1A	(R,E)-2-(5-((7-(4-(6-(azetidin-1-yl)-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-7-fluoro-1-isopropyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-5-fluoro-4,4-dimethylpent-2-enenitrile
2A	(R,E)-2-(5-((4-(4-(6-(azetidin-1-yl)-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-7-fluoro-1-isopropyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-5-fluoro-4,4-dimethylpent-2-enenitrile
3A	(R,E)-2-(5-((4-(4-(6-(azetidin-1-yl)-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-1-isopropyl-7-methoxy-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-5-fluoro-4,4-dimethylpent-2-enenitrile

Compound	Compound name
4A	(R,E)-2-(5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-1-isopropyl-7-methoxy-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-5-fluoro-4,4-dimethylpent-2-enenitrile
5A	(R,E)-2-(5-((7-(2,6-dimethoxy-4-(6-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[3,4-c]pyridin-4-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-1-isopropyl-7-methoxy-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-5-fluoro-4,4-dimethylpent-2-enenitrile
6A	(R,E)-2-(5-((4-(2,6-dimethoxy-4-(6-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[3,4-c]pyridin-4-yl)benzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-1-isopropyl-7-methoxy-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-5-fluoro-4,4-dimethylpent-2-enenitrile
7A	single enantiomer of unknown absolute configuration of (E/Z)-2-(5-((7-(2,6-dimethoxy-4-(6-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[3,4-c]pyridin-4-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-7-fluoro-1-isopropyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile
8A	single enantiomer of unknown absolute configuration of (E/Z)-2-(5-((7-(2,6-dimethoxy-4-(6-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[3,4-c]pyridin-4-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-7-fluoro-1-isopropyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile
9A	(R,E/Z)-2-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-1-isopropyl-7-methoxy-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-5-fluoro-4,4-dimethylpent-2-enenitrile

Compound	Compound name
10A	(R,E/Z)-2-(5-((7-(4-(6-(azetidin-1-yl)-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-1-isopropyl-7-methoxy-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-5-fluoro-4,4-dimethylpent-2-enenitrile
11A	(R,E/Z)-2-(5-((4-(4-(6-(azetidin-1-yl)-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-7-hydroxy-1-isopropyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-5-fluoro-4,4-dimethylpent-2-enenitrile
12A	(R,E/Z)-2-(5-((7-(4-(6-(azetidin-1-yl)-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-7-hydroxy-1-isopropyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-5-fluoro-4,4-dimethylpent-2-enenitrile
13A	(R,E/Z)-2-(5-((7-(2,6-dimethoxy-4-(6-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[3,4-c]pyridin-4-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-7-fluoro-1-isopropyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-5-fluoro-4,4-dimethylpent-2-enenitrile
14A	(R,E/Z)-2-(5-((7-(2,6-bis(methoxy-d_3)-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-1-isopropyl-7-methoxy-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-5-fluoro-4,4-dimethylpent-2-enenitrile

In an embodiment, the compound of formula (III) is a compound of formula (IIIc)



(IIIc)

wherein

X^1 is CR^{10} or N;

X^2 is CR^{11};

X^3 is CR^{12} or N; and

X^4 is CR^{13} or N;

R^{10}, R^{11}, R^{12}, and R^{13} are each H; and

R^1, R^4, R^5, R^6, R^7, R^8, R^9, R^{14} and L are as defined for the compound of formula (II);

wherein at least one of X^1, X^3 and X^4 is N; and

no more than three of X^1, X^2, X^3 and X^4 are N.

In embodiments of the compound of formula (IIc), one of X^1, X^2, X^3 and X^4 is N.

In embodiments of the compound of formula (IIc), at least two and not more than three (e.g. two) of X^1, X^2, X^3 and X^4 are N.

In embodiments of the compound of formula (IIc), three of X^1, X^2, X^3 and X^4 are N.

In embodiments of the compound of formula (IIIc), one of R^{10}, R^{11}, R^{12} and R^{13} is replaced by -L-R^{14}, and the others are as defined for the compound of formula (III).

In embodiments of the compound of formula (IIIc), R^{11} is replaced by -L-R^{14}, and R^{10}, R^{12}, and R^{13} are as defined for the compound of formula (III).

In embodiments of the compound of formula (IIIc), R^{10}, R^{11}, R^{12}, and R^{13} are H.

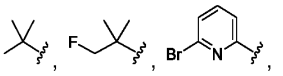
In embodiments of the compound of formula (IIIc), one of R^{10}, R^{11}, R^{12} and R^{13} is replaced by -L-R^{14}, and the others are H.

In embodiments of the compound of formula (IIIc), R^{11} is replaced by -L-R^{14}, and R^{10}, R^{12}, R^{13} are H.

In embodiments of the compound of formula (IIIc), R^1 is selected from C_1-C_6 alkyl and 5-10 membered heteroaryl comprising one or more heteroatoms selected from the group consisting of N, S and O, wherein the alkyl and heteroaryl are each optionally substituted with one or more groups independently selected from halogen and C_1-C_6 alkyl.

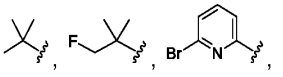
In embodiments of the compound of formula (IIIc), R^1 is selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, and 5-10 membered heteroaryl substituted with halogen.

In embodiments of compound of formula (IIIc), R^1 is selected from the following groups:



wherein the wavy line intersects the bond between R^1 and the rest of the compound.

In embodiments of compound of formula (IIIc), R^1 is selected from the following groups:



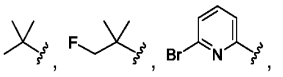
wherein the wavy line intersects the bond between R^1 and the rest of the compound;

R^4 is methyl;

R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, and R^{13} are H; and

R^{14} and L are as defined for compounds of formula (III).

In embodiments of compounds of formula (IIIc), R^1 is selected from the following groups:



wherein the wavy line intersects the bond between R^1 and the rest of the compound;

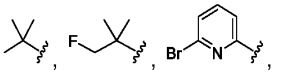
R^4 is methyl;

R^5, R^6, R^7, R^8, R^9,

R^{14} and L are as defined for compounds of formula (II); and

one of R^{10}, R^{11}, R^{12}, and R^{13} is replaced by -L-R^{14}, and the others are H.

In embodiments of the compound of formula (IIIc), R^1 is selected from the following groups:



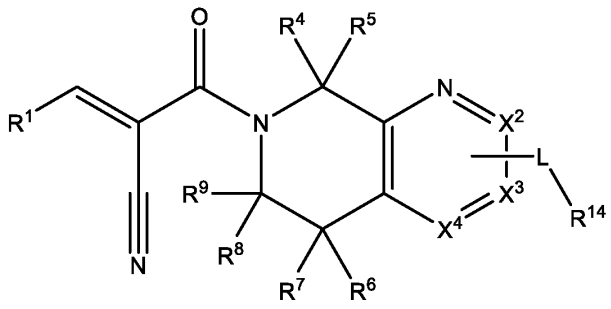
wherein the wavy line intersects the bond between R^1 and the rest of the compound;

R^4 is methyl;

R^5, R^6, R^7, R^8, R^9, R^{10}, R^{12}, and R^{13} are H; and

R^{11} is replaced by -L-R^{14}.

In an embodiment, the moiety of formula (III) is a moiety of formula (IIId)



(IIId)

wherein

X^2 is CR^{11};

X^3 is CR^{12};

X^4 is CR^{13}; and

R^1, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, and L are as defined for the moiety of formula (III).

In embodiments of compounds of formula (IIId), one of R^{11}, R^{12}, and R^{13} is replaced by -L-R^{14}, and the others are as defined for the moiety of formula (III).

In embodiments of compounds of formula (IIId), one of R^{11}, R^{12}, and R^{13} is replaced by -L-R^{14}, and the others are as defined for the moiety of formula (III).

In embodiments of compounds of formula (IIId), R^{11}, R^{12}, and R^{13} are H.

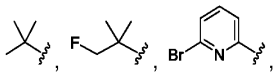
In embodiments of compounds of formula (IIId), one of R^{11}, R^{12}, and R^{13} is replaced by -L-R^{14}, and the others are H.

In embodiments of the compound of formula (IIId), R^{11} is replaced by -L-R^{14}, and R^{12} and R^{13} are H.

In embodiments of the compound of formula (IIId), R^1 is selected from C_1-C_6 alkyl and 5-10 membered heteroaryl comprising one or more heteroatoms selected from the group consisting of N, S and O, wherein the alkyl and heteroaryl are each optionally substituted with one or more groups independently selected from halogen and C_1-C_6 alkyl.

In embodiments of the compound of formula (IIId), R^1 is selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, and 5-10 membered heteroaryl substituted with halogen.

In embodiments of the compound of formula (IIId), R^1 is selected from the following groups:



wherein the wavy line intersects the bond between R^1 and the rest of the compound.

In embodiments of compounds of formula (IIId), R^1 is



wherein the wavy line intersects the bond between R^1 and the rest of the compound.

In embodiments of compounds of formula (IIId), R^1 is



wherein the wavy line intersects the bond between R^1 and the rest of the compound;

R^4 is methyl;

R^5, R^6, R^7, R^8, R^9, R^{11}, R^{12}, and R^{13} are H; and

R^{14} and L are as defined for compounds of formula (III).

In embodiments of compounds of formula (IIId), R^1 is



wherein the wavy line intersects the bond between R^1 and the rest of the compound;

R^4 is methyl;

R^5, R^6, R^7, R^8, and R^9 are H;

R^{14} and L are as defined for compounds of formula (II); and

one of R^{11}, R^{12}, and R^{13} is replaced by -L-R^{14}, and the others are H.

In embodiments of the compound of formula (IIId), R^1 is



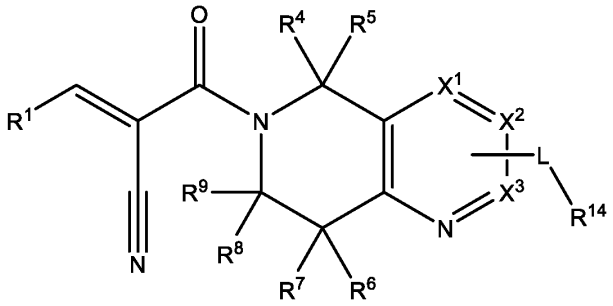
wherein the wavy line intersects the bond between R^1 and the rest of the compound;

R^4 is methyl;

R^5, R^6, R^7, R^8, R^9, R^{12}, and R^{13} are H; and

R^{11} is replaced by -L-R^{14}.

In an embodiment, the compound of formula (III) is a compound of formula (IIIe)



(IIIe)

wherein

X^1 is CR^{10};

X^2 is CR^{11};

X^3 is CR^{12}; and

R^1, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, and L are as defined for the moiety of formula (III).

In embodiments of the compound of formula (IIIe), one of R^{10}, R^{12}, and R^{13} is replaced by -L-R^{14}, and the others are as defined for the moiety of formula (III).

In embodiments of the compound of formula (IIIe), R^{11} is replaced by -L-R^{14}, and R^{10} and R^{12} are as defined for the moiety of formula (III).

In embodiments of the compound of formula (IIIe), R^{10}, R^{12}, and R^{13} are H.

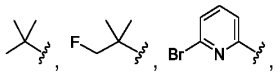
In embodiments of the compound of formula (IIIe), one of R^{10}, R^{12}, and R^{13} is replaced by -L-R^{14}, and the others are H.

In embodiments of the compound of formula (IIIe), R^{11} is replaced by -L-R^{14}, and R^{10} and R^{12} are H.

In embodiments of the compound of formula (IIIe), R^1 is selected from C_1-C_6 alkyl and 5-10 membered heteroaryl comprising one or more heteroatoms selected from the group consisting of N, S and O, wherein the alkyl and heteroaryl are each optionally substituted with one or more groups independently selected from halogen and C_1-C_6 alkyl.

In embodiments of the compound of formula (IIIe), R^1 is selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, and 5-10 membered heteroaryl substituted with halogen.

In embodiments of the compound of formula (IIIe), R^1 is selected from the following groups:



wherein the wavy line intersects the bond between R^1 and the rest of the compound.

In embodiments of the compound of formula (IIIe), R^1 is



wherein the wavy line intersects the bond between R^1 and the rest of the compound.

In embodiments of the compound of formula (IIIe), R^1 is



wherein the wavy line intersects the bond between R^1 and the rest of the compound;

R^4 is methyl;

R^5, R^6, R^7, R^8, R^9, R^{11}, R^{12}, and R^{13} are H; and

R^{14} and L are as defined for compounds of formula (III).

In embodiments of compounds of formula (IIe), R^1 is



wherein the wavy line intersects the bond between R^1 and the rest of the compound;

R^4 is methyl;

R^5, R^6, R^7, R^8, and R^9 are H;

R^{14} and L are as defined for compounds of formula (II); and

one of R^{11}, R^{12}, and R^{13} is replaced by -L-R^{14}, and the others are H.

In embodiments of the compound of formula (IIIe), R^1 is



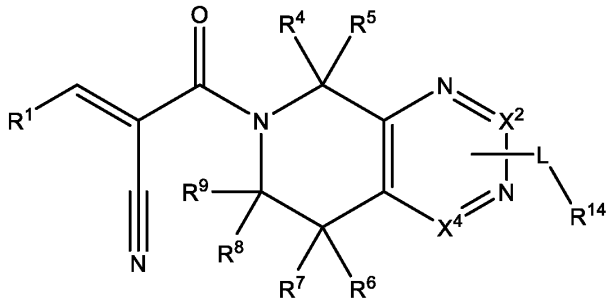
wherein the wavy line intersects the bond between R^1 and the rest of the compound;

R^4 is methyl;

R^5, R^6, R^7, R^8, R^9, R^{10}, and R^{12} are H;

R^{11} is replaced by -L-R^{14}.

In an embodiment, the compound of formula (III) is a compound of formula (IIIf)



(IIIf)

wherein

X^2 is CR^{11};

X^4 is CR^{13}; and

R^1, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, and L are as defined for the moiety of formula (III).

In embodiments of the compound of formula (IIIf), one of R^{11} and R^{13} is replaced by -L-R^{14}, and the other is as defined for the moiety of formula (III).

In embodiments of the compound of formula (IIIf), R^{11} is as defined for the moiety of formula (III), and R^{13} is replaced by -L-R^{14}.

In embodiments of the compound of formula (IIIf), R^{10} and R^{13} are H.

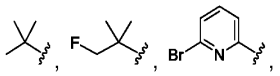
In embodiments of compounds of formula (IIIf), one of R^{10} and R^{13} is replaced by -L-R^{14}, and the other is H.

In embodiments of the compound of formula (IIIf), R^{11} is H, and R^{13} is replaced by -L-R^{14}.

In embodiments of the moiety of formula (If), R^1 is selected from C_1-C_6 alkyl and 5-10 membered heteroaryl comprising one or more heteroatoms selected from the group consisting of N, S and O, wherein the alkyl and heteroaryl are each optionally substituted with one or more groups independently selected from halogen and C_1-C_6 alkyl.

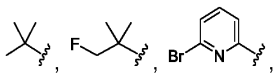
In embodiments of the moiety of formula (If), R^1 is selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, and 5-10 membered heteroaryl substituted with halogen.

In embodiments of the moiety of formula (If), R^1 is selected from the following groups:



wherein the wavy line intersects the bond between R^1 and the rest of the compound.

In embodiments of the compound of formula (IIIf), R^1 is selected from the following groups:



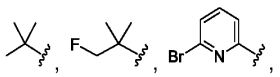
wherein the wavy line intersects the bond between R^1 and the rest of the compound;

R^4 is methyl;

R^5, R^6, R^7, R^8, R^9, R^{11} and R^{13} are each H; and

-L-R^{14} is as defined for compounds of formula (III).

In embodiments of compounds of formula (IIIf), R^1 is selected from the following groups:



wherein the wavy line intersects the bond between R^1 and the rest of the compound;

R^4 is methyl;

R^5, R^6, R^7, R^8, and R^9 are H;

X^1 is N;

X^2 is CR^{11};

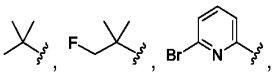
X^3 is N;

X^4 is CR^{13};

-L-R^{14} is as defined for compounds of formula (III); and

one of R^{11} and R^{13} is replaced by G, and the other is H.

In embodiments of the compound of formula (IIIf), R^1 is selected from the following groups:



wherein the wavy line intersects the bond between R^1 and the rest of the compound;

R^4 is methyl;

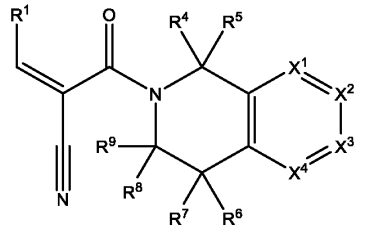
R^5, R^6, R^7, R^8, R^9, and R^{11} are H; and

R^{13} is replaced by -L-R^{14}.

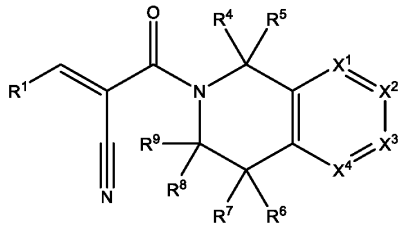
As shown in formulae (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (III), (IIIa), (IIIb), (IIIc), (IIId), (IIIe), or (IIIf), a double bond is present in the Z configuration. The stereochemistry of this double bond may, however, be either E or Z. In some examples, the compound or moiety of formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (III), (IIIa), (IIIb), (IIIc), (IIId), (IIIe), or (IIIf) may comprise a mixture of E and Z stereoisomers. Thus, the present disclosure includes within its scope the use of each individual E and Z stereoisomers of any of the disclosed compounds or moieties of formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (III), (IIIa), (IIIb), (IIIc), (IIId), (IIIe), or (IIIf) (e.g. in a substantially stereopure form), as well as the use of mixtures of these E and Z isomers. In some cases, the stereochemistry of the double bond and the moieties bound to it is Z, i.e. the Z stereoisomer. In other examples, the stereochemistry of the double bond and the moieties bound to it is E, i.e. the E stereoisomer.

For the avoidance of doubt, where the vinylic double bond of a compound or moiety of formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (III), (IIIa), (IIIb), (IIIc), (IIId), (IIIe), or (IIIf), for example that of formula (I), is shown in a structure herein to be a specific stereoisomer (E or Z) in any of the specific examples of this disclosure, it need not be in that specific stereoisomer. In other words, both E and Z stereoisomers and mixtures of the two are included within the scope of the structure irrespective of the specific stereoisomer shown.

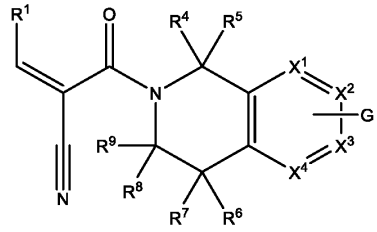
By way of further example, the moiety of formula (I) may be represented as either formula (I-E) or (I-Z), the compounds of formula (II) may be represented as either formula (II-E) or (II-Z), and the compounds of formula (III) maybe represented as either formula (III-E) or (III-Z):



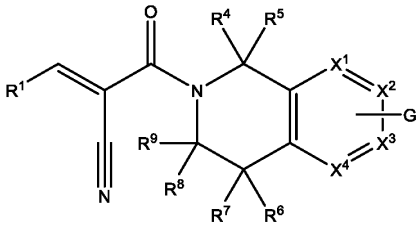
(I-E)



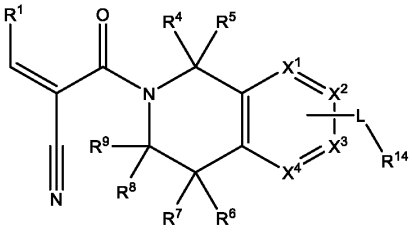
(I-Z)



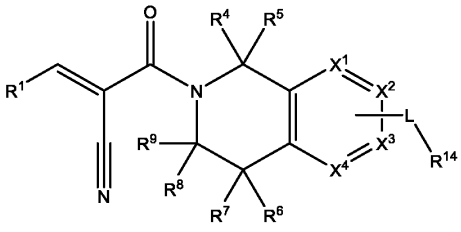
(II-E)



(II-Z)



(III-E)



(III-Z)

wherein R^1, R^4, R^5, R^6, R^7, R^8, R^9, X^1, X^2, X^3 and X^4 are as defined above and herein.

It will be appreciated that the compounds of the present disclosure may exist in different stereoisomeric forms. The present disclosure includes within its scope the use of all stereoisomeric forms, or the use of a mixture of stereoisomers of the compounds, By way of example, where the compound comprises one or more chiral centres, the present disclosure encompasses each individual enantiomer of the compound as well as mixtures of enantiomers including racemic mixtures of such enantiomers. By way of further example, where the compound comprises two or more chiral centres, the present disclosure encompasses each individual diastereomer of the compound, as well as mixtures of the various diastereomers.

Unless otherwise indicated, the various structures shown herein encompass all isomeric (e.g. enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure). For example, the present disclosure embraces the R and S configurations for each asymmetric centre, and Z and E double bond isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are to be understood to be within the scope of the present disclosure. Additionally, unless otherwise stated, where

present, all tautomeric forms of the compounds described herein are to be understood to be within the scope of the present disclosure.

As used herein, references to a compound of formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (III), (IIIa), (IIIb), (IIIc), (IIId), (IIIe), or (IIIf) may further embrace a pharmaceutically acceptable salt thereof.

It should be understood that throughout this specification, the terms “comprise”, “comprising” and/or “comprises” is/are used to denote that aspects, embodiments and examples of this disclosure “comprise” a particular feature or features. It should be understood that this/these terms may also encompass aspects, embodiments and/or examples which “consist essentially of” or “consist of” the relevant feature or features.

The disclosure also includes various deuterated forms of the compounds disclosed herein, or of any of the formulae disclosed herein, including Formulae (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (III), (IIIa), (IIIb), (IIIc), (IIId), (IIIe), or (IIIf) (inc. corresponding subgeneric formulae defined herein), respectively, or a pharmaceutically acceptable salt and/or a corresponding tautomer form thereof (including subgeneric formulas, as defined above) of the present disclosure. Each available hydrogen atom attached to a carbon atom may be independently replaced with a deuterium atom. A person of ordinary skill in the art will know how to synthesize deuterated forms of the compounds of any of the Formulae disclosed herein, including Formulae (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (III), (IIIa), (IIIb), (IIIc), (IIId), (IIIe), or (IIIf) (inc. corresponding subgeneric formulae defined herein), respectively, or a pharmaceutically acceptable salt and/or a corresponding tautomer form thereof (including subgeneric formulae, as defined above) of the present disclosure. For example, deuterated materials, such as alkyl groups may be prepared by conventional techniques (see for example: methyl-d_3 -amine available from Aldrich Chemical Co., Milwaukee, WI, Cat. No.489,689-2).

The disclosure also includes isotopically-labelled compounds which are identical to those recited in any of the Formulae disclosed herein, including Formulae (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (III), (IIIa), (IIIb), (IIIc), (IIId), (IIIe), or (IIIf) (inc. corresponding subgeneric formulae defined herein), respectively, or a pharmaceutically acceptable salt and/or a corresponding tautomer form thereof (including subgeneric formulae, as defined above) of the present disclosure but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number most commonly found in nature. Examples of isotopes that can be incorporated into compounds of the disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, fluorine, iodine and chlorine such as ^{3}H, ^{11}C, ^{14}C, ^{18}F, ^{123}I or ^{125}I. Compounds of the present disclosure and pharmaceutically acceptable salts of said compounds that contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of the present disclosure. Isotopically labelled compounds of the present disclosure, for example those into which radioactive isotopes such as ^{3}H or ^{14}C have been incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e. ^{3}H, and carbon-14, i.e. ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. ^{11}C and ^{18}F isotopes are particularly useful in PET (positron emission tomography).

Degradation may be determined by measuring the amount of a target protein in the presence of a compound of formula (III) as described herein and/or comparing this to the amount of the target protein observed in the absence of the compound of formula (III). For example, the amount of target protein in a cell that has been contacted and/or treated with a compound of formula (III) as described herein may be determined. This amount may be compared to the amount of target protein in a cell that has not been contacted and/or treated with the compound of formula (III) (e.g. as a control). If the amount of target protein is decreased in the cell contacted and/or treated with the compound of formula (III), the compound of formula (III) may be considered as facilitating and/or promoting the degradation and/or proteolysis of the target protein.

The amount of the target protein can be determined using methods known in the art, for example, by performing immunoblotting assays, Western blot analysis and/or ELISA with cells that have been contacted and/or treated with a compound of formula (III).

Selective degradation and/or increased proteolysis may be considered to have occurred if at least a 10% decrease in the amount of a target protein is observed compared to the control, for example, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or 100% following administration of the compound of formula (III) to the cell.

For example, selective degradation and/or increased proteolysis may be considered to have occurred if at least a 10% decrease in the amount of a target protein is observed, (e.g. at least 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or 100% decrease) within 4 hours or more (e.g. 4 hours, 8 hours, 12 hours, 24 hours, 30 hours, 36 hours, 42 hours, 48 hours, 54 hours, 60 hours, 66 hours and 72 hours) following administration of the compound of formula (III) to the cell. The compound of formula (III) may be administered at any concentration, e.g. a concentration between 0.01 nM to 10 mM , such as 0.01nM, 0.1nM, 1 nM, 10nM, 100 nM, 1 mM, and 10 mM. In some instances, an increase of at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, or approximately 100% in the degradation of the target protein is observed following administration of the compound of formula (III) at a concentration of approximately 100 nM (e.g. following an incubation period of approximately 8 hours).

One measure of degrader activity of the compounds of formula (III) is the DC_{50} value. As used herein, DC_{50} is the concentration required to reach 50% of the maximal degradation of the target protein. The compounds of formula (III) described herein may exhibit a DC_{50} of less than or equal to 10000 nM, less than or equal to 1000 nM, less than or equal to 500 nM, less than or equal to 100 nM or less than or equal to 75 nM. In some cases, the compounds of formula (III) exhibit a DC_{50} less than or equal to 50 nM, less than or equal to 25 nM, or less than or equal to 10 nM.

Another measure of the degrader activity of the compounds of formula (III) is the D_{max} value. As used herein, D_{max} represents the maximal percentage of target protein degradation. The compounds of formula (III) described herein may exhibit a D_{max} of at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95% or about 100%.

Yet another measure of the efficacy of the described compounds of formula (III) may be their effect on cell viability and/or their IC_{50} value. For example, an anti-proliferative effect of a compound of formula (III) as described herein may be assessed in a cell viability assay to provide an IC_{50} value. As

used herein, the IC_{50} value represents the concentration at which 50% cell viability was observed in the cell viability assay (following administration of a compound of formula (III) as described herein). In terms of cell viability, the compounds of formula (III) described herein may exhibit an IC_{50} of less than 1000nM, less than 500nM, less than 100 nM, less than 50 nM, less than 25 nM, less than 20 nM, or less than 10 nM. In some cases, the compounds of formula (III) described herein may exhibit an IC50 value of less than 5 nM.

The present disclosure provides a pharmaceutical composition comprising the compounds of formula (III) described herein. In such compositions, the compound of formula (III) may be suitably formulated such that it can be introduced into the environment of the cell by a means that allows for a sufficient portion of the molecule to enter the cell to induce degradation of the target protein.

Accordingly, there is provided a pharmaceutical composition comprising a compound of formula (III) as described herein together with a pharmaceutically acceptable carrier. Optionally the compound of formula (III) is present in the pharmaceutical composition as a pharmaceutically acceptable salt, solvate or derivative

Pharmaceutically acceptable carriers are well known to those skilled in the art and include, but are not limited to, phosphate buffer solutions and/or saline. Pharmaceutically acceptable carriers may be aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Parenteral vehicles include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's or fixed oils. Preservatives and other additives may also be present, such as, for example, antimicrobials, antioxidants, chelating agents, inert gases and the like.

In addition to the aforementioned carrier ingredients the pharmaceutical compositions described above may alternatively or additionally include, an appropriate one or more additional carrier ingredients such as diluents, buffers, flavouring agents, binders, surface active agents, thickeners, lubricants, preservatives (including anti-oxidants) and the like, and substances included for the purpose of rendering the formulation isotonic with the blood of the intended recipient.

Pharmaceutical compositions may be present in any formulation typical for the administration of a pharmaceutical compound to a subject. Representative examples of typical formulations include, but are not limited to, capsules, granules, tablets, powders, lozenges, suppositories, pessaries, nasal sprays, gels, creams, ointments, sterile aqueous preparations, sterile solutions, aerosols, implants etc.

A pharmaceutical composition is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, e.g., intravenous, intradermal, subcutaneous, oral, transdermal, topical, transmucosal, vaginal and rectal administration.

The pharmaceutical compositions may include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular and intravenous), topical (including dermal, buccal and sublingual), rectal, nasal and pulmonary administration e.g., by inhalation. The composition may, where

appropriate, be conveniently presented in discrete dosage units and may be prepared by any of the methods well known in the art of pharmacy. Methods typically include the step of bringing into association an active compound with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Pharmaceutical compositions suitable for oral administration wherein the carrier is a solid are most preferably presented as unit dose formulations such as boluses, capsules or tablets each containing a predetermined amount of active compound. A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine an active compound in a free-flowing form such as a powder or granules optionally mixed with a binder, lubricant, inert diluent, lubricating agent, surface-active agent or dispersing agent. Moulded tablets may be made by moulding an active compound with an inert liquid diluent. Tablets may be optionally coated and, if uncoated, may optionally be scored. Capsules may be prepared by filling an active compound, either alone or in admixture with one or more accessory ingredients, into the capsule shells and then sealing them in the usual manner. Cachets are analogous to capsules wherein an active compound together with any accessory ingredient(s) is sealed in a rice paper envelope. The compounds of formula (III) may also be formulated as dispersible granules, which may for example be suspended in water before administration, or sprinkled on food. The granules may be packaged, e.g., in a sachet. Compositions suitable for oral administration wherein the carrier is a liquid may be presented as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water liquid emulsion. Compositions for oral administration include controlled release dosage forms, e.g., tablets wherein an active compound is formulated in an appropriate release-controlling matrix, or is coated with a suitable release-controlling film.

Pharmaceutical compositions suitable for parenteral administration include sterile solutions or suspensions of an active compound in aqueous or oleaginous vehicles. Injectable preparations may be adapted for bolus injection or continuous infusion. Such preparations are conveniently presented in unit dose or multi-dose containers, which are sealed after introduction of the formulation until required for use. Alternatively, the compound of formula (III) may be in powder form, which is constituted with a suitable vehicle, such as sterile, pyrogen-free water, before use.

The pharmaceutical composition may also be formulated as long-acting depot preparations, which may be administered by intramuscular injection or by implantation, e.g., subcutaneously or intramuscularly. Depot preparations may include, for example, suitable polymeric or hydrophobic materials, or ion-exchange resins.

Pharmaceutical compositions suitable for topical formulation may be provided for example as gels, creams or ointments.

The compound of formula (III) described herein may be present in the pharmaceutical compositions as a pharmaceutically and/or physiologically acceptable salt, solvate or derivative.

The compound comprising a moiety of formula (I) described herein may be present in the pharmaceutical compositions as a pharmaceutically and/or physiologically acceptable salt, solvate or derivative.

As used herein, the term “pharmaceutically acceptable salt” refers to those salts, which are generally considered suitable for use in medicine (including in a veterinary context). For example, pharmaceutically acceptable salts may be those which can be contacted with the tissues of a mammalian subject (e.g. humans) without undue toxicity, irritation, allergic response or the like. By way of further example of suitable pharmaceutically acceptable salts, S. M. Berge et al., describe pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66, 1–19, the entire contents of which are incorporated herein by reference.

Representative examples of pharmaceutically and/or physiologically acceptable salts of the compounds of the disclosure may include, but are not limited to, acid addition salts formed with organic carboxylic acids such as acetic, lactic, tartaric, maleic, citric, pyruvic, oxalic, malonic, fumaric, oxaloacetic, isethionic, lactobionic and succinic acids; organic sulfonic acids such as methanesulfonic, ethanesulfonic, benzenesulfonic and p-toluenesulfonic acids and inorganic acids such as hydrochloric, hydrobromic, sulfuric, perchloric, phosphoric and sulfamic acids. Other pharmaceutically acceptable salts include (but are not limited to) adipate, alginate, ascorbate, aspartate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2– hydroxy–ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, 2–naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3–phenylpropionate, pivalate, propionate, stearate, thiocyanate, undecanoate, valerate salts, and the like.

In some examples, salts that may be derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. Representative alkali or alkaline earth metal salts include, but are not limited to, sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts may include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate and aryl sulfonate.

Pharmaceutically and/or physiologically functional derivatives of compounds of the present invention are derivatives, which may be converted in the body into the parent compound. Such pharmaceutically and/or physiologically functional derivatives may also be referred to as “pro-drugs” or “bioprecursors”. Pharmaceutically and/or physiologically functional derivatives of compounds of the present disclosure may include hydrolysable esters or amides, particularly esters, *in vivo*.

It may be convenient or desirable to prepare, purify, and/or handle a corresponding pharmaceutically and/or physiologically acceptable solvate of the compounds described herein, which may be used in the any one of the uses/methods described. The term solvate is used herein to refer to a complex of solute, such as a compound or salt of the compound, and a solvent. If the solvent is water, the solvate may be termed a hydrate, for example a mono-hydrate, di-hydrate, tri-hydrate etc, depending on the number of water molecules present per molecule of substrate.

The compounds of formula (III) or compounds comprising a moiety of formula (I) of the present disclosure may modulate, facilitate and/or promote proteasomal degradation of a target protein. As such, there is provided a method of selectively degrading and/or increasing proteolysis of a target protein in a cell, the method comprising contacting and/or treating the cell with a compound of formula (III) or a compound comprising a moiety of formula (I) or a pharmaceutical composition comprising a compound of formula (III) or a compound comprising a moiety of formula (I) as described herein. The method may be carried out *in vivo* or *in vitro*.

In particular, there is provided a method of selectively degrading and/or increasing proteolysis of a target protein in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of formula (III) or a compound comprising a moiety of formula (I) or a pharmaceutical composition comprising a compound of formula (III) or a compound comprising a moiety of formula (I) of the present disclosure.

As such, the compound of formula (III) or compound comprising a moiety of formula (I) (or a pharmaceutical composition comprising a compound of formula (III) or a compound comprising a moiety of formula (I)) of the present disclosure may find application in medicine and/or therapy. Specifically, the compound of formula (III) or the compound comprising a moiety of formula (I) (or a pharmaceutical composition comprising a compound of formula (III) or a compound comprising a moiety of formula (I)) of the present disclosure may find use in the treatment and/or prevention of any disease or condition, which is modulated through the target protein. For example, the compounds of formula (III) or the compound comprising a moiety of formula (I) of the present disclosure may be useful in the treatment of any disease, which is modulated through the target protein by lowering the level of that protein in the cell, e.g. cell of a subject. Reduction of target protein levels in a cell following administration of a compound of formula (III) or a compound comprising a moiety of formula (I) of the present invention wherein activity of the selected protein is implicated in a disease state or a disorder, then it is to be understood that the compound of formula (III) or the compound comprising a moiety of formula (I) is useful in the treatment of that disease.

There is further provided the use of the compounds of formula (III) or the compounds comprising a moiety of formula (I) (or a pharmaceutical composition comprising a compound of formula (III) or a compound comprising a moiety of formula (I)) as described herein in the manufacture of a medicament for the treatment and/or prevention of any disease or condition, which is modulated through the target protein. Additionally, there is provided the use of a compound of formula (III) or a compound comprising a moiety of formula (I) (or a pharmaceutical composition comprising a compound of formula (III) or a compound comprising a moiety of formula (I)) in the manufacture of a medicament for the treatment and/or prevention of any disease or condition, which is modulated through the target protein.

Diseases and/or conditions that may be treated and/or prevented by the compounds of formula (III) or the compounds comprising a moiety of formula (I) (or a pharmaceutical composition comprising a compound of formula (III) or a compound comprising a moiety of formula (I)) of the disclosure include any disease, which is associated with and/or is caused by an abnormal level of protein activity (e.g. an abnormal level of BRD9 activity).

Such diseases and conditions include those whose pathology is related at least in part to an abnormal (e.g. elevated) level of a protein and/or the overexpression of a protein. For example, the compounds of formula (III) or the compounds comprising a moiety of formula (I) may find use in the treatment and/or prevention of diseases where an elevated level of a protein is observed in a subject suffering from the disease. In other examples, the diseases and/or conditions may be those whose pathology is related at least in part to inappropriate protein expression (e.g., expression at the wrong time and/or in the wrong cell), excessive protein expression or expression of a mutant protein. In one example, a mutant protein disease is caused when a mutant protein interferes with the normal biological activity of a cell, tissue, or organ.

Accordingly, there is provided a method of treating and/or preventing a disease or condition, which is associated with and/or is caused by an abnormal level of protein activity (e.g. an abnormal level of BRD9 activity), which comprises administering a therapeutically effective amount of a compound of formula (III) or a compound comprising a moiety of formula (I) as described herein.

Representative examples of the diseases and/or conditions that may be treated and/or prevented by the use of the described compounds of formula (III) or the compounds comprising a moiety of formula (I) (or a pharmaceutical composition comprising a compound of formula (III) or a compound comprising a moiety of formula (I)) include (but are not limited to) cancer, asthma, multiple sclerosis, ciliopathies, cleft palate, diabetes, heart disease, hypertension, inflammatory bowel disease, mental retardation, mood disorder, obesity, refractive error, infertility, Angelman syndrome, Canavan disease, Coeliac disease, Charcot-Marie-Tooth disease, Cystic fibrosis, Duchenne muscular dystrophy, Haemochromatosis, Haemophilia, Klinefelter's syndrome, Neurofibromatosis, Phenylketonuria, Polycystic kidney disease, (PKDl) or 4 (PKD2) Prader-Willi syndrome, Sickle-cell disease, Tay-Sachs disease, and Turner syndrome.

Further examples include, Alzheimer's disease, Amyotrophic lateral sclerosis (Lou Gehrig's disease), Anorexia nervosa, Anxiety disorder, Atherosclerosis, Attention deficit hyperactivity disorder, Autism, Bipolar disorder, Chronic fatigue syndrome, Chronic obstructive pulmonary disease, Crohn's disease, Coronary heart disease, Dementia, Depression, Diabetes mellitus type 1, Diabetes mellitus type 2, Epilepsy, Guillain-Barre syndrome, Irritable bowel syndrome, Lupus, Metabolic syndrome, Multiple sclerosis, Myocardial infarction, Obesity, Obsessive-compulsive disorder, Panic disorder, Parkinson's disease, Psoriasis, Rheumatoid arthritis, Sarcoidosis, Schizophrenia, Stroke, Thromboangiitis obliterans, Tourette syndrome, and Vasculitis.

Yet further examples include aceruloplasminemia, Achondrogenesis type II, achondroplasia, Acrocephaly, Gaucher disease type 2, acute intermittent porphyria, Canavan disease, Adenomatous Polyposis Coli, ALA dehydratase deficiency, adenylosuccinate lyase deficiency, Adrenogenital syndrome, Adrenoleukodystrophy, ALA-D porphyria, ALA dehydratase deficiency, Alkaptonuria, Alexander disease, Alkaptonuric ochronosis, alpha 1-antitrypsin deficiency, alpha-1 proteinase inhibitor, emphysema, amyotrophic lateral sclerosis, Alstrom syndrome, Alexander disease, Amelogenesis imperfecta, ALA dehydratase deficiency, Anderson-Fabry disease, androgen insensitivity syndrome, Anemia, Angiokeratoma Corporis Diffusum, Angiomatosis retinae (von Hippel-Lindau disease), Apert

syndrome, Arachnodactyly (Marfan syndrome), Stickler syndrome, Arthrochalasis multiplex congenital (Ehlers-Danlos syndrome arthrochalasia type), ataxia telangiectasia, Rett syndrome, primary pulmonary hypertension, Sandhoff disease, neurofibromatosis type II, Beare-Stevenson cutis gyrata syndrome, Mediterranean fever, familial, Benjamin syndrome, beta-thalassemia, Bilateral Acoustic Neurofibromatosis (neurofibromatosis type II), factor V Leiden thrombophilia, Bloch-Sulzberger syndrome (incontinentia pigmenti), Bloom syndrome, X-linked sideroblastic anemia, Bonnevie-Ullrich syndrome (Turner syndrome), Bourneville disease (tuberous sclerosis), prion disease, Birt-Hogg-Dube syndrome, Brittle bone disease (osteogenesis imperfecta), Broad Thumb-Hallux syndrome (Rubinstein-Taybi syndrome), Bronze Diabetes/Bronzed Cirrhosis (hemochromatosis), Bulbospinal muscular atrophy (Kennedy's disease), Burger-Grutz syndrome (lipoprotein lipase deficiency), CGD Chronic granulomatous disorder, Campomelic dysplasia, biotinidase deficiency, Cardiomyopathy (Noonan syndrome), Cri du chat, CAVD (congenital absence of the vas deferens), Caylor cardiofacial syndrome (CBAVD), CEP (congenital erythropoietic porphyria), cystic fibrosis, congenital hypothyroidism, Chondrodystrophy syndrome (achondroplasia), otospondylomegaepiphyseal dysplasia, Lesch-Nyhan syndrome, galactosemia, Ehlers-Danlos syndrome, Thanatophoric dysplasia, Coffin-Lowry syndrome, Cockayne syndrome, (familial adenomatous polyposis), Congenital erythropoietic porphyria, Congenital heart disease, Methemoglobinemia/Congenital methaemoglobinaemia, achondroplasia, X-linked sideroblastic anemia, Connective tissue disease, Conotruncal anomaly face syndrome, Cooley's Anemia (beta-thalassemia), Copper storage disease (Wilson's disease), Copper transport disease (Menkes disease), hereditary coproporphyria, Cowden syndrome, Craniofacial dysarthrosis (Crouzon syndrome), Creutzfeldt-Jakob disease (prion disease), Cockayne syndrome, Cowden syndrome, Curschmann-Batten-Steinert syndrome (myotonic dystrophy), Beare-Stevenson cutis gyrata syndrome, primary hyperoxaluria, spondyloepimetaphyseal dysplasia (Strudwick type), muscular dystrophy, Duchenne and Becker types (DBMD), Usher syndrome, Degenerative nerve diseases including de Grouchy syndrome and Dejerine-Sottas syndrome, developmental disabilities, distal spinal muscular atrophy, type V, androgen insensitivity syndrome, Diffuse Globoid Body Sclerosis (Krabbe disease), Di George's syndrome, Dihydrotestosterone receptor deficiency, androgen insensitivity syndrome, Down syndrome, Dwarfism, erythropoietic protoporphyria, Erythroid 5-aminolevulinate synthetase deficiency, Erythropoietic porphyria, erythropoietic protoporphyria, erythropoietic uroporphyria, Friedreich's ataxia,, familial paroxysmal polyserositis, porphyria cutanea tarda, familial pressure sensitive neuropathy, primary pulmonary hypertension (PPH), Fibrocystic disease of the pancreas, fragile X syndrome, galactosemia, genetic brain disorders, Giant cell hepatitis (Neonatal hemochromatosis), Gronblad-Strandberg syndrome (pseudoxanthoma elasticum), Gunther disease (congenital erythropoietic porphyria), haemochromatosis, Hallgren syndrome, sickle cell anemia, hemophilia, hepatoerythropoietic porphyria (HEP), Hippel-Lindau disease (von Hippel- Lindau disease), Huntington's disease, Hutchinson-Gilford progeria syndrome (progeria), Hyperandrogenism, Hypochondroplasia, Hypochromic anemia, Immune system disorders, including X-linked severe combined immunodeficiency, Insley-Astley syndrome, Jackson- Weiss syndrome, Joubert syndrome, Lesch-Nyhan syndrome, Jackson-Weiss syndrome, Kidney diseases, including hyperoxaluria, Klinefelter's

syndrome, Kniest dysplasia, Lacunar dementia,Langer-Saldino achondrogenesis, ataxia telangiectasia, Lynch syndrome, Lysyl- hydroxylase deficiency, Machado-Joseph disease, Metabolic disorders, including Kniest dysplasia, Marfan syndrome, Movement disorders, Mowat-Wilson syndrome, cystic fibrosis, Muenke syndrome, Multiple neurofibromatosis, Nance-Insley syndrome, Nance-Sweeney chondrodysplasia, Niemann-Pick disease, Noack syndrome (Pfeiffer syndrome), Osler- Weber-Rendu disease, Peutz-Jeghers syndrome, Polycystic kidney disease, polyostotic fibrous dysplasia (McCune-Albright syndrome), Peutz-Jeghers syndrome, Prader-Labhart- Willi syndrome, hemochromatosis, primary hyperuricemia syndrome (Lesch-Nyhan syndrome), primary pulmonary hypertension, primary senile degenerative dementia, prion disease, progeria (Hutchinson Gilford Progeria Syndrome), progressive chorea, chronic hereditary (Huntington) (Huntington's disease), progressive muscular atrophy, spinal muscular atrophy, propionic acidemia, protoporphyria, proximal myotonic dystrophy, pulmonary arterial hypertension, PXE (pseudoxanthoma elasticum), Rb (retinoblastoma), Recklinghausen disease (neurofibromatosis type I), Recurrent polyserositis, Retinal disorders, Retinoblastoma, Rett syndrome, RFALS type 3, Ricker syndrome, Riley-Day syndrome, Roussy-Levy syndrome, severe achondroplasia with developmental delay and acanthosis nigricans (S ADD AN), Li-Fraumeni syndrome, sarcoma, breast, leukemia, and adrenal gland (SBLA) syndrome, sclerosis tuberose (tuberous sclerosis), SDAT, SED congenital (spondyloepiphyseal dysplasia congenita), SED Strudwick (spondyloepimetaphyseal dysplasia, Strudwick type), SEDc (spondyloepiphyseal dysplasia congenita), SEMD, Strudwick type (spondyloepimetaphyseal dysplasia, Strudwick type), Shprintzen syndrome, Skin pigmentation disorders, Smith-Lemli-Opitz syndrome, South-African genetic porphyria (variegate porphyria), infantile-onset ascending hereditary spastic paralysis, Speech and communication disorders, sphingolipidosis, Tay-Sachs disease, spinocerebellar ataxia, Stickler syndrome, stroke, androgen insensitivity syndrome, tetrahydrobiopterin deficiency, beta- thalassemia, Thyroid disease Tomaculous neuropathy (hereditary neuropathy with liability to pressure palsies) Treacher Collins syndrome, Triplo X syndrome (triple X syndrome), Trisomy 21 (Down syndrome), Trisomy X, VHL syndrome (von Hippel-Lindau disease), Vision impairment and blindness (Alstrom syndrome), Vrolik disease, Waardenburg syndrome, Warburg Sjo Fledelius Syndrome, Weissenbacher-Zweymüller syndrome, Wolf- Hirschhorn syndrome, Wolff Periodic disease, Weissenbacher-Zweymüller syndrome and Xeroderma pigmentosum.

Representative examples of cancers that may be treated and/or prevented using the described compounds of formula (III) or the compounds comprising a moiety of formula (I) include but, are not limited to squamous-cell carcinoma, basal cell carcinoma, adenocarcinoma, hepatocellular carcinomas, and renal cell carcinomas, cancer of the bladder, bowel, breast, cervix, colon, esophagus, head, kidney, liver, lung, neck, ovary, pancreas, prostate, and stomach; leukemias; benign and malignant lymphomas, particularly Burkitt's lymphoma and Non-Hodgkin's lymphoma; benign and malignant melanomas; myeloproliferative diseases; multiple myeloma, sarcomas, including Ewing's sarcoma, hemangiosarcoma, Kaposi's sarcoma, liposarcoma, myosarcomas, peripheral neuroepithelioma, synovial sarcoma, gliomas, astrocytomas, oligodendrogliomas, ependymomas, gliobastomas, neuroblastomas, ganglioneuromas, gangliogliomas, medulloblastomas, pineal cell tumors,

meningiomas, meningeal sarcomas, neurofibromas, and Schwannomas; bowel cancer, breast cancer, prostate cancer, cervical cancer, uterine cancer, lung cancer, ovarian cancer, testicular cancer, thyroid cancer, astrocytoma, esophageal cancer, pancreatic cancer, stomach cancer, liver cancer, colon cancer, melanoma; carcinosarcoma, Hodgkin's disease, Wilms' tumor and teratocarcinomas. Further examples include, T-lineage Acute lymphoblastic Leukemia (T-ALL), T-lineage lymphoblastic Lymphoma (T-LL), Peripheral T-cell lymphoma, Adult T-cell Leukemia, Pre-B ALL, Pre-B Lymphomas, Large B-cell Lymphoma, Burkitts Lymphoma, B-cell ALL, Philadelphia chromosome positive ALL and Philadelphia chromosome positive CML.

In embodiments wherein R^{14} is a BRD9 binder, representative examples of the diseases and/or conditions that may be treated and/or prevented by the use of the described compounds of formula (III) or the compounds comprising a moiety of formula (I) include (but are not limited to) cancer.

A recent review article summarises the potential mechanisms of action of BRD9 in carcinogenesis and also describes various strategies for targeting BRD9 for use as cancer treatments (Zhu et al, OncoTargets and Therapy, 2020, Vol. 13, pages 13191-13200). Previous studies have shown that BRD9 is essential for the proliferation of SMARCB1-deficient cancer cell lines, suggesting it is a therapeutic target for these cancers. (Xiaofeng Wang et. al., Nature Communications, 2019, 10 (1881)). Recent studies also highlight a role of BRD9 in leukemia growth: BRD9 was shown to be required for the proliferation of acute myeloid leukemia (AML) cells (Nature Chemical Biology, 2016, 101038/nchembio.2115). In addition to the role of BRD9 as a functional dependency in certain cancers, BRD9 also plays a pivotal role in immune cells as a regulator of regulatory T cells (Tregs) via transcriptional control of Foxp3 target genes, "BioRxiv, 10.1101/2020.02.26.964981.

In embodiments wherein R^{14} is a BRD9 binder, representative examples of cancers that may be treated and/or prevented using the described compounds of formula (III) or compounds comprising a moiety of formula (I) include, but are not limited to:

(i) brain tumours such as for example acoustic neurinoma, astrocytomas such as pilocytic astrocytomas, fibrillary astrocytoma, protoplasmic astrocytoma, gemistocytary astrocytoma, anaplastic astrocytoma and glioblastoma, brain lymphomas, brain metastases, hypophyseal tumour such as prolactinoma, HGH (human growth hormone) producing tumour and ACTH producing tumour (adrenocorticotropic hormone), craniopharyngiomas, medulloblastomas, meningeomas and oligodendrogliomas;

(ii) nerve tumours (neoplasms) such as for example tumours of the vegetative nervous system such as neuroblastoma sympathicum, ganglioneuroma, paraganglioma (pheochromocytoma, chromaffinoma) and glomus-caroticum tumour, tumours on the peripheral nervous system such as amputation neuroma, neurofibroma, neurinoma (neurilemmoma, Schwannoma) and malignant Schwannoma, as well as tumours of the central nervous system such as brain and bone marrow tumours;

(iii) intestinal cancer such as for example carcinoma of the rectum, colon carcinoma, colorectal carcinoma, anal carcinoma, carcinoma of the large bowel, tumours of the small intestine and duodenum;

(iv) eyelid tumours such as basalioma or basal cell carcinoma;

(v) pancreatic cancer or carcinoma of the pancreas;

(vi) bladder cancer or carcinoma of the bladder;

(vii) lung cancer (bronchial carcinoma) such as for example small-cell bronchial carcinomas (oat cell carcinomas) and non-small cell bronchial carcinomas (NSCLC) such as plate epithelial carcinomas, adenocarcinomas and large-cell bronchial carcinomas;

(viii) breast cancer such as for example mammary carcinoma such as infiltrating ductal carcinoma, colloid carcinoma, lobular invasive carcinoma, tubular carcinoma, adenocystic carcinoma and papillary carcinoma;

(ix) non-Hodgkin's lymphomas (NHL) such as for example Burkitt's lymphoma, low-malignancy non-Hodgkin's lymphomas (NHL) and mucosis fungoides;

(x) uterine cancer or endometrial carcinoma or corpus carcinoma;

(xi) CUP syndrome (Cancer of Unknown Primary);

(xii) ovarian cancer or ovarian carcinoma such as mucinous, endometrial or serous cancer;

(xiii) gall bladder cancer;

(xiv) bile duct cancer such as for example Klatskin tumour;

(xv) testicular cancer such as for example seminomas and non-seminomas;

(xvi) lymphoma (lymphosarcoma) such as for example malignant lymphoma, Hodgkin's disease, non-Hodgkin's lymphomas (NHL) such as chronic lymphatic leukaemia, leukaemic reticuloendotheliosis, immunocytoma, plasmocytoma (multiple myeloma (MM)), immunoblastoma, Burkitt's lymphoma, T-zone mycosis fungoides, large-cell anaplastic lymphoblastoma and lymphoblastoma;

(xvii) laryngeal cancer such as for example tumours of the vocal cords, supraglottal, glottal and subglottal laryngeal tumours;

(xviii) bone cancer such as for example osteochondroma, chondroma, chondroblastoma, chondromyxoid fibroma, osteoma, osteoid osteoma, osteoblastoma, eosinophilic granuloma, giant cell tumour, chondrosarcoma, osteosarcoma, Ewing's sarcoma, reticulo-sarcoma, plasmocytoma, fibrous dysplasia, juvenile bone cysts and aneurysmatic bone cysts;

(xix) head and neck tumours such as for example tumours of the lips, tongue, floor of the mouth, oral cavity, gums, palate, salivary glands, throat, nasal cavity, paranasal sinuses, larynx and middle ear;

(xx) liver cancer such as for example liver cell carcinoma or hepatocellular carcinoma (HCC);

(xxi) leukaemias, such as for example acute leukaemias such as acute lymphatic/lymphoblastic leukaemia (ALL), acute myeloid leukaemia (AML); chronic leukaemias such as chronic lymphatic leukaemia (CLL), chronic myeloid leukaemia (C ML);

(xxii) stomach cancer or gastric carcinoma such as for example papillary, tubular and mucinous adenocarcinoma, signet ring cell carcinoma, adenosquamous carcinoma, small-cell carcinoma and undifferentiated carcinoma;

(xxiii) melanomas such as for example superficially spreading, nodular, lentigo -maligna and acral-lentiginous melanoma;

(xxiv) renal cancer such as for example kidney cell carcinoma or hypernephroma or Grawitz's tumour;

(xxv) oesophageal cancer or carcinoma of the oesophagus;

(xxvi) penile cancer;

(xxvii) prostate cancer;

(xxviii) throat cancer or carcinomas of the pharynx such as for example nasopharynx carcinomas, oropharynx carcinomas and hypopharynx carcinomas;

(xxix) retinoblastoma such as for example vaginal cancer or vaginal carcinoma;

(xxx) plate epithelial carcinomas, adenocarcinomas, in situ carcinomas, malignant melanomas and sarcomas;

(xxxi) thyroid carcinomas such as for example papillary, follicular and medullary thyroid carcinoma, as well as anaplastic carcinomas;

(xxxii) spinalioma, epidormoid carcinoma and plate epithelial carcinoma of the skin;

(xxxiii) thymomas, cancer of the urethra and cancer of the vulva.

In specific examples wherein R^{14} is a BRD9 binder, the cancer is any one selected from the group consisting of hematopoietic malignancies (including but not limited to AML, MM) and solid tumors including but not limited to lung, liver, colon, brain, thyroid, pancreas, breast, ovary and prostate cancer.

Other particular examples of cancers that may be treated by a targeted protein degradation of BRD9 may include cancers that harbour SMARCB1 abnormalities, for example SMARCB1-deficient cancers, such as malignant rhabdoid tumors and several specific types of sarcoma, as well as leukemia such as acute myeloid leukemia (AML).

As used herein, the term “patient” or “subject” is used to describe an animal, such as a mammal (e.g. a human or a domesticated animal), to whom treatment, including prophylactic treatment, with the compositions according to the present disclosure is provided. For treatment of those infections, conditions or disease states which are specific to a specific animal such as a human patient, the term patient refers to that specific animal, including a domesticated animal such as a dog or cat or a farm animal such as a horse, cow, sheep, etc. In general, in the present invention, the term patient refers to a human patient unless stated or implied from the context of the use of the term.

The disclosure also encompasses a method of screening compounds of formula (III) to identify suitable moieties for use at R^{14} and as linkers for use in the compounds of formula (III) described herein, e.g. a compound of formula (III) that is able to effectively modulate, facilitate and/or promote proteolysis of a target protein. This method may assist in identifying suitable linkers for a particular R^{14} such that the level of degradation is further optimised.

The method may comprise:

a. providing a compound of formula (III) comprising:

(i) a first ligand comprising a moiety of formula (I) as defined herein;

(ii) R^{14} as defined for a compound of formula (III) herein; and

(iii) a linker that covalently attaches the first and second ligands;

b. contacting a cell with the compound of formula (III); and

c. detecting degradation of the target protein in the cell.

This method may further comprise the steps of:

d. detecting degradation of the target protein in the cell in the absence of the compound of formula (III); and

e. comparing the level of degradation of the target protein in the cell contacted with the compound of formula (III) to the level of degradation of the target protein in the absence of the compound of formula (III);

wherein an increased level of degradation of the target protein in the cell contacted with the compound of formula (III) indicates that the compound of formula (III) has facilitated and/or promoted the degradation of the target protein.

In such methods, a step of detecting degradation of the target protein may comprise detecting changes in levels of a target protein in a cell. For example, a reduction in the level of the target protein indicates degradation of the target protein. An increased reduction in the level of the target protein in the cell contacted with the compound of formula (III) (compared to any reduction in the levels of target protein observed in the cell in the absence of the compound of formula (III)) indicates that the compound of formula (III) has facilitated and/or promoted the degradation of the target protein.

The method may further comprise providing a plurality of linkers, each one being used to covalently attach the moiety of formula (I) and R^{14} together to form a plurality of compounds of formula (III). The level of degradation provided by each one of the plurality of compounds of formula (III) may be detected and compared. Those compounds of formula (III) showing higher levels of target protein degradation indicate preferred and/or optimal linkers for use with the selected R^{14}.

The method may be carried out *in vivo* or *in vitro*.

The disclosure also provides a library of compounds of formula (III), the library comprising a plurality of compounds of formula (III), the plurality of compounds of formula (III) comprising a plurality of moieties of formula (I) covalently linked to a selected R^{14}. Alternatively, the disclosure provides a library of compounds of formula (III), the library comprising a plurality of compounds of formula (III), the plurality of compounds of formula (III) comprising a plurality of R^{14} covalently linked to a selected moiety of formula (I).

As such, the R^{14} may be pre-selected and the moiety of formula (I) may not be determined in advance, or vice versa. The library may be used to determine the activity of a candidate moiety of formula (I) in modulating, promoting and/or facilitating selective protein degradation of a target protein. The library may be used to determine the activity of a candidate R^{14} in modulating, promoting and/or facilitating selective protein degradation of a target protein.

The disclosure also includes a library of compounds e.g. a library of compounds of formula (III), the library comprising a plurality of compounds of formula (III), the plurality of compounds of formula (III) comprising a plurality of R^{14} and a selected moiety of formula (I). As such, the moiety of formula (I) may be pre-selected and the target protein may not be determined in advance. The library may be used to

determine the activity of a putative R^{14} and its value as a binder of a target protein to facilitate target protein degradation.

According to a further aspect of the disclosure, there is provided a method of making a compound of formula (III) as described herein.

The method of making the compound of formula (III) may comprise the steps of:

(a) providing a compound of formula (II) as described herein;

(b) providing a second ligand or moiety that binds to a target protein (e.g. a target protein binding ligand as defined herein); and

c) linking (e.g. covalently linking) the first and second ligands or moieties using a linker as defined herein.

In other examples, the method of making the compounds of formula (III) may comprise the steps of:

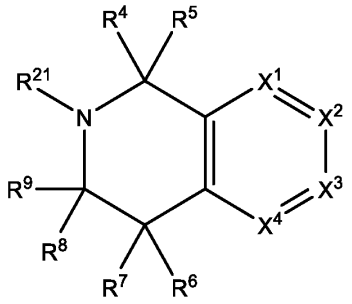
(a) providing a target protein binding ligand (as defined herein);

(b) linking (e.g. covalently linking) a linker (as defined herein) to the target protein binding ligand to provide a R^{14}-linker conjugate (-L-R^{14});

c) further reacting the linker moiety of the conjugate to add and/or form a moiety of formula (I) to provide the compound of formula (III) .

According to a further aspect, the present invention provides intermediate compounds in the synthesis of a compound of formula (III) as defined herein (e.g. a compound of any one of formulae A1 to A7, B1 to B18, C1 to C19, D1 to D19, E1 to E19, F1, G1, H1 to H22, J1 to J4, K1 to K4, M1 to M4, N1 to N4, P1 to P28, Q1 to Q28, R1, S1 to S29, T1 to T4, U1 to U4, V1 to V45 (including the separated enantiomers thereof), W1 to W78 and X1).

According to a further aspect, the present invention provides a compound of formula (IV):



(IV)

wherein

R^4, R^5, R^6, R^7, R^8, and R^9 are each independently selected from H and C_1-C_6 alkyl, wherein each alkyl is optionally substituted with one or more groups independently selected from halogen, OR^2, C_1-C_6 alkyl, CN, and $N(R^3)_2$;

X^1 is selected from N and CR^{10};

X^2 is selected from N and CR^{11};

X^3 is selected from N and CR^{12};

X^4 is selected from N and CR^{13};

R^{10}, R^{11}, R^{12}, and R^{13} are each independently selected from H, halogen, OR^2, C_1-C_6 alkyl, and $N(R^3)_2$ wherein each alkyl is optionally substituted with one or more groups independently selected from halogen, OR^2, and $N(R^3)_2$;

R^{21} is a H or a protecting group (e.g. tert-butoxycarbonyl);

each R^2 is independently selected from H, C_1-C_6 alkyl and C_1-C_6 haloalkyl;

each R^3 is independently selected from H, C_1-C_6 alkyl and C_1-C_6 haloalkyl;

or a pharmaceutically acceptable salt thereof;

wherein:

- at least one of R^{10}, R^{11}, R^{12}, and R^{13} is halogen;
- at least one of X^1, X^2, X^3 and X^4 is N; and
- no more than three of X^1, X^2, X^3 and X^4 are N.

In embodiments of the compounds of formula (IV), R^{10}, R^{11}, R^{12}, and R^{13} are each selected from H or halogen, wherein at least one of R^{10}, R^{11}, R^{12}, and R^{13} is halogen.

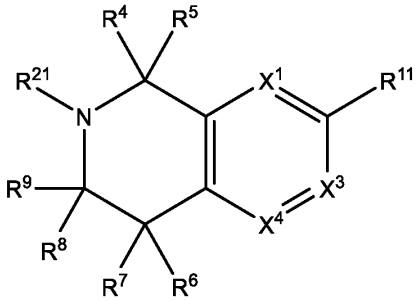
In embodiments of the compounds of formula (IV), one of R^{10}, R^{11}, R^{12}, and R^{13} is halogen and the rest are H.

In embodiments of the compounds of formula (IV), at least one of R^{10}, R^{11}, R^{12}, and R^{13} is F, Cl, or Br, and the rest are H.

In embodiments of the compounds of formula (IV), R^{10}, R^{11}, R^{12}, and R^{13} are each selected from H or Br, wherein at least one of R^{10}, R^{11}, R^{12}, and R^{13} is Br.

For example, one of R^{10}, R^{11}, R^{12}, and R^{13} is Br and the rest are H.

In an embodiment, the compound of formula (IV) is a compound of formula (IVa):



(IVa)

wherein

X^1 is N or CH;

X^3 is N or CH;

X^4 is N or CH;

R^{11} is a halogen (e.g. F, Cl, or Br); and

R^4, R^5, R^6, R^7, R^8, R^9, and R^{21} are as defined for compounds of formula (IV); and

wherein at least one of X^1, X^3 and X^4 is N.

In embodiments of the compounds of formula (IVa), R^{11} is Br.

In embodiments of the compounds of formula (IV) and (IVa), one of X^1, X^2, X^3 and X^4 is N (e.g. X^4 is N; and X^1 is CR^{10}, X^2 is CR^{11}, and X^3 is CR^{12}).

In embodiments of the compounds of formula (IV) and (IVa), at least one of R^4, R^5, R^6, R^7, R^8, and R^9 is methyl or isopropyl.

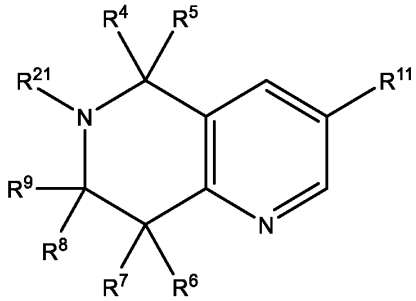
In embodiments of the compounds of formula (IV) and (IVa), one of R^4, R^5, R^6, R^7, R^8, and R^9 is methyl or isopropyl, and the rest are H.

In embodiments of the compounds of formula (IV) and (IVa), one of R^4, R^5, R^6, R^7, R^8, and R^9 is methyl, and the others are H.

In embodiments of the compounds of formula (IV) and (IVa), R^4 is methyl or isopropyl; and R^5, R^6, R^7, R^8, and R^9 are H.

In embodiments of the compounds of formula (IV) and (IVa), R^4 is methyl; and R^5, R^6, R^7, R^8, and R^9 are H.

In an embodiment, the compound of formula (IVa) is a compound of formula (IVb):



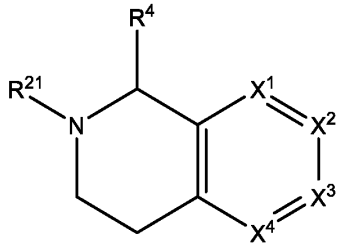
(IVb)

wherein

R^{11} is halogen (e.g. Br); and

R^4, R^5, R^6, R^7, R^8, R^9, and R^{21} are as defined for compounds of formula (IV).

In an embodiment, the compound of formula (IV) is a compound of formula (IVc):



(IVc)

wherein

X^1, X^2, X^3, X^4, R^{10}, R^{11}, R^{12}, R^{13}, and R^{21} are as defined for the compound of formula (IV);

R^4 is methyl or isopropyl; and

wherein:

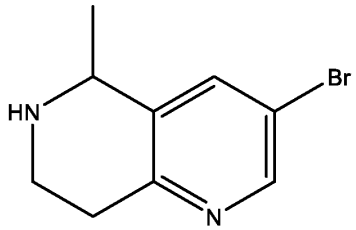
- at least one of R^{10}, R^{11}, R^{12}, and R^{13} is halogen;

- at least one of X^1, X^2, X^3 and X^4 is N; and
- no more than three of X^1, X^2, X^3 and X^4 are N.

In embodiments of the compounds of formula (IVc), R^4 is methyl.

In embodiments of the compounds of formulae (IV), (IVa), (IVb) and (IVc), R^{21} is H.

In an embodiment, the compound of formula (IV) is H17:



H17

In the discussion above, reference is made to a number of terms, which are to be understood to have the meanings provided below, unless a context indicates to the contrary. The nomenclature used herein for defining compounds, in particular the compounds described herein, is intended to be in accordance with the rules of the International Union of Pure and Applied Chemistry (IUPAC) for chemical compounds, specifically the "IUPAC Compendium of Chemical Terminology (Gold Book)" (see A. D. Jenkins *et al.*, Pure & Appl. Chem., 68, 2287-2311 (1996)). For the avoidance of doubt, if an IUPAC rule is contrary to a definition provided herein, the definition herein is to prevail.

As used herein, the term "aryl" refers to a mono- or polycyclic aromatic hydrocarbon system having 6 to 14 carbon atoms, in some cases having 6 to 10 carbon atoms. Representative examples of suitable "aryl" groups include, but are not limited to, phenyl, biphenyl, naphthyl, 1-naphthyl, 2-naphthyl and anthracenyl. As used herein, "substituted aryl" refers to an aryl group as defined herein which comprises one or more substituents on the aromatic ring. When an aryl group is substituted, any hydrogen atom(s) may be replaced with the substituent(s), providing valencies are satisfied.

As used herein, "heteroaryl" may be a single or fused ring system having one or more aromatic rings containing 1 or more, in some cases 1 to 3, in some cases 1 to 2, in some cases a single O, N and/or S heteroatom(s). The term "heteroaryl" may refer to a mono- or polycyclic heteroaromatic system having 5 to 10 ring atoms. Representative examples of heteroaryl groups may include, but are not limited to, pyrrolyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, indolyl, benzofuranyl, benzothiazolyl, benzimidazolyl, indazolyl, benzoxazolyl, benzisoxazolyl etc. As used herein, "substituted heteroaryl" refers to a heteroaryl group as defined herein which comprises one or more substituents on the heteroaromatic ring.

As used herein, the term "alkyl" refers to a straight or branched chain hydrocarbyl group. The chain may be saturated or unsaturated, e.g. in some cases the chain may contain one or more double or triple bonds.

As used herein, "C_1-C_6 alkyl" refers to a straight or branched chain hydrocarbyl group containing from 1 to 6 carbon atoms. As used herein, a "C_1-C_3 alkyl" refers to a straight or branched chain hydrocarbyl group containing from 1 to 3 carbon atoms. Representative examples are methyl, ethyl, n-

propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, isohexyl, neohexyl, etc. When an alkyl group is substituted, any hydrogen atom(s), CH_3,CH_2 or CH group(s) may be replaced with the substituent(s), providing valencies are satisfied.

As used herein, the term “alkylene” refers to an alkanediyl group, i.e. a divalent straight or branched chain saturated hydrocarbyl group. Representative examples are methylene (i.e. -CH_2-), ethylene (i.e. -CH_2CH_2-), n-propylene (i.e. -$CH_2CH_2CH_2$-), iso-propylene (e.g.-$CH(CH_3)CH_2$-), n-butylene (i.e. -$CH_2CH_2CH_2CH_2$-), sec-butylene (i.e. -$CH(CH_3)CH_2CH_2$-), iso-butylene (i.e. -$CH_2CH(CH_3)CH_2$-), tert-butylene (i.e. -$C(CH_3)_2CH_2$-), n-pentylene (i.e. -$CH_2CH_2CH_2CH_2CH_2$-), n-hexylene (i.e. -$CH_2CH_2CH_2CH_2CH_2CH_2$-), etc. When an alkylene group is substituted, any hydrogen atom(s), CH_3,CH_2 or CH group(s) may be replaced with the substituent(s), providing valencies are satisfied.

As used herein, a “cycloalkyl” is a ring containing 3 to 10 carbon atoms, in some cases 3 to 8, or in some cases 5 to 6 carbon atoms. The ring may be saturated or unsaturated, e.g. in some cases the ring may contain one or more double or triple bonds. As used herein, a C_3-C_7 cycloalkyl is a cycloalkyl containing 3 to 7 carbon atoms in the ring. As used herein, a C_3-C_6 cycloalkyl is a cycloalkyl containing 3 to 6 carbon atoms in the ring.

Representative examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclooctynl etc. As used herein, “substituted cycloalkyl” refers to a cycloalkyl group as defined herein which comprises one or more substituents on the cycloalkyl ring. When a cycloalkyl group is substituted, any hydrogen atom(s) may be replaced with the substituent(s), providing valencies are satisfied.

The term “alkenyl” defines monovalent groups derived from alkenes by removal of a hydrogen atom from any carbon atom, wherein the term “alkene” is intended to define acyclic branched or unbranched hydrocarbons having the general formula CnH_{2n}, wherein n is an integer ≥2. Examples of alkenyl groups include ethenyl, n-propylenyl, iso-propylenyl, n-butylenyl, sec-butylenyl, iso-butylenyl and tert-butylenyl. When an alkenyl group is substituted, any hydrogen atom(s) may be replaced with the substituent(s), providing valencies are satisfied. Where the alkenyl comprises a divalent hydrocarbon radical, this moiety may sometimes be referred to herein as an alkenylene.

The term “alkynyl” defines monovalent groups derived from alkynes by removal of a hydrogen atom from any carbon atom, wherein the term “alkyne” is intended to define acyclic branched or unbranched hydrocarbons having the general formula CnH_{2n-2}, wherein n is an integer ≥2. Examples of alkynyl groups include ethynyl, n-propylynyl, iso-propylynyl, n-butylynyl, sec-butylynyl, iso-butylynyl and tert-butylynyl. When an alkynyl group is substituted, any hydrogen atom(s) may be replaced with the substituent(s), providing valencies are satisfied. Where the alkynyl comprises a divalent hydrocarbon radical, this moiety may sometimes be referred to herein as an alkynylene.

“Benzyl” as used herein refers to a -CH_2Ph group. As used herein, a “substituted benzyl” refers to a benzyl group as defined herein which comprises one or more substituents on the aromatic ring. When a benzyl group is substituted, any hydrogen atom(s) may be replaced with the substituent(s), providing valencies are satisfied.

As used herein, “heterocycloalkyl” refers to a monocyclic or polycyclic ring having in one or more rings of the ring system at least one heteroatom selected from O, N and S (e.g. from one to five ring heteroatoms independently selected from the group consisting of O, N and S). The one or more rings may also contain one or more double bonds provided that the one or more rings are not fully aromaticized. The one or more rings of the heterocycloalkyl may comprise 3 to 10 atoms, in some cases 3 to 8 atoms. The one or more rings may be aliphatic. The one or more rings may be saturated or unsaturated, e.g. in some cases the one or more rings may contain one or more double or triple bonds. Any N heteroatom present in the heterocycloalkyl group may be C_1 to C_6 alkyl-substituted. In some cases, the heterocycloalkyl is a monocyclic or bicyclic ring, such as a monocyclic ring. Representative examples of heterocycloalkyl groups include, but are not limited to, pyrrolidinyl, tetrahydrofuranyl, dioxolanyl, dithiolanyl, thiazolidinyl, isothiazolidinyl, oxazolidinyl, isoxazolidinyl, pyrazolidinyl, imidazolidinyl, piperidinyl, piperazinyl, N-alkylpiperazinyl, morpholinyl, dioxanyl, oxazolidinyl, tetrahydropyranyl, diazaspiroundecane, diazaspiroheptane, azaspiroheptane, diazaspirodecane, octahydropyrrolopyrrole, etc. As used herein, “substituted heterocycloalkyl” refers to a heterocycloalkyl group as defined herein which comprises one or more substituents on the heterocycloalkyl ring. Where the heterocycloalkyl comprises a divalent radical, this moiety may sometimes be referred to herein as heterocycloalkylene.

As used herein, -CH(aryl)-, –CH(substituted aryl)-, -CH(heteroaryl)- and –CH(substituted heteroaryl) refers to a methylene moiety that comprises an aryl, substituted aryl, heteroaryl or substituted heteroarylsubstituent and is the attachment point for the linker L.

As used herein, where a group comprising carbon atoms is defined as “saturated”, only single bonds bind the carbon atoms to one another. Where a group comprising carbon atoms is defined as “unsaturated”, at least two of the carbon atoms are connected by a double or triple bond.

The term “spiro” is used to refer to moieties comprising two or more ring systems, wherein at least two of the ring systems are connected by just one atom (typically a quaternary carbon atom).

“Monocyclic” is used herein to refer to moieties comprising one ring of atoms. “Bicyclic” is used herein to refer to moieties that feature two joined rings of atoms. “Tricyclic” is used herein to refer to moieties that feature three joined rings of atoms. “Polycyclic” is used herein to refer to moieties that comprise two or more joined rings. Unless the context indicates otherwise, bicyclic and polycyclic systems may comprise a fused ring system (in which at least two rings share a common bond). In other examples, the two or more rings may be joined by a bond between atoms on each of the two or more rings. In other examples, the bicyclic system may comprise a spiro centre (as defined above).

The term “bridged” is used herein to refer to a cyclic compound, or ring, comprising two bridgehead atoms (typically two carbon atoms of the cyclic compound or ring) that are connected by one or more atoms lying outside of the ring (such as one to three atoms lying outside of the ring). Bridged rings comprise two rings sharing three or more atoms. In some examples, the bridgehead atoms are separated within the ring by at least one carbon atom. In some examples, a ring may be bridged by between 1 and 3 bridging atoms which lie outside of the ring to form a bridging group (optionally wherein

the bridging atoms are selected from C, N, O and S). As used herein, a "C_{1-3} bridge" is a bridging group comprising between 1 and 3 carbon bridging atoms. The bridging group may comprise one to three atoms lying outside of the ring, of which one, two or three of those atoms are carbon. In some cases, the bridging group may additionally comprise non-carbon atoms (such as a heteroatom selected from N, O and S). By way of example, as used herein, a "C_{1-3} bridge" may refer to a bridging group comprising between 1 and 3 atoms of which one, two or three are carbon and the remainder (if any) are selected from N, O and S. The bridging group may be a C_1 to C_3 alkylene (such as methylene, ethylene or propylene). The C_1 to C_3 alkylene bridging group may be optionally substituted with any suitable substituent as described herein. For example, C_1 to C_3 alkylene bridging group may be optionally substituted with one or two substituents each independently selected from the group consisting of halo, C_1 to C_3 alkyl, C_1 to C_3 haloalkyl and C_1 to C_3 alkoxy.

The term "fused" is used to refer to moieties comprising two or more ring systems, wherein at least two of the ring systems are connected by a [1,2] ring junction, i.e. a moiety comprising two or more ring systems wherein two, or more, of the rings present share a bond in each respective ring structure.

The term "aliphatic" refers to acyclic or cyclic, saturated or unsaturated compounds, excluding aromatic compounds, where "aromatic" defines a cyclically conjugated molecular entity with a stability (due to delocalisation) significantly greater than that of a hypothetical localised structure. The Hückel rule is often used in the art to assess aromatic character; monocyclic planar (or almost planar) systems of trigonally (or sometimes digonally) hybridised atoms that contain (4n+2) π-electrons (where n is a non-negative integer) will exhibit aromatic character. The rule is generally limited to n = 0 to 5.

As used herein, an alkoxy refers to an alkyl group, as defined above, appended to the parent molecular moiety through an oxy group, -O-. As used herein, a C_{1-4}alkoxy refers to a C_{1-4} alkyl group (as defined above), appended to the parent molecular moiety through a oxy group, -O-. Representative examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy, tert-butoxy, pentyloxy, hexyloxy etc.

The term "alkylamino" is used herein to refer to a moiety derived from an amino (NH_2) moiety in which one or both hydrogen atom(s) of the amino is/are substituted with one or two alkyl moieties. Examples of alkylamino groups include dimethylamino, diethylamino and the like.

As used herein, a "substituent" may include, but is not limited to, hydroxy, thiol, carboxyl, cyano (CN), nitro (NO_2), halo, haloalkyl (e.g. a C_1 to C_6 haloalkyl or a C_1 to C_4 haloalkyl), an alkyl group (e.g. C_1 to C_{10} or C_1 to C_6), an alkenyl group (e.g. C_2 to C_6), an alkynyl group (e.g. C_2 to C_6), aryl (e.g. phenyl and substituted phenyl for example benzyl or benzoyl), morpholino, N-C_{1-6}alkylenylmorpholine, alkoxy group (e.g. C_1 to C_6 alkoxy or C_1 to C_4 alkoxy), haloalkoxy (e.g. C_1 to C_4 haloalkoxy), aryloxy (e.g. phenoxy and substituted phenoxy), hydroxyalkynyl (e.g. C_2 to C_6). Thioether (e.g. C_1 to C_6 alkyl or aryl thioether), alkylthio (e.g. C_1 to C_6alkylthio), cyanoalkyl (e.g. C_1 to C_6), oxo, keto (e.g. C_1 to C_6 keto), ester (e.g. C_1 to C_6 alkyl or aryl ester, which may be present as an oxyester or carbonylester on the substituted moiety), thioester (e.g. C_1 to C_6 alkyl or aryl thioester), alkylene ester (such that attachment is on the alkylene group, rather than at the ester function which is optionally substituted with a C_1 to C_6 alkyl or aryl group), amine (including monoalkylamino, dialkylamino, a five- or six-membered cyclic alkylene

amine optionally substituted with one or more halo, further including a C_1 to C_6 alkyl amine or a C_1 to C_6 dialkyl amine which alkyl groups may be substituted with one or two hydroxyl groups, and also including alkylphenylamino or alkylphenyl(alkyl)amino groups), amido (including $–C(O)NH_2$, -C(O)NH(alkyl) such as -C(O)NH(C_{1-4}alkyl), –C(O)N(alkyl)$_2$ such as –C(O)N(C_{1-4}alkyl)$_2$, -NHC(O)alkyl such as -NHC(O)C_{1-4}alkyl, -NHC(O)(phenyl), -N(alkyl)C(O)(alkyl) such as -N(C_{1-4}alkyl)C(O)(C_{1-4}alkyl), -N(alkyl)C(O)(phenyl) such as -N(C_{1-4}alkyl)C(O)(phenyl), N-C_{1-6}alkylenylamino, amido (e.g. which may be substituted with one or two C_1 to C_6 alkyl groups (including a carboxamide which is optionally substituted with one or two C_1 to C_6 alkyl groups), aminoalkyl (e.g. C_1 to C_4 aminoalkyl), alkanol (e.g. C_1 to C_6 alkyl, C_1 to C_4 alkyl or aryl alkanol), or carboxylic acid (e.g. C_1 to C_6 alkyl or aryl carboxylic acid), sulfoxide, sulfone, sulfinimide, sulfonamide, and urethane (such as -O-C(O)-NR_2 or–NI-C(O)-O-R, wherein each R in this context is independently selected from C_1 to C_6 alkyl or aryl), a heteroaryl, arylalkyl (such as an arylC_{1-4}alkyl), heteroarylalkyl (such as a heteroarylC_{1-4}alkyl), -OC_{1-4}alkylphenyl, -C(O)alkyl such as –C(O)(C_{1-4}alkyl), -C(O)alkylphenyl such as C(O)(C_{1-4}alkylphenyl), -C(O)haloalkyl such as –C(O)(C_{1-4}haloalkyl), -SO_2(alkyl) such as –SO_2(C_{1-4}alkyl), -SO_2(phenyl), -SO_2haloalkyl such as OSO_2(C_{1-4}haloalkyl), -SO_2NH_2, -SO_2NH(alkyl) such as –SO_2NH(C_{1-4}alkyl), -SO_2NH(phenyl), -$NHSO_2$(alkyl) such as –$NHSO_2$(C_{1-4}alkyl), -$NHSO_2$(phenyl), -$NHSO_2$(haloalkyl) such as –$NHSO_2$(C_{1-4}haloalkyl), -S-C_{1-3}haloalkyl, -$CH_2C(O)N(R^C)_2$, -C_{3-4}alkynyl($NR^C)_2$, deuteroC_{2-4}alkynyl, (C_{1-3}alkoxy)haloC_{1-3}alkyl-, C_{3-6}cycloalkyl (wherein said C_{3-6}cycloalkyl is optionally substituted with halo or C_{1-3}alkyl), HC(O)-, -CO_2R^C, or -$CO_2N(R^C)_2$, wherein R^C is hydrogen or C_{1-3}alkyl.

In some examples, and unless the context indicates otherwise, a “substituent” may include, but is not limited to, halo, C_1 to C_6 alkyl, C_1 to C_6 haloalkyl, C_1 to C_6 alkoxy, hydroxyl, oxo, amino (such as $NR^{1'}R^{2'}$), amido (such as –(C=O)$NR^{1'}R^{2'}$ or $NR^{1'}$(C=O)C_1-C_6 alkyl), keto (such as –(C=O)C_1-C_6 alkyl), and ester (such as -O(C=O)C_1-C_6 alkyl or –(C=O)OC_1-C_6 alkyl); and wherein $R^{1'}$ and $R^{2'}$ are each independently selected from H and C_1 to C_6 alkyl.

In further examples, and unless the context indicates otherwise, a “substituent” may include, but is not limited to, halo, C_1 to C_6 alkyl, C_1 to C_6 haloalkyl and C_1 to C_6 alkoxy.

As used herein, a “halo” or “halogen” group may be F, Cl, Br, or I. In some examples, halo or halogen may be F.

As used herein, “haloalkyl” may be an alkyl group in which one or more hydrogen atoms thereon have been replaced with a halogen atom, e.g. a C_1-C_6 haloalkyl may be a C_1 to C_6 alkyl in which one or more hydrogen atoms thereon have been replaced with a halogen atom. By way of a representative example, a C_1-C_6 haloalkyl may be a fluoroalkyl, such as fluoromethyl (-CH_2F), difluoromethyl (-CHF_2), trifluoromethyl (-CF_3) or 1,1-difluoroethyl (-CH_2CHF_2), and in particular fluoromethyl (-CH_2F), difluoromethyl (-CHF_2), or trifluoromethyl (-CF_3).

Cycloalkyl in which one or more hydrogen atoms thereon have been replaced with a halogen atom.

As used herein, a “haloalkoxy” (e.g. C_{1-4} haloalkoxy) refers to an alkoxy (e.g. C_1-C_4 alkoxy) as defined above, in which one or more hydrogen atoms thereon have been replaced with a halogen atom.

As used herein, the terms “aryl”, “substituted aryl”, “heteroaryl”, “substituted heteroaryl”, “cycloalkyl”, “C_1 to C_6 alkyl”, “heterocycloalkyl”, and “substituted heterocycloalkyl” may refer to either a monovalent radical species or a divalent radical species.

It should be understood that throughout this specification, the terms “comprise”, “comprising” and/or “comprises” is/are used to denote that aspects, embodiments and examples of this disclosure “comprise” a particular feature or features. It should be understood that this/these terms may also encompass aspects, embodiments and/or examples which “consist essentially of” or “consist of” the relevant feature or features.

EXAMPLES

List of Abbreviations:

μL = microliter

μM = micromolar

NMR = Nuclear Magnetic Resonance

ACN = acetonitrile

Ac = acetate

AcOH or HOAc = acetic acid

AIBN = azobisisobutyronitrile

BINAP = (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl)

Boc = tert-butoxycarbonyl

bs = broad singlet

°C = degrees Celsius

Cbz = benzyl carbamate

d = doublet

δ = chemical shift

DCE = dichloroethane

DCM = dichloromethane

dba =dibenzylideneacetone

DIPEA = N, N-diisopropylethylamine, or Hünig's base

DMAP = 4-dimethylaminopyridine

DMF = N,N-dimethylformamide

DMSO = dimethylsulfoxide

dppf = 1,1′-ferrocenediyl-bis(diphenylphosphine)

EtOAc = ethyl acetate

EtOH = ethanol

Et_3N = triethylamine

g or G = gram

h or H = hour(s)

HATU = 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate

HPLC = high performance liquid chromatography

Hz = hertz

iPr = isopropyl

J = coupling constant (given in Hz unless otherwise indicated)

LCMS = liquid chromatography mass spectrometry

LDA = lithium diisopropylamide

m = multiplet

M = molar

$M+H^+$ = parent mass spectrum peak plus H^+

MeCN = acetonitrile

MeOH = methanol

mg = milligram

min = minutes

mL = milliliter

mM = millimolar

mmol = millimole

MP-$CNBH_3$ = macroporous polymer supported cyanoborohydride

MS = mass spectrum

MsCl = methanesulfonyl chloride

MTBE = methyl tert-butyl ether

NBS = N-bromosuccinimide

nM = nanomolar

NMP = N-methyl-2-pyrrolidone

pTsOH = p-toluenesulfonic acid

q = quartet

RT or r.t. = room temperature

STAB = sodium triacetoxyborohydride

t = triplet

TBAF = tetra-n-butylammonium fluoride

TFA = trifluoroacetic acid

THF = tetrahydrofuran

TLC = thin layer chromatography

TMSCl = trimethylsilyl chloride

XPhos = 2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

Chemistry - Materials and Methods

All chemicals, unless otherwise stated were commercially available and used without further purification. Solvents were anhydrous and reactions preformed under positive pressure of nitrogen or argon.

Flash column chromatography (FCC) was performed using a Teledyne Isco Combiflash Rf or Rf200i. Prepacked columns RediSep Rf Normal Phase Disposable Columns were used. NMR data was acquired in Bruker Avance Neo nano bay 400 MHz NMR Spectrometer. Chemical Shifts are reported in ppm relative to dimethyl Sulfoxide (δ 2.50), methanol (δ 3.31), chloroform (δ7.26) or other solvent as indicated in NMR spectral data. A small amount (1-5 mg) of sample is dissolved in an appropriate deuterated solvent (0.6 mL).

Preparative HPLC was performed on a Gilson Preparative HPLC System with a Waters X-Bridge C18 column (100 mm x 19 mm; 5 µm particle size) and a gradient of 5% to 95% acetonitrile in water over 10 min, flow 25 mL/min, with 0.1% formic acid in the aqueous phase.

Liquid Chromatography Mass Spectra (LC-MS) were recorded using positive ion electron spray ionisation (ESI^+) on an Agilent InfinityLab Single Quadrupole LC/MSD with a Waters XBridge® C18 3.5µm column (2.1mm × 50mm) using H_2O+MeCN (5-95%) + 0.1% HCO_2H or H_2O+MeCN (20-95%) + 0.1% HCO_2H as eluent, using a linear gradient over 3 minutes. Alternatively, a Shimadzu LC; Prominence-I series instrument was used, with the following set up:

HPLC Method A	
Column: X-Bridge C8 (150 × 4.6 mm, 5.0 µm)	
Detection: UV @ 210-400 nm(Max Plot)	
Sample Diluent: Acetonitrile and Water	
Mobile Phase A: 10mM Ammonium Acetate in water	
Mobile Phase B: Acetonitrile	
Flow rate:1.5mL/Min	
Runtime:12.0 Min	
Elution: Gradient elution	
Time in Min	%of Mobile Phase B
0.01	10
8.0	100
10.0	100
10.01	10
12.0	10

HPLC Method B	
Column: X-select CSH C18 (150 × 4.6 mm, 5.0 µm)	
Column Temperature: Ambient	
Detection: UV @ 210-400 nm(Max Plot)	
Sample Diluent: Acetonitrile and Water	
Mobile Phase A: 0.1% Formic acid in water	
Mobile Phase B: Acetonitrile	
Runtime:10.0Min	
Flowrate:2.0mL/Min	
Elution: Gradient elution	
Time in Min	%of Mobile Phase B
0	5
8	100
8.01	5
10	5

Example 1: Synthesis of compounds A1 to A7

Compounds A1 to A7 (shown in Table 1) were prepared by the following procedure:

To a suspension of *t*BuOK (2.5 eq) in THF, was added a solution of 1-(isocyanomethylsulfonyl)-4-methyl-benzene (1.5 eq) in THF at -78 °C. The reaction mixture was stirred at -78 °C for 30 min and a solution of the starting aldehyde (1 eq) in THF was added. After stirring for 1 h at -78 °C, MeOH (0.3M) was added and the reaction mixture was warmed up to RT, and heated to 60 °C for 2 h. The reaction progress was monitored by TLC. The reaction mixture was allowed to cool to RT, diluted with water, extracted with ethyl acetate and the organic layer was washed with brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The resulting crude residue was purified by column chromatography (EtOAc in hexane) to yield the product.

Table 1: Compounds A1 to A7

Compound number	Starting material	Product name	LCMS m/z $[M-H]^-$
A1	2-bromo-4-methylbenzaldehyde	2-(2-bromo-4-methylphenyl)acetonitrile	208.1$^-$
A2	3-bromo-4-fluorobenzaldehyde	2-(3-bromo-4-fluorophenyl)acetonitrile	no m/z
A3	2-bromo-4-chlorobenzaldehyde	2-(2-bromo-4-chlorophenyl)acetonitrile	228.0$^-$
A4	2-bromo-4-methoxybenzaldehyde	2-(2-bromo-4-methoxyphenyl)acetonitrile	Used crude
A5	2-bromo-3-fluorobenzaldehyde	2-(2-bromo-3-fluorophenyl)acetonitrile	212.0$^-$
A6	2-bromo-5-methylbenzaldehyde	2-(2-bromo-5-methylphenyl)acetonitrile	207.9$^-$
A7	2-bromo-5-fluoro-4-methylbenzaldehyde	2-(2-bromo-5-fluoro-4-methylphenyl)acetonitrile	228.2$^-$

Example 2: Synthesis of compounds B1 to B12

Compounds B1 to B12 (shown in Table 2) were prepared by the following procedure:

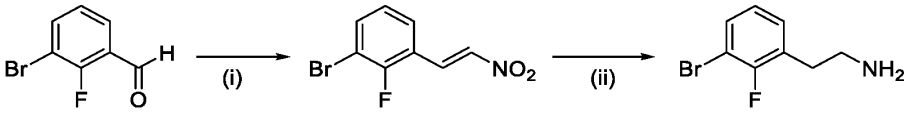
To a stirred solution of the starting compound (1 eq) in THF at 0 °C was added BH_3·THF (1 M in THF, 3 eq). The reaction was allowed to warm to RT, and stirred for 12 h. The reaction mixture was cooled to 0 °C and quenched with MeOH. The reaction was concentrated *in vacuo*. H_2O was added and the organic phase was extracted with EtOAc. The combined organic fractions were dried over with sodium sulphate, filtered and concentrated to yield the product. The crude material was used in the next step without any further purification.

Table 2: Compounds B1 to B12

Compound number	Starting material	Product name	LCMS m/z $[M+H]^+$
B1	A1	2-(2-bromo-4-methylphenyl)ethan-1-amine	216.0
B2	2-(4-bromo-3-fluorophenyl)acetonitrile	2-(4-bromo-3-fluorophenyl)ethan-1-amine	220.0
B3	2-(4-bromo-2-fluorophenyl)acetonitrile	2-(4-bromo-2-fluorophenyl)ethan-1-amine	220.0
B4	2-(2-bromo-4-fluorophenyl)acetonitrile	2-(2-bromo-4-fluorophenyl)ethan-1-amine	220.2

Compound number	Starting material	Product name	LCMS m/z $[M+H]^+$
B5	2-(2-bromo-5-fluorophenyl)acetonitrile	2-(2-bromo-5-fluorophenyl)ethan-1-amine	220.2
B6	A2	2-(3-bromo-4-fluorophenyl)ethan-1-amine	220.0
B7	A3	2-(2-bromo-4-chlorophenyl)ethan-1-amine	234.2
B8	A4	2-(2-bromo-4-methoxyphenyl)ethan-1-amine	230.0
B9	A5	2-(2-bromo-3-fluorophenyl)ethan-1-amine	220.0
B10	A6	2-(2-bromo-5-methylphenyl)ethan-1-amine	216.2
B11	A7	2-(2-bromo-5-fluoro-4-methylphenyl)ethan-1-amine	234.0
B12	2-(4-bromo-2-methoxyphenyl)acetonitrile	2-(4-bromo-2-methoxyphenyl)ethan-1-amine	Used crude

Example 3: Synthesis of compound B13



B13

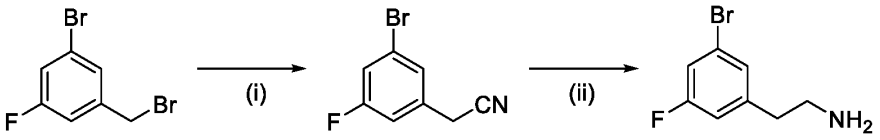
Step (i) Preparation of (E)-1-bromo-2-fluoro-3-(2-nitrovinyl)benzene

To a stirred solution of 3-bromo-2-fluorobenzaldehyde (20 g, 99 mmol) in nitromethane (100 mL) was added ammonium acetate (3.8 g, 49.3 mmol) at RT. The reaction mixture was heated at 100 °C for 3 h. The progress of reaction was monitored by TLC. Upon completion, the reaction mixture was allowed to cool to RT, and the solvent was evaporated under vacuum. The crude residue was diluted with H_2O, the aqueous phase was extracted with EtOAc (2 x 500 mL). The combined organic layer was dried over sodium sulphate, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (10% EtOAc in hexane) to give (E)-1-bromo-2-fluoro-3-(2-nitrovinyl)benzene (13.5 g, 50.9 mmol, 52%). LCMS: m/z: 245.2 $[M+H]^+$

Step (ii): Preparation of 2-(3-bromo-2-fluorophenyl)ethan-1-amine (B13)

To a solution of lithium aluminium hydride (2 M in THF, 123 mL, 246 mmol) in THF (220 mL) at -78 °C was added H_2SO_4 (10 mL) dropwise. After 15 min, a solution of (E)-1-bromo-2-fluoro-3-(2-nitrovinyl)benzene (12.1 g, 49.2 mmol) in THF (120 mL) was added at -78 °C. The reaction mixture was allowed to warm to RT and stirred for 1hr. The progress of reaction was monitored by TLC. The reaction mixture was quenched by addition of an aq. solution of NaOH at 0 °C. The aqueous phase was extracted with EtOAc. The combined organic layer was dried over sodium sulphate, filtered, and concentrated in vacuo to afford 2-(3-bromo-2-fluorophenyl)ethan-1-amine (8.6 g, 29.3 mmol, 60%). The crude material was used in the next step without any further purification. LCMS: m/z 218.2 $[M+H]^+$

Example 4: Synthesis of compound B14



B14

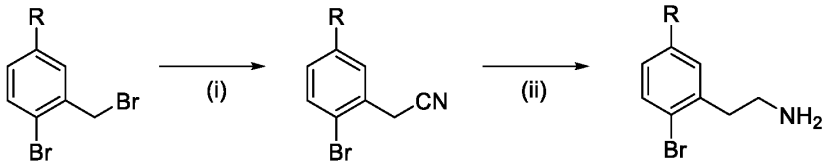
Step (i): Preparation of 2-(3-bromo-5-fluorophenyl)acetonitrile

To a stirred solution of 1-bromo-3-(bromomethyl)-5-fluorobenzene (12 g, 44.8 mmol) in THF (120 mL) was added dropwise trimethylsilyl cyanide (6.72 mL, 53.7 mmol) at RT. The reaction mixture was cooled to 0 °C, TBAF (44.8 mL, 44.8 mmol) was slowly added, and stirred for 10 mins at 0 °C. The reaction mixture was allowed to warm to RT and stirred for 18 h. The progress of the reaction was monitored by TLC. The reaction mixture was quenched with ice-cold water. The aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organic layer was dried over sodium sulphate and concentrated under vacuum to afford the crude product which was purified by column chromatography (8 % EtOAc in hexane) to give 2-(3-bromo-5-fluorophenyl)acetonitrile (7 g, 32.7 mmol, 73%). LCMS: m/z 214.0 $[M+H]^+$

Step (ii): Preparation of 2-(3-bromo-5-fluorophenyl)ethan-1-amine (B14)

To a stirred solution of 2-(3-bromo-5-fluorophenyl)acetonitrile (14 g, 65.4 mmol) in THF (140 mL) was added BH_3·THF (1M in THF, 196 mL, 196 mmol) dropwise, under nitrogen, at 0 °C. The reaction mixture was allowed to warm to RT, and stirred for 12 h. The reaction mixture was cooled to 0 °C, and quenched by adding MeOH (50 mL). The solvent was evaporated under vacuum. The residue was partitioned between H_2O and DCM. The aqueous phase was extracted with DCM (2 x 150 mL). The combined organic fractions were dried over with sodium sulphate, filtered and concentrated *in vacuo* to give 2-(3-bromo-5-fluorophenyl)ethan-1-amine (13 g, 59.6 mmol, 91%). The crude material was used in the next step without any further purification. LCMS: m/z: 218.0 $[M+H]^+$

Example 5: Synthesis of compounds B15 and B16



R=OMe (B15)
Cl (B16)

Step (i): Preparation of 2-(2-bromo-5-methoxyphenyl)acetonitrile or 2-(2-bromo-5-chlorophenyl)acetonitrile

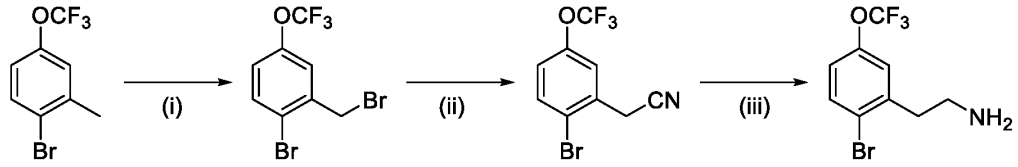
To a stirred solution of the appropriate benzylbromide (1 eq), and trimethylsilyl cyanide (1.3 eq) in THF was added slowly *tetra-n*-butylammonium fluoride (1 M in THF, 1 eq) at 0° C under inert atmosphere. The reaction mixture was stirred at RT overnight. The progress of the reaction was monitored by LCMS. After completion, the reaction mixture was quenched with ice-water and extracted with EtOAc. The combined organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (EtOAc: petrol ether) to give 2-(2-bromo-5-methoxyphenyl)acetonitrile (3.6 g, 15.8 mmol, 88%) as a

white solid. LCMS m/z = NA or 2-(2-bromo-5-chlorophenyl)acetonitrile (70 g, 267 mmol, 76%) as a white solid. LCMS m/z = 228.0 $[M-2H]^+$.

Step (ii): Preparation of 2-(2-bromo-5-methoxyphenyl)ethan-1-amine or 2-(2-bromo-5-chlorophenyl)ethan-1-amine (B15 or B16)

To a stirred solution of the appropriate benzyl cyanide (1 eq) in THF was added borane tetrahydrofuran complex (2 eq) dropwise at 0 °C under inert atmosphere. The reaction mixture was allowed to warm to RT and stirred for 10 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was quenched with MeOH at 0° C, partitioned between EtOAc and H_2O. The aqueous layer was extracted with EtOAc. The combined organic extract was washed with H_2O and brine, dried (Na_2SO_4), and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (EtOAc in *n*-hexane) to afford 2-(2-bromo-5-methoxyphenyl)ethan-1-amine (B15; 3.6 g, 11.6 mmol, 75%) as a white solid. **LCMS m/z** = 280.1 $[M+H]^+$ or 2-(2-bromo-5-chlorophenyl)ethan-1-amine (B16; 30 g, 102 mmol, 79%) as a white gum. **LCMS m/z** = 236.0 $[M+2H]^+$.

Example 6: Synthesis of B17



B17

Step (i): Preparation of 1-bromo-2-(bromomethyl)-4-(trifluoromethoxy)benzene

To a stirred solution of 1-bromo-2-methyl-4-(trifluoromethoxy)benzene (19 g, 74.5 mmol) in DCE (190 mL) was added NBS (15.9 g, 89 mmol) and AIBN (1.2 g, 7.5 mmol) at RT. The reaction mixture was heated to 65 °C for 12 h. The reaction mixture was allowed to cool to RT and quenched by addition of ice-cold water. The aqueous layer was separated and extracted with DCM (3 x 250 mL). The combined organic layer was dried over sodium sulphate and concentrated in vacuo. The crude product was purified by column chromatography (1% EtOAc in hexane) to afford 1-bromo-2-(bromomethyl)-4-(trifluoromethoxy)benzene (16 g, 47.9 mmol, 64%).

Step (ii): Preparation of 2-(2-bromo-5-(trifluoromethoxy)phenyl)acetonitrile

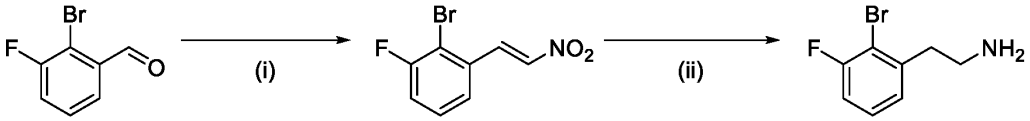
To a stirred solution of 1-bromo-2-(bromomethyl)-4-(trifluoromethoxy)benzene (16 g, 47.9 mmol) in THF (160 mL) was added trimethylsilyl cyanide (7.2 mL, 57.5 mmol) dropwise at RT. The reaction mixture was cooled to 0 °C, TBAF (47.9 mL, 47.9 mmol) was slowly added and stirred for 10 mins. The reaction mixture was allowed to warm to RT and stirred for 18 h. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was quenched with ice-cold water. The aqueous phase was separated and extracted with EtOAc (3 x 250 mL). The combined organic layer was dried over sodium sulphate and concentrated in vacuo. The crude product was purified by column chromatography (8% EtOAc in hexane) to afford 2-(2-bromo-5-(trifluoromethoxy)phenyl)acetonitrile (10 g, 33.9 mmol, 71%). **LCMS m/z** = 277.9 $[M-H]^-$.

Step (iii): Preparation of 2-(2-bromo-5-(trifluoromethoxy)phenyl)ethan-1-amine (B17)

To a stirred solution of 2-(2-bromo-5-(trifluoromethoxy)phenyl)acetonitrile (10 g, 35.7 mmol) in THF (100 mL) was added a solution of $BH_3 \cdot THF$ (1M in THF, 71.4 mL, 71.4 mmol) slowly under nitrogen

at 0 °C. The reaction mixture was allowed to warm to RT and stirred for 16 h. The reaction mixture was cooled to 0 °C and quenched with MeOH (50 mL). The solvent was removed in vacuo and the crude residue was partitioned between H_2O and DCM. The aqueous phase was separated and extracted with DCM (2 x 200 mL). The combined organic fractions were dried over with sodium sulphate, filtered and concentrated to obtain 2-(2-bromo-5-(trifluoromethoxy)phenyl)ethan-1-amine (B17; 8.5 g, 21.24 mmol, 60%). The crude material was used in the next step without any further purification. **LCMS m/z** = 283.9 $[M+H]^+$

Example 7: Synthesis of B18



B18

Step (i): Synthesis of (E)-2-bromo-1-fluoro-3-(2-nitrovinyl)benzene

To a stirred solution of 2-bromo-3-fluorobenzaldehyde (25 g, 123 mmol) in nitromethane (250 mL), was added ammonium acetate (6.64 g, 86 mmol) at room temperature and stirred for 10 min. The resulting solution was stirred at reflux for 2 hours. The reaction was monitored by TLC (10% EtOAc/hexanes). After completion of the reaction, water was added and the reaction mixture was extracted with EtOAc (2 x 750 mL). The combined organic fractions were washed with brine solution and dried over sodium sulphate, filtered and concentrated under reduced pressure to provide crude (E)-2-bromo-1-fluoro-3-(2-nitrovinyl)benzene (23 g, 44.7 mmol, 36.3% yield) as a yellow solid.

Step (ii): Synthesis of 2-(2-bromo-3-fluorophenyl)ethan-1-amine (B18):

To a stirred solution of lithium aluminium hydride (174 mL, 348 mmol) in THF (200 mL) was added H_2SO_4 (8.23 mL, 154 mmol) at 0°C. After stirring for 20 min, a solution of a (E)-2-bromo-1-fluoro-3-(2-nitrovinyl)benzene (19 g, 77 mmol) in THF (17 mL) was added dropwise over 20 min at 0°C. The resulting reaction mixture was stirred at room temperature for 16 h. Reaction was monitored by TLC (10% EtOAc/hexanes) and LCMS. The reaction mixture was quenched with 2M KOH solution (160 mL) and extracted with EtOAc (300 mL x 2). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford 2-(2-bromo-3-fluorophenyl)ethan-1-amine (B18; 15 g, 48.1 mmol, 62.3% yield) as a colourless liquid. **LCMS: m/z**: MM-ES+APCI, positive $[M+2H]^+$ 220.0.

Example 8: Synthesis of compounds C1 to C17

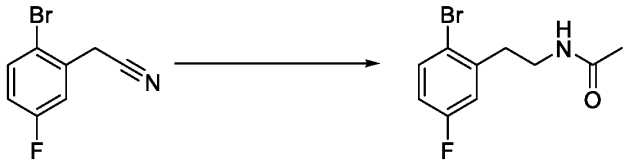
Compounds C1 to C17 (shown in Table 3) were prepared by the following procedure:

To a stirred solution of the starting material (1 eq) in DCM was added Et_3N (1.5 eq) followed by an appropriate acid chloride or anhydride (shown in Table 3) at 0 °C. The reaction was warmed to RT and stirred for 16 h. The reaction mixture was cooled to -78 °C and iron(III) chloride (3 eq) was added. The reaction mixture was quenched with cold water and extracted with DCM. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford the desired product (II). The resulting crude solid was used without further purification.

Table 3: Compounds C1 to C17

Compound number	Starting material	Reagent	Product name	LCMS m/z $[M+H]^+$, yield
C1	B1	Ac_2O (1.2 eq)	N-(2-bromo-4-methylphenethyl)acetamide	258.2, 70%
C2	B2	Ac_2O (1 eq)	N-(4-bromo-3-fluorophenethyl)acetamide	262.0, 67%
C3	B2	isobutyryl chloride (1.2 eq)	N-(4-bromo-3-fluorophenethyl) isobutyramide	288.2, 69%
C4	B3	Ac_2O (1 eq)	N-(4-bromo-2-fluorophenethyl)acetamide	262.0, 50%
C5	B6	Ac_2O (1.2 eq)	N-(3-bromo-4-fluorophenethyl)acetamide	262.0, 69%
C6	B7	Ac_2O (1.2 eq)	N-(2-bromo-4-chlorophenethyl)acetamide	278.0, 86%
C7	B8	Ac_2O (1 eq)	N-(2-bromo-4-methoxyphenethyl)acetamide	272.0, 85%
C8	B14	Ac_2O (1 eq)	N-(3-bromo-5-fluorophenethyl)acetamide	262.0, 77%
C9	B13	Ac_2O (1.2 eq)	N-(3-bromo-2-fluorophenethyl)acetamide	262.1, 49%
C10	B10	Ac_2O (1 eq)	N-(2-bromo-5-methylphenethyl)acetamide	258.1, 57%
C11	B4	Ac_2O (1.5 eq)	N-(2-bromo-4-fluorophenethyl)acetamide	262.2, 75%
C12	B15	Ac_2O (1.3 eq)	N-(2-bromo-5-methoxyphenethyl) acetamide	272.0, 47%
C13	B16	Ac_2O (1.2 eq)	N-(2-bromo-5-chlorophenethyl)acetamide	278.0, 64%
C14	B17	Ac_2O (1.2 eq)	N-(2-bromo-5-(trifluoromethoxy)phenethyl)acetamide	326.0, 70%
C15	B11	Ac_2O (1.1 eq)	N-(2-bromo-5-fluoro-4-methylphenethyl)acetamide	274.0, 70%
C16	B18	Ac_2O (1.1 eq)	N-(2-bromo-3-fluorophenethyl)acetamide	262.2 ($[M+2H]^+$), 64%
C17	B12	Ac_2O (1.1 eq)	N-(4-bromo-2-methoxyphenethyl)acetamide	272.0, 67%

Example 9: Synthesis of N-(2-bromo-5-fluorophenethyl)acetamide (C18)



C18

To a stirred solution of 2-(2-bromo-5-fluorophenyl) acetonitrile (10 g, 46.7 mmol) in MeOH (100 mL) was added Ac_2O (4.4 mL, 46.7 mmol), nickel(II) chloride hexahydrate (2.2 g, 9.3 mmol) and sodium borohydride (8.8 g, 234 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. The reaction was monitored by TLC. After completion of the reaction, the solvent was removed in vacuo. To the crude residue was added a solution of ammonium chloride and the aqueous phase was extracted with EtOAc (2 x 250 mL). The combined organic fractions were washed with water (200 mL) and brine (200 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (100-200 silica mesh, 25-30% EtOAc in Hexane) to afford N-(2-bromo-5-fluorophenethyl)acetamide (4.5 g, 17.3 mmol, 37%) as a pale brown solid. LCMS m/z = 262.1 $[M+H]^+$

Example 10: Synthesis of N-(2-bromo-3-methylphenethyl)acetamide (C19)



C19

To a stirred solution of 2-(2-bromo-3-methyl-phenyl)acetonitrile (5g, 23.80 mmol, 1 eq) in methanol (70 mL) was added acetic anhydride (12.15 g, 119.01mmol, 5 eq) and nickel (II) chloride hexahydrate (0.56 g, 2.38 mmol, 0.1 eq) at 0°C added $NaBH_4$ (4.5g, 119.01mmol, 5 eq) portionwise at 0 °C. The reaction mixture was stirred overnight at RT. The reaction was monitored by LCMS. The reaction mixture distilled in vacuo then quenched with ice-water and extracted with ethyl acetate. The organic layer was washed with brine and dried over sodium sulphate and concentrated under reduced pressure to obtain crude N-(2-bromo-3-methylphenethyl)acetamide (C19). The crude C19 was used for the next step. LCMS m/z = 258.2$[M+2H]^+$.

Example 11: Synthesis of compounds D1 to D19

Compounds D1 to D19 (shown in Table 4) were prepared by the following procedure:

To a stirred solution of the starting material (1 eq) in DCM was added oxalyl chloride (4 eq) dropwise at 0-5 °C. The reaction mixture was allowed to warm to RT and stirred for 2 h. The reaction mixture was cooled to -78 °C, iron(III) chloride (2 eq) was added in two portions. The reaction mixture was allowed to warm to RT, and stirred for 16 h at RT. The reaction mixture was quenched with ice-cold water and extracted with DCM. The combined organic layer was dried over sodium sulphate, and concentrated under reduced pressure to yield the crude product which was used in the next step without any further purification.

Table 4: Compounds D1 to D19

Compound number	Starting material	Product name	LCMS m/z $[M+H]^+$ [a]
D1	C1	7-bromo-9,10b-dimethyl-6,10b-dihydro-5H-oxazolo[2,3-a]isoquinoline-2,3-dione	311.9
D2	C2	9-bromo-8-fluoro-10b-methyl-6,10b-dihydro-5H-oxazolo[2,3-a]isoquinoline-2,3-dione	316.2
D3	C3	9-bromo-8-fluoro-10b-isopropyl-6,10b-dihydro-5H-oxazolo[2,3-a]isoquinoline-2,3-dione	344.2
D4	C4	9-bromo-7-fluoro-10b-methyl-6,10b-dihydro-5H-oxazolo[2,3-a]isoquinoline-2,3-dione	244.0[(a)]
D5	C5	8-bromo-9-fluoro-10b-methyl-6,10b-dihydro-5H-oxazolo[2,3-a]isoquinoline-2,3-dione	244.2[(a)]
D6	C6	7-bromo-9-chloro-10b-methyl-6,10b-dihydro-5H-oxazolo[2,3-a]isoquinoline-2,3-dione	332.0
D7	C7	7-bromo-9-methoxy-10b-methyl-6,10b-dihydro-5H-oxazolo[2,3-a]isoquinoline-2,3-dione	256.2[(a)]
D8	C8	Inseparable mixture of 10-bromo-8-fluoro-10b-methyl-6,10b-dihydro-5H-oxazolo[2,3-a]isoquinoline-2,3-dione and 8-bromo-10-fluoro-10b-methyl-6,10b-dihydro-5H-oxazolo[2,3-a]isoquinoline-2,3-dione	244.0[(a)]
D9	C9	8-bromo-7-fluoro-10b-methyl-6,10b-dihydro-5H-oxazolo[2,3-a]isoquinoline-2,3-dione	244.2[(a)]

Compound number	Starting material	Product name	LCMS m/z [M+H]+ a
D10	C10	7-bromo-10,10b-dimethyl-6,10b-dihydro-5H-oxazolo[2,3-a]isoquinoline-2,3-dione	240.2(a)
D11	C11	7-bromo-9-fluoro-10b-methyl-6,10b-dihydro-5H-oxazolo[2,3-a]isoquinoline-2,3-dione	316.0
D12	NC12	7-bromo-10-methoxy-10b-methyl-6,10b-dihydro-5H-oxazolo[2,3-a]isoquinoline-2,3-dione	328.0
D13	C13	7-bromo-10-chloro-10b-methyl-6,10b-dihydro-5H-oxazolo[2,3-a]isoquinoline-2,3-dione	no m/z
D14	C14	7-bromo-10b-methyl-10-(trifluoromethoxy)-6,10b-dihydro-5H-oxazolo[2,3-a]isoquinoline-2,3-dione	310.2(a)
D15	C15	7-bromo-10-fluoro-9,10b-dimethyl-6,10b-dihydro-5H-oxazolo[2,3-a]isoquinoline-2,3-dione	no m/z
D16	C18	7-bromo-10-fluoro-10b-methyl-6,10b-dihydro-5H-oxazolo[2,3-a]isoquinoline-2,3-dione	244.0
D17	C16	7-bromo-8-fluoro-10b-methyl-6,10b-dihydro-5H-oxazolo[2,3-a]isoquinoline-2,3-dione	244.2
D18	C17	9-bromo-7-methoxy-10b-methyl-6,10b-dihydro-5H-oxazolo[2,3-a]isoquinoline-2,3-dione	256.0
D19	C19	7-bromo-8,10b-dimethyl-6,10b-dihydro-5H-oxazolo[2,3-a]isoquinoline-2,3-dione	Used crude

(a) Note: corresponding imine mass ion was observed from compound fragmentation by LCMS.

Example 12: Synthesis of compounds E1 to E19

Compounds E1 to E19 (shown in Table 5) were prepared by the following procedure:

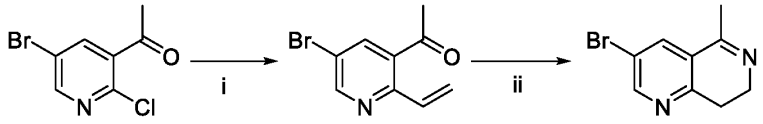
To a stirred solution of crude starting material (1 eq) in MeOH was added H_2SO_4 (6 eq) dropwise at 0 °C. The reaction mixture was heated to 85 °C and stirred for 16 h. The reaction was monitored by TLC and LCMS. After completion of the reaction, MeOH was removed under reduced pressure. The crude residue was taken up in water and basified with a solution of aqueous ammonia. The aqueous phase was extracted with DCM. The combined organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield the product. The crude was used in the next step without further purification.

Table 5: Compounds E1 to E19

Compound number	Starting material	Product name	LCMS m/z [M+H]+ a
E1	D1	5-bromo-1,7-dimethyl-3,4-dihydroisoquinoline	240.2
E2	D2	7-bromo-6-fluoro-1-methyl-3,4-dihydroisoquinoline	244.0
E3	D3	7-bromo-6-fluoro-1-isopropyl-3,4-dihydroisoquinoline	272.2
E4	D4	7-bromo-5-fluoro-1-methyl-3,4-dihydroisoquinoline	244.0
E5	D5	6-bromo-7-fluoro-1-methyl-3,4-dihydroisoquinoline	244.0
E6	D6	5-bromo-7-chloro-1-methyl-3,4-dihydroisoquinoline	260.0
E7	D7	5-bromo-7-methoxy-1-methyl-3,4-dihydroisoquinoline	256.0
E8	D8	Inseparable mixture of 8-bromo-6-fluoro-1-methyl-3,4-dihydroisoquinoline and 6-bromo-8-fluoro-1-methyl-3,4-dihydroisoquinoline	244.0
E9	D9	6-bromo-5-fluoro-1-methyl-3,4-dihydroisoquinoline	244.0

Compound number	Starting material	Product name	LCMS m/z $[M+H]^+$ [a]
E10	D10	5-bromo-1,8-dimethyl-3,4-dihydroisoquinoline	240.0
E11	D11	5-bromo-7-fluoro-1-methyl-3,4-dihydroisoquinoline	244.2
E12	D12	5-bromo-8-methoxy-1-methyl-3,4-dihydroisoquinoline	256.0
E13	D13	5-bromo-8-chloro-1-methyl-3,4-dihydroisoquinoline	260.2
E14	D14	5-bromo-1-methyl-8-(trifluoromethoxy)-3,4-dihydroisoquinoline	310.0
E15	D15	5-bromo-8-fluoro-1,7-dimethyl-3,4-dihydroisoquinoline	256.0
E16	D16	5-bromo-8-fluoro-1-methyl-3,4-dihydroisoquinoline	244.0
E17	D17	5-bromo-6-fluoro-1-methyl-3,4-dihydroisoquinoline	242.0
E18	D18	7-bromo-5-methoxy-1-methyl-3,4-dihydroisoquinoline	254.2
E19	D19	5-bromo-1,6-dimethyl-3,4-dihydroisoquinoline	238.2

Example 13: Synthesis of compound F1



(F1)

Reaction conditions: i) $Pd(PPh_3)_2Cl_2$, potassium trifluoro(vinyl)borate, Et_3N, EtOH; ii) aq. ammonia, NH_4Cl, EtOH, H_2O

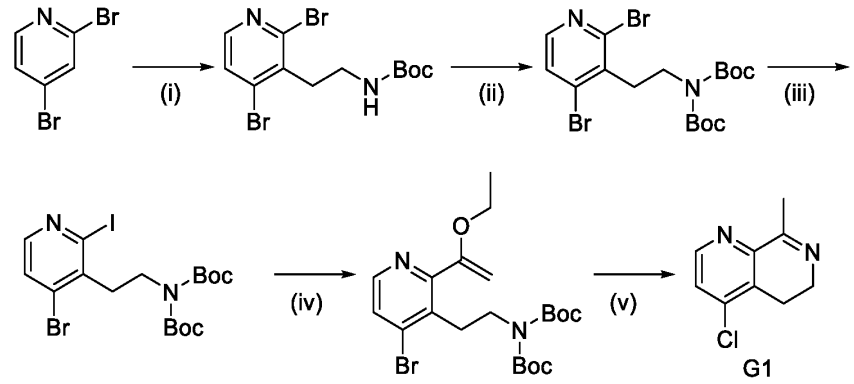
Step (i): Preparation of 1-(5-bromo-2-vinylpyridin-3-yl)ethan-1-one

To a stirred solution of 1-(5-bromo-2-chloropyridin-3-yl)ethan-1-one (3.0 g, 12.8 mmol) in EtOH (30 mL) was added potassium trifluoro(vinyl)borate (1.5 g, 11.5 mmol) and Et_3N (1.3 g, 12.8 mmol) at RT. The reaction mixture was degassed with N_2 for 10 min. Bis(triphenylphosphine)palladium(II) dichloride (0.9 g, 1.3 mmol) was added and the reaction mixture was degassed with N_2 for 2 min and heated to 85 °C for 3 h. The reaction mixture was allowed to cool to RT, quenched with H_2O and extracted with DCM (3 x 15 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The resulting crude residue was purified by flash column chromatography (10% EtOAc in *n*-hexane) to afford the title compound (2 g, 8.8 mmol, 69%). **LCMS m/z** = 226.0 $[M+H]^+$

Step (ii): Preparation of 3-bromo-5-methyl-7,8-dihydro-1,6-naphthyridine (F1)

To a stirred solution of 1-(5-bromo-2-vinylpyridin-3-yl)ethan-1-one (6.0 g, 26.5 mmol) in EtOH (60 mL) was added aqueous ammonia (60 mL) and a solution of NH_4Cl (2.8 g, 53.1 mmol) in H_2O (10 mL). The reaction mixture was heated to 90 °C for 16 h in a sealed vessel. After completion of the reaction, the solvent was removed under reduced pressure. The aqueous phase was extracted with DCM (5 x 50 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The resulting crude residue was purified by flash column chromatography (10% MeOH in DCM) to afford F1 (2.7 g, 11.0 mmol, 42%). **LCMS m/z** = 226.9 $[M+H]^+$

Example 14: Synthesis of compound G1



Reaction conditions: i) LDA, THF, tert-butyl 1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide; ii) $(Boc)_2O$, DMAP, 1,4-dioxane; iii) CuI, NaI, N,N'-dimethylcyclohexanediamine, 1,4-dioxane; iv) $Pd(dppf)Cl_2$, 1-ethoxyvinyltri-n-butyltin, 1,4-dioxane; v) 3N aq. HCl

Step (i): Preparation of *tert*-butyl (2-(2,4-dibromopyridin-3-yl)ethyl)carbamate

To a stirred solution of 2,4-dibromopyridine (5 g, 21.1 mmol) in THF (100 mL) was added LDA (12.7 mL, 25.3 mmol) at -70° C under N_2 atmosphere and was stirred at for 1h. Then, a solution of tert-butyl 1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (5.7 g, 25.3 mmol) in THF (100 mL) was added and the reaction mixture was stirred at -70° C for 3 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl at -70° C and was allowed to warm to RT. The reaction mixture was diluted with EtOAc (100 mL). The aqueous phase was separated and extracted with 10% MeOH in DCM (200 mL x 2). The combined organic layer was dried over sodium sulphate, filtered, and concentrated in vacuo. The crude residue was purified by column chromatography (17% EtOAc in hexane) to give *tert*-butyl (2-(2,4-dibromopyridin-3-yl)ethyl)carbamate (4.5 g, 11.8 mmol, 56%) as white solid. **LCMS m/z** = 381.0 $[M+H]^+$

Step (ii): Preparation of *tert*-butyl (*tert*-butoxycarbonyl)(2-(2,4-dibromopyridin-3-yl)ethyl)carbamate

To stirred solution of tert-butyl (2-(2,4-dibromopyridin-3-yl)ethyl)carbamate (6 g, 15.8 mmol) in 1,4-dioxane (60 mL) was added DMAP (0.19 g, 1.58 mmol) and Boc anhydride (14.7 mL, 63.1 mmol) at 0 °C. The reaction mixture was heated to 100 °C for 14 h and was allowed to cool to RT. The reaction mixture was quenched with a saturated solution of $NaHCO_3$. The aqueous phase was extracted with EtOAc (100 mL x 2) and the combined organic layer was dried over sodium sulphate, filtered and concentrated in vacuo. The solvent was removed in vacuo and the crude residue was purified by flash column chromatography to afford *tert*-butyl (*tert*-butoxycarbonyl)(2-(2,4-dibromopyridin-3-yl)ethyl)carbamate (7.3 g, 15.2 mmol, 96%). **LCMS m/z** = 481.0 $[M+H]^+$

Step (iii): Preparation of *tert*-butyl (2-(4-bromo-2-iodopyridin-3-yl)ethyl)(*tert*-butoxycarbonyl)carbamate

To a degassed solution of *tert*-butyl (*tert*-butoxycarbonyl)(2-(2,4-dibromopyridin-3-yl)ethyl)carbamate (7.2 g, 15.0 mmol) in 1,4-dioxane (75 mL) was added copper(I) iodide (0.14 g, 0.75 mmol), sodium iodide (4.5 g, 30.0 mmol) and N,N'-dimethylcyclohexanediamine (0.21 g, 1.5 mmol). The reaction mixture was heated at 100 °C for 16 h, was allowed to cool to RT, quenched with a solution of 30% aqueous ammonia. The aqueous phase was separated and extracted with DCM (2 x 200 mL). The combined organic layer was dried over sodium sulphate, filtered, and concentrated in vacuo. The crude

material was purified by column chromatography to give (2-(4-bromo-2-iodopyridin-3-yl)ethyl)(*tert*-butoxycarbonyl)carbamate (7.5 g, 14.2 mmol, 95%). **LCMS m/z** = 527.0 $[M+H]^+$

Step (iv): Preparation of *tert*-butyl (2-(4-bromo-2-(1-ethoxyvinyl)pyridin-3-yl)ethyl)(*tert*-butoxycarbonyl)carbamate

To a degassed solution of *tert*-butyl (2-(4-bromo-2-iodopyridin-3-yl)ethyl)(*tert*-butoxycarbonyl)carbamate (7 g, 13.3 mmol) and 1,4-dioxane (70 mL) was added 1-ethoxyvinyltri-*n*-butyltin (6.2 g, 17.3 mmol) and $PdCl_2$(dppf) (2.9 g, 4.0 mmol). The reaction mixture was heated at 100 °C for 12 h and was allowed to cool to RT. The reaction mixture was diluted with ice-cold H_2O, the aqueous phase was separated and extracted with EtOAc (2 x 100 mL). The combined organic layer was dried over sodium sulphate, filtered, and concentrated in vacuo. The crude residue was purified by column chromatography (7% EtOAc in hexane) to afford *tert*-butyl (2-(4-bromo-2-(1-ethoxyvinyl)pyridin-3-yl)ethyl)(*tert*-butoxycarbonyl)carbamate (2 g, 4.2 mmol, 32%). **LCMS m/z** = 471.0 $[M+H]^+$

Step (v): Preparation of 4-chloro-8-methyl-5,6-dihydro-1,7-naphthyridine (G1)

To a stirred solution of *tert*-butyl (2-(4-bromo-2-(1-ethoxyvinyl)pyridin-3-yl)ethyl)(tert-butoxycarbonyl)carbamate (1.9 g, 4.0 mmol) in H_2O (12 mL) was added concentrated HCl (6 mL, 4.0 mmol). The reaction mixture was stirred at 100 °C for 12 h and was allowed to cool to RT. The reaction mixture was neutralized with a saturated solution of $NaHCO_3$. The aqueous phase was separated and extracted with DCM (2 x 100 mL). The combined organic layer was dried over sodium sulphate, filtered, and concentrated in vacuo. The crude residue was purified by column chromatography (17% EtOAc in hexane) to afford 4-chloro-8-methyl-5,6-dihydro-1,7-naphthyridine (G1; 0.6 g, 3.3 mmol, 82%). LCMS m/z = 181.2 $[M+H]^+$

Example 15: Synthesis of compounds H1 to H22

Compounds H1 to H22 (shown in Table 6) were prepared by the following procedure:

To a stirred solution of the starting material (1 eq) in MeOH was added sodium borohydride (2 eq) and acetic acid (1 eq) at 0 °C. The reaction mixture was stirred at RT for 12 h. The reaction was monitored by TLC and LCMS. After completion of the reaction, the solvent was removed under reduced pressure, ice-cold water was added and the aqueous phase was extracted with DCM. The combined organic layer was washed with brine, dried over sodium sulphate, filtered, and concentrated in vacuo to give the title compound. The crude was used in the next step without further purification.

Table 6: Compounds H1 to H22

Compound number	Starting material	Product name	LCMS m/z $[M+H]^+$
H1	E1	5-bromo-1,7-dimethyl-1,2,3,4-tetrahydroisoquinoline	242.2
H2	E2	7-bromo-6-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline	246.2
H3	E3	7-bromo-6-fluoro-1-isopropyl-1,2,3,4-tetrahydroisoquinoline	274.0
H4	E4	7-bromo-5-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline	246.0
H5	E5	6-bromo-7-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline	246.0
H6	E6	5-bromo-7-chloro-1-methyl-1,2,3,4-tetrahydroisoquinoline	262.1

Compound number	Starting material	Product name	LCMS m/z $[M+H]^+$
H7	E7	5-bromo-7-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline	258.2
H8	E8	8-bromo-6-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline	246.0
H9	E8	6-bromo-8-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline	246.0
H10	E9	6-bromo-5-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline	246.2
H11	E10	5-bromo-1,8-dimethyl-1,2,3,4-tetrahydroisoquinoline	242.2
H12	E11	5-bromo-7-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline	246.0
H13	E12	5-bromo-8-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline	258.0
H14	E13	5-bromo-8-chloro-1-methyl-1,2,3,4-tetrahydroisoquinoline	no m/z
H15	E14	5-bromo-1-methyl-8-(trifluoromethoxy)-1,2,3,4-tetrahydroisoquinoline	311.7
H16	E15	5-bromo-8-fluoro-1,7-dimethyl-1,2,3,4-tetrahydroisoquinoline	260.0
H17	F1	3-bromo-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine	226.9
H18	G1	4-chloro-8-methyl-5,6,7,8-tetrahydro-1,7-naphthyridine	183.1
H19	E16	5-bromo-8-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline	246.2 ($[M+2H]^+$)
H20	E17	5-bromo-6-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline	246.2 ($[M+2H]^+$)
H21	E18	7-bromo-5-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline	256.2
H22	E19	5-bromo-1,6-dimethyl-1,2,3,4-tetrahydroisoquinoline	240.2

Example 16: Synthesis of compounds J1 to J4

Compounds J1 to J4 (shown in Table 7) were prepared by either procedure A or B, as indicated in the table below:

A) A solution of the starting material (1 eq) in ethyl formate (1M) was refluxed for 18 h. The reaction progress was monitored by TLC. The reaction mixture was concentrated under reduced pressure, the obtained crude material was purified by flash column chromatography (MeOH/DCM) to afford the product.

B) To a solution of the starting material (1 eq) in ethyl formate (1 eq) was added pivalic acid (1 eq) at RT. The reaction mixture was refluxed for 48 h. The reaction progress was monitored by TLC. The reaction was allowed to cool to RT and concentrated under reduced pressure. The crude residue was basified (pH: 8-10) with a solution of sodium bicarbonate and the aqueous phase was extracted with DCM (3 x 150 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (EtOAc in hexane) to afford the product.

Table 7: Compounds J1 to J4

Compound number	Starting material	Product name	Procedure	LCMS m/z $[M+H]^+$
J1	B2	N-(4-bromo-2-fluorophenethyl)formamide	A	248.1

Compound number	Starting material	Product name	Procedure	LCMS m/z $[M+H]^+$
J2	B4	N-(2-bromo-4-fluorophenethyl)formamide	B	248.1
J3	B5	N-(2-bromo-5-fluorophenethyl)formamide	A	248.2
J4	B9	N-(2-bromo-3-fluorophenethyl)formamide	A	248.0

Example 17: Synthesis of compounds K1 to K4

Compounds K1 to K4 (shown in Table 8) were prepared by the following procedure:

To a stirred solution of the starting material (1 eq) in DCM was added oxalyl chloride (4 eq) dropwise at 0 °C. The reaction mixture was allowed to warm to RT and stirred for 2 h. The reaction mixture was cool to -78 °C and iron(III) chloride (2 eq) was added in two portions. The reaction mixture was allowed to warm up to RT and stirred for 16 h. The reaction mixture was filtered through Celite, washed with DCM, and concentrated under reduced pressure to give the crude product which was used in the next step without any further purification.

Table 8: Compounds K1 to K4

Compound number	Starting material	Product name	LCMS m/z $[M+H]^+$ [a]
K1	J1	9-bromo-7-fluoro-6,10b-dihydro-5H-oxazolo[2,3-a]isoquinoline-2,3-dione	230.2[(a)]
K2	J2	7-bromo-9-fluoro-6,10b-dihydro-5H-oxazolo[2,3-a]isoquinoline-2,3-dione	230.2[(a)]
K3	J3	7-bromo-10-fluoro-6,10b-dihydro-5H-oxazolo[2,3-a]isoquinoline-2,3-dione	230.2[(a)]
K4	J4	7-bromo-8-fluoro-6,10b-dihydro-5H-oxazolo[2,3-a]isoquinoline-2,3-dione	230.0[(a)]

[(a)] Note: corresponding imine mass ion was observed from compound fragmentation by LCMS.

Example 18: Synthesis of compounds M1 to M4

Compounds M1 to M4 (Table 9) were prepared by the following procedure:

The crude starting material (I) (1 eq) was dissolved in MeOH. H_2SO_4 (9 eq) was added at 0 °C and the reaction mixture was heated to 70 °C for 16 h. The reaction mixture was allowed to cool to RT. The solvent was removed in vacuo. Ice-cold water was slowly added, and pH was adjusted to 8-9 with a solution of 25% aq. NH_3 solution. The aqueous layer was extracted with DCM. The organic layer was washed with H_2O, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by chromatography (gradient of EtOAc in hexane) to afford the product.

Table 9: Compounds M1 to M4

Compound number	Starting material	Product name	LCMS m/z $[M+H]^+$ [a]
M1	K1	7-bromo-5-fluoro-3,4-dihydroisoquinoline	230.2
M2	K2	5-bromo-7-fluoro-3,4-dihydroisoquinoline	230.1
M3	K3	5-bromo-8-fluoro-3,4-dihydroisoquinoline	230.2
M4	K4	5-bromo-6-fluoro-3,4-dihydroisoquinoline	230.0

Example 19: Synthesis of compounds N1 to N4

Compounds N1 to N4 (shown in Table 10) were prepared by the following procedure:

To a stirred solution of the starting material (1 eq) in THF at 0 °C was added boron trifluoride etherate (1 eq). The reaction mixture was stirred for 15 min, and isopropylmagnesium chloride (2M in THF, 1.5 eq) was added dropwise at 0 °C. The reaction mixture was allowed to warm to RT and stirred for 16 h. The progress of the reaction was monitored by TLC. The reaction mixture was quenched with a solution of NH_4Cl and the aqueous phase was extracted with EtOAc. The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (gradient of EtOAc in hexane) to afford the product.

Table 10: Compounds N1 to N4

Compound number	Starting material	Product name	LCMS m/z $[M+H]^+$ [a]
N1	M1	7-bromo-5-fluoro-1-isopropyl-1,2,3,4-tetrahydroisoquinoline	274.0
N2	M2	5-bromo-7-fluoro-1-isopropyl-1,2,3,4-tetrahydroisoquinoline	274.2
N3	M3	5-bromo-8-fluoro-1-isopropyl-1,2,3,4-tetrahydroisoquinoline	274.1
N4	M4	5-bromo-6-fluoro-1-isopropyl-1,2,3,4-tetrahydroisoquinoline	274.0

Example 20: Synthesis of compounds P1 to P28

Compounds P1 to P28 (shown in Table 11) were prepared by the following procedure:

To a stirred solution of the starting material (1 eq) in DCM was added triethylamine (3 eq) and Boc-anhydride (1.5 eq) at 0 °C. The reaction mixture was allowed to warm up to RT and was stirred for 12 h. The reaction progress was monitored by TLC and LCMS. The reaction mixture was diluted with water and the aqueous phase was extracted with DCM. The combined organic layer was washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (EtOAc/hexane) to give the title compound.

Table 11: Compounds P1 to P27

Compound number	Starting material	Product name	LCMS m/z $[M-Boc+H]^+$
P1	H19	tert-butyl 5-bromo-8-fluoro-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	246.2
P2	H20	tert-butyl 5-bromo-6-fluoro-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	246.2
P3	H12	tert-butyl 5-bromo-7-fluoro-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	246.2
P4	H1	tert-butyl 5-bromo-1,7-dimethyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	242.0
P5	H13	tert-butyl 5-bromo-8-methoxy-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	256.2
P6	H14	tert-butyl 5-bromo-8-chloro-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	262.0
P7	H4	tert-butyl 7-bromo-5-fluoro-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	246.2
P8	H3	tert-butyl 7-bromo-6-fluoro-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	246.2
P9	H7	tert-butyl 5-bromo-7-methoxy-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	256.2
P10	H6	tert-butyl 5-bromo-7-chloro-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	262.0
P11	H10	tert-butyl 6-bromo-5-fluoro-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	246.0
P12	H5	tert-butyl 6-bromo-7-fluoro-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	246.2
P13	H11	tert-butyl 5-bromo-1,8-dimethyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	242.2
P14	H8	tert-butyl 8-bromo-6-fluoro-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	246.2
P15	H3	tert-butyl 7-bromo-6-fluoro-1-isopropyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	274.0
P16	N1	tert-butyl 7-bromo-5-fluoro-1-isopropyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	316.2 ($[M-tBu+H]^+$)
P17	N3	tert-butyl 5-bromo-8-fluoro-1-isopropyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	274.0
P18	N4	tert-butyl 5-bromo-6-fluoro-1-isopropyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	274.0
P19	N2	tert-butyl 5-bromo-7-fluoro-1-isopropyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	274.2
P20	H21	tert-butyl 7-bromo-5-methoxy-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	256.0
P21	H6	tert-butyl 5-bromo-7-chloro-3,4-dihydroisoquinoline-2(1H)-carboxylate	248.0
P22	H9	tert-butyl 6-bromo-8-fluoro-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	287.7 $[M-tBu+H]^+$
P23	H22	tert-butyl 5-bromo-1,6-dimethyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	242.2
P24	N/A	tert-butyl 3-bromo-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate	commercially available [CAS:1184950-48-8]
P25	H15	tert-butyl 5-bromo-1-methyl-8-(trifluoromethoxy)-3,4-dihydroisoquinoline-2(1H)-carboxylate	353.7 ($[M-tBu+H]^+$)
P26	H16	tert-butyl 5-bromo-8-fluoro-1,7-dimethyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	258.0
P27	H17	tert-butyl 3-bromo-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate	329.0 $[M+H]^+$
P28	H18	tert-butyl 4-chloro-8-methyl-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate	238.2 ($[M-tBu+H]^+$)

Example 21: Synthesis of compounds Q1 to Q28

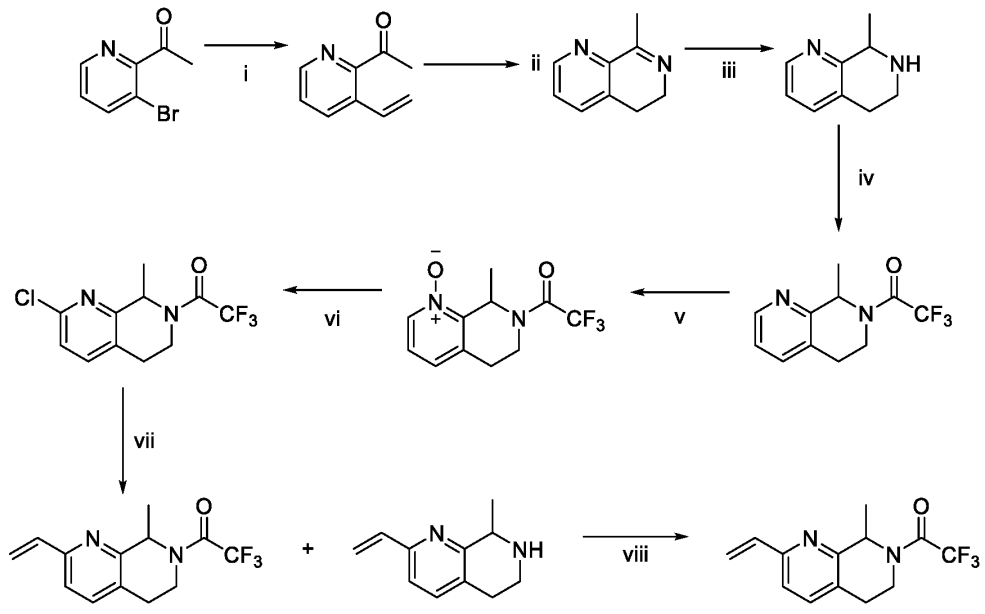
Compounds Q1 to Q28 (shown in Table 12) were prepared by the following procedure:

To a degassed solution of starting material (1 equiv.), potassium trifluoro(vinyl)borate (1 equiv.) and Cs_2CO_3 (2 equiv.) in 1,4-dioxane:water (4:1) was added $Pd(dppf)Cl_2.CH_2Cl_2$ (0.1 equiv.) at room temperature. The reaction mixture was degassed for 10 mins before being heated at 90 ^oC for 16 h. The reaction mixture was filtered through celite and the celite was washed with EtOAc. The combined washings were concentrated in vacuo and the resulting residue was purified by silica gel column chromatography. The appropriate fractions were concentrated in vacuo to give the product.

Table 12: Compounds Q1 to Q28

Compound number	Starting material	Product name	LCMS m/z $[[M-Boc+H]^+$
Q1	P1	tert-butyl 8-fluoro-1-methyl-5-vinyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	192.2
Q2	P2	tert-butyl 6-fluoro-1-methyl-5-vinyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	192.2
Q3	P3	tert-butyl 7-fluoro-1-methyl-5-vinyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	192.2
Q4	P4	tert-butyl 1,7-dimethyl-5-vinyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	188.2
Q5	P5	tert-butyl 8-methoxy-1-methyl-5-vinyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	204.3
Q6	P6	tert-butyl 8-chloro-1-methyl-5-vinyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	208.2
Q7	P7	tert-butyl 5-fluoro-1-methyl-7-vinyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	192.0
Q8	P8	tert-butyl 6-fluoro-1-methyl-7-vinyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	192.3
Q9	P9	tert-butyl 7-methoxy-1-methyl-5-vinyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	204.2
Q10	P10	tert-butyl 7-chloro-1-methyl-5-vinyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	208.2
Q11	P11	tert-butyl 5-fluoro-1-methyl-6-vinyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	192.3
Q12	P12	tert-butyl 7-fluoro-1-methyl-6-vinyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	192.2
Q13	P13	tert-butyl 1,8-dimethyl-5-vinyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	188.3
Q14	P14	tert-butyl 6-fluoro-1-methyl-8-vinyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	192.2
Q15	P15	tert-butyl 6-fluoro-1-isopropyl-7-vinyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	220.2
Q16	P16	tert-butyl 5-fluoro-1-isopropyl-7-vinyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	220.4
Q17	P17	tert-butyl 8-fluoro-1-isopropyl-5-vinyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	264.2 ($[M-tBu+H]^+$)
Q18	P18	tert-butyl 6-fluoro-1-isopropyl-5-vinyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	220.4
Q19	P19	tert-butyl 7-fluoro-1-isopropyl-5-vinyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	264.2$[M-tBu+H]^+$
Q20	P20	tert-butyl 5-methoxy-1-methyl-7-vinyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	204.2
Q21	P21	tert-butyl 7-chloro-5-vinyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	194.2
Q22	P22	tert-butyl 8-fluoro-1-methyl-6-vinyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	192.2
Q23	P27	tert-butyl 5-methyl-3-vinyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate	275.2 $[M+H]^+$
Q24	P23	tert-butyl 1,6-dimethyl-5-vinyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	188
Q25	P24	tert-butyl 3-vinyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate	261.4 ($[M+H]^+$)
Q26	P25	tert-butyl 1-methyl-8-(trifluoromethoxy)-5-vinyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	258.2
Q27	P26	tert-butyl 8-fluoro-1,7-dimethyl-5-vinyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	206.2
Q28	P28	tert-butyl 8-methyl-4-vinyl-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate	275.2 ($[M+H]^+$)

Example 22: Synthesis of compound R1



(R1)

Reaction conditions: i) $Pd(PPh_3)_2Cl_2$, potassium trifluoro(vinyl)borate, Et_3N, EtOH; ii) aq. ammonia, NH_4Cl, EtOH, H_2O; iii) $NaBH_4$, MeOH; iv) $(COCF_3)_2$, Et_3N, DCM; v) mCPBA, DCM; vi) $POCl_3$; vii) potassium trifluoro(vinyl)borate, $Pd(dppf)Cl_2.CH_2Cl_2$, Cs_2CO_3, 1,4-dioxane:H_2O; viii) $(COCF_3)_2$, Et_3N, DCM

Step (i): Preparation of 1-(3-vinylpyridin-2-yl)ethan-1-one

To a stirred solution of 1-(3-bromopyridin-2-yl)ethan-1-one (5 g, 25 mmol) in EtOH (40 mL) were added potassium trifluoro(vinyl)borate (4.0 g, 30.0 mmol) and Et_3N (3.5 mL, 25 mmol) at RT under N_2. To the reaction mixture was added bis(triphenylphosphine)palladium(II) dichloride (1.7 g, 2.5 mmol) with N_2 bubbling through for 2 min. The reaction mixture was heated to 85 °C and stirred for 2 h. The reaction mixture was cooled to RT and quenched by addition of H_2O. The aqueous phase was separated and extracted with DCM. The organic layer was dried over sodium sulphate and concentrated in vacuo. The crude residue was purified by column chromatography (10% EtOAc in hexane) to afford 1-(3-vinylpyridin-2-yl)ethan-1-one (3.5 g, 23.8 mmol, 95%). **LCMS m/z** = 148.1 $[M+H]^+$

Step (ii): Preparation of 8-methyl-5,6-dihydro-1,7-naphthyridine

To a stirred solution of 1-(3-vinylpyridin-2-yl)ethan-1-one (3.5 g, 23.8 mmol) in EtOH (35 mL) were added ammonia (70 mL, 23.8 mmol) and a solution of NH_4Cl (2.5 g, 47.6 mmol) in H_2O (7 mL) at RT. The reaction was heated to 110 °C in a sealed vessel (the internal pressure was raised up to 3.5 - 4.0 kg/cm^2) and stirred for 48 h. The reaction mixture was allowed to cool to RT and H_2O was added. The aqueous phase was separated and extracted with DCM. The combined organic layer was dried over sodium sulphate, filtered and concentrated in vacuo. The crude material was purified by column chromatography (10% MeOH in DCM) to afford 8-methyl-5,6-dihydro-1,7-naphthyridine (2.6 g, 17.8 mmol, 75%). **LCMS m/z** = 147.2 $[M+H]^+$

Step (iii): Preparation of 8-methyl-5,6,7,8-tetrahydro-1,7-naphthyridine

To a stirred solution of 8-methyl-5,6-dihydro-1,7-naphthyridine (2.6 g, 17.8 mmol) in MeOH (15 mL) was added $NaBH_4$ (1.3 g, 35.6 mmol) portionwise at 0 °C. The reaction mixture was allowed to warm to RT and stirred for 16 h. The reaction mixture was quenched with a solution of NH_4Cl. The aqueous phase was separated and extracted with DCM (150 mL x 2). The combined organic layer was dried over sodium sulphate, and concentrated in vacuo to yield 8-methyl-5,6,7,8-tetrahydro-1,7-naphthyridine (2.1 g, 14.2 mmol, 80%). The crude material was used in the next step without further purification. **LCMS m/z** = 149.2 $[M+H]^+$

Step (iv): Preparation of 2,2,2-trifluoro-1-(8-methyl-5,8-dihydro-1,7-naphthyridin-7(6H)-yl)ethan-1-one

To a stirred solution of 8-methyl-5,6,7,8-tetrahydro-1,7-naphthyridine (2.1 g, 14.2 mmol) in DCM (10 mL) were added triethylamine (2.8 mL, 34.0 mmol) and trifluoroacetic anhydride (2.0 mL, 14.2 mmol) dropwise at 0-5 °C. The reaction mixture was allowed to warm to RT and stirred for 12 h. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was diluted with H_2O (5 mL) and extracted with DCM (50 mL x 2). The combined organic layer was washed with H_2O (10 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography (20% EtOAc in hexane) to yield 2,2,2-trifluoro-1-(8-methyl-5,8-dihydro-1,7-naphthyridin-7(6H)-yl)ethan-1-one (1.6 g, 6.6 mmol, 46%). **LCMS m/z** = 245.2 $[M+H]^+$

Step (v): Preparation of 8-methyl-7-(2,2,2-trifluoroacetyl)-5,6,7,8-tetrahydro-1,7-naphthyridine 1-oxide

To a stirred solution of 2,2,2-trifluoro-1-(8-methyl-5,8-dihydro-1,7-naphthyridin-7(6H)-yl)ethan-1-one (1.6 g, 6.6 mmol) in DCM (15 mL) was added m-CPBA (1.8 g, 7.9 mmol) and the reaction mixture was stirred at RT for 12 h. The reaction mixture was quenched with an aqueous solution of $NaHCO_3$. The aqueous phase was separated and extracted with DCM (20 mL x 2). The combined organic layer was washed with H_2O (10 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (5% MeOH in DCM) to give 8-methyl-7-(2,2,2-trifluoroacetyl)-5,6,7,8-tetrahydro-1,7-naphthyridine 1-oxide (1.2 g, 4.6 mmol, 70%). **LCMS m/z** = 261.0 $[M+H]^+$

Step (vi): Preparation of 1-(2-chloro-8-methyl-5,8-dihydro-1,7-naphthyridin-7(6H)-yl)-2,2,2-trifluoroethan-1-one

$POCl_3$ (10 mL, 4.6 mmol) was added to 8-methyl-7-(2,2,2-trifluoroacetyl)-5,6,7,8-tetrahydro-1,7-naphthyridine 1-oxide (1.2 g, 4.6 mmol) under N_2 at 0-5 °C. The resulting solution was heated to 100 °C and stirred for 12 h under N_2. The reaction mixture was cooled to RT. $POCl_3$ was removed in vacuo and the crude material was dissolved in DCM (30 mL), then a cooled solution of aq. $NaHCO_3$ was slowly added to adjust pH to 8-10. The aqueous layer was separated and further extracted with DCM (30 mL x 2). The combined organic layer was washed with H_2O (10 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was purified by column chromatography (8 % EtOAc in pet ether) to obtain 1-(2-chloro-8-methyl-5,8-dihydro-1,7-naphthyridin-7(6H)-yl)-2,2,2-trifluoroethan-1-one (1.1 g, 4.0 mmol, 86%). **LCMS m/z** = 278.9 $[M+H]^+$

Step (vii): Preparation of 2,2,2-trifluoro-1-(8-methyl-2-vinyl-5,8-dihydro-1,7-naphthyridin-7(6H)-yl)ethan-1-one and 8-methyl-2-vinyl-5,6,7,8-tetrahydro-1,7-naphthyridine

To a stirred solution of 1-(2-chloro-8-methyl-5,8-dihydro-1,7-naphthyridin-7(6H)-yl)-2,2,2-trifluoroethan-1-one (0.2 g, 0.72 mmol) and potassium trifluoro(vinyl)borate (115 mg, 0.861 mmol) in

1,4-dioxane (16 mL) and H_2O (4 mL) was added Cs_2CO_3 (0.47 g, 1.4 mmol) and the resulting reaction mixture was degassed with argon gas for 5 min then $PdCl_2(dppf)\cdot DCM$ complex (53 mg, 0.07 mmol) was added and the reaction mixture was heated to 100 °C for 16 h. The reaction mixture was cooled to RT, diluted with H_2O (50 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layer was washed with brine, dried over anhydrous sodium sulphate, and concentrated under reduced pressure to afford 2,2,2-trifluoro-1-(8-methyl-2-vinyl-5,8-dihydro-1,7-naphthyridin-7(6H)-yl)ethan-1-one and 8-methyl-2-vinyl-5,6,7,8-tetrahydro-1,7-naphthyridine (200 mg). The crude material was used in the next step without further purification. **LCMS m/z** = 271.2 $[M+H]^+$ and **LCMS m/z** = 175.2 $[M+H]^+$

Step (viii): Preparation of 2,2,2-trifluoro-1-(8-methyl-2-vinyl-5,8-dihydro-1,7-naphthyridin-7(6H)-yl)ethan-1-one (R1)

To a stirred solution of 2,2,2-trifluoro-1-(8-methyl-2-vinyl-5,8-dihydro-1,7-naphthyridin-7(6H)-yl)ethan-1-one and 8-methyl-2-vinyl-5,6,7,8-tetrahydro-1,7-naphthyridine (200 mg) in DCM (10 mL) was added triethylamine (0.22 mL, 2.75 mmol) and the reaction mixture was stirred for 30 min at 0-5 °C. Then, trifluoroacetic anhydride (0.19 mL, 1.38 mmol) was added dropwise at 0-5 °C. The reaction mixture was allowed to warm to RT and stirred for 16 h. The reaction mixture was quenched with cold water and extracted with DCM (2 x 50 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude residue was purified by flash column chromatography by using neutral alumina (15-20% EtOAc in hexane) to afford 2,2,2-trifluoro-1-(8-methyl-2-vinyl-5,8-dihydro-1,7-naphthyridin-7(6H)-yl)ethan-1-one (R1; 60 mg, 0.21 mmol). **LCMS m/z** = 271.2 $[M+H]^+$

Example 23: Synthesis of compounds S1 to S29

Compounds S1 to S29 (shown in Table 13) were prepared by the following procedure:

To a solution of the starting material (1 equiv.), sodium periodate (2 equiv.) and N-methyl morpholine (1 equiv.) in 1,4-dioxane:water (2:1) was added osmium tetroxide (4 wt% aqueous solution, 1 equiv.) dropwise at room temperature. The reaction mixture was stirred for 2 h at room temperature before being quenched with cold water and extracted with ethyl acetate. The combined organic layers were washed with brine and dried over anhydrous sodium sulphate, filtered and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography. The appropriate fractions were concentrated in vacuo to give the product.

Table 13: Compounds S1 to S29

Compound number	Starting material	Product	LCMS m/z [M-Boc+H]$^+$
S1	Q1	tert-butyl 8-fluoro-5-formyl-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	194.2
S2	Q2	tert-butyl 6-fluoro-5-formyl-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	194.2
S3	Q3	tert-butyl 7-fluoro-5-formyl-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	194.2
S4	Q4	tert-butyl 5-formyl-1,7-dimethyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	190.4
S5	Q5	tert-butyl 5-formyl-8-methoxy-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	206.0

Compound number	Starting material	Product	LCMS m/z [M-Boc+H]$^+$
S6	Q6	tert-butyl 8-chloro-5-formyl-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	210.2
S7	Q7	tert-butyl 5-fluoro-7-formyl-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	238.3 [M-tBu+H]$^+$
S8	Q8	tert-butyl 6-fluoro-7-formyl-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	194.2
S9	Q9	tert-butyl 5-formyl-7-methoxy-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	206.3
S10	Q10	tert-butyl 7-chloro-5-formyl-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	210.2
S11	Q11	tert-butyl 5-fluoro-6-formyl-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	194.3
S12	Q12	tert-butyl 7-fluoro-6-formyl-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	194.2
S13	Q13	tert-butyl 5-formyl-1,8-dimethyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	234.3
S14	Q14	tert-butyl 6-fluoro-8-formyl-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	194.2
S15	Q15	tert-butyl 6-fluoro-7-formyl-1-isopropyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	222.2
S16	Q16	tert-butyl 5-fluoro-7-formyl-1-isopropyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	222.2
S17	Q17	tert-butyl 8-fluoro-5-formyl-1-isopropyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	222.2
S18	Q18	tert-butyl 6-fluoro-5-formyl-1-isopropyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	222.4
S19	Q19	tert-butyl 7-fluoro-5-formyl-1-isopropyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	222.2
S20	Q20	tert-butyl 7-formyl-5-methoxy-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	206.3
S21	Q21	tert-butyl 7-chloro-5-formyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	190.2
S22	Q22	tert-butyl 8-fluoro-6-formyl-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	194.3
S23	Q23	tert-butyl 3-formyl-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate	277.2 ([M+H]$^+$)
S24	Q24	tert-butyl 5-formyl-1,6-dimethyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	190
S25	Q25	tert-butyl 3-formyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate	263.2 ([M+H]$^+$)
S26	Q26	tert-butyl 5-formyl-1-methyl-8-(trifluoromethoxy)-3,4-dihydroisoquinoline-2(1H)-carboxylate	260.2
S27	R1	8-methyl-7-(2,2,2-trifluoroacetyl)-5,6,7,8-tetrahydro-1,7-naphthyridine-2-carbaldehyde	273.1 ([M+H]$^+$)
S28	Q27	tert-butyl 8-fluoro-5-formyl-1,7-dimethyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	208.1
S29	Q28	tert-butyl 4-formyl-8-methyl-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate	277.1 ([M+H]$^+$)

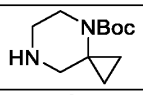
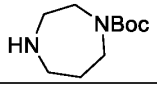
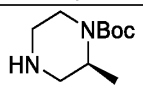
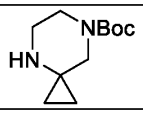
Example 24: Synthesis of compounds T1 to T4

Compounds T1 to T4 (shown in Table 14) were prepared by the following procedure:

A solution of the commercially available mono protected diamine shown in the table below (1 equiv.) and 2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzaldehyde (synthesized according to WO2021178920A1) (1 equiv.) in DCM (0.05 M) was treated with Et_3N (1.5 equiv.). The reaction mixture was stirred for 1 h, then was treated with MP-$CNBH_3$ (5.0 equiv.). The reaction mixture

was stirred at room temperature until the reaction was complete by LCMS. The reaction was quenched by addition of H_2O and extracted with DCM. The combined organic extracts were washed with water, brine, dried over $MgSO_4$ and concentrated in vacuo. Purification by silica gel column chromatography yielded the desired product (III).

Table 14: Compounds T1 to T4

Compound number	Mono protected diamine	Product Name	LCMS m/z $[M+H]^+$
T1		*tert*-butyl 7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octane-4-carboxylate	498.3
T2		*tert*-butyl 4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-1,4-diazepane-1-carboxylate	486.4
T3		*tert*-butyl (S)-4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-2-methylpiperazine-1-carboxylate	486.3
T4		*tert*-butyl 4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octane-7-carboxylate	498.4

Example 25: Synthesis of compounds U1 to U4

Compounds U1 to U4 (shown in Table 15) were prepared by the following procedure:

A solution of the starting material (1.0 equiv.) in DCM or 1,4-dioxane (0.05 M) was treated with HCl (4 M in 1,4-dioxane, 50 equiv.) and the mixture was stirred for 2 h. The volatiles were evaporated *in vacuo* to yield the product.

Table 15: Compounds U1 to U4

Compound number	Starting material	Product Name	LCMS m/z $[M+H]^+$
U1	T1	5-(4-((4,7-diazaspiro[2.5]octan-7-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt	398.3
U2	T2	5-(4-((1,4-diazepan-1-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt	386.3
U3	T3	(S)-5-(3,5-dimethoxy-4-((3-methylpiperazin-1-yl)methyl)phenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt	386.2
U4	T4	5-(4-((4,7-diazaspiro[2.5]octan-4-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt	398.4

Example 26: Synthesis of compounds V1 to V45

Compounds V1 to V45 (shown in Table 16) were prepared by the following procedure:

A solution of starting material (I) (1 equiv.) and starting material (II) (1 equiv.) in DCM (0.05 M) was treated with Et_3N (1.5 equiv.). The reaction mixture was stirred for 1 h, then was treated with $NaBH(OAc)_3$ (2.0 equiv.) or MP-$CNBH_3$ (5.0 equiv.) . The reaction mixture was stirred at room temperature until the reaction was complete by LCMS. The reaction was quenched by addition of H_2O and extracted with DCM. The combined organic extracts were washed with water, brine, dried over

$MgSO_4$ and concentrated in vacuo. Purification by silica gel column chromatography yielded the desired product (III).

Table 16: Compounds V1 to V45

Compound number	Starting material (I)	Starting material (II)	Product name	LCMS m/z $[M+H]^+$/ Yield
V1	U1	S1	tert-butyl 5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-8-fluoro-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	675.4/51%
V2	U1	S24	tert-butyl 5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-1,6-dimethyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	671.0/89%
V3	U1	S2	tert-butyl 5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-6-fluoro-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	675.4/60%
V4	U1	S3	tert-butyl 5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-7-fluoro-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	675.4/44%
V5	U1	S4	tert-butyl 5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-1,7-dimethyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	671.4/83%
V6	U1	S5	tert-butyl 5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-8-methoxy-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	687.2/40%
V7	U1	S6	tert-butyl 8-chloro-5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	691.2/59%
V8	U2	S1	tert-butyl 5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-1,4-diazepan-1-yl)methyl)-8-fluoro-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	663.4/54%
V9	U2	S2	tert-butyl 5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-1,4-diazepan-1-yl)methyl)-6-fluoro-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	663.4/63%
V10	U1	S7	tert-butyl 7-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-5-fluoro-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	675.2/31%
V11	U1	S8	tert-butyl 7-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-6-fluoro-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	675.3/68%
V12	U1	S9	tert-butyl 5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-7-methoxy-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	687.3/53%
V13	U1	S10	tert-butyl 7-chloro-5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	691.2/63%
V14	U2	S4	tert-butyl 5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-1,4-diazepan-1-yl)methyl)-1,7-dimethyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	659.4/47%
V15	U3	S2	tert-butyl 5-(((S)-4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-2-methylpiperazin-1-yl)methyl)-6-fluoro-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	663.4/51%
V16	U4	S4	tert-butyl 5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-1,7-dimethyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	671.6/53%
V17	U4	S1	tert-butyl 5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-8-fluoro-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	675.4/47%

Compound number	Starting material (I)	Starting material (II)	Product name	LCMS m/z $[M+H]^+$/ Yield
V18	U1	S11	tert-butyl 6-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-5-fluoro-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	675.2/32%
V19	U1	S12	tert-butyl 6-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-7-fluoro-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	675.3/25%
V20	U1	S13	tert-butyl 5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-1,8-dimethyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	671.3/70%
V21	U1	S14	tert-butyl 8-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-6-fluoro-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	675.3/71%
V22	U1	S15	tert-butyl 7-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-6-fluoro-1-isopropyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	703.4/16%
V23	U1	S16	tert-butyl 7-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-5-fluoro-1-isopropyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	703.3/33%
V24	U1	S17	tert-butyl 5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-8-fluoro-1-isopropyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	703.3/46%
V25	U4	S2	tert-butyl 5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-6-fluoro-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	675.3/62%
V26	U1	S18	tert-butyl 5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-6-fluoro-1-isopropyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	703.3/44%
V27	U1	S19	tert-butyl 5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-7-fluoro-1-isopropyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	703.3/38%
V28	U1	S20	tert-butyl 7-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-5-methoxy-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	687.4/60%
V29	U4	S3	tert-butyl 5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-7-fluoro-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	675.7/47%
V30	U4	S6	tert-butyl 8-chloro-5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	687.4/52%
V31	U1	S21	tert-butyl 7-chloro-5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate	677.6/81%
V32	U1	S22	tert-butyl 6-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-8-fluoro-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	675.3/54%
V33	U1	S23	tert-butyl 3-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate	-
V34	U4	9	tert-butyl 5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-7-methoxy-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	687.4/80%

Compound number	Starting material (I)	Starting material (II)	Product name	LCMS m/z $[M+H]^+$/ Yield
V35	U4	S18	tert-butyl 5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-6-fluoro-1-isopropyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	703.3/28%
V36	U4	S10	tert-butyl 7-chloro-5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	691.4/71%
V37	U4	S21	tert-butyl 7-chloro-5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate	677.3/98%
V38	U4	S19	tert-butyl 5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-7-fluoro-1-isopropyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	703.3/37%
V39	U4	S17	tert-butyl 5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-8-fluoro-1-isopropyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	-
V40	U1	S25	tert-butyl 3-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate	644.5/52%
V41	U4	S25	tert-butyl 3-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate	644.2/26%
V42	U1	S26	tert-butyl 5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-1-methyl-8-(trifluoromethoxy)-3,4-dihydroisoquinoline-2(1H)-carboxylate	741.3/41%
V43	U1	S27	5-(3,5-dimethoxy-4-((4-((8-methyl-7-(2,2,2-trifluoroacetyl)-5,6,7,8-tetrahydro-1,7-naphthyridin-2-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)phenyl)-1,3,4-trimethylpyridin-2(1H)-one	654.4/40%
V44	U1	S28	tert-butyl 5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-8-fluoro-1,7-dimethyl-3,4-dihydroisoquinoline-2(1H)-carboxylate	689.6/54%
V45	U1	S29	tert-butyl 4-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-8-methyl-5,8-dihydro-1,7-naphthyridine-7(6H)-carboxylate	658.5/40%

Example 27: Separation of enantiomers

The compounds shown in Table 17 were prepared by separating the parent racemic compound using the conditions presented in below.

Table 17: Separated enantiomers

Racemic compound	Enantiomer number	SFC separation conditions and isolated peak
V1	V1-1	A - isolated peak-1
V4	V4-1	B - isolated peak 1
V4	V4-2	B - Isolated peak 2
V8	V8-1	C - isolated peak 1
V9	V9-1	C - isolated peak 1
V11	V11-1	E - isolated peak 1
V11	V11-2	E - isolated peak 2
V3	V3-2	F - isolated peak 2
V3	V3-1	F - isolated peak 1
V13	V13-1	G - isolated peak 1
V13	V13-2	G - isolated peak 2
V14	V14-1	H - isolated peak 1
V14	V14-2	H - isolated peak 2
V15	V15-1	J - isolated peak 1
V15	V15-2	J - isolated peak 2
V16	V16-1	K - isolated peak 1
V16	V16-2	K - isolated peak 2
V17	V17-2	L - isolated peak 2
V7	V7-2	M - isolated peak 2
V7	V7-1	M - isolated peak 1
V10	V10-1	N - isolated peak 1
V10	V10-2	N - isolated peak 2
V5	V5-2	P - isolated peak 2
V5	V5-1	P - isolated peak 1
V18	V18-2	Q - isolated peak 2
V12	V12-1	R - isolated peak 1
V12	V12-2	R - isolated peak 2
V19	V19-1	S - isolated peak 1
V19	V19-2	S - isolated peak 2
V22	V22-1	T - isolated peak 1
V22	V22-2	T - isolated peak 2
V23	V23-1	U - isolated peak 1
V23	V23-2	U - isolated peak 2
V25	V25-1	V - isolated peak 1
V25	V25-2	V - isolated peak 2
V26	V26-1	W - isolated peak 1
V26	V26-2	W - isolated peak 2
V27	V27-1	X - isolated peak 1
V27	V27-2	X - isolated peak 2
V28	V28-1	Y - isolated peak 1
V28	V28-2	Y - isolated peak 2
V29	V29-1	Z - isolated peak 1
V29	V29-2	Z - isolated peak 2
V30	V30-1	Ai - isolated peak 1
V16	V16-1	Bi - isolated peak 1
V16	V16-2	Bi - isolated peak 2
V32	V32-2	Ci - isolated peak-2
V33	V33-1	Di - isolated peak 1
V33	V33-	Di - isolated peak 2
V34	V34-2	Ei - isolated peak 2

Racemic compound	Enantiomer number	SFC separation conditions and isolated peak
V24	V24-1	Fi - isolated peak 1
V24	V24-2	Fi - isolated peak 2
V35	V35-1	Gi - isolated peak 1
V35	V35-2	Gi - isolated peak 2
V36	V36-1	Hi - isolated peak 1
V36	V36-2	Hi - isolated peak 2
V38	V38-1	Ji - isolated peak 1
V38	V38-2	Ji - isolated peak 2
V39	V39-1	Ki - isolated peak 1
V39	V39-2	Ki - isolated peak 2
V42	V42-1	Li - isolated peak 1
V42	V42-2	Li - isolated peak 2
V44	V44-1	Mi - isolated peak 1

Table 18: SFC separation conditions A to Mi

SFC conditions	Column (see Table 19)	Mobile phase (see Table 20)	Flow rate (mL/min)	Back pressure (bar)	Wavelength (nm)	Cycle time (min)
A	Ac	Am	50	20	254	7
B	Bc	Am	100	120	220	10
C	Bc	Bm	120	120	220	6
E	Cc	Cm	100	100	254	6.5
F	Dc	Dm	100	100	220	6.5
G	Ac	Em	50	120	220	16
H	Dc	Dm	100	100	210	11
J	Ec	Fm	70	100	220	12
K	Dc	Dm	120	120	220	5.7
L	Fc	Gm	50	100	254	5
M	Bc	Dm	120	120	254	5
N	Gc	Hm	100	100	220	4
P	Bc	Dm	120	120	254	9.5
Q	Ac	Bm	60	100	220	8.5
R	Ac	Dm	50	100	220	8
S	Ac	Am	60	100	210	8.5
T	Dc	Jm	100	120	210	11
U	Dc	Lm	120	120	210	10
V	Cc	Cm	100	100	254	6.5
W	Bc	Am	60	100	220	8.5
X	Bc	Em	100	100	210	7
Y	Hc	Dm	50	100	254	8.5
Z	Bc	Mm	100	100	254	11
Ai	Bc	Mm	120	120	254	8
Bi	Dc	Nm	100	100	220	10
Ci	Jc	Pm	120	100	220	12
Di	Ac	Am	60	100	220	6
Ei	Ac	Am	50	120	254	7
Fi	Bc	Qm	120	100	220	14.5
Gi	Dc	Fm	120	100	220	7.5
Hi	Ac	Am	50	120	254	7
Ji	Bc	Bm	100	120	254	4.5
Ki	Kc	Gm	50	120	210	6
Li	Dc	Jm	100	100	220	12
Mi	Bc	Am	100	100	220	9

Table 19: Columns used in SFC separation

Column reference	Column
Ac	WHELK RR-(250*20)mm, 5μm
Bc	I Cellulose-Z (250*30)mm, 5μm
Cc	Chiral Pak ASH-(250*30)mm, 5μm
Dc	WHELK RR-(250*30)mm, 5μm
Ec	Lux A3-(250*20)mm, 5μm
Fc	I Cellulose B (250*21)mm, 5μm
Gc	DIOL-(250*30)mm, 5μm
Hc	WHELK RR-(250*21)mm, 5μm
Jc	Chiral Pak IK-(250*30)mm, 5μm
Kc	C Cellulose B (250*21) mm, 5μm

Table 20: Mobile phase used in SFC separation

Mobile phase reference	Mobile phase
Am	CO_2: 0.5% isopropylamine in MeOH:MeCN [60:40]
Bm	CO_2: 0.5% isopropylamine in MeOH:MeCN [70:30]
Cm	CO_2: 0.5% isopropylamine in IPA:MeCN [75:25]
Dm	CO_2: 0.5% isopropylamine in MeOH:MeCN [55:45]
Em	CO_2: 0.5% isopropylamine in MeOH:MeCN [50:50]
Fm	CO_2: 0.5% isopropylamine in MeOH:MeCN [75:25]
Gm	CO_2: 0.5% isopropylamine in MeOH:MeCN [80:20]
Hm	CO_2: 0.5% isopropylamine in IPA:MeCN [80:20]
Jm	CO_2: 0.5% isopropylamine in IPA:MeCN [60:40]
Lm	CO_2: 0.5% isopropylamine in IPA:MeCN [55:45]
Mm	CO_2: 0.5% isopropylamine in IPA:MeCN [70:30]
Nm	CO_2: 0.5% isopropylamine in IPA:MeCN [50:50]
Pm	CO_2: 0.5% isopropylamine in IPA:MeCN [65:35]
Qm	CO_2: 0.5% isopropylamine in MeOH:MeCN [65:35]

Example 28: Synthesis of compounds W1 to W78

Compounds W1 to W78(shown in Table 21) were prepared by the following procedure:

A solution of the starting material (1.0 equiv.) in DCM or 1,4-dioxane (0.05 M) was treated with HCl (4 M in 1,4-dioxane, 50 equiv.) and the mixture was stirred for 2 h. The volatiles were evaporated *in vacuo* to yield the corresponding amine hydrochloride (II).

Table 21: Compounds W1 to W78

Compound number	Starting material	Product name[b]	LCMS m/z $[M+H]^+$/Yield
W1	V1	5-(4-((4-((8-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt	575.4/used crude
W2	V2	5-(4-((4-((1,6-dimethyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt	571.4/used crude
W3	V4	5-(4-((4-((7-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt	575.4/used crude
W4	V3	5-(4-((4-((6-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt	575.4/used crude
W5	V1-1	5-(4-((4-((8-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 1)	575.3/98%
W6	V4-1	5-(4-((4-((7-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 1)	575.3/used crude
W7	V4-2	5-(4-((4-((7-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 2)	571.2/89%
W8	V5	5-(4-((4-((1,7-dimethyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt	587.2/used crude
W9	V6	5-(3,5-dimethoxy-4-((4-((8-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)phenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt	591.2/used crude
W10	V7	5-(4-((4-((8-chloro-1-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt	563.3/used crude
W11	V8-1	5-(4-((4-((8-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-1,4-diazepan-1-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 1)	563.3/used crude
W12	V9-1	5-(4-((4-((6-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-1,4-diazepan-1-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 1)	575.2/86%
W13	V10	5-(4-((4-((5-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt	575.2/91%
W14	V11	5-(4-((4-((6-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt	575.2/used crude
W15	V11-1	5-(4-((4-((6-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 1)	575.2/used crude
W16	V11-2	5-(4-((4-((6-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 2)	no m/z/used crude
W17	V12	5-(3,5-dimethoxy-4-((4-((7-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)phenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt	591.3/used crude

Compound number	Starting material	Product name[b]	LCMS m/z $[M+H]^+$/Yield
W18	V13	5-(4-((4-((7-chloro-1-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt	575.4/used crude
W19	V3-2	5-(4-((4-((6-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 2)	575.3/used crude
W20	V3-1	5-(4-((4-((6-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 1)	591.4/used crude
W21	V13-1	5-(4-((4-((7-chloro-1-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 1)	591.5/used crude
W22	V13-2	5-(4-((4-((7-chloro-1-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 2)	559.4/used crude
W23	V14-1	5-(4-((4-((1,7-dimethyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-1,4-diazepan-1-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 1)	559.4/used crude
W24	V14-2	5-(4-((4-((1,7-dimethyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-1,4-diazepan-1-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 2)	575.4/used crude
W25	V15-1	5-(4-(((3S)-4-((6-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 1)	575.4/used crude
W26	V15-2	5-(4-(((3S)-4-((6-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-3-methylpiperazin-1-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 2)	571.4/used crude
W27	V16-1	5-(4-((7-((1,7-dimethyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 1)	571.3/used crude
W28	V16-2	5-(4-((7-((1,7-dimethyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 2)	575.6/used crude
W29	V17-2	5-(4-((7-((8-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 2)	591.3/used crude
W30	V7-2	5-(4-((4-((8-chloro-1-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 2)	591.3/used crude
W31	V7-1	5-(4-((4-((8-chloro-1-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 1)	575.2/used crude
W32	V10-1	5-(4-((4-((5-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 1)	575.6/used crude
W33	V10-2	5-(4-((4-((5-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 2)	571.6/used crude
W34	V5-2	5-(4-((4-((1,7-dimethyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 2)	571.6/used crude
W35	V5-1	5-(4-((4-((1,7-dimethyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 1)	575.6/96%

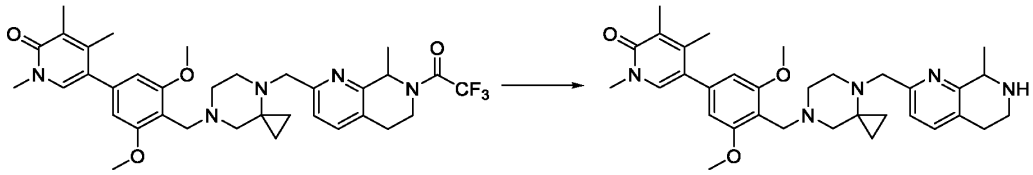
Compound number	Starting material	Product name[b]	LCMS m/z $[M+H]^+$/Yield
W36	V18-2	5-(4-((4-((5-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 2)	575.3/97%
W37	V19-1	5-(4-((4-((7-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 1)	575.4/97%
W38	V19-2	5-(4-((4-((7-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 2)	571.4/88%
W39	V20	5-(4-((4-((1,8-dimethyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt	575.2/84%
W40	V21	5-(4-((4-((6-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinolin-8-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt	603.4/87%
W41	V22-1	5-(4-((4-((6-fluoro-1-isopropyl-1,2,3,4-tetrahydroisoquinolin-7-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 1)	603.4/88%
W42	V22-2	5-(4-((4-((6-fluoro-1-isopropyl-1,2,3,4-tetrahydroisoquinolin-7-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 2)	603.4/89%
W43	V23-1	5-(4-((4-((5-fluoro-1-isopropyl-1,2,3,4-tetrahydroisoquinolin-7-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 1)	603.2/92%
W44	V23-2	5-(4-((4-((5-fluoro-1-isopropyl-1,2,3,4-tetrahydroisoquinolin-7-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 2)	603.3/73%
W45	V24	5-(4-((4-((8-fluoro-1-isopropyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt	575.4/97%
W46	V25-1	5-(4-((7-((6-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 1)	575.4/90%
W47	V25-2	5-(4-((7-((6-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 2)	603.3/77%
W48	V26-1	5-(4-((4-((6-fluoro-1-isopropyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 1)	603.3/66%
W49	V26-2	5-(4-((4-((6-fluoro-1-isopropyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 2)	603.4/98%
W50	V27-1	5-(4-((4-((7-fluoro-1-isopropyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 1)	603.2/92%
W51	V27-2	5-(4-((4-((7-fluoro-1-isopropyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 2)	No m/z/85%
W52	V28-1	5-(3,5-dimethoxy-4-((4-((5-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)phenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 1)	No m/z/78%
W53	V28-2	5-(3,5-dimethoxy-4-((4-((5-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)phenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 2)	575.2/used crude

Compound number	Starting material	Product name[b]	LCMS m/z $[M+H]^+$/Yield
W54	V29-1	5-(4-((7-((7-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 1)	575.2/used crude
W55	V29-2	5-(4-((7-((7-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 2)	591.3/99%
W56	V30-1	5-(4-((7-((8-chloro-1-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one (enantiomer 1)	577.5/used crude
W57	V31	5-(4-((4-((7-chloro-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt	587.3/96%
W58	V12-1	5-(3,5-dimethoxy-4-((4-((7-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)phenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 1)	587.3/98%
W59	V12-2	5-(3,5-dimethoxy-4-((4-((7-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)phenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 2)	NA/87%
W60	V32-2	5-(4-((4-((8-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 2)	558.2/78%
W61	V33-1	5-(3,5-dimethoxy-4-((4-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)phenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 1)	558.4/77%
W62	V33-2	5-(3,5-dimethoxy-4-((4-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)phenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 2)	587.6/94%
W63	V34-2	5-(3,5-dimethoxy-4-((7-((7-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)phenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 2)	603.5/used crude
W64	V24-1	5-(4-((4-((8-fluoro-1-isopropyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 1)	603.6/used crude
W65	V24-2	5-(4-((4-((8-fluoro-1-isopropyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 2)	603.4/used crude
W66	V35-1	5-(4-((7-((6-fluoro-1-isopropyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 1)	591.6/97%
W67	V13-2	R/S)-5-(4-((7-((7-chloro-1-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 2)	577.5/used crude
W68	V37	5-(4-((7-((7-chloro-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt	603.3/used crude
W69	V38-1	5-(4-((7-((7-fluoro-1-isopropyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 1)	603.3/used crude
W70	V38-2	5-(4-((7-((7-fluoro-1-isopropyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 2)	603.3/used crude
W71	V39-2	5-(4-((7-((8-fluoro-1-isopropyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 2)	544.5/92%

Compound number	Starting material	Product name[b]	LCMS m/z $[M+H]^+$/Yield
W72	V40	5-(3,5-dimethoxy-4-((4-((5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)phenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt	544.6/94%
W73	V41	5-(3,5-dimethoxy-4-((7-((5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)methyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)phenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt	641.5/89%
W74	V42-1	5-(3,5-dimethoxy-4-((4-((1-methyl-8-(trifluoromethoxy)-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)phenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 1)	641.5/81%
W75	V42-2	5-(3,5-dimethoxy-4-((4-((1-methyl-8-(trifluoromethoxy)-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)phenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 2)	589.4/97%
W76	V44-1	5-(4-((4-((8-fluoro-1,7-dimethyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt (enantiomer 1)	558.3/95%
W77	V45	5-(3,5-dimethoxy-4-((4-((8-methyl-5,6,7,8-tetrahydro-1,7-naphthyridin-4-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)phenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt	
W78	V35-2	5-(4-((7-((6-fluoro-1-isopropyl-1,2,3,4-tetrahydroisoquinolin-5-yl)methyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one, HCl salt	603.4

[b]"Enantiomer 1" indicates that the compound is one of the single enantiomers of the compound of unknown absolute configuration, and "enantiomer 2" that the compound is the other single enantiomer of the compound

Example 29: Synthesis of compound X1



(X1)

To a stirred solution of 5-(3,5-dimethoxy-4-((4-((8-methyl-7-(2,2,2-trifluoroacetyl)-5,6,7,8-tetrahydro-1,7-naphthyridin-2-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)phenyl)-1,3,4-trimethylpyridin-2(1H)-one (60 mg, 0.09 mmol) in MeOH (4 mL) was added K_2CO_3 (38 mg, 0.28 mmol) in H2O (1 mL) at RT. The reaction mixture was stirred at RT for 4 h. The solvent was removed in vacuo. The crude residue was partitioned between H_2O (20 mL) and DCM (2 x 50 mL). The combined organic layers was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to give 5-(3,5-dimethoxy-4-((4-((5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-2-yl)methyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)phenyl)-1,3,4-trimethylpyridin-2(1H)-one (X1; 50 mg, 0.09 mmol, 96%). **LCMS m/z** = 558.4 $[M+H]^+$.

Example 30: Synthesis of compounds Y1 to Y78

Compounds Y1 to Y78 (shown in Table 20) were prepared by the following procedure:

To a stirred solution of (E/Z)-2-cyano-4,4-dimethylpent-2-enoic acid (reported in WO2016210165A1; 1.0 equiv.) in DMF was added DIPEA (2.5 equiv.) and HATU (1.5 equiv.). The reaction mixture was stirred for 5 min, then starting material (1.5 equiv.) was added and the reaction mixture was stirred for 16 h at RT. The reaction was quenched with ice cold water and extracted with EtOAc. The combined organic layers were concentrated *in vacuo* to afford the crude product. If necessary, the crude product was purified by silica gel column chromatography/reverse phase preparative HPLC to give the product.

Table 22: Compounds Y1 to Y78

Compound number	Starting material	Product name[b]	LCMS m/z $[M+H]^+$/Yield
Y1	W1	(E/Z)-2-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-8-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile	710.4/ 34%
Y2	W2	(E/Z)-2-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-1,6-dimethyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile	706.4/ 5%
Y3	W3	(E/Z)-2-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-7-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile	710.4/ 50%
Y4	W4	(E/Z)-2-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-6-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile	710.4/ 20%
Y5	W5	(E/Z)-2-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-8-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 1)	710.3/ 21%
Y6	W6	(E/Z)-2-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-7-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 1)	710.4/ 49%
Y7	W7	(E/Z)-2-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-7-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 2)	710.3/ 46%
Y8	W8	(E/Z)-2-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-1,7-dimethyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile	706.3/ 12%
Y9	W9	(E/Z)-2-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-8-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile	722.3/ 17%
Y10	W10	(E/Z)-2-(8-chloro-5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile	726.2/ 19%
Y11	W11	(E/Z)-2-(5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-1,4-diazepan-1-yl)methyl)-8-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 1)	698.3/ 31%
Y12	W12	(E/Z)-2-(5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-1,4-diazepan-1-yl)methyl)-6-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 1)	698.4/ 42%
Y13	W13	(E/Z)-2-(7-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-5-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile	710.3/ 2%
Y14	W14	(E/Z)-2-(7-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-6-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile	710.2/ 48%
Y15	W15	(E/Z)-2-(7-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-6-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 1)	710.3/ 54%
Y16	W16	(E/Z)-2-(7-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-6-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 2)	710.3/ 60%
Y17	W17	(E/Z)-2-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-7-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile	722.4/ 18%

Compound number	Starting material	Product name[b]	LCMS m/z $[M+H]^+$/Yield
Y18	W18	(E/Z)-2-(7-chloro-5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile	726.2/ 49%
Y19	W19	(E/Z)-2-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-6-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 1)	710.4/ 41%
Y20	W20	(E/Z)-2-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-6-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 2)	710.4/ 51%
Y21	W21	(E/Z)-2-(7-chloro-5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 1)	726.2/ 54%
Y22	W22	(E/Z)-2-(7-chloro-5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 2)	726.2/ 57%
Y23	W23	(E/Z)-2-(5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-1,4-diazepan-1-yl)methyl)-1,7-dimethyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 1)	694.4/ 32%
Y24	W24	(E/Z)-2-(5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-1,4-diazepan-1-yl)methyl)-1,7-dimethyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 2)	694.4/ 32%
Y25	W25	(E/Z)-2-(5-(((S)-4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-2-methylpiperazin-1-yl)methyl)-6-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 1)	698.4/ 49%
Y26	W26	(E/Z)-2-(5-(((S)-4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-2-methylpiperazin-1-yl)methyl)-6-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 2)	698.4/ 35%
Y27	W27	(E/Z)-2-(5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-1,7-dimethyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 1)	706.4/ 48%
Y28	W28	(E/Z)-2-(5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-1,7-dimethyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 2)	706.3/ 43%
Y29	W29	(E/Z)-2-(5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-8-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 1)	710.3/ 49%
Y30	W30	(E/Z)-2-(8-chloro-5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 1)	726.2/ 41%
Y31	W31	(E/Z)-2-(8-chloro-5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 2)	726.2/ 41%
Y32	W32	(E/Z)-2-(7-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-5-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 1)	710.4/ 26%
Y33	W33	(E/Z)-2-(7-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-5-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 2)	710.4/ 43%

Compound number	Starting material	Product name[b]	LCMS m/z $[M+H]^+$/Yield
Y34	W34	(E/Z)-2-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-1,7-dimethyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 1)	706.3/ 44%
Y35	W35	(E/Z)-2-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-1,7-dimethyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 2)	706.3/ 39%
Y36	W3	(E/Z)-2-(6-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-5-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 1)	710.2/ 55%
Y37	W58	(E/Z)-2-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-7-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 1)	722.4/ 43%
Y38	W59	(E/Z)-2-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-7-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 2)	722.4/ 32%
Y39	W37	(E/Z)-2-(6-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-7-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 1)	710.3/ 67%
Y40	W38	(E/Z)-2-(6-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-7-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 2)	710.4/ 64%
Y41	W39	(E/Z)-2-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-1,8-dimethyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile	706.4/ 55%
Y42	W40	(E/Z)-2-(8-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-6-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile	710.4/ 21%
Y43	W41	(E/Z)-2-(7-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-6-fluoro-1-isopropyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 1)	738.4/ 27%
Y44	W42	(E/Z)-2-(7-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-6-fluoro-1-isopropyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 2)	738.4/ 31%
Y45	W43	(E/Z)-2-(7-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-5-fluoro-1-isopropyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 1)	738.4/ 80%
Y46	W44	(E/Z)-2-(7-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-5-fluoro-1-isopropyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 2)	738.4/ 55%
Y47	W45	(E/Z)-2-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-8-fluoro-1-isopropyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile	738.4/ 14%
Y48	W46	(E/Z)-2-(5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-6-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 1)	710.3/ 45%
Y49	W47	(E/Z)-2-(5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-6-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 2)	710.4/ 39%
Y50	W48	(E/Z)-2-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-6-fluoro-1-isopropyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 1)	738.3/ 40%
Y51	W49	(E/Z)-2-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-6-fluoro-1-isopropyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 2)	738.3/ 32%

Compound number	Starting material	Product name[b]	LCMS m/z [M+H]+/Yield
Y52	W50	(E/Z)-2-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-7-fluoro-1-isopropyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 1)	738.2/ 25%
Y53	W51	(E/Z)-2-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-7-fluoro-1-isopropyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 2)	738.2/ 55%
Y54	W52	(E/Z)-2-(7-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-5-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 1)	722.4/ 35%
Y55	W53	(E/Z)-2-(7-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-5-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 2)	722.3/ 41%
Y56	W56	(E/Z)-2-(8-chloro-5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 1)	726.2/ 33%
Y57	W57	(E/Z)-2-(7-chloro-5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile	712.2/ 14%
Y58	W60	(E/Z)-2-(6-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-8-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 1)	710.4/ 41%
Y59	W61	(E/Z)-2-(3-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine-6-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 1)	693.2/ 71%
Y60	W62	(E/Z)-2-(3-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine-6-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 2)	693.3/ 71%
Y61	W63	(E/Z)-2-(5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-7-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 1)	722.3/ 37%
Y62	W64	(E/Z)-2-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-8-fluoro-1-isopropyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 1)	738.4/ 28%
Y63	W65	(E/Z)-2-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-8-fluoro-1-isopropyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 2)	738.3/ 23%
Y64	W66	(E/Z)-2-(5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-6-fluoro-1-isopropyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 1)	738.3/ 14%
Y65	W55	(E/Z)-2-(5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-7-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 1)	710.4/ 5%
Y66	W54	(E/Z)-2-(5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-7-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 2)	710.3/ 5%
Y67	W67	(E/Z)-2-(7-chloro-5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 1)	726.2/ 61%
Y68	W68	(E/Z)-2-(7-chloro-5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile	712.2/ 20%

Compound number	Starting material	Product name[b]	LCMS m/z [M+H]+/Yield
Y69	W69	(E/Z)-2-(5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-7-fluoro-1-isopropyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 1)	738.4/ 9%
Y70	W70	(E/Z)-2-(5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-7-fluoro-1-isopropyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 2)	738.3/ 9%
Y71	W71	(E/Z)-2-(5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-8-fluoro-1-isopropyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 1)	738.3/ 12%
Y72	W72	(E/Z)-2-(3-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-6-carbonyl)-4,4-dimethylpent-2-enenitrile	679.2/ 21%
Y73	W73	(E/Z)-2-(3-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-6-carbonyl)-4,4-dimethylpent-2-enenitrile	679.2/ 16%
Y74	W74	(E/Z)-2-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-1-methyl-8-(trifluoromethoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 1)	776.2/ 59%
Y75	W75	(E/Z)-2-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-1-methyl-8-(trifluoromethoxy)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 2)	776.2/ 45%
Y76	X1	(E/Z)-2-(2-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-8-methyl-5,6,7,8-tetrahydro-1,7-naphthyridine-7-carbonyl)-4,4-dimethylpent-2-enenitrile	693.3/ 20%
Y77	W76	(E/Z)-2-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-8-fluoro-1,7-dimethyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 1)	724.3/ 60%
Y78	W77	(E/Z)-2-(4-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-8-methyl-5,6,7,8-tetrahydro-1,7-naphthyridine-7-carbonyl)-4,4-dimethylpent-2-enenitrile	693.3/ 21%

[b]"Enantiomer 1" indicates that the compound is one of the single enantiomers of the compound of unknown absolute configuration, and "enantiomer 2" that the compound is the other single enantiomer of the compound

Example 31: Synthesis of compounds Z1 to Z27

Compounds Z1 to Z27 (shown in Table 23) were prepared by the following procedure:

To a suspension of the starting material (1.0 equiv.) in MeCN (0.05 M) was added Et_3N (3 equiv.) and 3-(3,5-dimethyl-1H-pyrazol-1-yl)-3-oxopropanenitrile (1.1 equiv.). The reaction mixture was heated to 55 °C for 16 h. The volatiles were concentrated *in vacuo* and purified by flash chromatography to yield the product.

Table 23: Compounds Z1 to Z26

Compound number	Starting material	Product name[b]	LCMS m/z $[M+H]^+$/Yield
Z1	W1	3-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-8-fluoro-1-methyl-3,4-dihydroisoquinolin-2(1H)-yl)-3-oxopropanenitrile (enantiomer 1)[c]	642.3/72%
Z2	W1	3-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-8-fluoro-1-methyl-3,4-dihydroisoquinolin-2(1H)-yl)-3-oxopropanenitrile (enantiomer 2)[c]	642.3/72%
Z3	W12	3-(5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-1,4-diazepan-1-yl)methyl)-7-fluoro-1-methyl-3,4-dihydroisoquinolin-2(1H)-yl)-3-oxopropanenitrile (enantiomer 1)	630.3/31%
Z4	W35	3-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-1,7-dimethyl-3,4-dihydroisoquinolin-2(1H)-yl)-3-oxopropanenitrile (enantiomer 1)	638.3/98%
Z5	W34	3-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-1,7-dimethyl-3,4-dihydroisoquinolin-2(1H)-yl)-3-oxopropanenitrile (enantiomer 2)	638.2/97%
Z6	W54	3-(5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-7-fluoro-1-methyl-3,4-dihydroisoquinolin-2(1H)-yl)-3-oxopropanenitrile (enantiomer 1)	642.5/59%
Z7	W55	3-(5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-7-fluoro-1-methyl-3,4-dihydroisoquinolin-2(1H)-yl)-3-oxopropanenitrile (enantiomer 2)	642.5/62%
Z8	W46	3-(5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-6-fluoro-1-methyl-3,4-dihydroisoquinolin-2(1H)-yl)-3-oxopropanenitrile (enantiomer 1)	642.6/95%
Z9	W47	3-(5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-6-fluoro-1-methyl-3,4-dihydroisoquinolin-2(1H)-yl)-3-oxopropanenitrile (enantiomer 2)	642.6/93%
Z10	W28	3-(5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-1,7-dimethyl-3,4-dihydroisoquinolin-2(1H)-yl)-3-oxopropanenitrile (enantiomer 1)	638.3/94%
Z11	W27	3-(5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-1,7-dimethyl-3,4-dihydroisoquinolin-2(1H)-yl)-3-oxopropanenitrile (enantiomer 2)	638.3/94%
Z12	W58	3-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-7-methoxy-1-methyl-3,4-dihydroisoquinolin-2(1H)-yl)-3-oxopropanenitrile (enantiomer 1)	654.2/84%
Z13	W59	3-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-7-methoxy-1-methyl-3,4-dihydroisoquinolin-2(1H)-yl)-3-oxopropanenitrile (enantiomer 2)	654.2/84%
Z14	W19	3-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-6-fluoro-1-methyl-3,4-dihydroisoquinolin-2(1H)-yl)-3-oxopropanenitrile (enantiomer 1)	642.4/62%
Z15	W20	3-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-6-fluoro-1-methyl-3,4-dihydroisoquinolin-2(1H)-yl)-3-oxopropanenitrile (enantiomer 2)	642.4/100%
Z16	W63	3-(5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-7-methoxy-1-methyl-3,4-dihydroisoquinolin-2(1H)-yl)-3-oxopropanenitrile (enantiomer 1)	654.5/94%
Z17	W23	3-(5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-1,4-diazepan-1-yl)methyl)-1,7-dimethyl-3,4-dihydroisoquinolin-2(1H)-yl)-3-oxopropanenitrile (enantiomer 1)	626.2/18%

Compound number	Starting material	Product name[b]	LCMS m/z $[M+H]^+$/Yield
Z18	W24	3-(5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-1,4-diazepan-1-yl)methyl)-1,7-dimethyl-3,4-dihydroisoquinolin-2(1H)-yl)-3-oxopropanenitrile (enantiomer 2)	626.3/23%
Z19	W31	3-(8-chloro-5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-1-methyl-3,4-dihydroisoquinolin-2(1H)-yl)-3-oxopropanenitrile (enantiomer 1)	659.9/95%
Z20	W30	3-(8-chloro-5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-1-methyl-3,4-dihydroisoquinolin-2(1H)-yl)-3-oxopropanenitrile (enantiomer 2)	659.9/92%
Z21	W3	3-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-7-fluoro-1-methyl-3,4-dihydroisoquinolin-2(1H)-yl)-3-oxopropanenitrile	642.3/31%
Z22[d]	W6	3-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-7-fluoro-1-methyl-3,4-dihydroisoquinolin-2(1H)-yl)-3-oxopropanenitrile (enantiomer 1)	642.3/78%
Z23	W66	3-(5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-6-fluoro-1-isopropyl-3,4-dihydroisoquinolin-2(1H)-yl)-3-oxopropanenitrile (enantiomer 1)	668.4/85%
Z24	W78	3-(5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-6-fluoro-1-isopropyl-3,4-dihydroisoquinolin-2(1H)-yl)-3-oxopropanenitrile (enantiomer 2)	668.4/79%
Z25	W21	3-(7-chloro-5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-1-methyl-3,4-dihydroisoquinolin-2(1H)-yl)-3-oxopropanenitrile (enantiomer 1)	658.2/97%
Z26	W22	3-(7-chloro-5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-1-methyl-3,4-dihydroisoquinolin-2(1H)-yl)-3-oxopropanenitrile (enantiomer 2)	658.2/94%
Z27	W7	3-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-7-fluoro-1-methyl-3,4-dihydroisoquinolin-2(1H)-yl)-3-oxopropanenitrile (enantiomer 2)	642.3/20%

[b]"Enantiomer 1" indicates that the compound is one of the single enantiomers of the compound of unknown absolute configuration, and "enantiomer 2" that the compound is the other single enantiomer of the compound

[c]These enantiomers were obtained from the racemic compound using the following SFC conditions:

Instrument	PIC 22-028
Column	LUX A1
Mobile Phase	CO_2: 0.5% isopropylamine in MeOH:MeCN [60:40]
Flow rate	4 mL/min
Back pressure	100 bar
Wavelength	254 nm
Cycle time	8 min

[d] Compound Z22 was prepared using 1.5 equiv. rather than 1.1 equiv. of 3-(3,5-dimethyl-1H-pyrazol-1-yl)-3-oxopropanenitrile (1.5 equiv.)

Example 32: Synthesis of compounds Y80 to Y97, Y99 to Y108 and Y110 to Y115

Compounds Y80 to Y97, Y99 to Y108 and Y110 to Y115 (shown in Table 24) were prepared by either procedure A or B, as indicated in Table 25:

A) A solution of the starting material in EtOH was treated with an aldehyde and piperidine as noted in the “procedure” column of the table below. The reaction mixture was stirred at RT or heated to reflux for 72 h or until the reaction was complete. The volatiles were concentrated in vacuo and purified by silica gel column chromatography to yield the product.

B) A solution of the starting material in DMF (0.1 M) was treated with pyrrolidine and TMS-Cl and followed by addition of an aldehyde as noted in the “procedure” column of the table below. The reaction mixture was stirred at RT or heated to 55 °C for 16 h until the reaction was complete. The volatiles were concentrated *in vacuo* (at low temperature where appropriate) and purified by silica gel column chromatography to yield the product.

Table 24:Compounds Y80 to Y97, Y99 to Y108 and Y110 to Y115

Compound number	Product name[b]
Y80	(E/Z)-2-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-8-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-5-fluoro-4,4-dimethylpent-2-enenitrile (enantiomer 1)
Y81	(E/Z)-2-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-8-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-5-fluoro-4,4-dimethylpent-2-enenitrile (enantiomer 2)
Y82	(E/Z)-2-(5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-1,4-diazepan-1-yl)methyl)-7-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (enantiomer 1)
Y83	(E/Z)-2-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-1,7-dimethyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-5-fluoro-4,4-dimethylpent-2-enenitrile (enantiomer 1)
Y84	(E/Z)-2-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-1,7-dimethyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-5-fluoro-4,4-dimethylpent-2-enenitrile (enantiomer 2)
Y85	(E/Z)-2-(5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-7-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-5-fluoro-4,4-dimethylpent-2-enenitrile (enantiomer 1)
Y86	(E/Z)-2-(5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-7-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-5-fluoro-4,4-dimethylpent-2-enenitrile (enantiomer 2)
Y87	(E/Z)-2-(5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-6-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-5-fluoro-4,4-dimethylpent-2-enenitrile (enantiomer 1)
Y88	(E/Z)-2-(5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-6-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-5-fluoro-4,4-dimethylpent-2-enenitrile (enantiomer 2)
Y89	(E/Z)-2-(5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-1,7-dimethyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-5-fluoro-4,4-dimethylpent-2-enenitrile (enantiomer 1)
Y90	(E/Z)-2-(5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-1,7-dimethyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-5-fluoro-4,4-dimethylpent-2-enenitrile (enantiomer 2)
Y91	(E/Z)-2-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-7-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-5-fluoro-4,4-dimethylpent-2-enenitrile (enantiomer 1)
Y92	(E/Z)-2-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-7-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-5-fluoro-4,4-dimethylpent-2-enenitrile (enantiomer 2)
Y93	(E/Z)-2-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-6-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-5-fluoro-4,4-dimethylpent-2-enenitrile (enantiomer 1)
Y94	(E/Z)-2-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-6-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-5-fluoro-4,4-dimethylpent-2-enenitrile (enantiomer 2)
Y95	(E/Z)-2-(5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-7-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-3-(3-methyloxetan-3-yl)acrylonitrile (enantiomer 1)
Y96	(E/Z)-2-(5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-7-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-3-(thiazol-2-yl)acrylonitrile (enantiomer 1)

Compound number	Product name[b]
Y97	(E/Z)-2-(5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-7-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethyl-5-morpholinopent-2-enenitrile (enantiomer 1)
Y99	(E/Z)-2-(5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-7-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-5-fluoro-4,4-dimethylpent-2-enenitrile (enantiomer 1)
Y100	(E/Z)-2-(5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-1,4-diazepan-1-yl)methyl)-1,7-dimethyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-5-fluoro-4,4-dimethylpent-2-enenitrile (enantiomer 1)
Y101	(E/Z)-2-(5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-1,4-diazepan-1-yl)methyl)-1,7-dimethyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-5-fluoro-4,4-dimethylpent-2-enenitrile (enantiomer 2)
Y102	(E/Z)-2-(8-chloro-5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-3-(3-methyloxetan-3-yl)acrylonitrile (enantiomer 1)
Y103	(E/Z)-2-(8-chloro-5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-3-(3-methyloxetan-3-yl)acrylonitrile (enantiomer 2)
Y104	(E/Z)-2-(8-chloro-5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-5-fluoro-4,4-dimethylpent-2-enenitrile (enantiomer 1)
Y105	(E/Z)-2-(8-chloro-5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-5-fluoro-4,4-dimethylpent-2-enenitrile (enantiomer 2)
Y106	(E/Z)-2-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-7-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-5-fluoro-4,4-dimethylpent-2-enenitrile (enantiomer 1)
Y107	(E/Z)-2-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-7-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-5-fluoro-4,4-dimethylpent-2-enenitrile (enantiomer 2)
Y108	(E/Z)-2-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-7-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-3-(3-(fluoromethyl)oxetan-3-yl)acrylonitrile (enantiomer 1)
Y110	(E/Z)-2-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-7-fluoro-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-3-(3-methyloxetan-3-yl)acrylonitrile (enantiomer 1)
Y111	(E/Z)-2-(5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-6-fluoro-1-isopropyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-3-(3-methyloxetan-3-yl)acrylonitrile (enantiomer 1)
Y112	(E/Z)-2-(5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-7-yl)methyl)-6-fluoro-1-isopropyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-3-(3-methyloxetan-3-yl)acrylonitrile (enantiomer 2)
Y113	(E/Z)-2-(5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-7-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-3-(3-methyloxetan-3-yl)acrylonitrile (enantiomer 1)
Y114	(E/Z)-2-(7-chloro-5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-5-fluoro-4,4-dimethylpent-2-enenitrile (enantiomer 1)
Y115	(E/Z)-2-(7-chloro-5-((7-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-5-fluoro-4,4-dimethylpent-2-enenitrile (enantiomer 2)

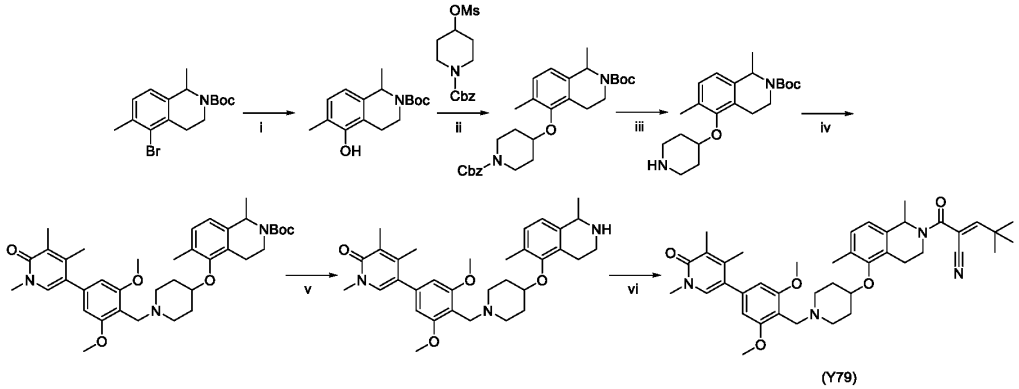
[b]"Enantiomer 1" indicates that the compound is one of the single enantiomers of the compound of unknown absolute configuration, and "enantiomer 2" that the compound is the other single enantiomer of the compound

Table 25: Procedures for preparation of compounds Y80 to Y97, Y99 to Y108 and Y110 to Y115

Compound number	Starting material	Procedure	LCMS m/z $[M+H]^+$/Yield
Y80	Z1	B: 3-fluoro-2,2-dimethylpropanal (5 eq), TMSCl (4 eq), pyrrolidine (6 eq), DMF	728.2/9%
Y81	Z2	B: 3-fluoro-2,2-dimethylpropanal (5 eq), TMSCl (4 eq), pyrrolidine (6 eq), DMF	728.2/26%
Y82	Z3	B: Pivalaldehyde (5 eq), TMSCl (4 eq), pyrrolidine (6 eq), DMF	698.3/37%
Y83	Z4	B: 3-fluoro-2,2-dimethylpropanal (4 eq), TMSCl (4 eq), pyrrolidine (6 eq), DMF	724.4/11%
Y84	Z5	B: 3-fluoro-2,2-dimethylpropanal (4 eq), TMSCl (4 eq), pyrrolidine (6 eq), DMF	724.3/21%
Y85	Z6	B: 3-fluoro-2,2-dimethylpropanal (2 eq), TMSCl (4 eq), pyrrolidine (6 eq), DMF	728.4/9%
Y86	Z7	B: 3-fluoro-2,2-dimethylpropanal (2 eq), TMSCl (4 eq), pyrrolidine (6 eq), DMF	728.2/5%
Y87	Z8	B: 3-fluoro-2,2-dimethylpropanal (4 eq), TMSCl (4 eq), pyrrolidine (6 eq), DMF	728.4/16%
Y88	Z9	B: 3-fluoro-2,2-dimethylpropanal (4 eq), TMSCl (4 eq), pyrrolidine (6 eq), DMF	728.3/14%
Y89	Z10	B: 3-fluoro-2,2-dimethylpropanal (4 eq), TMSCl (4 eq), pyrrolidine (6 eq), DMF	724.3/43%
Y90	Z11	B: 3-fluoro-2,2-dimethylpropanal (4 eq), TMSCl (4 eq), pyrrolidine (6 eq), DMF	724.3/47%
Y91	Z12	B: 3-fluoro-2,2-dimethylpropanal (4 eq), TMSCl (4 eq), pyrrolidine (6 eq), DMF	740.3/24%
Y92	Z13	B: 3-fluoro-2,2-dimethylpropanal (4 eq), TMSCl (4 eq), pyrrolidine (6 eq), DMF	740.3/27%
Y93	Z14	B: 3-fluoro-2,2-dimethylpropanal (5 eq), TMSCl (3 eq), pyrrolidine (4 eq), DMF	728.2/14%
Y94	Z15	B: 3-fluoro-2,2-dimethylpropanal (5 eq), TMSCl (3 eq), pyrrolidine (4 eq), DMF	728.4/32%
Y95	Z16	B: 3-methyloxetane-3-carbaldehyde (3 eq), TMSCl (4 eq), pyrrolidine (5 eq), DMF	736.4/9%
Y96	Z16	A: thiazole-2-carbaldehyde (3 eq), piperidine (5 eq), EtOH	749.2/14%
Y97	Z16	B: 2,2-dimethyl-3-morpholinopropanal (3 eq), TMSCl (4 eq), pyrrolidine (5 eq), DMF	807.4/25%
Y99	Z16	B: 3-fluoro-2,2-dimethylpropanal (6 eq), TMSCl (4 eq), pyrrolidine (5 eq), DMF	740.4/21%
Y100	Z17	B: 3-fluoro-2,2-dimethylpropanal (2 eq), TMSCl (5 eq), pyrrolidine (4 eq), DMF	712.3/11%
Y101	Z18	B: 3-fluoro-2,2-dimethylpropanal (5 eq), TMSCl (5 eq), pyrrolidine (4 eq), DMF	712.3/13%
Y102	Z19	B: 3-methyloxetane-3-carbaldehyde (7 eq), TMSCl (4 eq), pyrrolidine (6 eq), DMF	740.3/19%
Y103	Z19	B: 3-methyloxetane-3-carbaldehyde (7 eq), TMSCl (4 eq), pyrrolidine (6 eq), DMF	740.3/19%
Y104	Z19	B: 3-fluoro-2,2-dimethylpropanal (7 eq), TMSCl (4 eq), pyrrolidine (3 eq), DMF	744.2/22%
Y105	Z20	B: 3-fluoro-2,2-dimethylpropanal (7 eq), TMSCl (4 eq), pyrrolidine (3 eq), DMF	744.2/22%
Y106	Z27	B: 3-fluoro-2,2-dimethylpropanal (4 eq), TMSCl (6 eq), pyrrolidine (3 eq), DMF	728.2/11%
Y107	Z22	B: 3-fluoro-2,2-dimethylpropanal (8 eq), TMSCl (5 eq), pyrrolidine (5 eq), DMF	728.2/45%
Y108	Z22	B: 3-(fluoromethyl)oxetane-3-carbaldehyde (15 eq), TMSCl (4 eq), pyrrolidine (6 eq), DMF	742.2/14%
Y110	Z22	B: 3-methyloxetane-3-carbaldehyde (19 eq), TMSCl (8 eq), pyrrolidine (18 eq), DMF	724.4/36%
Y111	Z23	A: 3-methyloxetane-3-carbaldehyde (3 eq), piperidine (5 eq), EtOH	744.2/10%
Y112	Z24	A: 3-methyloxetane-3-carbaldehyde (3 eq), piperidine (5 eq), EtOH	752.4/6%
Y113	Z16	B: 3-methyloxetane-3-carbaldehyde (5 eq), TMSCl (4 eq), pyrrolidine (6 eq), DMF	736.3/13%

Compound number	Starting material	Procedure	LCMS m/z $[M+H]^+$/Yield
Y114	Z25	B: 3-fluoro-2,2-dimethylpropanal (4 eq), TMSCl (5 eq), pyrrolidine (5 eq), DMF	744.2/22%
Y115	Z26	B: 3-fluoro-2,2-dimethylpropanal (4 eq), TMSCl (5 eq), pyrrolidine (5 eq), DMF	744.2/12%

Example 33: Synthesis of compound Y79



Reaction conditions: i) KOH, tBuXPhos-Pd-G3, 1,4-dioxane; ii) Cs_2CO_3, MeCN; iii) Pd/C, MeOH; iv) AcOH, $MPCNBH_4$, MeOH; v) HCl in 1,4-dioxane, DCM; vi) HATU, DIPEA, DMF

Step (i): Preparation of tert-butyl 5-hydroxy-1,6-dimethyl-3,4-dihydroisoquinoline-2(1H)-carboxylate

A solution of aryl-bromide (1 equiv.), tBuXPhos-Pd-G3 (0.05 equiv.) and KOH (1M, 6 equiv.) in 1,4-dioxane was heated to 110 °C for 2 h. The reaction was quenched with ice-water and extracted with ethyl acetate. The organic phases were dried over anhydrous Na_2SO_4 and concentrated in vacuo to afford the crude product which was purified by silica gel column chromatography. Obtained 500 mg, 64% yield. **LCMS m/z** = 178.0 $[M\text{-}Boc+H]^+$

Step (ii): Preparation of tert-butyl 5-((1-((benzyloxy)carbonyl)piperidin-4-yl)oxy)-1,6-dimethyl-3,4-dihydroisoquinoline-2(1H)-carboxylate

To a solution of phenol (1.1 equiv.) and methylsulfonyl)oxy)piperidine-1-carboxylate (1.7 equiv., reported in WO2019034686A1) in acetonitrile was added cesium carbonate (3 equiv.). The reaction mixture was stirred at RT overnight before being concentrated in vacuo and partitioned between ice-water and DCM. The aqueous phase was extracted with DCM and the combined organic phases were dried over anhydrous sodium sulphate, filtered, and concentrated in vacuo. The crude product was purified by silica gel column chromatography to yield the desired product. Obtained 500 mg (crude), 56% yield. **LCMS m/z** = 395.3 $[M\text{-}Boc+H]^+$

Step (iii): Preparation of tert-butyl 1,6-dimethyl-5-(piperidin-4-yloxy)-3,4-dihydroisoquinoline-2(1H)-carboxylate

To a solution of Cbz-amine (1 equiv.) in MeOH was added Pd/C under nitrogen atmosphere. The atmosphere was replace with hydrogen gas (1 atm) and the reaction mixture was stirred at RT overnight. The reaction mixture was filtered through celite and the celite bed was washed with MeOH. The filtrate was concentrated in vacuo to afford crude product which was used in the next step without further purification. Obtained 250 mg, 74% yield. **LCMS m/z** = 361.4 $[M+H]^+$

Step (iv): Preparation of tert-butyl 5-((1-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)piperidin-4-yl)oxy)-1,6-dimethyl-3,4-dihydroisoquinoline-2(1H)-carboxylate

A solution of amine (1 equiv.) and 2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzaldehyde (1 equiv.) in MeOH (0.05 M) was treated with Et_3N (1.5 equiv.). The reaction mixture was stirred for 1 h, then was treated with $MP\text{-}CNBH_3$ (5.0 equiv.). The reaction mixture was stirred at

room temperature until the reaction was complete by LCMS. The reaction was quenched by addition of H_2O and extracted with DCM. The combined organic extracts were washed with water, brine, dried over $MgSO_4$ and concentrated in vacuo. Purification by silica gel column chromatography yielded the desired product (III). Obtained 500 mg, 78% yield. **LCMS m/z** = 646.4 $[M+H]^+$

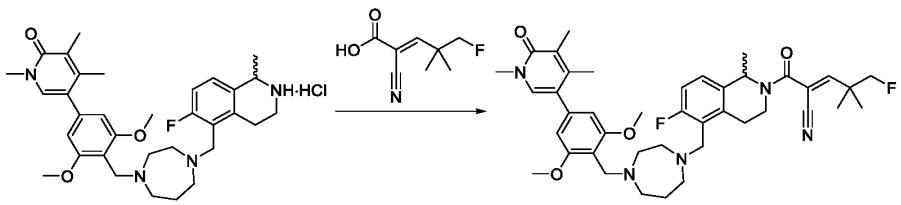
Step (v): Preparation of 5-(4-((4-((1,6-dimethyl-1,2,3,4-tetrahydroisoquinolin-5-yl)oxy)piperidin-1-yl)methyl)-3,5-dimethoxyphenyl)-1,3,4-trimethylpyridin-2(1H)-one hydrochloride

A solution of Boc protected amine (1.0 equiv.) in DCM or 1,4-dioxane (0.05 M) was treated with HCl (4 M in 1,4-dioxane, 50 equiv.) and the mixture was stirred for 2 h. The volatiles were evaporated *in vacuo* to yield the corresponding amine hydrochloride. Obtained 217 mg (crude). **LCMS m/z** = 546.4 $[M+H]^+$

Step (vi): Preparation of (E/Z)-2-(5-((1-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)piperidin-4-yl)oxy)-1,6-dimethyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (Y79)

To a stirred solution (E/Z)-2-cyano-4,4-dimethylpent-2-enoic acid (1.3 eq) in DMF was added DIPEA (2.5 equiv.) and HATU (1.5 equiv.). The reaction mixture was stirred for 5 min, then relevant amine (1.5 equiv.) was added and the reaction mixture was stirred for 16 h at RT. The reaction was quenched with ice cold water and extracted with EtOAc. The combined organic layers were concentrated *in vacuo* to afford the crude product. Where stated, the crude product was purified by silica gel column chromatography/reverse phase preparative HPLC to give (E/Z)-2-(5-((1-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)piperidin-4-yl)oxy)-1,6-dimethyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4,4-dimethylpent-2-enenitrile (Y79). Obtained 50 mg, 19% yield. **LCMS m/z** = 681.3 $[M+H]^+$

Example 34: Synthesis of compound Y117



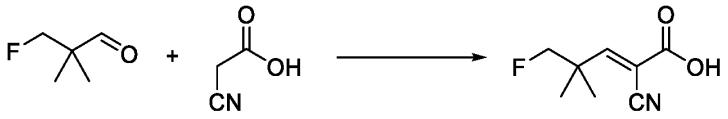
(W12) (Y117)

The wavy bonds in the scheme above indicate that the compound is a single enantiomer of unknown absolute configuration.

To a stirred solution of (E/Z)-2-cyano-5-fluoro-4,4-dimethylpent-2-enoic acid (1.5 equiv.) in DMF was added DIPEA (2.5 equiv.) and HATU (1.5 equiv.). The reaction mixture was stirred for 5 min, then compound W12 (1.5 equiv.) was added and the reaction mixture was stirred for 16 h at RT. The reaction was quenched with ice cold water and extracted with EtOAc. The combined organic layers were concentrated *in vacuo* to afford the crude product. Where stated, the crude product was purified by silica gel column chromatography/reverse phase preparative HPLC to give (E/Z)-2-(5-((4-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-1,4-diazepan-1-yl)methyl)-6-fluoro-1-methyl-

1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-5-fluoro-4,4-dimethylpent-2-enenitrile (Y117). Obtained 18 mg, 42% yield. **LCMS m/z** = 716.4 $[M+H]^+$

Preparation of (E/Z)-2-cyano-5-fluoro-4,4-dimethylpent-2-enoic acid



To a stirred solution of 2-cyanoacetic acid (1 g, 11.8 mmol, 1 eq) in methanol (5 mL) was added piperidine (3 g, 35.3 mmol, 3 eq) and the reaction mixture was stirred for 5 min at 25 °C. 3-fluoro-2,2-dimethylpropanal (2.4 g, 23.5 mmol, 2 eq) was added and the reaction mixture was stirred at 45 °C for 16 h. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL x 2). The aqueous layer pH was adjusted to ~3 using HCl (1.5 M) and the mixture was extracted with EtOAc (10 mL x 2). The combined organic layers were dried over anhydrous sodium sulphate, filtered, and concentrated in vacuo. The resulting residue was purified by reverse phase column chromatography (C18, flow rate = 20 mL/min, gradient = 30% MeCN in water). The appropriate fractions were concentrated in vacuo to afford (E/Z)-2-cyano-5-fluoro-4,4-dimethylpent-2-enoic acid (230 mg, 1.34 mmol, 11%). **LCMS m/z** = 170.2 $[M-H]^-$

Example 35: Degradation of BRD9 (IF)

A suspension of MV4-11 cells (ATCC CRL-9591) was prepared in phenol red-free assay media (IMDM Thermo Scientific 21056023 + 10% FBS ATCC 302025) and cells were seeded at 20,000 cells per well (45 µL) in sterile black poly-d-lysine coated 384 well plates (Greiner 781948). Compounds were prepared at 1000x final concentration in DMSO, diluted 1:100 in assay media, and 5 µL compound was added to each well of the cell plate. Cells were incubated for 24 hours at 37°C with 5% CO_2. All the following incubations for immunofluorescence staining were at room temperature. 15 µL of 16% PFA was added to each well (3.7% final concentration) and the cells were fixed for 15 min then washed twice with DPBS. Cells were permeabilised with 0.1% Triton X-100 for 10 min, Triton X-100 was removed, then blocked with 1% BSA in DPBS for 1 hour. Cells were stained with 25 µL anti-BRD9 E4Q3F antibody (CST 48306) diluted 1:25600 in 1% BSA in DPBS for 2-3 hours. Wells were washed twice with DPBS then incubated in the dark with 25 µL of 1% BSA containing a 1:1000 dilution of Anti-rabbit Alexa Fluor™ 647 secondary antibody (Thermo Scientific A21244) and 1 µg/mL Hoechst nuclear counter stain (Abcam ab228551) for 1 hour. Wells were washed twice with DPBS and then 60 µL of DPBS was left in the wells. The plate was imaged on a Perkin Elmer Operetta CLS with 10X air lens. Images were processed using Harmony High-Content Imaging and Analysis Software (Perkin Elmer) and the mean contrast ratio of Alexa Fluor™ 647 in central nuclei was used to quantify BRD9 protein levels. Data was further analysed using Dotmatics software and % BRD9 remaining was calculated by normalisation to average data from high and low control wells (cells treated with DMSO or 100 nM CFT-8634 respectively).

BRD9 degradation results

The degradation of BRD9 was detected according to the procedure outlined above for a number of exemplary compounds of the invention. The results are shown in Table 26. In particular, the table shows the degradation efficiency of 1 µM of indicated example compound at 6 h of treatment.

Table 26: Degradation of BRD9

Compound	DC_{50} (nm)	D_{max} (%)
Y1	+++	+++
Y2	+	+
Y3	+++	+++
Y4	++	+++
Y79	++	+
Y5	+++	+++
Y6	+++	+++
Y7	*	+
Y8	+++	+++
Y9	*	+
Y10	+++	+++
Y11	++	+++
Y12	+++	+++
Y13	+++	+++
Y14	++	+++
Y15	++	+++
Y16	++	+++
Y17	+++	+++
Y18	+++	+++
Y19	++	+++
Y20	*	+
Y21	*	++
Y22	+++	+++
Y23	+	+
Y24	++	+++
Y25	*	++
Y26	++	+++
Y27	*	+
Y28	++	+++
Y29	++	+++
Y30	+++	+++
Y31	*	+++
Y32	+++	+++
Y33	++	+
Y34	*	+
Y35	+++	+++
Y36	*	+
Y37	*	+
Y38	+++	+++
Y39	++	+++
Y40	*	+
Y41	+++	+++
Y42	*	+
Y43	*	+
Y44	+	++
Y45	++	+++
Y46	+	++
Y47	+++	+++
Y48	++	+++
Y49	*	+
Y50	++	+++
Y51	*	+++
Y52	+++	+++
Y53	*	++
Y54	+++	+++
Y55	+	+

Compound	DC_{50} (nm)	D_{max} (%)
Y56	++	+++
Y57	++	+++
Y58	++	+
Y59	+++	+++
Y60	++	+
Y61	++	+++
Y62	+++	+++
Y63	*	+
Y64	++	+++
Y65	++	+++
Y66	*	+
Y67	++	+++
Y68	*	+++
Y69	++	+++
Y70	*	+
Y71	++	+++
Y72	++	+++
Y73	+	+++
Y74	+++	+++
Y75	*	+
Y76	+	+++
Y77	+++	+++
Y78	+++	+++
Y80	++	++
Y81	+++	+++
Y82	++	+++
Y83	+++	+++
Y84	+	+
Y85	++	+++
Y86	*	+
Y87	+++	+++
Y88	*	+
Y89	++	+++
Y90	*	+
Y91	*	+
Y92	+++	+++
Y93	++	+++
Y94	*	+
Y95	+++	+++
Y96	+++	+++
Y97	+	+
Y99	+++	+++
Y100	++	+++
Y101	++	+
Y102	+++	+++
Y103	+	+
Y104	+++	+++
Y105	+++	+++
Y106	+	+
Y107	+++	+++
Y108	+++	+++
Y110	+++	+++
Y111	++	+++
Y112	*	+

Compound	DC_{50} (nm)	D_{max} (%)
Y113	+++	+++
Y114	*	++
Y115	+++	+++

NA = degradation does not reach 50%, / = not tested.

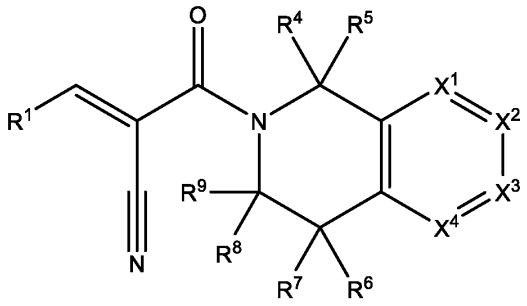
DC_{50} key: * = 25n M to 1000 nM, + = >10 nM and < 25 nM, ++ = 1.25 to 10 nM, +++ = <1.25 nM.

D_{max} key: + = >40% and <70%, ++ = ≥70 and <75%, +++ = ≥75%

5

CLAIMS

1. A compound comprising a moiety of formula (I)



(I)

wherein

R^1 is selected from C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_1-C_6 alkyl-(C_3-C_8cycloalkyl), 3-8 membered heterocycloalkyl, C_1-C_6 alkyl-(3-8 membered heterocycloalkyl), C_6-C_{10} aryl, C_1-C_6 alkyl-(C_6-C_{10} aryl), 5-10 membered heteroaryl, and C_1-C_6 alkyl-(5-10 membered heteroaryl), wherein each heterocycloalkyl and heteroaryl comprises one or more heteroatoms selected from the group consisting of N, S and O, and wherein the alkyl, cycloalkyl, alkyl(cycloalkyl), heterocycloalkyl, alkyl(heterocycloalkyl), aryl, alkyl(aryl), heteroaryl, and alkyl(heteroaryl) are each optionally substituted with one or more groups independently selected from halogen, OR^2, C_1-C_6 alkyl, and $N(R^3)_2$;

each R^2 is independently selected from H, C_1-C_6 alkyl and C_1-C_6 haloalkyl;

each R^3 is independently selected from H, C_1-C_6 alkyl and C_1-C_6 haloalkyl;

R^4, R^5, R^6, R^7, R^8, and R^9 are each independently selected from H and C_1-C_6 alkyl, wherein each alkyl is optionally substituted with one or more groups independently selected from halogen, OR^2, C_1-C_6 alkyl, CN, and $N(R^3)_2$;

X^1 is selected from N and CR^{10};

X^2 is selected from N and CR^{11};

X^3 is selected from N and CR^{12};

X^4 is selected from N and CR^{13};

R^{10}, R^{11}, R^{12}, and R^{13} are each independently selected from H, halogen, OR^2, C_1-C_6 alkyl, and $N(R^3)_2$ wherein each alkyl is optionally substituted with one or more groups independently selected from halogen, OR^2, and $N(R^3)_2$;

or a pharmaceutically acceptable salt thereof;

wherein:

- if X^1 is CR^{10}, X^2 is CR^{11}, X^3 is CR^{12} and X^4 is CR^{13}, then at least one of R^{10}, R^{11}, R^{12}, and R^{13} is not H; and
- no more than three of X^1, X^2, X^3 and X^4 are N.

2. The compound according to claim 1, wherein R^1 is selected from C_1-C_6 alkyl, 3-8 membered heterocycloalkyl, C_1-C_6alkyl(3-8 membered heterocycloalkyl), and 5-10 membered heteroaryl, wherein each heterocycloalkyl and heteroaryl comprises one or more heteroatoms selected from the group consisting of N, S and O, and wherein the alkyl, cycloalkyl, heterocycloalkyl,

alkyl(heterocycloalkyl), and heteroaryl are each optionally substituted with one or more groups independently selected from halogen and C_1-C_6 alkyl.

3. The compound according to claim 1 or claim 2, wherein R^1 is selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, 3-8 membered heterocycloalkyl, 3-8 membered heterocycloalkyl substituted with C_1-C_6 alkyl, C_1-C_6alkyl(3-8 membered heterocycloalkyl), 5-10 membered heteroaryl, and 5-10 membered heteroaryl substituted with halogen, wherein each heterocycloalkyl and heteroaryl comprises one or more heteroatoms selected from the group consisting of N, S and O.

4. The compound according to any preceding claim, wherein R^1 is selected from the following groups:



wherein the wavy line intersects the bond between R^1 and the rest of the compound.

5. The compound according to any preceding claim, wherein R^4, R^5, R^6, R^7, R^8, and R^9 are each independently selected from H, C_1-C_6 alkyl and, C_1-C_6 haloalkyl.

6. The compound according to any preceding claim, wherein R^4 and R^5 are each independently selected from H, C_1-C_6 alkyl, and C_1-C_6 haloalkyl; and

R^6, R^7, R^8, and R^9 are H.

7. The compound according to any preceding claim, wherein R^4 and R^5 are each independently selected from H, methyl, and isopropyl; and

R^6, R^7, R^8, and R^9 are H.

8. The compound according to any preceding claim, wherein R^4 is selected from H, methyl and isopropyl; and

R^5, R^6, R^7, R^8, and R^9 are H.

9. The compound according to any preceding claim, wherein R^{10}, R^{11}, R^{12}, and R^{13} are each independently selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy and C_1-C_6 haloalkoxy.

10. The compound according to any preceding claim, wherein

X^1 is CR^{10};

X^2 is CR^{11};

X^3 is CR^{12}; and

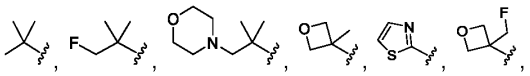
X^4 is CR^{13};

wherein at least one of R^{10}, R^{11}, R^{12}, and R^{13} is not H.

11. The compound according to any preceding claim, wherein no more than two of R^{10}, R^{11}, R^{12}, and R^{13} are H.

12. The compound according to any preceding claim, wherein

R^1 is selected from the following groups:



wherein the wavy line intersects the bond between R^1 and the rest of the compound;

R^4 is selected from H, methyl and isopropyl;

R^5, R^6, R^7, R^8, and R^9 are H;

X^1 is CR^{10};

X^2 is CR^{11};

X^3 is CR^{12};

X^4 is CR^{13};

R^{10} is selected from H, chlorine, fluorine, methyl, methoxy, and trifluoromethoxy;

R^{11} is selected from H, chlorine, fluorine, methyl, and methoxy;

R^{12} is selected from H, fluorine, and methyl; and

R^{13} is selected from H, fluorine, and methoxy;

wherein at least one of R^{10}, R^{11}, R^{12}, and R^{13} is not H.

13. The compound according to any one of claims 1 to 9, wherein

X^1 is CH or N;

X^2 is CH;

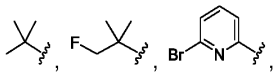
X^3 is CH or N; and

X^4 is CH or N;

wherein at least one of X^1, X^3 and X^4 is N.

14. The compound according to claim 13, wherein

R^1 is selected from the following groups:



wherein the wavy line intersects the bond between R^1 and the rest of the compound;

R^4 is methyl;

R^5, R^6, R^7, R^8, and R^9 are H;

X^1 is CH or N;

X^2 is CH;

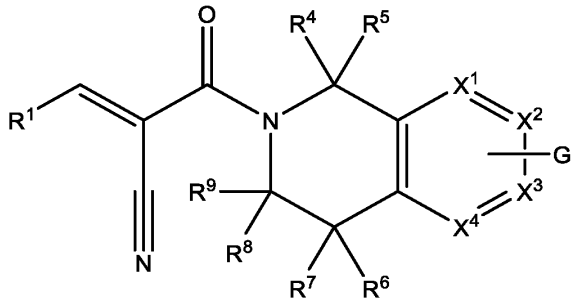
X^3 is CH or N; and

X^4 is CH or N;

wherein at least one of X^1, X^3 and X^4 is N.

15. The compound according to any preceding claim, wherein one of R^{10}, R^{11}, R^{12}, and R^{13} is replaced by a covalent bond to the rest of the compound.

16. A compound of formula (II)



(II)

wherein R^1, R^4, R^5, R^6, R^7, R^8, R^9, X^1, X^2, X^3, and X^4 are as defined in claims 1 to 14; and

G is a moiety which enables the attachment of the compound to another chemical structure via formation of a new covalent bond;

or a pharmaceutically acceptable salt thereof;

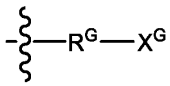
wherein if X^1 is CR^{10}, X^2 is CR^{11}, X^3 is CR^{12} and X^4 is CR^{13}, then at least one of R^{10}, R^{11}, R^{12}, and R^{13} is not H; and

wherein no more than three of X^1, X^2, X^3 and X^4 are N.

17. The compound according to claim 16, wherein no more than two of R^{10}, R^{11}, R^{12}, and R^{13} are H.

18. The compound according to claim 16 or claim 17, wherein G comprises a functional group that is able to facilitate the formation of an amide, ester, thioester, keto, urethane, amine, or ether linkage, or a carbon-carbon bond or carbon-nitrogen bond).

19. The compound according to any one of claims 16 to 18, wherein G is



wherein R^G is absent or is C_1-C_6 alkylene, optionally substituted with one or more groups independently selected from halogen, OR^2, C_1-C_6 alkyl, and $N(R^3)_2$;

each R^2 is independently selected from H and C_1-C_6 alkyl;

each R^3 is independently selected from H and C_1-C_6 alkyl;

X^G is a group that is selected from $-CO_2H$, -(CO)-N-hydroxysuccinimide, -(CO)-pentafluorphenol esters, -CHO, $-COR^{G1}$, -OH, $-OR^{G1}$, $-NH_2$, $-NHR^{G2}$, $-N(R^{G1}R^{G2})$, halo, O-leaving group, alkynyl, azide, dienyl, aminoxy, tetrazinyl, l-cyclooctenyl, cyclooctynyl, norbornyl, boronic acid, boronate ester, alkylboranes, an organometallic group, or C_1-C_6 alkyl optionally substituted by CO_2H, $O-NH_2$, or azide; and

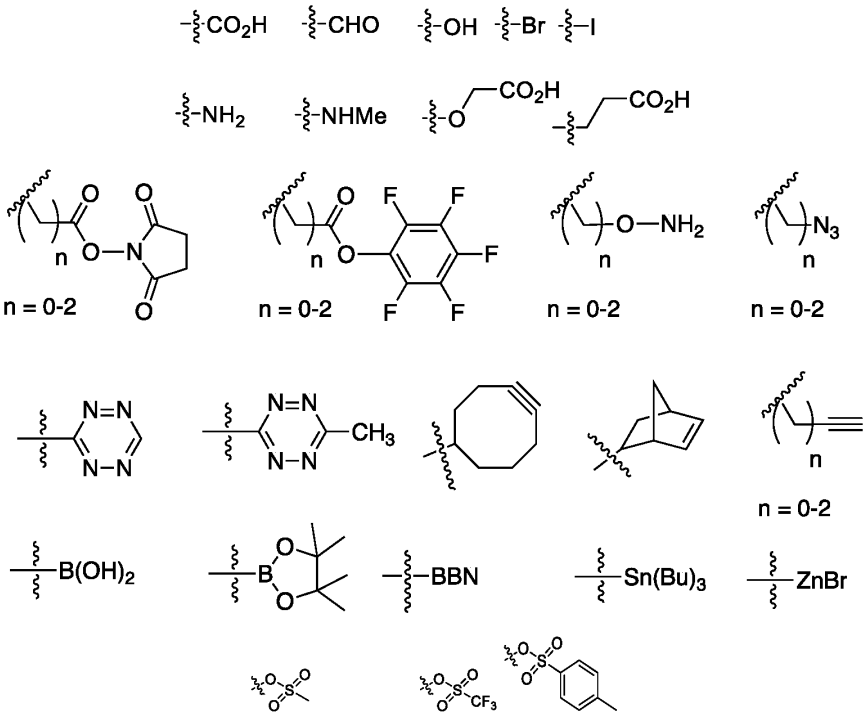
R^{G1} and R^{G2} are each independently selected from C_1-C_6 alkyl; and

wherein wavy line intersects the bond between G and the rest of the compound.

20. The compound according to claim 19, wherein R^G is absent or is C_1-C_6 alkylene.

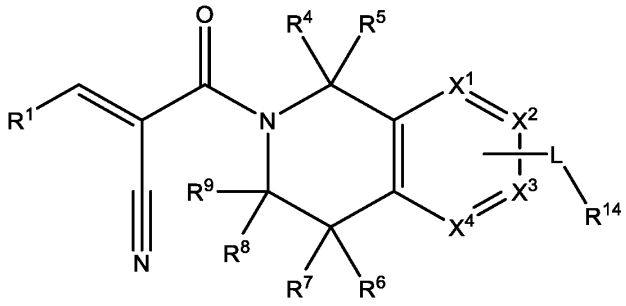
21. The compound according to claim 19 or claim 20, wherein X^G is a group that is selected from -CO_2H, -(CO)-N-hydroxysuccinimide, -(CO)-pentafluorphenol esters, -CHO, -COR^{G1}, -OH, -OR^{G1}, -NH_2, -NHR^{G2}, -$N(R^{G1}R^{G2})$, halogen (e.g. iodine or bromine), -Ots (tosylate), Oms (mesylate), –Otf (triflate), alkynyl, azide, dienyl, aminoxy, tetrazinyl, l-cyclooctenyl, cyclooctynyl, norbornyl, boronic acid, boronate ester, alkylboranes, an organometallic group (e.g. organotin or zinc), or C_1-C_6 alkyl optionally substituted by CO_2H, O-NH_2, or azide.

22. The compound according to anyone of claims 16 to 21, wherein G is selected from:



wherein wavy line intersects the bond that forms the link with the aromatic moiety of the compound of formula (II).

23. A compound of formula (III)



(III)

wherein

R^1, R^4, R^5, R^6, R^7, R^8, R^9, X^1, X^2, X^3, and X^4 are as defined in claims 1 to 14;

L is a covalent bond or a linker; and

R^{14} is a ligand that binds to a protein;

or a pharmaceutically acceptable salt thereof;

wherein if X^1 is CR^{10}, X^2 is CR^{11}, X^3 is CR^{12} and X^4 is CR^{13}, then at least one of R^{10}, R^{11}, R^{12}, and R^{13} is not H; and

wherein no more than three of X^1, X^2, X^3 and X^4 are N.

24. The compound according to claim 23, wherein no more than two of R^{10}, R^{11}, R^{12}, and R^{13} are H.

25. The compound according to claim 23 or claim 24, wherein L is a linker comprising 1 to 25 or 1 to 18 atoms in a single linear chain.

26. The compound according to any one of claims 23 to 25, wherein L is a linker comprising 1 to 10 or 1 to 8 rotatable bonds.

27. The compound according to anyone of claims 23 to 26, wherein:

(i) L is a covalent bond or a linker of formula $(L_x)_q$,

wherein each L_x represents a subunit of L that is independently selected from $CR^{L1}R^{L2}$, O, C=O, S, SO, SO_2, NR^{L3}, $SONR^{L4}$, $SONR^{L5}C{=}O$, $CONR^{L6}$, $NR^{L7}CO$, $C(R^{L8})=C(R^{L9})$, C≡C, C_6-C_{10}aryl, 5-10 membered heteroaryl, C_3-C_8cycloalkyl, and 3-8 membered heterocycloalkyl, wherein each heterocycloalkyl and heteroaryl comprises one or more heteroatoms selected from the group consisting of N, S and O, and wherein the aryl, heteroaryl, cycloalklyl, and heterocycloalkyl are each optionally substituted with one or more groups independently selected from halogen, OR^{15}, C_1-C_6 alkyl, and $N(R^{16})_2$;

each R^{15} is independently selected from H and C_1-C_6 alkyl;

each R^{16} is independently selected from H and C_1-C_6 alkyl;

each R^{L1}, R^{L2}, R^{L3}, R^{L4}, R^{L5}, R^{L6}, R^{L7}, R^{L8} and R^{L9} are each independently selected from H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, OH, C_1-C_6 alkoxy, NH_2, $NH(C_1$-C_6 alkyl), NO_2, CN, $CONH_2$, $CONH(C_1$-C_6 alkyl), $CON(C_1$-C_6 alkyl)$_2$, $SO_2(C_1$-C_6 alkyl), $CO_2(C_1$-C_6 alkyl), and $CO(C_1$-C_6 alkyl); and

q is an integer between 1 and 30; or

(ii) L is a linker of formula (L1a):

$$\mathbf{L^{1A}\text{-}L^{2A}\text{-}L^{3A}}$$

(L1a)

wherein L^{1A} is absent or is selected from C_1-C_6 alkylene, C_1-C_6 alkoxy and C_1-C_6 alkylamino;

L^{2A} is $-NR^{L2A}C{=}O-$ or $-C{=}ONR^{L2A}-$;

L^{3A} is selected from C_1-C_3 alkylene, C_1-C_6 alkoxy and C_1-C_6 alkylamino; and

R^{L2A} is H or C_1-C_6 alkyl; or

(iii) L is a linker of formula (L1b):

$$\mathbf{L^{1B}\text{-}L^{2B}\text{-}L^{3B}\text{-}L^{4B}\text{-}L^{5B}}$$

(L1b)

wherein L^{1B} is absent or is selected from C_1-C_3 alkylene, C_1-C_6 alkoxy and C_1-C_6 alkylamino;

L^{2B} is $-NR^{L2A}C{=}O-$ or $-C{=}ONR^{L2A}-$;

L^{3B} is selected from C_1-C_{15} alkylene, and $–[(CH_2)_2O]_{1-6}(CH_2)_2$-;

L^{4B} is -$NR^{L2A}C$=O- or -C=ONR^{L2A}-;

L^{5B} is selected from C_1-C_3 alkylene, C_1-C_6 alkoxy and C_1-C_6 alkylamino; and

R^{L2A} is H or C_1-C_6 alkyl; or

(iv) L is a linker of formula (L1c):

$$L^{1C}\text{-}L^{2C}\text{-}L^{3C}\text{-}L^{4C}$$

(L1c)

wherein L^{1C} is a 4- to 7-membered monocyclic N-heterocycloalkyl, a 7- to 12-membered bicyclic N-heterocycloalkyl, or an 8- to 18-membered tricyclic N-heterocycloalkyl, wherein the monocyclic, bicyclic, and tricyclic N-heterocycloalkyl each optionally containing one or two additional ring heteroatoms selected from N, O and S, and are each optionally substituted with one or more groups independently selected from halogen, OR^{15}, C_1-C_6 alkyl, and $N(R^{16})_2$;

L^{2C} is absent or is selected from C_1-C_3 alkylene, C_1-C_6 alkoxy, and C_1-C_6 alkylamino;

L^{3C} is -$R^{L2B}C$=O- or –(C=O)R^{L2B}-; and

L^{4C} is selected from C_1-C_3 alkylene, C_1-C_6 alkoxy, and C_1-C_6 alkylamino;

each R^{15} is independently selected from H and C_1-C_6 alkyl;

each R^{16} is independently selected from H and C_1-C_6 alkyl;

R^{L2A} is H or C_1-C_6 alkyl;

R^{L2B} is NR^{L2A}; or an N-linked 4- to 7-membered monocyclic N-heterocycloalkyl, a 7- to 12-membered bicyclic N-heterocycloalkyl, or an 8- to 18-membered tricyclic N-heterocycloalkyl, wherein the monocyclic, bicyclic, and tricyclic N-heterocycloalklyl each optionally containing one or two additional ring heteroatoms selected from N, O and S, and are each optionally substituted with one or more groups independently selected from halogen, OR^{17}, C_1-C_6 alkyl, and $N(R^{18})_2$; or

(v) L is a linker of formula (L1d):

$$L^{1D}\text{-}L^{2D}\text{-}L^{3D}$$

(L1d)

wherein L^{1D} is absent or is selected from C_1-C_3 alkylene, CO, C_1-C_3 alkylene(N(C_1-C_3 alkyl);

L^{2D} is NR^{L2A} or a 4- to 7-membered monocyclic N-heterocycloalkyl, a 7- to 12-membered bicyclic N-heterocycloalkyl, or an 8- to 18-membered tricyclic N-heterocycloalkyl, wherein the monocyclic, bicyclic, and tricyclic N-heterocycloalkyl each optionally contain one or two additional ring heteroatoms selected from N, O and S, and are each optionally substituted with one or more groups independently selected from halogen, OR^{15}, C_1-C_6 alkyl, and $N(R^{16})_2$;

L^{3D} is absent or is selected from C_1-C_3 alkylene, –O-, -N(C_1-C_3 alkyl)-, and CO;

each R^{15} is independently selected from H and C_1-C_6 alkyl;

each R^{16} is independently selected from H and C_1-C_6 alkyl; and

R^{L2A} is H or C_1-C_6 alkyl.

(vi) L is a linker of formula (L1e):

$$L^{1E}\text{-}L^{2E}\text{-}L^{3E}$$

(L1e)

wherein L^{1E} is C_1-C_3 alkylene or CO;

L^{2E} is a 4- to 7-membered monocyclic N-heterocycloalkyl, or a 7- to 12-membered bicyclic N-heterocycloalkyl, wherein the monocyclic, and bicyclic N-heterocycloalkyl each optionally contain one

or two additional ring heteroatoms selected from N, O and S, and are each optionally substituted with one or more groups independently selected from halogen, OR^{15}, C_1-C_6 alkyl, and $N(R^{16})_2$;

each R^{15} is independently selected from H and C_1-C_6 alkyl;

each R^{16} is independently selected from H and C_1-C_6 alkyl; and

L^{3E} is selected from C_1-C_3 alkylene; or

(vii) L is a linker of formula (L1f):

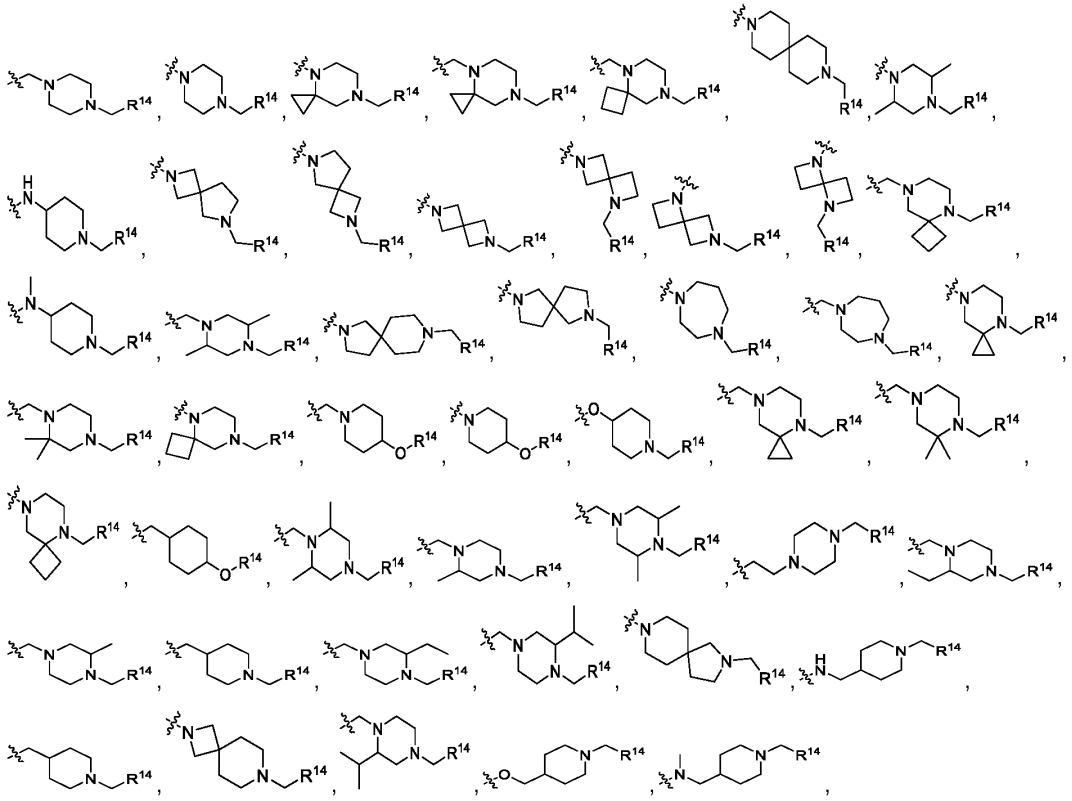
L^{1F}

(L1f)

wherein L^{1F} is selected from C_1-C_3 alkylene, CO, and C_1-C_3 alkylene(NR^{L1C}); and

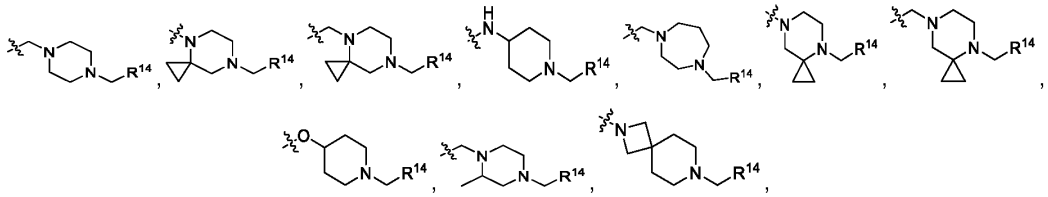
R^{L1C} is H or C_1-C_3 alkyl.

28. The compound according to anyone of claims 23 to 27, wherein the -L-R^{14} moiety comprises a structure selected from:



wherein the wavy line intersects the bond between L and the rest of the compound.

29. The compound according to anyone of claims 23 to 28, wherein the -L-R^{14} moiety comprises a structure selected from:

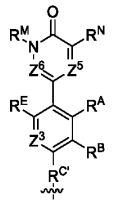


wherein the wavy line intersects the bond between L and the rest of the compound.

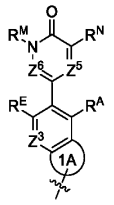
30. The compound according to any one of claims 23 to 29, wherein R^{14} is selected from the group consisting of: binders to kinases; binders to bromodomain-containing proteins; epigenetic modulator compounds; binders to transcription factors; binders to phosphatases, binders to ubiquitin E3 ligases and/or deubiquitinase enzymes; binders to nuclear hormone receptors; binders to aggregation-prone proteins; binders to apoptotic and anti-apoptotic factors; and binders to polymerases.

31. The compound according to claim 30, wherein R^{14} is a BRD9 binder.

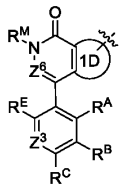
32. The compound of any one of claims 23 to 31, wherein R^{14} is a moiety of formula (1e), (1f) or (1g)



(1e)



(1f)



(1g)

wherein the wavy line intersects the bond between R^{14} and the linker;

R^A and R^E are each independently selected from the group consisting of H, C_{1-3} alkoxy and C_{1-3}alkyl;

R^B and R^D are each independently selected from the group consisting of C_{1-3} alkoxy, H, OH, halogen, NH_2, C_{1-3}alkyl, C_{1-3} haloalkoxy, C_{1-3}alkyl-O-C_{1-3}alkyl, 4-7 membered heterocycloalkyl, C_{1-3}alkyl-SO_2-C_{1-3}alkyl, C_{1-3}alkyl-NH_2, C_{1-3}alkyl-N(-C_{1-3}alkyl)$_2$, N(C_{1-3}alkyl)$_2$, NH-R^F, wherein the heterocycloalkyl comprises one or more heteroatoms selected from the group consisting of N, S and O;

alternatively, R^A and R^B taken together form a benzene ring;

R^C is selected from the group consisting of H, -Y-R^{G3}, NH_2, C_{1-3} alkyl and 4-7 membered heterocycloalkyl comprising one or more heteroatoms selected from the group consisting of N, S and O;

alternatively, R^C and Z^2 or R^C and Z^3 taken together form a 5-7 membered heterocycloalkyl comprising one or more heteroatoms selected from the group consisting of N, S and O, optionally substituted with C_{1-3} alkyl;

wherein when R^C is Y-R^{G3}, R^B and R^D are each independently selected from H, OH, halogen, NH_2, CN, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy and C_{1-3}alkoxy-C_{1-3}alkyl; wherein at least one of the substituents R^A to R^E is not hydrogen;

$R^{C'}$ is absent, or is as defined for R^C

R^F is selected from SO_2-C_{1-3}alkyl and C_{1-3} alkyl, wherein the C_{1-3} alkyl is optionally substituted with a 5 to 6 membered heteroaryl comprising one or more heteroatoms selected from the group consisting of N, S and O;

R^{G3} is selected from the group consisting of NH_2, OH, C_{1-3} alkyl, N(R^JR^K), OR^L, aryl, 5-6 membered heteroaryl, wherein the aryl and heteroaryl are optionally and independently substituted with one or more halogen, optionally substituted 4- to 7-membered monocyclic heterocycloalkyl, and

optionally substituted 7- to 12-membered bicyclic heterocycloalkyl, which monocyclic or bicyclic heterocycloalkyl comprise one or more heteroatoms selected from the group consisting of N, S and O, and are optionally substituted with one or more groups independently selected from halogen, OH, NH_2, C_{1-3} alkyl, NHC_{1-3}alkyl, $N(C_{1-3}alkyl)_2$, C_{1-3} alkoxy and CH_2-R^{M1};

R^H and R^I are each independently selected from H or C_{1-3} alkyl; or R^H and R^I taken together form a C_{3-4}cycloalkyl;

R^J is H or C_{1-3}alkyl;

R^K is selected from the group consisting of C_{1-3} alkyl, C_{2-3}alkyl-$N(C_{1-3}alkyl)_2$, C_{2-3}alkyl-NHC_{1-3}alkyl, 4- to 7- membered monocyclic heterocycloalkyl, and 7- to 12-membered bicyclic heterocycloalkyl, wherein each monocyclic and bicyclic heterocycloalkyl comprises one or more heteroatoms selected from the group consisting of N, S and O, and is optionally substituted with C_{1-3}alkyl;

R^L is C_{1-3} alkyl or a 4-7 membered heterocycloalkyl, wherein the heterocycloalkyl comprises one or more heteroatoms selected from the group consisting of N, S and O, and is optionally substituted with C_{1-3} alkyl;

R^M is selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} heteroalkyl comprising one or more heteroatoms selected from the group consisting of N, S and O, C_{3-10} cycloalkyl, C_{2-6} alkynyl and H, wherein the alkyl, alkenyl, heteroalkyl and cycloalkyl are each optionally substituted with C_1-C_3 alkyl;

R^{M1} is selected from 5-10 membered mono- or bicyclic aryl or heteroaryl comprising one or more heteroatoms selected from the group consisting of N, S and O, which is optionally substituted with NH_2, OH, halogen, CN, C_{1-3} alkyl, C_{1-3} alkoxy;

R^N is selected from the group consisting of H, halogen, C_{1-6}alkyl, $C(O)C_{1-5}$alkyl, NH_2, optionally substituted amino, OH, cyano, C_{1-6}heteroalkyl, C_{3-10} cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{2-9}heteroaryl, C_{2-6}alkenyl, C_{2-6}heteroalkenyl and thiol, wherein each heteroalkyl and heteroalkenyl comprises one or more heteroatoms selected from the group consisting of N, S and O, each heterocycloalkyl and heteroaryl comprises one or more heteroatoms selected from the group consisting of N, S and O, and the alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkenyl and heteroalkenyl are each optionally substituted with C_1-C_3 alkyl;

R^O is H, halogen, cyano, C_{1-6}alkyl, C_{1-6}heteroalkyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{2-9}heteroaryl, C_{2-6}alkenyl, C_{2-6}heteroalkenyl, hydroxy, and thiol, wherein each heteroalkyl and heteroalkenyl comprises one or more heteroatoms selected from the group consisting of N, S and O, each heterocycloalkyl and heteroaryl comprises one or more heteroatoms selected from the group consisting of N, S and O, and the alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkenyl and heteroalkenyl are each optionally substituted with C_1-C_3 alkyl;

alternatively, R^N and Z^5 taken together, combine to form a C_{6-10}arene or C_{2-9}heteroarene, wherein the heteroarene comprises one or more heteroatoms selected from the group consisting of N, S and O, and the arene or heteroarene are each optionally substituted with C_1-C_3 alkyl; optionally wherein R^N and R^O taken together with the carbon atoms to which they are joined, combine to form a C_{6-10}arene or C_{2-9}heteroarene, wherein the heteroarene comprises one or more heteroatoms selected from the group consisting of N, S and O, and the arene or heteroarene are each optionally substituted with C_1-C_3 alkyl;

R^P is selected from the group consisting of H, halogen, C_{1-6} alkyl, C_{1-6} heteroalkyl comprising one or more heteroatoms selected from the group consisting of N, S and O, C_{3-10} cycloalkyl and C_{6-10} aryl, wherein the alkyl, heteroalkyl, cycloalkyl, and aryl are each optionally substituted with C_1-C_3 alkyl;

Z^3 is N or CR^D;

Z^5 is N or CR^O;

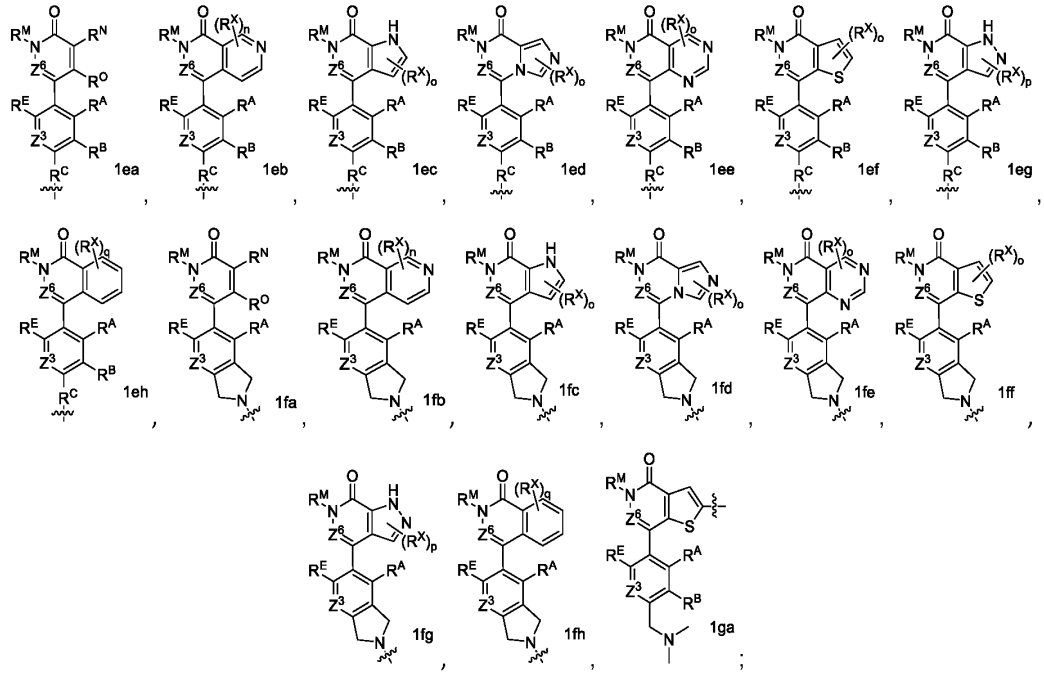
Z^6 is N or CR^P;

Y is absent or is selected from the group consisting of $-CR^HR^I-$, $-SO_2-$ and -CO-;

ring 1A is a 5-7 membered heterocycloalkane comprising one or two heteroatoms selected from the list consisting of N, S and O, optionally substituted with C_{1-3}alkyl; and

ring 1D is a C_{6-10}aryl or C_{2-9}heteroaryl comprising one or more heteroatoms selected from the group consisting of N, S and O, each of which are optionally substituted with C_{1-3}alkyl.

33. The compound of any one of claims 23 to 32, wherein R^{14} is a moiety selected from formulae (1ea) to (1eh), (1fa) to (1fi) and (1ga)



wherein the wavy line intersects the bond between R^{14} and L;

R^A, R^B, R^E, R^M, Z^3 and Z^6 are as defined in claim 28;

R^C is absent or as defined in claim 28;

R^N is selected from the group consisting of halogen, C_{1-5} alkyl, C_{1-3} haloalkyl, H, $C(O)C_{1-5}$alkyl, NH_2, NHC_{1-3}alkyl and OH;

R^O is H or C_{1-3} alkyl;

each R^X is independently selected from the group consisting of halogen, OH, NH_2, NH-C_{1-3}alkyl, C_{1-5} alkyl, C_{1-5} haloalkyl, C_{1-5} alkoxy and C_{1-4} haloalkoxy;

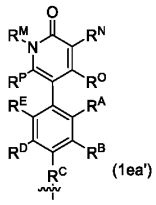
n is 0 to 3;

o is 0 to 2;

p is 0 or 1; and

q is 0 to 4.

34. The compound of any one of claims 23 to 33, wherein R^{14} is a moiety according to formula (1ea')



(1ea')

wherein the wavy line intersects the bond between R^{14} and L;

R^A and R^E are each independently selected from H and C_{1-3} alkoxy;

R^B and R^D are each independently selected from C_{1-3} alkoxy, H, halogen, C_{1-3} alkyl, and C_{1-3} haloalkoxy;

R^C is absent, or is Y-R^{G3};

Y is selected from the group consisting of -CR^HR^I-, and -CO-;

R^H and R^I are each independently selected from H or C_{1-3} alkyl; or R^H and R^I taken together form a C_{3-4} cycloalkyl;

R^{G3} is selected from the group consisting of N(R^JR^K), N(C_{1-3}alkyl)(4- to 7-membered monocyclic heterocycloalkylene), or -N(C_{1-3}alkyl)(7- to 12-membered bicyclic heterocycloalkylene)); -O-; 4- to 7-membered monocyclic heterocycloalkylene; and 7- to 12-membered heterocycloalkylene, wherein each heterocycloalkene comprises one or more heteroatoms selected from the group consisting of N, S and O, and is optionally substituted with C_1-C_3 alkyl;

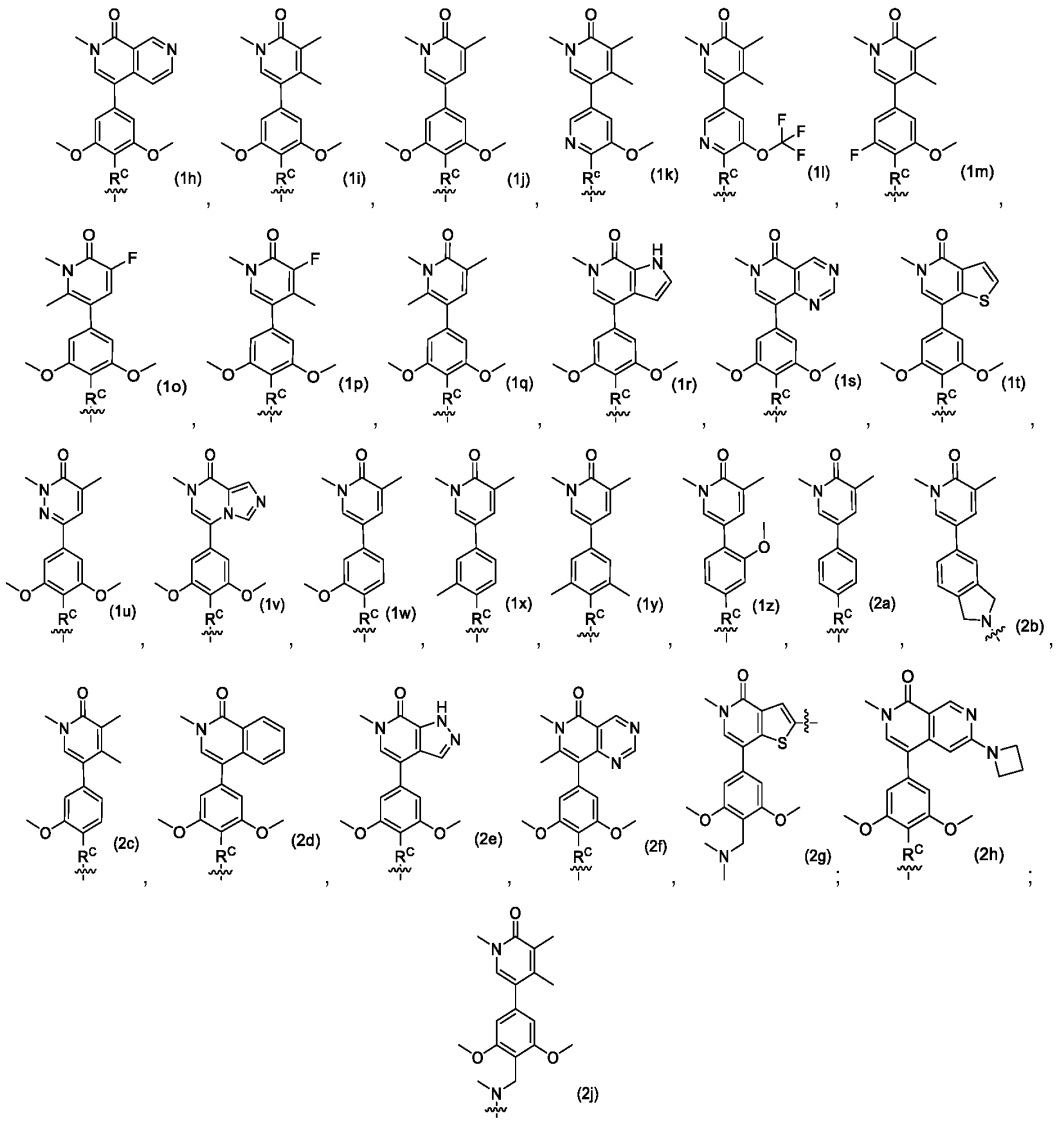
R^J is H or C_{1-3}alkyl;

R^K is selected from the group consisting of C_{1-3} alkyl, C_{2-3}alkyl-N(C_{1-3}alkyl)$_2$, C_{2-3}alkyl-NHC_{1-3}alkyl, 4- to 7-membered monocyclic heterocycloalkyl, and 7- to 12-membered bicyclic heterocycloalkyl, wherein each monocyclic or bicyclic heterocycloalkyl comprises one or more heteroatoms selected from the group consisting of N, S and O, and is optionally substituted with C_{1-3} alkyl;

R^M is C_{1-3} alkyl; and

R^N, R^O and R^P are each independently selected from the group consisting of halogen, C_{1-3} alkyl, and C_{1-3} haloalkyl.

35. The compound of any one of claims 23 to 34, wherein R^{14} is a moiety of formulae (1h) to (1m), (1o) to (1z) or (2a) to (2j)



wherein the wavy line intersects the bond between R^{14} and L;

R^C is absent, or is -Y-R^{G3};

Y is selected from the group consisting of -CR^HR^I-, and -CO-;

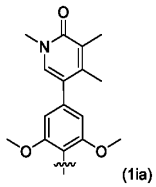
R^H and R^I are each H; or R^H and R^I taken together form a C_{3-4}cycloalkyl;

R^{G3} is selected from the group consisting of N(R^JR^K), N(C_{1-3}alkyl)(4- to 7-membered monocyclic heterocycloalkylene), or N(C_{1-3}alkyl)(7- to 12-membered bicyclic heterocycloalkylene)); -O-; 4- to 7-membered monocyclic heterocycloalkylene; and 7- to 12-membered bicyclic heterocycloalkylene, wherein each monocyclic or bicyclic heterocycloalkyl comprises one or more heteroatoms selected from the group consisting of N, S and O, and is optionally substituted with C_{1-3} alkyl;

R^J is H or C_{1-3}alkyl;

R^K is selected from the group consisting of C_{1-3} alkyl, C_{2-3}alkyl-N(C_{1-3}alkyl)$_2$, C_{2-3}alkyl-NHC_{1-3}alkyl, 4- to 7- membered monocyclic heterocycloalkyl, and 7- to 12-membered bicyclic heterocycloalkyl, wherein each monocyclic or bicyclic heterocycloalkyl comprises one or more heteroatoms selected from the group consisting of N, S and O, and is optionally substituted with C_{1-3}alkyl.

36. The compound of any one of claims 23 to 35, wherein R^{14} is a moiety of formula (1ia)



(1ia)

wherein the wavy line intersects the bond between R^{14} and L.

37. The compound according to claim 23, wherein the compound is any one of compounds Y1 to Y115.

38. A pharmaceutical composition comprising a compound of formula (III) according to any one of claims 23 to 37, together with a pharmaceutically acceptable carrier, optionally wherein the compound of formula (III) is present in the composition as a pharmaceutically acceptable salt, solvate or derivative.

39. A compound according to any one of claims 23 to 37, or a pharmaceutical composition of claim 38, for use in medicine.

40. The compound or pharmaceutical composition for use of claim 39, wherein the use comprises the treatment and/or prevention of any disease or condition which is associated with and/or is caused by an abnormal level of protein activity (e.g. an abnormal level of BRD9 activity).

41. The compound or pharmaceutical composition for use of claim 39 or 40, for use in the treatment and/or prevention of cancer.

42. A method of selectively degrading and/or increasing proteolysis of a target protein (e.g. BRD9) in a cell or a subject in need thereof, the method comprising contacting and/or treating the cell with a compound of formula (III) as defined in any one of claims 23 to 37 or the pharmaceutical composition of claim 38.

43. A method of making a compound of formula (III) as defined in any one of claims 23 to 37.

44. A compound library comprising a plurality of compounds according to any one of claims 1 to 37.