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(54) Title: BIFUNCTIONAL MOLECULES FOR TARGETED PROTEIN DEGRADATION

(57) Abstract: The present disclosure relates to a novel class of bifunctional molecules that are useful in a targeted or selective degradation of a protein.



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BIFUNCTIONAL MOLECULES FOR TARGETED PROTEIN DEGRADATION

FIELD

- 5 The present disclosure relates to a novel class of bifunctional molecules that are useful in a targeted or selective degradation of a protein, the protein being selected from an: (i) estrogen receptor; and (ii) androgen receptor.

BACKGROUND

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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.

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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.

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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.

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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.

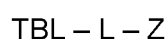
Because of these limitations, there remains a need to identify novel degrading mechanisms and warheads able to deliver new bifunctional degrader molecules, which show efficient degradation across a range of targets and cellular systems and/or with improved profiles suitable for drug development.

Further bifunctional degrader molecules have been described in WO 2019/238886, WO 2019/238817, WO 2019/238816, and WO 2022/129925.

SUMMARY

The present disclosure is based on the identification of a novel class of bifunctional molecules 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 bifunctional molecules, which facilitate proteasomal degradation of selected target protein(s) using a novel class of warhead. Within the context of the present disclosure, a “target protein” is selected from an: (i) estrogen receptor; and (ii) androgen receptor.

The bifunctional molecules described herein comprise a general structure of:

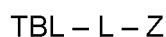


wherein TBL is a target protein binding ligand and L is a linker. The moiety “Z” (a “warhead”) modulates, facilitates and/or promotes proteasomal degradation of the target protein and may, in some cases, be referred to as a modulator, facilitator and/or promoter of proteasomal degradation. For example, in use, the TBL moiety of the bifunctional molecule binds to a target protein. The moiety Z (which is joined or otherwise connected to the TBL via the linker) then modulates, facilitates and/or promotes the degradation of this target protein, e.g. by acting to bring the target protein into proximity with a proteasome and/or by otherwise causing the target protein to be marked for proteasomal degradation within a cell.

Thus, the bifunctional molecules described in the present disclosure may be considered to comprise: a target protein binding ligand (TBL) (i.e. a ligand capable of binding (e.g. specifically binding) to a target protein; a warhead or degradation tag (Z) (e.g. moiety Z which acts to modulate, facilitate and/or promote the degradation of this target protein) and a linker (e.g. a chemical linker) which conjugates, joins or connects TBL and Z.

The bifunctional molecules described in the present disclosure have been shown to be effective degraders against a wide range of target proteins. Without being bound by theory, it is hypothesised that the Z moiety of the bifunctional molecules described herein does not bind to the ubiquitin E3 ligases typically relied on in the classical PROTAC approaches discussed above (such as CRBN and VHL). Accordingly, the bifunctional molecules described herein are believed to modulate, facilitate and/or promote proteasomal degradation via an alternative mechanism. Thus, the present class of bifunctional molecules may be useful against a wider range of diseases (including those that are resistant to many PROTAC degraders).

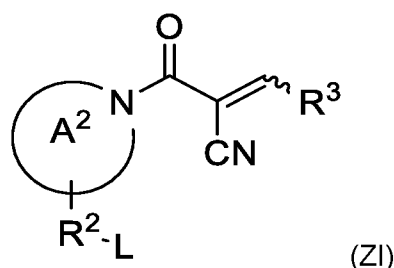
According to a first aspect of the invention, there is provided a bifunctional molecule comprising the general formula:



wherein TBL is a target protein binding ligand selected from an: (i) estrogen receptor binding ligand; and (ii) androgen receptor binding ligand;

L is a linker; and

Z comprises a structure according to formula (ZI):



wherein:

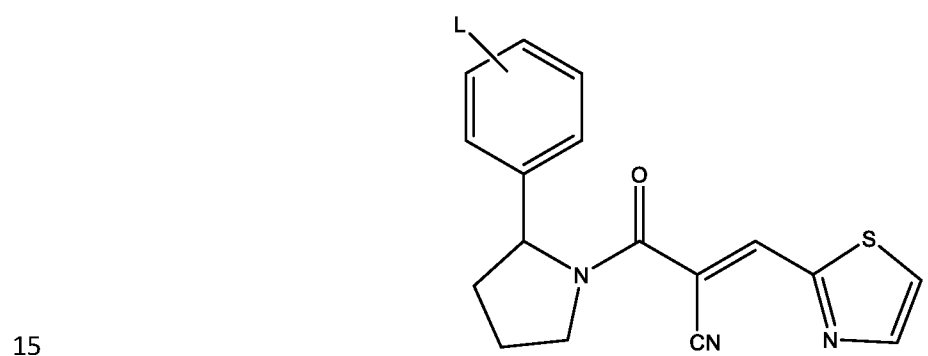
ring A² is an optionally substituted 4- to 7-membered monocyclic N-heterocycloalkyl or an optionally substituted 7- to 12-membered bicyclic N-heterocycloalkyl, each optionally containing one or two additional ring heteroatoms selected from N, O and S;

- 5 R² is absent or is selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, substituted heterocycloalkyl, NR^y, -CH(aryl)-, -CH(substituted aryl)-, -CH(heteroaryl)- and -CH(substituted heteroaryl)-;

wherein R^y is optionally substituted C₁₋₆alkyl or H;

- 10 R³ is selected from C₁₋₆ alkyl, cycloalkyl, substituted cycloalkyl, alkylcycloalkyl, substituted alkylcycloalkyl, alkyl heterocycloalkyl, substituted alkylcycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, optionally wherein the C₁₋₆ alkyl is substituted with one or more heteroatoms selected from halo, N, O and S; and L shows the point of attachment of the linker;

and further wherein Z is not:



or a pharmaceutically acceptable salt thereof.

- In a second aspect, the invention provides a pharmaceutical composition comprising the bifunctional molecule of the first aspect, together with a pharmaceutically acceptable carrier,
 20 optionally wherein the bifunctional molecule is present in the composition as a pharmaceutically acceptable salt, solvate or derivative.

- In a third aspect, the invention provides a bifunctional molecule of the first aspect, or the pharmaceutical composition of the second aspect, for use in medicine. suitably, wherein the
 25 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 of the estrogen receptor or androgen receptor.

- In a fourth aspect, the invention provides a method of treating and/or preventing any disease
 30 or condition which is associated with and/or is caused by an abnormal level of protein activity

of the estrogen receptor or androgen receptor, the method comprising administering a therapeutically effective amount of a bifunctional molecule of the first aspect, or the pharmaceutical composition of the second aspect to a subject in need thereof.

- 5 In a fifth aspect, the invention provides 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 bifunctional molecule of the first aspect or the pharmaceutical composition of the second aspect, wherein the target protein is selected from an: (i) estrogen receptor; and (ii) androgen receptor.

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In a sixth aspect, the invention provides 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 bifunctional molecule of the first aspect or the pharmaceutical composition of the second aspect, wherein the target

15 protein is selected from an: (i) estrogen receptor; and (ii) androgen receptor.

In a seventh aspect, the invention provides for use of a moiety Z as defined herein in a method of targeted protein degradation of a target protein selected from an: (i) estrogen receptor; and (ii) androgen receptor.

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In a seventh aspect, the invention provides for use of a moiety Z as defined herein in the manufacture of a bifunctional molecule suitable for targeted protein degradation of a target protein selected from an: (i) estrogen receptor; and (ii) androgen receptor.

- 25 In an eighth aspect, the invention provides a method of making a bifunctional molecule the first aspect.

In a ninth aspect, the invention provides a method of screening the bifunctional molecules of the first aspect, comprising:

- 30 a. providing a bifunctional molecule comprising:
(i) a first ligand comprising a structure according to Z as defined herein;
(ii) a second ligand that binds to a target protein selected from an: (i) estrogen receptor; and (ii) androgen receptor; and
(iii) a linker that covalently attaches the first and second ligands;
- 35 b. contacting a cell with the bifunctional molecule;
c. detecting degradation of the target protein in the cell;

d. detecting degradation of the target protein in the cell in the absence of the bifunctional molecule; and

e. comparing the level of degradation of the target protein in the cell contacted with the bifunctional molecule to the level of degradation of the target protein in the absence of the bifunctional molecule;

wherein an increased level of degradation of the target protein in the cell contacted with the bifunctional molecule indicates that the bifunctional molecule has facilitated and/or promoted the degradation of the target protein,

optionally wherein detecting degradation of the target protein comprises detecting changes in the levels of the target protein in the cell.

In a tenth aspect, the invention provides a compound library comprising a plurality of bifunctional molecules of the first aspect.

As shown in formula (ZI) above, the linker may be appended to moiety Z via the R^2 group. In such examples, the linker may be attached to moiety Z by way of a covalent bond between an atom on the linker and an atom contained in the ring system of the aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl or substituted heterocycloalkyl of the R^2 group. Alternatively, the linker may be attached to moiety Z by way of a covalent bond to the nitrogen atom of NR^y or the benzylic carbon atom of the $-CH(aryl)-$ or $-CH(substituted\ aryl)-$, for example by way of a covalent bond to the benzylic carbon atom of the $-CH(aryl)-$ or $-CH(substituted\ aryl)-$.

As described above, in some examples R^2 may be absent. In such examples, the linker may be appended to moiety Z by way of a covalent bond between an atom on the linker and an atom contained in the heterocyclic ring (e.g. ring A^2).

In all of the examples, the linker may be attached at any suitable position e.g. provided it has the correct valency and/or is chemically suitable. For example, the linker may be bonded at any position on the aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, substituted heterocycloalkyl, NR^y , $-CH(aryl)-$ or $-CH(substituted\ aryl)-$ of the R^2 group or may replace a hydrogen atom at any position on the heterocyclic ring shown, for example, in formula (ZI).

As described above, ring A^2 is an optionally substituted 4- to 7-membered monocyclic N-heterocycloalkyl, an optionally substituted 7- to 12-membered bicyclic N-heterocycloalkyl, or an optionally substituted 8- to 18-membered tricyclic N-heterocycloalkyl, each optionally

containing one or two additional ring heteroatoms selected from N, O and S, such as N and O.

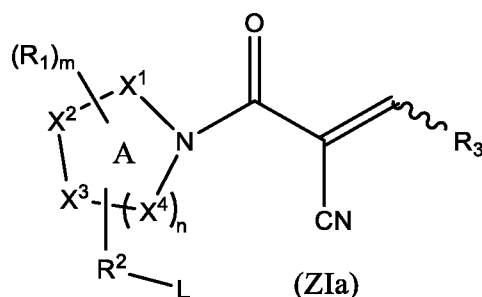
5 When ring A² is bicyclic or tricyclic, and unless otherwise stated, it may comprise rings that are joined by a bond, rings that are fused, a bridged ring and/or rings that are joined at a spiro centre.

10 When ring A² 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).

15 When ring A² is a bridged bicyclic ring, it may be an optionally substituted 7- to 12-membered bridged bicyclic N-heterocycloalkyl optionally containing one or two additional ring heteroatoms selected from N, O and S. In some examples, ring A² is 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, ring A² is a 7- or 8-membered bridged bicyclic N-heterocycloalkyl optionally containing one additional ring atom selected from N.

20 When ring A² is a spirocyclic bicyclic ring, it may be an optionally substituted 7- to 12-membered spirocyclic bicyclic N-heterocycloalkyl optionally containing one or two additional ring heteroatoms selected from N, O and S. In some examples, ring A² is 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, ring A² is bicyclic and comprises a first 5- to 7-membered ring and a second 3- to 7-membered ring. For example, ring A² 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, ring A² 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 embodiments, Z comprises a structure according to formula (ZIa):



wherein:

R^1 is absent (i.e. when m is 0) or is selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, C_1 to C_6 alkyl and substituted C_1 to C_6 alkyl, and/or wherein two R^1 groups combine to form an optionally substituted C_{1-3} bridge, optionally substituted C_{3-5} cycloalkyl or optionally substituted 5- to 7-membered heterocycloalkyl (e.g. 5- to 7-membered N-heterocycloalkyl), optionally wherein the C_{3-5} cycloalkyl or the 5- to 7-membered heterocycloalkyl are joined to ring A at a spiro centre;

R^2 is absent or is selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, substituted heterocycloalkyl, NR^y , $-CH(aryl)-$, $-CH(substituted\ aryl)-$, $-CH(heteroaryl)-$ and $-CH(substituted\ heteroaryl)-$;

wherein R^y is optionally substituted C_{1-6} alkyl or H;

R^3 is selected from C_1 - C_6 alkyl, cycloalkyl, substituted cycloalkyl, alkylcycloalkyl, substituted alkylcycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, alkyl heterocycloalkyl, substituted alkylheterocycloalkyl, aryl, substituted aryl, alkyl aryl, substituted alkylaryl, heteroaryl, substituted heteroaryl, alkyl heteroaryl, substituted alkylheteroaryl, optionally wherein the C_1 - C_6 alkyl is substituted with one or more heteroatoms selected from halo, N, O and S;

X^1 is CH_2 ;

X^2 , X^3 and X^4 are each independently CH_2 , O or NR^x ;

R^x is H or C_1 to C_6 alkyl, or wherein one R^1 group and one R^x group combine to form an optionally substituted C_{1-3} bridge;

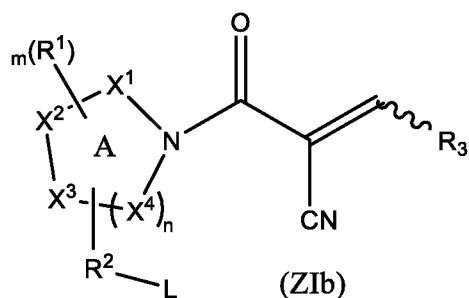
n is 0, 1, 2, or 3;

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

L shows the point of attachment of the linker.

In some examples, where n is 1, 2 or 3 (i.e. when 1, 2 or 3 X^4 groups are present), an X^4 group adjacent to (or directly bonded to) the N of the heterocyclic ring shown in formula (ZIa) is CH_2 .

In some examples, Z comprises a structure according to formula (ZIb):



wherein:

R¹ is absent (i.e. when m is 0) or is selected from aryl, substituted aryl, heteroaryl,

- 5 substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, C₁ to C₆ alkyl and substituted C₁ to C₆ alkyl, and/or wherein two R¹ groups combine to form an optionally substituted C₁₋₃ bridge, optionally substituted C₃₋₅cycloalkyl or optionally substituted 5- to 7-membered heterocycloalkyl (e.g. a 5- to 7-membered N-heterocycloalkyl), optionally wherein the C₃₋₅cycloalkyl or the 5- to 7-membered
- 10 heterocycloalkyl are joined to ring A at a spiro centre;

R² is absent or is selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, substituted heterocycloalkyl, NR^y, -CH(aryl)-, -CH(substituted aryl)-, -CH(heteroaryl)- and -CH(substituted heteroaryl)-;

wherein R^y is optionally substituted C₁₋₆alkyl or H;

- 15 R³ is selected from C₁-C₆ alkyl, cycloalkyl, substituted cycloalkyl, alkylcycloalkyl, substituted alkylcycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, alkyl heterocycloalkyl, substituted alkylheterocycloalkyl, aryl, substituted aryl, alkyl aryl, substituted alkylaryl, heteroaryl, substituted heteroaryl, alkyl heteroaryl, substituted alkylheteroaryl, optionally wherein the C₁-C₆ alkyl is substituted with one or more heteroatoms selected from halo, N, O
- 20 and S;

X¹ and X⁴ are each CH₂;

X² and X³ are each independently CH₂, O or NR^x; with the proviso that none or only 1 of X² and X³ is O;

R^x is H or C₁ to C₆ alkyl; or wherein one R¹ group and one R^x group combine to form an

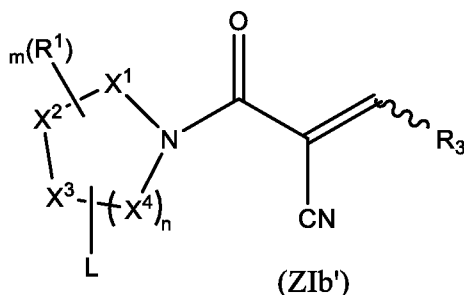
25 optionally substituted C₁₋₃ bridge;

n is 0, 1, 2 or 3;

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

L shows the point of attachment of the linker.

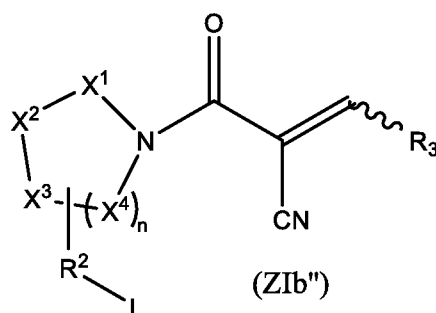
- 30 In some examples, Z comprises a structure according to formula (ZIb'):



wherein:

R^1 , R^3 , X^1 , X^2 , X^3 , X^4 , n , m and L are as defined above in respect of formula (ZIa) and (Zlb).

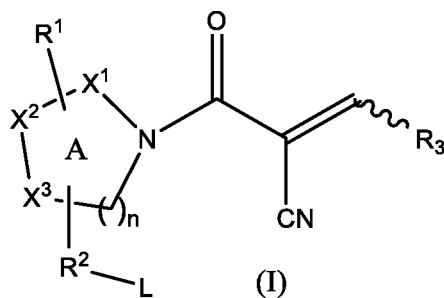
- 5 In some examples, Z comprises a structure according to formula (ZIb''):



wherein:

R^2 , R^3 , X^1 , X^2 , X^3 , X^4 , n and L are as defined above in respect of formula (ZIa) and (Zlb).

- 10 As stated above, in some embodiments of formulae (ZIa), (Zlb), (ZIb'), and (ZIb'') (and other formulae as described herein), an optionally substituted C_{1-3} bridge may be formed by two R^1 groups or, in some cases, by one R^1 group and one R^x group. The C_{1-3} bridge may be a C_1 - C_3 alkylene bridging group, such as methylene, ethylene or propylene. In some examples, the C_1 - C_3 bridge may be methylene or ethylene. Where the C_{1-3} bridge is substituted, it may
- 15 comprise from one to three (e.g. one or two) substituents (selected from any suitable substituent as described herein). For example, the 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.
- 20 In further embodiments, Z may comprise a structure according to formula (I):



wherein R^1 is absent or is selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, C_1 to C_6 alkyl and substituted C_1 to C_6 alkyl;

R^2 is absent or is selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, substituted heterocycloalkyl, $-NR^y$, $-\text{CH}(\text{aryl})-$, $-\text{CH}(\text{substituted aryl})-$, $-\text{CH}(\text{heteroaryl})-$ and $-\text{CH}(\text{substituted heteroaryl})-$;

wherein R^y is H or C_1 to C_6 alkyl;

R^3 is selected from C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

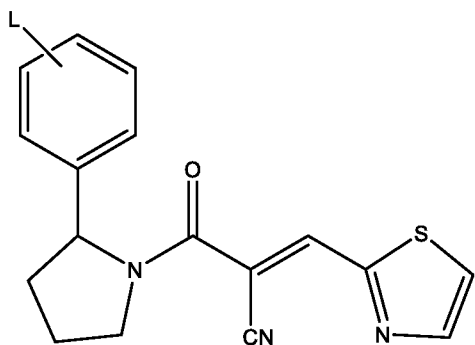
10 X^1 is CH_2 ;

X^2 and X^3 are each independently CH_2 , or a heteroatom selected from O and NR^x , wherein R^x is H or C_1 to C_6 alkyl;

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

L shows the point of attachment of the linker;

15 and further wherein Z is not:



In alternative examples of formula (I), the list of options for R^3 given above, may be replaced with C_1 to C_6 alkyl, cycloalkyl, substituted cycloalkyl, alkylcycloalkyl, substituted alkylcycloalkyl, alkyl heterocycloalkyl, substituted alkylcycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, optionally wherein the C_1 to C_6 alkyl is substituted with one or more heteroatoms selected from halo, N, O and S. In some embodiments, R^2 may be absent or selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, substituted heterocycloalkyl, $-\text{CH}(\text{aryl})-$, $-\text{CH}(\text{substituted aryl})-$, $-\text{CH}(\text{heteroaryl})-$ and $-\text{CH}(\text{substituted heteroaryl})-$.

In some examples, at least one of R^1 or R^2 is present.

For example, where R^1 is absent, R^2 may be present and selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, substituted heterocycloalkyl, $-NR^y$, $-CH(aryl)-$, $-CH(substituted\ aryl)-$, $-CH(heteroaryl)-$ and $-CH(substituted\ heteroaryl)-$. For example, where R^1 is absent, R^2 may be present and selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, substituted heterocycloalkyl, $-CH(aryl)-$, $-CH(substituted\ aryl)-$, $-CH(heteroaryl)-$ and $-CH(substituted\ heteroaryl)-$.

By way of further example, where R^2 is absent, R^1 may be present and selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, C_1 to C_6 alkyl and substituted C_1 to C_6 alkyl. By way of even further example, where R^2 is absent, at least one R^1 may be selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, C_1 to C_6 alkyl and substituted C_1 to C_6 alkyl, and/or wherein two R^1 groups combine to form an optionally substituted C_{1-3} bridge, optionally substituted C_{3-6} cycloalkyl or optionally substituted 5- to 7-membered N-heterocycloalkyl, optionally wherein the C_{3-5} cycloalkyl or the 5-7-membered N-heterocycloalkyl are joined to ring A at a spiro centre.

In some examples, both of R^1 and R^2 are present. For example, in some cases, R^2 is present and at least one R^1 is selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, C_1 to C_6 alkyl and substituted C_1 to C_6 alkyl, and/or wherein two R^1 groups combine to form a optionally substituted C_{1-3} bridge, optionally substituted C_{3-6} cycloalkyl or optionally substituted 5- to 7-membered N-heterocycloalkyl.

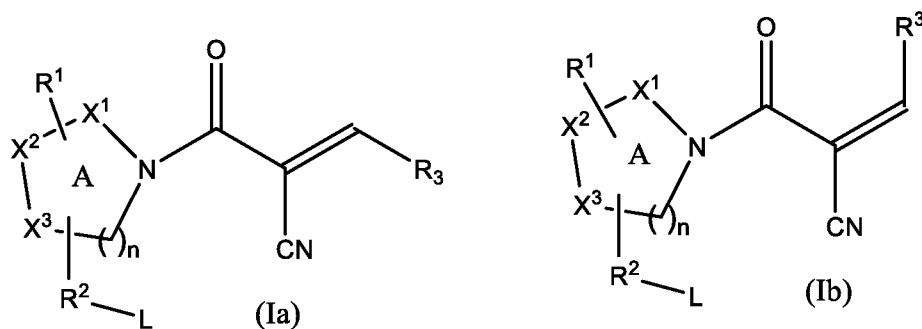
In the compounds described herein, R^1 and/or R^2 may be covalently attached to the heterocyclic ring (e.g. ring A) at any suitable position e.g. provided it has the correct valency and/or is chemically suitable. For example, R^1 and/or R^2 may replace a hydrogen atom at any position on the heterocyclic core, e.g. that shown in formula (I).

Where both R^1 and R^2 are present, they may be covalently attached to the heterocyclic ring (e.g. ring A) at the same or different positions. For example, in some cases R^1 and R^2 may be covalently attached to the heterocyclic core by way of different carbon atoms. In other cases, R^1 and R^2 may be covalently attached to the heterocyclic core by way of the same carbon atom.

As shown in the formulae described herein in relation to the Z moiety, a double bond is present in Z. The stereochemistry of this double bond may be either E or Z and this is indicated by the wavy line bond in formula (I) (and is similarly shown on the other formulae and structures disclosed herein). The designation of this moiety as either E or Z may depend on the identity of the R³ group. In some examples, Z 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 Z moieties according to formula (I) and any of the other formulae described herein (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 Z, 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, Z may be represented as either formula (Ia) or (Ib):



wherein R¹, R², R³, X¹, X², X³ and n are as defined above and herein.

It will be appreciated that the bifunctional molecules 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 bifunctional molecules, By way of example, where the bifunctional molecule comprises one or more chiral centres, the present disclosure encompasses each individual enantiomer of the bifunctional molecule as well as mixtures of enantiomers including racemic mixtures of such enantiomers. By way of further example, where the bifunctional molecule comprises two or more chiral centres, the

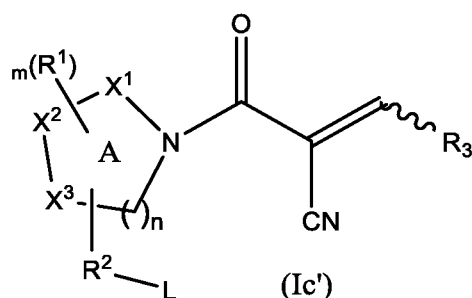
present disclosure encompasses each individual diastereomer of the bifunctional molecule, as well as mixtures of the various diastereomers.

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 bifunctional molecules described herein are to be understood to be within the scope of the present disclosure.

Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, bifunctional molecules as described herein in which one or more hydrogen atoms have been replaced by deuterium or tritium, or in which one or more carbon atoms have been replaced by a ^{13}C - or ^{14}C -enriched carbon are to be understood to be within the scope of the present disclosure. Such molecules may be useful, for example, as analytical tools, as probes in biological assays, or as therapeutic agents in accordance with the present disclosure. By way of further example, a bifunctional molecule as described herein, may be substituted with one or more deuterium atoms.

As used herein, references to “a bifunctional molecule” may further embrace a pharmaceutically acceptable salt thereof.

By way of further example, Z may be represented as formula (Ic'):



wherein:

R^1 is absent (i.e. m is 0) or is selected from the group consisting of: aryl having 6 to 10 carbon ring atoms that is optionally substituted with one to three substituents; heteroaryl having 5 to 10 ring atoms containing 1 to 3 heteroatoms each independently selected from N,

O and S, the heteroaryl being optionally substituted with one to three substituents; C₃ to C₈ cycloalkyl being optionally substituted with one to three substituents; heterocycloalkyl having 3 to 10 ring atoms and containing 1 to 3 ring heteroatoms each independently selected from N, O and S, the heterocycloalkyl being optionally substituted with one to three substituents;
 5 C₁ to C₆ alkyl optionally substituted with one to three substituents; and/or wherein two R¹ groups combine to form a C₁₋₃ bridge optionally substituted with one to three substituents, C₃₋₅cycloalkyl optionally substituted with one to three substituents or 5- to 7-membered N-heterocycloalkyl optionally substituted with one to three substituents (e.g wherein the C₃₋₅cycloalkyl or the 5-7-membered N-heterocycloalkyl are joined to ring A at a spiro centre);

10 R² is absent or is selected from the group consisting of: aryl having 6 to 10 carbon ring atoms, the aryl being optionally substituted with one to three substituents; heteroaryl having 5 to 10 ring atoms and containing 1 to 3 heteroatoms each independently selected from N, O and S, the heteroaryl being optionally substituted with one to three substituents; heterocycloalkyl having 3 to 10 ring atoms and containing 1 to 3 heteroatoms each
 15 independently selected from N, O and S, the heterocycloalkyl being optionally substituted with one to three substituents; -NR^y; -CH(aryl)-, wherein the aryl has 6 to 10 carbon ring atoms and is optionally substituted with one to three substituents-; and -CH(heteroaryl)-, wherein the heteroaryl has 5 to 10 ring atoms and contains 1 to 3 heteroatoms each independently selected from N, O and S, the heteroaryl being optionally substituted with one to three
 20 substituents;

wherein R^y is H or C₁ to C₆ alkyl;

R³ is selected from the group consisting of: C₁ to C₆ alkyl optionally substituted with one to three substituents; C₃ to C₈ cycloalkyl optionally substituted with one to three substituents; heterocycloalkyl having 3 to 10 ring atoms and containing 1 to 3 heteroatoms
 25 each independently selected from N, O and S, the heterocycloalkyl being optionally substituted with one to three substituents; aryl having 6 to 10 carbon ring atoms, the aryl being optionally substituted with one to three substituents; heteroaryl having 5 to 10 ring atoms and containing 1 to 3 heteroatoms each independently selected from N, O and S, the heteroaryl being optionally substituted with one to three substituents;

30 X¹ is CH₂;

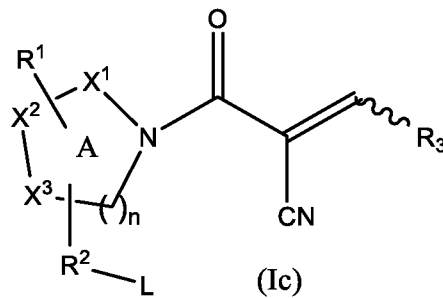
X² and X³ are each independently CH₂, or a heteroatom selected from O and NR^x, wherein R^x is H or C₁ to C₆ alkyl, or wherein one R¹ group and one R^x group combine to form a C₁₋₃ bridge optionally substituted with one to three substituents; with the proviso that none, or only 1 or 2 X² and X³ is a heteroatom; and

35 m is 0, 1, 2 or 3;

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

L shows the point of attachment of the linker.

By way of further example, Z may be represented as formula (lc):



wherein:

5 R¹ is absent or is selected from the group consisting of: aryl having 6 to 10 carbon ring atoms that is optionally substituted with one to three substituents; heteroaryl having 5 to 10 ring atoms containing 1 to 3 heteroatoms each independently selected from N, O and S, the heteroaryl being optionally substituted with one to three substituents; C₃ to C₈ cycloalkyl; C₁ to C₆ alkyl optionally substituted with one to three substituents;

10 R² is absent or is selected from the group consisting of: aryl having 6 to 10 carbon ring atoms, the aryl being optionally substituted with one to three substituents; heteroaryl having 5 to 10 ring atoms and containing 1 to 3 heteroatoms each independently selected from N, O and S, the heteroaryl being optionally substituted with one to three substituents; heterocycloalkyl having 3 to 10 ring atoms and containing 1 to 3 heteroatoms each
15 independently selected from N, O and S, the heterocycloalkyl being optionally substituted with one to three substituents; -NR^y; -CH(aryl)-, wherein the aryl has 6 to 10 carbon ring atoms and is optionally substituted with one to three substituents-; and -CH(heteroaryl)-, wherein the heteroaryl has 5 to 10 ring atoms and contains 1 to 3 heteroatoms each independently selected from N, O and S, the heteroaryl being optionally substituted with one to three
20 substituents;

wherein R^y is H or C₁ to C₆ alkyl;

R³ is selected from the group consisting of: C₁ to C₆ alkyl optionally substituted with one to three substituents; C₃ to C₈ cycloalkyl optionally substituted with one to three substituents; heterocycloalkyl having 3 to 10 ring atoms and containing 1 to 3 heteroatoms each independently selected from N, O and S, the heterocycloalkyl being optionally substituted with one to three substituents; aryl having 6 to 10 carbon ring atoms, the aryl being optionally substituted with one to three substituents; heteroaryl having 5 to 10 ring atoms and containing 1 to 3 heteroatoms each independently selected from N, O and S, the heteroaryl being optionally substituted with one to three substituents;

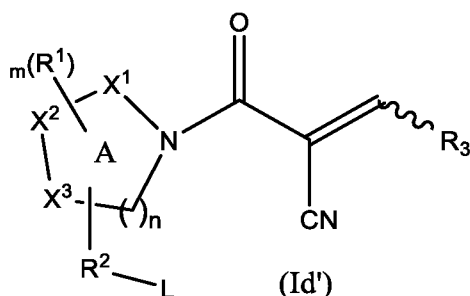
30 X^1 is CH_2 ;

X^2 and X^3 are each independently CH_2 , or a heteroatom selected from O and NR^x , wherein R^x is H or C_1 to C_6 alkyl; with the proviso that none, or only 1 or 2 X^2 and X^3 is a heteroatom; and

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

5 L shows the point of attachment of the linker.

By way of further example, Z may be represented as formula (Id'):



wherein:

10 R^1 is absent (i.e. when m is 0) or is selected from the group consisting of: phenyl that is optionally substituted with one to three substituents selected from the group consisting of halo, C_1 to C_6 alkyl, C_1 to C_6 haloalkyl and C_1 to C_6 alkoxy; heteroaryl having 5 to 6 ring atoms containing 1 to 3 heteroatoms each independently selected from N, O and S, the heteroaryl being optionally substituted with one to three substituents selected from the group consisting of halo, C_1 to C_6 alkyl, C_1 to C_6 haloalkyl and C_1 to C_6 alkoxy; heterocycloalkyl having 5 to 7 ring atoms and containing 1 to 3 ring heteroatoms each independently selected from N, O and S; C_3 to C_8 cycloalkyl; C_1 to C_6 alkyl and C_1 to C_6 haloalkyl;

and/or wherein two R^1 groups combine to form a C_{1-3} bridge, C_{3-5} cycloalkyl or 5- to 7-membered N-heterocycloalkyl (e.g. wherein the C_{3-5} cycloalkyl or the 5-7-membered N-heterocycloalkyl are joined to ring A at a spiro centre);

25 R^2 is absent or is selected from the group consisting of: phenyl that is optionally substituted with one to three substituents selected from the group consisting of halo, C_1 to C_6 alkyl, C_1 to C_6 haloalkyl and C_1 to C_6 alkoxy; heteroaryl having 5 to 6 ring atoms containing 1 to 3 heteroatoms each independently selected from N, O and S, the heteroaryl being optionally substituted with one to three substituents each independently selected from the group consisting of halo, C_1 to C_6 alkyl, C_1 to C_6 haloalkyl and C_1 to C_6 alkoxy; heterocycloalkyl having 5 to 7 ring atoms and containing 1 to 3 heteroatoms each independently selected from N, O and S, the heterocycloalkyl being optionally substituted with one to three substituents each independently selected from the group consisting of halo, C_1 to C_6 alkyl, C_1 to C_6 haloalkyl and C_1 to C_6 alkoxy; $-\text{NR}^y$; $-\text{CH}(\text{phenyl})-$, wherein the phenyl is optionally substituted with one to three substituents each independently selected from the group consisting of halo, C_1 to C_6

alkyl, C₁ to C₆ haloalkyl and C₁ to C₆ alkoxy; and –CH(heteroaryl), wherein the heteroaryl has 5 to 6 ring atoms and contains 1 to 3 heteroatoms each independently selected from N, O and S, the heteroaryl being optionally substituted with one to three substituents each independently selected from the group consisting of halo, C₁ to C₆ alkyl, C₁ to C₆ haloalkyl and

C₁ to C₆ alkoxy;

wherein R^y is H or C₁ to C₆ alkyl;

R³ is selected from the group consisting of C₁ to C₆ alkyl optionally wherein the C₁ to C₆ alkyl is substituted with a heterocycloalkyl group; C₃ to C₆ cycloalkyl optionally wherein the C₃ to C₆ cycloalkyl is substituted with one to three substituents each independently selected from the group consisting of halo, C₁ to C₆ alkyl, C₁ to C₆ haloalkyl and C₁ to C₆ alkoxy; phenyl that is optionally substituted with one to three substituents each independently selected from the group consisting of halo, C₁ to C₆ alkyl, C₁ to C₆ haloalkyl and C₁ to C₆ alkoxy; and heteroaryl having 5 to 6 ring atoms containing 1 to 3 heteroatoms each independently selected from N, O and S, the heteroaryl being optionally substituted with one to three substituents each independently selected from the group consisting of halo, C₁ to C₆ alkyl, C₁ to C₆ haloalkyl and C₁ to C₆ alkoxy;

X¹ is CH₂;

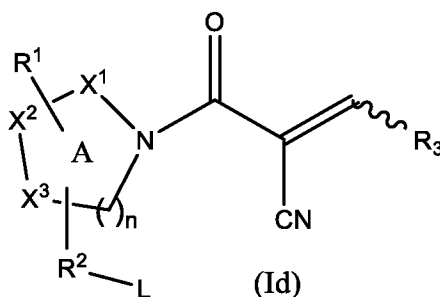
X² and X³ are each independently CH₂, or a heteroatom selected from O and NR^x, wherein R^x is H or C₁ to C₆ alkyl, or wherein one R¹ group and one R^x group combine to form a C₁₋₃ bridge; with the proviso that none or only 1 of X² and X³ is a heteroatom; and

m is 0, 1, 2 or 3;

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

L shows the point of attachment of the linker.

By way of further example, Z may be represented as formula (Id):



wherein:

R¹ is absent or is selected from the group consisting of: phenyl that is optionally substituted with one to three substituents selected from the group consisting of halo, C₁ to C₆ alkyl, C₁ to C₆ haloalkyl and C₁ to C₆ alkoxy; heteroaryl having 5 to 6 ring atoms containing 1 to 3 heteroatoms each independently selected from N, O and S, the heteroaryl being optionally

substituted with one to three substituents selected from the group consisting of halo, C₁ to C₆ alkyl, C₁ to C₆ haloalkyl and C₁ to C₆ alkoxy; C₃ to C₈ cycloalkyl; C₁ to C₆ alkyl and C₁ to C₆ haloalkyl;

R² is absent or is selected from the group consisting of: phenyl that is optionally substituted with one to three substituents selected from the group consisting of halo, C₁ to C₆ alkyl, C₁ to C₆ haloalkyl and C₁ to C₆ alkoxy; heteroaryl having 5 to 6 ring atoms containing 1 to 3 heteroatoms each independently selected from N, O and S, the heteroaryl being optionally substituted with one to three substituents each independently selected from the group consisting of halo, C₁ to C₆ alkyl, C₁ to C₆ haloalkyl and C₁ to C₆ alkoxy; heterocycloalkyl having 5 to 7 ring atoms and containing 1 to 3 heteroatoms each independently selected from N, O and S, the heterocycloalkyl being optionally substituted with one to three substituents each independently selected from the group consisting of halo, C₁ to C₆ alkyl, C₁ to C₆ haloalkyl and C₁ to C₆ alkoxy; -NR^y; -CH(phenyl)-, wherein the phenyl is optionally substituted with one to three substituents each independently selected from the group consisting of halo, C₁ to C₆ alkyl, C₁ to C₆ haloalkyl and C₁ to C₆ alkoxy; and -CH(heteroaryl), wherein the heteroaryl has 5 to 6 ring atoms and contains 1 to 3 heteroatoms each independently selected from N, O and S, the heteroaryl being optionally substituted with one to three substituents each independently selected from the group consisting of halo, C₁ to C₆ alkyl, C₁ to C₆ haloalkyl and C₁ to C₆ alkoxy;

wherein R^y is H or C₁ to C₆ alkyl;

R³ is selected from the group consisting of C₁ to C₆ alkyl optionally wherein the C₁ to C₆ alkyl is substituted with a heterocycloalkyl group; C₃ to C₈ cycloalkyl optionally substituted with one to three substituents; heterocycloalkyl having 3 to 10 ring atoms and containing 1 to 3 heteroatoms each independently selected from N, O and S, the heterocycloalkyl being optionally substituted with one to three substituents; phenyl that is optionally substituted with one to three substituents each independently selected from the group consisting of halo, C₁ to C₆ alkyl, C₁ to C₆ haloalkyl and C₁ to C₆ alkoxy; and heteroaryl having 5 to 6 ring atoms containing 1 to 3 heteroatoms each independently selected from N, O and S, the heteroaryl being optionally substituted with one to three substituents each independently selected from the group consisting of halo, C₁ to C₆ alkyl, C₁ to C₆ haloalkyl and C₁ to C₆ alkoxy;

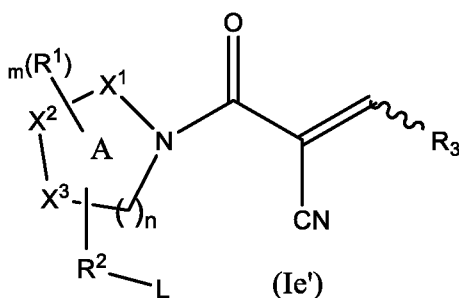
X¹ is CH₂;

X² and X³ are each independently CH₂, or a heteroatom selected from O and NR^x, wherein R^x is H or C₁ to C₆ alkyl; with the proviso that none or only 1 of X² and X³ is a heteroatom; and

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

L shows the point of attachment of the linker.

By way of further example, Z may be represented as formula (Ie'):



wherein:

R^1 is absent (i.e. when m is 0) or is selected from the group consisting of: phenyl; heteroaryl having 5 to 6 ring atoms containing 1 or 2 heteroatoms each independently selected from N, O and S; C_3 to C_7 cycloalkyl; heterocycloalkyl having 5 to 7 ring atoms and containing 1 or 2 heteroatoms each independently selected from N, O and S; C_1 to C_6 alkyl and C_1 to C_6 haloalkyl; wherein the phenyl or heteroaryl is optionally substituted with one substituent 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; and/or wherein two R^1 groups combine to form a C_{1-3} bridge, C_{3-5} cycloalkyl or 5- to 7-membered N-heterocycloalkyl (e.g. wherein the C_{3-5} cycloalkyl or the 5- to 7-membered N-heterocycloalkyl are joined to ring A at a spiro centre);

R^2 is absent or is selected from the group consisting of: phenyl; heteroaryl having 5 to 6 ring atoms and containing 1 or 2 heteroatoms each independently selected from N, O and S; heterocycloalkyl having 5 to 7 ring atoms and containing 1 or 2 heteroatoms each independently selected from N, O and S; $-NR^y$; $-\text{CH}(\text{phenyl})-$; and $-\text{CH}(\text{heteroaryl})$ wherein the heteroaryl has 5 to 6 ring atoms and contains 1 or 2 heteroatoms each independently selected from N, O and S; and further wherein the phenyl, heteroaryl, heterocycloalkyl, $-\text{CH}(\text{phenyl})-$ and $-\text{CH}(\text{heteroaryl})$ are each optionally substituted with one substituent 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;

wherein R^y is H or C_1 to C_6 alkyl;

R^3 is selected from the group consisting of C_1 to C_6 alkyl optionally wherein the C_1 to C_6 alkyl is substituted with a heterocycloalkyl group the heterocycloalkyl having 5 to 7 ring atoms and containing 1 or 2 heteroatoms each independently selected from N, O and S; C_3 to C_6 cycloalkyl; phenyl; and heteroaryl having 5 to 6 ring atoms containing 1 to 3 heteroatoms each independently selected from N, O and S; wherein the C_3 to C_6 cycloalkyl, phenyl and heteroaryl are optionally substituted with one or two substituents 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;

X^1 is CH_2 ;

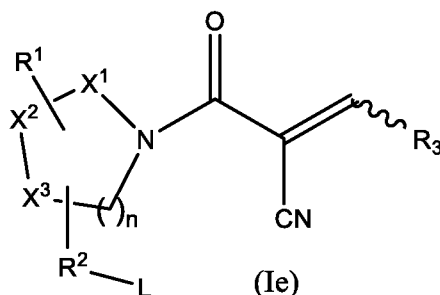
X^2 and X^3 are each independently CH_2 or O; with the proviso that none or only 1 of X^2 and X^3 is O;

m is 0, 1, 2 or 3;

n is 1, 2, or 3; and

L shows the point of attachment of the linker.

- 5 By way of further example, Z may be represented as formula (Ie):



wherein:

R¹ is absent or is selected from the group consisting of: phenyl; heteroaryl having 5 to 6 ring atoms containing 1 or 2 heteroatoms each independently selected from N, O and S; C₃ to C₇ cycloalkyl; C₁ to C₆ alkyl and C₁ to C₆ haloalkyl; wherein the phenyl or heteroaryl is optionally substituted with one substituent selected from the group consisting of halo, C₁ to C₃ alkyl, C₁ to C₃ haloalkyl and C₁ to C₃ alkoxy;

R² is absent or is selected from the group consisting of: phenyl; heteroaryl having 5 to 6 ring atoms and containing 1 or 2 heteroatoms each independently selected from N, O and S; heterocycloalkyl having 5 to 7 ring atoms and containing 1 or 2 heteroatoms each independently selected from N, O and S; -NR^y; -CH(phenyl)-; and -CH(heteroaryl) wherein the heteroaryl has 5 to 6 ring atoms and contains 1 or 2 heteroatoms each independently selected from N, O and S; and further wherein the phenyl, heteroaryl, heterocycloalkyl, -CH(phenyl)- and -CH(heteroaryl) are each optionally substituted with one substituent selected from the group consisting of halo, C₁ to C₃ alkyl, C₁ to C₃ haloalkyl and C₁ to C₃ alkoxy;

wherein R^y is H or C₁ to C₆ alkyl;

R³ is selected from the group consisting of C₁ to C₆ alkyl optionally wherein the C₁ to C₆ alkyl is substituted with a heterocycloalkyl group the heterocycloalkyl having 5 to 7 ring atoms and containing 1 or 2 heteroatoms each independently selected from N, O and S; C₃ to C₆ cycloalkyl; phenyl; and heteroaryl having 5 to 6 ring atoms containing 1 to 3 heteroatoms each independently selected from N, O and S; wherein the C₃ to C₆ cycloalkyl, phenyl and heteroaryl are optionally substituted with one or two substituents selected from the group consisting of halo, C₁ to C₃ alkyl, C₁ to C₃ haloalkyl and C₁ to C₃ alkoxy;

X¹ is CH₂;

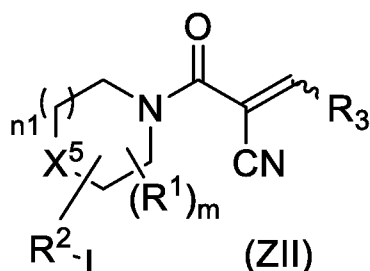
X² and X³ are each independently CH₂ or O; with the proviso that none or only 1 of X² and X³ is O;

and

n is 1, 2, or 3; and

L shows the point of attachment of the linker.

- 5 In further embodiments, Z comprises a structure according to formula (ZII):



wherein R² is absent or is as described in any one of the embodiments disclosed herein;

R³ is as described in any one of the embodiments disclosed herein;

- 10 X⁵ is CR^b₂, NR^b, O or a 5- to 7-membered heterocycloalkyl (e.g. a 5- to 7-membered heterocycloalkyl);

each R¹ is independently selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, C₁ to C₆ alkyl and substituted C₁ to C₆ alkyl, and/or wherein two R¹ groups combine to form an optionally substituted C₁₋₃ bridge or optionally substituted C₃₋₅cycloalkyl (optionally wherein the

- 15 C₃₋₅cycloalkyl is joined to the heterocyclic ring shown in formula (ZII) at a spiro centre);

R^b is H or optionally substituted C₁₋₃alkyl;

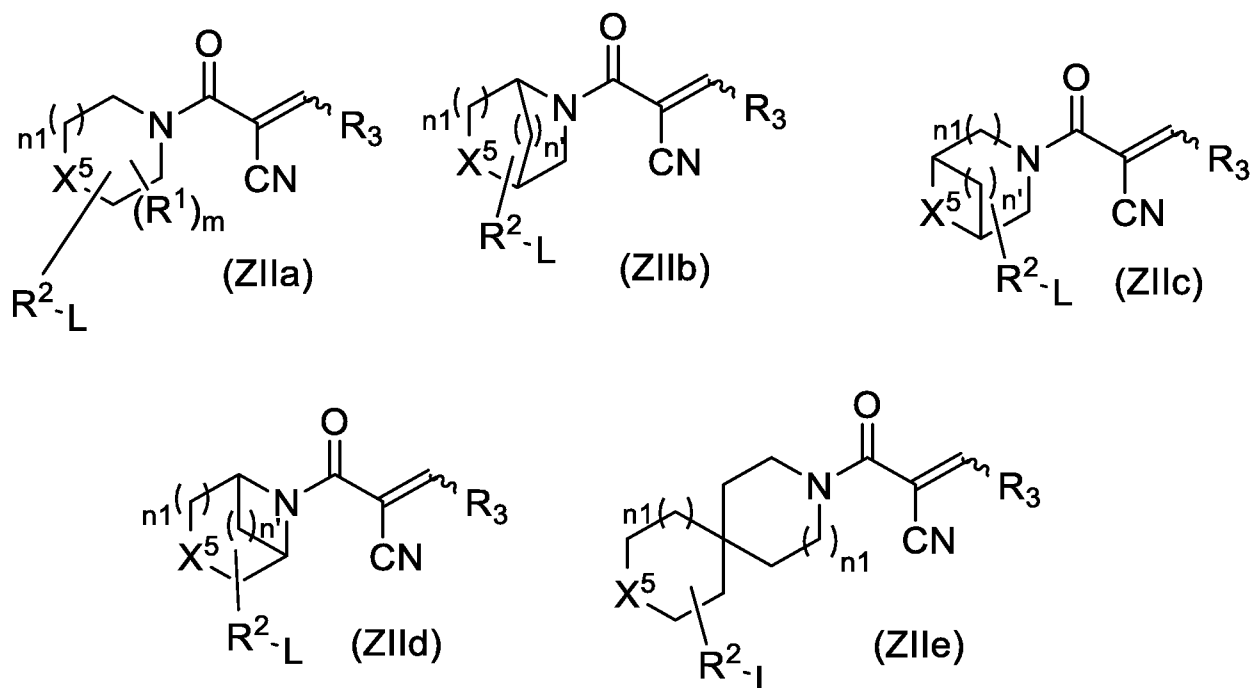
n₁ is 0, 1, 2 or 3;

m is 0, 1 or 2; and

L shows the point of attachment of the linker.

20

In yet further embodiments, Z comprises a structure according to any one of formulae (ZIIa) to (ZIIe):



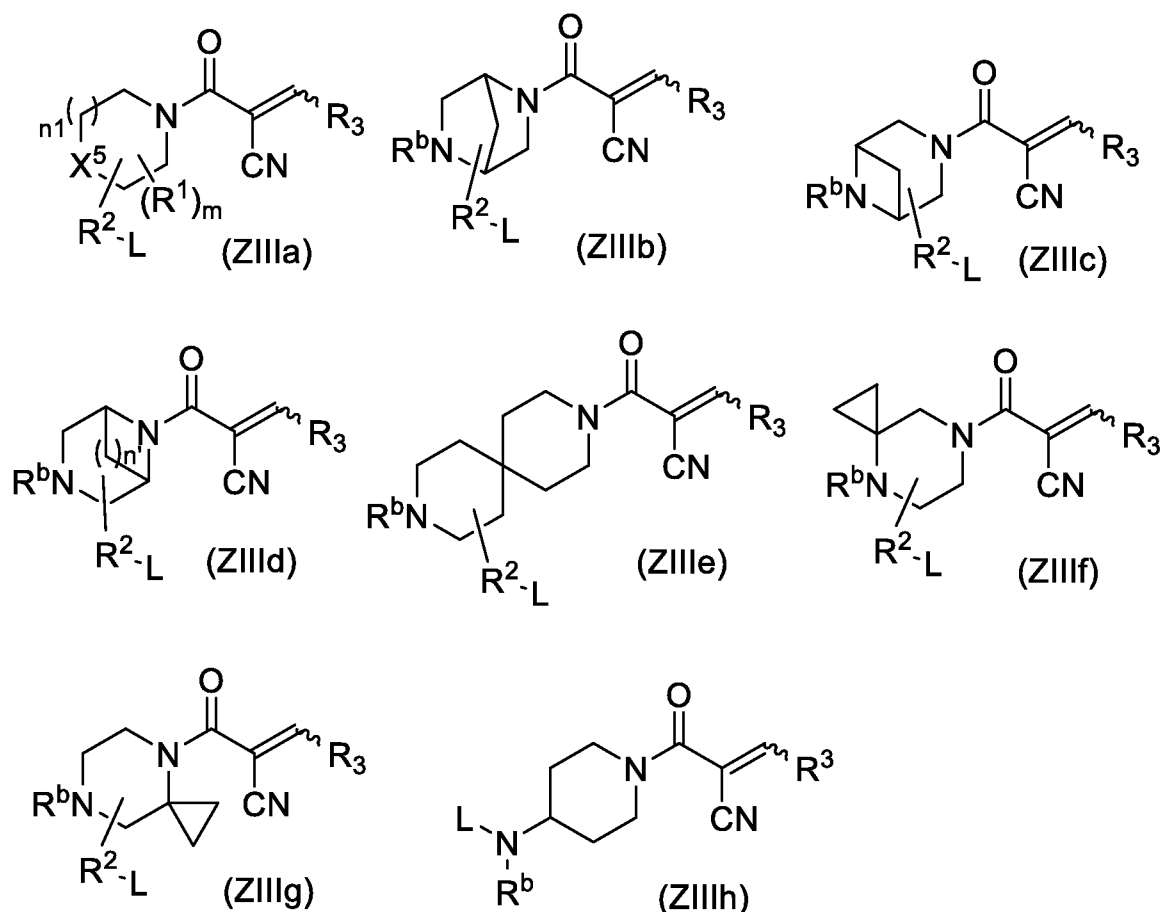
wherein:

R^2 is as described in any one of the embodiments disclosed herein;

R^3 is as described in any one of the embodiments disclosed herein;

- 5 each R^1 is independently selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, C_1 to C_6 alkyl and substituted C_1 to C_6 alkyl, and/or wherein two R^1 groups combine to form an optionally substituted C_{3-5} cycloalkyl (optionally wherein the C_{3-5} cycloalkyl is joined to the heterocyclic ring shown in formula (ZIIa) at a spiro centre);
- 10 X^5 is $C(R^b)_2$, NR^b or O;
 R^b is H or optionally substituted C_{1-3} alkyl;
 n_1 is 0, 1, 2 or 3;
 n' is 1 or 2;
 m is 0, 1 or 2; and
- 15 L shows the point of attachment of the linker.

For example, Z may comprise a structure according to formula (ZIIa) to (ZIIh):



wherein:

R^2 is as described in any one of the embodiments disclosed herein;

R^3 is as described in any one of the embodiments disclosed herein;

- 5 each R^1 is independently selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, C_1 to C_6 alkyl and substituted C_1 to C_6 alkyl;

X^5 is CH_2 , NR^b or O;

R^b is H or optionally substituted C_{1-3} alkyl;

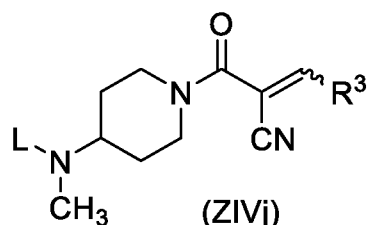
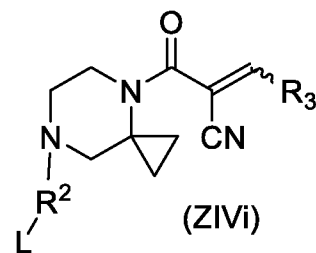
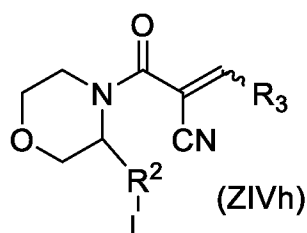
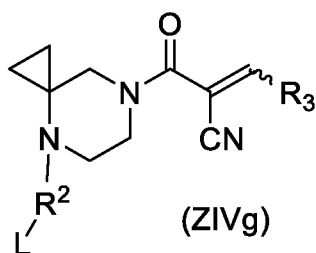
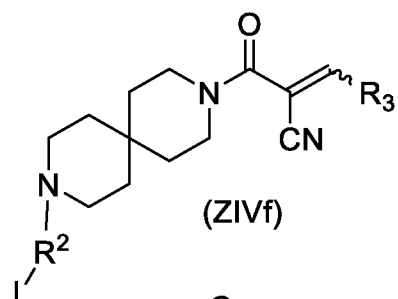
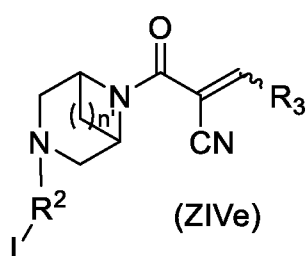
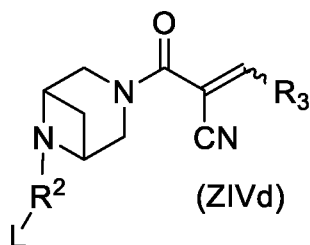
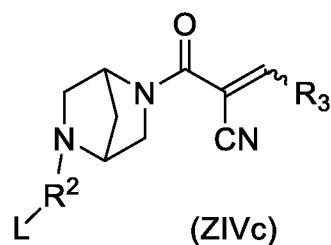
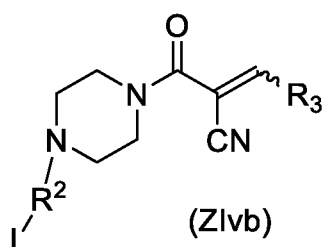
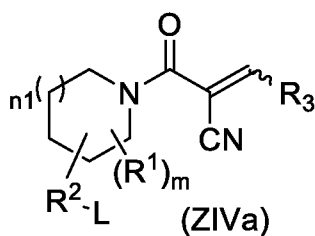
n_1 is 0, 1 or 2;

- 10 n' is 1 or 2;

m is 0, 1 or 2; and

L shows the point of attachment of the linker.

In even further embodiments, Z comprises a structure according to formula (ZIVa) to (ZIVj):



wherein:

R² is absent or is as described in any one of the embodiments disclosed herein;

R³ is as described in any one of the embodiments disclosed herein;

- 5 each R¹ is independently selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, C₁ to C₆ alkyl and substituted C₁ to C₆ alkyl;

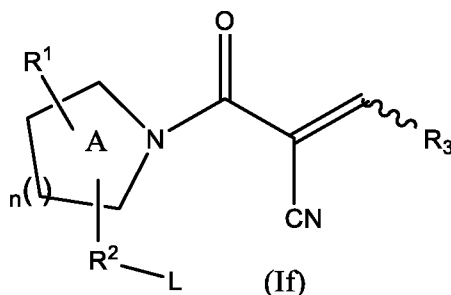
n₁ is 0, 1 or 2;

n' is 1 or 2;

m is 0, 1 or 2; and

- 10 L shows the point of attachment of the linker.

In further examples, Z comprises a structure according to formula (If):



wherein R^1 is absent or is selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, C_1 to C_6 alkyl and substituted C_1 to C_6 alkyl;

R^2 is absent or is selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, substituted heterocycloalkyl, $-\text{CH}(\text{aryl})-$ and $-\text{CH}(\text{substituted aryl})-$;

R^3 is selected from C_1 to C_6 alkyl, aryl, heteroaryl, substituted C_1 to C_6 alkyl, substituted aryl, and substituted heteroaryl; and

wherein at least one of R^1 and R^2 is present;

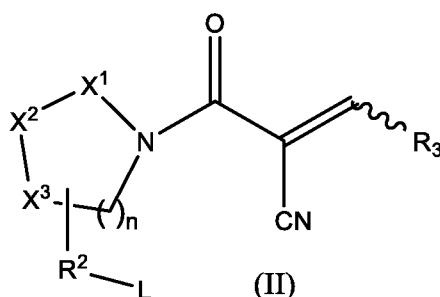
n is 0, 1, 2, or 3; and

L shows the point of attachment of the linker.

In some examples, R^1 , R^2 and R^3 of formula (If) may be selected from those groups defined above, e.g. for any one or more of formulae (Ic'), (Ic), (Id'), (Id), (Ie') or (Ie).

In some examples of the formulae described above and herein, n may be 1, 2 or 3 and/or n_1 may be 0, 1 or 2.

In those cases where R^1 is absent, Z may be represented by formula (II):



R^2 is selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, substituted heterocycloalkyl, $-\text{CH}(\text{aryl})-$, $-\text{CH}(\text{substituted aryl})-$, $-\text{CH}(\text{heteroaryl})-$ and $-\text{CH}(\text{substituted heteroaryl})-$;

R^3 is selected from C_1 to C_6 alkyl, aryl, heteroaryl, substituted aryl, and substituted heteroaryl, optionally wherein the C_1 to C_6 alkyl is substituted with a a heterocycloalkyl group;

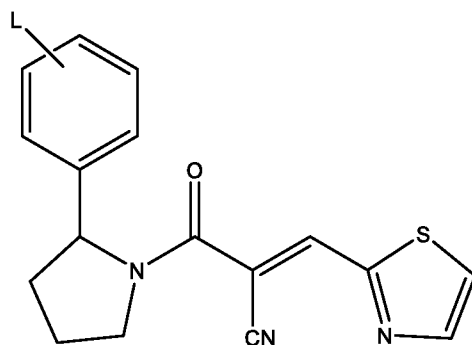
X^1 is CH_2 ;

X^2 and X^3 are each independently CH_2 or O; with the proviso that none or only 1 of X^2 and X^3 is O; and

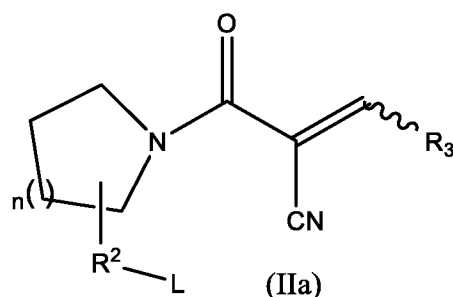
n is 0, 1, 2 or 3; and

L shows the point of attachment of the linker;

5 and wherein Z is not:



In those cases where R^1 is absent, Z may be represented by formula (IIa):



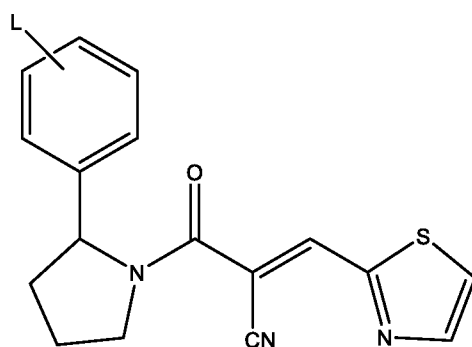
10 wherein R^2 is selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, substituted heterocycloalkyl, $-\text{CH}(\text{aryl})-$, $-\text{CH}(\text{substituted aryl})-$, $-\text{CH}(\text{heteroaryl})-$ and $-\text{CH}(\text{substituted heteroaryl})-$;

R^3 is selected from C_1 to C_6 alkyl, aryl, heteroaryl, substituted aryl, and substituted heteroaryl, optionally wherein the C_1 to C_6 alkyl is substituted with a heterocycloalkyl group; and

15 n is 0, 1, 2 or 3; and

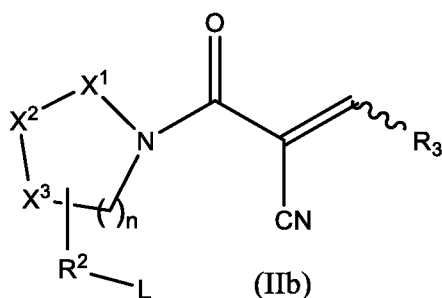
L shows the point of attachment of the linker;

and wherein Z is not:



By way of particular example, in formulae (II) or (IIa), n may be 1 or 2.

By way of further example, Z may be represented by formula (IIb):



5

wherein R^2 is selected from aryl substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, and substituted heterocycloalkyl;

R^3 is selected from C_1 to C_6 alkyl, aryl, heteroaryl, substituted aryl, and substituted heteroaryl, optionally wherein the C_1 to C_6 alkyl is substituted with a heterocycloalkyl group;

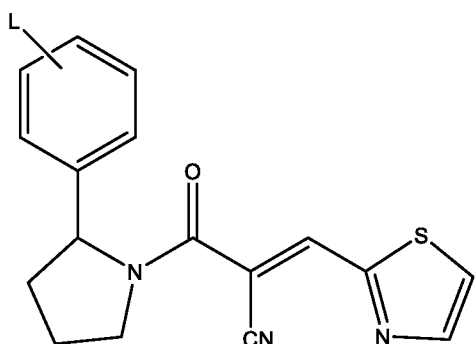
10 X^1 is CH_2 ;

X^2 and X^3 are each independently CH_2 or O; with the proviso that none or only 1 of X^2 and X^3 is O;

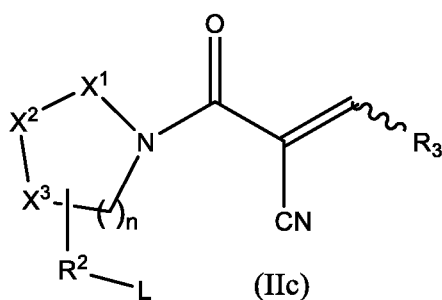
n is 1 or 2; and

L shows the point of attachment of the linker;

15 and wherein Z is not:



By way of further example, Z may be represented by formula (IIc):



20

wherein R^2 is selected from heterocycloalkyl and substituted heterocycloalkyl;

R^3 is selected from C_1 to C_6 alkyl, aryl, heteroaryl, substituted aryl, and substituted heteroaryl, optionally wherein the C_1 to C_6 alkyl is substituted with a heterocycloalkyl group;

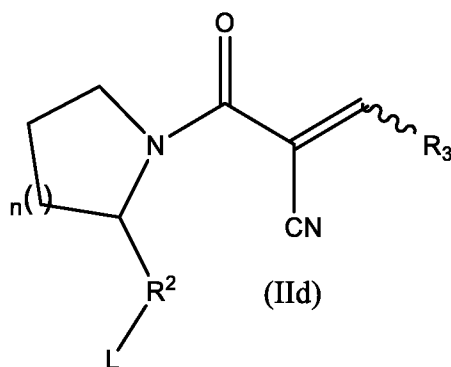
X^1 is CH_2 ;

- 5 X^2 and X^3 are each independently CH_2 or O; with the proviso that none or only 1 of X^2 and X^3 is O;

n is 1 or 2; and

L shows the point of attachment of the linker.

- 10 In some cases, Z may be represented by formula (IIId):



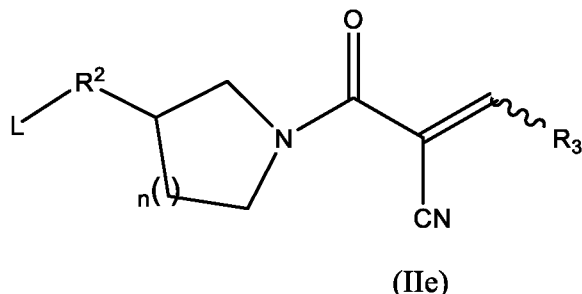
wherein R^2 is selected from heterocycloalkyl and substituted heterocycloalkyl;

R^3 is selected from C_1 to C_6 alkyl, aryl, heteroaryl, substituted aryl, and substituted heteroaryl, optionally wherein the C_1 to C_6 alkyl is substituted with a heterocycloalkyl group;

- 15 n is 1 or 2; and

L shows the point of attachment of the linker.

In other examples, Z may comprise a structure according to formula (IIe):



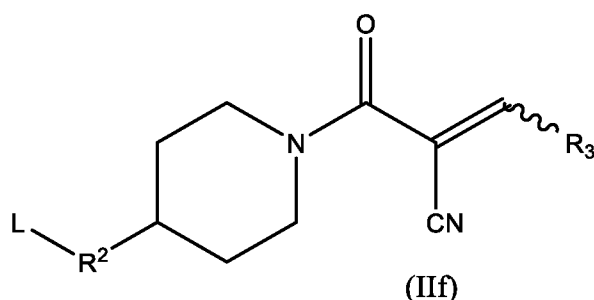
- 20 wherein R^2 is selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl and substituted heterocycloalkyl;

R^3 is selected from C_1 to C_6 alkyl, aryl, heteroaryl, substituted aryl, and substituted heteroaryl, optionally wherein the C_1 to C_6 alkyl is substituted with a heterocycloalkyl group;

n is 1 or 2; and

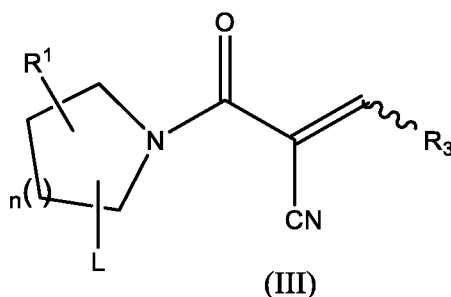
- 25 L shows the point of attachment of the linker.

In other examples, Z may comprise a structure according to formula (IIf):



wherein R^2 is selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl and substituted heterocycloalkyl;
 R^3 is selected from C_1 to C_6 alkyl, aryl, heteroaryl, substituted aryl, and substituted heteroaryl, optionally wherein the C_1 to C_6 alkyl is substituted with a heterocycloalkyl group; and
 L shows the point of attachment of the linker.

In those cases where R^2 is absent, Z may comprise a structure according to formula (III):



wherein R^1 is selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl and C_1 to C_6 alkyl;

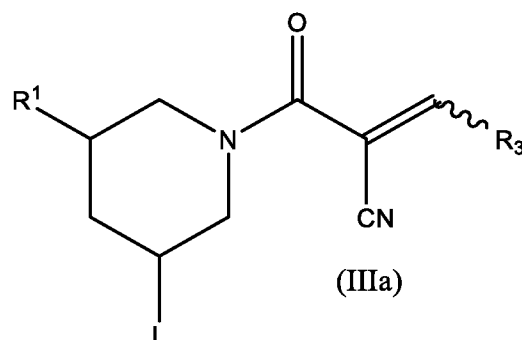
R^3 is selected from C_1 to C_6 alkyl, aryl, heteroaryl, substituted aryl, and substituted heteroaryl, optionally wherein the C_1 to C_6 alkyl is substituted with a heterocycloalkyl group; and

n is 0, 1, 2 or 3; and

L shows the point of attachment of the linker.

In some examples, n may be 1 or 2.

In some examples where n is 2, Z may be represented by formula (IIIa):

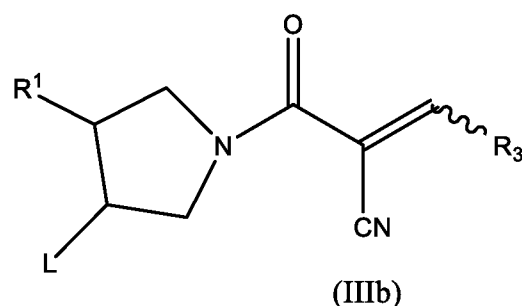


wherein R^1 is selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl and C_1 to C_6 alkyl;

R^3 is selected from C_1 to C_6 alkyl, aryl, heteroaryl, substituted aryl, and substituted heteroaryl,

- 5 optionally wherein the C_1 to C_6 alkyl is substituted with a heterocycloalkyl group; and
L shows the point of attachment of the linker.

In some examples where n is 1, Z may be represented by formula (IIIb):



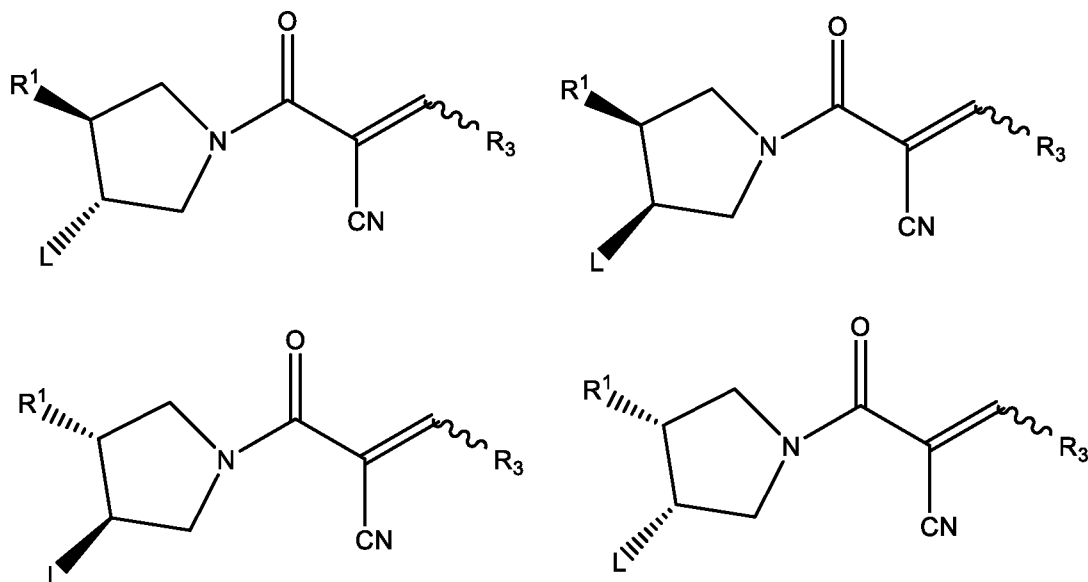
- 10 wherein R^1 is selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl and C_1 - C_6 alkyl;

R^3 is selected from C_1 to C_6 alkyl, aryl, heteroaryl, substituted aryl, and substituted heteroaryl, optionally wherein the C_1 to C_6 alkyl is substituted with a heterocycloalkyl group; and
L shows the point of attachment of the linker.

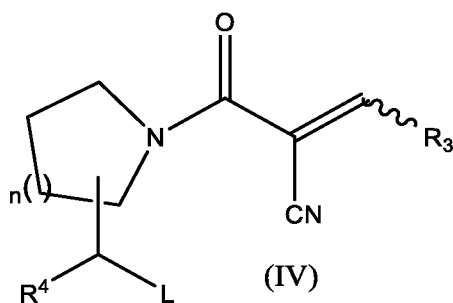
15

As illustrated above, bifunctional molecules of formula (IIIb) comprise at least two stereocentres and so exist in several diastereomeric (and enantiomeric) forms. In some examples, the groups R^1 and L may exist in a trans relationship (e.g. these groups are held and/or oriented on opposite sides of the heterocyclic core). In other examples, the groups R^1 and L may exist in a cis relationship (e.g. these groups are held and/or oriented on the same side of the heterocyclic core). By way of further example, bifunctional molecules of formula (IIIb) may encompass at least the following diastereomeric forms:

20



In those examples where R¹ is absent and R² is selected from CH(aryl)-, -CH(substituted aryl)-, -CH(heteroaryl)- and -CH(substituted heteroaryl)-, Z may be represented by formula (IV):

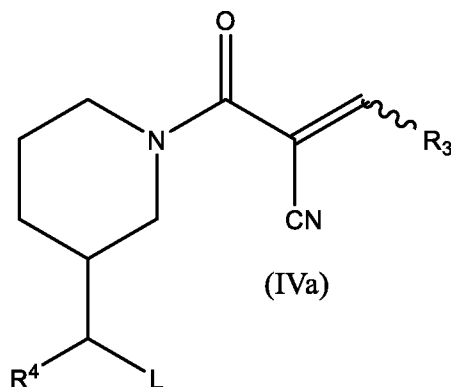


5

wherein R³ is selected from C₁ to C₆ alkyl, aryl, heteroaryl, substituted aryl, and substituted heteroaryl, optionally wherein the C₁ to C₆ alkyl is substituted with a heterocycloalkyl group; R⁴ is selected from aryl, substituted aryl, heteroaryl and substituted heteroaryl; and n is 0, 1, 2 or 3; and

10 L shows the point of attachment of the linker.

In some examples, Z may comprise a structure according to formula (IVa):



wherein R^3 is selected from C_1 to C_6 alkyl, aryl, heteroaryl, substituted aryl, and substituted heteroaryl, optionally wherein the C_1 to C_6 alkyl is substituted with a heterocycloalkyl group; R^4 is selected from aryl, substituted aryl, heteroaryl and substituted heteroaryl; and

5 L shows the point of attachment of the linker.

In either of formula (IV) or (IVa), R^4 may be selected from aryl or substituted aryl.

Representative examples of groups R^1 , R^2 , R^3 and R^4 are now provided below which are
10 applicable to any one or more of the formulae described herein (unless otherwise indicated).

With respect to the various structures for Z defined by the formulae herein (and unless otherwise stated), R^1 may be selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, C_1 to C_6 alkyl, and substituted C_1 to C_6 alkyl.

15

In some examples, R^1 is an optionally substituted aryl or an optionally substituted heteroaryl. Where R^1 is a substituted aryl or substituted heteroaryl, the aryl or heteroaryl may comprise one or more substituents selected from the group consisting of C_1 to C_6 alkyl (e.g. methyl), C_1 to C_6 alkoxy (e.g. methoxy), C_1 to C_6 haloalkyl and halo.

20

By way of further example, R^1 may be phenyl that is optionally substituted with one to three substituents selected from the group consisting of halo, C_1 to C_6 alkyl, C_1 to C_6 haloalkyl and C_1 to C_6 alkoxy. By way of a yet further example, R^1 may be heteroaryl having 5 to 6 ring atoms containing 1 to 3 heteroatoms each independently selected from N, O and S, the heteroaryl being optionally substituted with one to three substituents selected from the group
25 consisting of halo, C_1 to C_6 alkyl, C_1 to C_6 haloalkyl and C_1 to C_6 alkoxy; C_3 to C_8 cycloalkyl.

Representative examples of suitable R^1 groups include but are not limited to phenyl, substituted phenyl, pyrazolyl, and substituted pyrazolyl.

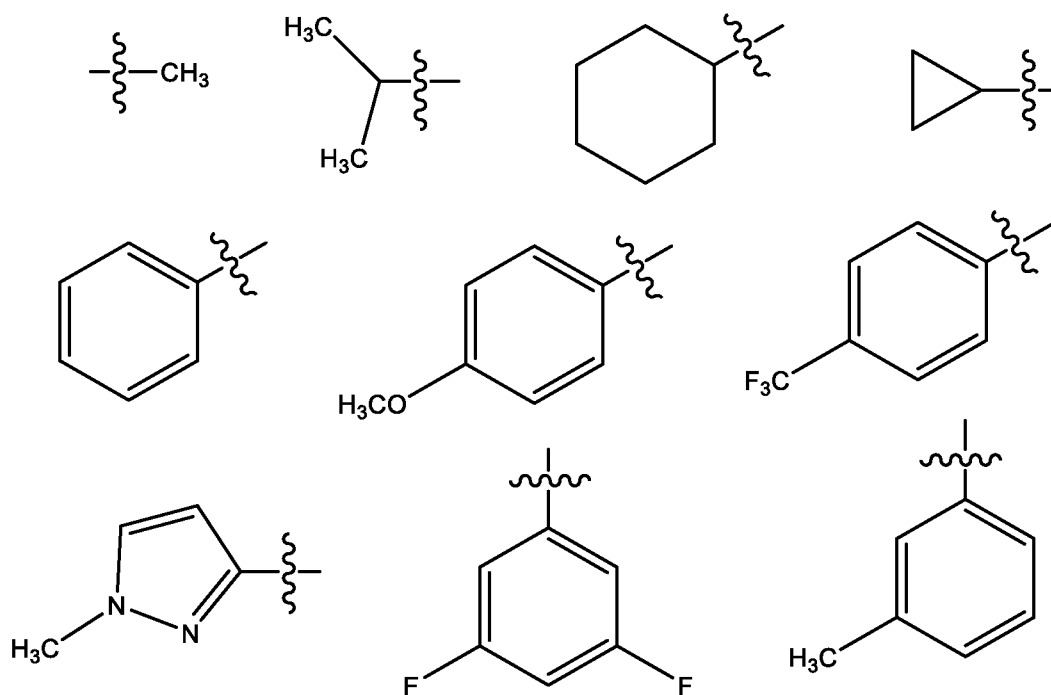
30

In some examples, R^1 is a cycloalkyl, such as a C_3 to C_7 cycloalkyl, or a C_3 to C_6 cycloalkyl.

In some examples, R^1 is a C_1 to C_6 alkyl, such as a C_1 to C_3 alkyl that is optionally substituted with one to three substituents as defined herein.

5

Further non-limiting examples of suitable R^1 groups are illustrated below:



- 10 In the structures shown above, the line intersected by a wavy line represents the covalent bond between the exemplary R^1 groups shown above and a carbon atom on the heterocycloalkyl core attached to the R^1 group in the parent structure of Z (as illustrated by the various formulae described herein). Although a particular substitution pattern is shown in the exemplary aryl and heteroaryl structures above, it will be appreciated that other
- 15 substitution patterns are also encompassed within the scope of the present disclosure.

In further examples, such as in respect of formulae (ZII), two R^1 groups may combine to form a C_{1-3} bridge or C_{3-5} cycloalkyl. For example, two R^1 groups may combine to form a C_{3-5} cycloalkyl. In such examples, the C_{3-5} cycloalkyl may be joined to the heterocyclic ring of the

20 parent structure at a spiro centre.

With respect to the various structures for Z defined by the formulae herein (and unless otherwise stated), R^2 may be selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, substituted heterocycloalkyl, NR^y , $-CH(aryl)-$, $-CH(substituted$

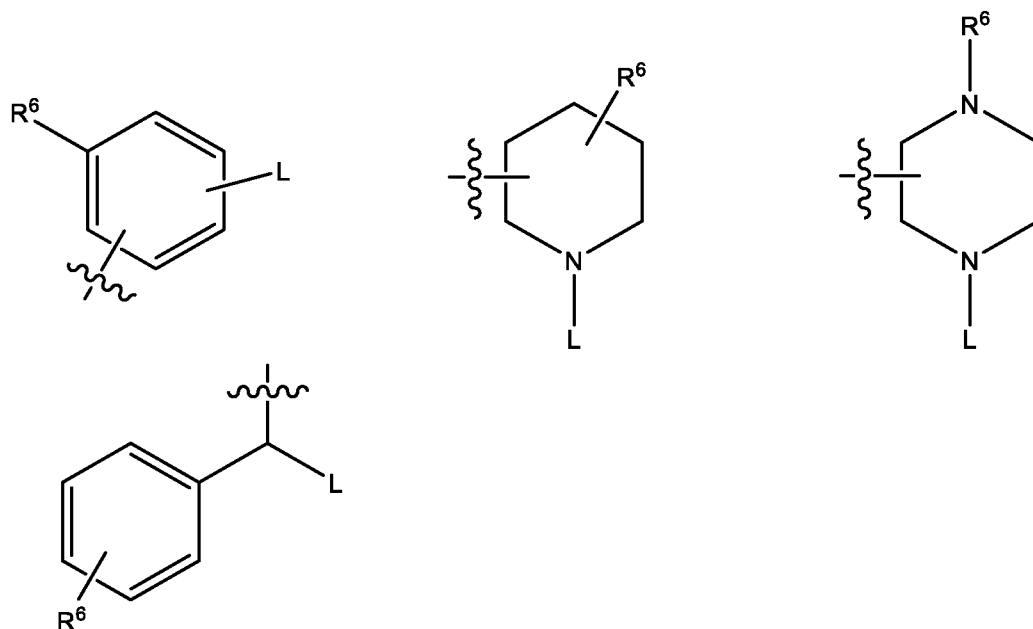
aryl)-, -CH(heteroaryl) and -CH(substituted heteroaryl); wherein R^y is optionally substituted C_{1-6} alkyl (such as methyl) or H

In some examples, R^2 is present in Z (and/or the bifunctional molecules described herein) as a divalent group. In other words, as shown in formulae (I) to (IVa) (and unless otherwise stated), the various groups defined for R^2 are covalently attached to an atom of the heterocyclic core of Z and also may be covalently attached to an atom of a linker. Thus, these groups may be considered as divalent radical species.

- 10 Where R^2 is selected from optionally substituted aryl and optionally substituted heteroaryl, R^2 may be selected from aryl having 6 to 10 carbon ring atoms, the aryl being optionally substituted with one to three substituents; and heteroaryl having 5 to 10 ring atoms and containing 1 to 3 heteroatoms each independently selected from N, O and S, the heteroaryl being optionally substituted with one to three substituents. By way of further example, R^2 may
- 15 be selected from phenyl optionally substituted with one to three substituents selected from H, C_1 to C_6 alkyl, halo, C_1 to C_6 haloalkyl and C_1 to C_6 alkoxy; and heteroaryl having 5 to 6 ring atoms and containing 1 or 2 N atoms, the heteroaryl being optionally substituted with one to three substituents selected from C_1 - C_6 alkyl (e.g. C_1 to C_3 alkyl), halo (e.g. F), C_1 - C_6 haloalkyl (e.g. C_1 to C_3 haloalkyl) and C_1 to C_6 alkoxy (e.g. C_1 to C_3 alkoxy). In some cases, suitable
- 20 examples of R^2 include (but are not limited to) optionally substituted phenyl, and optionally substituted pyrazolyl.

- Where R^2 is selected from optionally substituted heterocycloalkyl, the heterocycloalkyl may have 3 to 10 ring atoms and contain 1 to 3 heteroatoms each independently selected from N,
- 25 O and S, and the heterocycloalkyl may be optionally substituted with one to three substituents. In some examples, the heterocycloalkyl may have 5 to 8 ring atoms (e.g. 6 ring atoms) and may contain 1 or 2 N atoms. In some cases, suitable examples include (but are not limited to) optionally substituted piperidiny, and optionally substituted piperaziny.

- 30 Further examples of suitable R^2 groups are shown below:



wherein in the structures shown above, R^6 may be selected from H, C_1 - C_6 alkyl, halo, C_1 - C_6 haloalkyl and C_1 - C_6 alkoxy. In some examples, R^6 may be selected from H and C_1 - C_6 alkyl.

5

In the structures shown above, the line intersected by a wavy line represents the covalent bond between the exemplary R^2 groups shown above and a carbon atom on the heterocycloalkyl core attached to the R^2 group in the parent structure of Z (as illustrated by the various formulae described herein). Although a particular substitution pattern is shown in the exemplary structures above, it will be appreciated that other substitution patterns are also encompassed within the scope of the present disclosure.

10

In addition, the bond to L shows the point of attachment to the linker. In the exemplary aryl structure above, it will be appreciated that the linker may replace a hydrogen atom at any suitable position on the aryl ring (e.g. provided it is chemically suitable and has the correct valency).

15

With respect to the various structures for Z defined by the formulae herein, R^3 is selected from C_1 to C_6 alkyl, aryl, heteroaryl, substituted C_1 to C_6 alkyl, substituted aryl, and substituted heteroaryl.

20

In some examples, R^3 may be selected from the group consisting of: C_1 to C_6 alkyl optionally substituted with a heterocycloalkyl group having 5 to 7 ring atoms and containing 1 or 2 heteroatoms each independently selected from N, O and S; aryl having 6 to 10 carbon ring atoms; and heteroaryl having 5 to 10 ring atoms and containing 1 to 3 heteroatoms each

25

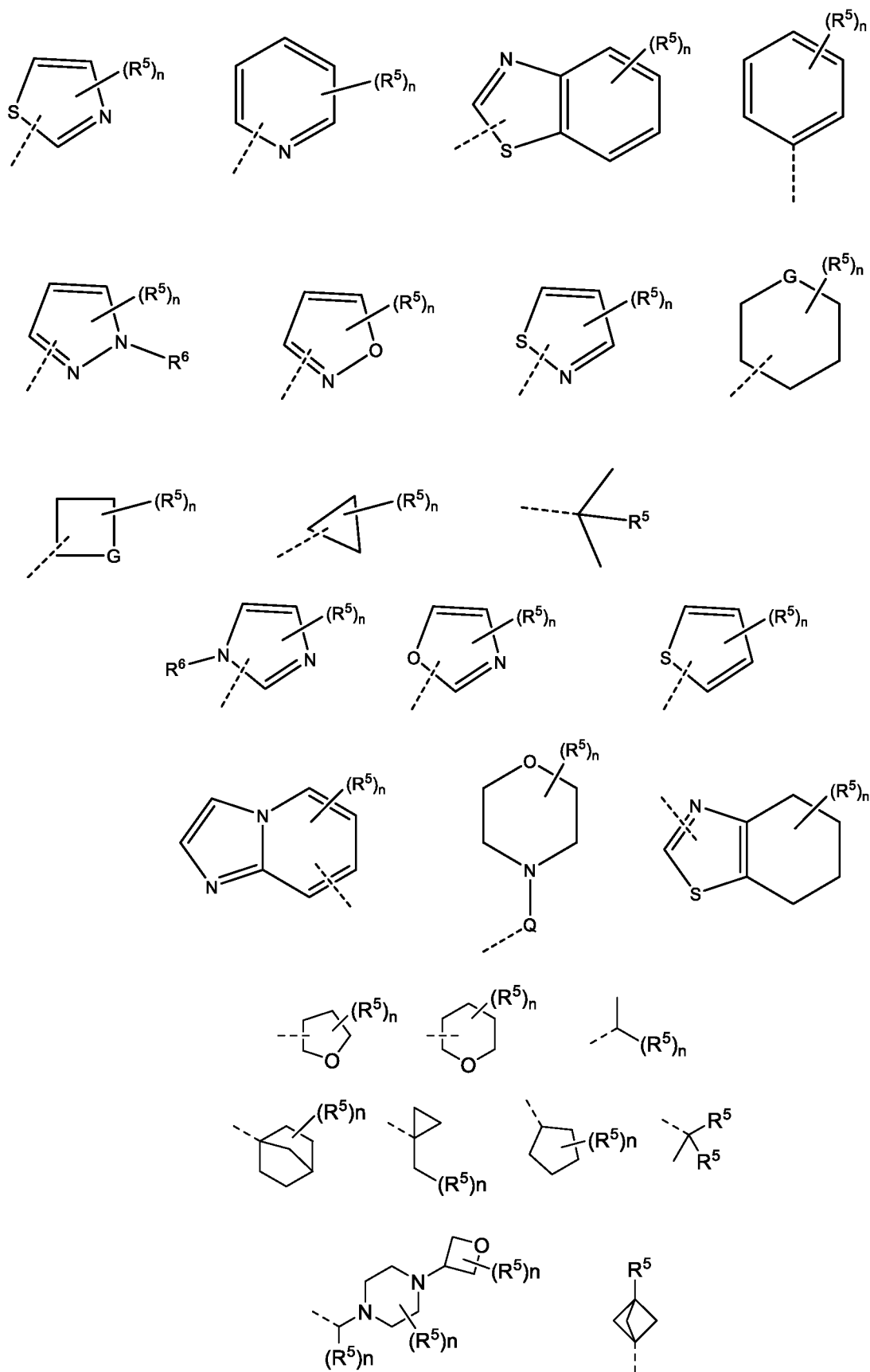
independently selected from N, O and S; wherein the aryl and the heteroaryl are optionally substituted with one or two substituents selected from the group consisting of halo, C₁ to C₃ alkyl, C₁ to C₃ haloalkyl and C₁ to C₃ alkoxy. By way of further example, in some cases the aryl and heteroaryl may be optionally substituted with one or two substituents selected from halo (e.g. F) and C₁ to C₃ alkyl (e.g. methyl).

Representative examples of suitable R³ groups include, but are not limited to, thiazolyl, pyridinyl, benzothiazolyl, phenyl, pyrazolyl, isoxazolyl, isothiazolyl, oxetanyl, cyclobutanyl, cyclopropanyl, tert-butyl, imidazolyl, oxazolyl, thiophenyl, imidazo(1,2-a)pyridinyl, N-C₁ to C₆ alkylenemorpholine, and 4,5,6,7-tetrahydro-1,3-benzothiazolyl, such as thiazolyl, pyridinyl, benzothiazolyl, phenyl, pyrazolyl, isoxazolyl, isothiazolyl, tetrahydropyranyl, tetrahydrofuranyl, oxetanyl, cyclobutanyl, cyclopropanyl and tert-butyl.

In each case, these R³ groups may be substituted, such as substituted thiazolyl, substituted pyridinyl, substituted benzothiazolyl, substituted phenyl, substituted pyrazolyl, substituted isoxazolyl, substituted isothiazolyl, substituted tetrahydropyranyl, substituted tetrahydrofuranyl, substituted oxetanyl, substituted cyclobutanyl, substituted cyclopropanyl and substituted tert-butyl. Where R³ is a substituted heteroaryl or aryl group, there may be one or more substituents on the aromatic ring e.g. it may be mono-, di- or tri-substituted. Where R³ is optionally substituted pyrazolyl or imidazolyl, a nitrogen atom of the pyrazolyl or imidazolyl ring may be substituted with C₁ to C₆ alkyl, such as methyl.

Representative examples of suitable R³ groups include, but are not limited to, optionally substituted phenyl, optionally substituted thiazolyl, optionally substituted pyrazolyl, optionally substituted oxazolyl, optionally substituted isoxazolyl, tert-butyl, C₁-C₆ alkyl comprising a morpholino substituent, optionally substituted benzothiazolyl and optionally substituted pyridinyl. Where R³ is a substituted aryl or heteroaryl group, there may be one or more substituents on the aromatic ring e.g. it may be mono-, di- or tri-substituted.

Further examples of suitable R³ groups are shown below:



wherein the dotted line on the structures indicates the position that each of the respective R^3 groups may be joined to the structure shown in the formulae described herein. Where the dotted line is not shown connected directly to an atom, the R^3 group may be connected to the structure shown in formulae by a covalent bond to an atom at any position on the aromatic ring (provided that it has the correct valency and/or is chemically suitable). For example, a hydrogen at any position on the R^3 group may be replaced with a bond to the parent structures as shown in the formulae described herein.

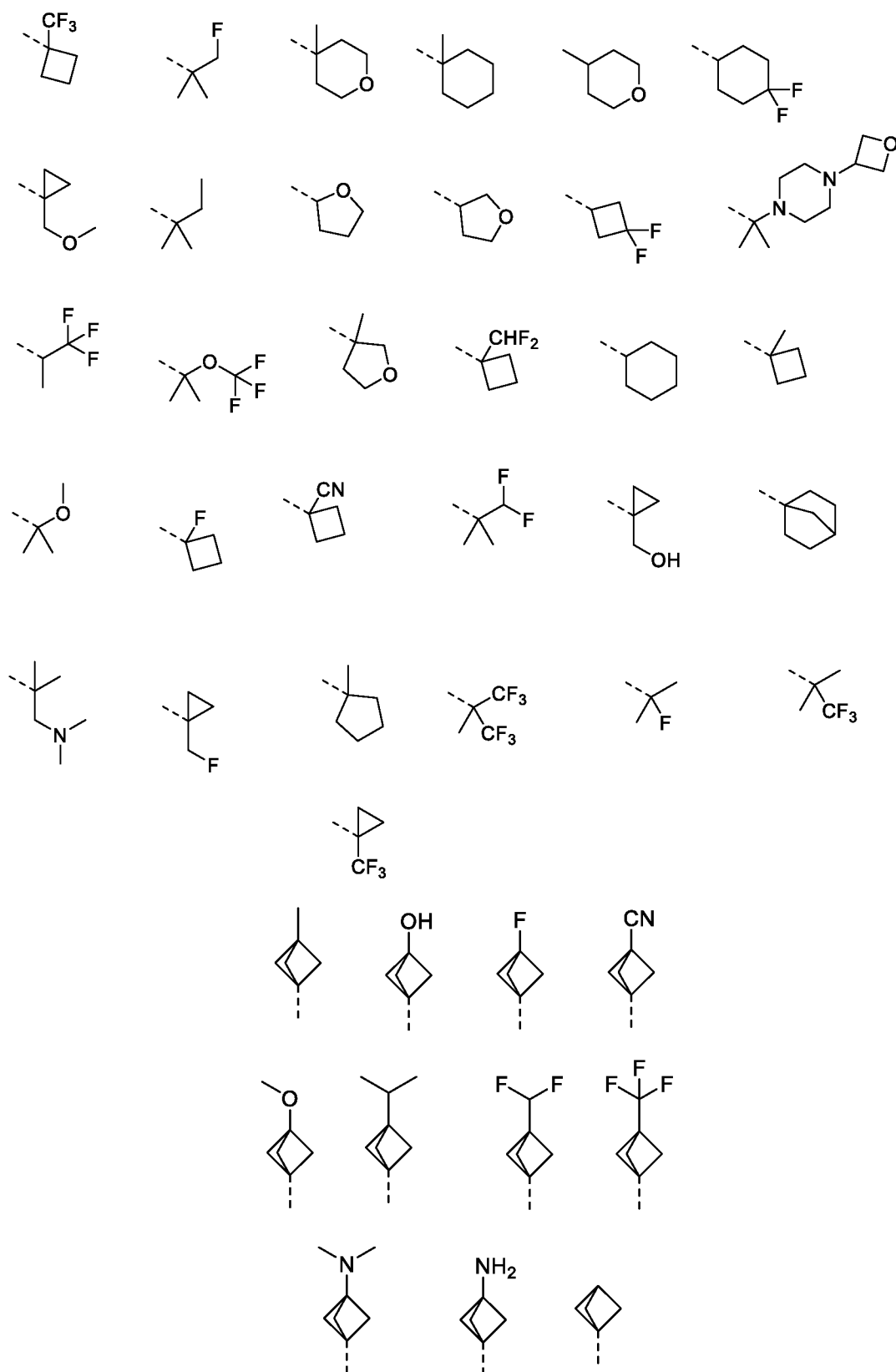
R^5 may be any substituent as described herein or may be absent. In some examples, R^5 may be selected from halo (e.g. F, Cl, Br, I), CF_3 , $-CH_2F$, $-CHF_2$, OCF_3 , $-OCH_2F$, $-OCHF_2$, C_1 to C_6 alkyl, $-CN$, $-OH$, $-OMe$, $-SMe$, $-SOMe$, $-SO_2Me$, $-NH_2$, $-NHMe$, $-NMe_2$, CO_2Me , $-NO_2$, CHO , and $COMe$. As stated above, there may be one or more substituents on the aromatic ring (e.g. n may be 0 to 5, such as 0 to 4, 0 to 3, or 0 to 2). Where more than one substituent is present, each substituent may be independently selected from the R^5 groups noted above.

R^6 may be C_1 to C_6 alkyl, such as methyl.

G may be selected from CH_2 , O and NH.

Q may be C_1 to C_6 alkylene such as dimethylmethylene ($-C(CH_3)_2-$) or dimethylethylene ($-C(CH_3)_2CH_2-$).

In further embodiments, R^3 is selected from the group consisting of:

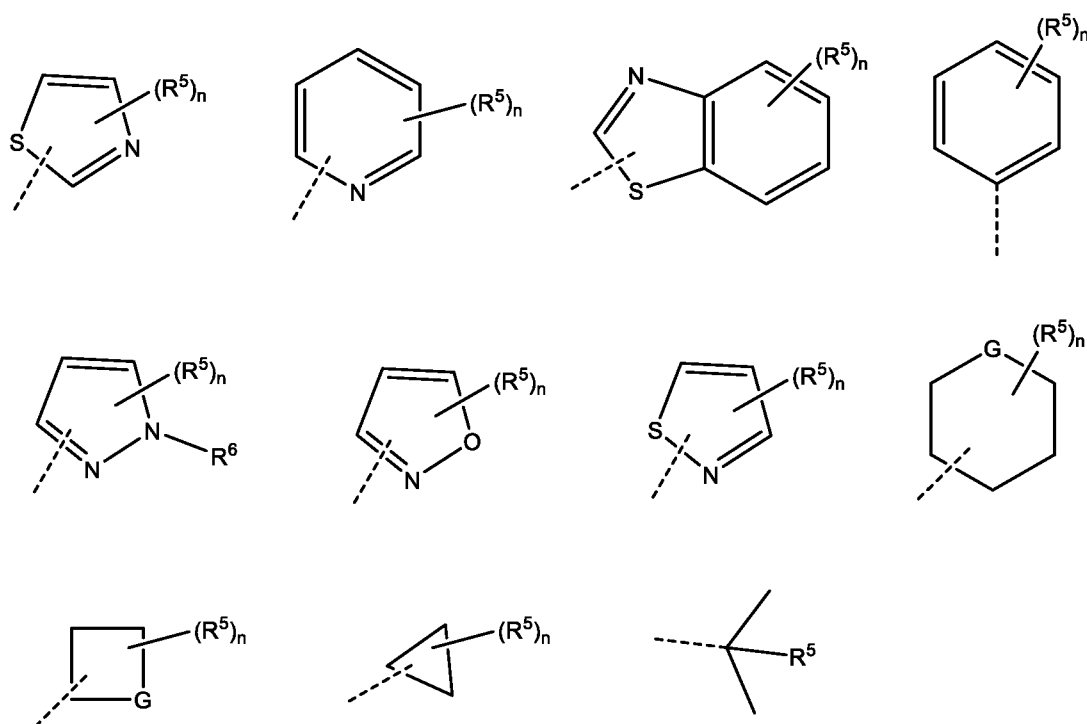


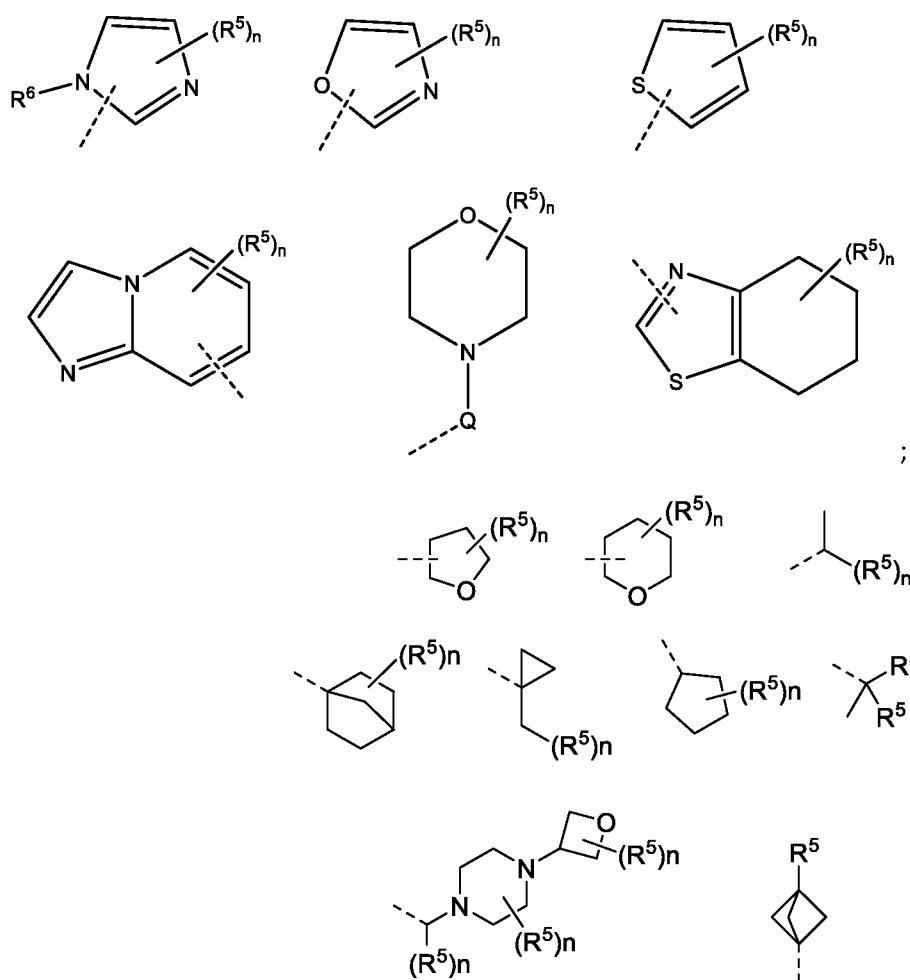
wherein the dotted line indicates the position at which each of the respective R^3 groups is joined to the structure in the formulae described herein.

By way of further example, R^5 may be selected from C_1 to C_6 alkyl (e.g. methyl) and halo (e.g. F). As stated above, there may be one or more substituents on the aromatic ring. Where two or more substituents are present, each substituent may be independently selected from the R^5 groups noted above. Again, where present and unless otherwise indicated, R^5 may be appended to the aryl or heteroaryl ring at any position (provided that it has the correct valency and/or is chemically suitable).

In the structures shown above, the line intersected by a wavy line represents the covalent bond between the exemplary R^3 groups shown above and the carbon atom of the parent structure of Z (as illustrated by the various formulae described herein). In those cases where R^3 is an aryl or heteroaryl group, this covalent bond (as illustrated in the various formulae described herein) may be formed at any position on the aromatic ring (provided that it has the correct valency and/or is chemically suitable). For example, a hydrogen at any position on the R^3 groups shown above may be replaced with a bond to the structure shown in formula (I).

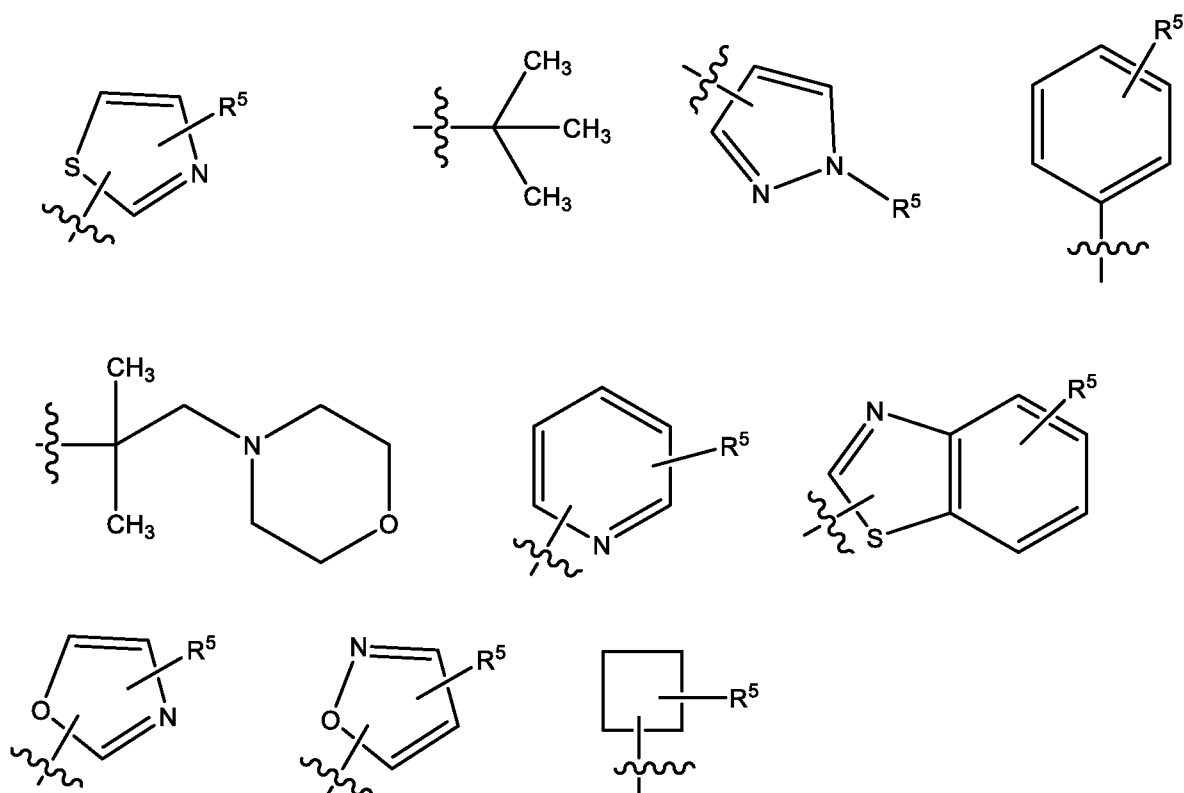
By way of further example, a suitable R^3 group may be selected from the following:





- 5 wherein the dotted line on the structures indicates the position that each of the respective R^3 groups may be joined to the structure shown in formulae described herein, and R^5 , R^6 , n and G are as defined above.

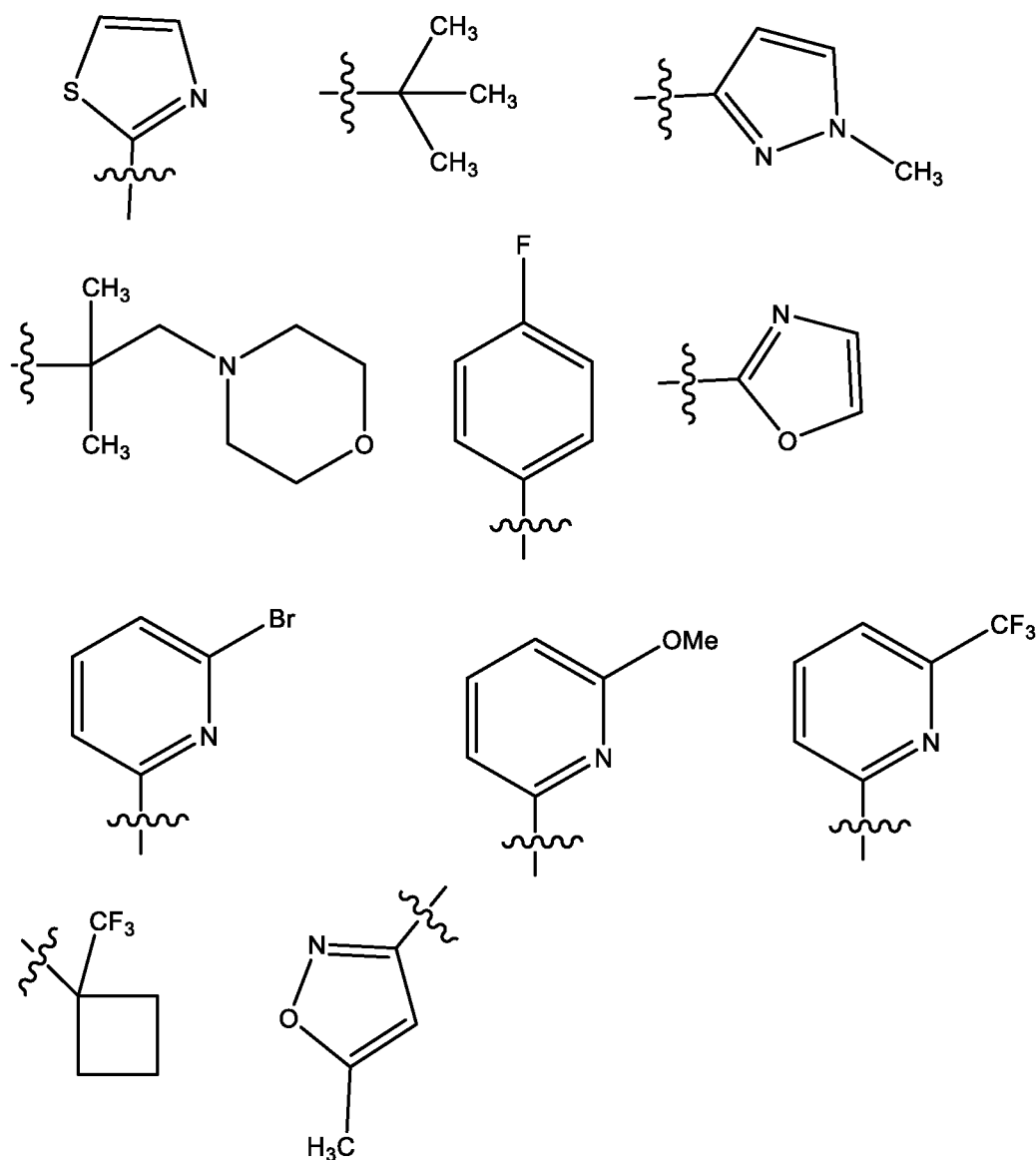
In other examples, a suitable R^3 group may be selected from the following:



wherein the line intersected by a wavy line represents the covalent bond between the exemplary R^3 groups shown above and the carbon atom of the parent structure of Z (as illustrated by the various formulae described herein), and R^5 is as defined above.

5

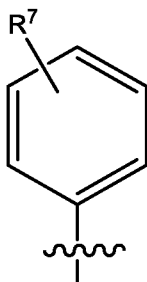
By way of further example, a suitable R^3 group may be selected from the following:



Again, in the structures shown above, the line intersected by a wavy line represents the covalent bond between the exemplary R³ groups shown above and the carbon atom of the parent structure of Z (as illustrated by the various formulae described herein).

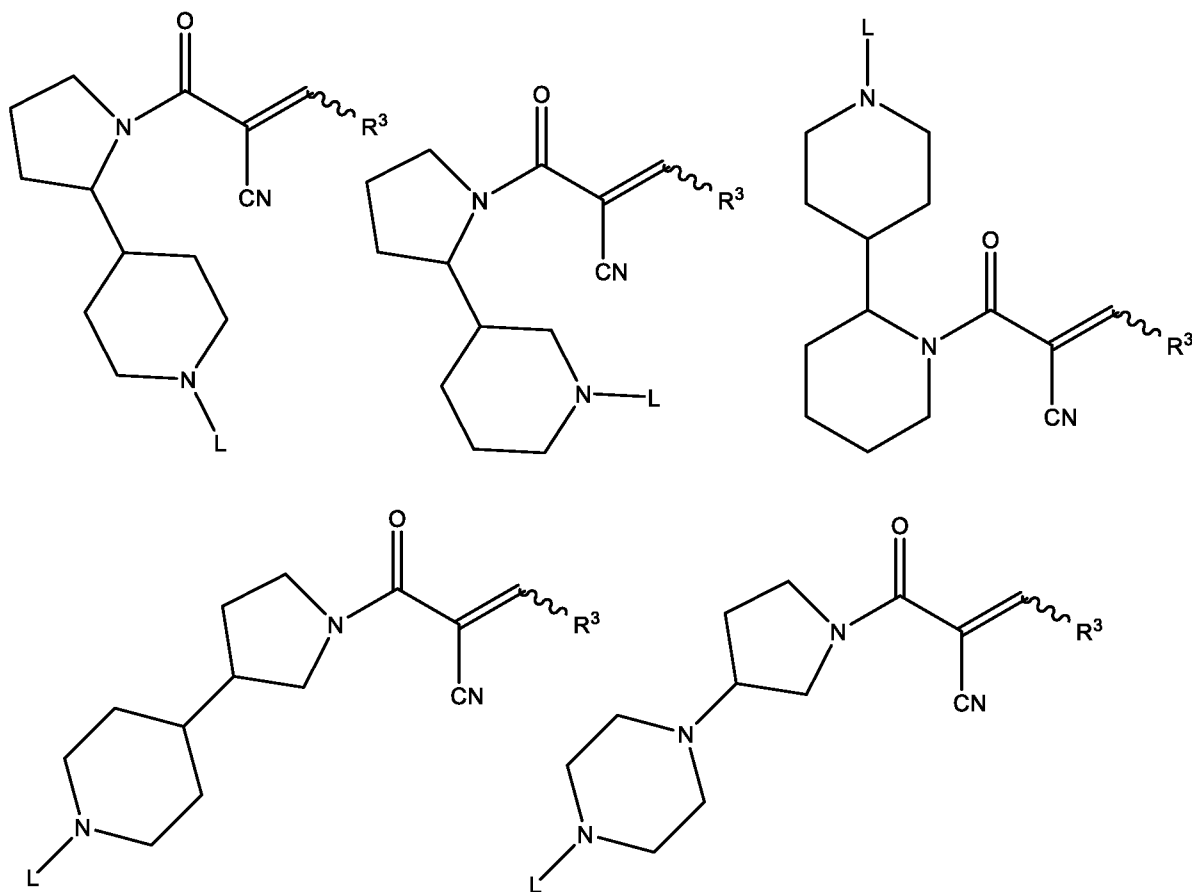
As stated above, R⁴ may be selected from aryl, substituted aryl, heteroaryl and substituted heteroaryl. In some examples, R⁴ may be selected from aryl having 6 to 10 carbon ring atoms; and heteroaryl having 5 to 10 ring atoms and containing 1 to 3 heteroatoms each independently selected from N, O and S; wherein the aryl and the heteroaryl are optionally substituted with one or two substituents selected from the group consisting of halo, C₁ to C₃ alkyl, C₁ to C₃ haloalkyl and C₁ to C₃ alkoxy. In some examples, R⁴ may be an optionally substituted phenyl.

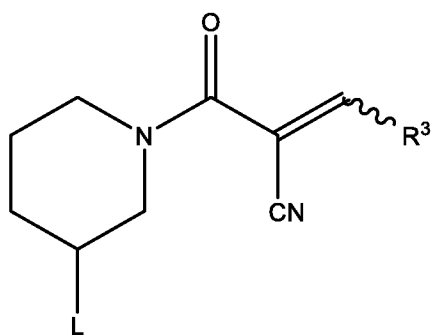
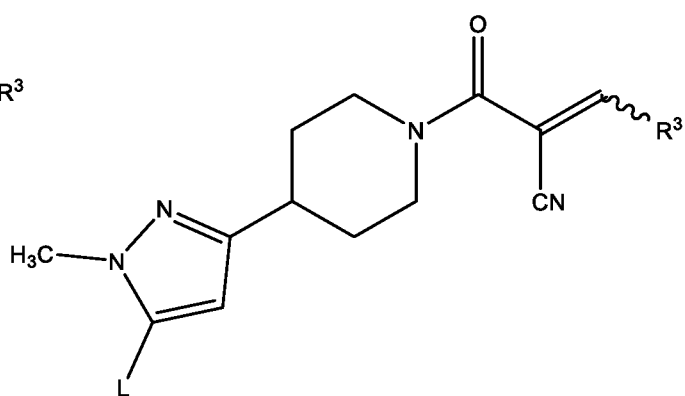
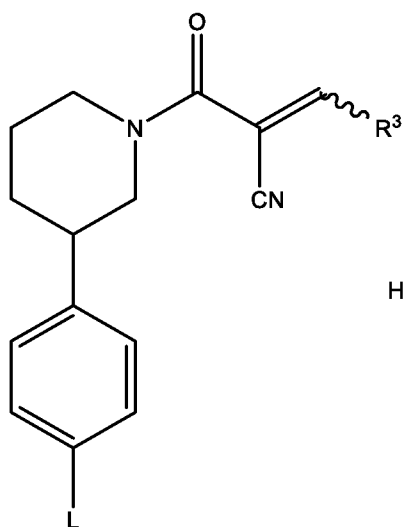
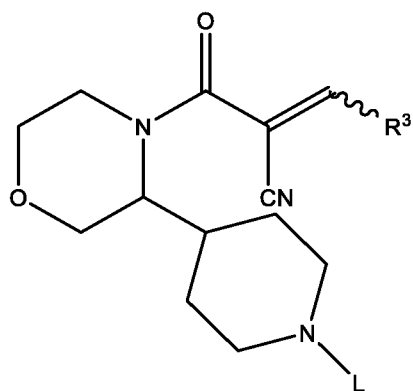
By way of further example, a suitable R^4 group may be selected from the following:

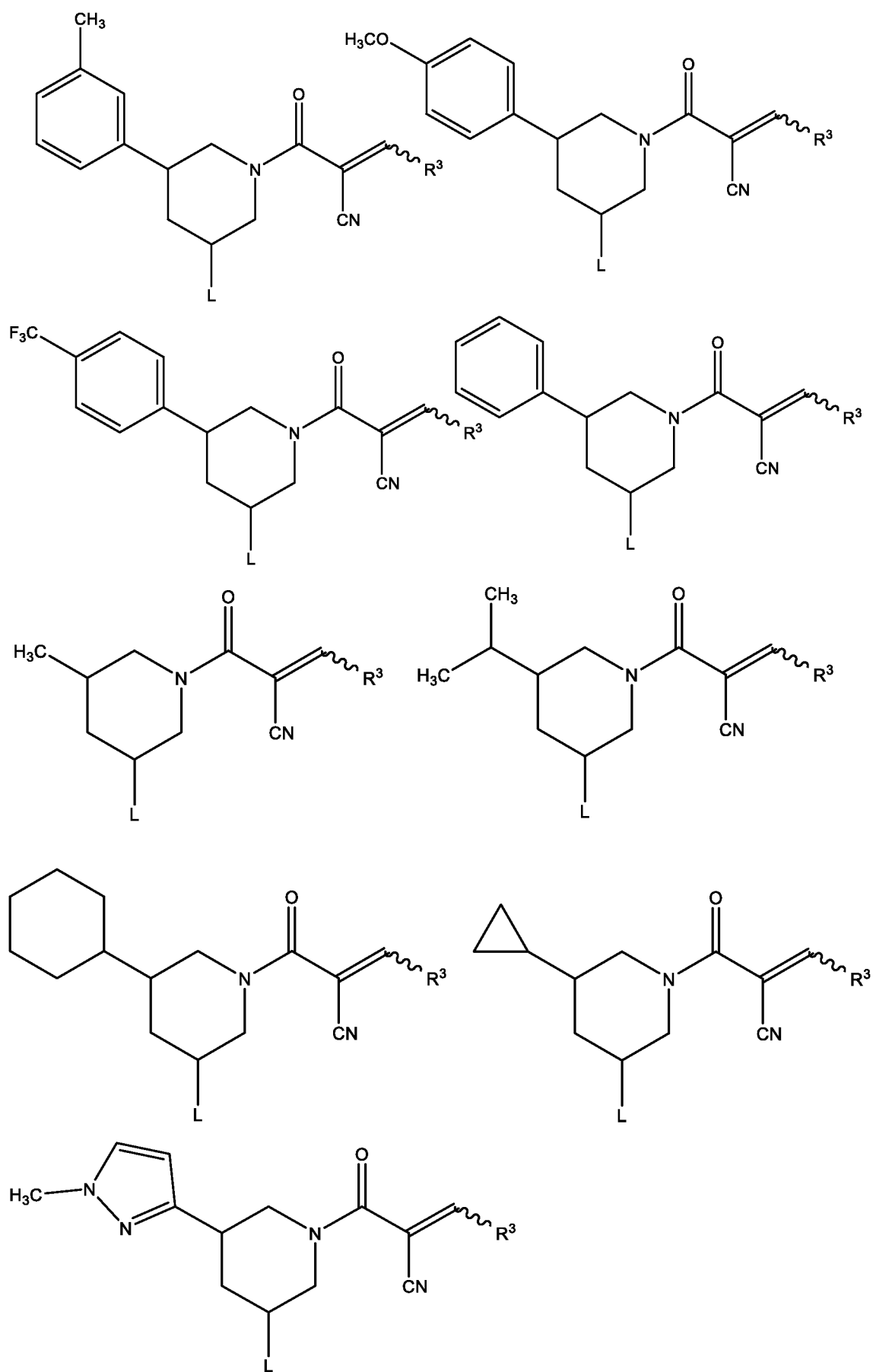


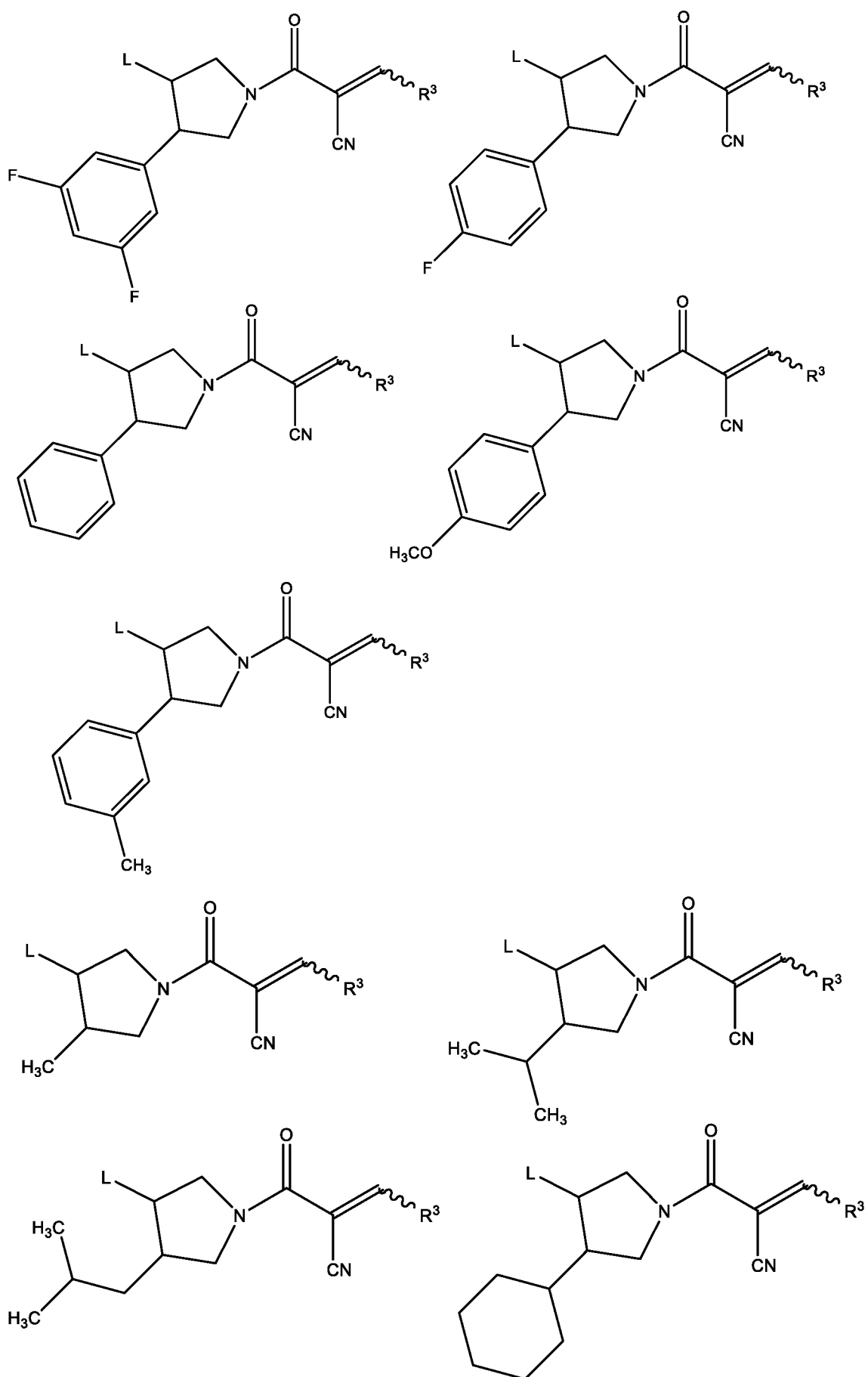
R^7 may be any substituent as described herein or may be absent. In some examples, R^7 may be selected from C_1 to C_6 alkyl, halo, C_1 to C_6 haloalkyl and C_1 to C_6 alkoxy. In some examples, R^6 may be C_1 to C_6 alkyl or C_1 to C_3 alkyl (e.g. methyl). As stated above, there may be one or more substituents on the aromatic ring. Where two or more substituents are present, each substituent may be independently selected from the R^7 groups noted above. Again, where present and unless otherwise indicated, R^7 may be covalently bonded to the aryl or heteroaryl ring at any position (provided that it has the correct valency and/or is chemically suitable).

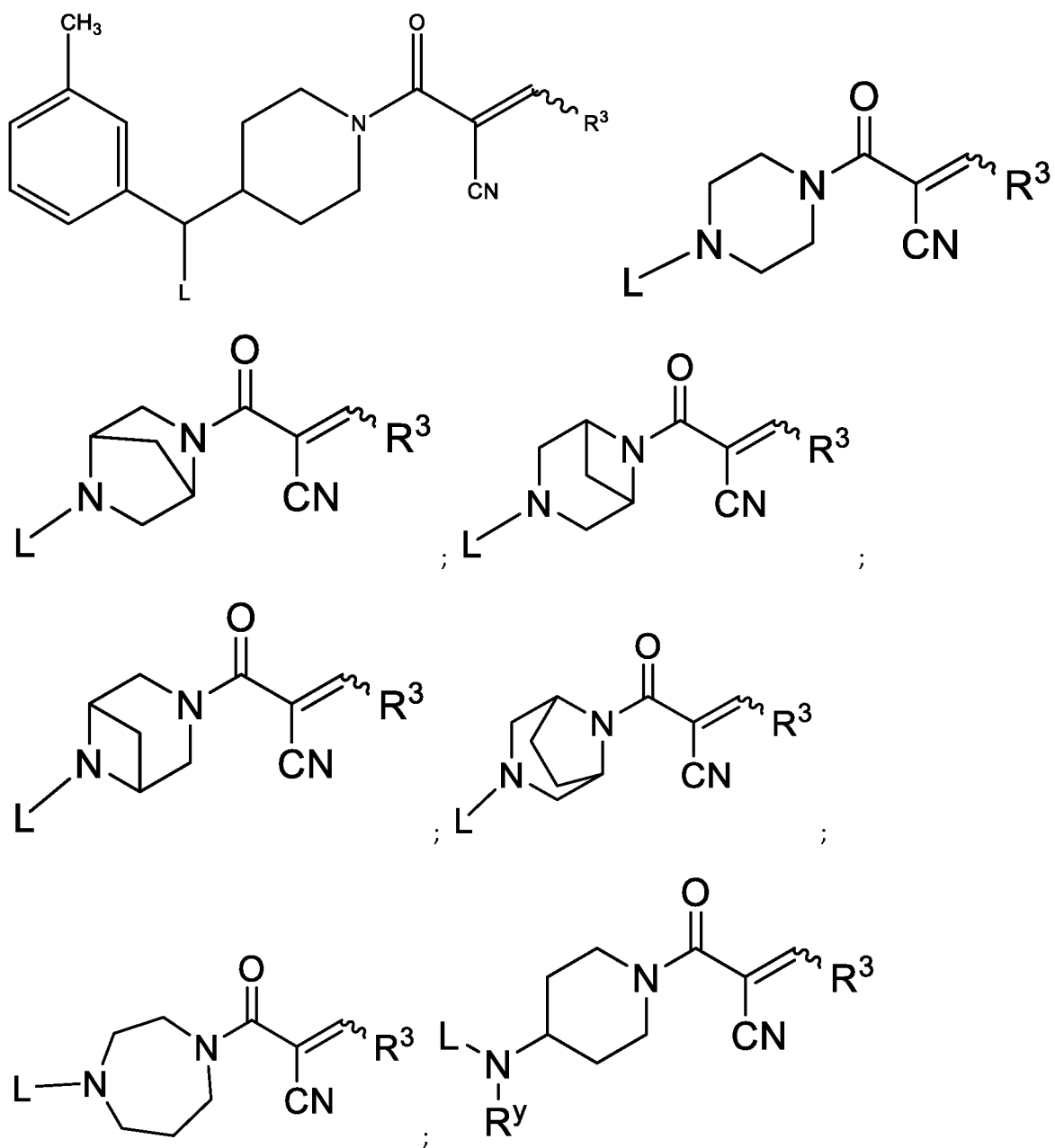
By way of further example, representative examples of Z are illustrated below:

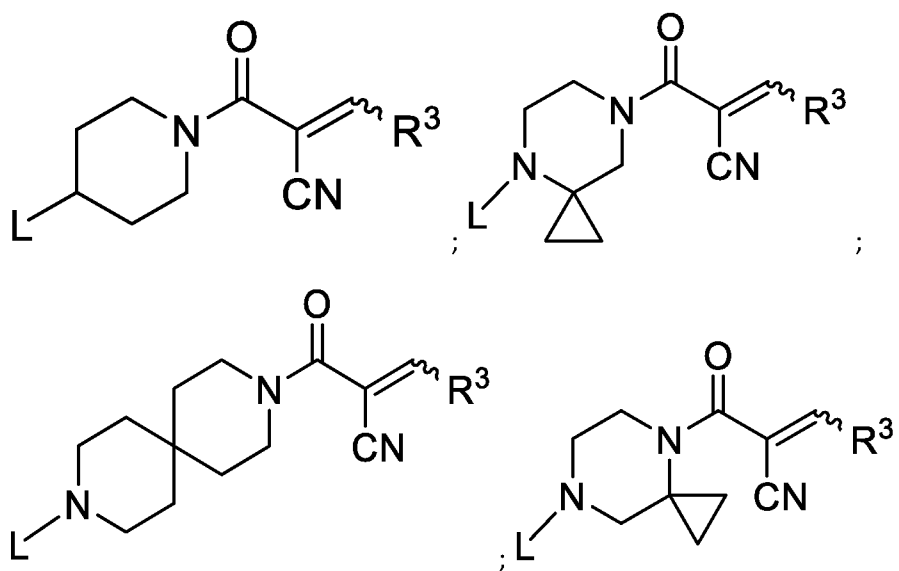






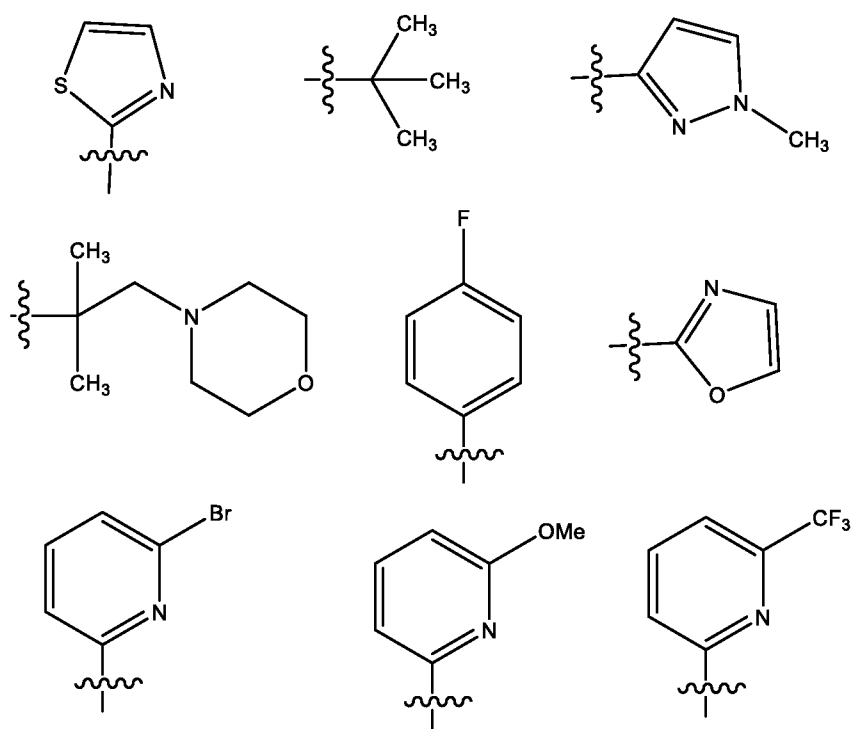


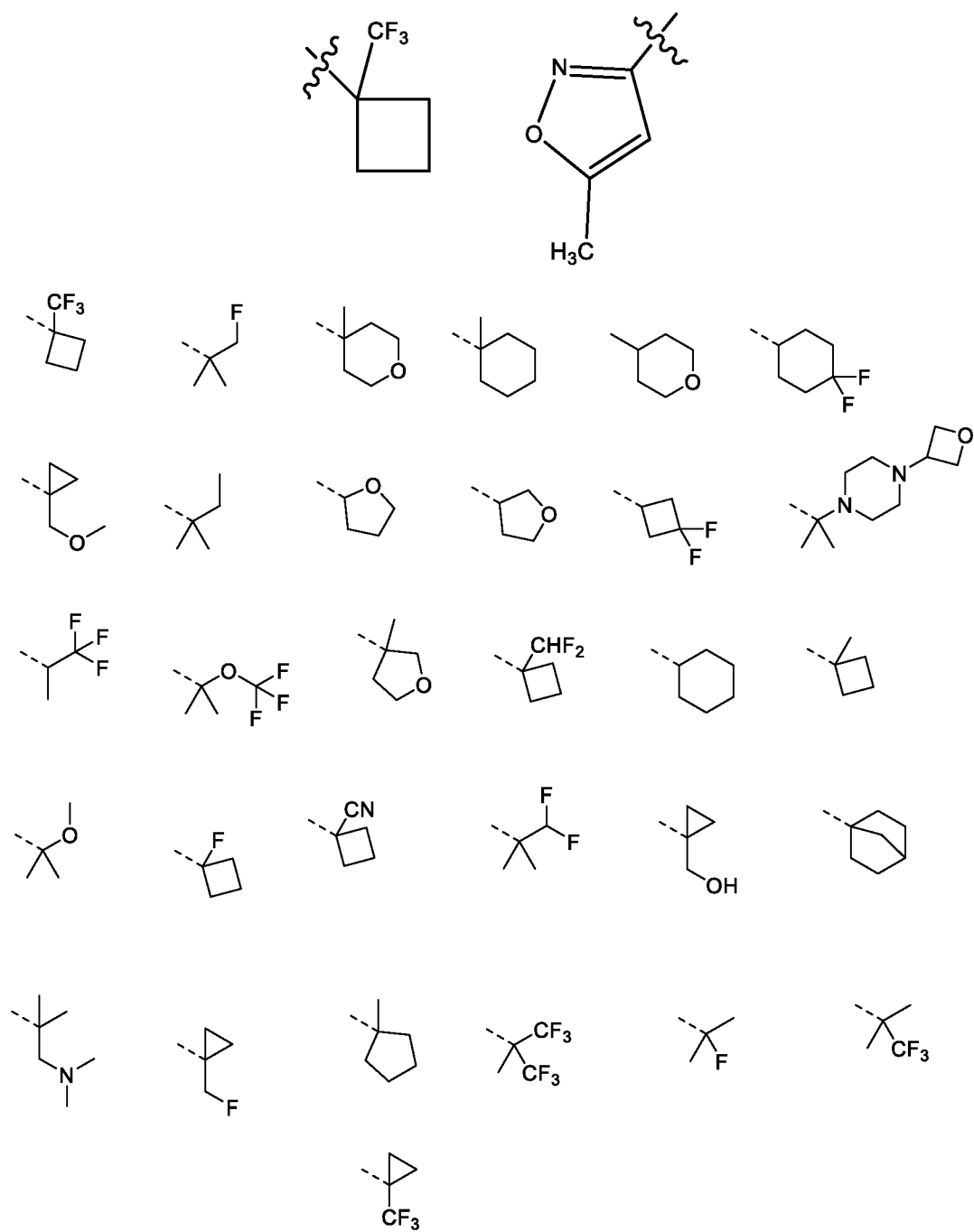


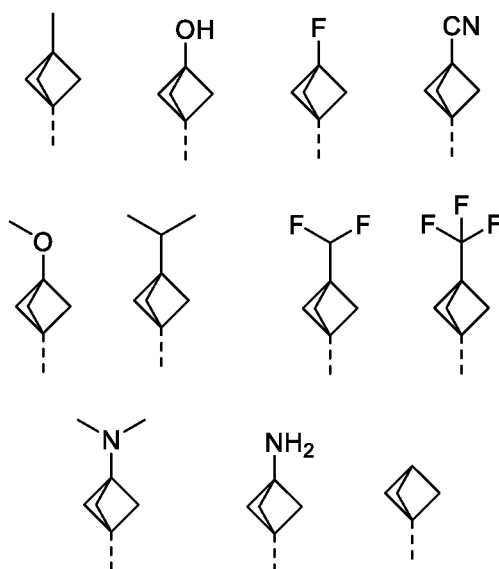


- 5 In the exemplary structures shown above, R^3 may be selected from any of those R^3 groups disclosed herein. In some cases, in the exemplary structures shown above, R^3 may be selected from the group consisting of:

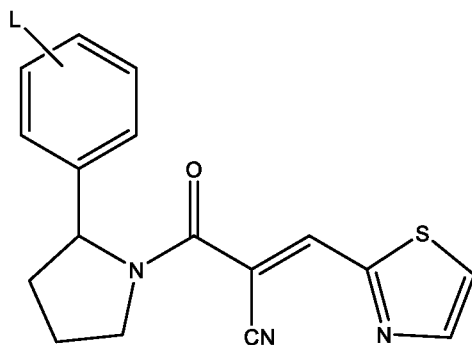
10





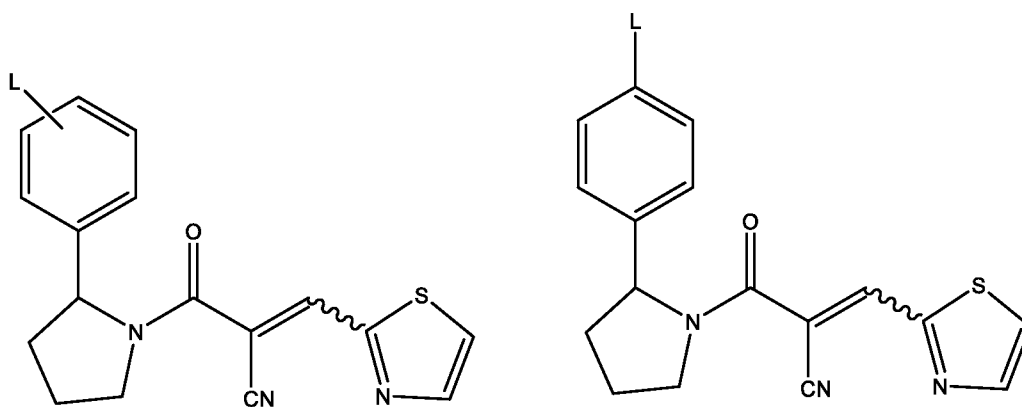


As noted above, Z is not:

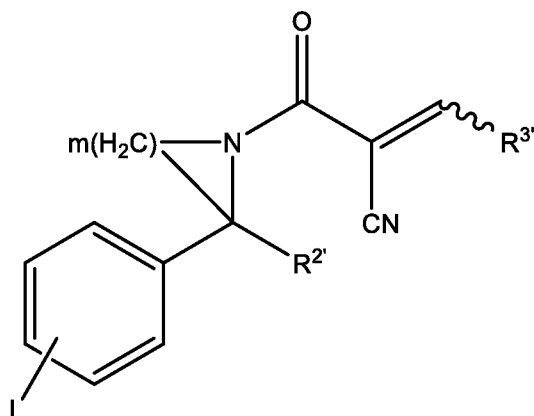


5

In some examples, Z is not (or does not comprise) a structure selected from one or more of the following:



10 In some examples, Z is not (or does not comprise) the following structure:



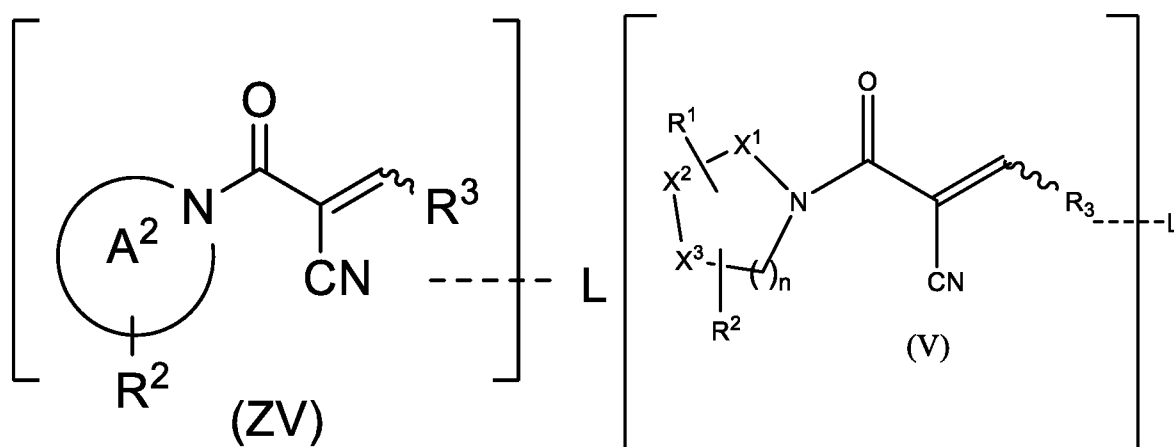
wherein $R^{2'}$ is selected from H and C_1 to C_6 alkyl;

$R^{3'}$ is selected from C_1 to C_6 alkyl, aryl, heteroaryl, substituted aryl, and substituted heteroaryl, optionally wherein the C_1 to C_6 alkyl is substituted with a heterocycloalkyl group;

5 m is 3, 4 or 5; and

L shows the point of attachment of the linker.

Alternatively it is noted, that whilst the various formulae described herein indicate that the linker is joined to the Z moiety via the heterocyclic core (either directly or indirectly via the R^2 group), the present disclosure also extends to examples wherein the linker is attached at any other position in the Z moiety (provided that it has the correct valency and/or is chemically suitable). For example, the linker may replace a hydrogen atom at any position in the Z moiety. Thus, in some examples, Z may be represented as shown in formula (ZV) or (V):



wherein ring A^2 , R^1 , R^2 , R^3 , X^1 , X^2 , X^3 , n and L are as defined in any one of the embodiments disclosed above.

The dotted line shown through the square brackets on formulae (ZV) and (V) indicates that the linker may be joined via a covalent bond to any atom on the Z moiety provided that it has the correct valency, is chemically suitable and/or provided that the attachment of the linker at

this alternative position does not disrupt the function of the Z moiety in promoting and/or facilitating proteasomal degradation.

Linker (L)

5

As described herein, the TBL is linked or coupled to moiety Z via a linker L. The linker 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 Z and/or TBL by a covalent bond.

10 The linker acts to tether the target protein binding ligand and Z moieties to one another whilst also allowing both of these portions to bind to their respect targets and/or perform their intended function. In particular, the linker may act to tether the target protein binding ligand to Z whilst also mitigating the possibility of the Z moiety disrupting, interfering with and/or inhibiting the binding of the target protein binding ligand to the target protein. Additionally or
15 alternatively, the linker may act to tether Z to the target protein binding ligand whilst also mitigating the possibility of the target protein binding ligand disrupting, interfering with and/or inhibiting the cellular interactions of Z (e.g. its function in modulating, facilitating and/or promoting the proteasomal degradation of the target protein).

20 In other words, the linker may function to facilitate targeted protein degradation by allowing each end of the bifunctional molecule to be available for binding (or another type of interaction) with various components of the cellular environment. For example, the linker may be configured to allow the target protein binding ligand to bind to the target protein without interference, disruption and/or inhibition from the Z moiety of the bifunctional molecule.
25 Additionally or alternatively, the linker may be configured to allow the Z moiety 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 the target protein binding ligand of the bifunctional molecule.

30 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 target protein binding ligand.

The linker may be selected to provide a particular length and/or flexibility, e.g. such that the
35 target protein binding ligand and the Z moiety 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 the

linker may be varied dependent upon the structure and/or nature of the target protein binding ligand.

In some examples, the TBL is connected directly to moiety Z by a covalent bond i.e, the linker 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, the linker 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 the linker 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, the linker 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.

The degree of flexibility of the linker may depend upon the number of rotatable bonds present in the linker. 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, the linkers may comprise one or more moieties selected from rings, double bonds and amides to reduce the flexibility of the linker. In other cases, the linker 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 the linker. It may also be appreciated that the length of the linker may affect the degree of flexibility. For example, a shorter linker comprising fewer bonds may also reduce the flexibility of a linker.

In some examples, the number of rotatable bonds present in the linker may be any number between 1 and 20, between 1 and 15, 1 and 10 or between 1 and 8. In some examples, the number of rotatable bonds present in the linker may be any number between 2 and 9, between 2 and 8, or between 3 and 6.

In some examples, the linker may comprise any number of atoms in a single linear chain between 10 and 20; and/or the number of rotatable bonds present in the linker may be any number between 2 and 8.

The structure of the linker (L) may be represented as follows:



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.

5

By way of example, in the case where q is 1, the linker comprises only one L_x subunit and may be represented as L_1 . In the case where q is 2, the linker 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, the linker 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 .

10

Each of L_x may be independently selected from $CR^{L1}R^{L2}$, O, C=O, S, S=O, SO_2 , NR^{L3} , $SONR^{L4}$, $SONR^{L5}C=O$, $CONR^{L6}$, $NR^{L7}CO$, $C(R^{L8})=C(R^{L9})$, $C\equiv C$, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl and substituted heterocycloalkyl groups.

15

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, halo, C_1 to C_6 alkyl, C_1 to C_6 haloalkyl, -OH, -O(C_1 to C_6 alkyl), - NH_2 , -NH(C_1 to C_6 alkyl), - NO_2 , -CN, -CONH $_2$, -CONH(C_1 to C_6 alkyl), -CON(C_1 to C_6 alkyl) $_2$, -S(O)OC $_1$ to C_6 alkyl, -C(O)OC $_1$ to C_6 alkyl, and -CO(C_1 to 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 and C_1 to C_6 alkyl.

20

The terms aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl and substituted heterocycloalkyl groups are defined above.

25

The terminal L_x subunits may link or couple the linker moiety to the TBL and Z moieties of the bifunctional molecule. For example, if the terminal L_x subunits are designated as L_1 and L_q , L_1 may link the linker to the TBL moiety and L_q may link the linker to the Z moiety. In those cases where q is 1, the one L_x subunit (e.g. L_1) provides the link between the TBL and Z moieties of the bifunctional molecule.

30

The TBL and Z moieties may be covalently linked to L through any group which is appropriate and stable to the chemistry of the linker. By way of example only, the linker may be covalently bonded to the TBL moiety via a carbon-carbon bond, keto, amino, amide, ester or ether linkage. Similarly, the linker may be covalently bonded to the Z moiety via a carbon-carbon bond, carbon-nitrogen bond, keto, amino, amide, ester or ether linkage.

35

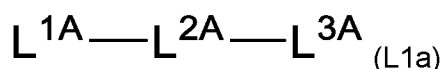
In some cases, each terminal L_x subunit (e.g. L_1 and L_q) is independently selected from O, C=O, $CR^{L1}R^{L2}$, NR^{L3} , $CONR^{L6}$, $NR^{L7}CO$, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl and substituted heterocycloalkyl groups.

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, the linker may be or 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, the linker may be or comprise a polyalkylene glycol. By way of example only, the linker may be or 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 the linker (L) may be, or comprise, a structure represented as shown in formula (L1a):



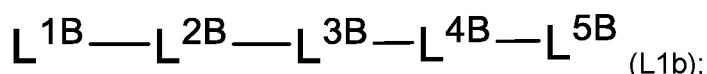
wherein L^{1A} is absent or is selected from C_1 - C_6 alkylene (e.g. ethylene), C_1 - C_6 alkoxy (e.g. $-O(CH_2)-$, $-O(CH_2)_2-$, $-O(CH_2)_5-$, $-CH_2OCH_2-$) and C_1 - C_6 alkylamino (e.g. $-NR^{L2A}(CH_2)-$, $-R^{L2A}(CH_2)_2-$, $-R^{L2A}(CH_2)_5-$, $-CH_2R^{L2A}CH_2-$);

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 the linker (L) may be, or comprise, a structure represented as shown in formula (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 $-C=ONR^{L2A}-$;

5 L^{3B} is selected from C_1 - C_{15} alkylene, $-[(CH_2)_2O]_{1-6}(CH_2)_2-$;

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. $-(CH_2)NR^{L2A}-$, $-NR^{L2A}(CH_2)_2-$, $-(CH_2)_5NR^{L2A}-$, $-CH_2NR^{L2A}CH_2-$);

10 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 the linker (L) may be, or comprise, a structure represented as shown in formula (L1c):



15 wherein L^{1C} is an optionally substituted 4- to 7-membered monocyclic N-heterocycloalkyl, an optionally substituted 7- to 12-membered bicyclic N-heterocycloalkyl, or an optionally substituted 8- to 18-membered tricyclic N-heterocycloalkyl, each optionally containing one or two additional ring heteroatoms selected from N, O and S;

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. $-(CH_2)NR^{L2A}-$, $-(CH_2)_2NR^{L2A}-$, $-(CH_2)_5NR^{L2A}-$, $-CH_2NR^{L2A}CH_2-$);

20 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. $-(CH_2)NR^{L2A}-$, $-(CH_2)_2NR^{L2A}-$, $-(CH_2)_5NR^{L2A}-$, $-CH_2NR^{L2A}CH_2-$);

25 wherein:

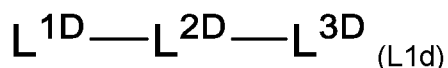
R^{L2A} is H or C_1 - C_6 alkyl (e.g. C_1 - C_3 alkyl); and

R^{L2B} is NR^{L2A} ; or an N-linked optionally substituted 4- to 7-membered monocyclic N-heterocycloalkyl, an optionally substituted 7- to 12-membered bicyclic N-heterocycloalkyl, or
30 an optionally substituted 8- to 18-membered tricyclic N-heterocycloalkyl, each optionally containing one or two additional ring heteroatoms selected from N, O and S.

In examples of Linker (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 optionally substituted 4- to 7-membered
35 monocyclic N-heterocycloalkyl, optionally containing one or two additional ring heteroatoms

selected from N, O and S, and L^{3C} is the terminal subunit of the linker attached, suitably covalently attached, to the TBL via R^{L2B}.

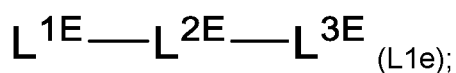
In some of the examples described herein, the structure of the linker (L) may be, or comprise, a structure represented as shown in formula (L1d):



wherein L^{1D} is absent or is selected from C₁-C₃ alkylene, CO, C₁-C₃ alkylene(N(C₁-C₃ alkyl)); L^{2D} is NR^{L2A} or an optionally substituted 4- to 7-membered monocyclic N-heterocycloalkyl, an optionally substituted 7- to 12-membered bicyclic N-heterocycloalkyl, or an optionally substituted 8- to 18-membered tricyclic N-heterocycloalkyl, each optionally containing one or two additional ring heteroatoms selected from N, O and S; wherein R^{L2A} is H or C₁-C₆ alkyl (e.g. C₁-C₃ alkyl); and

L^{3D} is absent or is selected from C₁-C₃ alkylene, -O-, -N(C₁-C₃ alkyl)-, and CO.

In further examples, the structure of the linker (L) may be, or comprise, a structure represented as shown in formula (L1e):



wherein L^{1E} is C₁-C₃ alkylene (e.g. methylene) or CO;

L^{2E} is an optionally substituted 4- to 7-membered monocyclic N-heterocycloalkyl, an optionally substituted 7- to 12-membered bicyclic N-heterocycloalkyl, each optionally containing one or two additional ring heteroatoms selected from N, O and S; and

L^{3E} is selected from C₁-C₃ 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 W moiety 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 the TBL portion.

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 W moiety. Where L^{3D} is absent, L^{2D} is directly attached (i.e. covalently bonded) to the TBL portion.

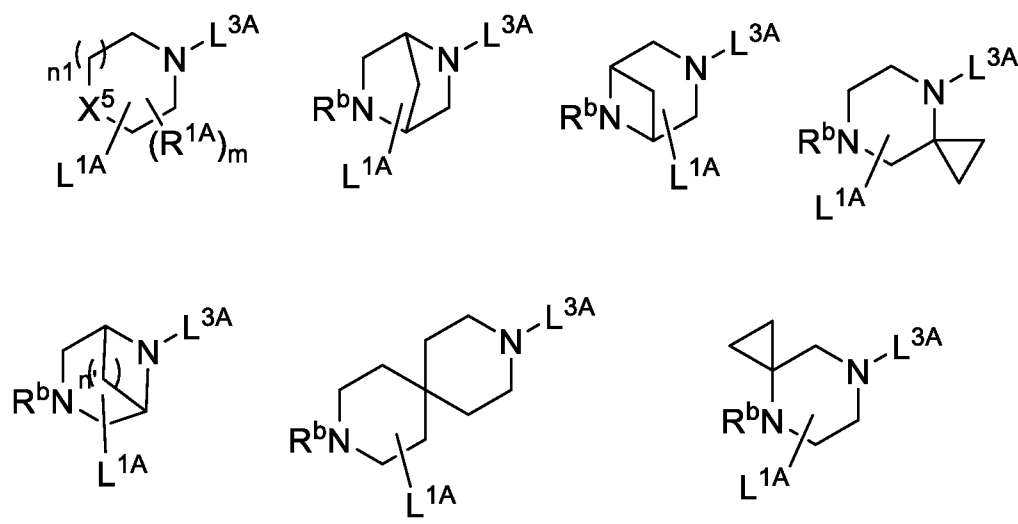
As stated above, a number of linker portions, such as L^{1C}, L^{2D}, L^{2E} examples of R^{L2B} and, may be bicyclic or tricyclic, and unless otherwise stated, these moieties may comprise rings that are joined by a bond, rings that are fused, a bridged ring and/or rings that are joined at a spiro centre.

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 an optionally substituted 7- to 12-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 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 an optionally substituted 7- to 12-membered spirocyclic 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- 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_{1-3} alkyl;

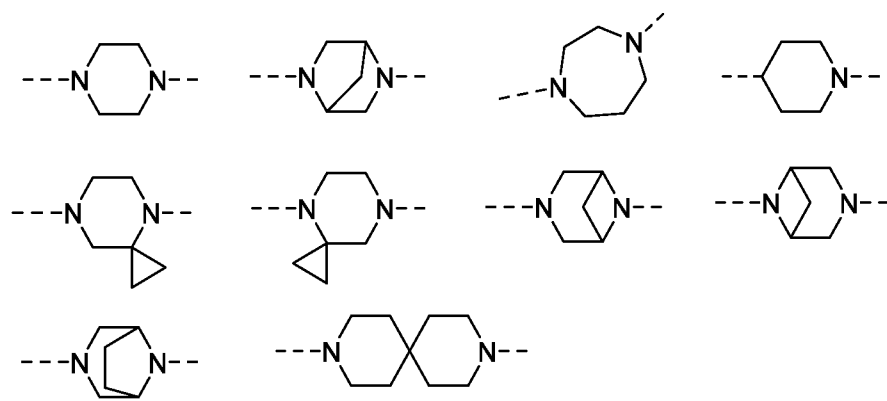
5 n_1 is 0, 1, 2 or 3;

n' is 1 or 2;

m is 0, 1 or 2

10 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:



As stated above, L^{1D} is absent or is selected from C_1 - C_3 alkylene, $-O-$, $-N(C_1-C_3 \text{ alkyl})-$, and CO . In some examples, L^{3D} is selected from C_1 - C_3 alkylene (e.g. methylene).

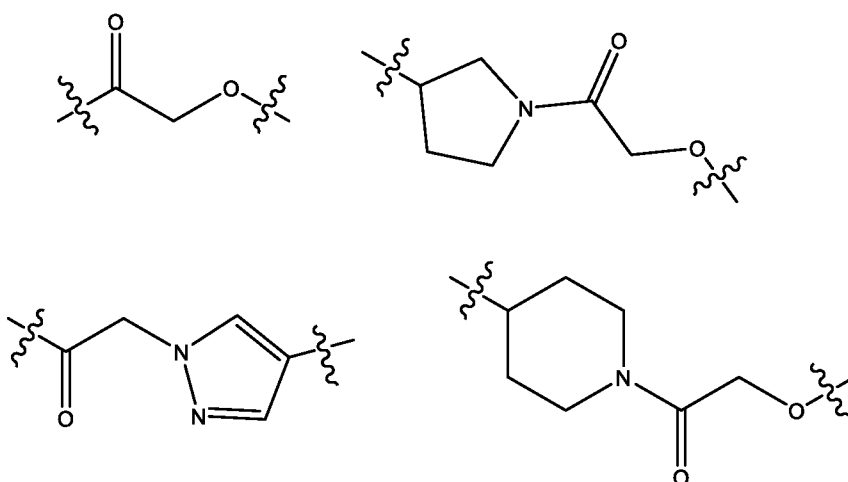
In some of the examples described herein, the linker (L) may be, or comprise, a structure represented as shown in formula (L1f):

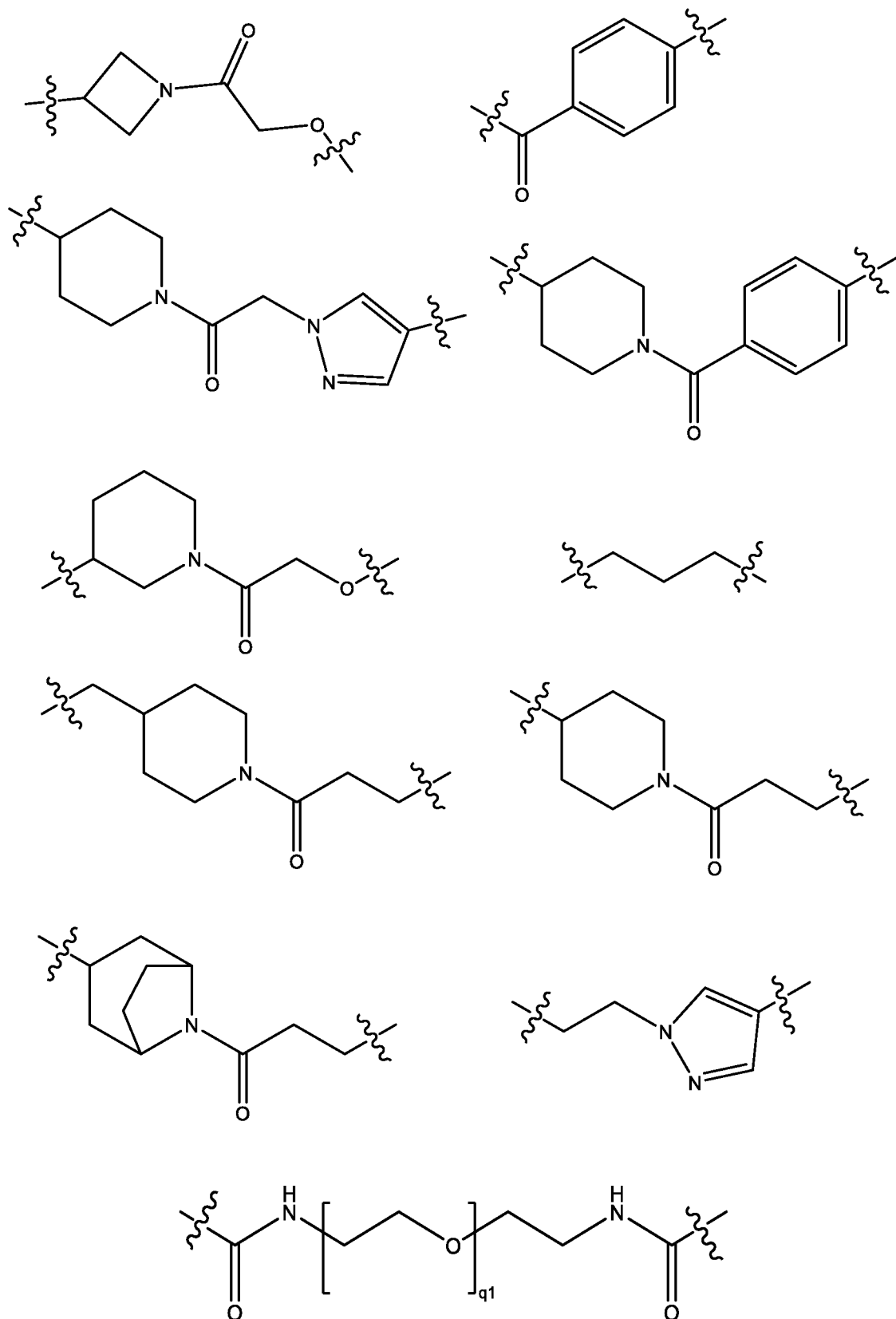
L^{1F} (L1f)

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.

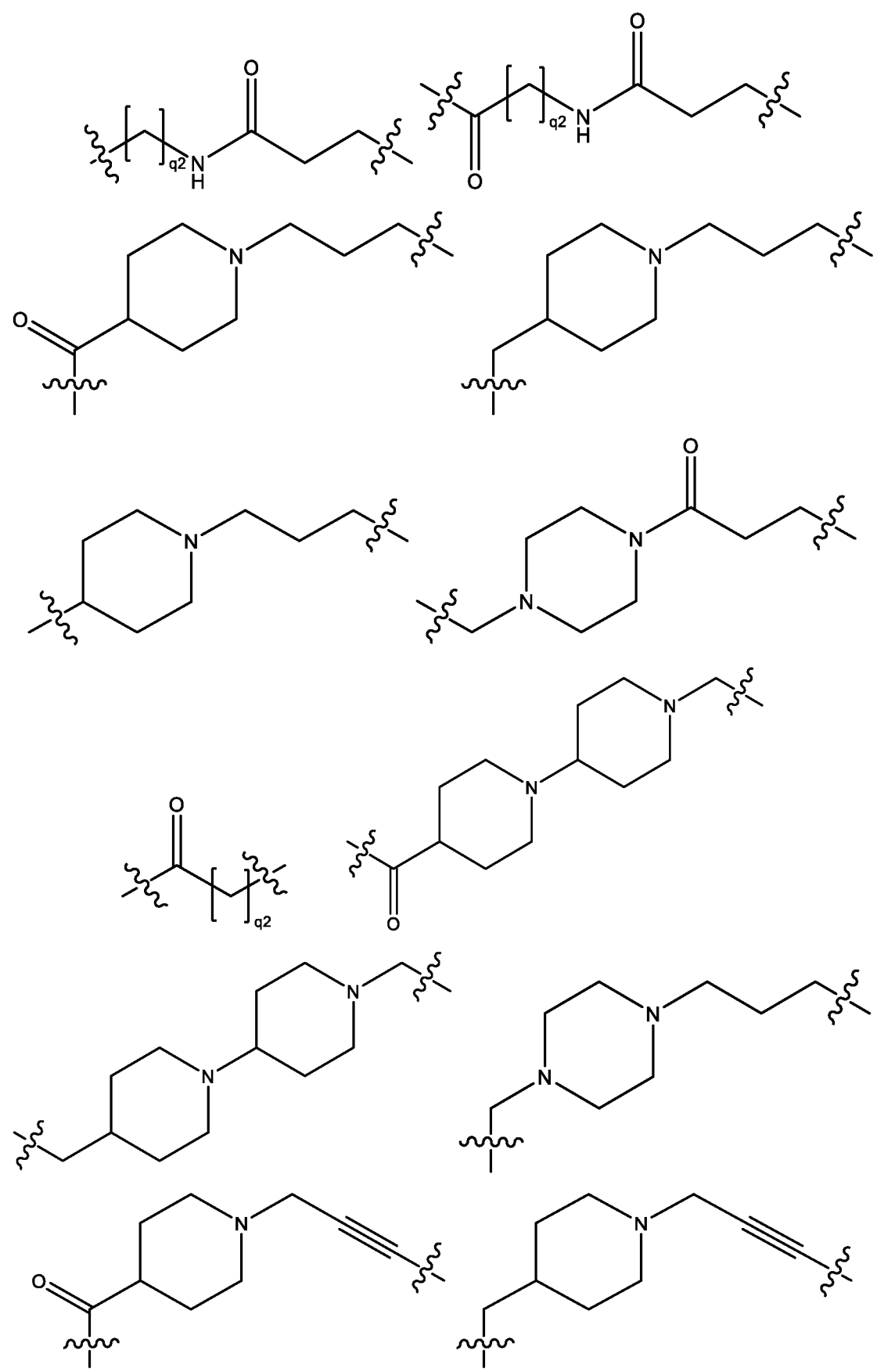
10 In some examples, L^{1F} is selected from C_1 - C_3 alkylene (such as methylene).

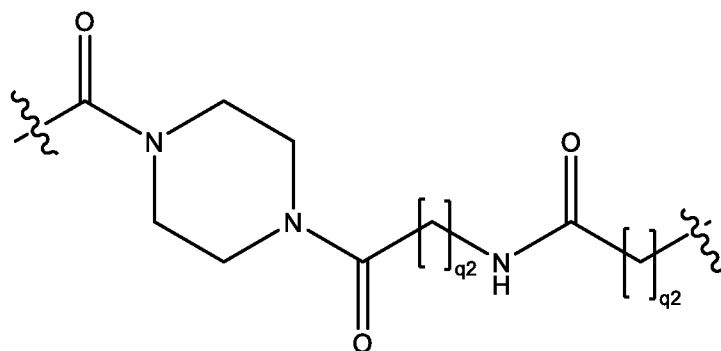
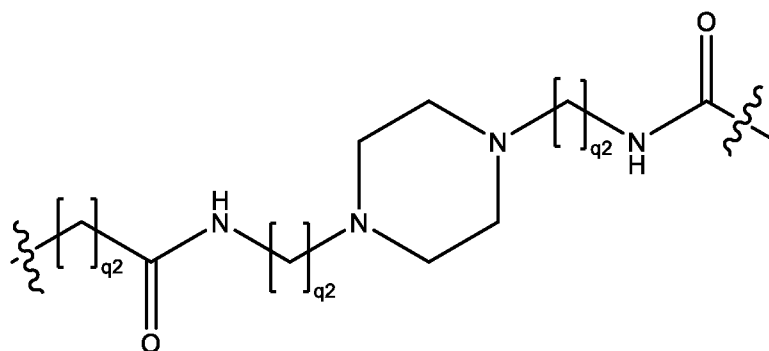
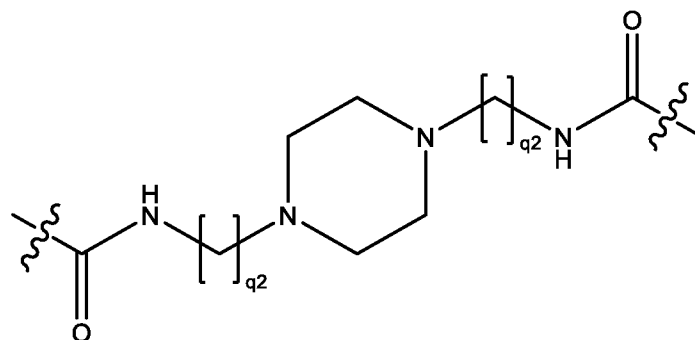
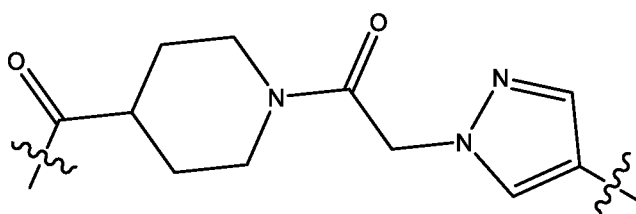
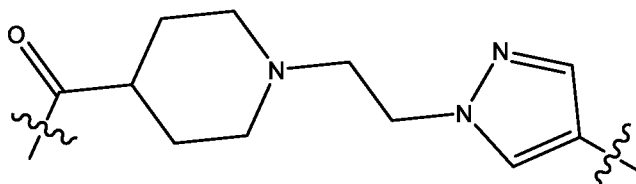
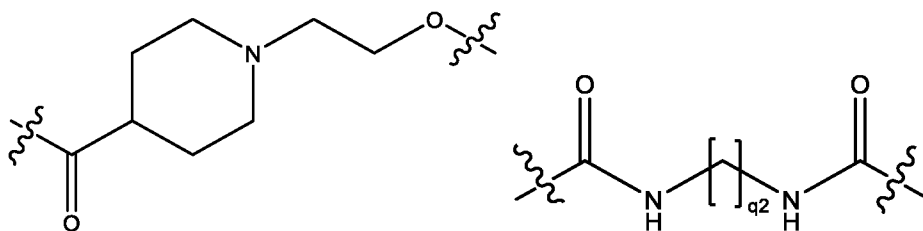
In any of the examples described herein, the linker is or comprises one or more of:

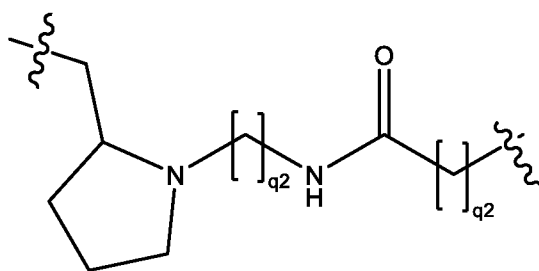




- 5 wherein q_1 is any integer between 1 and 20, or between 1 and 10 (e.g. between 1 and 5).
Alternatively, in any of the examples described herein, the linker is or comprises one or more of:

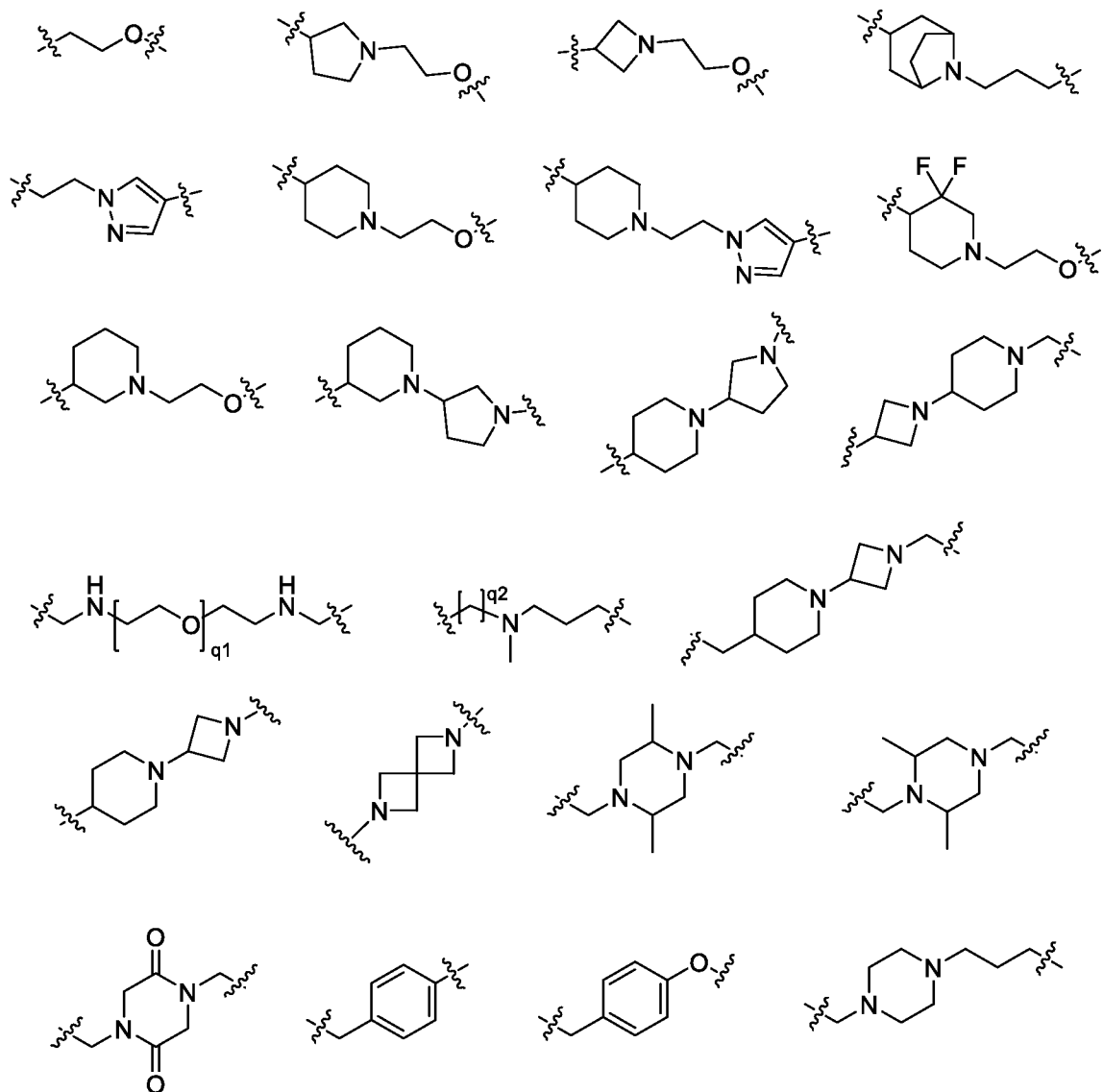


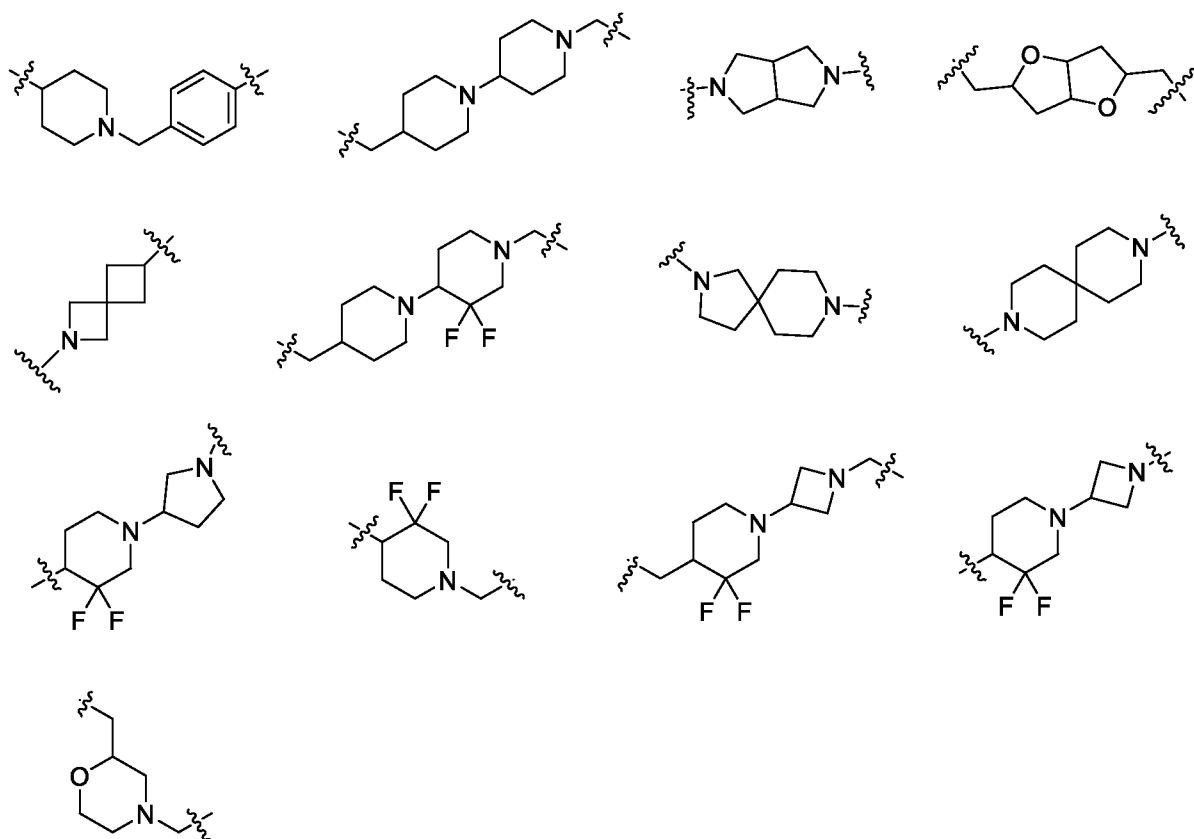




wherein q_2 is any integer between 1 and 20, or between 1 and 10 (e.g. 3, 4, 5, 6 or 10).

As a further alternative, in any of the examples described herein, the linker is or comprises
 5 one or more of:

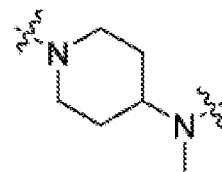
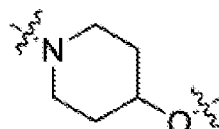
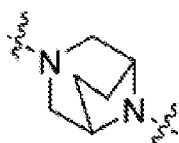
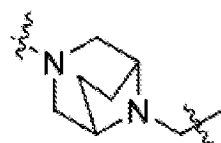
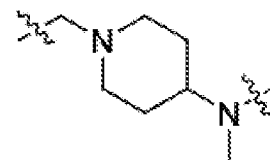
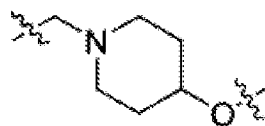
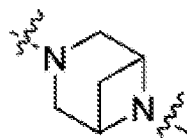
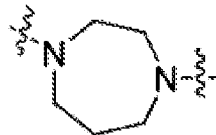
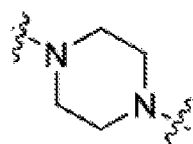
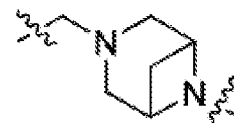
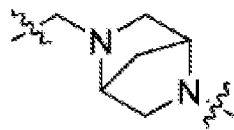
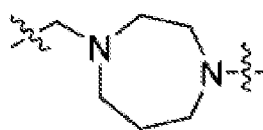
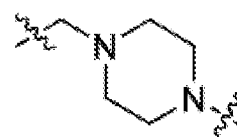
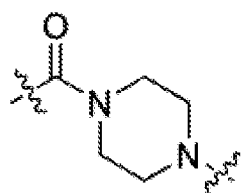
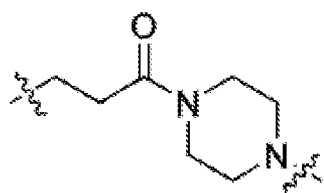


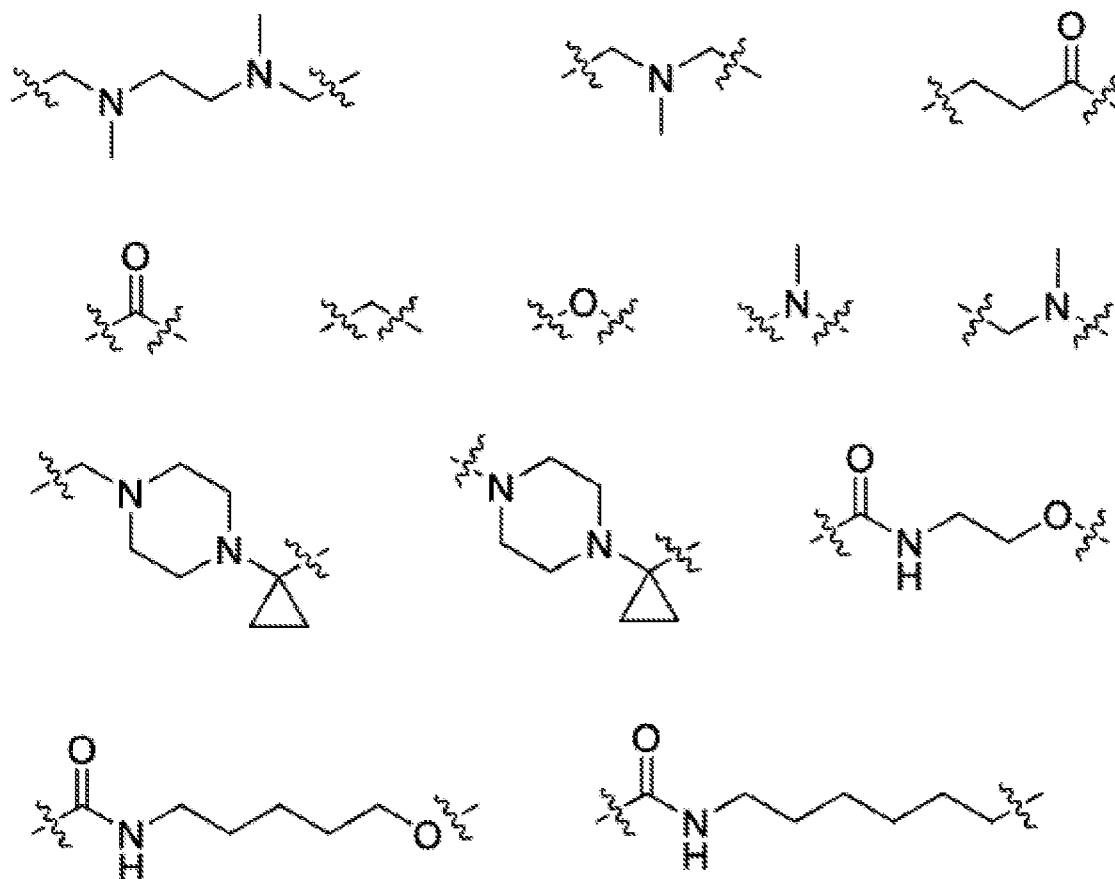


wherein q_1 is any integer between 1 and 20, or between 1 and 10 (e.g. between 1 and 5) and q_2 is any integer between 1 and 20, or between 1 and 10 (e.g. 3, 4, 5, 6 or 10).

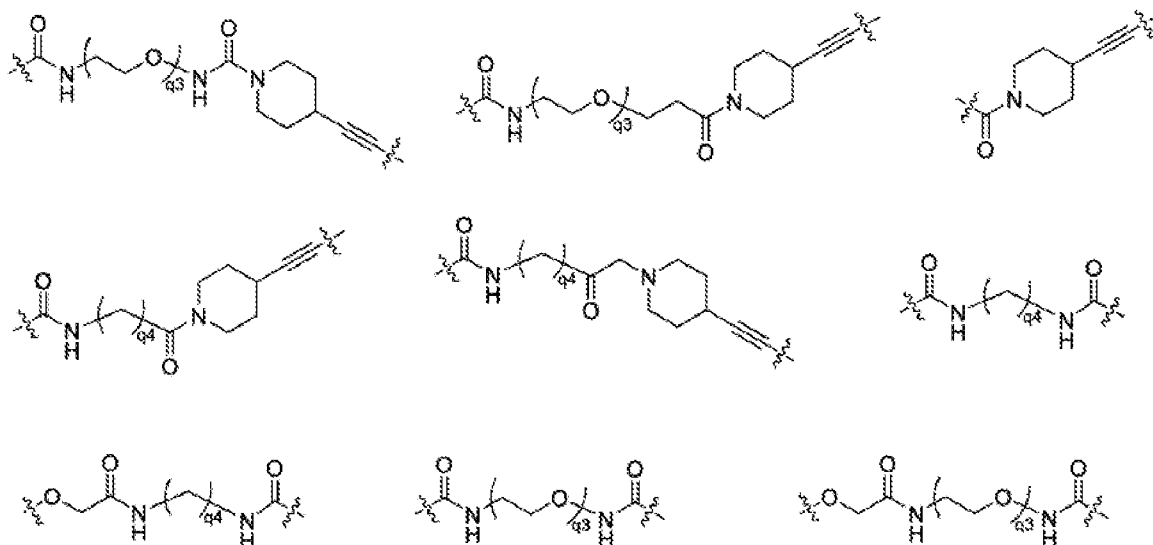
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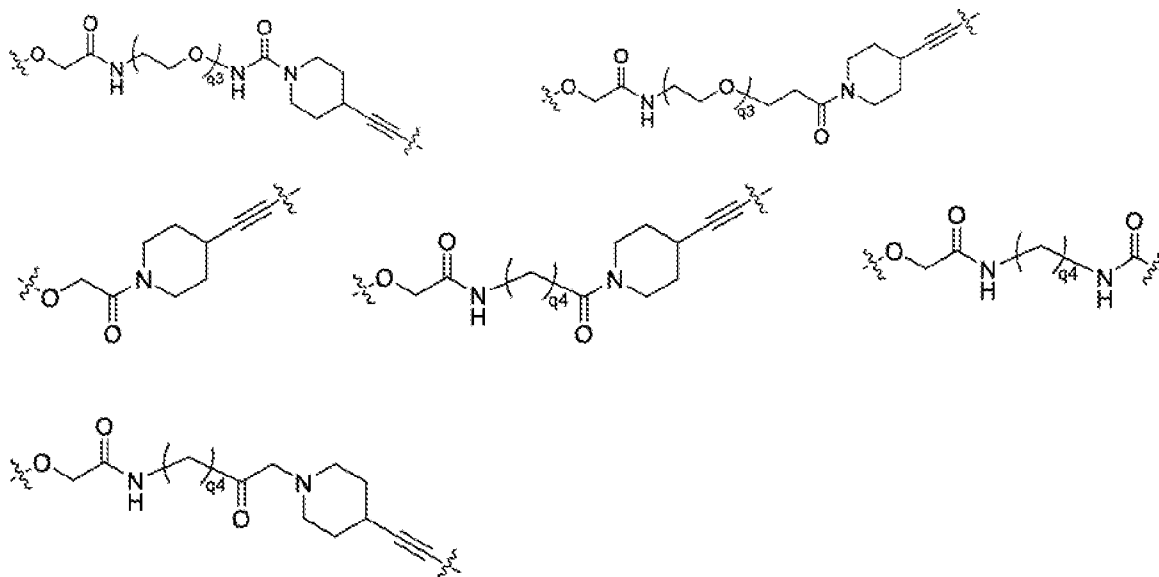
In particular examples, the linker is or comprises one or more of the following structures:



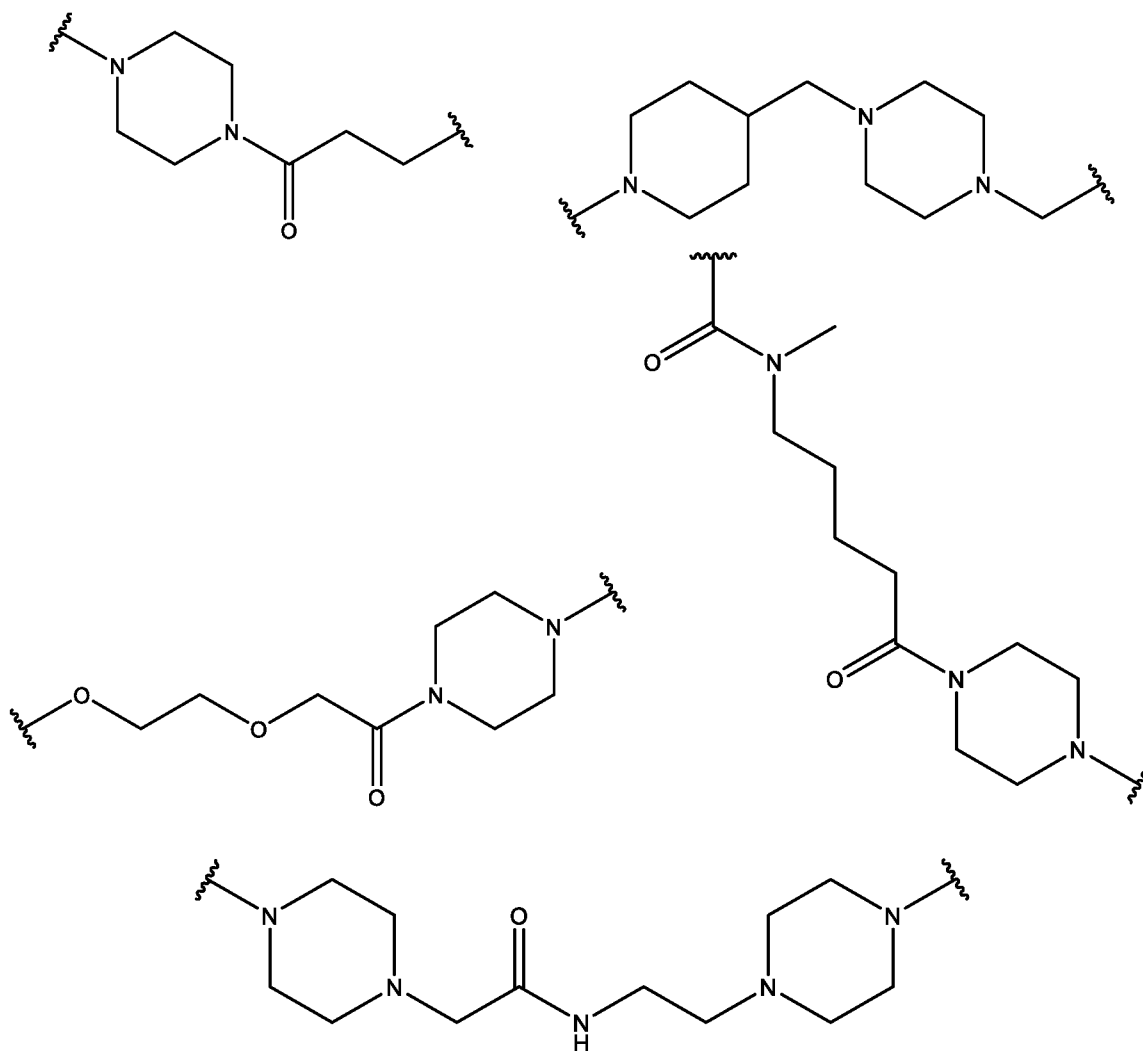


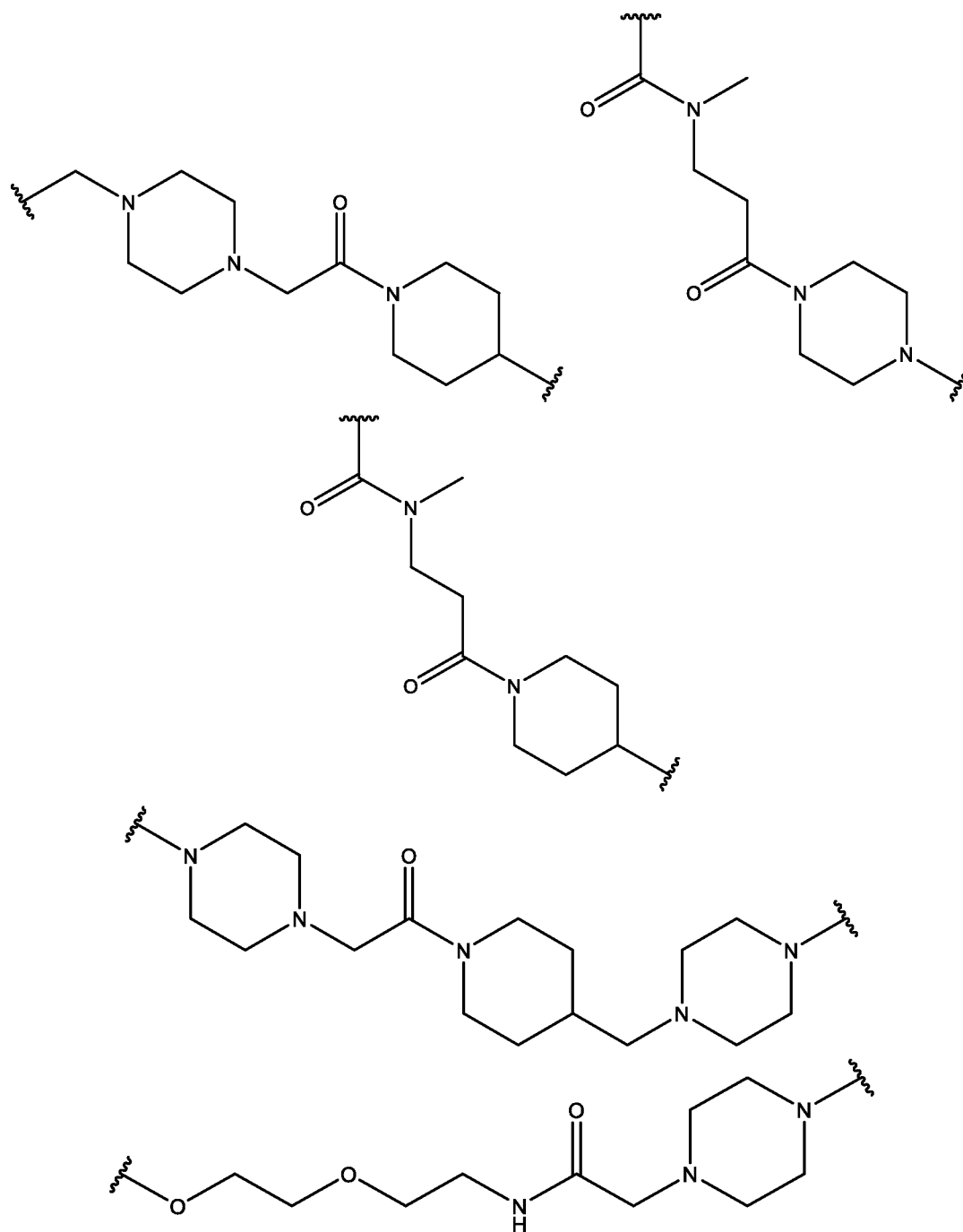
In yet further alternatives, in any of the examples described herein, the linker is or comprises one or more of:

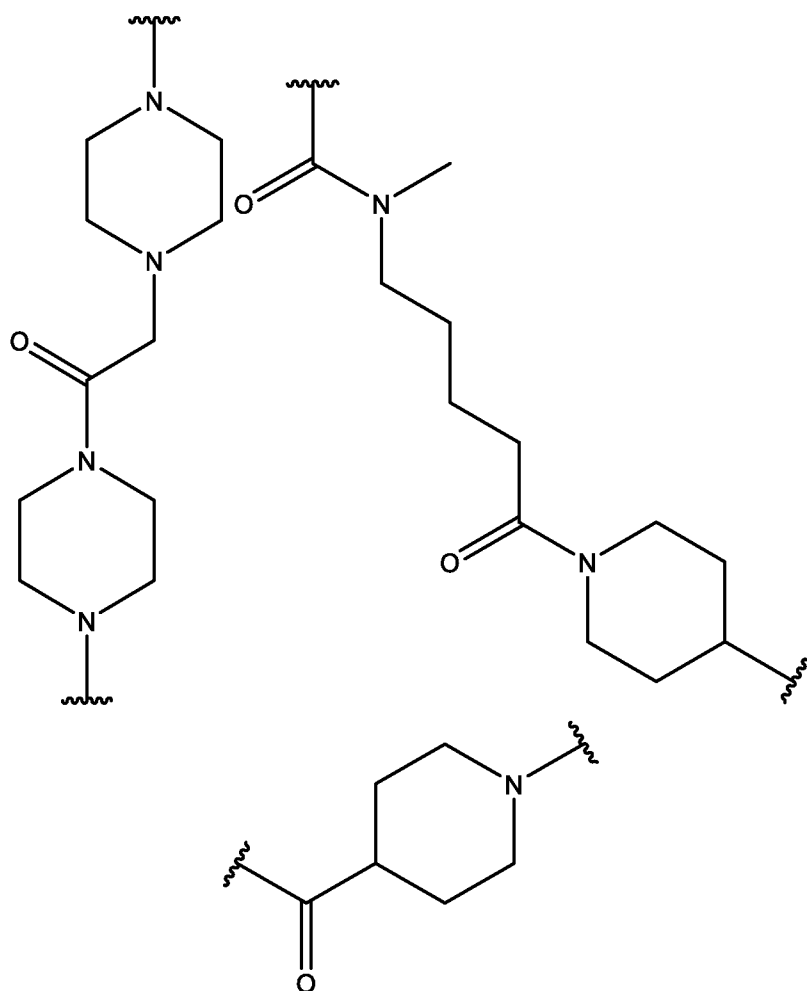




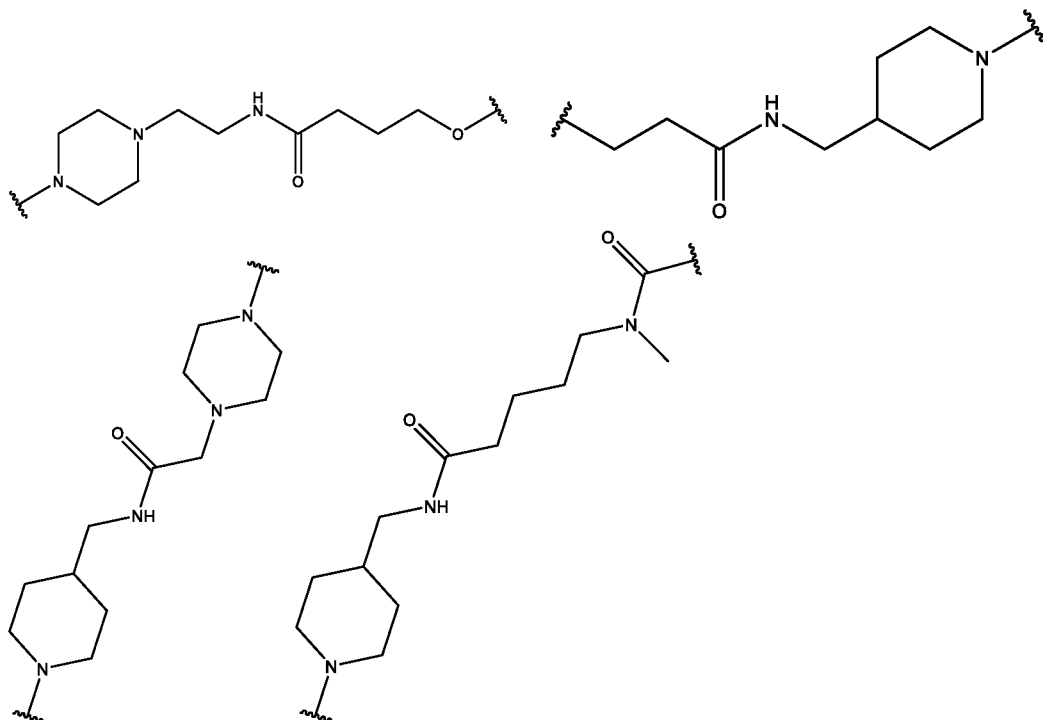
wherein q_3 is 1 to 8, such as 1 to 5, and q_4 is 1 to 12, such as 1 to 10.

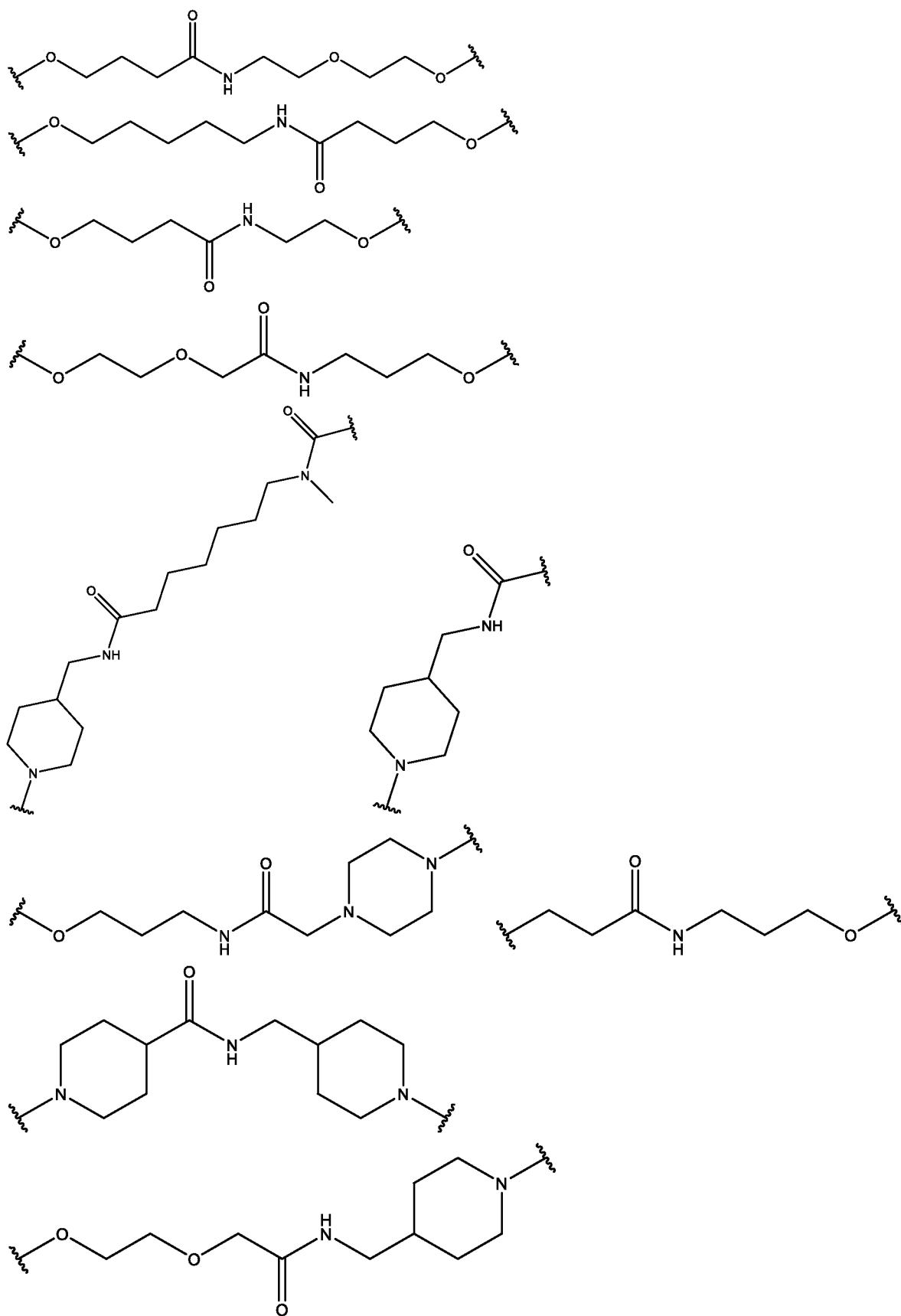


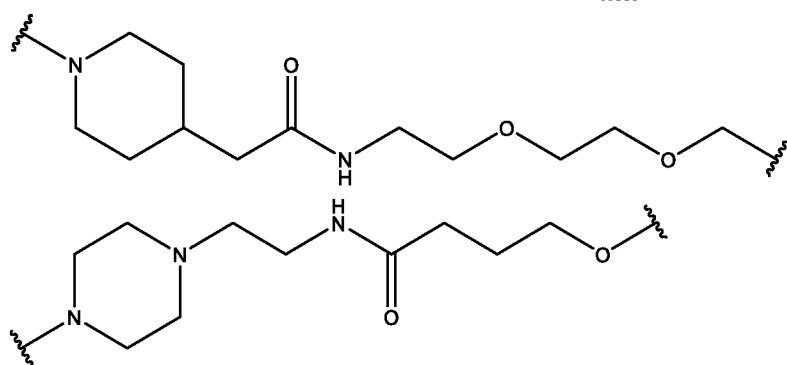
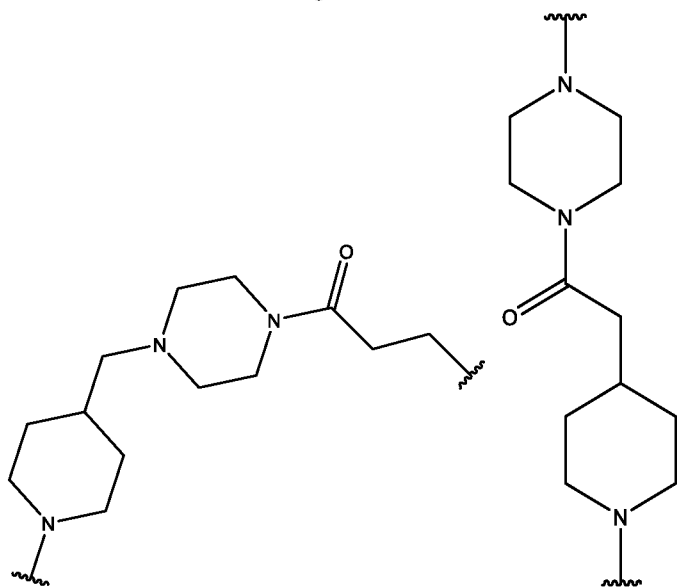
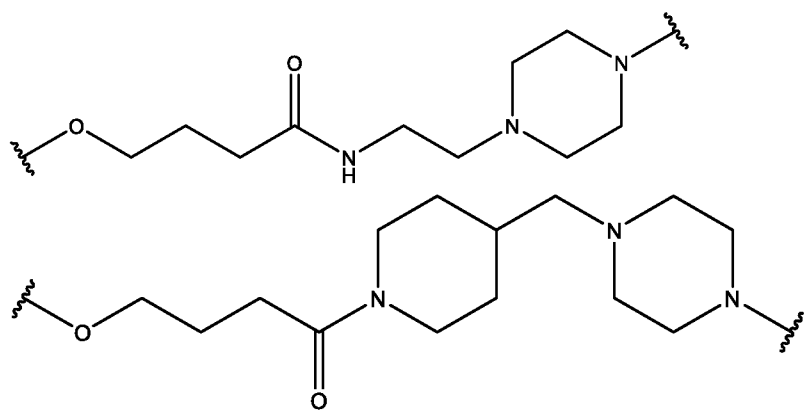




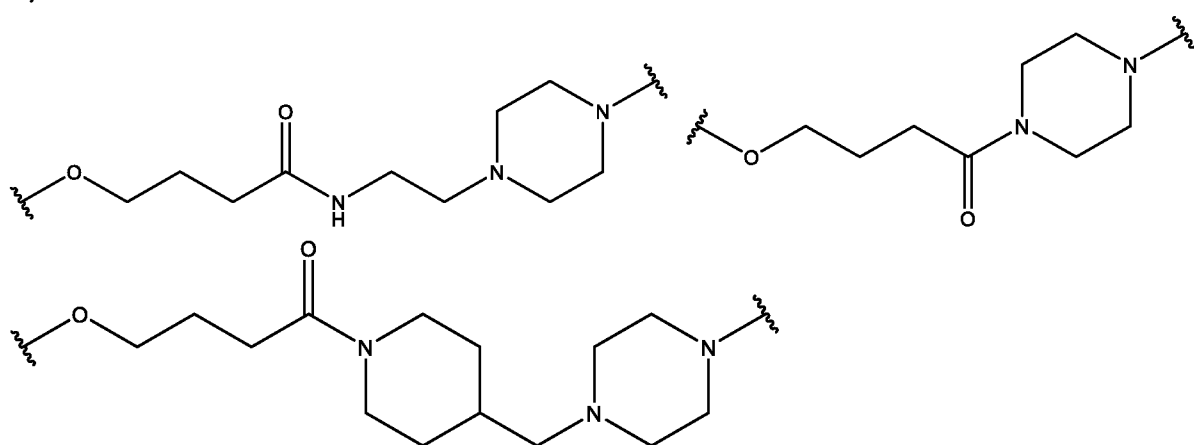
5 In particular examples, the linker is or comprises one or more of the following structures:



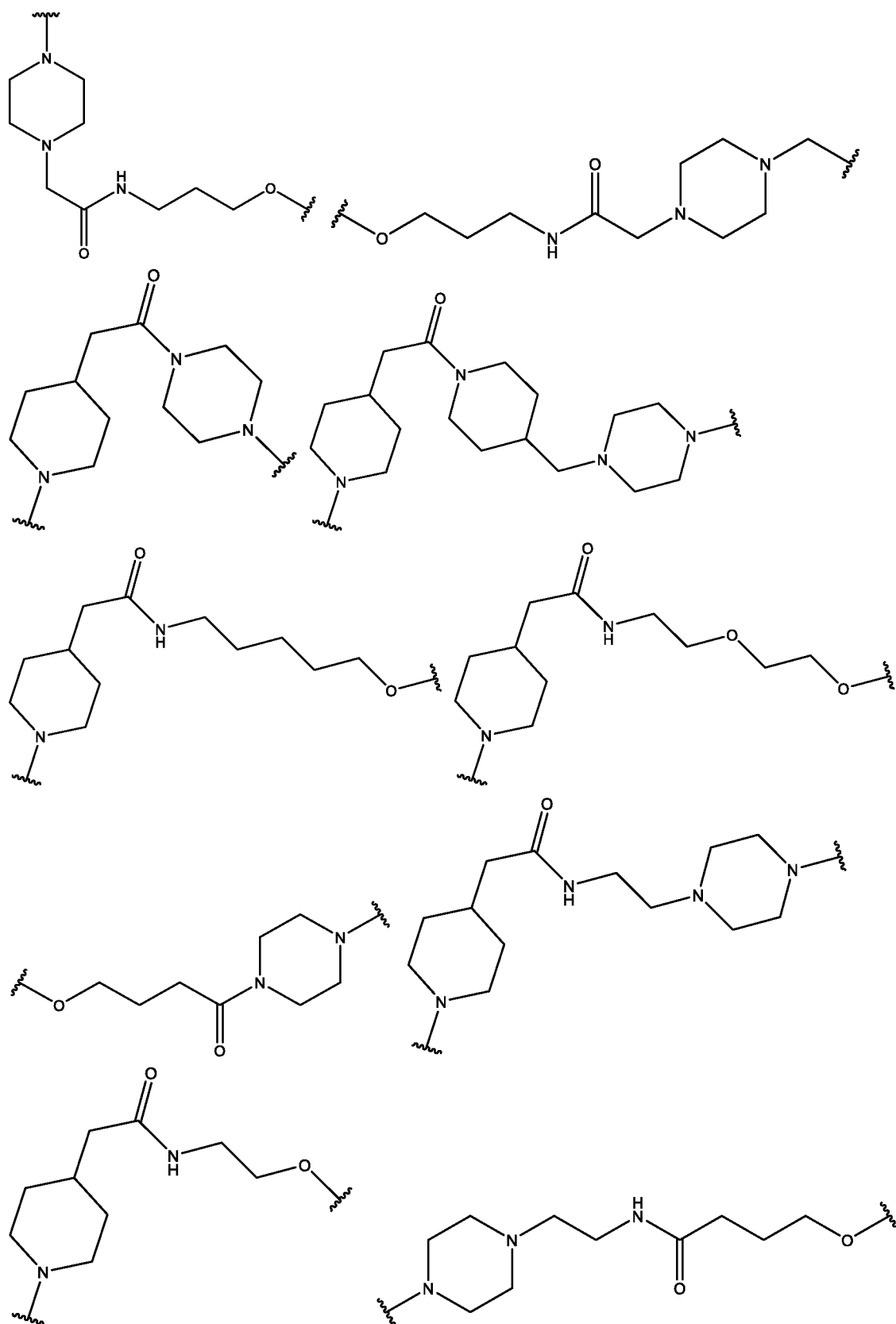


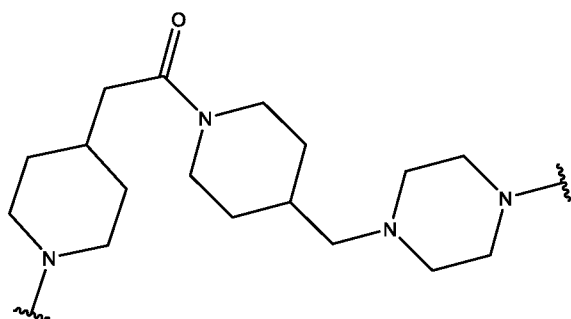
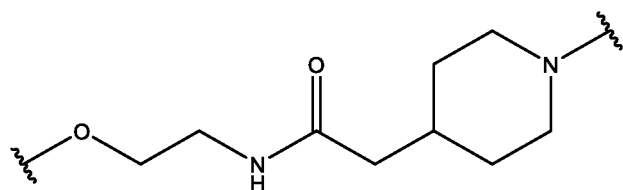
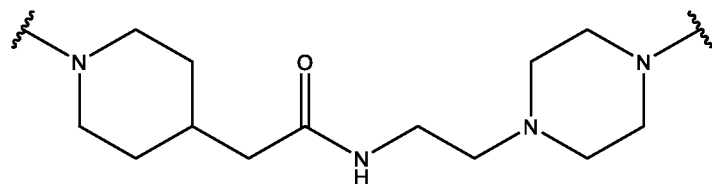
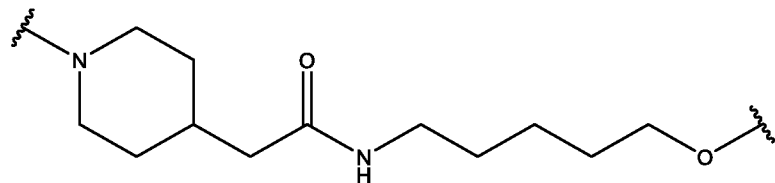
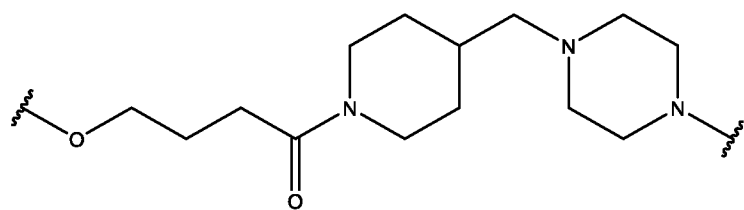


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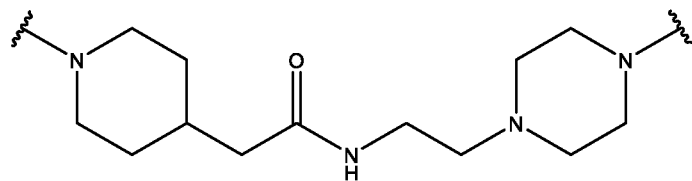
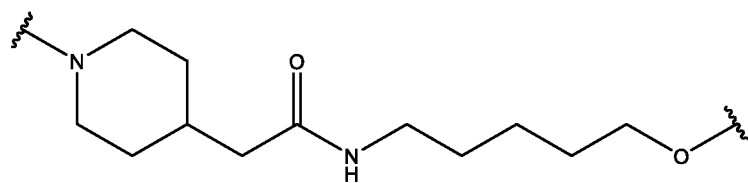
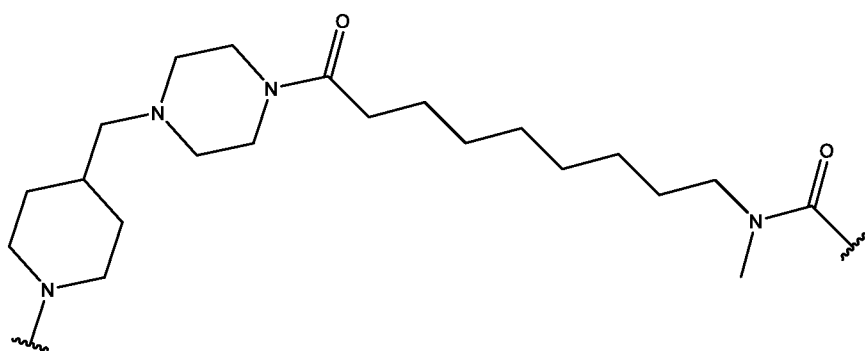




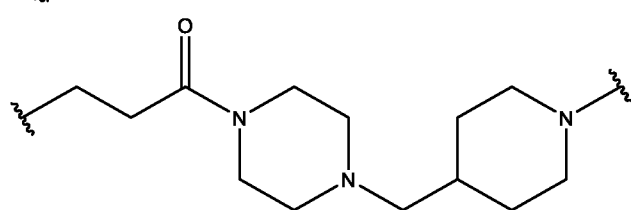
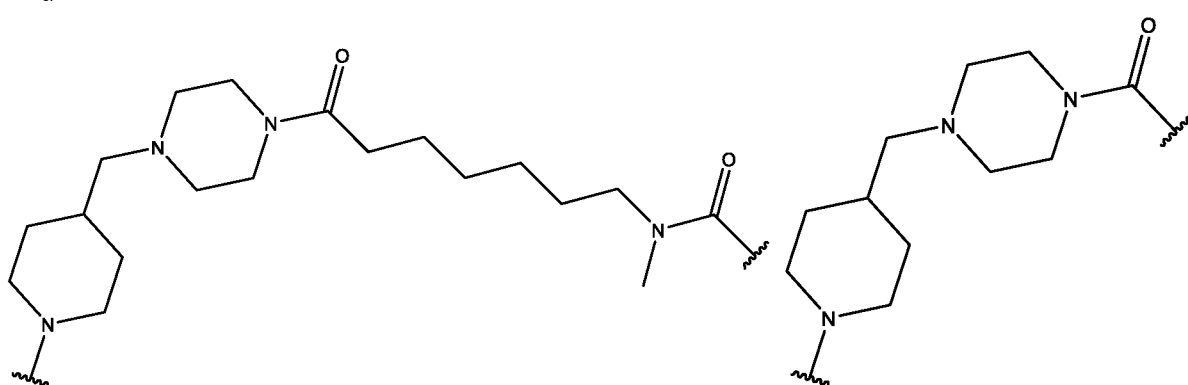
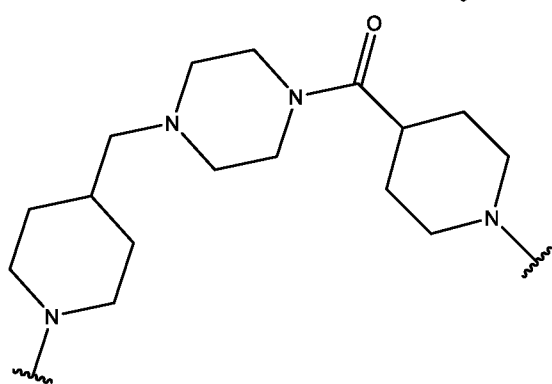
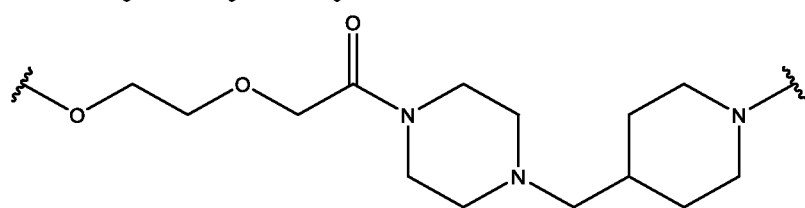
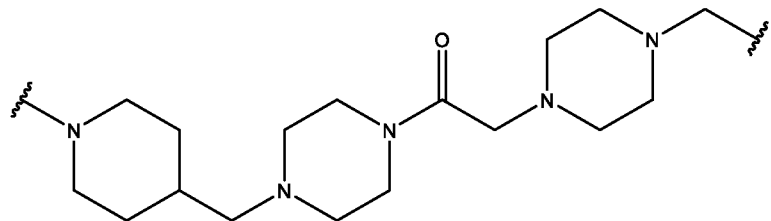
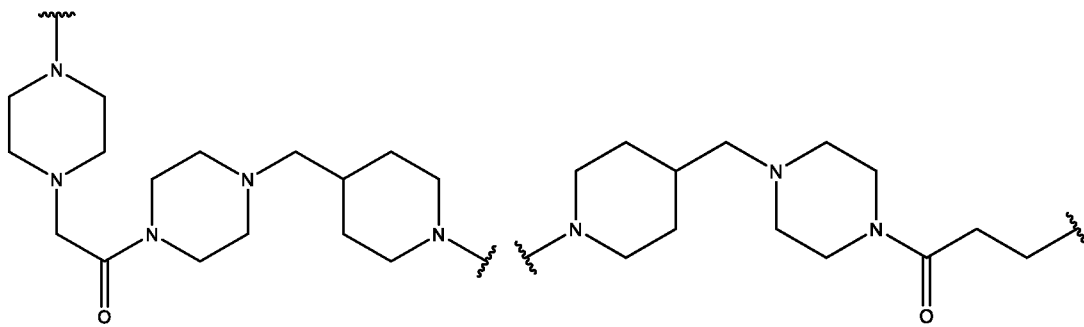


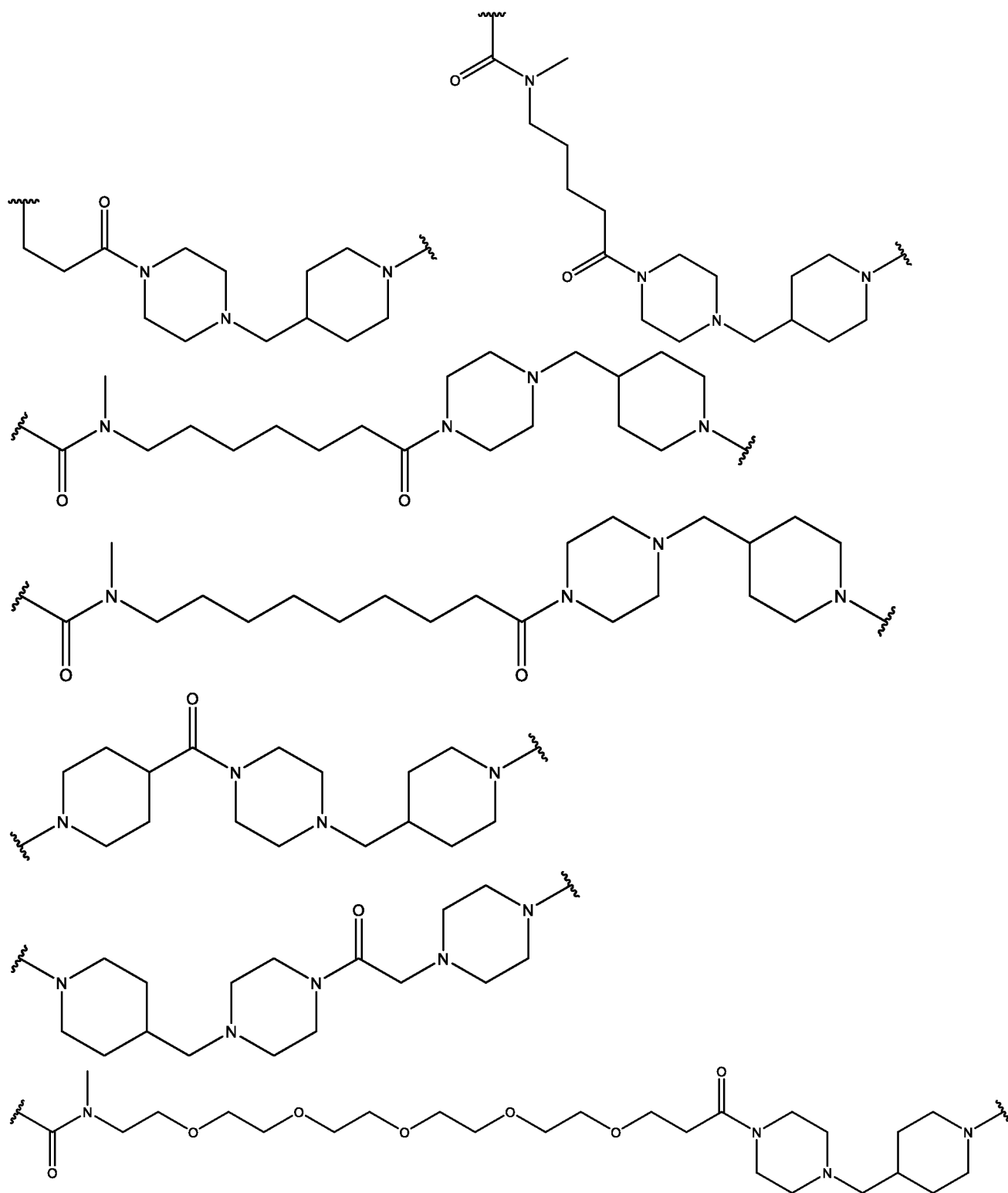


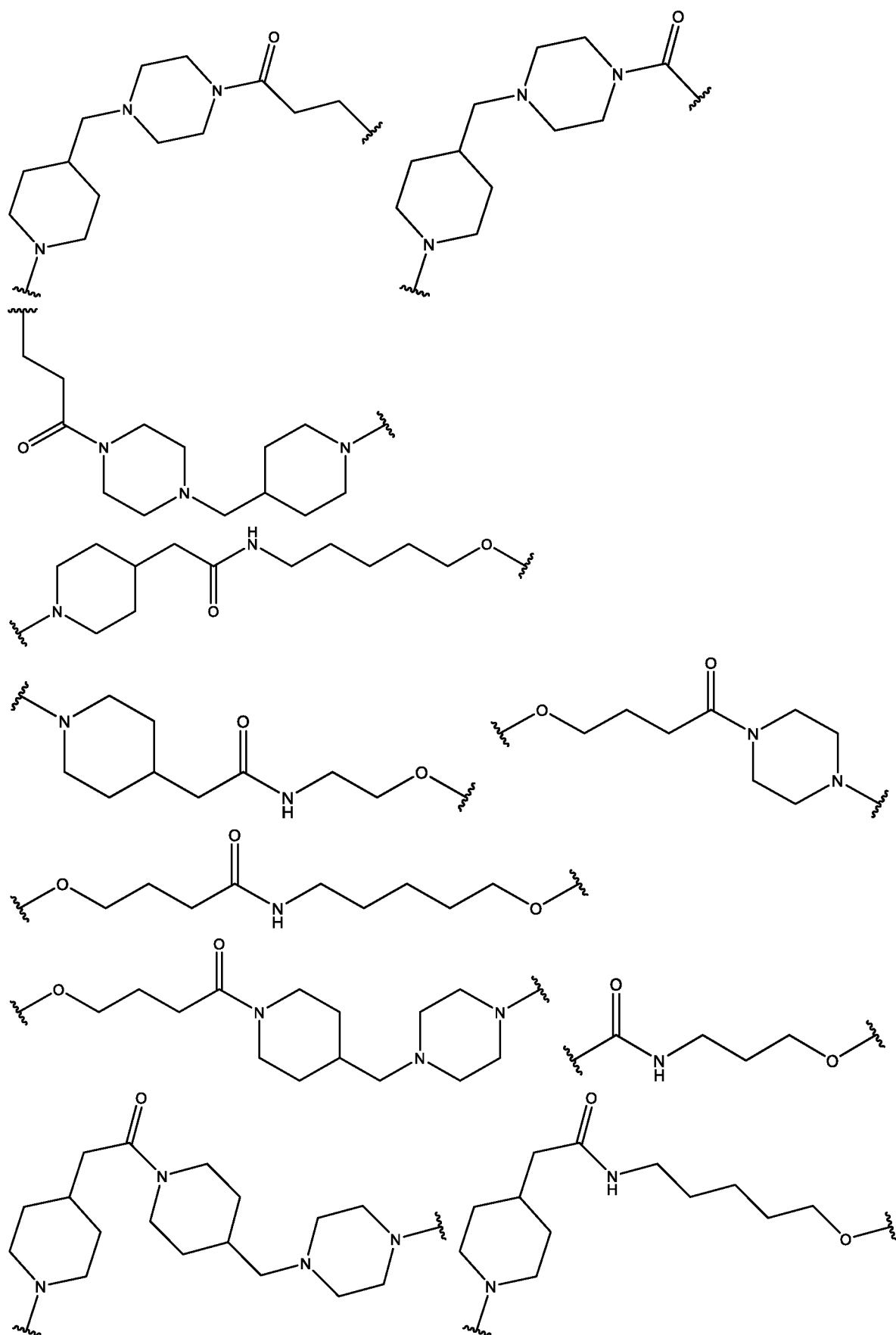
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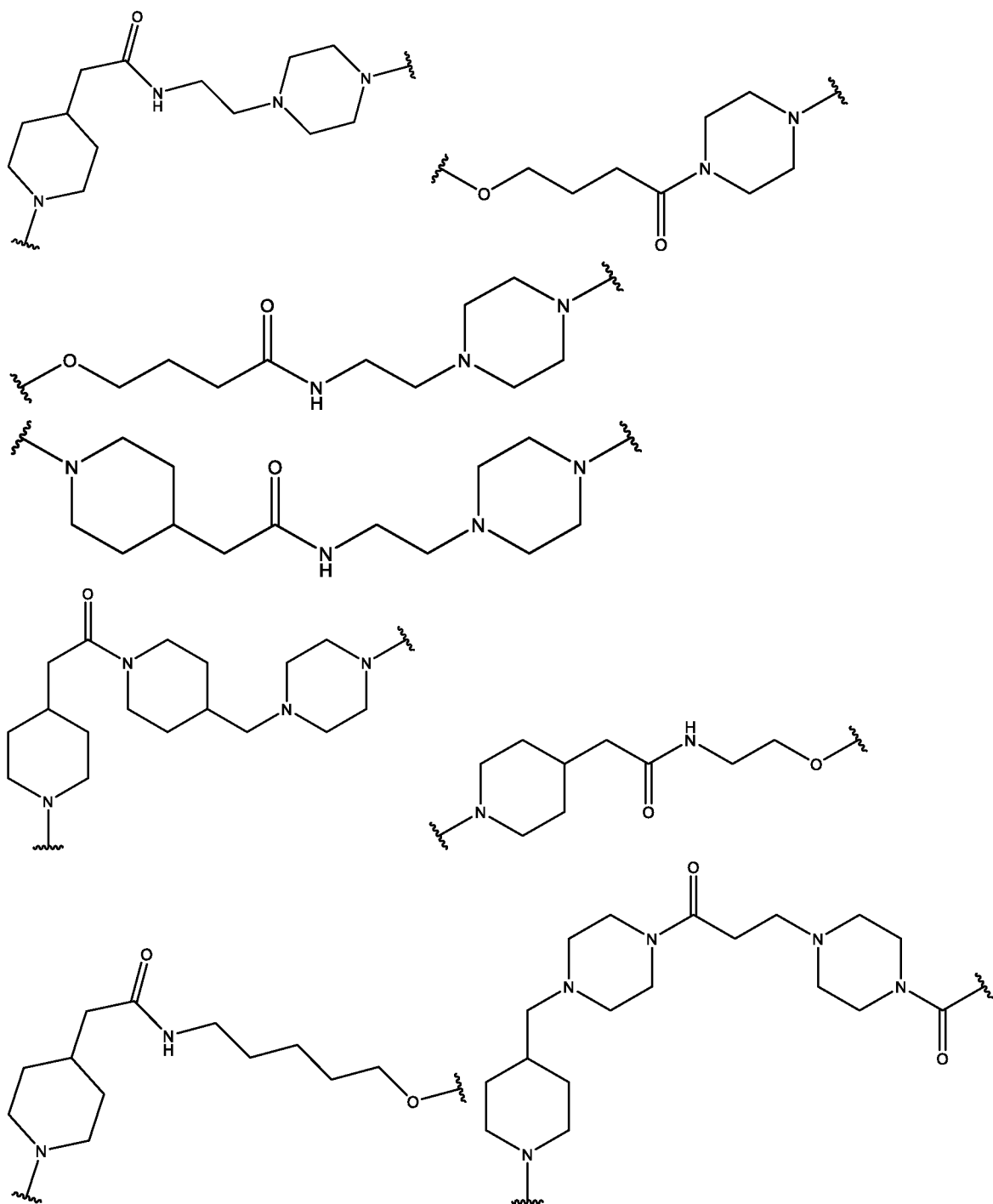




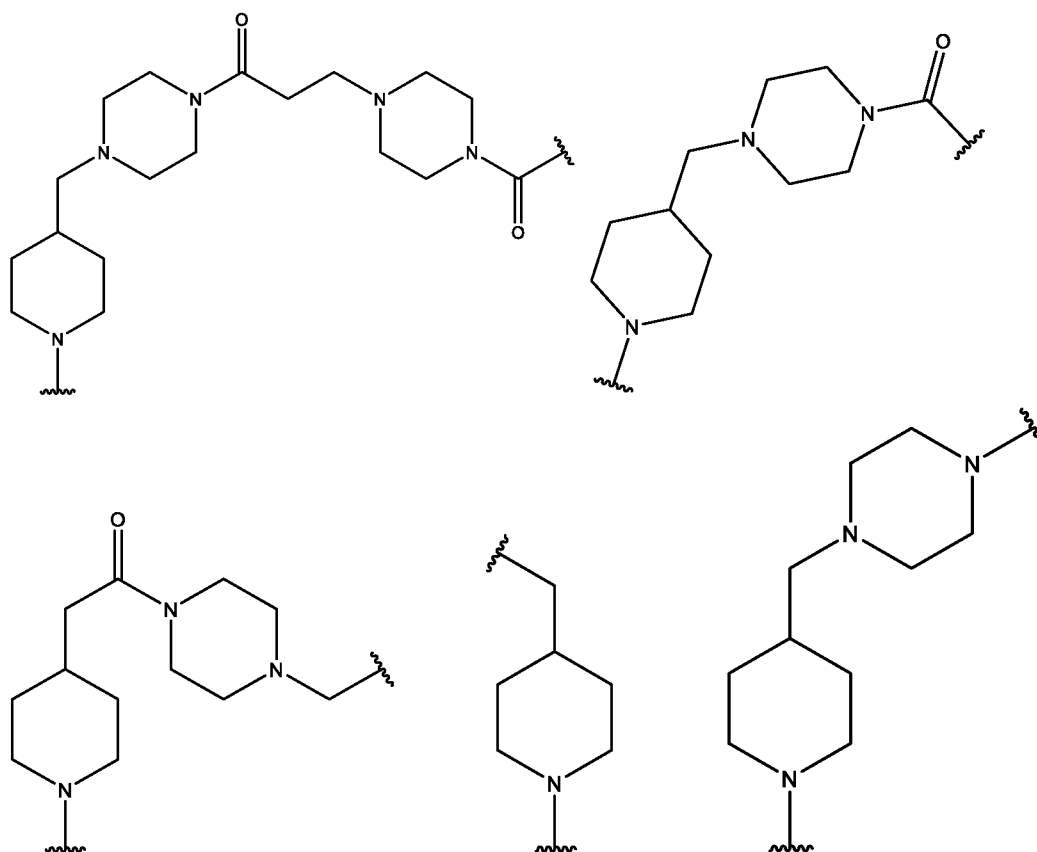








5



In some cases, the structures shown above represent the entire linker. In other examples, the linker of the bifunctional molecule 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 the TBL and Z moieties respectively.

In some examples, the bond(s) that forms the link with the TBL and/or Z moieties 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 TBL and Z moieties 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.

Target protein

As used herein, a "target protein" is: (i) an estrogen receptor; or (ii) an androgen receptor 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” is: (i) an estrogen receptor; or (ii) an androgen receptor that is selected by the skilled practitioner for increased proteolysis in a cell. The term “selected target protein” may be (i) an estrogen receptor; or (ii) an androgen receptor which has been selected to be targeted for protein degradation and/or increased proteolysis.

5

As used herein, “androgen receptor” means a protein with the UniProtKB designation of P10275 (ANDR_HUMAN).

As used herein, “estrogen receptor” means a protein with the UniProtKB designation of
10 P03372 (ESR1_HUMAN).

In other words, the bifunctional molecules disclosed herein are suitable for use and/or intended for use in the targeted degradation of a target protein selected from an: (i) estrogen receptor; and (ii) androgen receptor.

15

According to the disclosure, degradation of the target protein may occur when the target protein is subjected to and/or contacted with a bifunctional molecule as described herein, e.g. when the target protein is subjected to and/or contacted with any one of the bifunctional molecules in a cell.

20

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 bifunctional molecules described herein may provide treatment of a disease state or condition, which is modulated through or by the target protein
25 by lowering the level of that protein in the cells of a subject.

Target Protein Binding Ligand (TBL)

As stated above, the target protein binding ligand moiety is a target protein binding ligand
30 selected from an: (i) estrogen receptor binding ligand; and (ii) androgen receptor binding ligand. In particular, the target protein ligand comprised within the bifunctional molecules of the present disclosure is: (i) a ligand that selectively and/or specifically binds to an estrogen receptor; or (ii) is a ligand that selectively and/or specifically binds to an androgen receptor.

35 A bifunctional molecule according to this disclosure may comprise a target protein binding ligand, which binds to the target protein with sufficient binding affinity such that the target

protein (i.e. the estrogen receptor or androgen receptor) is more susceptible to degradation or proteolysis than if unbound by the bifunctional molecule.

The target protein binding ligand may bind to the androgen receptor or estrogen receptor 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 ligand may bind to the androgen receptor or estrogen receptor 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 target protein binding ligand binds to the target protein (i.e. the androgen receptor or estrogen receptor) to dissociate into separate components, i.e. the propensity of the target protein binding ligand to dissociate from the target protein.

The binding between the androgen receptor or the estrogen receptor and the target protein binding ligand 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 androgen receptor or the estrogen receptor and the target protein binding ligand may comprise a salt bridge (a combination of hydrogen and ionic bonding).

In particular, if the bifunctional molecules comprising an estrogen receptor binding ligand as described herein were to be contacted with an estrogen receptor, the observed DC_{50} values (for degradation of the estrogen receptor) would be less than about 1000 nM.

Additionally, if the bifunctional molecules comprising an androgen receptor binding ligand as described herein were to be contacted with an androgen receptor, the observed DC_{50} values (for degradation of the androgen receptor) would be less than about 1000 nM.

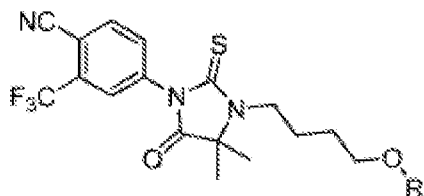
A target protein binding ligand may comprise or be derived from a small molecule (or analogue or fragment thereof) already known to act as a modulator, promoter and/or inhibitor of protein function (e.g. any small molecule known to bind to the estrogen receptor or androgen receptor). By way of example, the target protein binding ligand may comprise or be derived

from a small molecule that is known to inhibit activity of the estrogen receptor or androgen receptor.

Non-limiting examples of compounds known to bind to: (I) Androgen Receptor (AR); or (II)
5 Estrogen Receptor (ER) are described below.

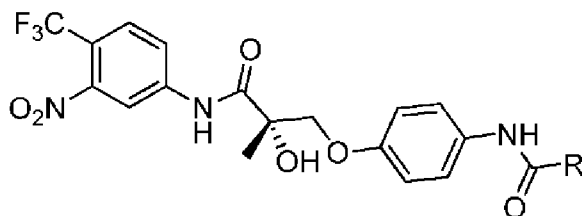
I. Compounds Targeting Androgen Receptor (AR)

1. RU59063 Ligand (derivatized) at Androgen Receptor



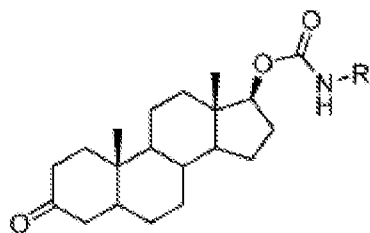
(Derivatized where "R" designates a site for linker attachment).

2. SARM Ligand (derivatized) of Androgen Receptor



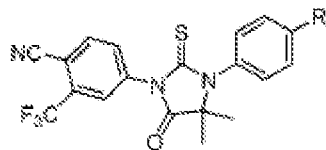
(Derivatized where "R" designates a site for linker attachment).

3. Androgen Receptor Ligand DHT (derivatized)

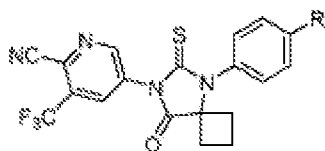


(Derivatized where "R" designates a site for linker attachment).

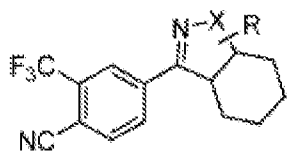
4. MDV3100 Ligand (derivatized)



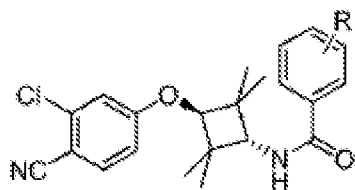
5. ARN-509 Ligand (derivatized)



6. Hexahydrobenzisoxazoles



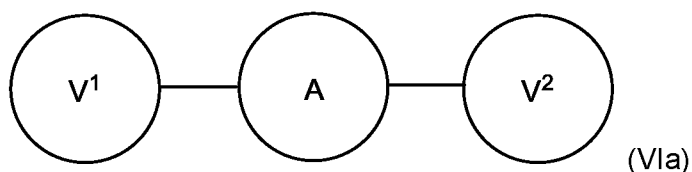
7. Tetramethylcyclobutanes



5

In the structures 1 to 7 above, R shows or indicates a site for linker attachment. However, the present disclosure also encompasses joining or coupling to the linker at any chemically suitable position on the various ligands.

10 In embodiments, the AR binder of the present disclosure is of formula VIa:

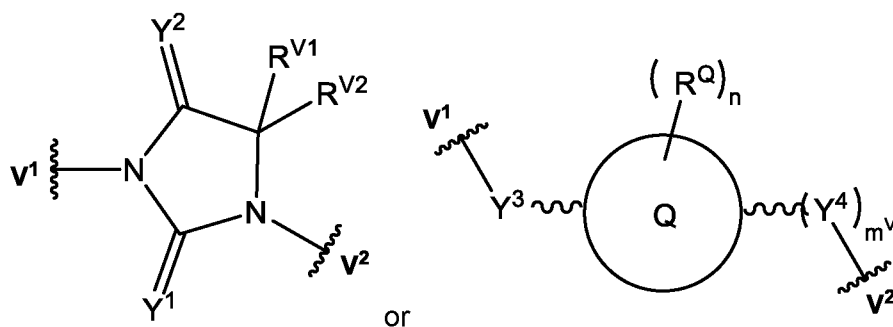


wherein:

15 V¹ is aryl or heteroaryl, wherein the aryl or heteroaryl is independently substituted by one or more R^{V1}, wherein each R^{V1} is independently selected from: halo; hydroxy; nitro; -CN; -C≡CH; C₁₋₆ alkyl optionally substituted by one or more halo; C₁₋₆ alkoxy optionally substituted by one or more halo, C₂₋₆ alkenyl, C₂₋₆ alkynyl;

V² is selected from: C₁₋₆ alkyl; C₁₋₈ cycloalkyl; heterocycloalkyl; aryl; or heteroaryl; each
20 optionally substituted by 1, 2 or 3 R^{V2}, wherein each R^{V2} is independently selected from: halo, C₁₋₆ alkyl optionally substituted by one or more halo; OC₁₋₃ alkyl optionally substituted by one or more halo, OH, NR^{Y1}R^{Y2}, CN, C₂₋₄ alkenyl C₂₋₄ alkynyl;

A is selected from:



wherein indicates the point of attachment to ring V¹, and indicates the point of attachment to ring V²; and

5 wherein:

Y¹ and Y² are each independently selected from NR^{Y1}, O and S;

R^{V1}, R^{V2} are each independently selected from: H, C₁₋₆ alkyl optionally substituted by one or more halo; or R^{V1} and R^{V2} taken together with the atom to which they are attached, form a 3-7-membered cycloalkyl ring containing 0-2 heteroatoms selected from N, O and S;

10 Y³ is selected from NR^{Y1}, O and S;

Y⁴ is selected from a bond, NR^{Y2}, CR^{Y3}R^{Y4}, O and S; -NR^{Y2}C=O-, -C=ONR^{Y2}-; -NR^{Y2}C=S-, -C=SNR^{Y2}-; S=O; SO₂; and C=O;

Q is a 3- to 7-membered cycloalkyl ring, wherein the cycloalkyl ring contains 0-4 heteroatoms selected from N, O or S;

15 each R^Q is independently selected from C₁₋₆ alkyl optionally substituted by one or more halo; or two R^Q groups taken together with the atom to which they are attached, form a 3-7-membered cycloalkyl ring containing 0-2 heteroatoms selected from N, O and S;

R^{Y1}, R^{Y2}, R^{Y3}, R^{Y4} are each independently selected from: H, C₁₋₆ alkyl optionally substituted by one or more halo;

20 n is 0, 1, 2, 3, 4, 5 or 6; and

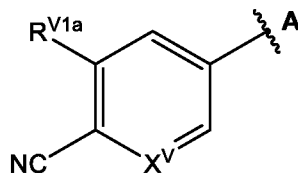
m is 0, 1, 2, 3, 4 or 5;

and

wherein the TBL is attached to the linker at any suitable position.

25 In some embodiments, the TBL is attached to the linker via covalent coupling to V².

In some embodiments, V¹ is:



wherein  indicates the point of attachment to ring A; and

R^{V1a} is selected from: halo; C_{1-4} alkyl optionally substituted with halo; $-OC_{1-4}$ alkyl

5 optionally substituted with halo;

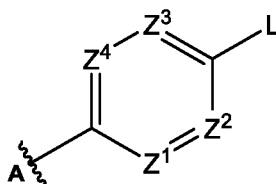
X^V is N, or CR^{V1b} , wherein R^{V1b} is selected from: H; halo; C_{1-4} alkyl optionally substituted with halo; $-OC_{1-4}$ alkyl optionally substituted with halo.

Suitably:

10 X^V is CH; and

R^{V1a} is selected from Cl and CF_3 .

In some embodiments, V^2 comprises:



15

wherein  indicates the point of attachment to ring A, and L indicates the point of attachment of the linker; and

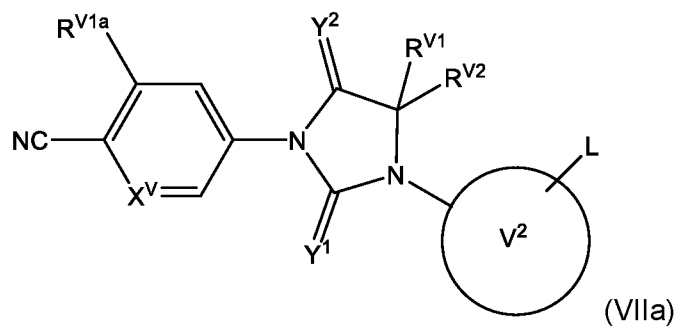
Z^1 , Z^2 , Z^3 and Z^4 are each independently selected from: N, or CR^{V2b} , wherein R^{V2b} is
20 selected from: H; halo; C_{1-4} alkyl optionally substituted with halo; $-OC_{1-4}$ alkyl optionally substituted with halo.

Suitably:

Z^1 is N, or CH; and

25 Z^2 , Z^3 and Z^4 are each CH.

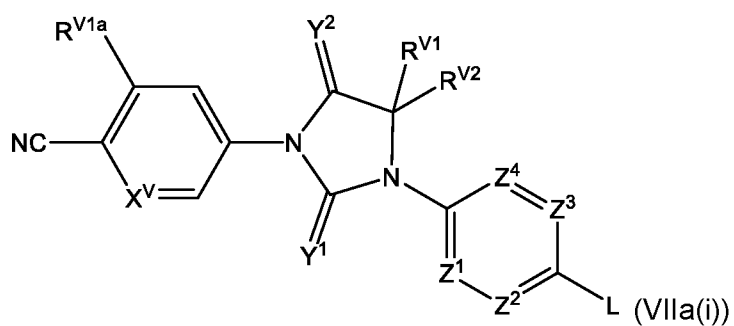
In some embodiments, the AR binder has the Formula VIIa:



wherein V^2 , X^V , Y^1 , Y^2 , R^{V1} , R^{V2} , R^{V1a} and L are as defined for formula VIa (and any sub-formula).

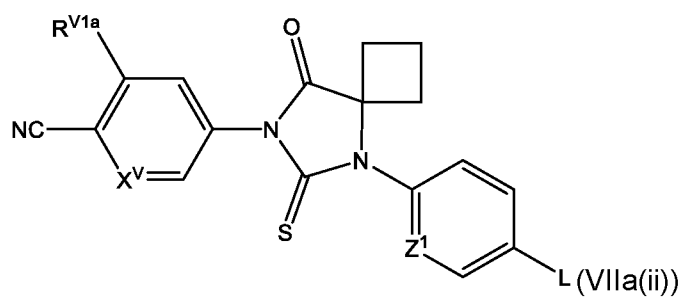
5

In some embodiments, the AR binder has the Formula VIIa(i):

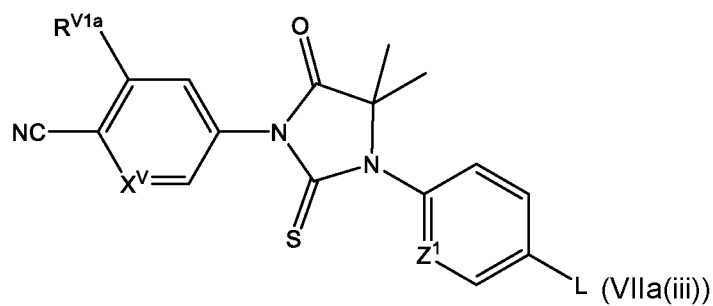


10 wherein X^V , Y^1 , Y^2 , R^{V1} , R^{V2} , R^{V1a} , Z^1 , Z^2 , Z^3 , Z^4 and L are as defined for formula VIa (and any sub-formula).

In some embodiments, the AR binder is of Formula VIIa(ii) or VIIa(iii):



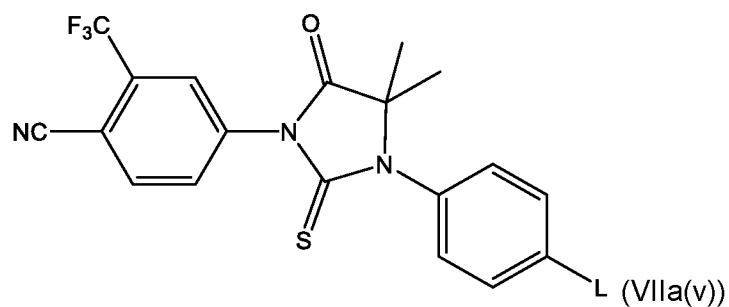
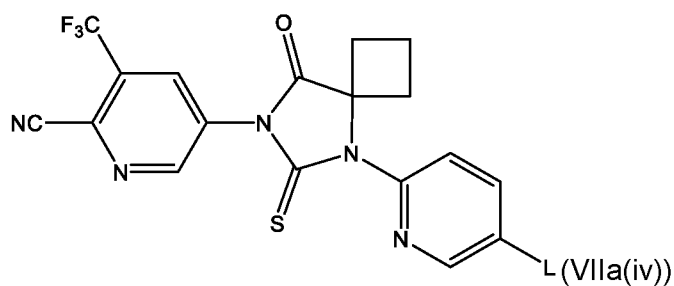
15



wherein X^V , R^{V1a} , Z^1 , Z^2 , Z^3 , Z^4 and L are as defined for formula VIa (and any sub-formula).

5

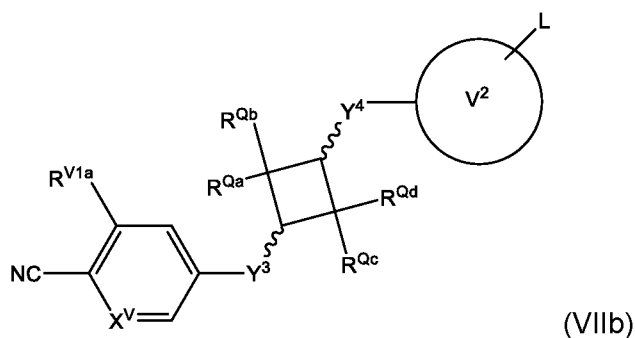
In some embodiments, the AR binder is of Formula VIIa(iv) or VIIa(v):



10

wherein L is as defined for formula VIa.

In some embodiments, the AR binder is of Formula VIIb:



15

wherein V^2 , X^V , Y^3 , Y^4 , R^{V1a} and L are as defined for formula VIa; and

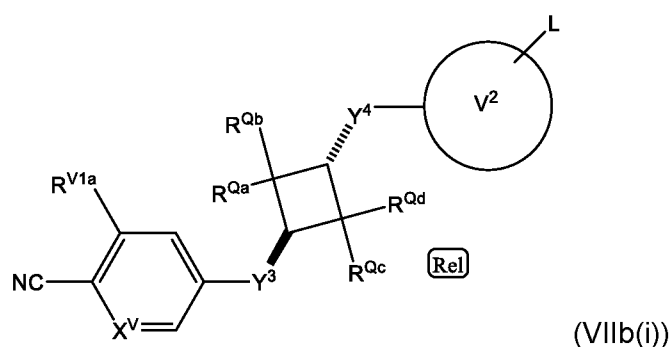
wherein:

R^{Qa} , R^{Qb} , R^{Qc} , R^{Qd} are each independently selected from C_{1-6} alkyl optionally

5 substituted by one or more halo; or

R^{Qa} and R^{Qb} , or R^{Qc} and R^{Qd} , taken together with the atom to which they are attached, form a 3-7-membered cycloalkyl ring containing 0-2 heteroatoms selected from N, O and S.

10 In some embodiments, the AR binder is of the Formula VIIb(i):



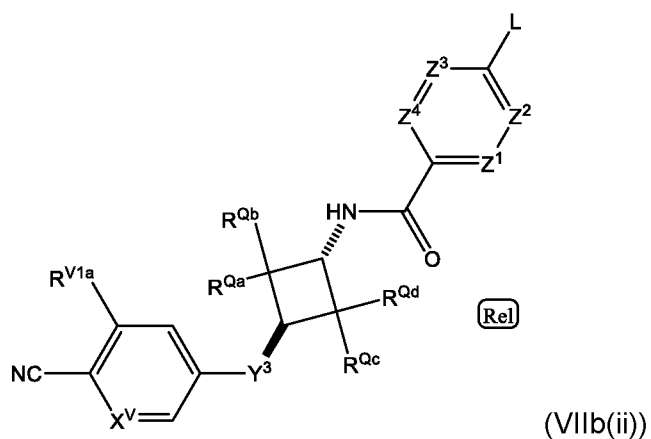
wherein X^V , Y^3 , R^{Qa} , R^{Qb} , R^{Qc} , R^{Qd} , R^{V1a} , Z^1 , Z^2 , Z^3 , Z^4 and L are as defined for formula

15 VIIb.

Here and throughout the symbol: Rel means the stereochemistry shown is relative and not absolute. As appropriate all specific enantiomers/diastereomers within such a definition are also explicitly encompassed.

20

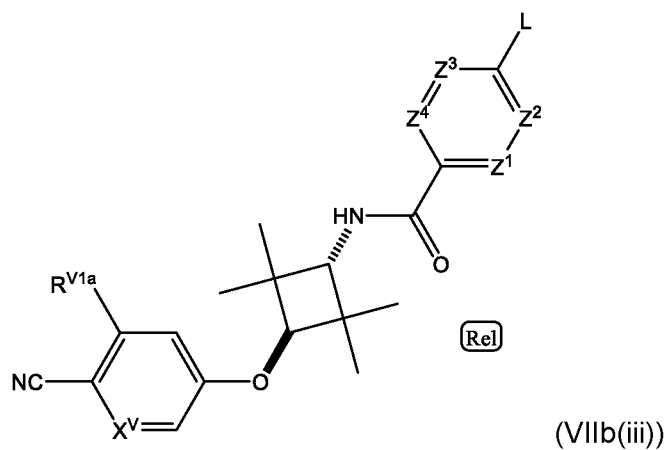
In some embodiments, the AR binder TBL is of Formula VIIb(ii):



wherein X^V , Y^3 , R^{Qa} , R^{Qb} , R^{Qc} , R^{Qd} , R^{V1a} , Z^1 , Z^2 , Z^3 , Z^4 and L are as defined for formula VIIb.

5

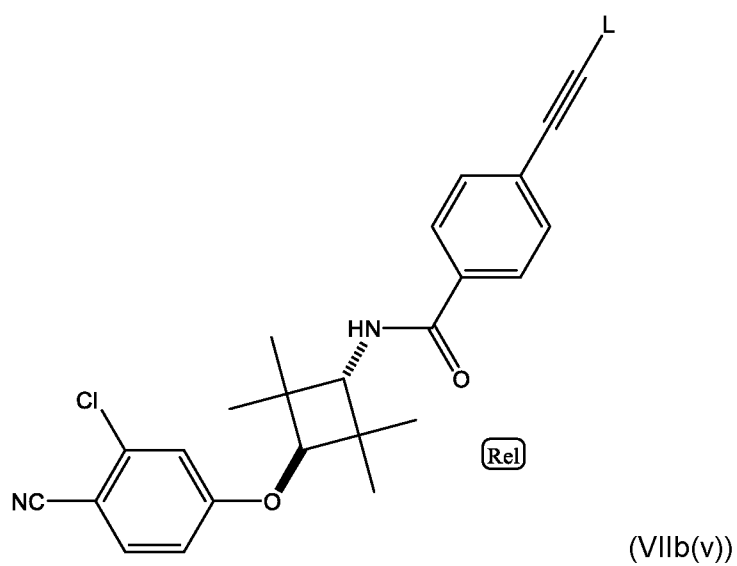
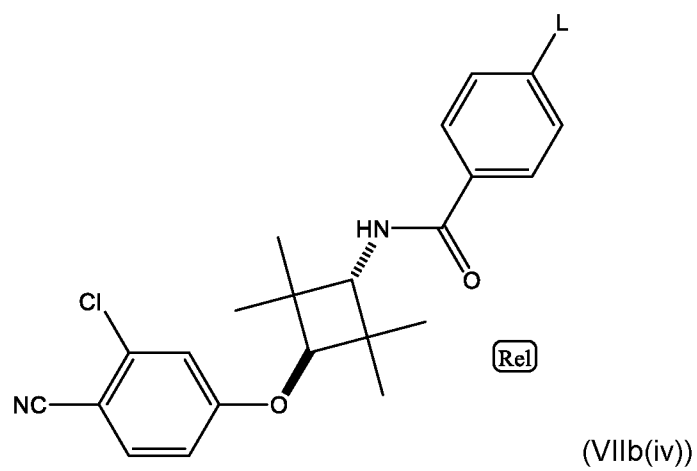
In some embodiments, the AR binder is of Formula VIIb(iii):



wherein X^V , Y^3 , R^{Qa} , R^{Qb} , R^{Qc} , R^{Qd} , R^{V1a} , Z^1 , Z^2 , Z^3 , Z^4 and L are as defined for formula VIIb.

10

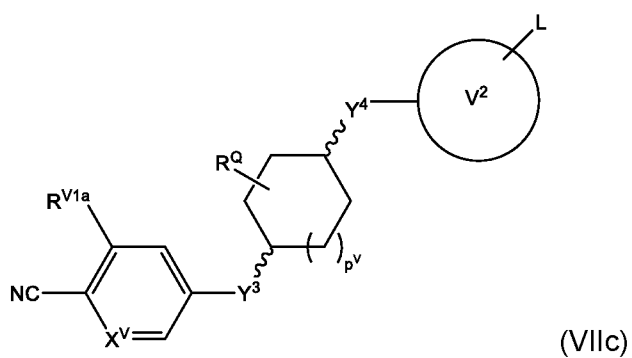
In some embodiments, the AR binder is of Formula VIIb(iv) or VIIb(v):



5

wherein L is as defined for formula VIIb.

In some embodiments, the AR binder is of Formula VIIc:

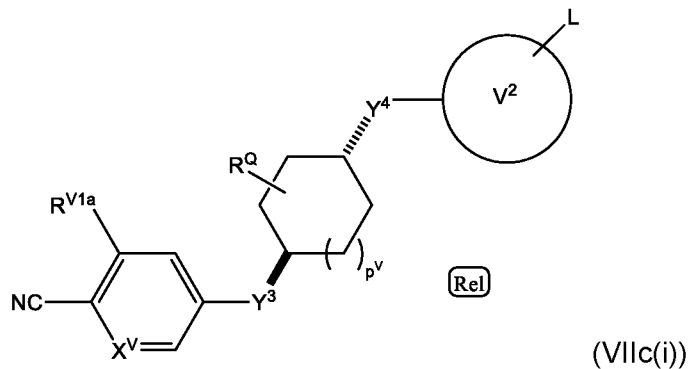


10

wherein X^V , V^2 , Y^3 , Y^4 , R^Q , R^{V1a} and L are as defined for formula VIIb; and

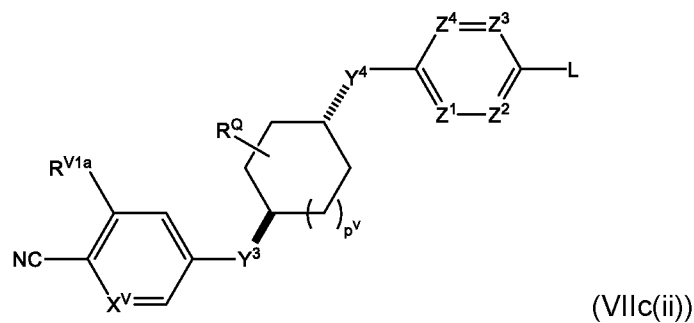
p^V is 0, 1 or 2.

In some embodiments, the AR binder is of Formula VIIc(i):



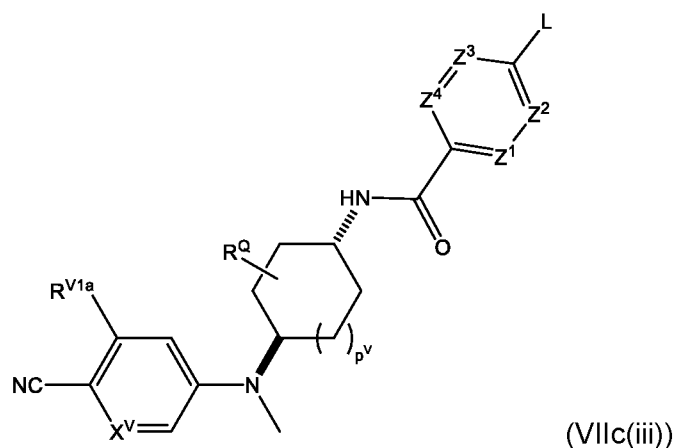
wherein X^V , V^2 , Y^3 , Y^4 , R^Q , R^{V1a} , p and L are as defined for formula VIIc.

In some embodiments, the AR binder is of Formula VIIc(ii):



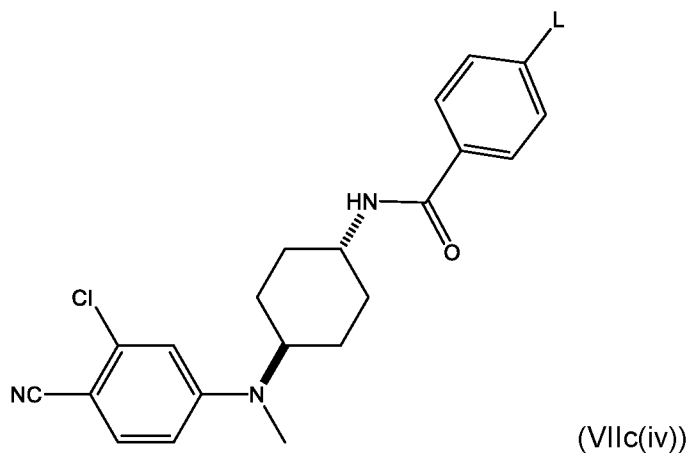
wherein X^V , Y^3 , Y^4 , R^Q , R^{V1a} , Z^1 , Z^2 , Z^3 , Z^4 , p^V and L are as defined for formula VIIc.

In some embodiments, the AR binder is of Formula VIIc(iii):



wherein X^V , R^Q , R^{V1a} , Z^1 , Z^2 , Z^3 , Z^4 , p^V and L are as defined for formula VIIc.

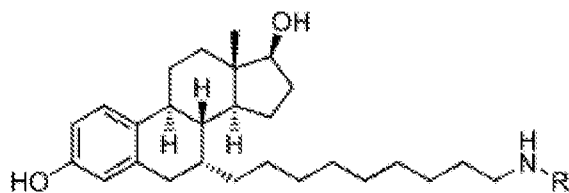
5 In some embodiments, the AR binder is of Formula VIIc(iv):



wherein L is as defined for formula VIIc.

10 II. Compounds Targeting Estrogen Receptor (ER) ICI-182780

1. Estrogen Receptor Ligand



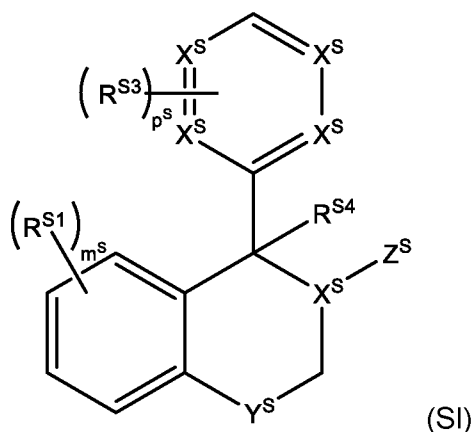
(Derivatized where "R" designates a site for linker attachment).

15 In the structure above, R shows or indicates a site for linker attachment. However, the present disclosure also encompasses joining or coupling the linker at any chemically suitable position on the various ligands.

In embodiments, the TBL or ER binder of the present disclosure has the structure of:

(a) Formula (SI):

5



wherein:

each X^S is independently selected from CH and N;

10

Y^S is CH_2 or NR_4 ;

Z^S is selected from C_{6-10} aryl; a 5- or 6- membered heteroaryl; C_{3-8} cycloalkyl; C_{5-8} cycloalkenyl; a 5- or 6- membered heterocycloalkyl containing up to two heteroatoms selected from the group consisting of -O-, $-(NR^{S5})_2$ -, $-S(O)-$ and $S(O)_2$; a bicyclic ring system consisting of a five or six membered alkyl or heterocycloalkyl ring fused to an aryl ring, the heterocyclic ring containing up to two heteroatoms selected from the group consisting of -O-, $-(NR^{S5})_2$ -, $-S(O)-$ and $S(O)_2$; wherein Z is optionally substituted with $(R^{S2})_n^S$;

15

each R^{S1} is independently selected from OH, $-O-C_{1-4}$ alkyl, $-O-C_{1-4}$ haloalkyl, halogen, $O(CO)R^{S6}$;

each R^{S2} is independently selected from halogen, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, C_{3-7} cyclohaloalkyl, OH, $-O-C_{1-4}$ alkyl, NH_2 , $-NR^{S5}-C_{1-4}$ alkyl, $-O-C_{1-4}$ haloalkyl, $-NR^{S5}-C_{1-4}$ haloalkyl, $-O-C_{3-7}$ cycloalkyl, $-NR^{S5}-C_{3-7}$ cycloalkyl;

20

each R^{S3} is independently selected from halogen, C_{1-4} alkyl, C_{1-4} haloalkyl;

R^{S4} is H, C_{1-4} alkyl, C_{1-4} haloalkyl;

each R^{S5} is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, C_{3-7} cyclohaloalkyl;

25

R^{S6} is selected from C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, heteroaryl;

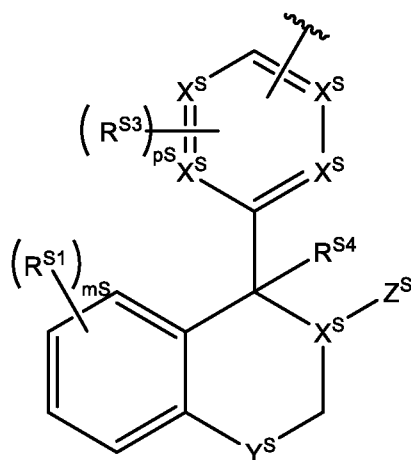
m^S is 0, 1, 2 or 3;

n^S is 0, 1, 2 or 3;

p^S is 0, 1, 2 or 3

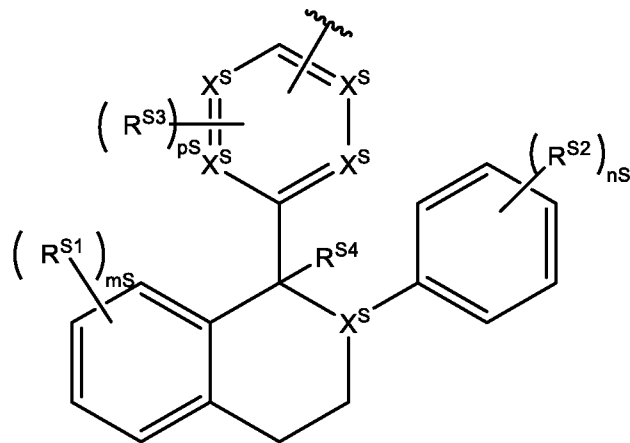
wherein the TBL is attached to the linker at any suitable position.

In embodiments of Formula (SI) above, the linker may be attached to the top aryl group. In other words, the linker (L) may substitute an H on the top aryl group, i.e. the TBL has the structure:



wherein  indicates the point of attachment of the linker.

In embodiments, the TBL is of formula SII:



(SII)

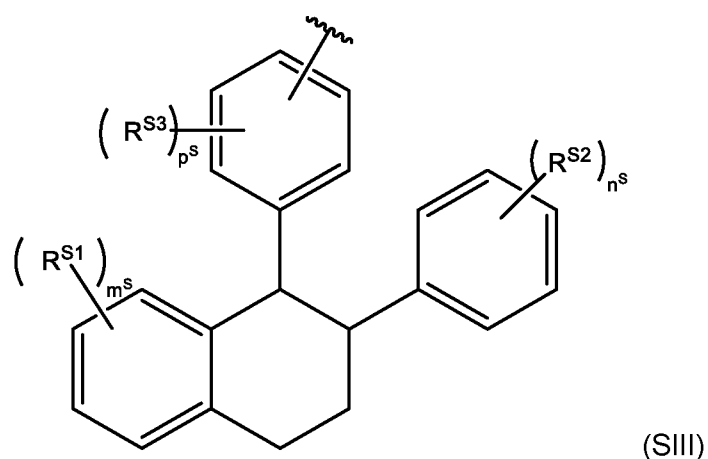
wherein:

X, R^{S1} , R^{S2} , R^{S3} , R^{S4} , R^{S5} , R^{S6} , m^S , n^S and p^S are as defined in Formula (SI);

wherein  indicates the point of attachment of the linker.

In embodiments of Formula (SI) or (SII), each X^S is CH.

As described above, in embodiments, the TBL is of formula SIII:



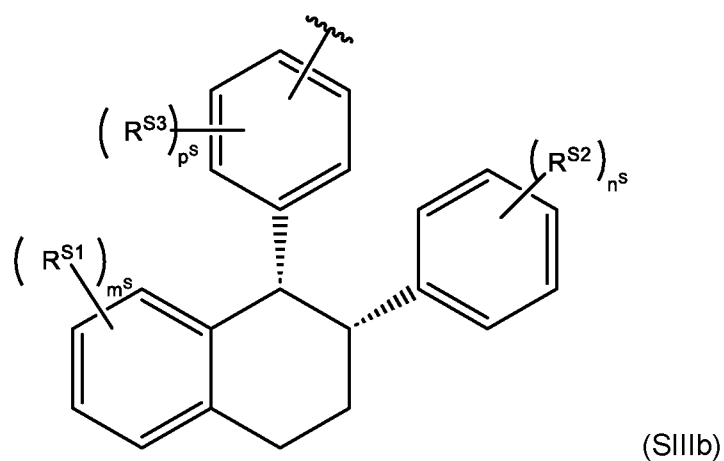
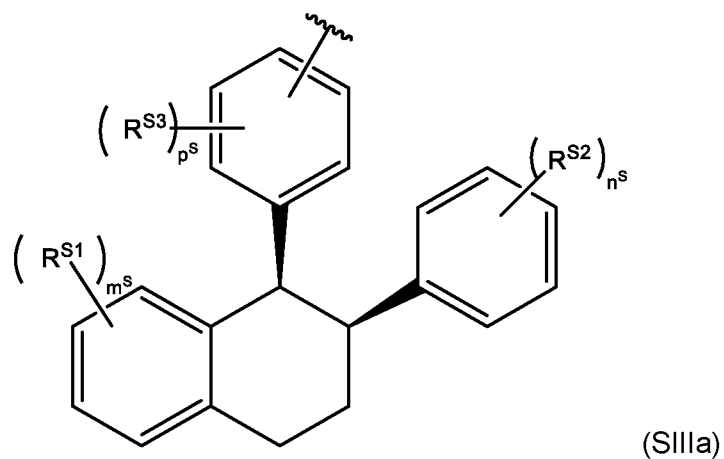
wherein:

R^{S1} , R^{S2} , R^{S3} , m^S , n^S and p^S are as defined in Formula (SI) or Formula (SII);

wherein indicates the point of attachment of the linker.

5

In embodiments, the TBL is of Formula SIIIa or SIIIb:



wherein:

10 R^{S1} , R^{S2} , R^{S3} , m^S , n^S and p^S are as defined in Formula (SI) or Formula (SII) or Formula (SIII);

wherein  indicates the point of attachment of the linker.

Suitably, the TBL is of Formula SIIIa.

5 In embodiments of Formula (SI), (SII) or (SIII), R^{S1} is OH.

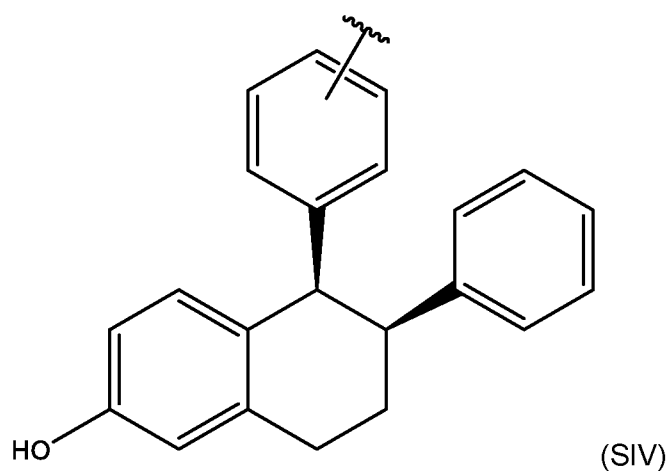
In embodiments of Formula (SI), (SII) or (SIII), m^S is 1.

In embodiments of Formula (SI), (SII) or (SIII), n^S is 0.

10

In embodiments of Formula (SI), (SII) or (SIII), p^S is 0.

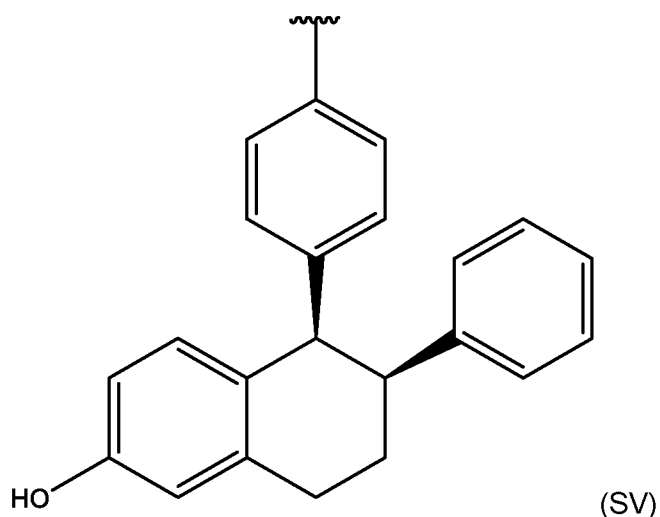
In embodiments, the TBL is of Formula SIV:



15

wherein  indicates the point of attachment of the linker.

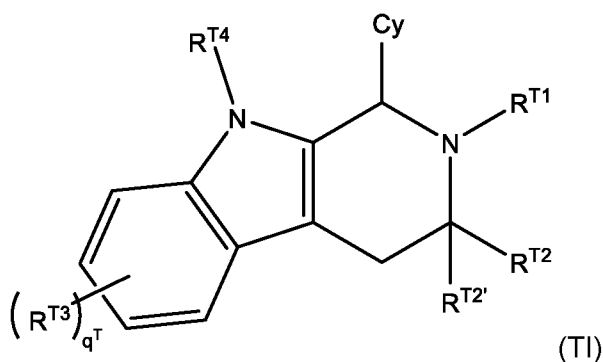
Suitably, the TBL is of Formula SV:



wherein indicates the point of attachment of the linker.

5 or,

(b) Formula T(I);



10 wherein:

Cy is selected from C₆₋₁₀ aryl; a 5- or 6-membered heteroaryl; C₃₋₇ cycloalkyl; a 5- or 6-membered heterocycloalkyl; wherein Cy is optionally substituted with 1-3 substituents independently selected from halogen, CN, OR^{Ta}, N(R^{Ta})₂, C₁₋₉ alkyl, C₃₋₇ cycloalkyl, 5- or 6-membered heterocycloalkyl, C₆₋₁₀ aryl, a 5- or 6-membered heteroaryl, C(O)R^{Ta}, C(O)NR^{Ta}, SO₂R^{Ta}, and SO₂NR^{Ta};

R^{T1} is selected from H, C₁₋₉ alkyl, C₁₋₉ haloalkyl; C₃₋₇ cycloalkyl, C₃₋₇ cyclohaloalkyl; a 5- or 6-membered heterocycloalkyl, C₆₋₁₀ aryl, a 5- or 6-membered heteroaryl, -(C₁₋₆ alkyl)-(C₃₋₇ cycloalkyl), -(C₁₋₆ alkyl)-(a 5- or 6-membered heterocycloalkyl), C(O)R^{Tb}, C(O)NR^{Ta}, SO₂R^{Ta}, and SO₂NR^{Ta}, wherein when R^{T1} is not H, R^{T1} is optionally substituted with 1-3 substituents

independently selected from halogen, CN, OR^a, N(R^a)₂, C₁₋₉ alkyl, C₃₋₇ cycloalkyl, 5- or 6-membered heterocyloalkyl, C₆₋₁₀ aryl, a 5- or 6-membered heteroaryl, C(O)R^{Ta}, C(O)NR^{Ta}, SO₂R^{Ta}, and SO₂NR^{Ta};

R^{Ta} is selected from H, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, and a 5- or 6-membered heterocyloalkyl, wherein R^{Ta} is optionally substituted with 1-3 substituents independently selected from halogen, CN, OH, OC₁₋₆ alkyl, and SO₂-C₁₋₆ alkyl;

R^{Tb} is independently selected from H, -OR^{Ta}, C₁₋₆ alkyl, -(C₁₋₆ alkyl)-(C₃₋₇ cycloalkyl), C₃₋₇ cycloalkyl, and 5- or 6-membered heterocyloalkyl, wherein R^{Tb} is optionally substituted with 1-3 substituents independently selected from halogen, CN, C₁₋₆ haloalkyl, OH, OC₁₋₆ alkyl, and SO₂-C₁₋₆ alkyl;

R^{T2} and R^{T2'} are independently selected from H, halogen, -CN, C₁₋₆ alkyl, -OR^{Ta}, -C₁₋₆ alkyl-OH, -C₁₋₆ alkyl-OR^{Ta}, -C₁₋₆ alkyl-SO₂-C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ cycloalkyl, 5- or 6-membered heterocyloalkyl, -N(R^{Ta})₂, -C₁₋₆ alkyl-NR^{Ta}-C₁₋₆ alkyl, -C₁₋₆ alkyl-NH₂, -C₁₋₆ alkyl-NHSO₂-C₁₋₆ alkyl, -C₁₋₆ alkyl-CN, -CO₂H, -COR^{Ta}, -CO₂R^{Ta}, -CON(R^{Ta})₂, -C₁₋₆ alkyl-CONH₂, -NR^{Ta}CO-C₁₋₆ alkyl, -NR^{Ta}S(O)₂-C₁₋₆ alkyl, -S(O)₂N(R^{Ta})₂;

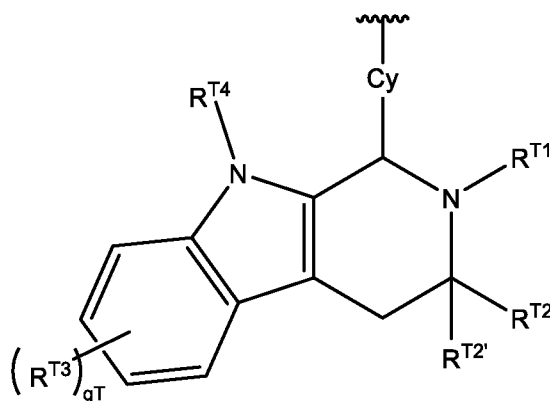
R^{T3} is selected from halogen, -CN, C₁₋₆ alkyl, CH₂OH, -C₁₋₆ alkyl-OR^{Ta}, -C₁₋₆ alkyl-SO₂-C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, C₃₋₇ cyclohaloalkyl, 5- or 6-membered heterocyloalkyl, -C₁₋₆ alkyl-NR^{Ta}-C₁₋₆ alkyl, -C₁₋₆ alkyl-NHSO₂-C₁₋₆ alkyl, -C₁₋₆ alkyl-CN, -CO₂H, -CO-C₁₋₆ alkyl, -CO₂-C₁₋₆ alkyl, -CON(R^{Ta})₂, -C₁₋₆ alkyl-CONH₂, -N(R^{Ta})₂, -NR^{Ta}CO-C₁₋₆ alkyl, -NR^{Ta}S(O)₂-C₁₋₆ alkyl;

R^{T4} is selected from H, C₁₋₃ alkyl, C₁₋₃ haloalkyl; and

q^T is 0, 1, 2 or 3;

wherein  indicates the point of attachment of the linker.

In embodiments of Formula (TI) above, the linker may be attached to the top aryl group. In other words, the linker (L) may substitute an H on the top aryl group, i.e. the TBL has the structure:

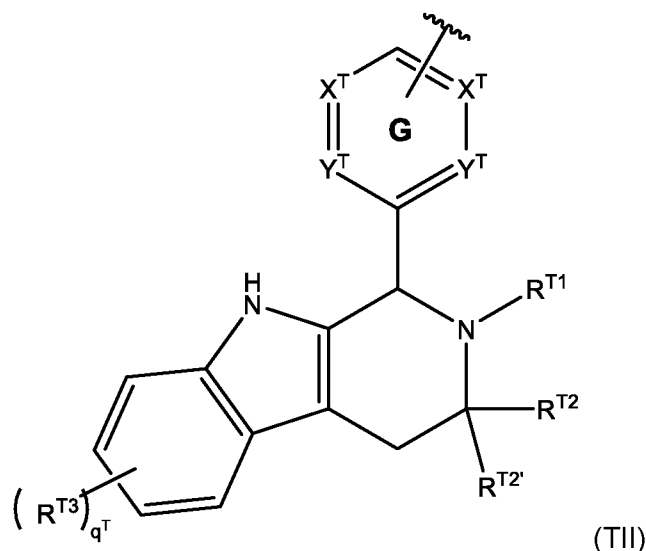


wherein  indicates the point of attachment of the linker.

In some embodiments of Formula (TI), Cy is C₆₋₁₀ aryl; a 5- or 6-membered heteroaryl.

5 In some embodiments of Formula (TI), R^{T4} is H.

In some embodiments, the TBL is of Formula TII:



10 wherein:

R^{T1}, R^{T2}, R^{T2'}, R^{T3} and q^T are as defined for Formula TI; and

Ring G is aryl or heteroaryl;

X^T is CH or N;

Y^T is CR^{Tc} or N, wherein R^{Tc} is halogen or C₁₋₃ alkyl;

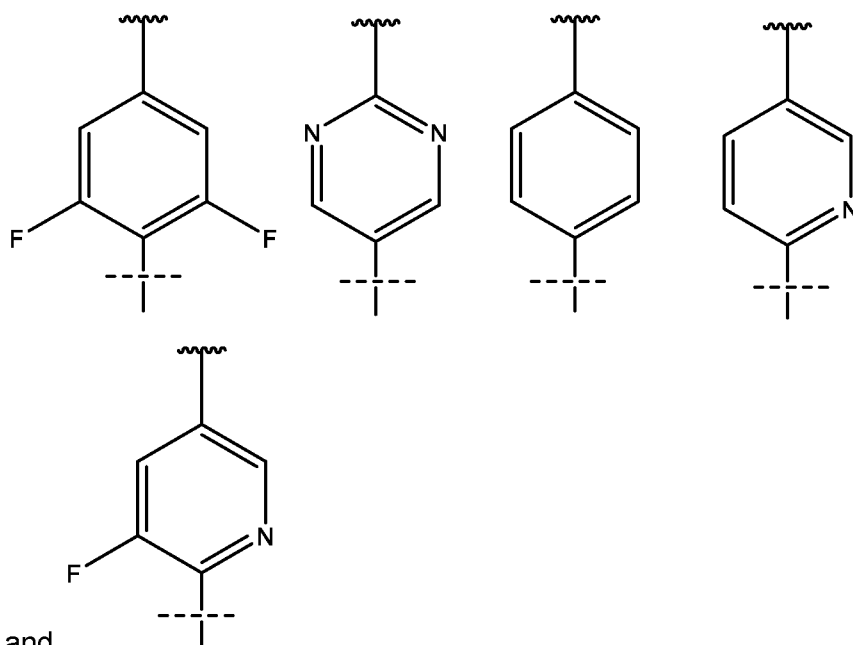
15 wherein  indicates the point of attachment of the linker.

In embodiments of Formula (TI) or (TII), each X^T is N and each Y^T is CH.

In embodiments of Formula (TI) or (TII), each X^T is CH and each Y^T is CR^{Tc}.

20

In embodiments, ring G is selected from:

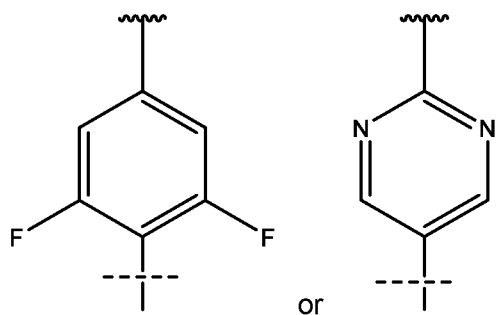


wherein  indicates the point of attachment of the linker; and

wherein  indicates the point of attachment to the remainder of the TBL structure.

5

Suitably, ring G is:



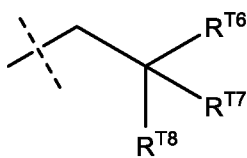
wherein  indicates the point of attachment of the linker; and

wherein  indicates the point of attachment to the remainder of the TBL structure.

10

In embodiments of Formula (TI) or (TII), R^{T2} is C_{1-6} alkyl and $R^{T2'}$ is H. Suitably, R^{T2} is Me and $R^{T2'}$ is H.

In embodiments of Formula (TI) or (TII), R^{T1} is

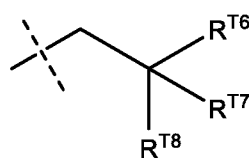


wherein:

R^{T6} and R^{T7} are each independently selected from H, Me or F, or R^{T6} and R^{T7} taken together with the carbon atom to which they are attached form a cyclopropyl ring or an oxetanyl ring;

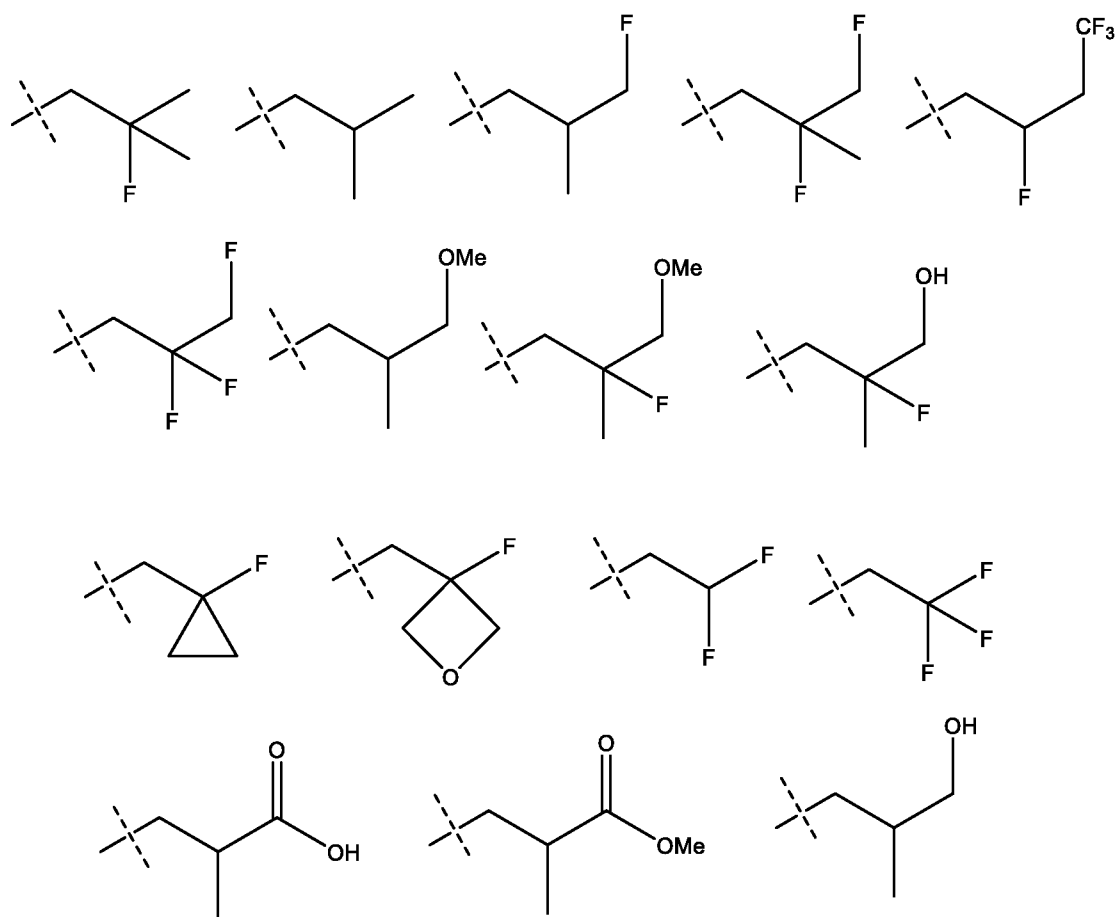
R^{T8} is selected from H, Me, F, CH_2F , CHF_2 , CF_3 , CN, CH_2CN , CH_2OMe , CH_2OH ,
 5 CO_2H , CO_2Me or SO_2Me ; and

wherein  indicates the point of attachment to the remainder of the TBL structure.



In embodiments of Formula (TI) or (TII), when R^{T1} is
 10 selected from:

R^{T1} has a structure



wherein  indicates the point of attachment to the remainder of the TBL structure.

15 In embodiments of Formula (TI) or (TII), R^{T6} is Me.

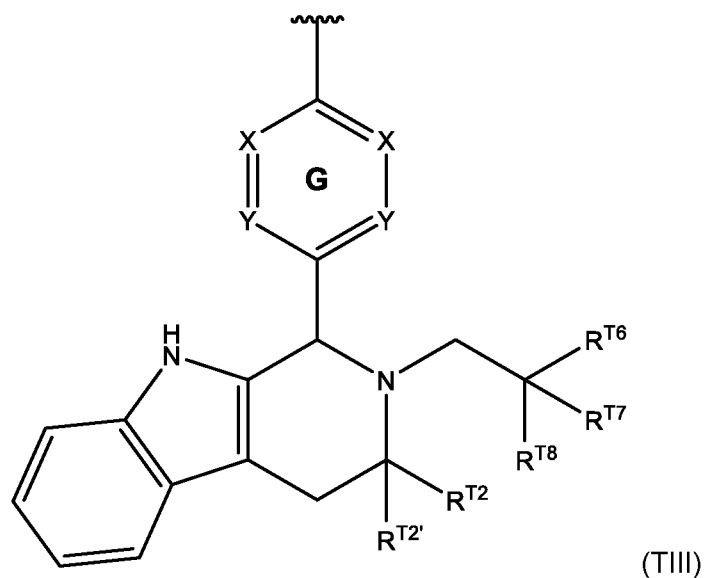
In embodiments of Formula (TI) or (TII), R^{T7} is Me.

In embodiments of Formula (TI) or (TII), R^{T8} is F.

5

In embodiments of Formula (TI) or (TII), q^T is 0.

In some embodiments, the TBL is of Formula TIII:



10

wherein:

Ring G, X^T , Y^T , R^{T2} , $R^{T2'}$, R^{T6} , R^{T7} and R^{T8} are as defined in Formula (TI) and Formula (TII); and

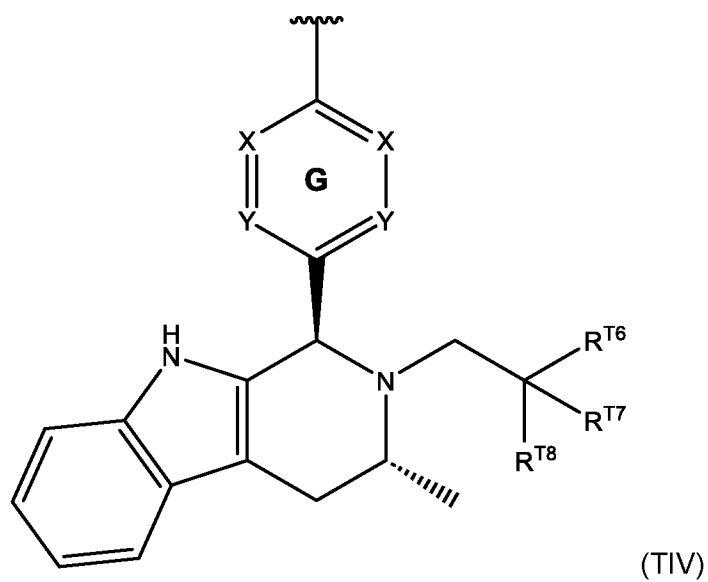
15

wherein  indicates the point of attachment of the linker.

In embodiments of Formula (TII) or Formula (TIII), when $R^{T2'}$ is H, R^{T2} and ring G have a trans relative stereochemistry.

20

In some embodiments, the TBL is of Formula TIV:

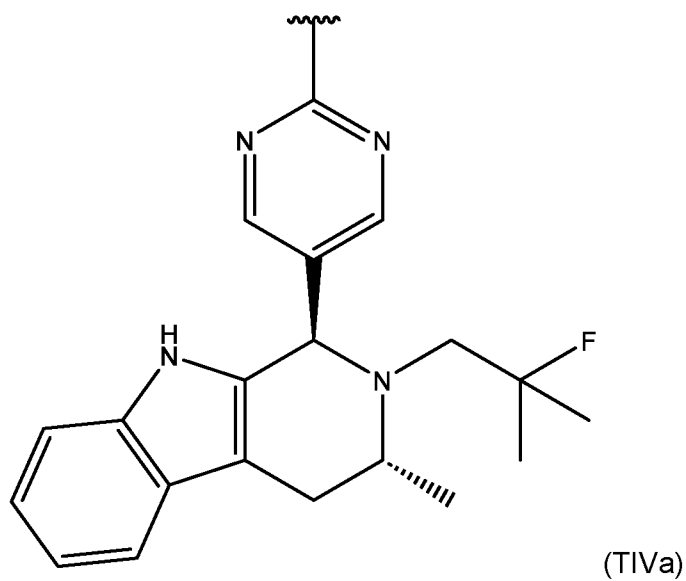


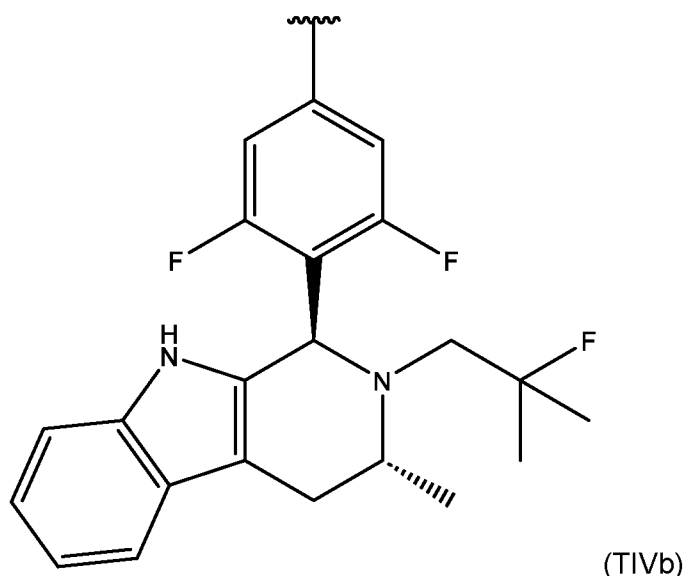
wherein:

Ring G, X^T, Y^T, R^{T6}, R^{T7} and R^{T8} are as defined in Formula (TII) or (TIII); and

5 wherein  indicates the point of attachment of the linker.

In embodiments, the TBL is of Formula TIVa or TIVb:





wherein indicates the point of attachment of the linker.

Exemplary Bifunctional Molecules

5

It will be appreciated that the bifunctional molecules 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 bifunctional molecules, By way of example, where the bifunctional molecule comprises one or more chiral centres, the present disclosure encompasses each individual enantiomer of the bifunctional molecule as well as mixtures of enantiomers including racemic mixtures of such enantiomers. By way of further example, where the bifunctional molecule comprises two or more chiral centres, the present disclosure encompasses each individual diastereomer of the bifunctional molecule, as well as mixtures of the various diastereomers.

15

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 bifunctional molecules described herein are to be understood to be within the scope of the present disclosure.

20

As used herein, references to “a bifunctional molecule” may further embrace a pharmaceutically acceptable salt thereof.

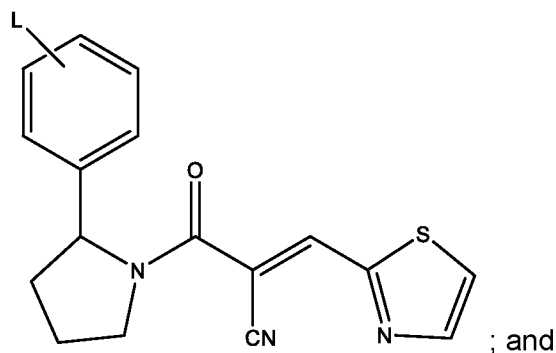
For the avoidance of doubt, the bifunctional molecule may comprise any combination of target binding protein (TBL), linker (L) and warhead (Z) (provided that it has the correct valency and/or is chemically suitable). For example, the bifunctional compound may comprise any combination of Z of formula (I), (II), (III), (IV), (V) (inc. corresponding subgeneric formulae defined herein, such as (Ia), (Ib), (Ic'), (Ic), (Id'), (Id), (Ie'), (Ie), (If), (IIa), (IIaa), (IIb), (IIc), (IId), (IIe), (IIIf), (IIIa), (IIIb) and IVa), L of any formula or subgeneric formula defined herein, such as any one of Formulae L1a to L1f, and TBL of any formula or subgeneric formula defined herein, for example any one of Formulae SI, SII, SIII, SIIIa, SIIIb, SIV, SV, TI, TII, TIII or TIV, TIVa, TIVb, VIa, VIIa, VIIa(i) to (v), VIIb, VIIb(i) to (v), VIIc or VIIc(i) to (iv). In other examples, the bifunctional compound comprises any combination of Z of formula (ZI), (ZII), (ZIII), (ZIV), (ZV) (inc. corresponding subgeneric formulae defined herein, such as (ZIa), (ZIb), (ZIb'), (ZIb'') (ZIIa to e), (ZIIIa-h) and (ZIVa-j), L, such as any one of Formulae L1a to L1f, and TBL of any formula or subgeneric formula defined herein, for example any one of Formulae SI, SII, SIII, SIIIa, SIIIb, SIV, SV, TI, TII, TIII or TIV, TIVa, TIVb, VIa, VIIa, VIIa(i) to (v), VIIb, VIIb(i) to (v), VIIc or VIIc(i) to (iv).

In some embodiments:

- i) Z is represented as formula (I), (II), (III), (IV), (V), (ZI), (ZII), (ZIII), (ZIV), (ZV) and (V) (inc. corresponding subgeneric formulae defined herein) as defined above; and
- ii) TBL is represented by formula SI, SII, SIII, SIIIa, SIIIb, SIV, SV, TI, TII, TIII or TIV, TIVa, TIVb, VIa, VIIa, VIIa(i) to (v), VIIb, VIIb(i) to (v), VIIc or VIIc(i) to (iv) as defined above.

In some embodiments:

- i) Z is represented as formula (I), (II), (III), (IV), (V), (ZI), (ZII), (ZIII), (ZIV), (ZV) and (V) (inc. corresponding subgeneric formulae defined herein) as defined above; wherein Z is not:



- ii) TBL is represented by formula SI, SII, SIII, SIIIa, SIIIb, SIV, SV, TI, TII, TIII or TIV, TIVa, TIVb, VIa, VIIa, VIIa(i) to (v), VIIb, VIIb(i) to (v), VIIc or VIIc(i) to (iv) as defined above.

5

In other particular embodiments:

- (i) Z is represented as formula (I), (II), (III), (IV), (V), (ZI), (ZII), (ZIII), (ZIV), (ZV) and (V) (inc. corresponding subgeneric formulae defined herein) as defined above; and
- 10 (ii) TBL is represented by formula SI, SII, SIII, SIIIa, SIIIb, SIV or SV as defined above.

In particular embodiments:

- i) Z is represented as formula (I), (II), (III), (IV), (V), (ZI), (ZII), (ZIII), (ZIV), (ZV) and
- 15 (V) (inc. corresponding subgeneric formulae defined herein) as defined above; and
- ii) TBL is represented by formula SIV or SV as defined above.

In other particular embodiments:

- 20 (i) Z is represented as formula (I), (II), (III), (IV), (V), (ZI), (ZII), (ZIII), (ZIV), (ZV) and (V) (inc. corresponding subgeneric formulae defined herein) as defined above; and
- (ii) TBL is represented by formula TI, TII, TIII, TIV, TIVa or TIVb as defined above.

In particular embodiments:

- 25 i) Z is represented as formula (I), (II), (III), (IV), (V), (ZI), (ZII), (ZIII), (ZIV), (ZV) and (V) (inc. corresponding subgeneric formulae defined herein) as defined above; and
- ii) TBL is represented by formula TIVa or TIVb as defined above.

30 In other particular embodiments:

- (iii) Z is represented as formula (I), (II), (III), (IV), (V), (ZI), (ZII), (ZIII), (ZIV), (ZV) and (V) (inc. corresponding subgeneric formulae defined herein) as defined above; and
- (iv) TBL is represented by formula VIa, VIIa, VIIa(i) to (v), VIIb, VIIb(i) to (v), VIIc or VIIc(i) to (iv) as defined above.

In particular embodiments:

- (iii) Z is represented as formula (I), (II), (III), (IV), (V), (ZI), (ZII), (ZIII), (ZIV), (ZV) and (V) (inc. corresponding subgeneric formulae defined herein) as defined above; and
- (iv) TBL is represented by formula VIIa(iv), VIIa(v), VIIb(v) or VIIc(iv) as defined above.

In these specific embodiments, L may be represented by formula L1a, L1b, L1c, L1d, L1e or L1f.

In yet further embodiments:

- i) (i) Z is represented as formula (I), (II), (III), (IV), (V), (ZI), (ZII), (ZIII), (ZIV), (ZV) and (V) (inc. corresponding subgeneric formulae defined herein) as defined above; and
- (ii) TBL is represented by any one of formulae Formulae SI, SII, SIII, SIIIa, SIIIb, SIV, SV, TI, TII, TIII or TIV, TIVa, TIVb, VIa, VIIa, VIIa(i) to (v), VIIb, VIIb(i) to (v), VIIc or VIIc(i) to (iv); and
- (iii) L is represented by formula L1a, L1b, L1c, L1d, L1e or L1f as defined above.

In some more specific examples, the bifunctional molecule is any one of compounds 1 and 2 or any combination of TBL, L and Z represented in compounds 1 and 2 as shown in Table 1 below:

Compd no.	Structure	Compound name
1		(Z)-2-(4-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)piperazine-1-carbonyl)-4,4-dimethylpent-2-enitrile
2		N-((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4-tetramethylcyclobutyl)-4-(4-(2-(4-((E)-2-cyano-4,4-dimethylpent-2-enoyl)piperazin-1-yl)acetyl)piperazin-1-yl)benzamide

Table 1 showing structures of exemplary bifunctional molecules 1 and 2.

5 Isotopically-labelled compounds

The disclosure also includes various deuterated forms of the compounds disclosed herein, or of any of the Formulae disclosed herein, including Formulae (ZI), (ZII), (ZIII), (ZIV), (ZV), (I), (II) (III), (IV) and (V) (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 (ZI), (ZII), (ZIII), (ZIV), (ZV), (I), (II) (III), (IV) and (V) (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 (ZI), (ZII), (ZIII), (ZIV), (ZV), (I), (II) (III), (IV) and (V) (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 ^2H , ^3H , ^{11}C , ^{13}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 ^3H or ^{14}C have been incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e. ^3H , 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 activity

Degradation may be determined by measuring the amount of a target protein (i.e. the estrogen receptor or the androgen receptor) in the presence of a bifunctional molecule as described herein and/or comparing this to the amount of the target protein observed in the absence of the bifunctional molecule. For example, the amount of target protein in a cell that has been contacted and/or treated with a bifunctional molecule 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 bifunctional molecule (e.g. as a control). If the amount of target protein is decreased in the cell contacted and/or treated with the bifunctional molecule, the bifunctional molecule 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 bifunctional molecule.

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 bifunctional molecule 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 bifunctional molecule to the cell. The bifunctional molecule may be administered at any concentration, e.g. a concentration between 0.01 nM to 10 μ M, such as 0.01nM, 0.1nM, 1 nM, 10nM, 100 nM, 1 μ M, and 10 μ M. 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 bifunctional molecule at a concentration of approximately 100 nM (e.g. following an incubation period of approximately 8 hours).

One measure of degrader activity of the bifunctional molecules 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 (i.e. the androgen receptor or the estrogen receptor). The bifunctional molecules described herein may comprise 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 bifunctional molecules comprise 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 bifunctional molecules is the D_{max} value. As used herein, D_{max} represents the maximal percentage of target protein degradation. The bifunctional molecules described herein may comprise 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 bifunctional molecules may be their effect on cell viability and/or their IC_{50} value. For example, an anti-proliferative effect of a bifunctional molecule 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 bifunctional molecule as described herein). In terms of cell viability, the bifunctional molecules described herein may comprise 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 bifunctional molecules described herein may comprise an IC_{50} value of less than 5 nM.

Pharmaceutical Compositions

The present disclosure provides a pharmaceutical composition comprising the bifunctional molecules described herein. In such compositions, the bifunctional molecule 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 bifunctional molecule as described herein together with a pharmaceutically acceptable carrier.

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 bifunctional molecules 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 bifunctional molecule may be in powder form, which is constituted with a suitable vehicle, such as sterile, pyrogen-free water, before use.

- 5 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.
- 10 Pharmaceutical compositions suitable for topical formulation may be provided for example as gels, creams or ointments.

The bifunctional molecules described herein may be present in the pharmaceutical compositions as a pharmaceutically and/or physiologically acceptable salt, solvate or
15 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
20 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.

25 Representative examples of pharmaceutically and/or physiologically acceptable salts of the bifunctional molecules 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
30 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,
35 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 bifunctional molecules 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.

Uses of moiety Z

As described herein, the moiety Z may form part of a bifunctional molecule intended for use in a method of targeted protein degradation, wherein the moiety Z acts to modulate, facilitate and/or promote proteasomal degradation of the target protein, wherein the target protein is selected from an: (i) estrogen receptor; and (ii) androgen receptor.

As such, according to a further aspect of the disclosure, there is provided a use of the moiety Z or a compound comprising moiety Z as described herein (e.g. as defined in any one of Formulae (ZI), (ZII), (ZIII), (ZIV), (ZV), (I), (II) (III), (IV) and (V)) in a method of targeted protein degradation of either the estrogen receptor or the androgen receptor (e.g. an *in vitro* or *in vivo*

method of targeted protein degradation). For example, moiety Z may find particular application as a promoter or facilitator of targeted protein degradation of either the estrogen receptor or androgen receptor.

- 5 There is also provided a use of moiety Z or a compound comprising moiety Z (e.g. as defined in any one of Formulae (ZI), (ZII), (ZIII), (ZIV), (ZV), (I), (II) (III), (IV) and (V)) in the manufacture of a bifunctional molecule suitable for targeted protein degradation.

Therapeutic Methods and Uses

10

The bifunctional molecules of the present disclosure may modulate, facilitate and/or promote proteasomal degradation of a target protein selected from an: (i) estrogen receptor; and (ii) androgen receptor. 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
15 treating the cell with a bifunctional molecule as described herein. The method may be carried out *in vivo* or *in vitro*.

20

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 bifunctional molecule of the present disclosure.

25

As such, the bifunctional molecules of the present disclosure may find application in medicine and/or therapy. Specifically, the bifunctional molecules of the present disclosure may find use in the treatment and/or prevention of any disease or condition, which is modulated through the estrogen receptor or androgen receptor. For example, the bifunctional molecules 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 degrader of the present invention wherein activity of the selected protein is implicated in a disease state or a disorder, then it is
30 to be understood that the degrader is useful in the treatment of that disease.

35

There is further provided the use of the bifunctional molecules 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 estrogen receptor or androgen receptor. Additionally, there is provided the use of a moiety Z (e.g. as defined in any one of Formulae (ZI), (ZII), (ZIII), (ZIV), (ZV), (I), (II) (III), (IV) and (V) in the manufacture of a medicament for the treatment and/or

prevention of any disease or condition, which is modulated through the estrogen receptor or androgen receptor.

Diseases and/or conditions that may be treated and/or prevented by the molecules of the disclosure include any disease, which is associated with and/or is caused by an abnormal level of protein activity of the estrogen receptor or androgen receptor.

Such diseases and conditions include those whose pathology is related at least in part to an abnormal (e.g. elevated) level of the protein and/or the overexpression of the protein. For example, the bifunctional molecules may find use in the treatment and/or prevention of diseases where an elevated level of the target 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 of the estrogen receptor or androgen receptor, which comprises administering a therapeutically effective amount of a bifunctional compound as described herein.

Representative examples of the diseases and/or conditions that may be treated and/or prevented by the use of the described bifunctional compounds for the targeted degradation of the estrogen receptor include (but are not limited to) bone disorders, e.g., osteoporosis (including glucocorticoid-induced osteoporosis), osteopenia, Paget's disease and periodontal disease; cardiovascular diseases (including fibroproliferative conditions); hypercholesterolemia; hypertriglyceridemia; vasomotor disorders (e.g., hot flashes); urogenital disorders (e.g., urinary incontinence); prostatic hypertrophy; endometrial hyperplasia; cancer, including prostate cancer, uterine cancer, ovarian cancer, breast cancer, and endometrial cancer; multiple CNS disorders, such as neurodegenerative diseases (e.g., improvement of cognitive function and the treatment of dementia, including Alzheimer's disease and short-term memory loss).

Representative examples of the diseases and/or conditions that may be treated and/or prevented by the use of the described bifunctional compounds for the targeted degradation of the androgen receptor include (but are not limited to) benign prostate hyperplasia, hirsutism,

acne, hyperpilosity, seborrhea, endometriosis, polycystic ovary syndrome, androgenic alopecia, adenomas and neoplasies of the prostate, benign or malignant tumor cells containing the androgen receptor, hypogonadism, osteoporosis, suppression of spermatogenesis, libido, cachexia, anorexia, androgen supplementation for age related decreased testosterone levels in men, prostate cancer, breast cancer, endometrial cancer, uterine cancer, hot flashes, and Kennedy's disease.

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 otherwise stated or implied from the context of the use of the term.

Assays

The disclosure also encompasses a method of screening bifunctional molecules to identify suitable target protein binding ligands and linkers for use in the bifunctional molecules described herein, e.g. a bifunctional molecule that is able to effectively modulate, facilitate and/or promote proteolysis of a target protein selected from an: (i) estrogen receptor; and (ii) androgen receptor. This method may assist in identifying suitable linkers for a particular target protein binding partner such that the level of degradation is further optimised.

The method may comprise:

- a. providing a bifunctional molecule comprising:
 - (i) a first ligand comprising a structure according to Z (as defined in any of the formulae for Z disclosed herein);
 - (ii) a second ligand that binds to a target protein selected from an: (i) estrogen receptor; and (ii) androgen receptor (a target protein binding ligand); and
 - (iii) a linker that covalently attaches the first and second ligands;
- b. contacting a cell with the bifunctional molecule; 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 bifunctional molecule; and

e. comparing the level of degradation of the target protein in the cell contacted with the bifunctional molecule to the level of degradation of the target protein in the

absence of the bifunctional molecule;

wherein an increased level of degradation of the target protein in the cell contacted with the bifunctional molecule indicates that the bifunctional molecule 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 bifunctional molecule (compared to any reduction in the levels of target protein observed in the cell in the absence of the bifunctional molecule) indicates that the bifunctional molecule 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 first and second ligands together to form a plurality of bifunctional molecules. The level of degradation provided by each one of the plurality of bifunctional molecules may be detected and compared. Those bifunctional molecules showing higher levels of target protein degradation indicate preferred and/or optimal linkers for use with the selected target protein binding partner.

The method may be carried out *in vivo* or *in vitro*.

Compound library

The disclosure also provides a library of bifunctional molecules, the library comprising a plurality of bifunctional molecules, the plurality of bifunctional molecules comprising a plurality of Z moieties covalently linked to a selected target protein binding partner.

As such, the target protein binding partner may be pre-selected and the Z moiety may not be determined in advance. The library may be used to determine the activity of a candidate Z moiety of a bifunctional molecule in modulating, promoting and/or facilitating selective protein degradation of a target protein.

The disclosure also includes a library of bifunctional molecules, the library comprising a plurality of bifunctional molecules, the plurality of bifunctional molecules comprising a plurality of target protein binding ligands and a selected Z moiety. As such, the Z moiety of the bifunctional molecule 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 target protein binding ligand and its value as a binder of a target protein to facilitate target protein degradation.

Methods of manufacture

According to a further aspect of the disclosure, there is provided a method of making a bifunctional molecule as described herein.

The method of making the bifunctional molecule may comprise the steps of:

- (a) providing a first ligand or moiety comprising a structure according to Z (as defined in any one of the formulae for Z disclosed herein);
- (b) providing a second ligand or moiety that binds to a target protein selected from an: (i) estrogen receptor binding ligand; and (ii) androgen receptor binding ligand (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 bifunctional molecule may comprise the steps of:

- (a) providing a target protein binding ligand selected from an: (i) estrogen receptor binding ligand; and (ii) androgen receptor 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 target protein binding ligand-linker conjugate (TBL-L);
- (c) further reacting the linker moiety of the conjugate to add and/or form a structure according to Z (as defined in any of formulae (I) to (III)) thereon to provide the bifunctional molecule having the general formula TBL-L-Z.

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.

Definitions

5 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
10 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
15 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),
20 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
25 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
30 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.

35 As used herein, "C₁-C₆ alkyl" refers to a straight or branched chain hydrocarbyl group containing from 1 to 6 carbon atoms. As used herein, a "C₁-C₃ alkyl" refers to a straight or

branched chain hydrocarbonyl 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), CH₃, CH₂ 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 C₃-C₇ cycloalkyl is a cycloalkyl containing 3 to 7 carbon atoms in the ring. As used herein, a C₃-C₆ 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, cyclooctynyl 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 C_nH_{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 C_nH_{2n-2}, wherein n is an integer ≥2. Examples of alkynyl groups include ethynyl, n-propylnyl, iso-propylnyl, n-butylnyl, sec-butylnyl, iso-butylnyl and tert-butylnyl. 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 $-\text{CH}_2\text{Ph}$ 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.

5

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, diazaspirooundecane, 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.

As used herein, $-\text{CH}(\text{aryl})-$, $-\text{CH}(\text{substituted aryl})-$, $-\text{CH}(\text{heteroaryl})-$ and $-\text{CH}(\text{substituted heteroaryl})$ refers to a methylene moiety that comprises an aryl, substituted aryl, heteroaryl or substituted heteroaryl substituent and is the attachment point for the linker L.

As used herein, the term “heterocyclyl” refers to a monovalent radical derived from a heterocycle. A heterocycle is a cyclic compound (a compound comprising one or more rings of connected atoms) having as ring members atoms of at least two different elements (such as carbon and nitrogen).

As used herein, a “carbocyclic ring” is a ring containing 3 to 10 carbon atoms, in some cases 3 to 8 carbon atoms, or in some cases 5 to 6 carbon atoms. The ring may be aliphatic. Thus, as used herein, references to “carbocyclyl” and “substituted carbocyclyl” groups may refer to aliphatic carbocyclyl groups and aliphatic substituted carbocyclyl groups. The ring may be saturated or unsaturated, e.g. in some cases the ring may contain one or more double or triple

bonds. Representative examples of carbocyclyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclooctynyl etc. As used herein, “substituted carbocyclyl” refers to a carbocyclyl group as defined herein which comprises one or more substituents on the carbocyclic ring. When a carbocyclyl group is substituted, any hydrogen atom(s) may be replaced with the substituent(s), providing valencies are satisfied.

As used herein, a “heterocyclic ring” (or heterocyclyl) may comprise at least 1 heteroatom selected from O, N and S. The heterocyclic ring may be a monocyclic or polycyclic ring, each ring comprising 3 to 10 atoms, in some cases 3 to 8 atoms. The one or more rings may be aliphatic. Thus, as used herein, references to “heterocyclyl” and “substituted heterocyclyl” groups may refer to aliphatic heterocyclyl groups and aliphatic substituted heterocyclyl groups. 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 heterocyclic group may be C₁ to C₆ alkyl-substituted. In some cases, the heterocyclyl is a monocyclic or bicyclic ring, such as a monocyclic ring. In other examples, the heterocyclyl may be a bicyclic ring, which may, in some cases be a fused ring. Representative examples of heterocyclyl 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, diazaspirooundecane, diazaspiroheptane, azaspiroheptane, diazaspirodecane, octahydropyrrolopyrrole, pyrrolizidinyl, etc. As used herein, “substituted heterocyclyl” refers to a heterocyclyl group as defined herein which comprises one or more substituents on the heterocyclic ring.

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. For the avoidance of doubt, unsaturated compounds may comprise any number of double and/or triple bonds.

“Cycloalkene” is used herein to refer to an unsaturated monocyclic hydrocarbon having one endocyclic double 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 “C₁₋₃ 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 “C₁₋₃ 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 C₁ to C₃ alkylene (such as methylene, ethylene or propylene). The C₁ to C₃ alkylene bridging group may be optionally substituted with any suitable substituent as described herein. For example, C₁ to C₃ alkylene bridging group may be optionally substituted with one or two substituents each independently selected from the group consisting of halo, C₁ to C₃ alkyl, C₁ to C₃ haloalkyl and C₁ to C₃ 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.

The term "hydrocarbyl" refers to a monovalent radical derived from a hydrocarbon by the removal of a hydrogen atom from the hydrocarbon. A hydrocarbon is any molecule comprising only the elements carbon and hydrogen. Hydrocarbons may be aliphatic, aromatic, unsaturated or saturated.

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.

As used herein, "alkoxyalkyl" may refer to a moiety derived from an alkyl moiety in which a hydrogen atom at any position of the alkyl is substituted with an alkoxy moiety. Examples of alkoxyalkyl groups include methoxyethyl, methoxypropyl, ethoxymethyl and the like.

As used herein, the term "alkylcarbonyl" refers to carbonyl having alkyl mentioned above. Examples of alkylcarbonyl include C_{1-6} alkylcarbonyl ($-C(O)C_{1-6}$ alkyl), such as methylcarbonyl, ethylcarbonyl, n-propylcarbonyl, isopropylcarbonyl, n-butylcarbonyl, isobutylcarbonyl, tert-butylcarbonyl, n-pentylcarbonyl, isopentylcarbonyl, and hexylcarbonyl, with methylcarbonyl being preferable.

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, the term "alkylcarbonylaminoalkyl" refers to aminoalkyl having alkylcarbonyl mentioned above. Examples of alkylcarbonylaminoalkyl include C_{1-6} alkylcarbonylaminoalkyl, such as methylcarbonylaminomethyl and ethylcarbonylaminomethyl.

As used herein, the term "alkylaminocarbonyl" refers to carbonyl having at least one alkylamino group. Examples of alkylaminocarbonyl include C₁₋₆alkylamino-C₁₋₆alkyl, such as methylaminocarbonyl, and ethylaminocarbonyl.

5 As used herein, the term "alkylaminoalkyl" refers to alkyl mentioned above having at least one alkylamino group mentioned above. Examples of alkylaminoalkyl include C₁₋₆alkylamino-C₁₋₆alkyl, such as methylaminomethyl, methylaminoethyl, ethylaminomethyl, and ethylaminopropyl.

10 The term "alkoxyalkylene" is used herein to refer to a moiety derived from an alkylene moiety in which a hydrogen atom at any position of the alkylene is substituted with an alkoxy moiety. Examples of alkoxyalkylene groups include methoxyethylene, methoxymethylene and the like.

The term "haloalkylene" is used herein to refer to a moiety derived from an alkylene moiety in
15 which one or more hydrogen atom(s) at any position(s) of the alkylene is/are substituted with one or more halo moieties. Examples of haloalkylene groups include fluoroethylene, difluoromethoxymethylene, dichloroethylene and the like.

The term "hydroxyalkylene" is used herein to refer to a moiety derived from an alkylene moiety
20 in which a hydrogen atom at any position of the alkylene is substituted a hydroxy moiety. Examples of hydroxyalkylene groups include hydroxyethylene, hydroxymethylene and the like.

The term "cycloalkoxy" is used herein to refer to a moiety derived from a linear alkoxy moiety
25 in which a bond forms between the oxygen atom of the OH moiety and the carbon atom at the end of the alkyl chain (by abstraction of the hydrogen atom of the OH moiety and a hydrogen atom at the end of the alkyl chain). Examples of cycloalkoxy groups include oxacyclohexanyl, oxacyclopentanyl and the like.

The term "carbocyclylamino" is used herein to refer to a moiety derived from an linear
30 monohydrocarbylamino moiety in which a bond forms between the nitrogen atom of the NH moiety and the carbon atom at the end of the hydrocarbyl chain (by abstraction of the hydrogen atom of the NH moiety and a hydrogen atom at the end of the hydrocarbyl chain). Examples of carbocyclylamino groups include piperidinyl, pyrrolidinyl, pyridinyl, pyrrolyl and the like.

35 As used herein, the term "substituted" means that the moiety comprises one or more substituents. As used herein, the "optionally substituted" means that the moiety may comprise one or more substituents.

As used herein, a “substituent” may include, but is not limited to, hydroxy, thiol, carboxyl, cyano (CN), nitro (NO₂), halo, haloalkyl (e.g. a C₁ to C₆ haloalkyl or a C₁ to C₄ haloalkyl), an alkyl group (e.g. C₁ to C₁₀ or C₁ to C₆), an alkenyl group (e.g. C₂ to C₆), an alkynyl group (e.g. C₂ to C₆), aryl (e.g. phenyl and substituted phenyl for example benzyl or benzoyl), morpholino, N-C₁₋₆alkylenylmorpholine, alkoxy group (e.g. C₁ to C₆ alkoxy or C₁ to C₄ alkoxy), haloalkoxy (e.g. C₁ to C₄ haloalkoxy), aryloxy (e.g. phenoxy and substituted phenoxy), hydroxyalkynyl (e.g. C₂ to C₆), thioether (e.g. C₁ to C₆ alkyl or aryl thioether), alkylthio (e.g. C₁ to C₆alkylthio), cyanoalkyl (e.g. C₁ to C₆), oxo, keto (e.g. C₁ to C₆ keto), ester (e.g. C₁ to C₆ alkyl or aryl ester, which may be present as an oxyester or carbonylester on the substituted moiety), thioester (e.g. C₁ to C₆ 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 C₁ to C₆ 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 C₁ to C₆ alkyl amine or a C₁ to C₆ 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)NH₂, -C(O)NH(alkyl) such as -C(O)NH(C₁₋₄alkyl), -C(O)N(alkyl)₂ such as -C(O)N(C₁₋₄alkyl)₂, -NHC(O)alkyl such as -NHC(O)C₁₋₄alkyl, -NHC(O)(phenyl), -N(alkyl)C(O)(alkyl) such as -N(C₁₋₄alkyl)C(O)(C₁₋₄alkyl), -N(alkyl)C(O)(phenyl) such as -N(C₁₋₄alkyl)C(O)(phenyl), N-C₁₋₆alkylenylamino, amido (e.g. which may be substituted with one or two C₁ to C₆ alkyl groups (including a carboxamide which is optionally substituted with one or two C₁ to C₆ alkyl groups), aminoalkyl (e.g. C₁ to C₄ aminoalkyl), alkanol (e.g. C₁ to C₆ alkyl, C₁ to C₄ alkyl or aryl alkanol), or carboxylic acid (e.g. C₁ to C₆ alkyl or aryl carboxylic acid), sulfoxide, sulfone, sulfinimide, sulfonamide, and urethane (such as -O-C(O)-NR₂ or -N(R)-C(O)-O-R, wherein each R in this context is independently selected from C₁ to C₆ alkyl or aryl), a heteroaryl, arylalkyl (such as an arylC₁₋₄alkyl), heteroarylalkyl (such as a heteroarylC₁₋₄alkyl), -OC₁₋₄alkylphenyl, -C(O)alkyl such as -C(O)(C₁₋₄alkyl), -C(O)alkylphenyl such as C(O)(C₁₋₄alkylphenyl), -C(O)haloalkyl such as -C(O)(C₁₋₄haloalkyl), -SO₂(alkyl) such as -SO₂(C₁₋₄alkyl), -SO₂(phenyl), -SO₂haloalkyl such as OSO₂(C₁₋₄haloalkyl), -SO₂NH₂, -SO₂NH(alkyl) such as -SO₂NH(C₁₋₄alkyl), -SO₂NH(phenyl), -NHSO₂(alkyl) such as -NHSO₂(C₁₋₄alkyl), -NHSO₂(phenyl), -NHSO₂(haloalkyl) such as -NHSO₂(C₁₋₄haloalkyl), -S-C₁₋₃haloalkyl, -CH₂C(O)N(R^C)₂, -C₃₋₄alkynyl(NR^C)₂, deuterioC₂₋₄alkynyl, (C₁₋₃alkoxy)haloC₁₋₃alkyl-, C₃₋₆cycloalkyl (wherein said C₃₋₆cycloalkyl is optionally substituted with halo or C₁₋₃alkyl), HC(O)-, -CO₂R^C, or -CO₂N(R^C)₂, wherein R^C is hydrogen or C₁₋₃alkyl.

In some examples, and unless the context indicates otherwise, a “substituent” may include, but is not limited to, halo, C₁ to C₆ alkyl, C₁ to C₆ haloalkyl, C₁ to C₆ alkoxy, hydroxyl, oxo,

amino (such as NR^1R^2), amido (such as $-(\text{C}=\text{O})\text{NR}^1\text{R}^2$ or $\text{NR}^1(\text{C}=\text{O})\text{C}_1\text{-C}_6$ alkyl), keto (such as $-(\text{C}=\text{O})\text{C}_1\text{-C}_6$ alkyl), and ester (such as $-\text{O}(\text{C}=\text{O})\text{C}_1\text{-C}_6$ alkyl or $-(\text{C}=\text{O})\text{OC}_1\text{-C}_6$ alkyl); and wherein R^1 and R^2 are each independently selected from H and C_1 to C_6 alkyl.

- 5 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” group may be F, Cl, Br, or I. In some examples, halo may be F.

- 10 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 $\text{C}_1\text{-C}_6$ 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 $\text{C}_1\text{-C}_6$ haloalkyl may be a fluoroalkyl, such as trifluoromethyl ($-\text{CF}_3$) or 1,1-difluoroethyl ($-\text{CH}_2\text{CHF}_2$).

- 15 As used herein, a cyclohaloalkyl refers to a cycloalkyl as defined above, in which one or more hydrogen atoms thereon have been replaced with a halogen atom. By way of example, a “ C_3 to C_7 cyclohaloalkyl” refers to a C_3 to C_7 cycloalkyl in which one or more hydrogen atoms thereon have been replaced with a halogen atom.

- 20 As used herein, a “ C_{1-4} haloalkoxy” refers to a C_{1-4} 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. For example, within the context of the various formulae for Z described herein, R^1 is typically a monovalent group that is attached to the heterocyclic core of Z and so the terms aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl and C_1 to C_6 alkyl should be understood to represent a monovalent radical moiety. By way of further example, R^2 for Z is typically a divalent group that is covalently attached to both the heterocyclic core of Z and also the linker. As such, in these examples, the terms aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, substituted heterocycloalkyl should be understood to represent divalent radical moiety.

- 35 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.

5 DETAILED DESCRIPTION

The present invention will now be described in detail with reference to the following non-limiting examples.

10 List of Abbreviations:

μL = Microliter

μM = Micromolar

NMR = Nuclear Magnetic Resonance

ACN = acetonitrile

15 AcOH or HOAc = acetic acid

Boc = tert-butoxycarbonyl

bs = broad singlet

°C = degrees Celsius

d = doublet

20 δ = chemical shift

DCM = Dichloromethane

DIPEA = N, N-Diisopropylethylamine, or Hünig's base

DMF = N,N-dimethylformamide

DMSO = Dimethylsulfoxide

25 dppf = 1,1'-Ferrocenediyl-bis(diphenylphosphine)

EtOAc = Ethyl acetate

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

30 hexafluorophosphate

HPLC = high performance liquid chromatography

Hz = Hertz

J = coupling constant (given in Hz unless otherwise indicated)

LCMS = liquid chromatography mass spectrometry

35 m = multiplet

M = Molar

M+H⁺ = parent mass spectrum peak plus H⁺

mg = Milligram

min = minutes

mL = Milliliter

mM = Millimolar

5 mmol = Millimole

MS = mass spectrum

MTBE = methyl tert-butyl ether

nM = nanomolar

q = quartet

10 RT or r.t. = room temperature

t = triplet

TFA = trifluoroacetic acid

THF = tetrahydrofuran

TLC = thin layer chromatography

15

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
20 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.

25 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 (δ 7.26) or other solvent as indicated in NMR spectral data. A small amount (1-5 mg) of sample is dissolved in an appropriate deuterated solvent (0.6ml).

30 Preparative HPLC was performed on a Gilson Preparative HPLC System with a Waters X-Bridge C18 column (100 mm x 19 mm; 5 μ m 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
35 spray ionisation (ESI⁺) on an Agilent InfinityLab Single Quadrupole LC/MSD with a Waters XBridge® C18 3.5 μ m column (2.1mm x 50mm) using H₂O+MeCN (5-95%) + 0.1% HCO₂H or H₂O+MeCN (20-95%) + 0.1% HCO₂H as eluent, using a linear gradient over 3 minutes.

Alternatively, a Shimadzu LC; Prominence-I series instrument was used, with the following set up:

LCMS

5

Method-A: Column: X-Select CSH C18(3.0*50mm,2.5um), Mobile Phase A:0.05% FA in H₂O
Mobile Phase B :0.05%FA in ACN, Gradient %B: 0/2,0.3/2,2.0/98,2.8/98,3.0/2,3.7/2 Flow
Rate:1.0ml/min

10 **Method-B:** Column: Bakerbond Q2100 C18 1.8um; 2.1x50mm Mobile Phase A :0.05% FA in
Water Mobile Phase B : 0.05% FA in ACN Flow Rate:0.6 ml Gradient Program (Time/B%):
0/5,0.2/5,2.3/98,3.3/98,3.8/5,4.5/5

Method-C: Column: X Select CSH C18 2.5um; 3.0x50mm Mobile Phase A :2.5 mM
15 Ammonium Bicarbonate Water + 5 %ACN Mobile Phase B : ACN Flow Rate:1.2 ml Gradient
Program (Time/B%): 0/0,1.5/100,2.4/100,2.6/0,3/0

Method-D: Column: X-Bridge BEH C18(3.0*50mm,2.5um), Mobile Phase A:0.05% FA in
H₂O:CAN (95:5), Mobile Phase B :0.05%FA in ACN, Gradient %B:
20 0/2,0.2/2,2.2/98,3/98,3.2/2,4/2 Flow Rate:1.2ml/min

Preparative purification method

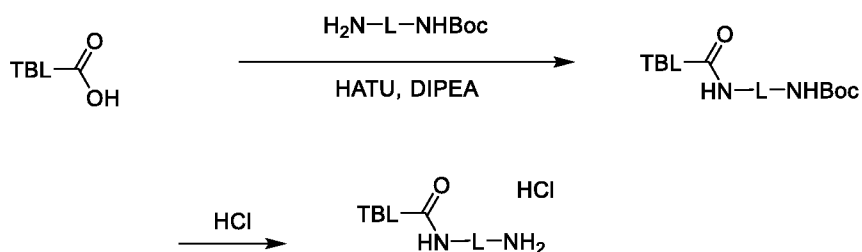
Method : Column: Synergy (150*20mm);5µm Mobile Phase A :0.1% FA in Water Mobile
25 Phase B : 100% ACN Flow Rate: 18 ml/min Gradient: linear gradient.

PART A – Synthetic methods

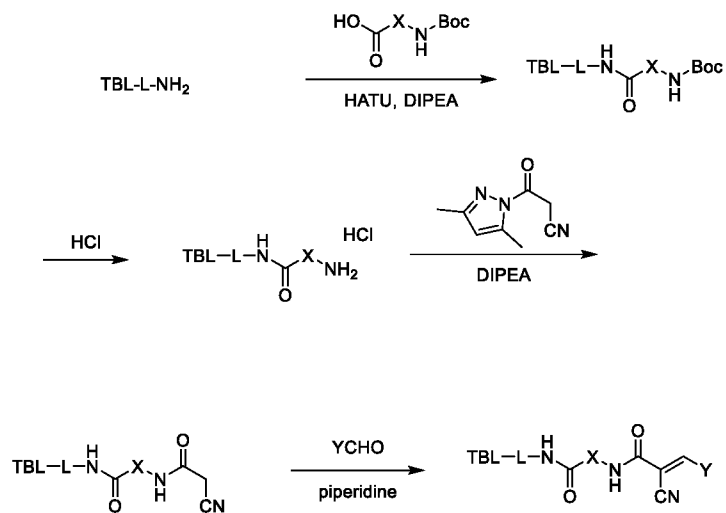
30 Overviews of various exemplary synthetic methods that may be used to provide the
compounds of the present disclosure are shown below.

Overview of Synthetic pathway - Scheme 1

35

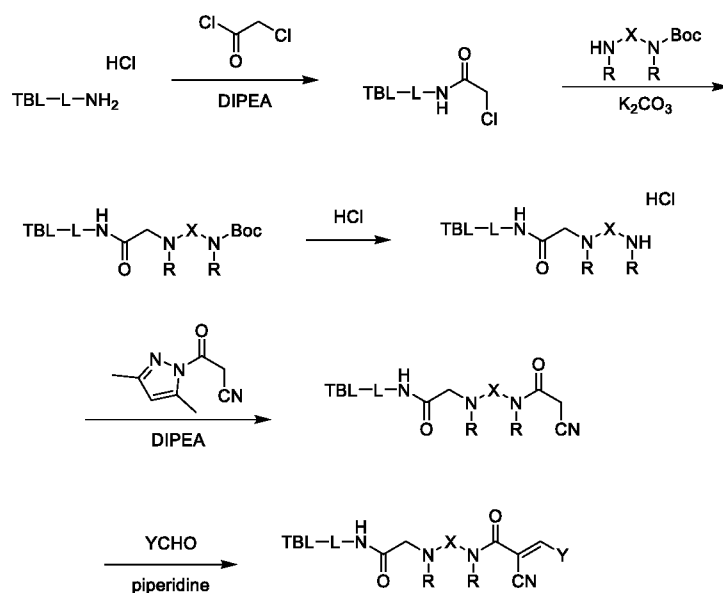


Overview of Synthetic pathway - Scheme 2

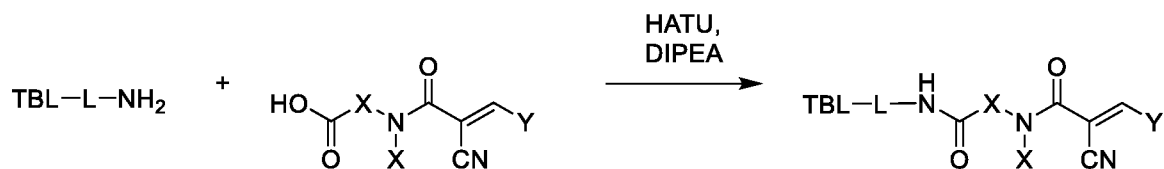


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Overview of Synthetic pathway - Scheme 3

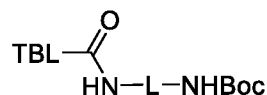


Overview of Synthetic pathway - Scheme 4



General Procedure 1A (see scheme 1)

5



To a stirred solution of TBL-Acid (1.1 equiv.) in DMF were added DIPEA (3 equiv.) and HATU (1.1 equiv.) at 0 °C and stirred for 10 min. To this reaction mixture was added Linker-Boc-amine (1.0 equiv.) dissolved in DMF at 0 °C and stirred for additional 24h at RT. The crude compound was purified by silica gel column chromatography using EtOAc/Hexane as eluents to afford the Linker-Boc-amine 1A.

10

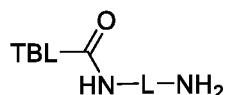
Examples:

15

Examples made in accordance with a method similar to that described above (and illustrated in scheme 1 is shown below).

Example number	Structure/Preparation
1a	$\text{TBL-C(=O)-NH-(CH}_2\text{)}_6\text{-NH-Boc}$
1b	$\text{TBL-C(=O)-NH-(CH}_2\text{)}_2\text{(O)}_5\text{(CH}_2\text{)}_2\text{-NH-Boc}$

General Procedure 2A: (see scheme 1)



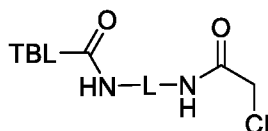
- 5 To a stirred solution of Linker-Boc-amine 1A (1 equiv.) in DCM was added HCl (4M in dioxane) (10.0 equiv.) slowly at 0 °C. The reaction was allowed to stir at RT for 2 h. After completion, the reaction mixture was concentrated under reduced pressure to get a crude solid, which was washed with MTBE and dried under vacuum, to afford Linker-amine.HCl 2A.

10 Examples:

Example made in accordance with a method similar to that described above (carried out on compound 1a and 1b) (and illustrated in scheme 1 is shown below).

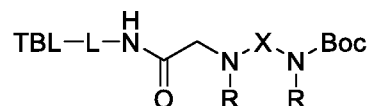
Example number	Structure/Preparation
2a	
2b	

General Procedure 3A: (see scheme 3)



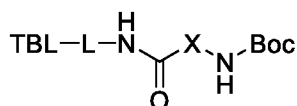
- 20 To a stirred solution of Linker-amine.HCl 2A (A2) (1 equiv.) in dichloromethane (DCM) at 0 °C were sequentially added Et₃N (5.0 equiv.) and chloroacetyl chloride (3.0 equiv.). The reaction was allowed to stir at room temperature for 16 h. After completion, the reaction was quenched by addition of NH₄Cl (saturated aqueous solution) the mixture was extracted with DCM. The organic phase was dried over MgSO₄ and concentrated under reduced pressure. Purification by column chromatography yielded TBL-L-alkyl chloride 3A .
- 25

General Procedure 4A: (see scheme 3)



To a stirred solution of TBL-L-alkyl chloride 3A (1 equiv.) in DMF at 0 °C were sequentially added Amino-Boc-amine (3 equiv.) and Potassium Carbonate (3 equiv.) and heated to 80 °C for 12 h. After cooling to room temperature the mixture was diluted with EtOAc. The organic phase was washed with LiCl (5% aqueous solution), dried over MgSO₄ and concentrated under reduced pressure. Purification by column chromatography yielded TBL-L-Boc amine 4A.

General Procedure 5A: (see, for example, scheme 2)



To a stirred solution of TBL-L-Acid (1.1 equiv.) in DMF was added DIPEA (4 equiv.) followed by HATU (1.5 equiv.) in DMF. Resulting solution was stirred for 10 min before the addition of TBL-L-amine (1 equiv.) in DMF and stirred for overnight. The reaction mixture was diluted by cold water and extracted with EtOAc, the organic layer was washed with water and brine, dried over Na₂SO₄ and concentrated to afford TBL-L-Boc amine 5A.

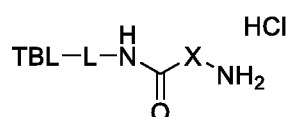
Examples:

Examples made in accordance with a method similar to that described above and illustrated in scheme 2 are shown below (carried out on compounds 2a and 2b with various commercially available carboxylic acids)

Example number	Structure/Preparation
5a	<chem>CC1=CC=C(C=C1)C2CCN(C2)C(=O)NCCCCCNC(=O)C(C)(C)C</chem>

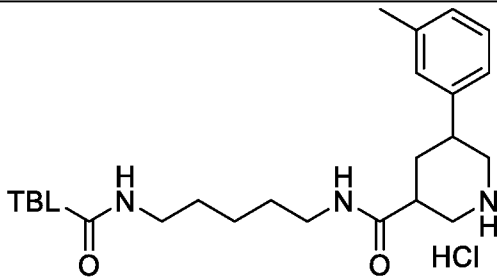
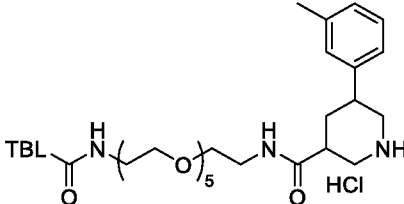
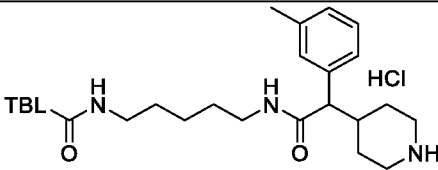
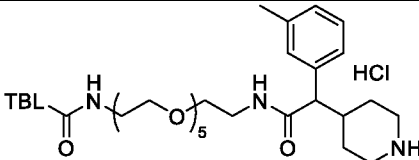
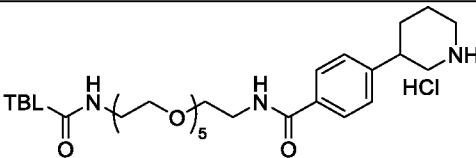
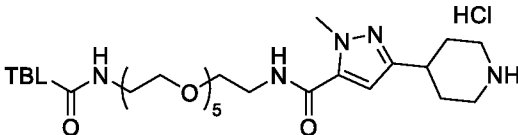
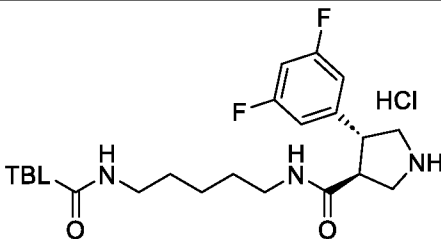
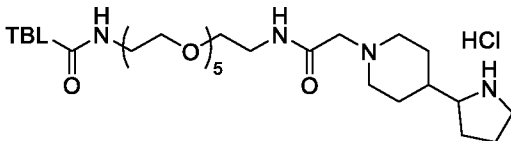
[illegible]

General Procedure 6A: (see for example, scheme 2)

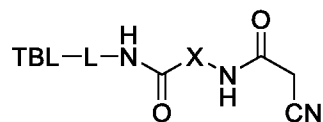


To a solution of TBL-L-Boc amine 5A (1 equiv.) in DCM was added HCl solution (4M in 1,4-dioxane) (10 equiv.) slowly at 0 °C and then warmed reaction slowly to room temperature and stirred for 3 h. The reaction mixture was concentrated under reduced pressure, washed with MTBE and dried under vacuum to afford the crude TBL-L-amine.HCl 6A. The crude was used for the next step without further purification.

Examples:

Example number	Structure/Preparation
6a	
6b	
6c	
6d	
6e	
6f	
6g	
6h	

General Procedure 7A: (see, for example, scheme 2)



- 5 To a stirred solution of TBL-L-amine.HCl 6A (1 equiv.) in 1,4-dioxane was added DIPEA (3 equiv.) taken in 1,4-dioxane and 1-cyanoacetyl-3,5-dimethyl-1H-pyrazole (2 equiv.) taken in 1,4-dioxane at room temperature and stirred at 80 °C for 6h. The crude obtained was dissolved in DCM and washed by H₂O, the organic layer was dried over Na₂SO₄ and concentrated to give Cyano-amide 7A as a crude product. The crude was used
10 for the next step without further purification.

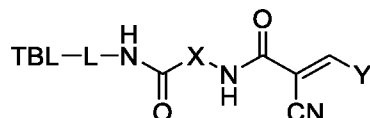
Examples:

- Examples made in accordance with a method similar to that described above and illustrated
15 in scheme 2 are shown below (carried out on compounds 6a to 6h).

Example number	Structure/Preparation
7a	
7b	
7c	

7d	
7e	
7f	
7g	
7h	

20 General Procedure 8A: (see, for example, scheme 2)



To a stirred solution of Cyano-amide 7A (1 equiv.) in EtOH at room temperature was added piperidine (1.5 equiv.) diluted with ethanol, followed by an aldehyde (3 equiv.) taken in 0.5 mL of EtOH. The resulting reaction mixture was stirred overnight at room temperature under nitrogen. The solvent in the reaction mixture was removed under reduced pressure to afford the crude compound. The crude compound was purified by column chromatography or mass directed prep HPLC to afford the Cyanoacrylamide 8A.

30 **Examples:**

Examples made in accordance with a method similar to that described above and illustrated in scheme 2 are shown below (carried out on compounds 7a to 7h).

Example number	Structure/Preparation
8a	
8b	
8c	
8d	
8e	
8f	
8g	
8h	

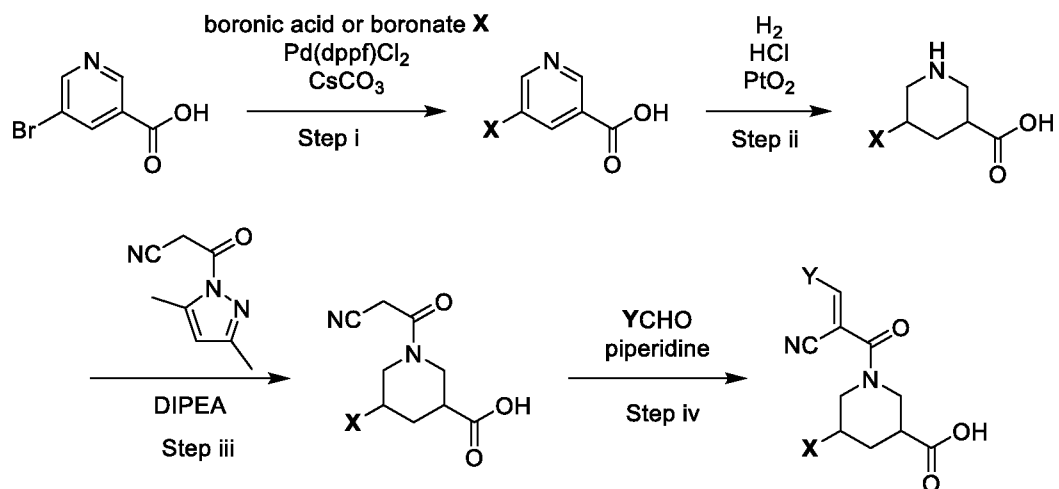
Piperidine-Aminoacid Based Warheads

Further examples of bifunctional degraders comprising a piperidine- amino acid derivative-based moiety as Z are illustrated below.

Overviews of various exemplary synthetic methods that may be used to provide these compounds are shown below.

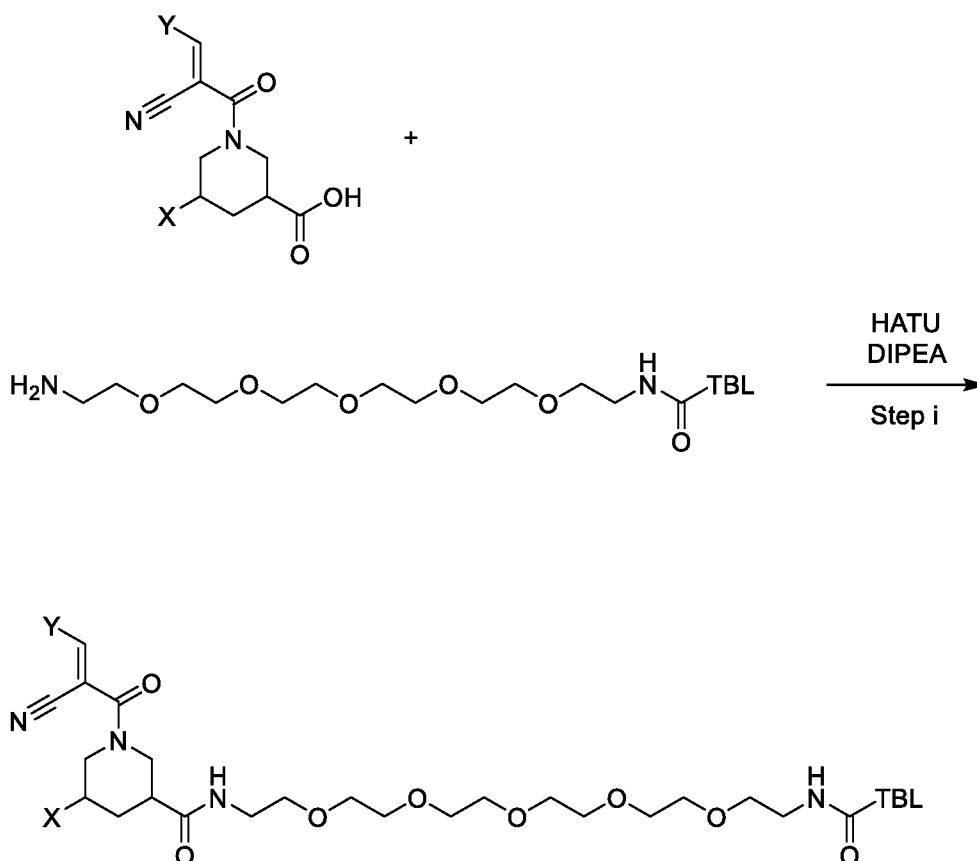
Overview of Synthetic Pathway – scheme 5

5



Overview of Synthetic Pathway – scheme 6

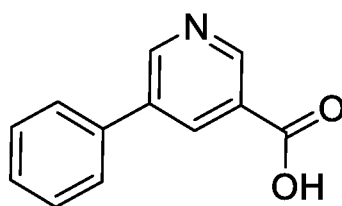
10



Synthesis of Piperidine-Amino acids (see scheme 5):

5-bromonicotinic acid is treated with the desired boronate or boronic acid **X** under Suzuki conditions ((PdCl₂(dppf).DCM, K₂CO₃ in dioxane/water at 100 °C) in order to obtain the 5 substituted nicotinic acids, unless commercially available. Hydrogenation under (H₂, PtO₂ in HCl or HOAc) affords the substituted nipecotic acids. Acylation using 1 cyanoacetyl-3,5-dimethylpyrazole and DIPEA in dioxane or DMF affords the precursors for the Knoevenagel reaction, which can be carried on using aldehydes **Y** in ethanol at r.t. (or THF at 40 to 70 °C) using piperidine as catalyst.

10 Example 9a: 5-phenylnicotinic acid

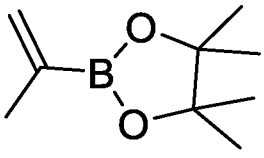
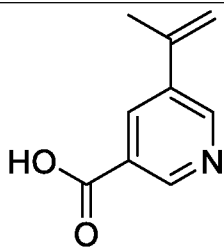
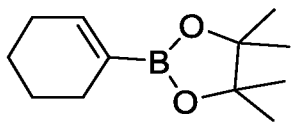
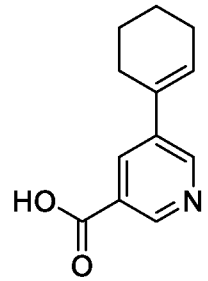
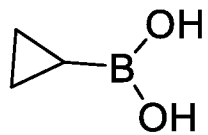
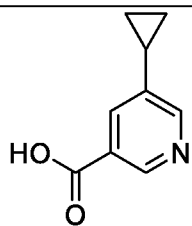
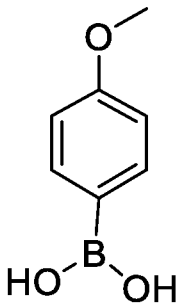
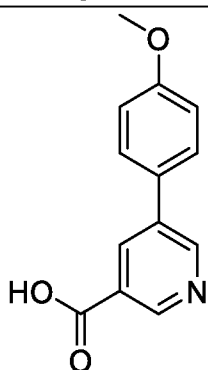
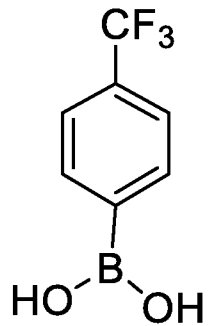
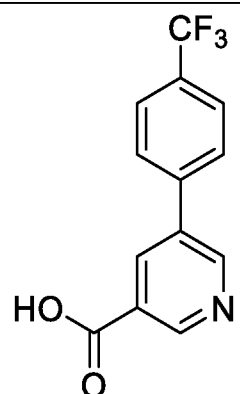


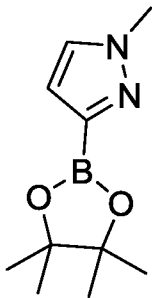
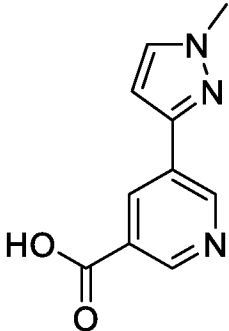
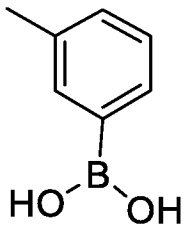
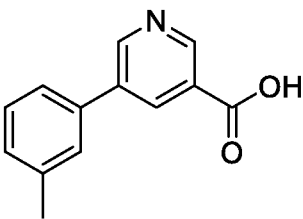
To a stirred solution of 5-bromonicotinic acid (1.0 equiv., 2.0 g, 9.90 mmol), phenylboronic acid (1.2 equiv., 1.4 g, 11.88 mmol) in Dioxane (20 ml) H₂O (4.0 ml) was added K₂CO₃ (2.0 equiv., 2.7 g, 19.80 mmol). After addition the reaction mixture was degassed with N₂ gas for 20 min and then added catalyst Pd(dppf)Cl₂ · CH₂Cl₂ (0.1 equiv., 0.80 g, 0.990 mmol) at RT and then stirred at 100 °C for 16 h. The progress of the reaction was monitored by LCMS. The reaction mixture was filtered through a celite bed and washed with EtOAc and water. The filtrate was concentrated completely and added ice cold water was added. The mixture was extracted with EtOAc. The aqueous layer was acidified with 1.5 N HCl at 0 °C and stirred for 30 min until precipitation was observed. The precipitate was filtered off and washed with water and dried thoroughly to afford 5-phenylnicotinic acid (1.10 g, 5.41 mmol, 54.7 % yield) as an off white solid. m/z = 200.1 [M+H]⁺; ¹H-NMR (400 MHz, DMSO-d₆): δ 13.57 (bs, 1H), 9.09 (dd, J = 2.00, 18.60 Hz, 2H), 8.45 (t, J = 2.40 Hz, 1H), 7.81-7.78 (m, 2H), 7.56-7.47 (m, 3H).

Additional examples:

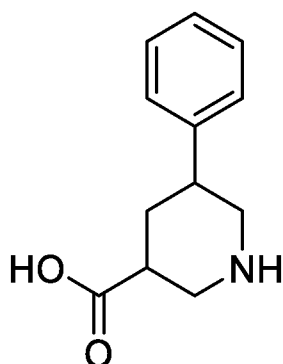
Additional examples made in accordance with a method similar to that described above and illustrated in scheme 5 are shown below.

Example number	Employed Boronate	Structure/Preparation	m/z (M+H) ⁺
----------------	-------------------	-----------------------	------------------------

9b			164.3
9c			204.2
9d			164.4
9e			230.1
9f			268.2

9g			204.3
9i			214.1

Example 10a: 5-phenylpiperidine-3-carboxylic acid (see, for example, scheme 5)



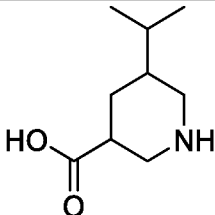
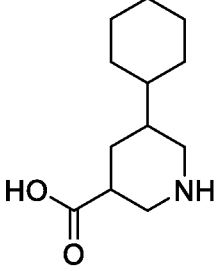
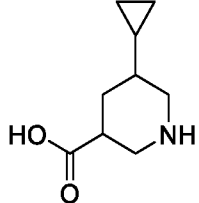
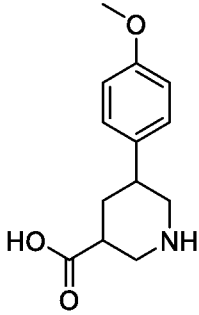
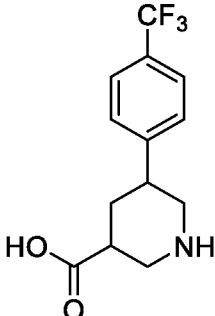
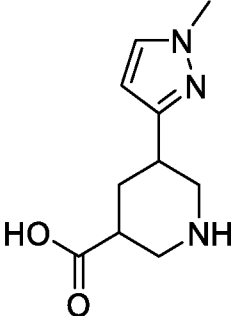
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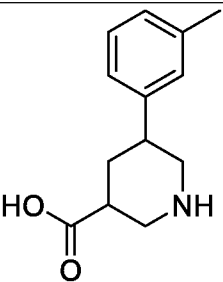
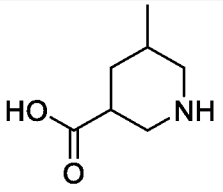
To a stirred solution of 5-phenylnicotinic acid (1.0 equiv., 0.500 g, 2.510 mmol) in acetic acid (20 ml) was added Platinum(IV) oxide (0.4 equiv., 0.285 g, 1.255 mmol) at room temperature and stirred under hydrogen gas bladder pressure for 48 h. The progress of the reaction was monitored by LCMS. Reaction mass was filtered through celite bed and washed with methanol. The filtrate was concentrated under reduced pressure. The crude residue was purified by reverse phase column chromatography in 0.1% formic acid: acetonitrile to give 5-phenylpiperidine-3-carboxylic acid (0.500 g, 1.949 mmol, 99 % yield) as gummy colourless compound. m/z = 206.2 $[M+H]^+$; 1H -NMR (400 MHz, DMSO- d_6): δ 11.37 (bs, 1H), 7.33-7.21 (m, 5H), 3.17-2.79 (m, 5H), 2.70-2.62 (m, 1H), 1.84-1.66 (m, 2H).

15

Additional examples:

Additional examples made in accordance with a method similar to that described above and illustrated in step ii, scheme 5 are shown below.

Example number	Structure/Preparation	m/z (M+H) ⁺
10b		172.2
10c		212.3
10d		170.1
10e		236.2
10f		274.2
10g		210.1

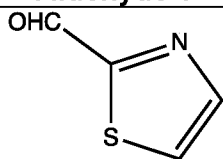
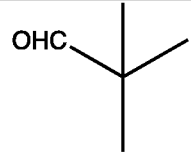
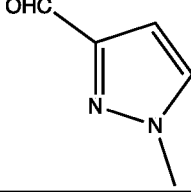
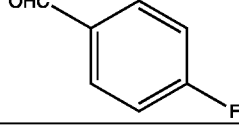
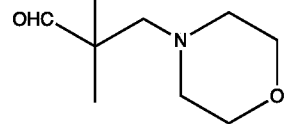
10i		220.1
10k		144.1

N.B. 3-piperidine carboxylic acid is commercially available and, for example, can be obtained from Sigma-Aldrich.

- 5 Compounds 10a to 10k and 3-piperidine carboxylic acid are then reacted with DIPEA and 1-cyanoacetyl-3,5-dimethyl-1H-pyrazole (as illustrated in step iii, scheme 5).

The resulting compounds are then reacted with the aldehydes shown below (as illustrated in step iv, scheme 5).

10

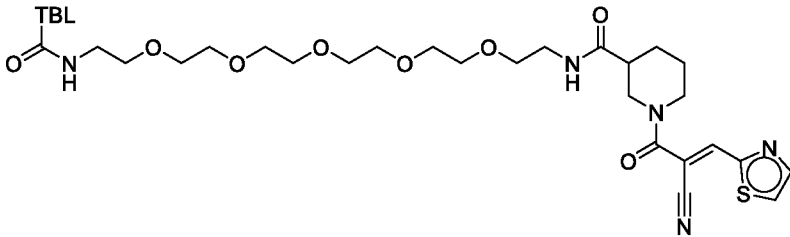
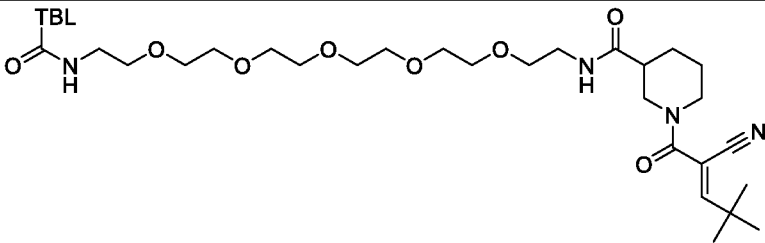
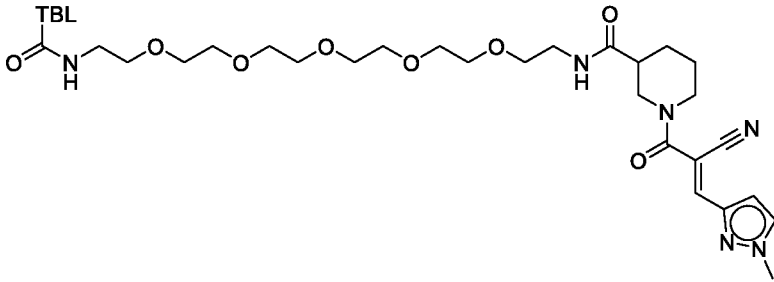
Aldehyde Y






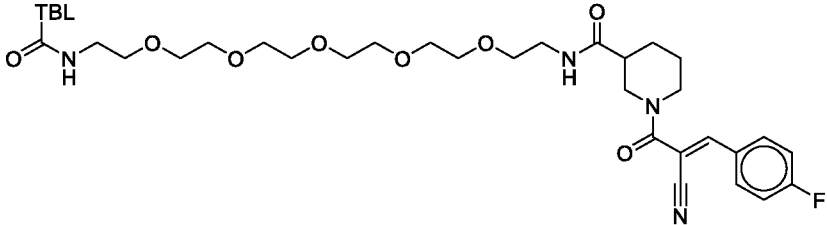
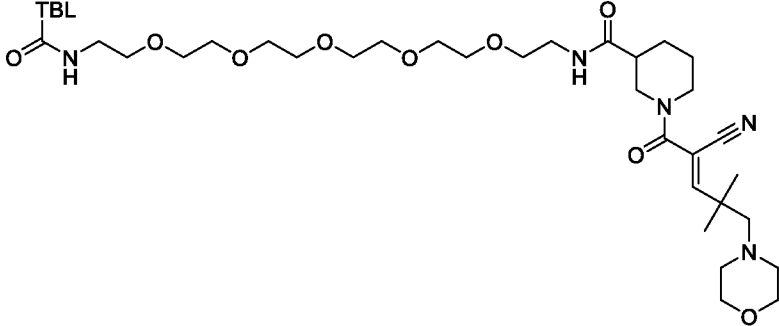
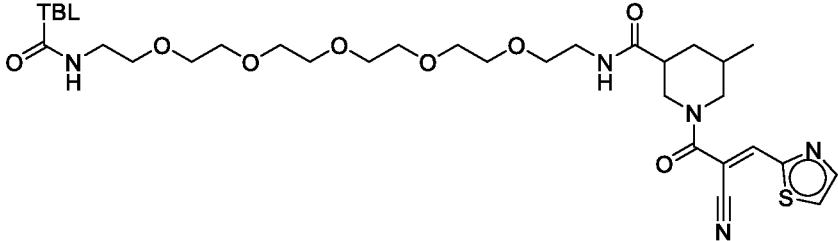
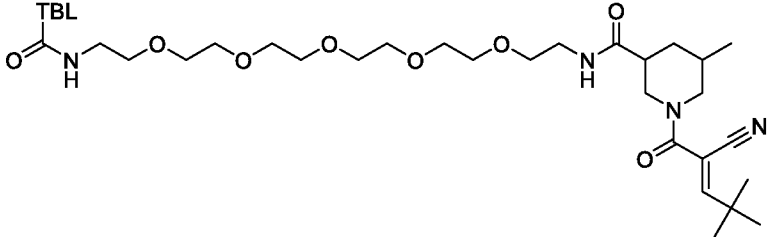
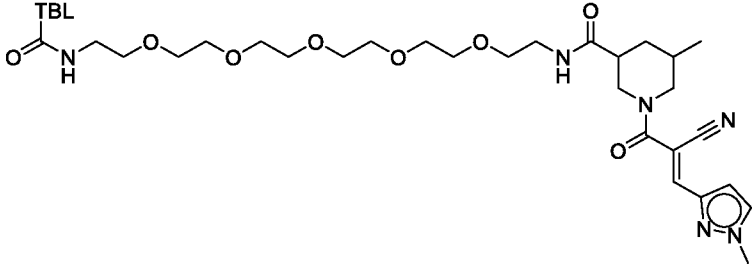
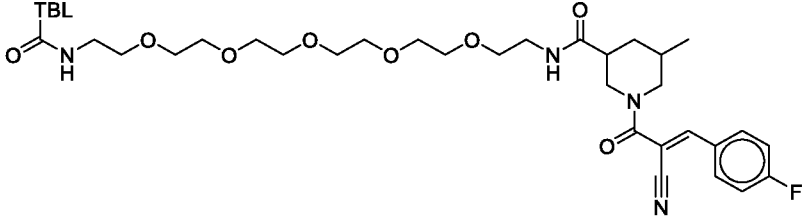
Synthesis of the final bifunctional degraders is illustrated in scheme 6

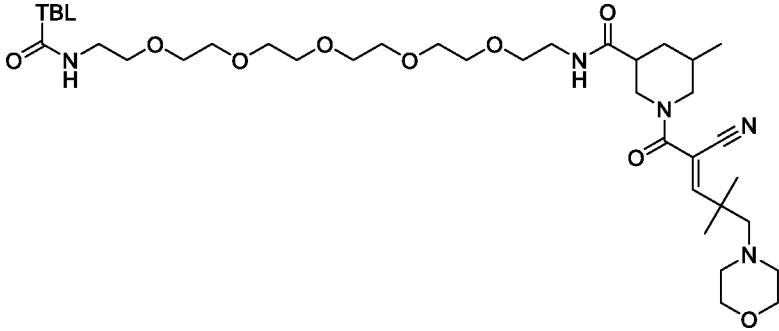
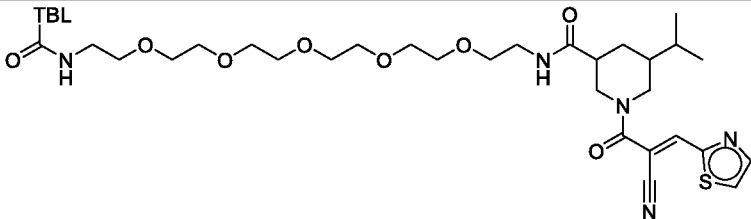
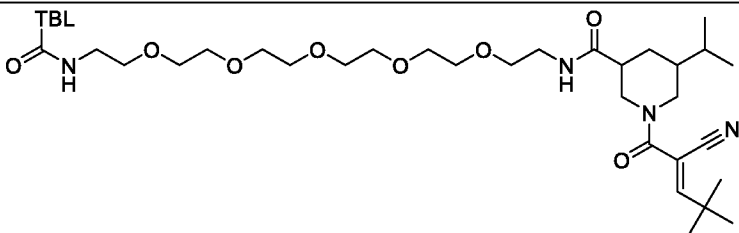
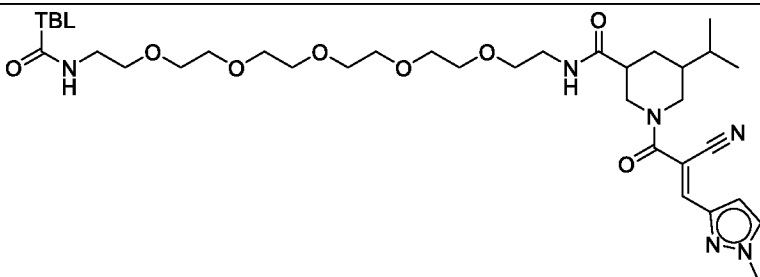
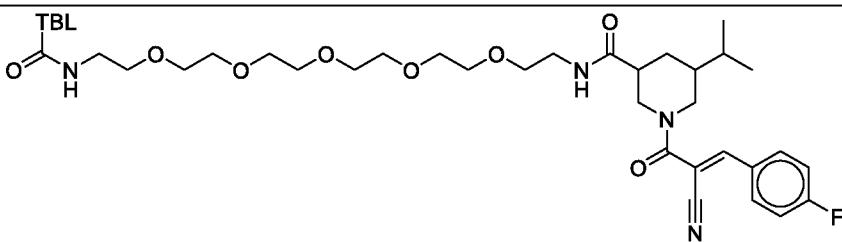
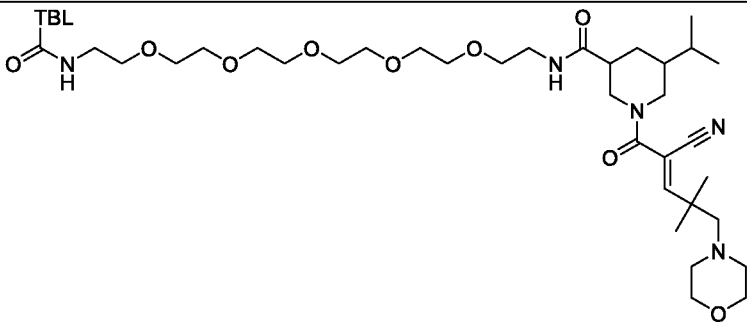
- 5 Piperidine-acrylamide acids and amine-linker functionalised target protein binding ligand are dissolved in DMF and treated with HATU and DIPEA at room temperature to afford the bifunctional compounds.

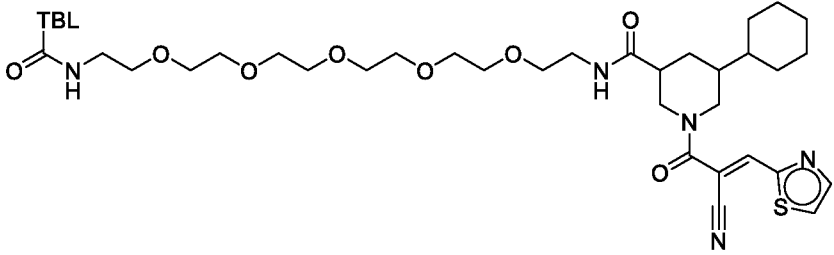
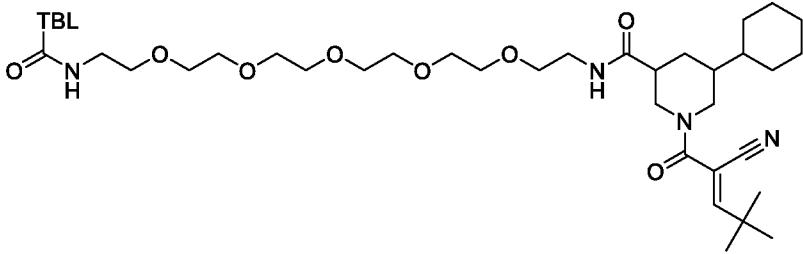
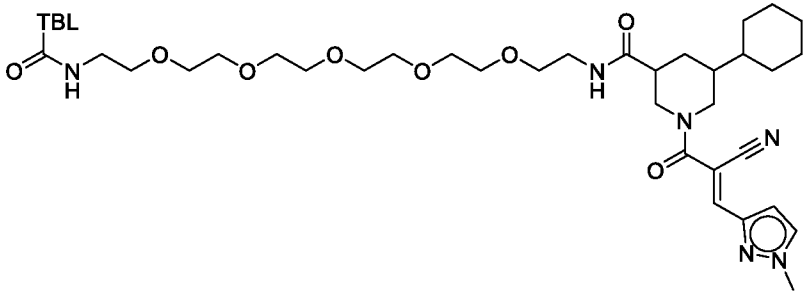
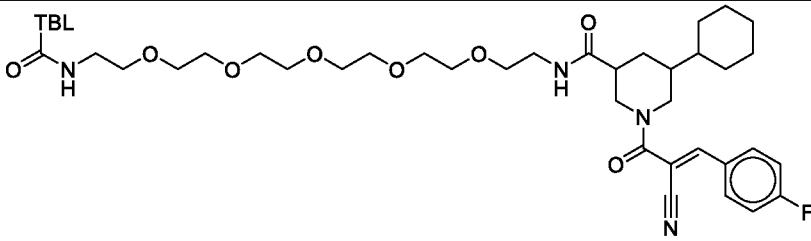
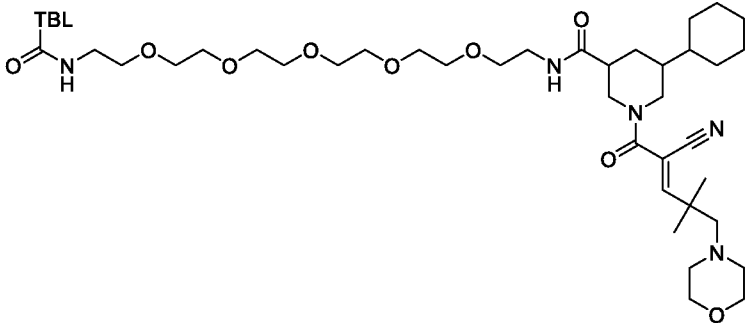
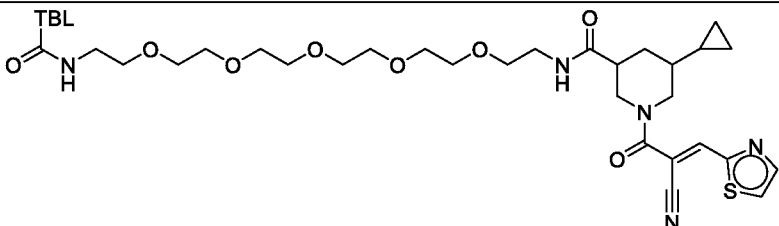
Example compounds that are made in accordance with the method illustrated in scheme 6 are shown below.

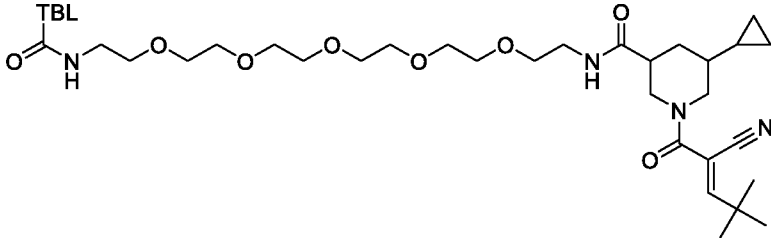
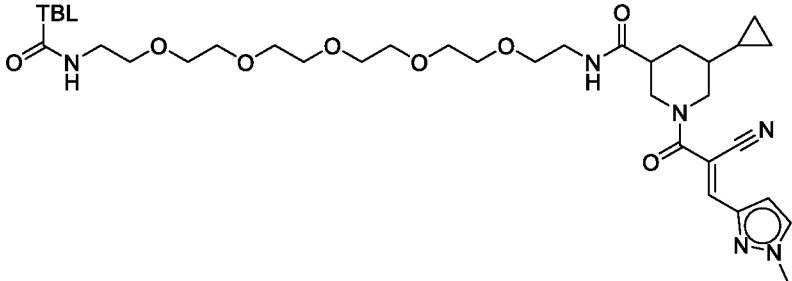
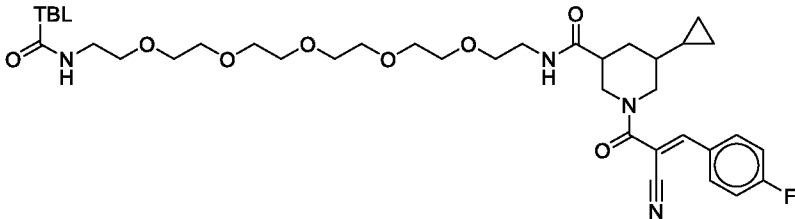
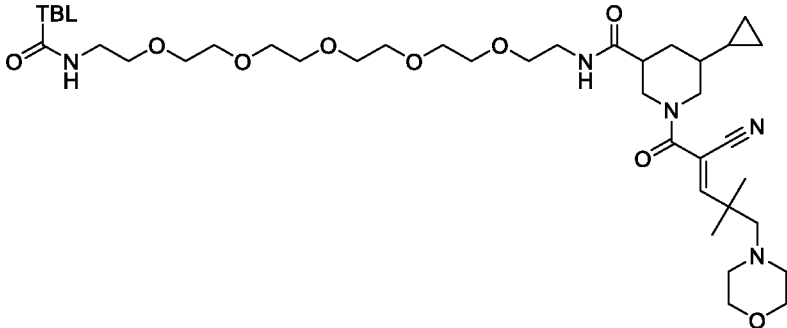
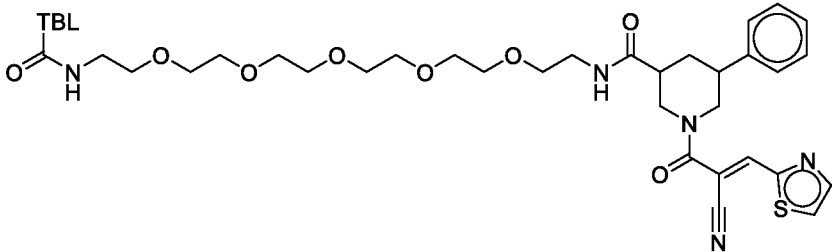
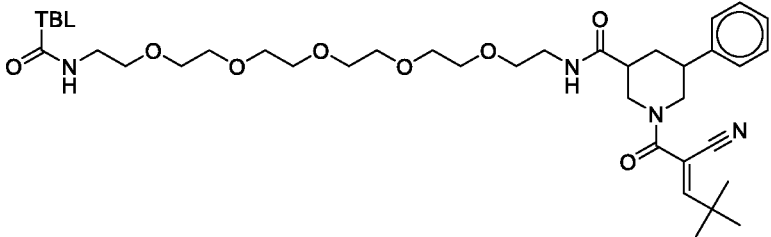
10

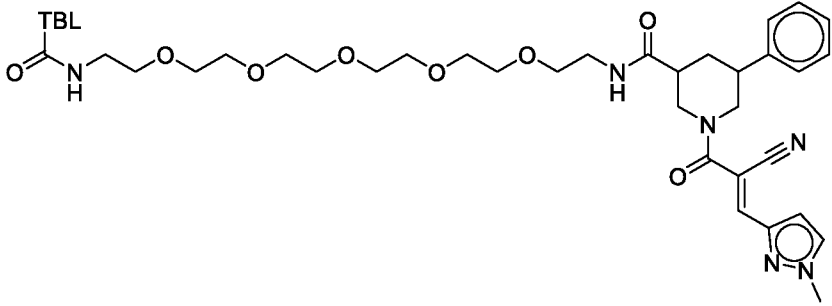
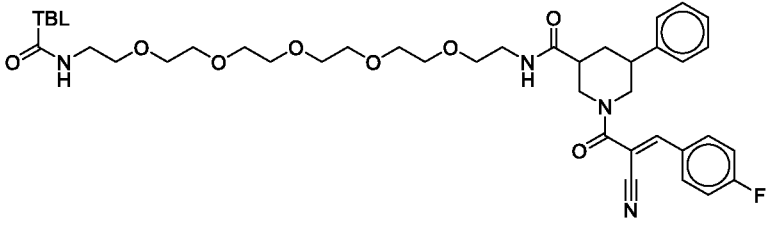
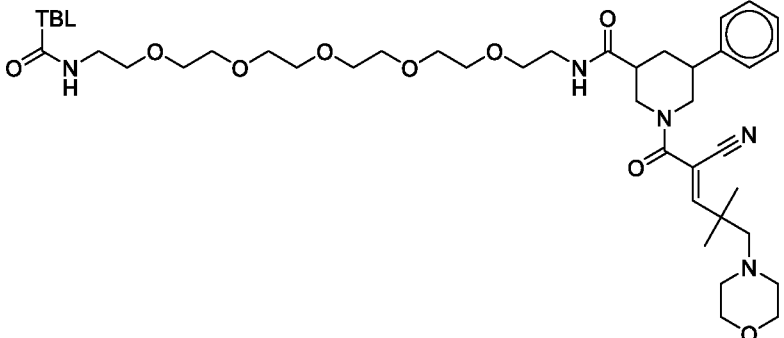
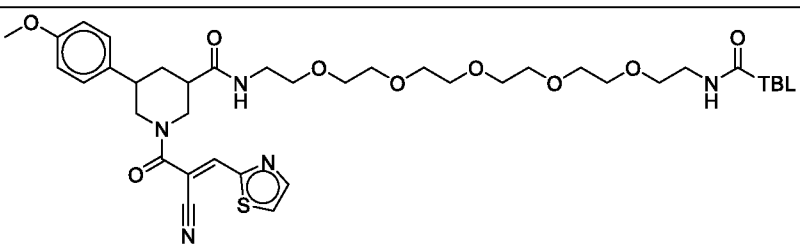
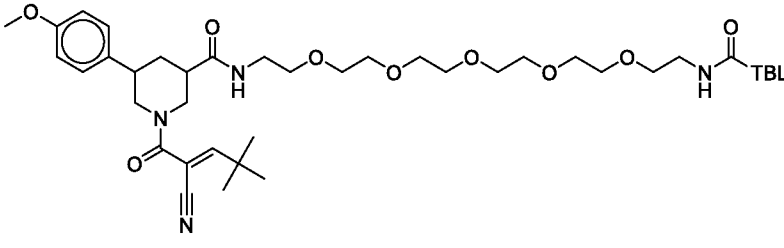
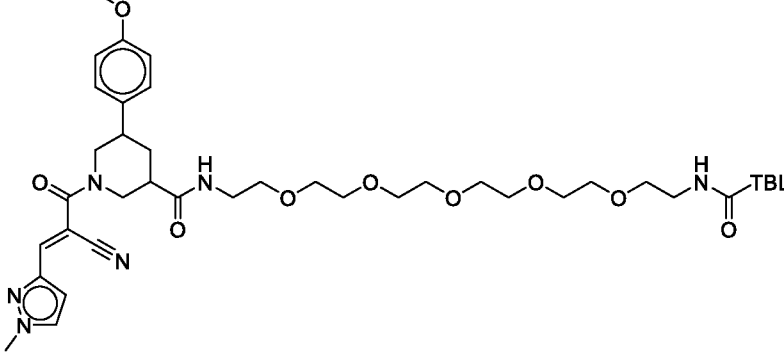
Example No.	Structure
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13b	
13c	

13d	
13e	
13f	
13g	
13h	
13i	

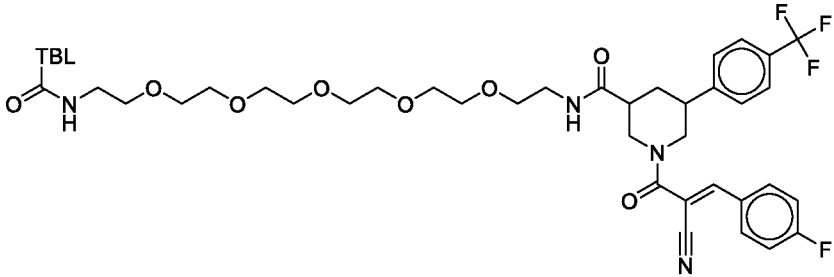
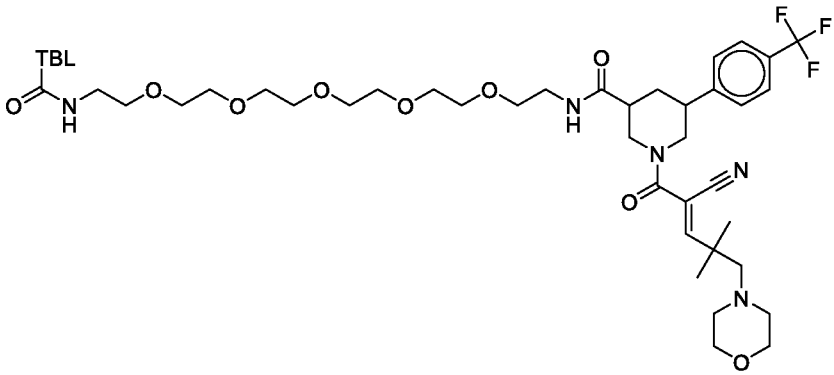
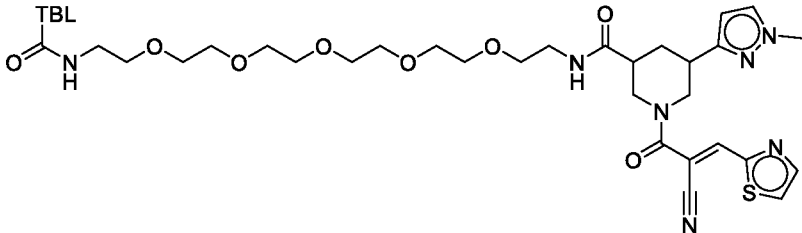
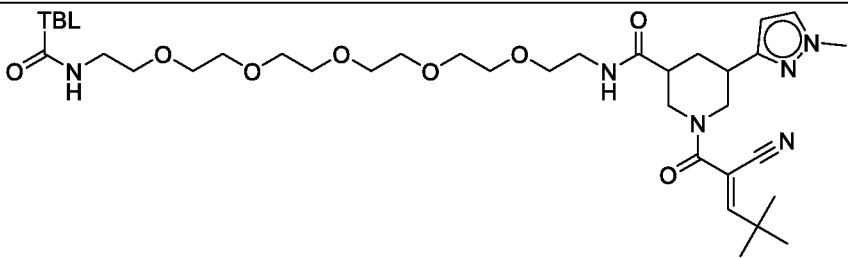
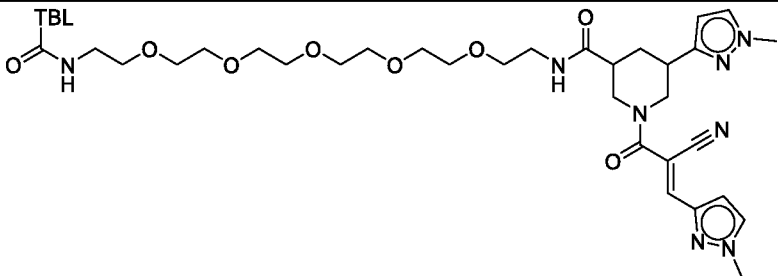
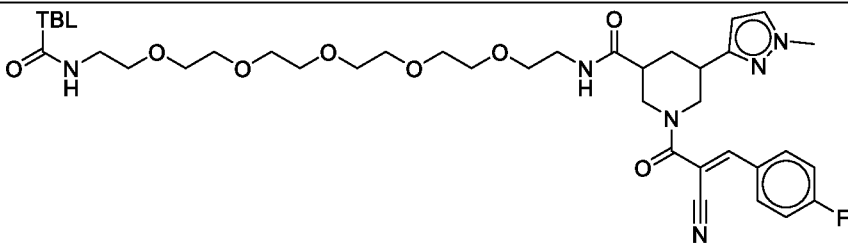
13j	
13k	
13l	
13m	
13n	
13o	

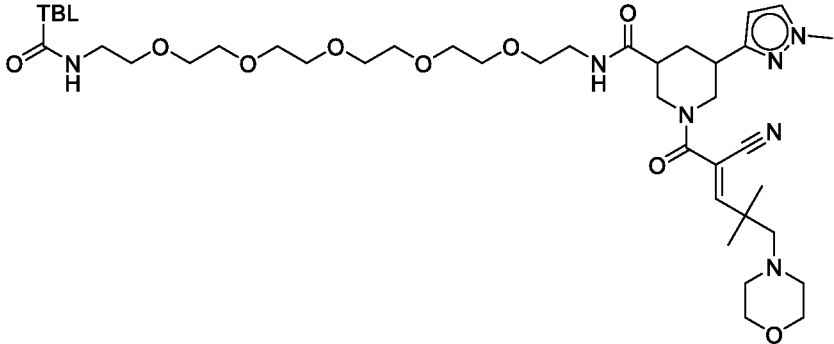
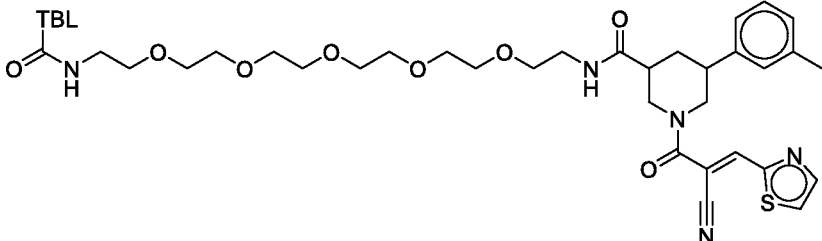
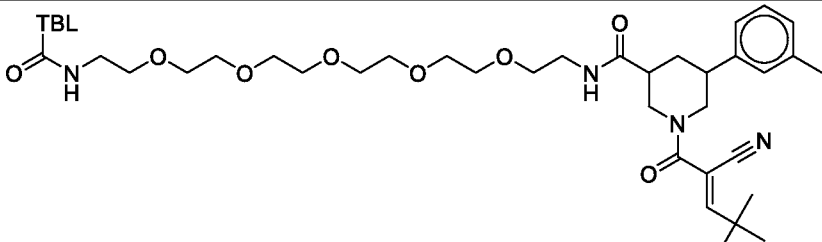
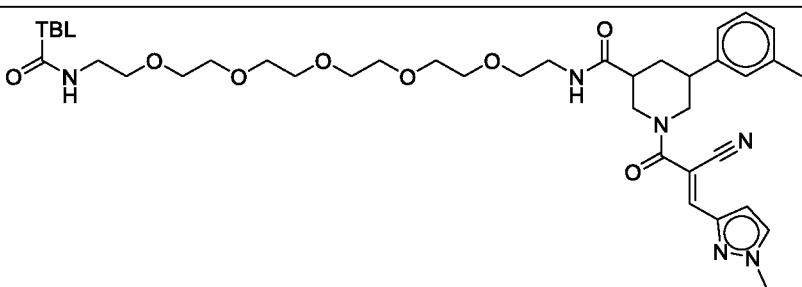
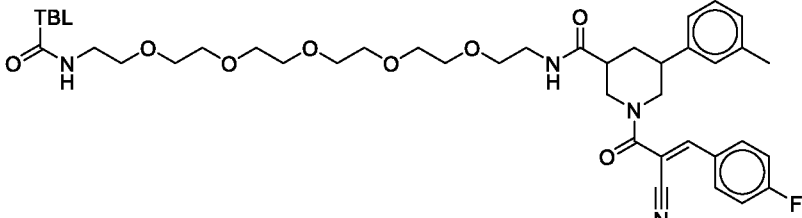
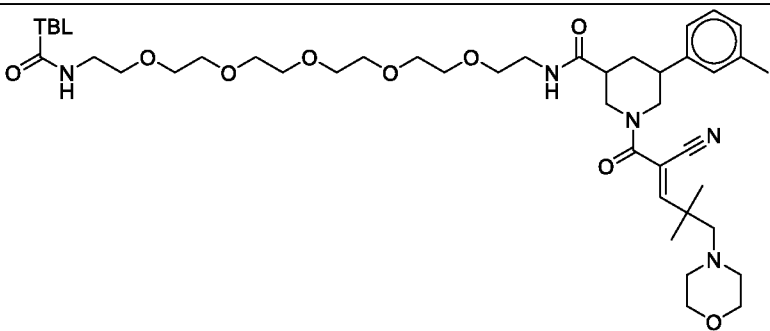
13p	
13q	
13r	
13s	
13t	
13u	

13v	
13w	
13x	
13y	
13z	
13aa	

13ab	
13ac	
13ad	
13ae	
13af	
13ag	

13ah	
13ai	
13aj	
13ak	
13al	

13am	
13an	
13ao	
13ap	
13aq	
13ar	

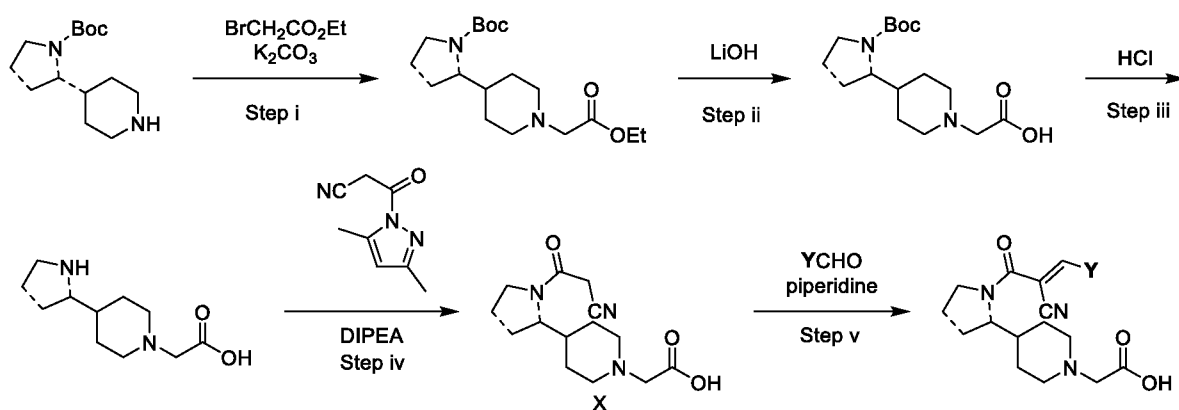
13as	
13at	
13au	
13av	
13aw	
13ax	

Piperidine–pyrrolidine-based warheads

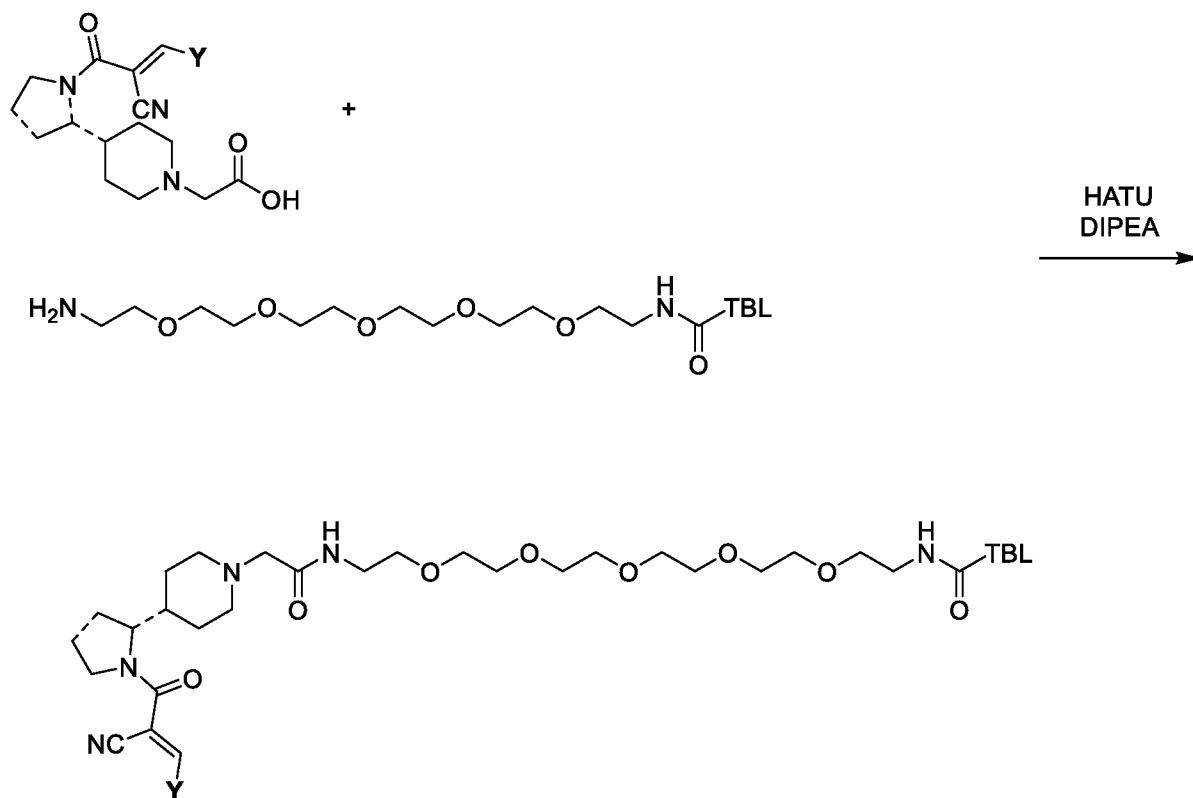
- 5 Further examples of bifunctional degraders comprising a piperidine-pyrrolidine-based moiety as Z are illustrated below.

Overviews of various exemplary synthetic methods that may be used to provide these compounds are shown below.

- 10 Overview of synthetic pathway – scheme 7



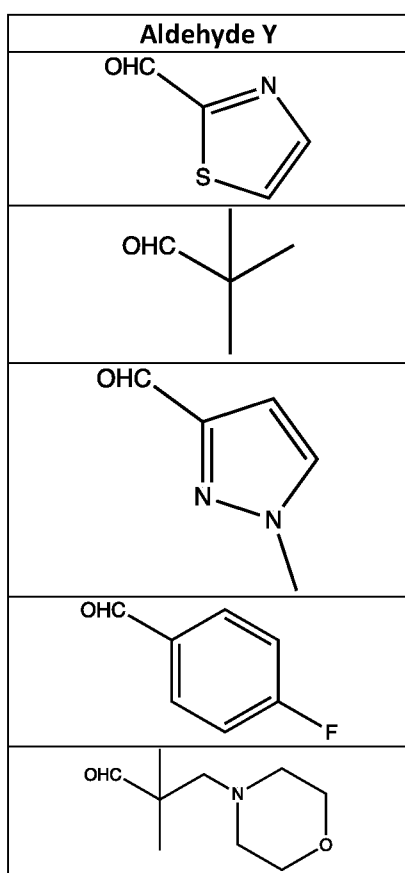
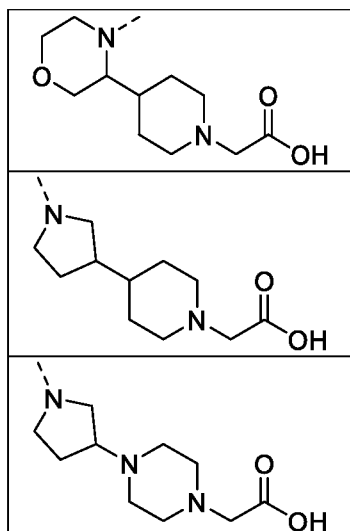
- 15 Overview of synthetic pathway – scheme 8



Synthesis from commercially available mono-Boc diamines (scheme 7)

Commercially available mono-*N*-Boc protected diamines are alkylated (ethyl bromoacetate, K₂CO₃ in DMF or MeCN). Hydrolysis of the ester group (LiOH in THF/H₂O) affords the carboxylic acid. Deprotection of the *N*-Boc amine (HCl in DCM/dioxane) delivers the free amino acid. Acylation using 1 cyanoacetyl-3,5-dimethylpyrazole and DIPEA in dioxane or DMF affords the precursors **X** for the Knoevenagel reaction, which can be carried on using aldehydes **Y** shown below in ethanol at r.t. (or THF at 40 to 70 °C) using piperidine as catalyst. Precursors **X** and aldehydes **Y** to be used in the Knoevenagel reaction (step v, Scheme 7) are shown below.

X

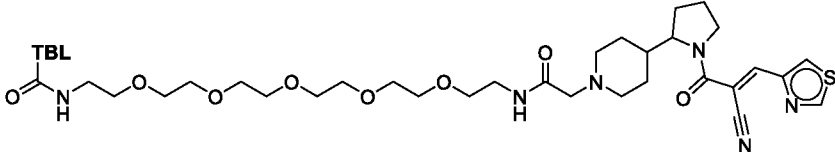
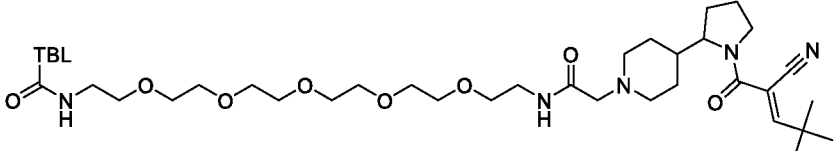
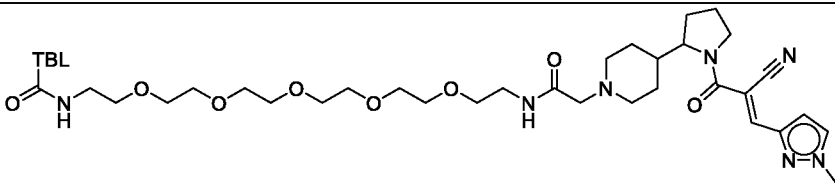
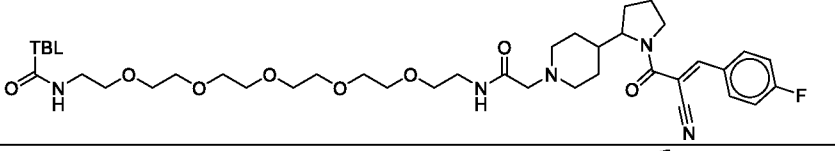
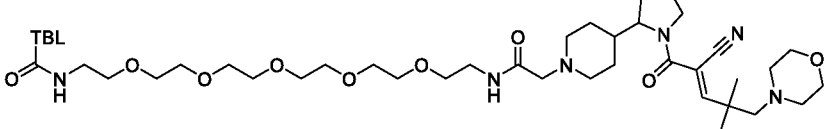
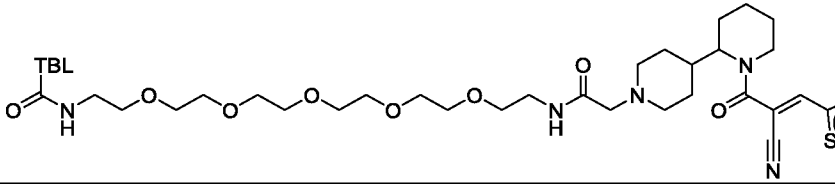
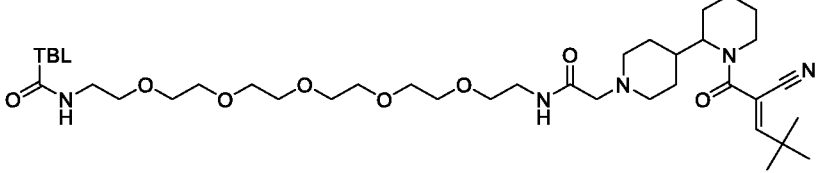
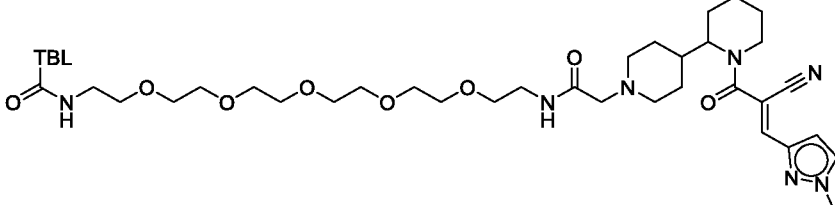
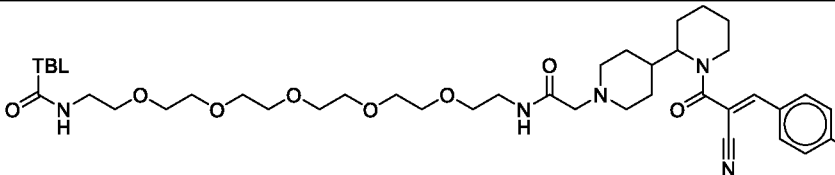


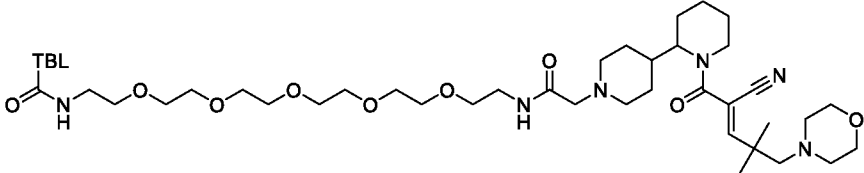
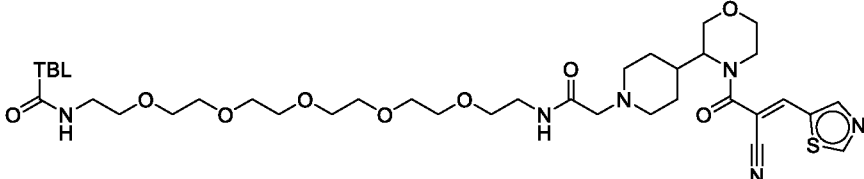
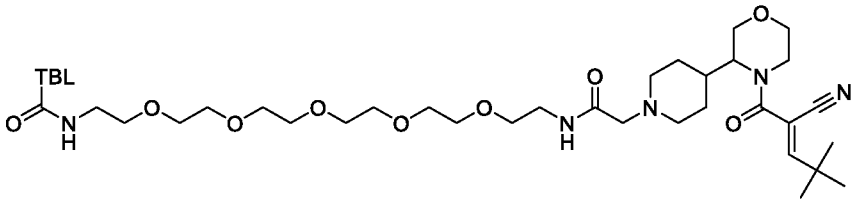
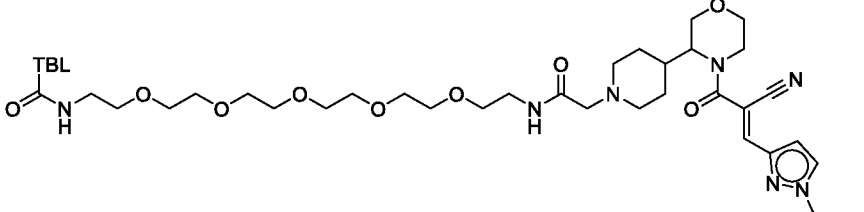
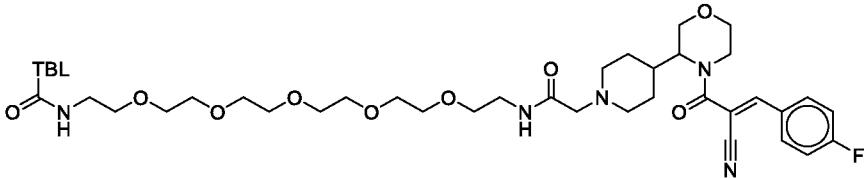
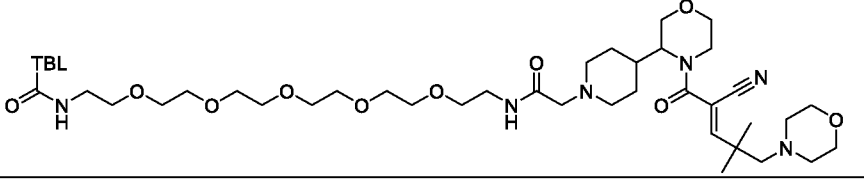
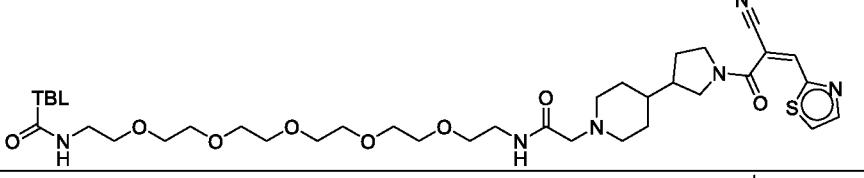
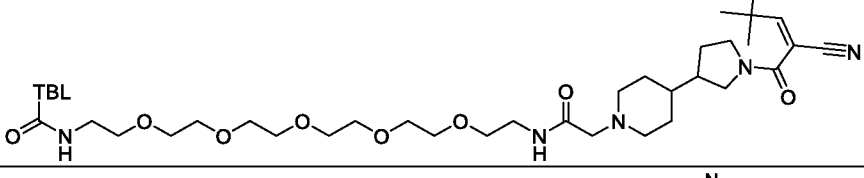
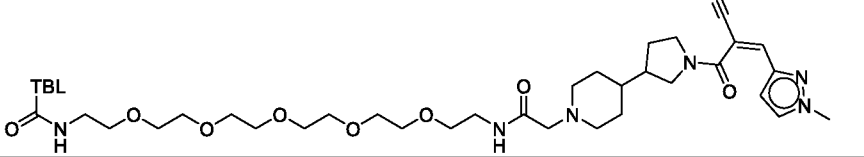
Examples of bifunctional compounds:

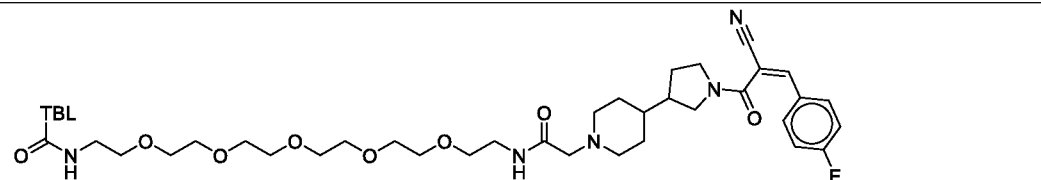
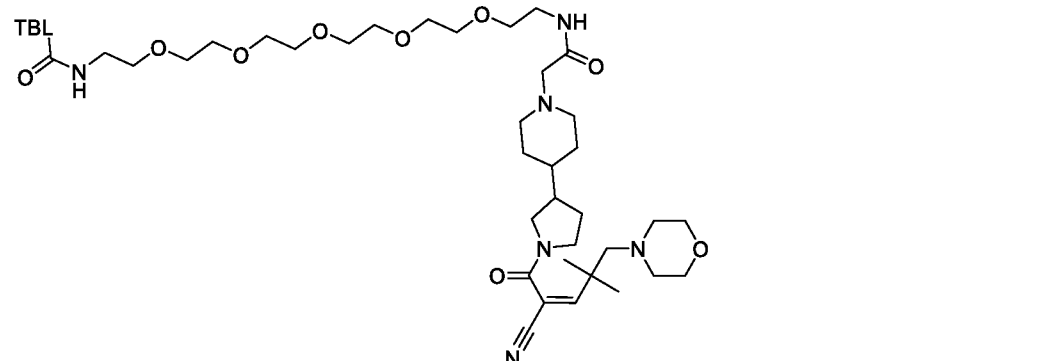
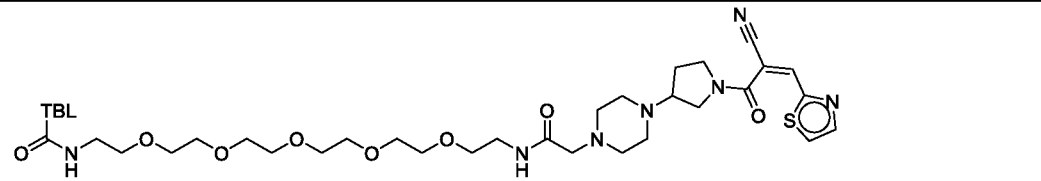
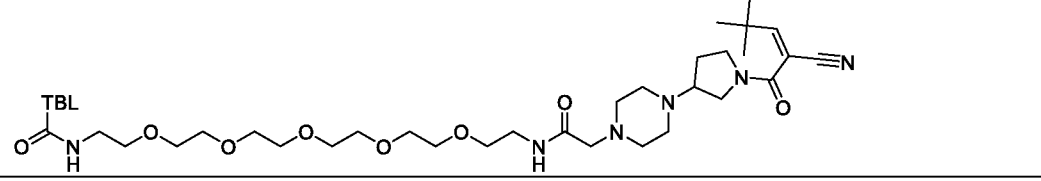
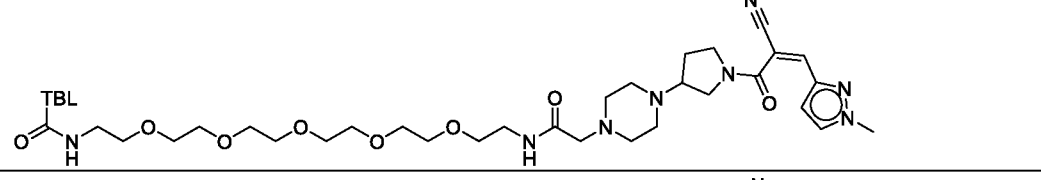
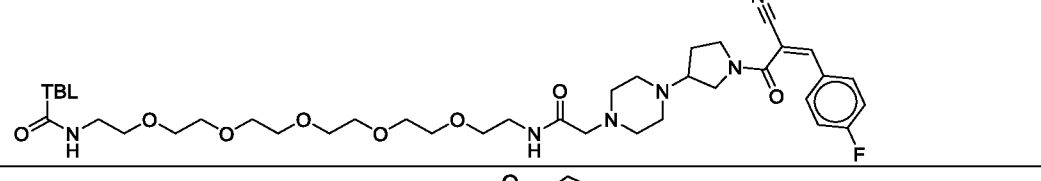
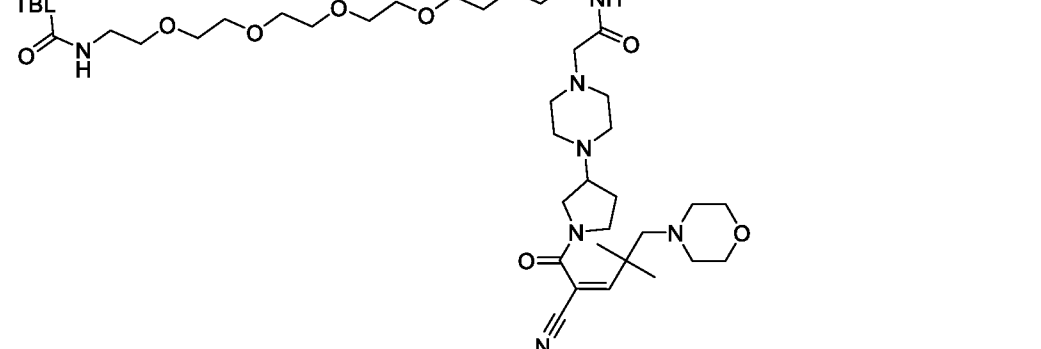
- 5 Synthesis of the final bifunctional degraders is illustrated in scheme 8.

Cyanoacrylamide acids and amine-linker functionalised target protein binding ligand are dissolved in DMF and treated with HATU and DIPEA at room temperature to afford the bifunctional compounds.

Example compounds that are made in accordance with the method illustrated in scheme 8 are shown below.

Example No.	Structure
14a	
14b	
14c	
14d	
14e	
14f	
14g	
14h	
14i	

14j	
14k	
14l	
14m	
14n	
14o	
14p	
14q	
14r	

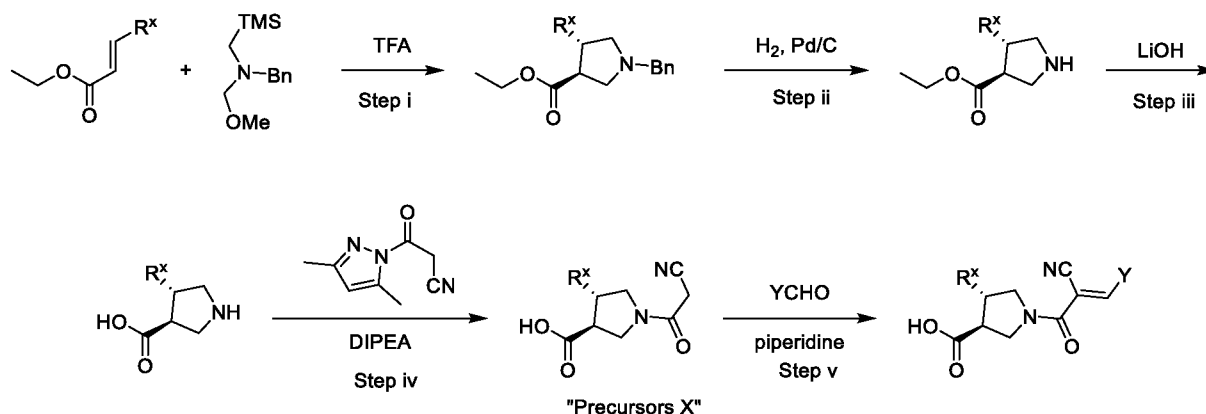
14s	
14t	
14u	
14v	
14w	
14x	
14y	

Pyrrolidine-based warheads

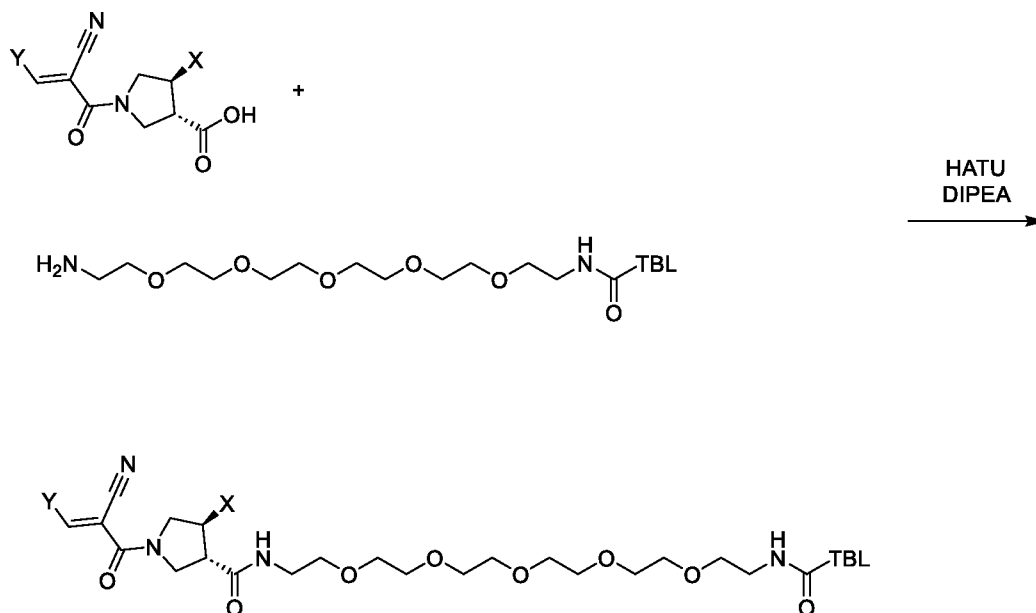
Further examples of bifunctional degraders comprising a pyrrolidine-based moiety as Z are illustrated below.

Overviews of various exemplary synthetic methods that may be used to provide these compounds are shown below.

Overview of synthetic pathway – scheme 9



Overview of synthetic pathway – scheme 10

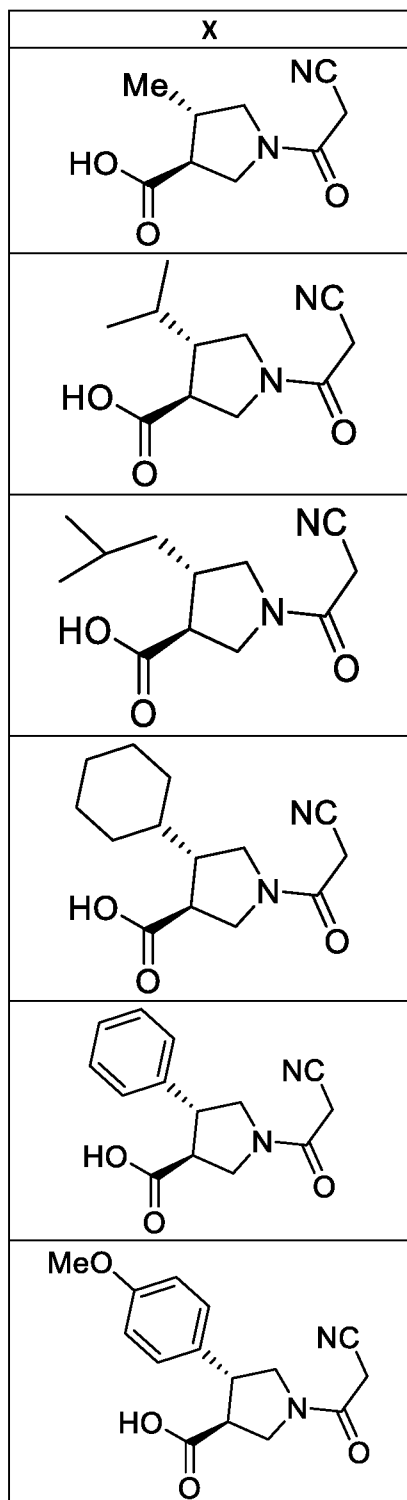


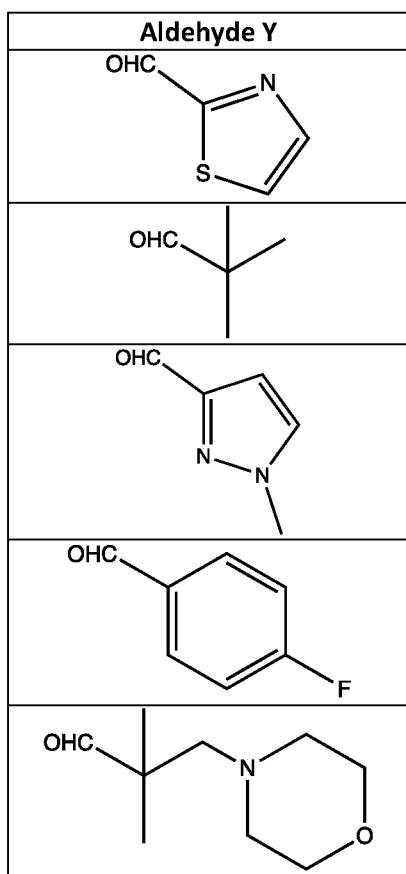
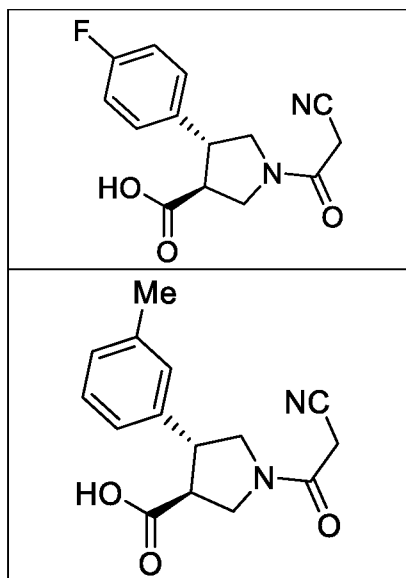
Synthesis from commercially available acrylate esters (scheme 9):

Acrylate esters are treated with *N*-benzyl-1-methoxy-*N*-((trimethylsilyl)methyl)ethanamine and TFA in toluene to afford the trans-3,4-disubstituted *N*-benzyl-pyrrolidines. Cleavage of the benzyl group (H_2 , $\text{Pd}(\text{OH})_2/\text{C}$ in ethanol or methanol) affords the free pyrrolidine analogues. Hydrolysis of the ester group (LiOH in $\text{THF}/\text{H}_2\text{O}$) affords the free amino acids. Acylation using 1 cyanoacetyl-3,5-dimethylpyrazole and DIPEA in dioxane or DMF affords the precursors X

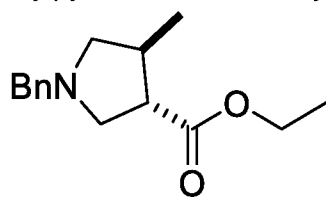
for the Knoevenagel reaction, which can be carried on using aldehydes **Y** shown below in ethanol at r.t. (or THF at 40 to 70 °C) using piperidine as catalyst.

Precursors **X** and aldehydes **Y** to be used in the Knoevenagel reaction (step v, Scheme 9) are shown below.



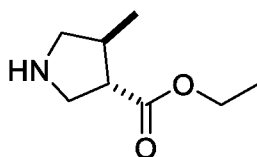


Example 11a Ethyl 1-benzyl-4-methylpyrrolidine-3-carboxylate (see step i, scheme 9)



To a stirred solution of ethyl (*E*)-but-2-enoate (1.154 g, 10.11 mmol) in toluene (20 ml) was added N-benzyl-1-methoxy-N-((trimethylsilyl)methyl)methanamine (3.00 g, 12.64 mmol) at 0 °C. The reaction mixture was stirred for 20 min and then a 1 M solution of TFA in DCM (0.097 ml, 1.264 mmol) was added slowly at 0 °C under inert atmosphere. Reaction mixture was stirred for 30 min at 0 °C and then stirred at RT for 12 h. The progress of the reaction mixture was monitored by LCMS. The reaction was quenched with H₂O, extracted with CHCl₃, and the organic extracts were dried over sodium sulphate. The solvent was evaporated to dryness, and the oily residue was subjected to column chromatography (silica gel, hexanes: ether = 6 : 1) to give ethyl 1-benzyl-4-methylpyrrolidine-3-carboxylate (2.6 g, yield 84%) as clear oil. LCMS: m/z = [M+H]⁺ 248.2; ¹H-NMR (400 MHz, DMSO-d₆): δ 7.32-7.28 (m, 5H), 4.16 (q, J = 1.60 Hz, 2H), 3.74-3.63 (m, 2H), 2.96-2.86 (m, 3H), 2.63-2.53 (m, 2H), 2.51-2.32 (m, 1H), 1.27 (t, J = 7.20 Hz, 3H), 1.17 (d, J = 6.80 Hz, 3H).

Example 12a: Ethyl 4-methylpyrrolidine-3-carboxylate (see step ii, scheme 9)



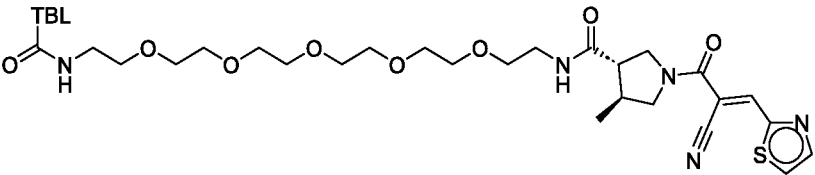
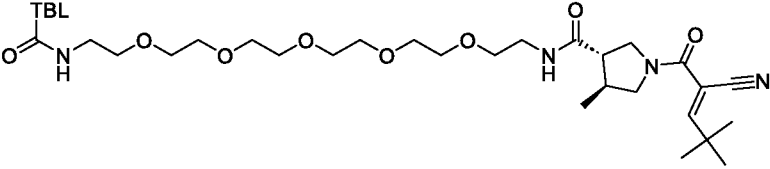
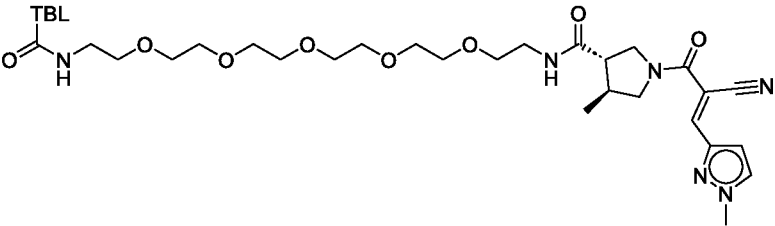
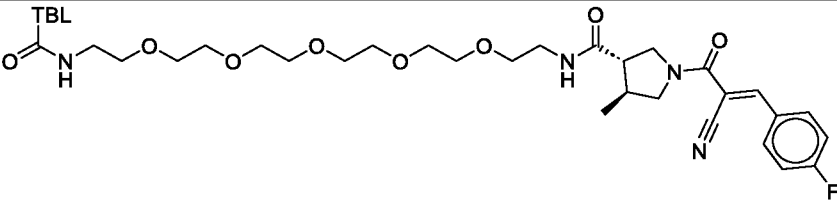
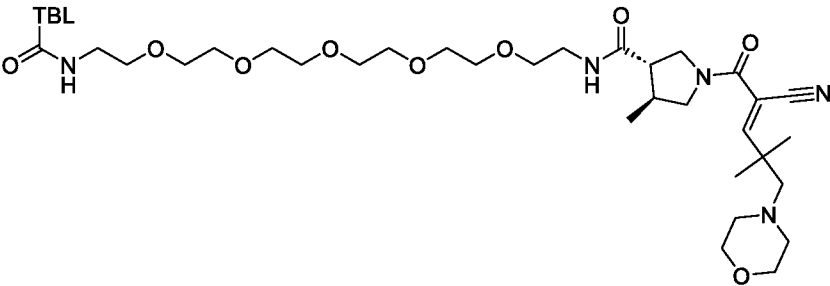
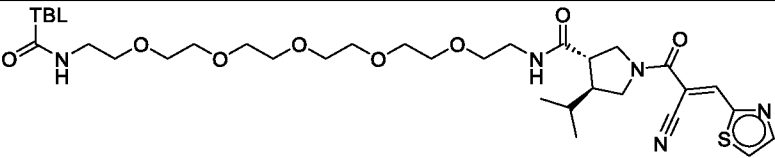
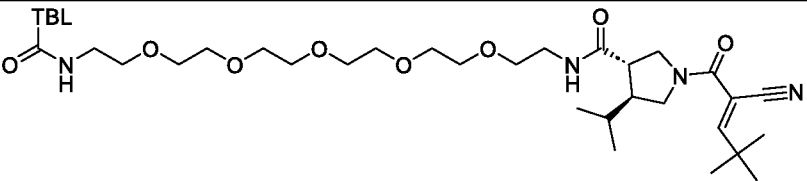
To a stirred solution of ethyl 1-benzyl-4-methylpyrrolidine-3-carboxylate (1.5 g, 6.06 mmol) in Ethanol (15.00 ml) was added palladium hydroxide on carbon (0.2 g, 1.424 mmol) and the reaction mixture was degassed and purged with hydrogen gas. The reaction mixture was stirred under hydrogen bladder pressure at room temperature for 48 h. The reaction progress was monitored by TLC. The suspension was filtered over a celite pad and washed with ethanol. The collected filtrate was concentrated under reduced pressure to afford ethyl 4-methylpyrrolidine-3-carboxylate (0.81 g, Yield- 85%) as a brown oil. LCMS: m/z = 158.2 [M+H]⁺; ¹H-NMR (400 MHz, DMSO-d₆): δ 4.05 (q, J = 1.20 Hz, 2H), 3.06-2.97 (m, 3H), 2.90-2.86 (m, 1H), 2.52-2.50 (m, 2H), 2.32-2.19 (m, 1H), 1.19 (t, J = 7.20 Hz, 3H), 1.02 (d, J = 6.80 Hz, 3H).

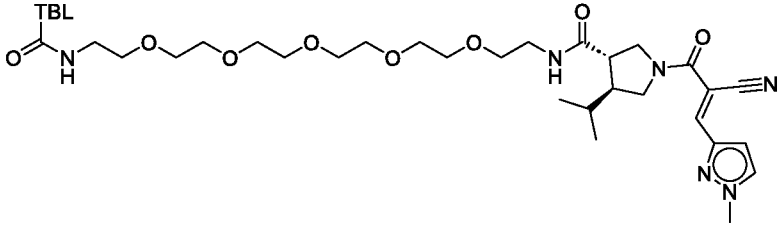
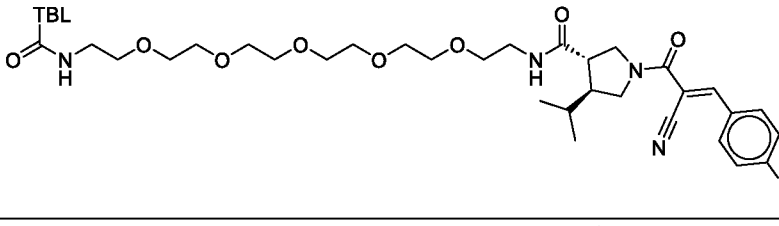
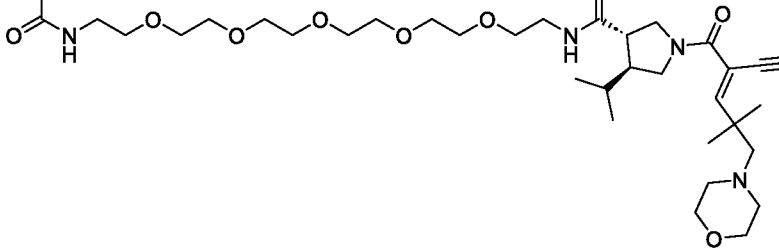
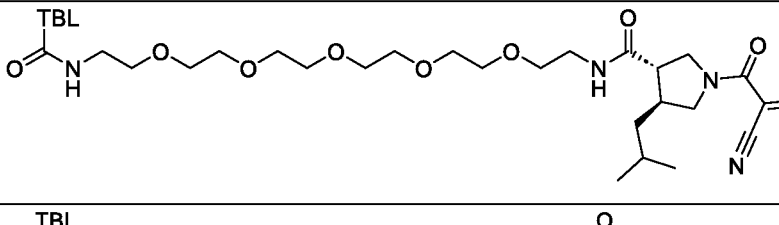
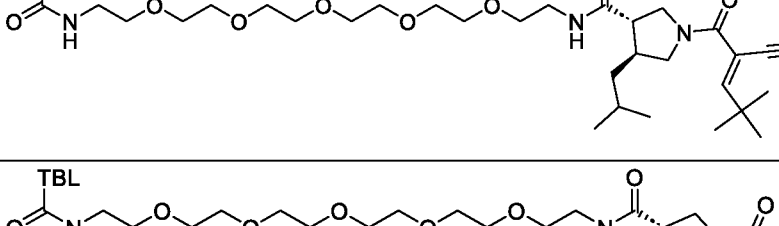
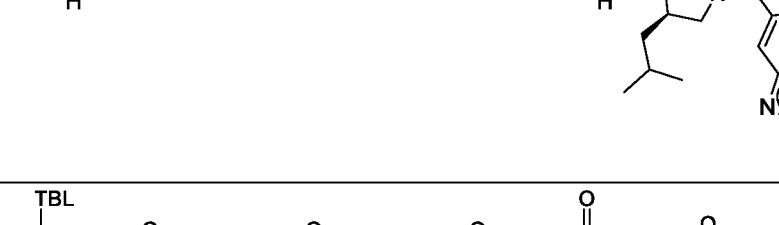
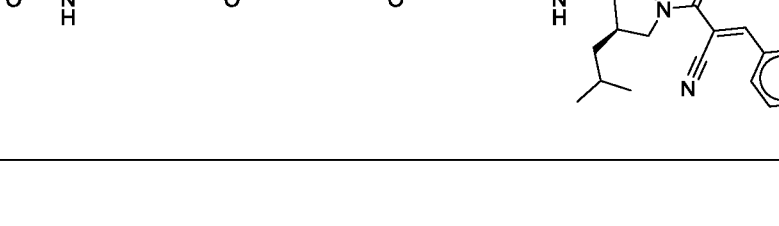
Examples of bifunctional compounds:

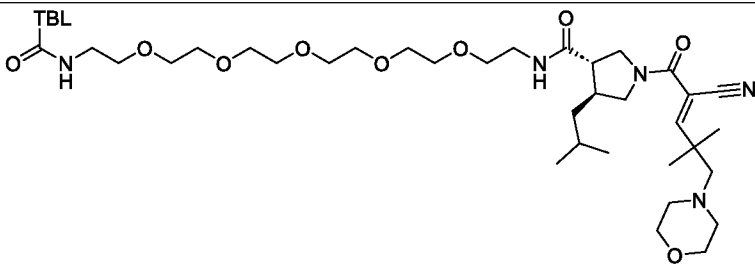
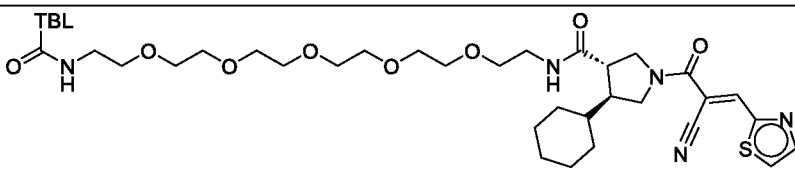
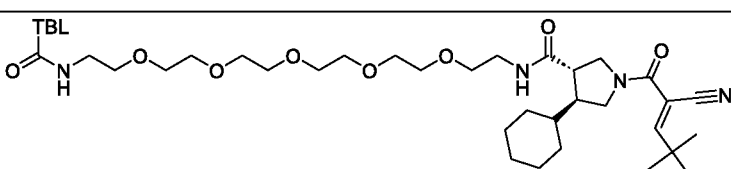
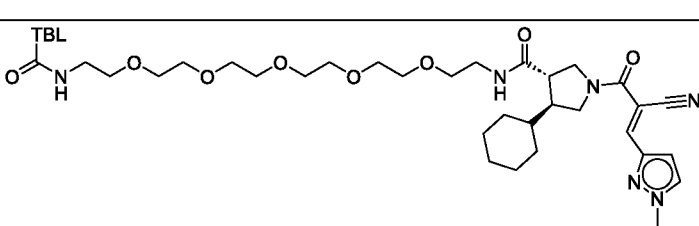
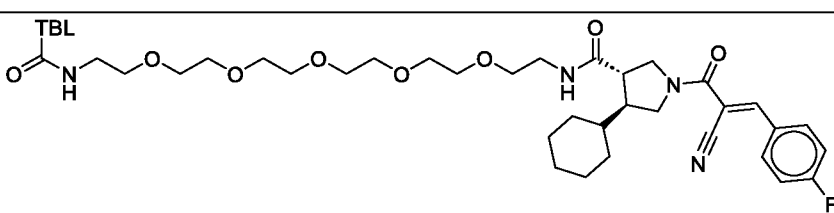
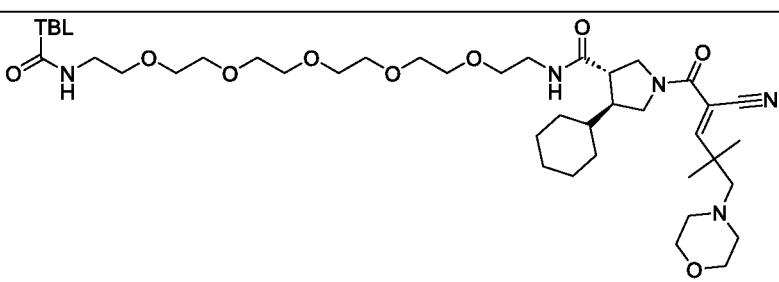
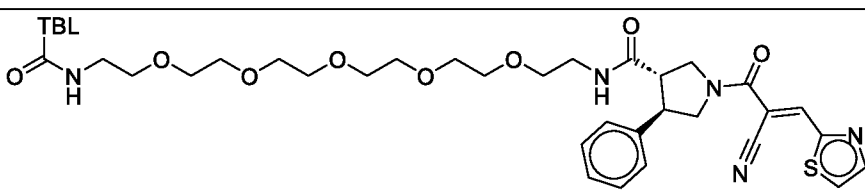
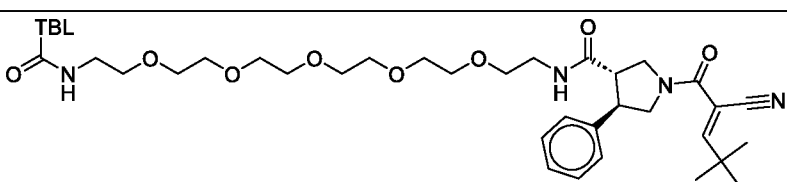
Synthesis of the final bifunctional degraders is illustrated in scheme 10.

Cyanoacrylamide acids and amine-linker functionalised target protein binding ligand are dissolved in DMF and treated with HATU and DIPEA at room temperature to afford the bifunctional compounds.

Example compounds that are made in accordance with the method illustrated in scheme 10 are shown below.

Example number	Structure
15a	
15b	
15c	
15d	
15e	
15f	
15g	

15h	
15i	
15j	
15k	
15l	
15m	
15n	

15o	
15p	
15q	
15r	
15s	
15t	
15u	
15v	

15w	
15x	
15y	
15z	
15aa	
15ab	
15ac	
15ad	

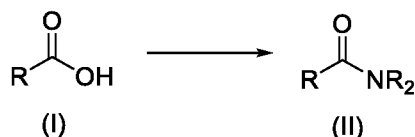
15ae	
15af	
15ag	
15ah	
15ai	
15aj	
15ak	

15al	
15am	
15an	

Further Synthetic Methods – ER degraders

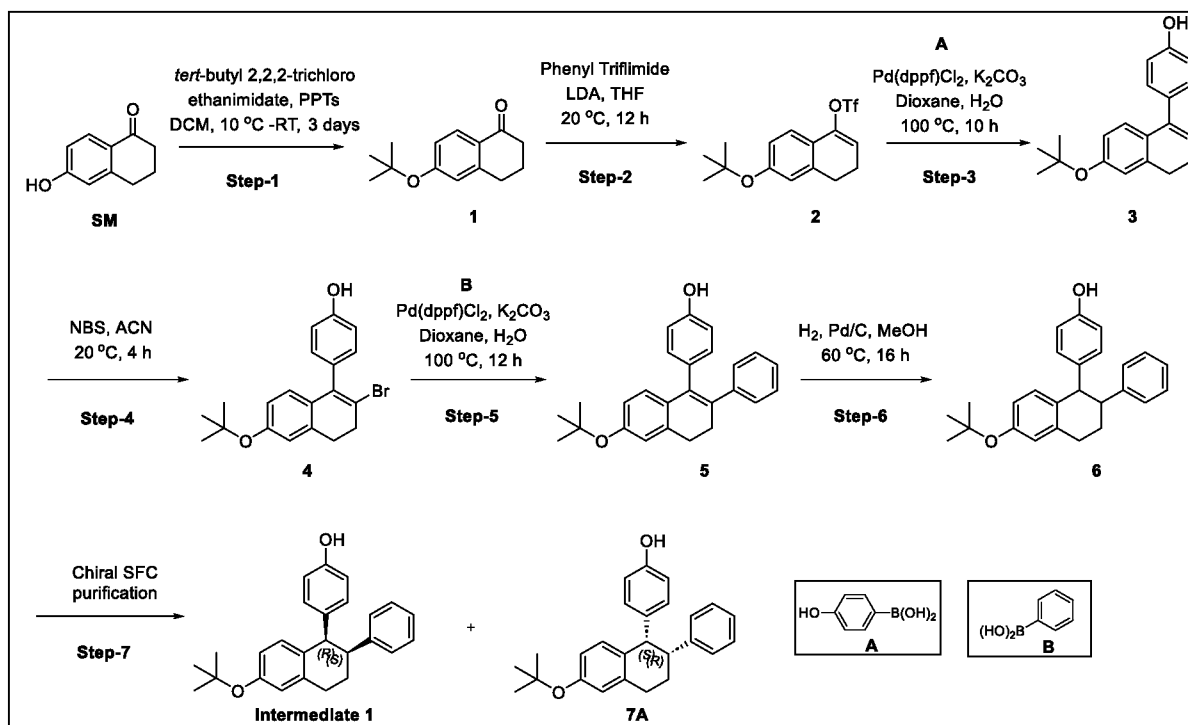
Overviews of various exemplary synthetic methods and general procedures that may be used to provide the compounds of the present disclosure are shown below.

Amide coupling – General procedure 1



To a stirring solution of carboxylic acid (I) (1.0 equiv.) in DMF (5 vol) was added DIPEA (2.5-3 equiv.) and HATU (1.2-1.5 equiv.). The reaction mixture was stirred for 5 min, then relevant amine (1.2 - 1.5 equiv.) was added and the reaction mixture was stirred at room temperature for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was quenched with ice cold water and extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄ filtered and concentrated under reduced pressure. The crude material was purified by preparative HPLC to afford the corresponding amide (II).

Scheme for synthesis of Intermediate 1



Synthesis of 6-(*tert*-butoxy)-3,4-dihydronaphthalen-1(2H)-one (1):

To a stirring solution of 6-hydroxy-3,4-dihydronaphthalen-1(2H)-one (SM) (1 g, 6.17 mmol) in DCM (40 mL) were added *tert*-butyl 2,2,2-trichloro ethanimidate (1.34 g, 6.17 mmol) and PPTS (0.15 g, 0.62 mmol) portion wise for every 6 h (5 times) at 10 °C and stirred at RT for 3 days. The reaction was monitored by TLC; after completion of reaction, the reaction mixture was quenched with aqueous NaHCO₃ and extracted with DCM. Combined organic layer was washed with brine and dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure give crude compound. The crude compound was purified by silica gel column chromatography, eluted with 10% petroleum ether/ ethyl acetate to afford **Int-1** (0.35 g, 26%) as pale yellow liquid.

¹H NMR (400 MHz, CDCl₃) δ = 7.98 (d, *J* = 8.8 Hz, 1H), 6.75 (d, *J* = 8.8 Hz, 1H), 6.68 (s, 1H), 2.90 (t, *J* = 6.0 Hz, 2H), 2.61 (t, *J* = 6.0 Hz, 2H), 2.11 (t, *J* = 6.0 Hz, 2H), 1.60 (s, 9H)

Synthesis of 6-(*tert*-butoxy)-3,4-dihydronaphthalen-1-yl trifluoromethanesulfonate (2):

To a stirring solution of **Int-1** (1 g, 4.58 mmol) in THF (20 mL) was added PhN(Tf)₂ (1.63 g, 4.58 mmol) followed by an addition of LDA (5 mL, 1 M) at -70 °C and stirred for 1 h. The resulting reaction mixture was allowed to warm up to 20 °C and stirred for 12 h. The reaction was monitored by TLC; after completion of reaction, the reaction mixture was quenched with saturated NH₄Cl, extracted with Ethyl acetate, washed with brine, dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure give crude compound. The crude compound was purified by silica gel column chromatography, eluted with 15% ethyl acetate/ heptane to afford **Int-2** (0.65 g, 40%) as an off white solid.

¹H NMR (400 MHz, CDCl₃) δ = 6.87 (d, *J* = 8.3 Hz, 1H), 6.80 (s, 1H), 5.91 (t, *J* = 4.4 Hz, 1H), 2.82 (t, *J* = 8.1 Hz, 2H), 2.54 - 2.44 (m, 2H), 1.58 (s, 1H), 1.37 (s, 9H)

Synthesis of 4-(6-(*tert*-butoxy)-3,4-dihydronaphthalen-1-yl)phenol (3):

- 5 To a stirring solution of **Int-2** (4.8 g, 13.714 mmol) in a mixture of 1,4-dioxane (60 mL) and water (20 mL) was added (4-hydroxyphenyl)boronic acid Compound **A** (1.89 g, 13.714 mmol) followed by K₂CO₃ (3.78 g, 27.42 mmol) under Argon atmosphere, de-gassed the reaction mixture for 10 min and added Pd(dppf)Cl₂.DCM (1.11 g, 1.37 mmol). The resulting reaction mixture was allowed to warm up to 100 °C and stirred for 10 h. The reaction was monitored
- 10 by TLC; after completion of reaction, the reaction mixture was diluted with water, extracted with EtOAc, washed with brine, dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure give crude compound. The crude compound was purified by silica gel column chromatography, eluted with 20% ethyl acetate/ heptane to afford **Int-3** (2.0 g, 50%) as a brown solid.
- 15 LC-MS: 60.22%; 293.1 (M-H)⁺; Column: X-Bridge BEH C18, (50mm*3.0mm,2.5μ) Mobile Phase A:2.5mM Ammonium Bicarbonate in Water+5% ACN Mobile Phase B: 100%ACN Flow rate: 1.2mL/min. Gradient Program (B%) :0.0/0, 1.4/100, 2.4/100, 2.6/0, 3.0/0

Synthesis of 4-(2-bromo-6-(*tert*-butoxy)-3,4-dihydronaphthalen-1-yl)phenol (4):

- 20 To a stirring solution of **Int-3** (2 g, 6.80 mmol) in CH₃CN (20 mL) was added NBS (1.0 g, 6.12 mmol) in portion wise. The resulting reaction mixture was allowed to warm up to 20 °C and stirred for 4 h. The reaction was monitored by TLC and LC-MS; after completion of reaction, the reaction mixture was diluted with water, extracted with EtOAc, washed with brine, dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure give crude
- 25 compound. The crude compound was purified by silica gel column chromatography, eluted with 15% ethyl acetate/ heptane to afford **Int-4** (2.5 g, 99%) as an off white solid.
- ¹H NMR (400 MHz, CDCl₃) δ = 7.13 - 7.11 (m, 1H), 7.10 - 7.09 (m, 1H), 6.90 - 6.89 (m, 1H), 6.88 - 6.87 (m, 1H), 6.76 (d, *J* = 2.4 Hz, 1H), 6.66 (d, *J* = 2.5 Hz, 1H), 6.63 (d, *J* = 2.5 Hz, 1H), 6.56 (s, 1H), 4.87 (s, 1H), 2.97 - 2.93 (m, 3H), 1.34 (s, 9H)
- 30 LC-MS: 51.07%; 317.17 (M-56+H)⁺; Column: X Select CSH C18 2.5um; 3.0x50mm Mobile Phase A :0.05% FA in Water + 5%ACN Mobile Phase B : 0.05% FA in ACN Flow Rate:1.2 mL Gradient Program (Time/B%): 0/2,1.5/98,2.2/98,2.5/2,3/2

Synthesis of 4-(6-(*tert*-butoxy)-2-phenyl-3,4-dihydronaphthalen-1-yl)phenol (5):

- 35 To a stirring solution of **Int-4** (6.0 g, 16.085 mmol) in a mixture of 1,4-dioxane (90 mL) and water (30 mL) was added phenyl boronic acid compound **B** (1.96 g, 16.085 mmol) followed by K₂CO₃ (4.37 g, 32.171 mmol) under Argon atmosphere, de-gassed the reaction mixture for 10

min and added Pd(dppf)Cl₂DCM (1.31 g, 1.608 mmol). The resulting reaction mixture was allowed to warm up to 100 °C and stirred for 12 h. The reaction was monitored by TLC; after completion of reaction, the reaction mixture was diluted with water, extracted with EtOAc, washed with brine, dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure give crude compound. The crude compound was purified by silica gel column chromatography, eluted with 20% ethyl acetate/ heptane to afford **Int-5** (4.5 g, 75%) as a brown solid.

¹H NMR (400 MHz, CDCl₃) δ = 7.11 - 7.10 (m, 1H), 7.09 (q, *J* = 1.4 Hz, 1H), 7.06 - 7.05 (m, 1H), 7.05 - 7.03 (m, 1H), 7.03 - 7.01 (m, 1H), 7.01 - 6.99 (m, 1H), 6.94 - 6.92 (m, 1H), 6.92 - 6.90 (m, 1H), 6.83 (dd, *J* = 0.8, 2.0 Hz, 1H), 6.70 - 6.68 (m, 3H), 6.67 - 6.66 (m, 1H), 2.95 - 2.89 (m, 2H), 2.79 (s, 1H), 2.78 - 2.76 (m, 1H), 1.36 (s, 9H)

LC-MS: 61.13%; 315.16 (M-56+H)⁺; Column: X Select CSH C18 2.5um; 3.0x50mm Mobile Phase A :0.05% FA in Water + 5%ACN Mobile Phase B : 0.05% FA in ACN Flow Rate:1.2 mL Gradient Program (Time/B%): 0/2,1.5/98,2.2/98,2.5/2,3/2

Synthesis of 4-(6-(*tert*-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenol (**6**):

To a stirring solution of **Int-5** (2.0 g, 5.40 mmol) in MeOH (30 mL) was added 10% Pd-C (400 mg) under Argon atmosphere, de-gassed the reaction mixture and stirred under H₂ gas atmosphere at 60 °C for 16 h. The reaction was monitored by TLC; after completion of reaction, the reaction mixture was filtered through celite-pad, washed with MeOH and the filtrate was concentrated under reduced pressure give crude compound. The crude compound was purified by silica gel column chromatography, eluted with 20% ethyl acetate/ heptane to afford **Int-6** (1.5 g, 74%) as an off-white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.98 (s, 1H), 7.19 - 7.08 (m, 3H), 6.83 (d, *J* = 8.3 Hz, 3H), 6.76 (d, *J* = 7.9 Hz, 1H), 6.68 (d, *J* = 7.9 Hz, 1H), 6.36 (d, *J* = 7.9 Hz, 2H), 6.16 (d, *J* = 7.9 Hz, 2H), 4.19 (d, *J* = 3.9 Hz, 1H), 3.10 - 2.90 (m, 3H), 2.12 (dd, *J* = 6.1, 12.3 Hz, 1H), 1.72 (d, *J* = 7.0 Hz, 1H), 1.29 (s, 9H)

LC-MS: 96.58%; 371.2 (M-H)⁻; Column: X-select CSH C18(3.0*50mm),2.5um Mobile Phase A:2.5mM Ammonium Bicarbonate in 950mL Water + 50mL ACN Mobile Phase B :100% ACN, Gradient %B:0.01/5,3.2/98,4.0/98,4.2/5,5/5 Flow Rate:1.0 mL/min

Synthesis of 4-((1*R*,2*S*)-6-(*tert*-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenol (Intermediate 1) and 4-((1*S*,2*R*)-6-(*tert*-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenol (**7A**):

The above product **Int-6** was purified by Chiral-SFC to afford Fraction-1 (**7A**) and Fraction-2 (Intermediate 1).

Fraction-1 (7A)-Data :

¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.00 (s, 1H), 7.18 - 7.10 (m, 3H), 6.85 - 6.79 (m, 3H), 6.78 - 6.73 (m, 1H), 6.71 - 6.64 (m, 1H), 6.36 (d, *J* = 8.4 Hz, 2H), 6.15 (d, *J* = 8.4 Hz, 2H), 4.19 (d, *J* = 4.8 Hz, 1H), 3.31 - 3.26 (m, 1H), 3.09 - 2.88 (m, 2H), 2.17 - 2.06 (m, 1H), 1.74 - 1.69 (m, 1H), 1.29 (s, 9H)

LC-MS: 94.86%; 371.1 (M-H)⁺; X-Bridge BEH C18, (50mm*3.0mm,2.5 μ) Mobile Phase A:2.5mM Ammonium Bicarbonate in Water+5% ACN Mobile Phase B: 100%ACN Flow rate: 1.2mL/min. Column temperature: 50°C Gradient Program (B%) :0.0/0, 1.4/100, 2.4/100, 2.6/0, 3.0/0

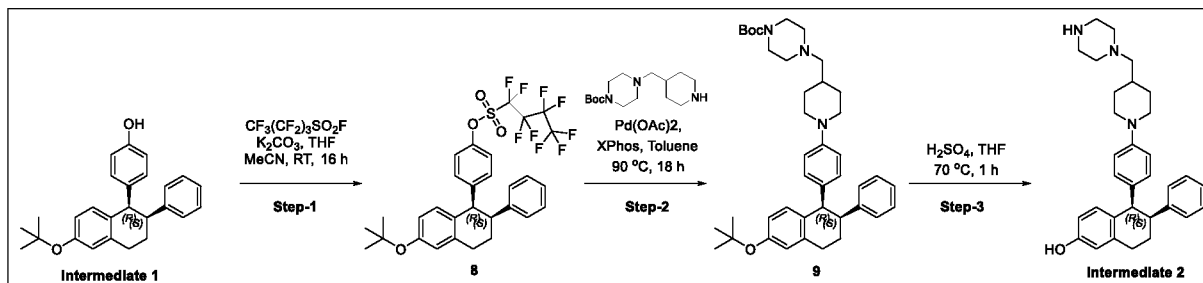
$[\alpha]_D^{25} = +376.15$ (C = 0.5 w/v% in ethyl acetate, 25 °C)

Fraction-2 (Intermediate 1)-Data:

¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.00 (s, 1H), 7.20 - 7.07 (m, 3H), 6.86 - 6.79 (m, 3H), 6.78 - 6.73 (m, 1H), 6.71 - 6.64 (m, 1H), 6.36 (d, *J* = 8.4 Hz, 2H), 6.15 (d, *J* = 8.4 Hz, 2H), 4.19 (d, *J* = 4.8 Hz, 1H), 3.31 - 2.27 (m, 1H), 3.09 - 2.89 (m, 2H), 2.17 - 2.06 (m, 1H), 1.74 - 1.69 (m, 1H), 1.29 (s, 9H)

LC-MS: 99.40%; 371.1 (M-H)⁺; X-Bridge BEH C18, (50mm*3.0mm,2.5 μ) Mobile Phase A:2.5mM Ammonium Bicarbonate in Water+5% ACN Mobile Phase B: 100%ACN Flow rate: 1.2mL/min. Column temperature: 50°C Gradient Program (B%) :0.0/0, 1.4/100, 2.4/100, 2.6/0, 3.0/0

$[\alpha]_D^{25} = -369.42$ (C = 0.5 w/v% in ethyl acetate, 25 °C)

Scheme for synthesis of Intermediate 2

Synthesis of 4-((1R,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (Int-8):

To a stirring solution of **Intermediate 1** (0.5 g, 1.34 mmol) in a mixture of solvents THF and ACN (5 mL, 1:1) were added K_2CO_3 (0.55 g, 4.02 mmol), perfluorobutane sulfonyl fluoride (0.81 g, 2.68 mmol) at room temperature and stirred for 16 h. The reaction was monitored by TLC; after completion of reaction, the reaction mixture was concentrated under reduced pressure give crude compound. The crude compound was purified by combiflash column

chromatography, eluted with 30% ethyl acetate/ heptane to afford **Int-8** (0.25 g, 28%) as colorless oil.

¹H NMR (400 MHz, DMSO-*d*₆) δ = 7.14 - 7.07 (m, 4H), 6.79 (d, *J* = 8.3 Hz, 4H), 6.59 - 6.51 (m, 3H), 3.43 (dd, *J* = 4.2, 12.5 Hz, 3H), 3.13 - 2.94 (m, 4H), 1.30 (s, 9H)

5

Synthesis of *tert*-butyl 4-((1-(4-((1*R*,2*S*)-6-(*tert*-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)piperazine-1-carboxylate (9):

To a stirring solution of **Int-8** (0.35 g, 0.579 mmol) in Toluene (8 mL) was added *tert*-butyl 4-(piperidin-4-ylmethyl)piperazine-1-carboxylate (0.245 g, 0.869 mmol) followed by NaOt-Bu (0.166 g, 1.738 mmol) under Argon atmosphere, de-gassed the reaction mixture for 10 min and added Pd(OAc)₂ (0.019 g, 0.0869 mmol) and X-Phos (0.055 g, 0.115 mmol). The resulting reaction mixture was allowed to warm up to 90 °C and stirred for 18 h. The reaction was monitored by TLC; after completion of reaction, the reaction mixture was diluted with water, extracted with EtOAc, washed with brine, dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure give crude compound. The crude compound was purified by silica gel column chromatography, eluted with 15% ethyl acetate/ heptane to afford **Int-9** (0.15 g, 40%) as a brown solid.

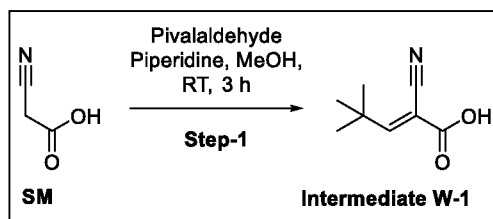
¹H NMR (400 MHz, CDCl₃) δ = 7.18 - 7.12 (m, 2H), 6.87 - 6.79 (m, 2H), 6.72 (d, *J* = 8.8 Hz, 2H), 6.57 (d, *J* = 7.9 Hz, 2H), 6.26 (d, *J* = 7.9 Hz, 2H), 5.30 (s, 3H), 4.22 (d, *J* = 4.4 Hz, 3H), 3.58 - 3.48 (m, 3H), 3.41 (br s, 3H), 3.04 (d, *J* = 5.3 Hz, 4H), 2.60 - 2.51 (m, 3H), 2.34 (br s, 3H), 2.19 (d, *J* = 7.0 Hz, 3H), 1.81 (d, *J* = 12.3 Hz, 2H), 1.46 (s, 9H), 1.36 (s, 9H)

Synthesis of (5*R*,6*S*)-6-phenyl-5-(4-(4-(piperazin-1-ylmethyl)piperidin-1-yl)phenyl)-5,6,7,8-tetrahydronaphthalen-2-ol (Intermediate 2):

To a stirring solution of **Int-9** (0.25 g, 0.391 mmol) in THF (10 mL) was added 2 M H₂SO₄ (10 mL). The resulting reaction mixture was allowed to warm up to 70 °C and stirred for 1 h. The reaction was monitored by TLC; after completion of reaction, the reaction mixture was diluted with water, neutralized with aqueous sodium bicarbonate solution, extracted with 10% MeOH in DCM, washed with brine, dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure give to afford **Intermediate 2** (0.15 g, 79%) as an off-white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.09 (s, 1H), 7.18 - 7.04 (m, 4H), 6.93 (s, 1H), 6.83 (d, *J* = 7.0 Hz, 2H), 6.66 - 6.57 (m, 2H), 6.55 - 6.45 (m, 3H), 6.19 (d, *J* = 8.3 Hz, 2H), 4.47 (d, *J* = 5.7 Hz, 1H), 4.15 - 4.05 (m, 2H), 3.74 - 3.67 (m, 1H), 3.65 - 3.57 (m, 1H), 3.49 (d, *J* = 11.4 Hz, 2H), 3.17 (d, *J* = 3.5 Hz, 1H), 2.98 - 2.83 (m, 4H), 2.66 (d, *J* = 5.3 Hz, 1H), 2.40 - 2.21 (m, 4H), 2.17 - 2.04 (m, 2H), 1.70 (d, *J* = 11.0 Hz, 2H), 1.24 (d, *J* = 7.0 Hz, 3H)

Synthesis of Intermediate W-1



Synthesis of (E)-2-cyano-4,4-dimethyl-pent-2-enoic acid

To a stirred solution of 2-cyanoacetic acid (**SM**) (6 g, 69.76 mmol) in methanol (60 mL) was added piperidine (6.51 g, 76.6 mmol) and pivaldehyde (11.86 g, 139 mmol) at RT. The resulting reaction mixture was stirred at RT for 3 h. The reaction was monitored by TLC; after completion, the reaction mixture was concentrated under reduced pressure and diluted with water (100 mL), extracted with DCM. Aqueous layer was then acidified with 2 M HCl to pH – 2 and extracted with DCM. Organic layer was dried over sodium sulphate, filtered and concentrated under reduced pressure to afford **Intermediate W-1** (1.5g, crude) as off white solid.

^1H NMR (400 MHz, CDCl_3) δ = 7.72 (s, 1H), 1.34 (s, 9H)

LC-MS: 154.3 $[\text{M}+\text{H}]^+$; 94.11% at RT = 1.21 min Method Details: Formic Acid (AMC-LCMS-15) Column: X Select CSH C18 2.5um; 3.0x50mm Mobile Phase A :0.05% FA in Water + 5%ACN Mobile Phase B : 0.05% FA in ACN Flow Rate:1.2 mL Oven Temperature:50 °C Gradient Program (Time/B%): 0/2,1.5/98,2.2/98,2.5/2,3/2.

Compound No	Intermediate A	Intermediate B	General Procedure	Analytical Data
1	2	W-1	1	LCMS: Method A, 617.4 $[\text{M}+\text{H}]^+$, 98.51% at RT: 1.629 min.

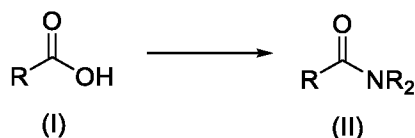
Intermediate A was coupled to Intermediate B via the method described in the General Procedure listed.

Further Synthetic Methods – AR degraders

Overviews of various exemplary synthetic methods and general procedures that may be used to provide the compounds of the present disclosure are shown below.

5

Amide coupling – General procedure 1

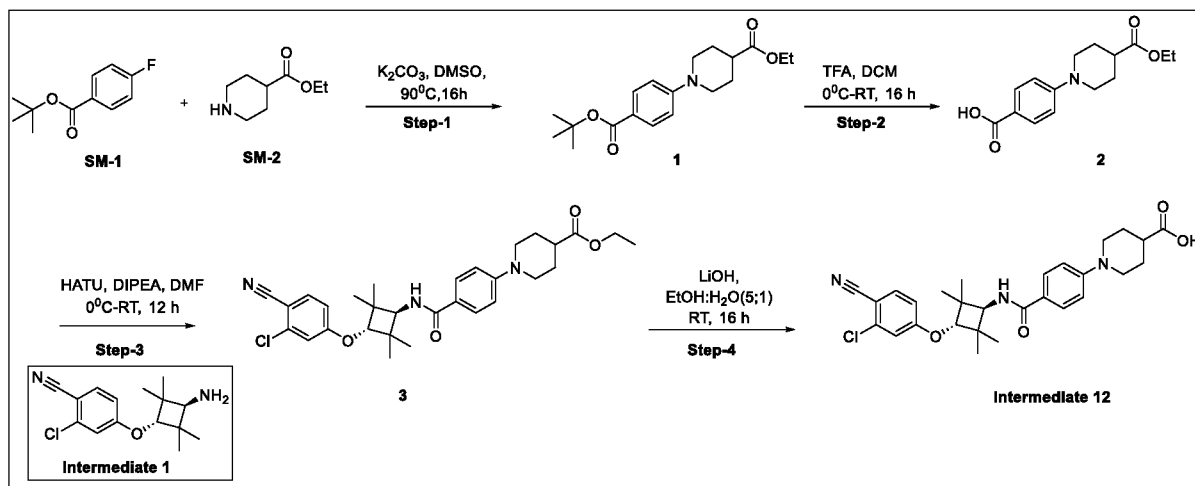


10

To a stirring solution of carboxylic acid (I) (1.0 equiv.) in DMF (5 vol) was added DIPEA (2.5-3 equiv.) and HATU (1.2-1.5 equiv.). The reaction mixture was stirred for 5 min, then relevant amine (1.2 - 1.5 equiv.) was added and the reaction mixture was stirred at room temperature for 16 h. The reaction was monitored by TLC; after completion of the reaction, the reaction mixture was quenched with ice cold water and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 filtered and concentrated under reduced pressure. The crude material was purified by preparative HPLC to afford the corresponding amide (II).

15

Synthesis of Intermediate 3



Synthesis of ethyl 1-(4-(tert-butoxycarbonyl)phenyl)piperidine-4-carboxylate (1)

20

To a stirred solution of *tert*-butyl 4-fluorobenzoate (SM-1) (3 g, 15.29 mmol) in DMSO (30 mL) was added K_2CO_3 (4.23 g, 30.58 mmol) and ethyl piperidine-4-carboxylate (SM-2) (2.4 g, 15.29 mmol) at RT. The resulting reaction mixture was stirred at $90^\circ C$ for 16 h. The reaction was monitored by TLC; after completion, the reaction mixture was cooled to RT, quenched with water (50 ml), extracted with ethyl acetate (3 x 50 ml) and washed with brine solution.

25

The combined organic layers were dried over Na_2SO_4 , filtered and concentrated under reduced pressure to get the residue. The residue was purified by flash column

chromatography (silica gel) using 50% EtOAc in heptane to obtain **1** (0.9 g, 17.6%) as a white solid.

LC-MS: 95.4 % 334.4, RT-2.43 min [M+H]⁺; Column: X-Select CSH C18, (50mm*3.0mm,2.5μ)
Mobile Phase A: 0.05% TFA in Water Mobile Phase B: 0.05% TFA in Acetonitrile Flow rate:
5 1.0mL/min. Column temperature: 40°C Gradient Program (B%) :0.0/2, 0.3/2,2.0/98, 3/98,
3.2/2,4.0/2

Synthesis of 4-(4-(ethoxycarbonyl)piperidin-1-yl)benzoic acid (**2**)

To a stirred solution of **1** (0.9 g, 2.70 mmol) in DCM (10 mL) was added TFA (2 mL, 16.2
10 mmol) drop wise at 0 °C. The resulting reaction mixture was stirred at RT for 16 h. The reaction
was monitored by TLC; after completion, the reaction mixture was distilled off to remove
solvent. The crude obtained was triturated with diethyl ether (2 x 5 mL) to afford **2** (0.7 g, 93%)
as an off white solid.

LC-MS: 97 % 278, RT-2.13 min [M+H]⁺; Column: Xselect CSH-C18(3.0X50mm,2.5μm) Mobile
15 Phase: A: 0.05% FA in water, Mobile Phase :B:0.05% FA in ACN
T/B%:0/2,0.3/2,2.0/98,3.0/98,3.2/2,4.0/2 Flow rate: 1.0ml/min(Gradient), Column Oven Temp:
40 °C

Synthesis of ethyl 1-(4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4- 20 tetramethylcyclobutyl) carbamoyl)phenyl)piperidine-4-carboxylate (**3**)

To a stirred solution of **2** (0.5 g, 1.80 mmol) in DMF (5 mL) was added HATU (0.82 g, 2.16
mmol), **1** (0.60 g, 2.16 mmol) and DIPEA (1.57 mL, 9 mmol) successively at 0 °C. The resulting
reaction mixture was stirred at room temperature for 12 h. The reaction was monitored by
TLC; after completion, the reaction mixture was quenched with cold water (10 mL), the
25 resulting precipitate was filtered-off, washed with cold water, and dried under vacuum. The
residue was purified by flash column chromatography (silica gel) using 50% EtOAc in heptane
to obtain **3** (0.8 g, 82.6%) as white solid.

LC-MS: 99.3% 537.8, RT-2.53 min [M+H]⁺; Column: Xselect CSH-C18(3.0X50mm,2.5μm)
Mobile Phase: A: 0.05% FA in water, Mobile Phase :B:0.05% FA in ACN
30 T/B%:0/2,0.3/2,2.0/98,2.8/98,3.0/2,3.7/2 Flow rate:1.0ml/min (Gradient),Column Oven
Temp:40°C

Synthesis of 1-(4-(((1r,3r)-3-(3-chloro-4-cyanophenoxy)-2,2,4,4- tetramethylcyclobutyl)carbamoyl)phenyl)piperidine-4-carboxylic acid (Intermediate 35 **12**):

To a stirred solution of **3** (0.8 g, 1.48 mmol) in EtOH:H₂O (5:1, 5 mL) was added LiOH (0.18
g, 7.44 mmol) at RT. The resulting reaction mixture was stirred at room temperature for 16 h.

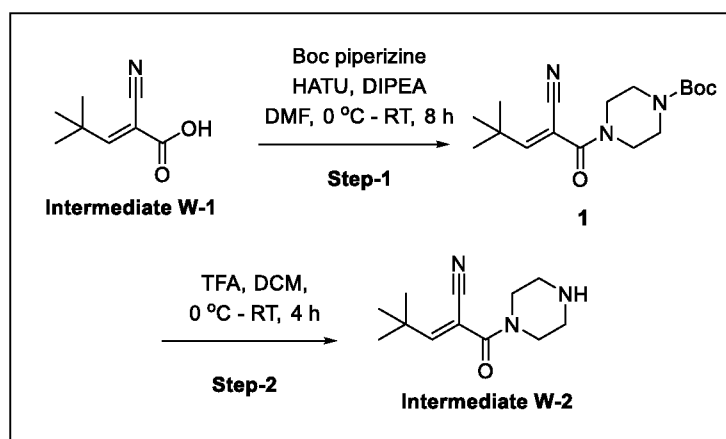
The reaction was monitored by TLC; after completion, the reaction mixture was distilled off to remove EtOH. Then, the residue obtained was diluted with cold water (3 mL) and acidified with 1N HCl (pH 2-3), the resulting precipitate was filtered-off, washed with cold water, and dried under vacuum to afford **Intermediate 3** (0.5 g, 65%) as white solid.

¹H NMR (400 MHz, DMSO-d₆) δ = 12.21 (br s, 1H), 7.90 (d, J = 8.8 Hz, 1H), 7.77 - 7.69 (m, 2H), 7.49 (d, J = 9.1 Hz, 1H), 7.20 (d, J = 2.5 Hz, 1H), 7.03 - 6.85 (m, 3H), 4.32 (s, 1H), 4.05 (d, J = 9.1 Hz, 1H), 3.79 (br d, J = 13.0 Hz, 2H), 2.97 - 2.81 (m, 2H), 2.47 - 2.44 (m, 1H), 1.95 - 1.82 (m, 2H), 1.67 - 1.56 (m, 2H), 1.34 - 1.19 (m, 6H), 1.16 - 1.00 (m, 6H)

LC-MS: 98.7% 510.33 [M+H]⁺; Column: X-Select CSH C18(3.0*50mm,2.5um), Mobile Phase A:0.05% FA in H₂O:ACN (95:5), Mobile Phase B :0.05%FA in ACN, Gradient %B: 0/2, 0.3/2, 2.0/98, 2.8/98, 3.0/2, 3.7/2 Flow rate:1.0 ml/min.

HPLC: 97.7%, RT-5.92; Column: X-Select CSH C18(3.0*50mm,2.5um), Mobile Phase A:0.05% FA in H₂O:ACN(95:5), Mobile Phase B :0.05%FA in ACN, Gradient %B: 0/2, 0.3/2, 2.0/98, 2.8/98, 3.0/2, 3.7/2 Flow rate:1.0 ml/min

Synthesis of Intermediate W-2



Synthesis of *tert*-butyl 4-[(*E*)-2-cyano-4,4-dimethyl-pent-2-enoyl]piperazine-1-carboxylate- (1)

To a stirred solution of **Intermediate W-1** (1 g, 6.530 mmol) and Boc-Piperazine (851 mg, 4.570 mmol) in DMF (10 ml) was added HATU (3.70 g, 9.75 mmol). Reaction mixture was cooled to 0 °C and DIPEA (2.11 ml, 16.5 mmol) was added dropwise. The resulting reaction mixture was stirred at RT for 8 h. The reaction was monitored by TLC; after completion, the reaction mixture was diluted with cold water (100 ml) and extracted the compound with ethyl acetate. The combined organic layer was dried over sodium sulphate, filtered and concentrated under reduced pressure. The crude was purified by flash chromatography to afford **1** (800 mg, 40%) as an off white solid.

LC-MS: 222.1 [M-Boc+H]⁺; 82.06% at RT = 1.36 min Method Conditions: Column:Xselect CSH-C18(3.0X50mm,2.5µm) Mobile Phase: A: 0.05% FA in Water+5% ACN, B: 0.05% FA in ACN

5 Synthesis of (E)-2-cyano-4,4-dimethyl-N-[2-(methylamino)ethyl]pent-2-enamide (Intermediate W-2)

To a stirred solution of **1** in DCM (4 ml) was added TFA (8 ml, 104.4 mmol) dropwise at 0 °C. The resulting reaction mixture was stirred at RT for 4 h. The reaction was monitored by TLC; after completion, the reaction mixture was concentrated under reduced pressure. Semi solid mass obtained was triturated with diethyl ether and dried under reduced pressure to afford **Intermediate W-2** (476 mg, crude) as brown semi solid.

¹H NMR (400 MHz, DMSO-d₆) δ = 3.75 - 3.55 (m, 4H), 3.17 – 3.13 (m, 4H), 2.67 (s, 1H), 1.22 (s, 9H)

LC-MS: 222.3 [M+H]⁺; 68.22% at RT = 1.158 min Column:Xselect CSH-C18(3.0X50mm,2.5µm) Mobile Phase: A: 0.05% FA in water, MobilePhase :B:0.05% FA in ACN T/B%:0./2,0.3/2,2.0/98,3.0/98,3.2/2,3.5/2 Flow rate:1.0ml/min(Gradient) ,Column Oven Temp:40°C.

Compound No	Intermediate A	Intermediate B	General Procedure	Analytical Data
2	3	W-2	1	LCMS: Method C, 834.2 [M+H] ⁺ , 90.98% at RT: 2.447 min.

Intermediate A was coupled to Intermediate B via the method described in the General Procedure listed.

PART B - Biological Data

The bifunctional compounds were assayed to investigate their ability to degrade target proteins in accordance with the following general procedures.

Assay Protocol (ER)

ER degradation:

MCF-7 cells were seeded at 5000 cells/well (45 μ L) in sterile 384 well Phenoplates (Perkin Elmer 6057302) and incubated overnight at 37°C with 5% CO₂. The next day, compounds were prepared at 1000x final concentration in DMSO and diluted 1:100 in media (Phenol red-free DMEM PAN Biotech P04-03591 + 10% Charcoal stripped FBS Life Technologies 12676-029). 5 μ L compound was added to each well of the cell plate and incubated for 24 h at 37°C with 5% CO₂. Cells were fixed by adding 15 μ L 16% paraformaldehyde (Thermo 28908) to every well and incubated at RT for 30 min. Well contents were aspirated using plate washer and 50 μ L PBS containing 0.5% BSA and 0.5% Triton X-100 (antibody dilution buffer) was added to each well. Plate was incubated at RT for 30 min. Well contents were aspirated, and plate washed 3 times with 70 μ L PBS. Immunofluorescence staining of ER was carried out using anti-ESR1 mAb (F10) (Santa Cruz sc-8002). Antibody was diluted 1:1000 in antibody dilution buffer and 25 μ L added to every well, plate was then incubated overnight at 4°C. The next day, plate was washed 3 times with 70 μ L PBS and secondary antibody solution was prepared by diluting Alexafluor 488 conjugate anti-mouse IgG (Life Technologies A2102) and 1 mg/mL Hoechst 33342 (Abcam ab228551) 1:1000 in antibody dilution buffer. 25 μ L was added to every well and plate incubated for 2 h in the dark at RT. Plate was washed 3 times with 70 μ L PBS and the final PBS dispensed was left in the plate. Quantitative fluorescence imaging was carried out on the Operetta (Perkin Elmer) using the Hoechst channel to define the nuclei and the Alexafluor 488 channel to measure ER signal. ER intensity per nuclei was calculated on the Harmony software and data was imported into Dotmatics software for analysis. DMSO and 1 μ M Fulvestrant were used to define 0% ER degradation and 100% ER degradation respectively.

ER degradation results

The degradation of ER was detected according to the procedure outlined in the Assay Protocol for a number of exemplary bifunctional molecules. The results are shown in Table 2 below.

Table 2: data showing ER degradation efficiency of an exemplary compound:

Compound	Activity MCF7 Assay	
	DC ₅₀	D _{max}
1	+++	+

DC₅₀ key: +++ = <10 nM, ++ = $\geq$ 10 nM and < 25 nM, + = $\geq$ 25 nM and < 100 nM.

D_{max} key: + = >50% and <65%, ++ = $\geq$ 65 and <80%, +++ = $\geq$ 80%

Assay Protocol (AR)

VCaP Assay

5 VCaP cells were seeded at 50000 cells into 96 well microplates in a final volume of 150ml (Corning CellBind #3300) and incubated. Compounds were prepared at 1000x final concentration in DMSO and diluted 1:100 in media (DMEM, 8% FBS, 1% Pen/Strep - Life Technologies). 20ml of diluted compound was transferred to the cell plate with DMSO (final concentration 0.10%) and Staurosporin (10mM) controls added manually and the plate
10 incubated for 24 h at 37°C with 5% CO₂.

Plates were removed from the incubator and the viability assessed using imaging on the Incucyte S3. Media was aspirated from all wells carefully and 120ml of Cell Lysis Buffer (Cell Signalling Technologies #9803) added before shaking for one hour at 4°C at 350rpm.
15 20ml of cell lysates were transferred to AR PathScan Total Androgen Receptor ELISA kit (Cell Signalling Technologies #12850), with sample buffer pipetted into negative control wells to support data analysis, additional sample buffer was added to lysate wells to give a total volume of 100ml. Plates were sealed and incubated overnight at 4°C. The following day, plates were removed and allowed to reach room temperature, well contents were aspirated and the plate
20 washed with PBS before the addition of 100ml of detection antibody from the ELISA kit (Cell Signalling Technologies #12850), plates were sealed and incubated at 37°C for one hour. Plates were washed with PBS and 100ml of HRP secondary antibody (Cell Signalling Technologies #12850) added to all wells, before incubation of the plate at 37°C for 30 minutes.

25 Well contents were aspirated and washed with PBS, before addition of 100ml of TMB substrate, followed by room temperature incubation for 10 minutes. Stop solution was added to each well, and the plate transferred to a Pherastar FSX plate reader where absorbance per well was measured. Percentage AR levels were calculated compared to DMSO control wells and data uploaded to Dotmatics for curve generation and DC₅₀ and D_{max} calculations.
30

AR degradation results

The degradation of AR was detected according to the procedure outlined in the Assay Protocol for a number of exemplary bifunctional molecules. The results are shown in Table 2 below.
35

Table 3: data showing AR degradation efficiency of exemplary compound.

Compound	Activity VCaP (Assay 2)	
	DC ₅₀	D _{max}
2	++	+

Key:

DC₅₀ key: +++ = <300 nM, ++ = ≥300 nM and < 500 nM, + = ≥500 nM.

5 D_{max} key: + = >50% and <65%, ++ = ≥65 and <80%, +++ = ≥80%

Although the present invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, the descriptions and examples should not
 10 be construed as limiting the scope of the invention. The disclosures of all patent and scientific literature cited herein are expressly incorporated herein in their entirety by reference.

CLAIMS

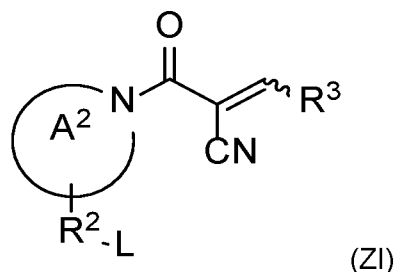
1. A bifunctional molecule comprising the general formula:



wherein TBL is a target protein binding ligand selected from an: (i) estrogen receptor binding ligand; and (ii) androgen receptor binding ligand;

L is a linker; and

Z comprises a structure according to formula (ZI):



wherein:

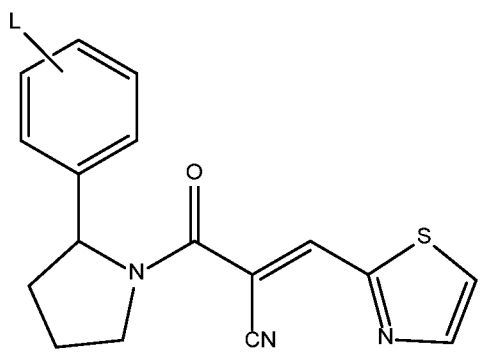
ring A² is an optionally substituted 4- to 7-membered monocyclic N-heterocycloalkyl or an optionally substituted 7- to 12-membered bicyclic N-heterocycloalkyl, each optionally containing one or two additional ring heteroatoms selected from N, O and S;

R² is absent or is selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, substituted heterocycloalkyl, NR^y, -CH(aryl)-, -CH(substituted aryl)-, -CH(heteroaryl)- and -CH(substituted heteroaryl)-;

wherein R^y is optionally substituted C₁₋₆alkyl or H;

R³ is selected from C₁₋₆ alkyl, cycloalkyl, substituted cycloalkyl, alkylcycloalkyl, substituted alkylcycloalkyl, alkyl heterocycloalkyl, substituted alkylcycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, optionally wherein the C₁₋₆ alkyl is substituted with one or more heteroatoms selected from halo, N, O and S; and L shows the point of attachment of the linker;

and further wherein Z is not:

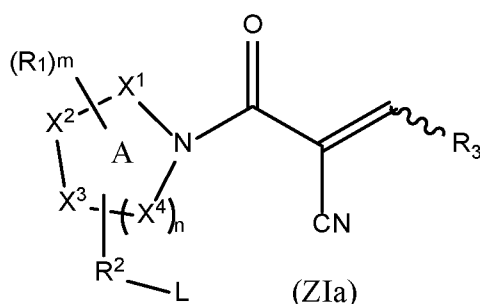


or a pharmaceutically acceptable salt thereof.

2. The bifunctional molecule of claim 1, wherein ring A² is an optionally substituted 5- to 7-membered monocyclic N-heterocycloalkyl, an optionally substituted 7- or 8-membered bridged bicyclic N-heterocycloalkyl, or an optionally substituted 7- to 12-membered spirocyclic bicyclic N-heterocycloalkyl, each optionally containing one or two additional ring heteroatoms selected from N, O and S.

3. The bifunctional molecule of claim 2, wherein the optionally substituted 7- to 12-membered spirocyclic bicyclic N-heterocycloalkyl comprises a first 5- to 7-membered ring and a second 3- to 7-membered ring.

4. The bifunctional molecule of any one of claims 1 to 3, wherein Z comprises a structure according to formula (ZIa):



wherein:

R¹ is absent or is selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, C₁ to C₆ alkyl and substituted C₁ to C₆ alkyl, and/or wherein two R¹ groups combine to form an optionally substituted C₁₋₃ bridge, optionally substituted C₃₋₅cycloalkyl or optionally substituted 5- to 7-membered heterocycloalkyl, optionally wherein the C₃₋₅cycloalkyl or the 5- to 7-membered heterocycloalkyl are joined to ring A at a spiro centre;

R² is absent or is selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, substituted heterocycloalkyl, NR^y, -CH(aryl)-, -CH(substituted aryl)-, -CH(heteroaryl)- and -CH(substituted heteroaryl)-;

wherein R^y is optionally substituted C₁₋₆alkyl or H;

R³ is selected from C₁₋₆ alkyl, cycloalkyl, substituted cycloalkyl, alkylcycloalkyl, substituted alkylcycloalkyl, alkyl heterocycloalkyl, substituted alkylcycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, optionally wherein the C₁₋₆ alkyl is substituted with one or more heteroatoms selected from halo, N, O and S;

X¹ is CH₂;

X², X³ and X⁴ are each independently CH₂, O or NR^x;

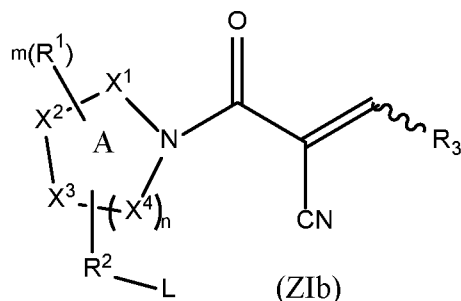
R^x is H or C_1 to C_6 alkyl, or wherein one R^1 group and one R^x group combine to form a C_{1-3} bridge;

n is 0, 1, 2, or 3;

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

L shows the point of attachment of the linker.

5. The bifunctional molecule of any one of claims 1 to 4, wherein Z comprises a structure according to formula (ZIb):



wherein:

R^1 is absent or is selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, C_1 to C_6 alkyl and substituted C_1 to C_6 alkyl, and/or wherein two R^1 groups combine to form an optionally substituted C_{1-3} bridge, optionally substituted C_{3-5} -cycloalkyl or optionally substituted 5- to 7-membered heterocycloalkyl, optionally wherein the C_{3-5} -cycloalkyl or the 5- to 7-membered heterocycloalkyl are joined to ring A at a spiro centre;

R^2 is absent or is selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, substituted heterocycloalkyl, NR^y , $-CH(aryl)-$, $-CH(substituted\ aryl)-$, $-CH(heteroaryl)-$ and $-CH(substituted\ heteroaryl)-$;

wherein R^y is optionally substituted C_{1-6} alkyl or H;

R^3 is selected from C_{1-6} alkyl, cycloalkyl, substituted cycloalkyl, alkylcycloalkyl, substituted alkylcycloalkyl, alkyl heterocycloalkyl, substituted alkylheterocycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, alkyl aryl, substituted alkylaryl, alkyl heteroaryl, substituted alkylheteroaryl, optionally wherein the C_{1-6} alkyl is substituted with one or more heteroatoms selected from halo, N, O and S;

X^1 and X^4 are each CH_2 ;

X^2 and X^3 are each independently CH_2 , O or NR^x ; with the proviso that none or only 1 of X^2 and X^3 is O;

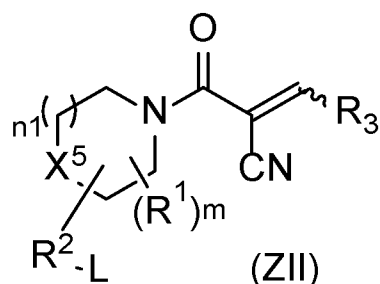
R^x is H or C_1 to C_6 alkyl; or wherein one R^1 group and one R^x group combine to form a C_{1-3} bridge;

n is 0, 1, 2 or 3;

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

L shows the point of attachment of the linker.

6. The bifunctional molecule of any one of claims 1 to 5, wherein Z comprises a structure according to formula (ZII):



wherein R^2 is absent or is selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, substituted heterocycloalkyl, NR^y , $-CH(aryl)-$, $-CH(substituted\ aryl)-$, $-CH(heteroaryl)-$ and $-CH(substituted\ heteroaryl)-$;

wherein R^y is optionally substituted C_{1-6} alkyl or H;

R^3 is selected from C_1 to C_6 alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted aryl, and substituted heteroaryl, optionally wherein the C_1 to C_6 alkyl is substituted with a heterocycloalkyl group;

X^5 is CR^{b_2} , NR^b , O or a 5- to 7-membered heterocycloalkyl;

each R^1 is independently selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, C_1 to C_6 alkyl and substituted C_1 to C_6 alkyl, and/or wherein two R^1 groups combine to form an optionally substituted C_{1-3} bridge or optionally substituted C_{3-5} cycloalkyl (optionally wherein the C_{3-5} cycloalkyl is joined to the heterocyclic ring shown in formula (ZII) at a spiro centre);

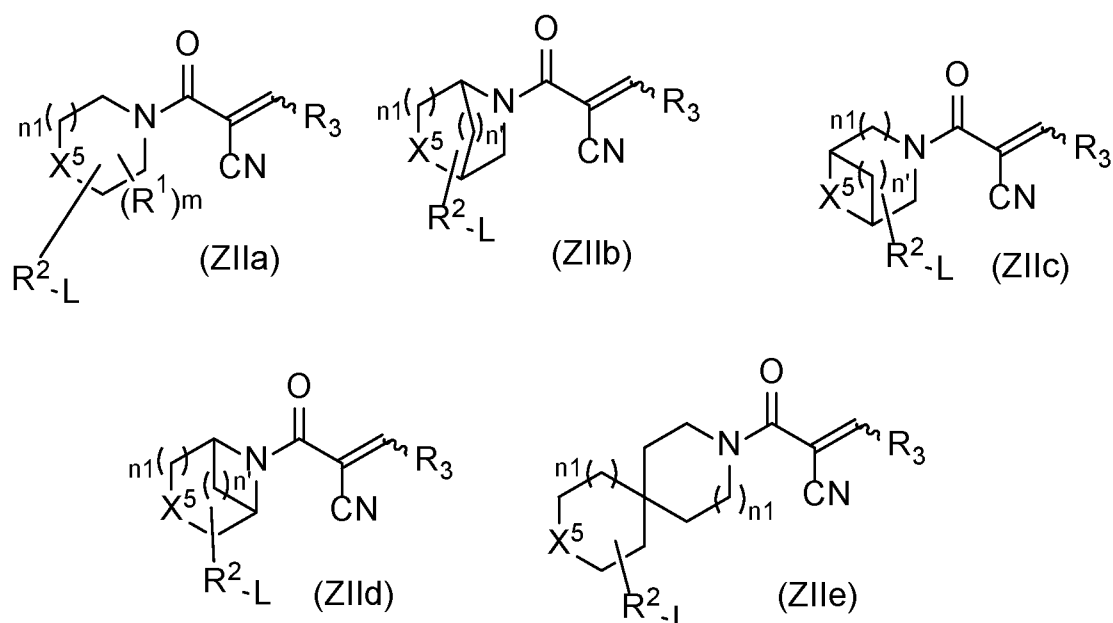
R^b is H or optionally substituted C_{1-3} alkyl;

n_1 is 0, 1, 2 or 3;

m is 0, 1 or 2; and

L shows the point of attachment of the linker.

7. The bifunctional molecule of any one of claims 1 to 6, wherein Z comprises a structure according to formula (ZIIa) to (ZIIe):



wherein R^2 is absent or is selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, substituted heterocycloalkyl, NR^y , $-CH(aryl)-$, $-CH(substituted\ aryl)-$, $-CH(heteroaryl)-$ and $-CH(substituted\ heteroaryl)-$;

wherein R^y is optionally substituted C_{1-6} alkyl or H;

R^3 is selected from C_1 to C_6 alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and substituted heteroaryl, optionally wherein the C_1 to C_6 alkyl is substituted with a heterocycloalkyl group;

each R^1 is independently selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, C_1 to C_6 alkyl and substituted C_1 to C_6 alkyl, and/or wherein two R^1 groups combine to form an optionally substituted C_{3-5} cycloalkyl, optionally wherein the C_{3-5} cycloalkyl is joined to the heterocyclic ring shown in formula (ZIIa) at a spiro centre;

X^5 is $C(R^b)_2$, NR^b or O;

R^b is H or optionally substituted C_{1-3} alkyl;

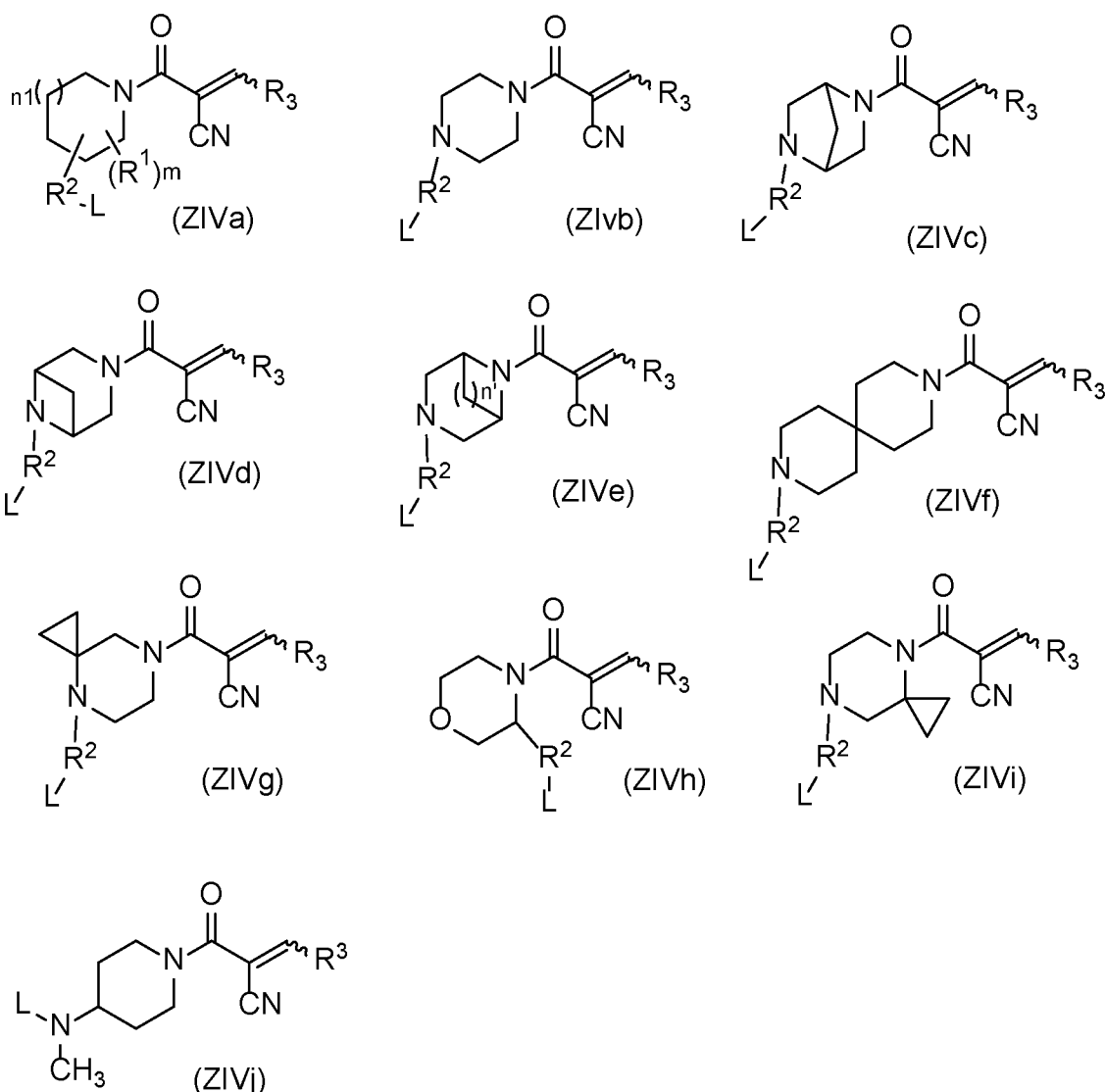
n_1 is 0, 1, 2 or 3;

n' is 1 or 2;

m is 0, 1 or 2; and

L shows the point of attachment of the linker.

8. The bifunctional molecule of any one of claims 1 to 7, wherein Z comprises a structure according to formula (ZIVa) to (ZIVj):



wherein R^2 is absent or is selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, substituted heterocycloalkyl, NR^y , $-\text{CH}(\text{aryl})-$, $-\text{CH}(\text{substituted aryl})-$, $-\text{CH}(\text{heteroaryl})-$ and $-\text{CH}(\text{substituted heteroaryl})-$;

wherein R^y is optionally substituted C_{1-6} alkyl or H;

R^3 is selected from C_1 to C_6 alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and substituted heteroaryl, optionally wherein the C_1 to C_6 alkyl is substituted with a heterocycloalkyl group;

each R^1 is independently selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, C_1 to C_6 alkyl and substituted C_1 to C_6 alkyl;

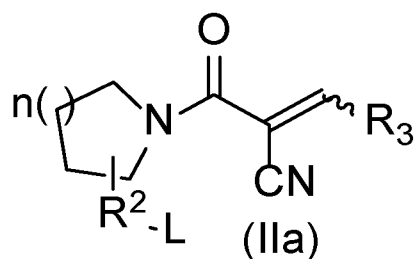
n_1 is 0, 1 or 2;

n' is 1 or 2;

m is 0, 1 or 2; and

L shows the point of attachment of the linker.

9. A bifunctional molecule according to claims 1 to 5, wherein Z comprises a structure according to formula (IIa):



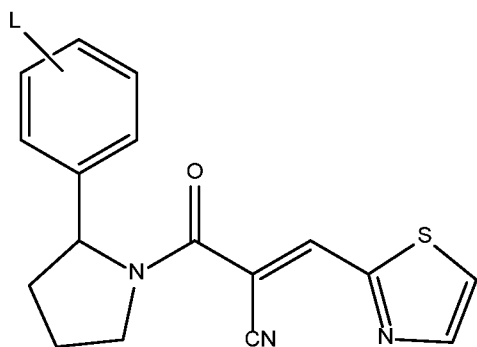
wherein R^2 is selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, substituted heterocycloalkyl, $-\text{CH}(\text{aryl})-$, $-\text{CH}(\text{substituted aryl})-$, $-\text{CH}(\text{heteroaryl})-$ and $-\text{CH}(\text{substituted heteroaryl})$;

R^3 is selected from C_1 to C_6 alkyl, aryl, heteroaryl, substituted aryl, and substituted heteroaryl, optionally wherein the C_1 to C_6 alkyl is substituted with a heterocycloalkyl group;

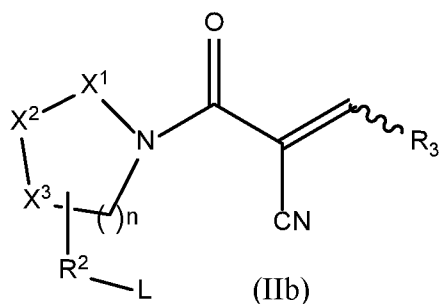
n is 0, 1, 2 or 3; and

L shows the point of attachment of the linker;

and wherein Z is not:



10. A bifunctional molecule according to claim 1, wherein Z comprises a structure according to formula (IIb):



wherein R^2 is selected from aryl substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, and substituted heterocycloalkyl;

R^3 is selected from C_1 to C_6 alkyl, aryl, heteroaryl, substituted aryl, and substituted heteroaryl, optionally wherein the C_1 to C_6 alkyl is substituted with a heterocycloalkyl group;

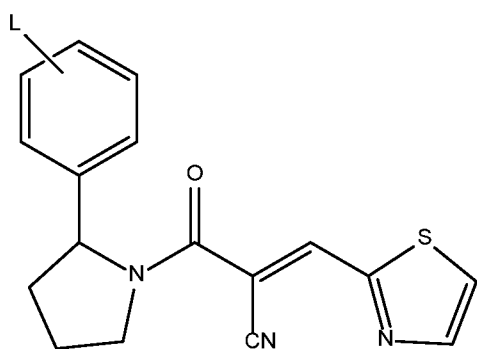
X^1 is CH_2 ;

X^2 and X^3 are each independently CH_2 or O; with the proviso that none or only 1 of X^2 and X^3 is O;

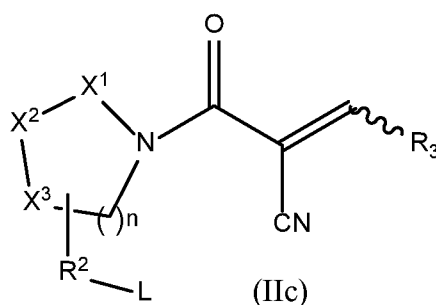
n is 1 or 2; and

L shows the point of attachment of the linker;

and wherein Z is not:



11. A bifunctional molecule according to claim 1, wherein Z comprises a structure according to formula (IIc):



wherein R^2 is selected from heterocycloalkyl and substituted heterocycloalkyl;

R^3 is selected from C_1 to C_6 alkyl, aryl, heteroaryl, substituted aryl, and substituted heteroaryl, optionally wherein the C_1 to C_6 alkyl is substituted with a heterocycloalkyl group;

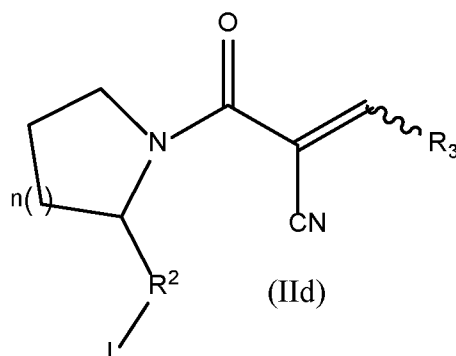
X^1 is CH_2 ;

X^2 and X^3 are each independently CH_2 or O; with the proviso that none or only 1 of X^2 and X^3 is O;

n is 1 or 2; and

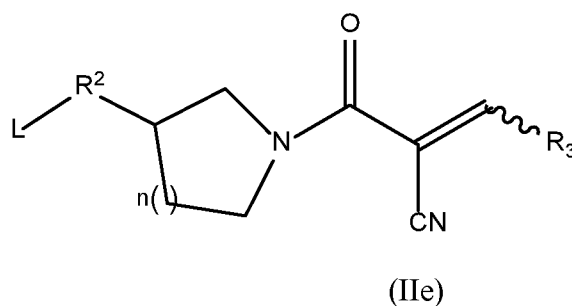
L shows the point of attachment of the linker.

12. A bifunctional molecule according to claim 1, wherein Z comprises a structure according to formula (IIId):



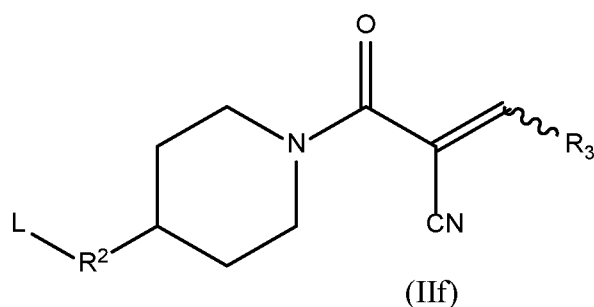
wherein R^2 is selected from heterocycloalkyl and substituted heterocycloalkyl;
 R^3 is selected from C_1 to C_6 alkyl, aryl, heteroaryl, substituted aryl, and substituted heteroaryl, optionally wherein the C_1 to C_6 alkyl is substituted with a heterocycloalkyl group;
 n is 1 or 2; and
 L shows the point of attachment of the linker.

13. A bifunctional molecule according to claim 1, wherein Z comprises a structure according to formula (IIe):



wherein R^2 is selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl and substituted heterocycloalkyl;
 R^3 is selected from C_1 to C_6 alkyl, aryl, heteroaryl, substituted aryl, and substituted heteroaryl, optionally wherein the C_1 to C_6 alkyl is substituted with a heterocycloalkyl group;
 n is 1 or 2; and
 L shows the point of attachment of the linker.

14. A bifunctional molecule according to claim 1, wherein Z comprises a structure according to formula (IIIf):

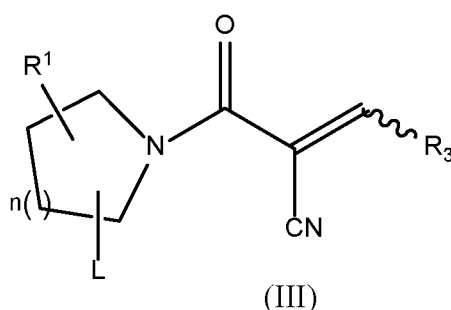


wherein R^2 is selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl and substituted heterocycloalkyl;

R^3 is selected from C_1 to C_6 alkyl, aryl, heteroaryl, substituted aryl, and substituted heteroaryl, optionally wherein the C_1 to C_6 alkyl is substituted with a heterocycloalkyl group; and

L shows the point of attachment of the linker.

15. A bifunctional molecule according to claim 1, wherein Z comprises a structure according to formula (III):



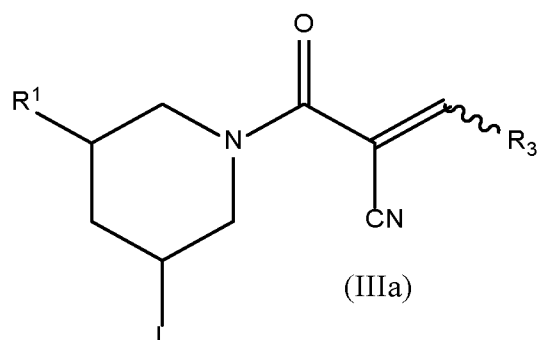
wherein R^1 is selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl and C_1 to C_6 alkyl;

R^3 is selected from C_1 to C_6 alkyl, aryl, heteroaryl, substituted aryl, and substituted heteroaryl, optionally wherein the C_1 to C_6 alkyl is substituted with a heterocycloalkyl group; and

n is 0, 1, 2 or 3; and

L shows the point of attachment of the linker.

16. A bifunctional molecule according to claim 1, wherein Z comprises a structure according to formula (IIIa):

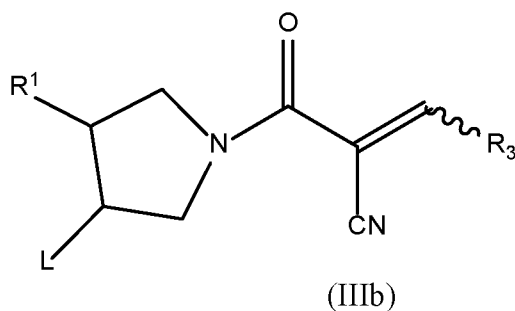


wherein R^1 is selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl and C_1 to C_6 alkyl;

R^3 is selected from C_1 to C_6 alkyl, aryl, heteroaryl, substituted aryl, and substituted heteroaryl, optionally wherein the C_1 to C_6 alkyl is substituted with a heterocycloalkyl group; and

L shows the point of attachment of the linker.

17. A bifunctional molecule according to claim 1, wherein Z comprises a structure according to formula (IIIb):

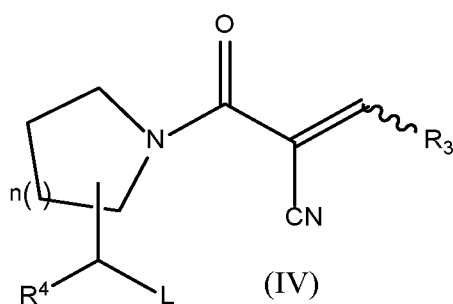


wherein R^1 is selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl and C_1 to C_6 alkyl;

R^3 is selected from C_1 to C_6 alkyl, aryl, heteroaryl, substituted aryl, and substituted heteroaryl, optionally wherein the C_1 to C_6 alkyl is substituted with a heterocycloalkyl group; and

L shows the point of attachment of the linker.

18. A bifunctional molecule according to claim 1, wherein Z comprises a structure according to formula (IV):



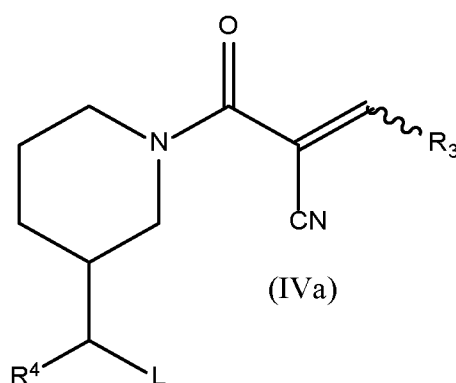
wherein R^3 is selected from C_1 to C_6 alkyl, aryl, heteroaryl, substituted aryl, and substituted heteroaryl, optionally wherein the C_1 to C_6 alkyl is substituted with a heterocycloalkyl group;

R^4 is selected from aryl, substituted aryl, heteroaryl and substituted heteroaryl; and

n is 0, 1, 2 or 3; and

L shows the point of attachment of the linker.

19. A bifunctional molecule according to claim 1, wherein Z comprises a structure according to formula (IVa):



wherein R^3 is selected from C_1 to C_6 alkyl, aryl, heteroaryl, substituted aryl, and substituted heteroaryl, optionally wherein the C_1 to C_6 alkyl is substituted with a heterocycloalkyl group; R^4 is selected from aryl, substituted aryl, heteroaryl and substituted heteroaryl; and L shows the point of attachment of the linker.

20. The bifunctional molecule of any one of claims 4 to 13, 15 and 18, wherein n is 1, 2 or 3 and n1 is 0, 1 or 2.

21. The bifunctional molecule of any one of claims 6 to 8, 15, 16 and 17, wherein each R^1 is independently:

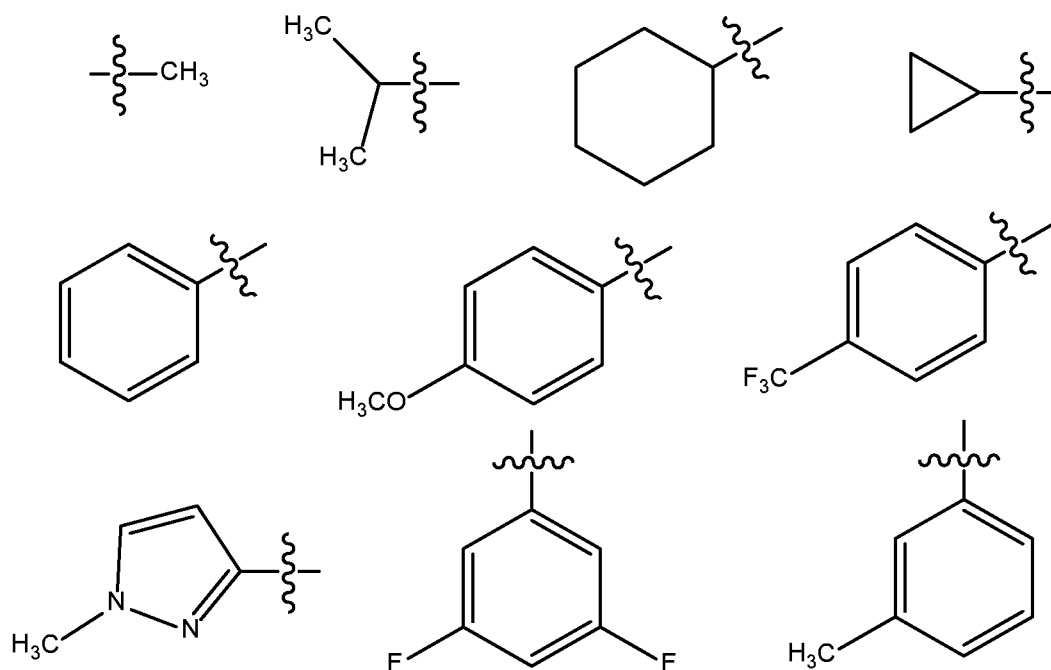
(i) selected from the group consisting of: phenyl that is optionally substituted with one to three substituents selected from the group consisting of halo, C_1 to C_6 alkyl, C_1 to C_6 haloalkyl and C_1 to C_6 alkoxy; and heteroaryl having 5 to 6 ring atoms containing 1 to 3 heteroatoms each independently selected from N, O and S, the heteroaryl being optionally substituted with one to three substituents selected from the group consisting of halo, C_1 to C_6 alkyl, C_1 to C_6 haloalkyl and C_1 to C_6 alkoxy; C_3 to C_8 cycloalkyl; or

(ii) selected from the group consisting of: phenyl, substituted phenyl, pyrazolyl, and substituted pyrazolyl.

22. The bifunctional molecule of claim 6 or claim 7 wherein two R^1 groups combine to form a C_{3-5} cycloalkyl.

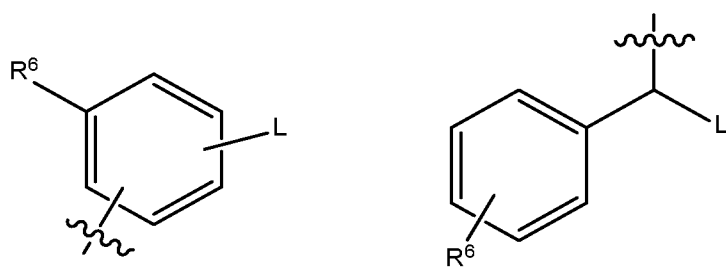
23. The bifunctional molecule of any one of claims 6 to 8, 15, 16 and 17, wherein R^1 is a C_3 to C_7 cycloalkyl or a C_1 to C_3 alkyl.

24. The bifunctional molecule of any one of claims 6 to 8, 15, 16 and 17, wherein R^1 is selected from one of the following structures:



25. The bifunctional molecule of any one of claims 1 to 14, wherein R^2 is:

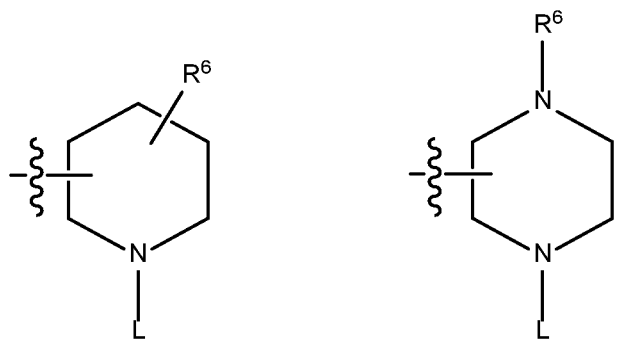
- (i) selected from phenyl optionally substituted with one to three substituents selected from H, C_1 to C_6 alkyl, halo, C_1 to C_6 haloalkyl and C_1 to C_6 alkoxy; and heteroaryl having 5 to 6 ring atoms and containing 1 or 2 N atoms, the heteroaryl being optionally substituted with one to three substituents selected from C_1 - C_6 alkyl, halo, C_1 - C_6 haloalkyl and C_1 to C_6 alkoxy;
- (ii) selected from optionally substituted phenyl, and optionally substituted pyrazolyl;
- (iii) selected from one of the following structures:



wherein R^6 is selected from H, C_1 - C_6 alkyl, halo, C_1 - C_6 haloalkyl and C_1 - C_6 alkoxy; or
 (iv) is absent.

26. The bifunctional molecule of any one of claims 1 to 14, wherein R^2 is:

- (i) an optionally substituted heterocycloalkyl, wherein the heterocycloalkyl has 3 to 10 ring atoms and contains 1 to 3 heteroatoms each independently selected from N, O and S;
- (ii) selected from optionally substituted piperidinyl, and optionally substituted piperazinyl;
- (iii) selected from one of the following structures:



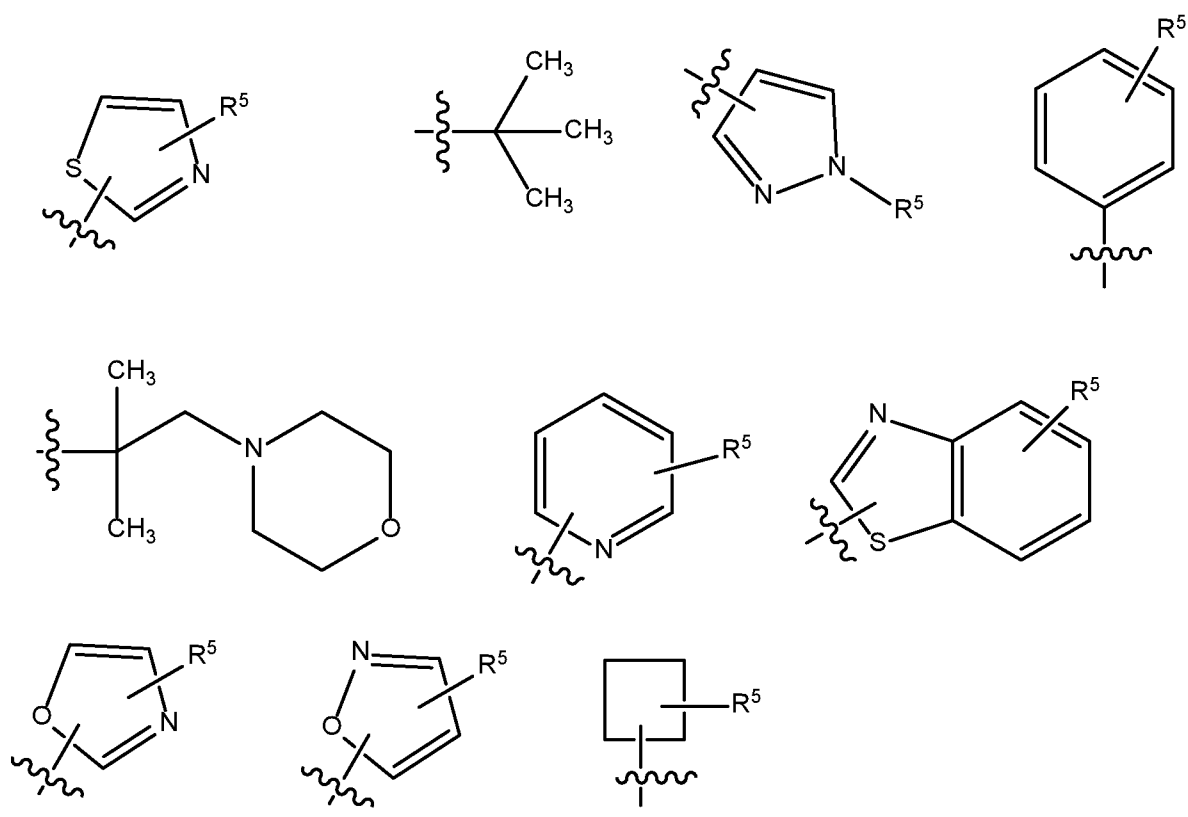
wherein R^6 is selected from H, C_1 to C_6 alkyl, halo, C_1 to C_6 haloalkyl and C_1 to C_6 alkoxy; or (iv) is absent.

27. The bifunctional molecule of any one of the preceding claims, wherein R^3 is:

(i) selected from C_1 to C_6 alkyl optionally substituted with a heterocycloalkyl group having 5 to 7 ring atoms and containing 1 or 2 heteroatoms each independently selected from N, O and S; aryl having 6 to 10 carbon ring atoms; and heteroaryl having 5 to 10 ring atoms and containing 1 to 3 heteroatoms each independently selected from N, O and S; wherein the aryl and the heteroaryl are optionally substituted with one or two substituents 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; or

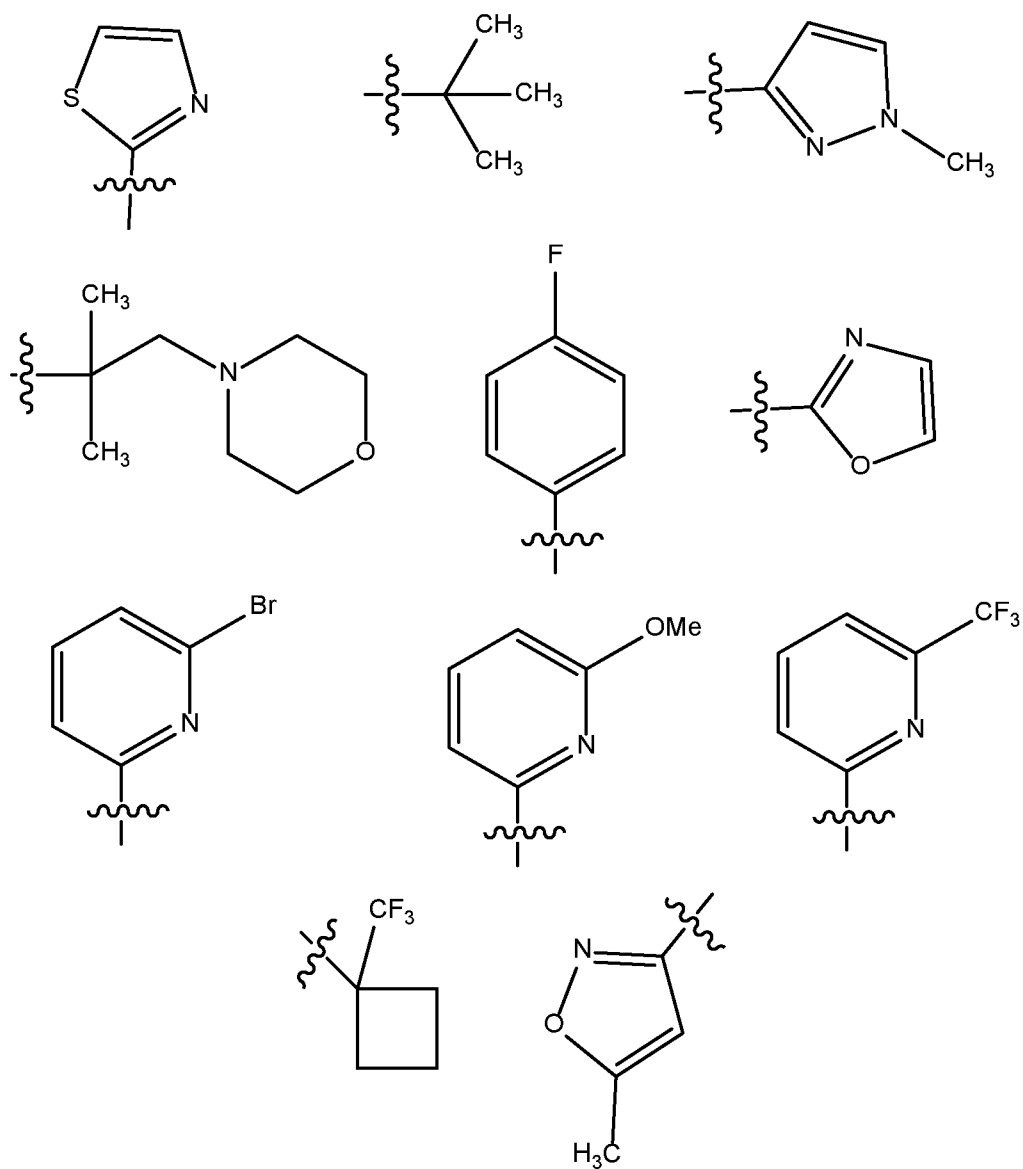
(ii) selected from optionally substituted phenyl, optionally substituted thiazolyl, optionally substituted pyrazolyl, optionally substituted oxazolyl, tert-butyl, C_1 - C_6 alkyl comprising a morpholino substituent, optionally substituted benzothiazolyl and optionally substituted pyridinyl.

28. The bifunctional molecule of any one of the preceding claims, wherein R^3 is selected from one of the following structures:

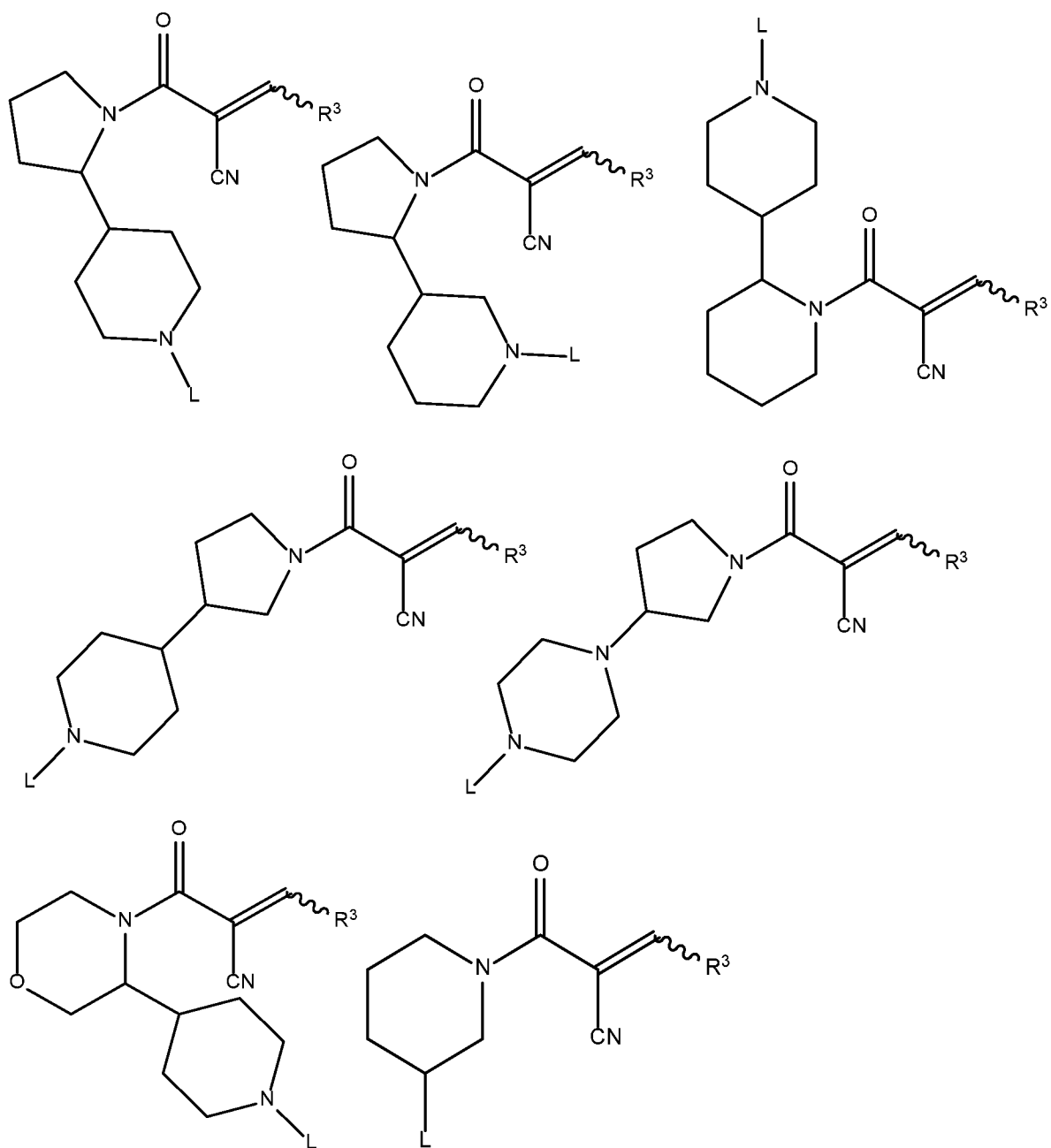


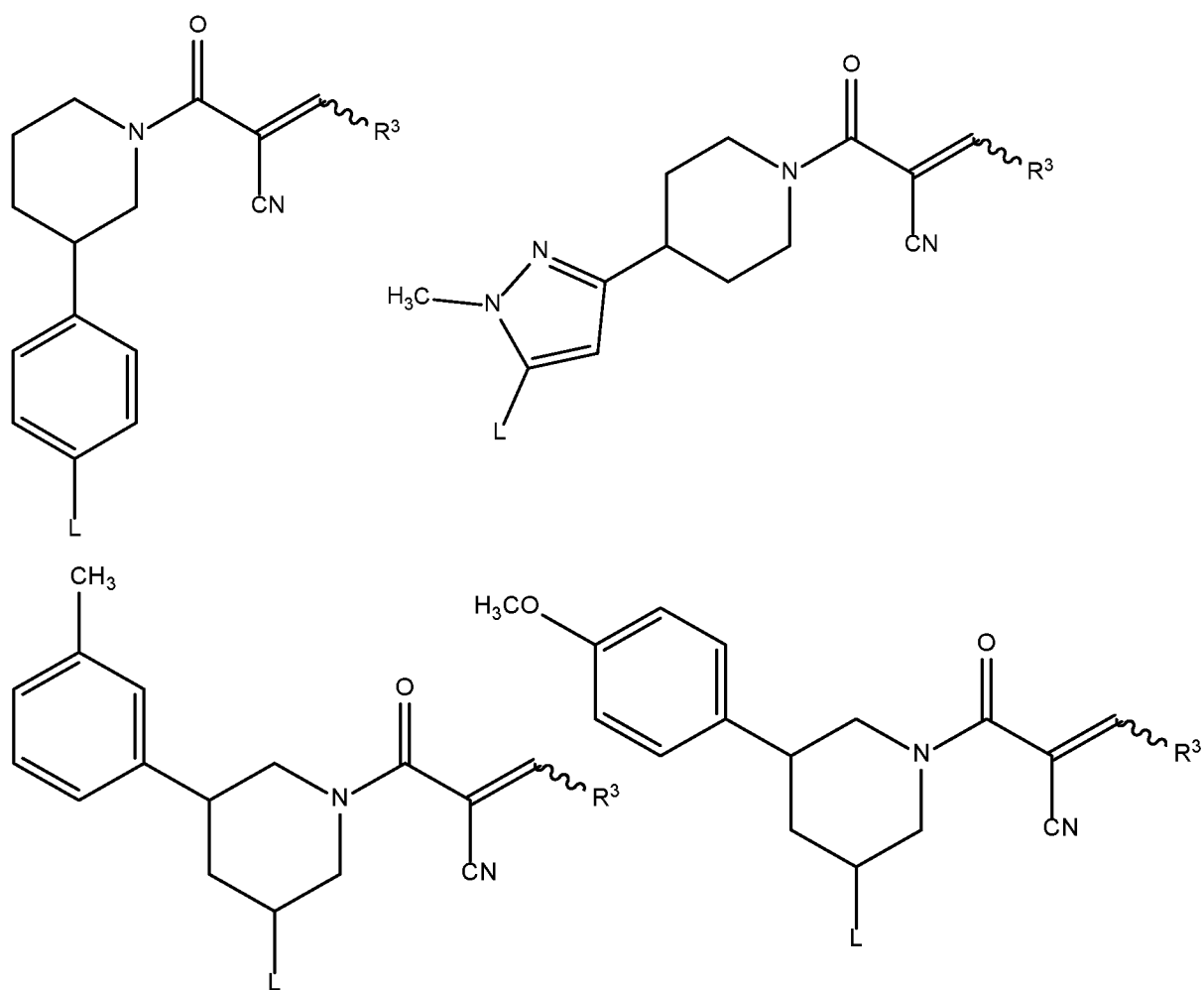
wherein R⁵ is selected from halo, CF₃, -CH₂F, -CHF₂, C₁ to C₆ alkyl, -CN, -OH, -OMe, -SMe, -SOMe, -SO₂Me, -NH₂, -NHMe, -NMe₂, CO₂Me, -NO₂, CHO, and COMe.

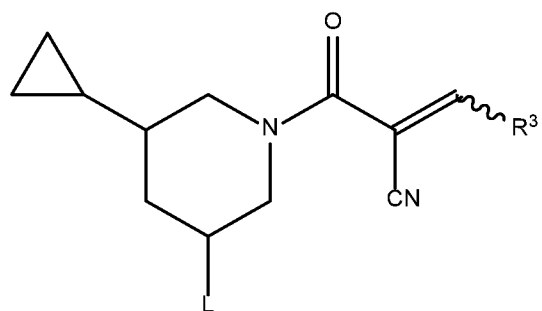
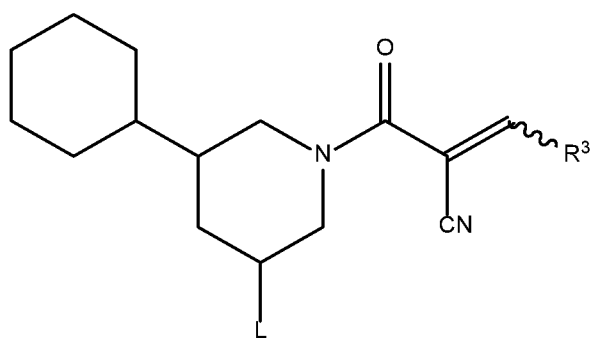
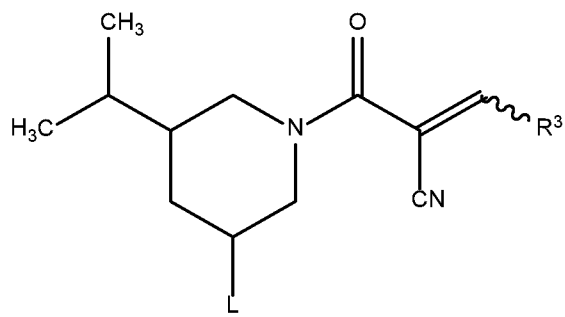
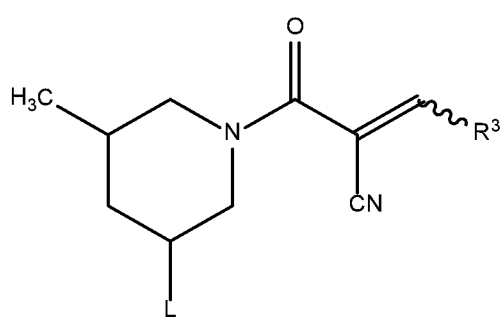
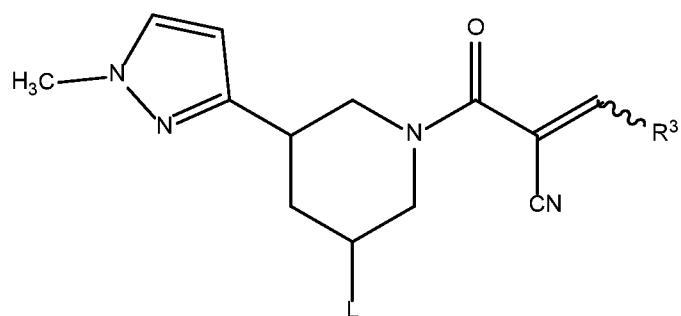
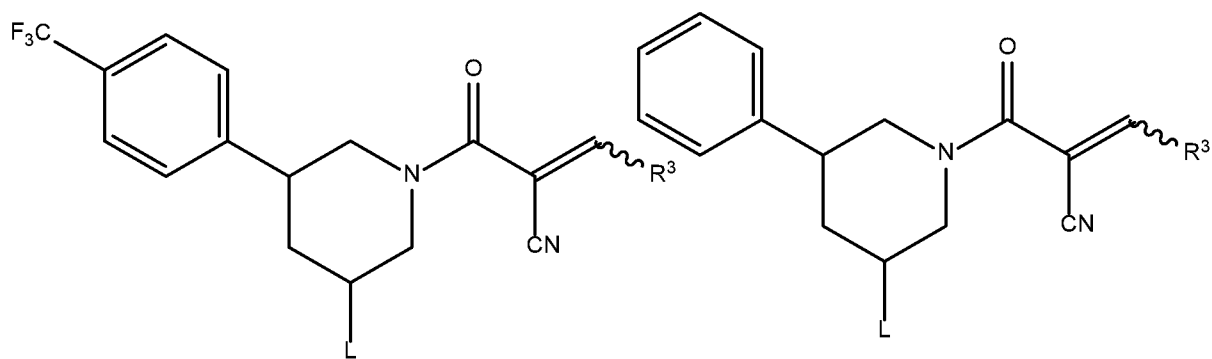
29. The bifunctional molecule of any one of the preceding claims, wherein R³ is selected from one of the following structures:

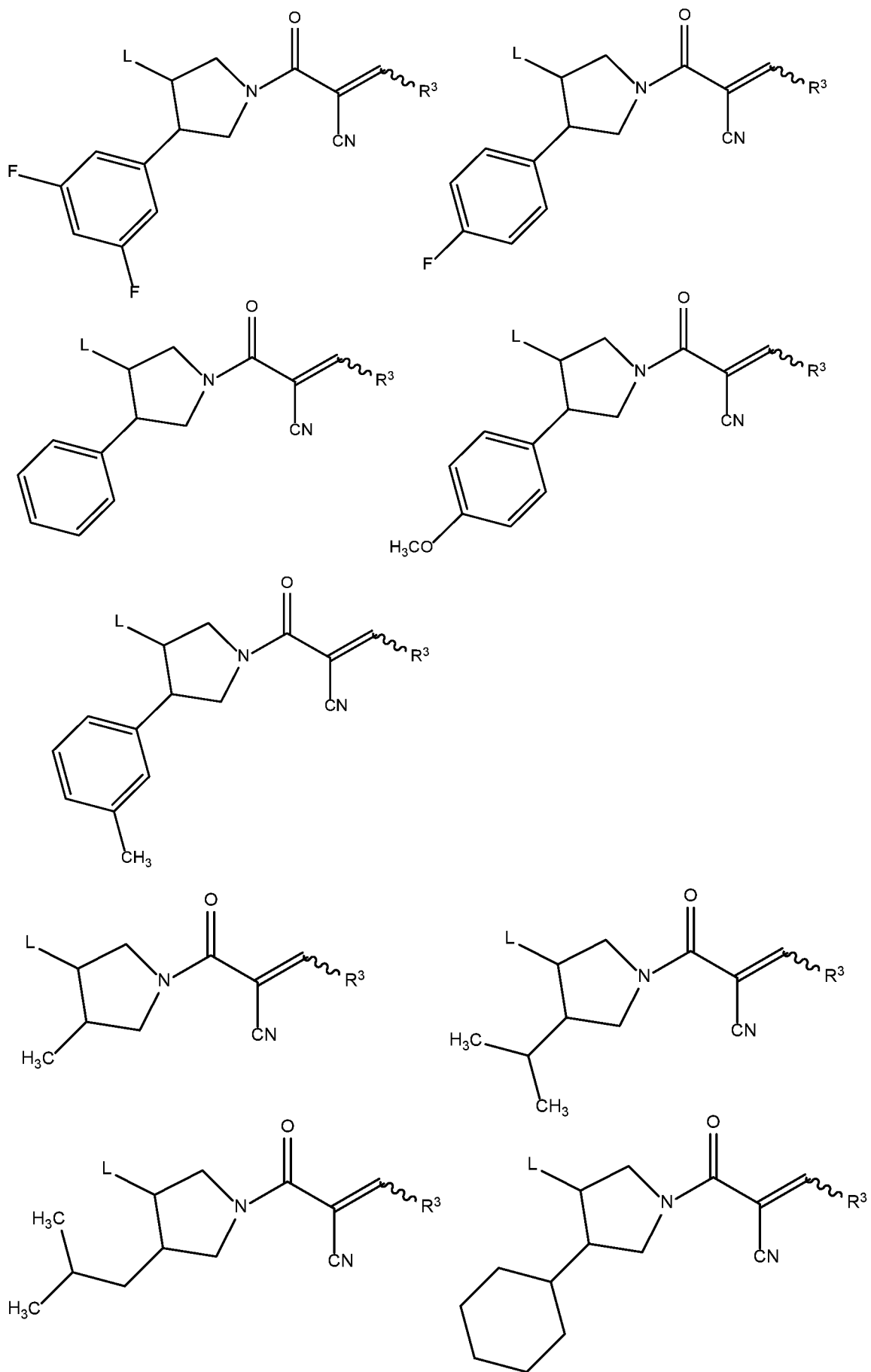


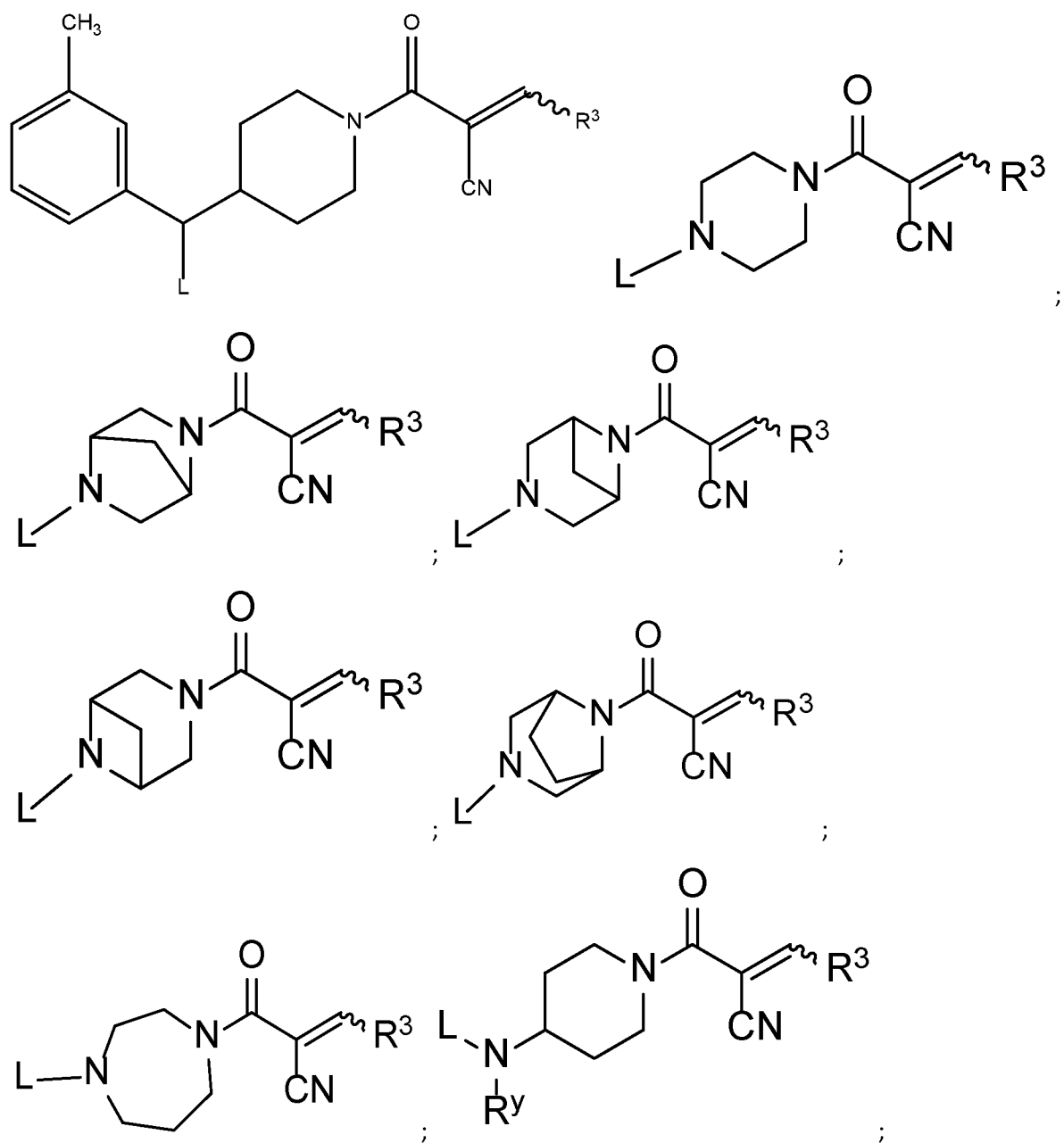
30. The bifunctional molecule of claim 1, wherein Z comprises one of the following structures:

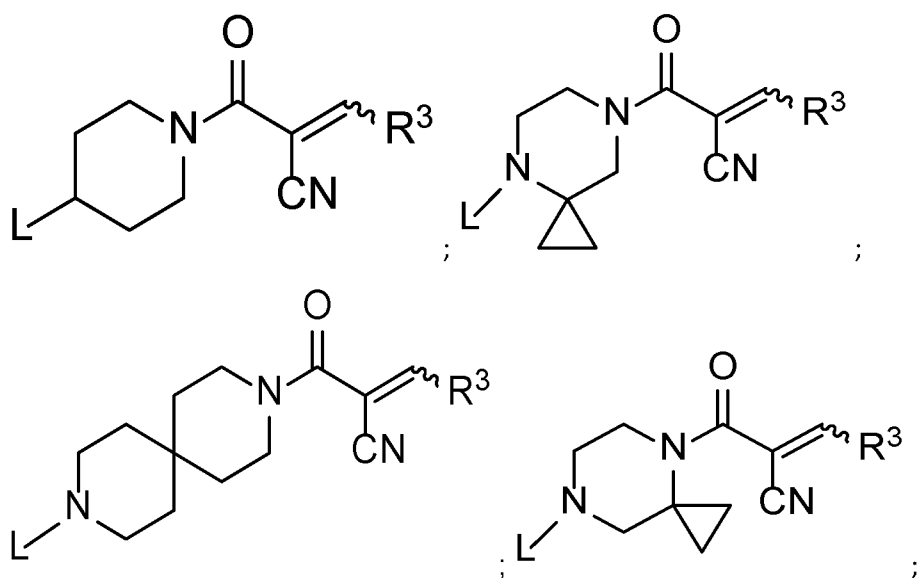




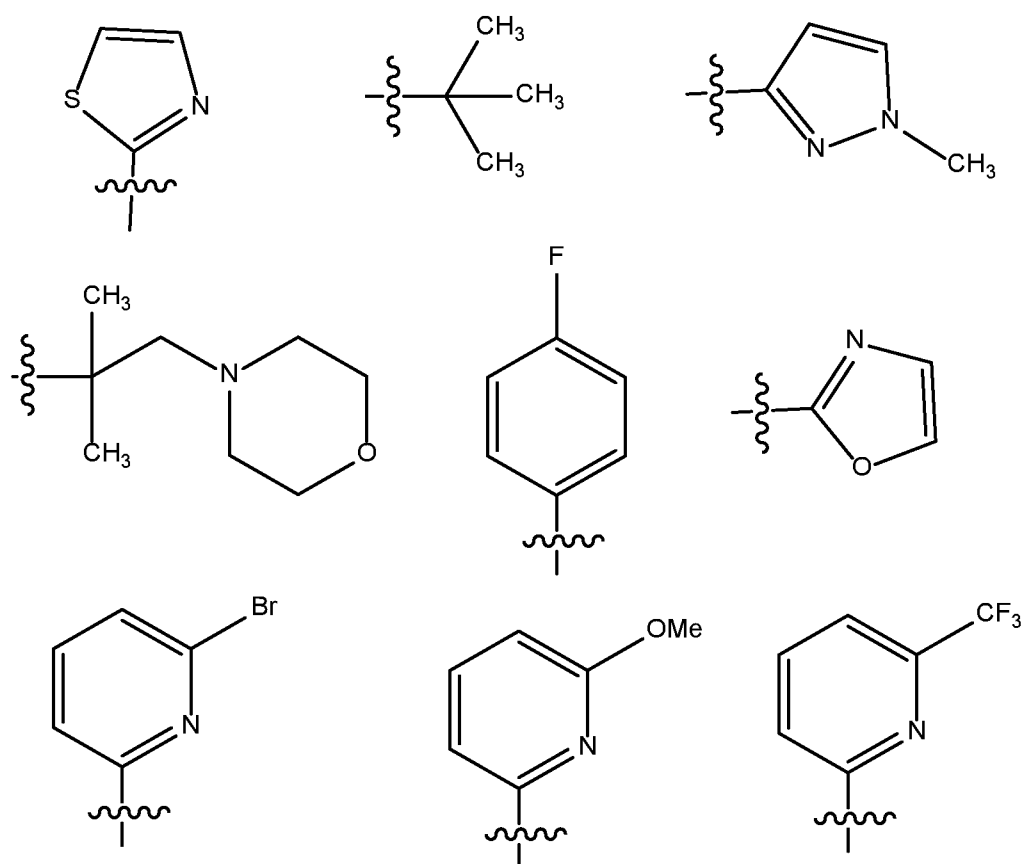


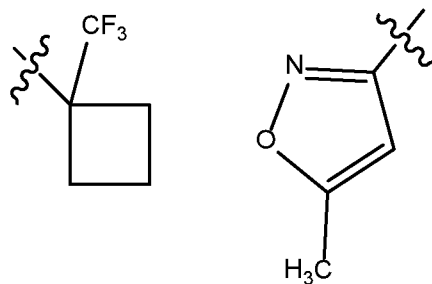






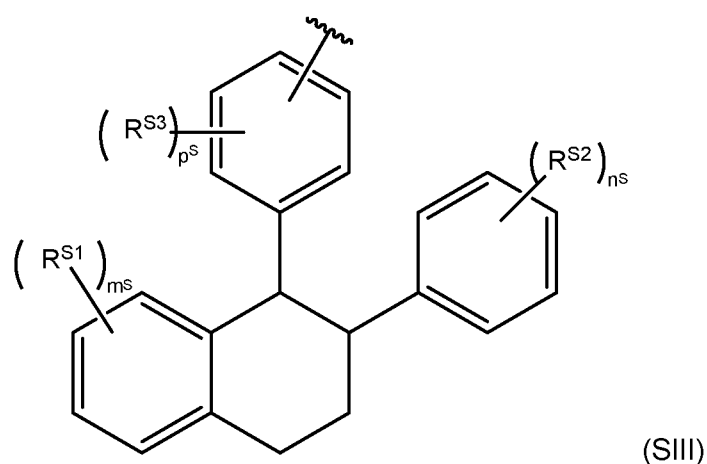
wherein R^3 in each of the structures above is one of the following:





31. The bifunctional molecule according to any one claims 1 to 30, wherein the TBL has the structure of:

(a) Formula (SIII):



wherein:

each R^{S1} is independently selected from OH, $-O-C_{1-4}$ alkyl, $-O-C_{1-4}$ haloalkyl, halogen, $O(CO)R^{S6}$;

each R^{S2} is independently selected from halogen, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, C_{3-7} cyclohaloalkyl, OH, $-O-C_{1-4}$ alkyl, NH_2 , $-NR^{S5}-C_{1-4}$ alkyl, $-O-C_{1-4}$ haloalkyl, $-NR^{S5}-C_{1-4}$ haloalkyl, $-O-C_{3-7}$ cycloalkyl, $-NR^{S5}-C_{3-7}$ cycloalkyl;

each R^{S3} is independently selected from halogen, C_{1-4} alkyl, C_{1-4} haloalkyl;

each R^{S5} is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, C_{3-7} cyclohaloalkyl;

R^{S6} is selected from C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, heteroaryl;

m^S is 0, 1, 2 or 3;

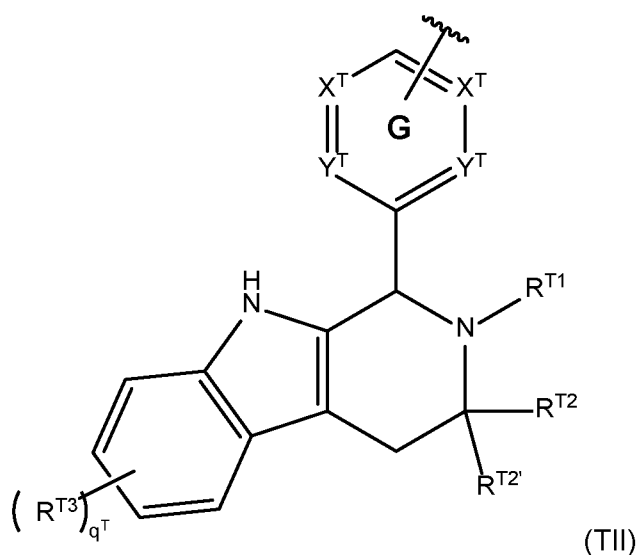
n^S is 0, 1, 2 or 3;

p^S is 0, 1, 2 or 3

wherein  indicates the point of attachment of the linker.

or,

(b) the TBL is of Formula T(II);



wherein:

Ring G is aryl or heteroaryl;

each X^T is independently CH or N;

each Y^T is independently CR^{Tc} or N, wherein R^{Tc} is halogen or C_{1-3} alkyl;

R^{T1} is selected from H, C_{1-9} alkyl, C_{1-9} haloalkyl; C_{3-7} cycloalkyl, C_{3-7} cyclohaloalkyl; a 5- or 6-membered heterocycloalkyl, C_{6-10} aryl, a 5- or 6-membered heteroaryl, $-(C_{1-6} \text{ alkyl})-(C_{3-7} \text{ cycloalkyl})$, $-(C_{1-6} \text{ alkyl})-(\text{a 5- or 6-membered heterocycloalkyl})$, $C(O)R^{Tb}$, $C(O)NR^{Ta}$, SO_2R^{Ta} , and SO_2NR^{Ta} , wherein when R^{T1} is not H, R^{T1} is optionally substituted with 1-3 substituents independently selected from halogen, CN, OR^a , $N(R^a)_2$, C_{1-9} alkyl, C_{3-7} cycloalkyl, 5- or 6-membered heterocycloalkyl, C_{6-10} aryl, a 5- or 6-membered heteroaryl, $C(O)R^{Ta}$, $C(O)NR^{Ta}$, SO_2R^{Ta} , and SO_2NR^{Ta} ;

R^{Ta} is selected from H, C_{1-6} alkyl, C_{3-7} cycloalkyl, and a 5- or 6-membered heterocycloalkyl, wherein R^{Ta} is optionally substituted with 1-3 substituents independently selected from halogen, CN, OH, OC_{1-6} alkyl, and SO_2-C_{1-6} alkyl;

R^{Tb} is independently selected from H, $-OR^{Ta}$, C_{1-6} alkyl, $-(C_{1-6} \text{ alkyl})-(C_{3-7} \text{ cycloalkyl})$, C_{3-7} cycloalkyl, and 5- or 6-membered heterocycloalkyl, wherein R^{Tb} is optionally substituted with 1-3 substituents independently selected from halogen, CN, C_{1-6} haloalkyl, OH, OC_{1-6} alkyl, and SO_2-C_{1-6} alkyl,

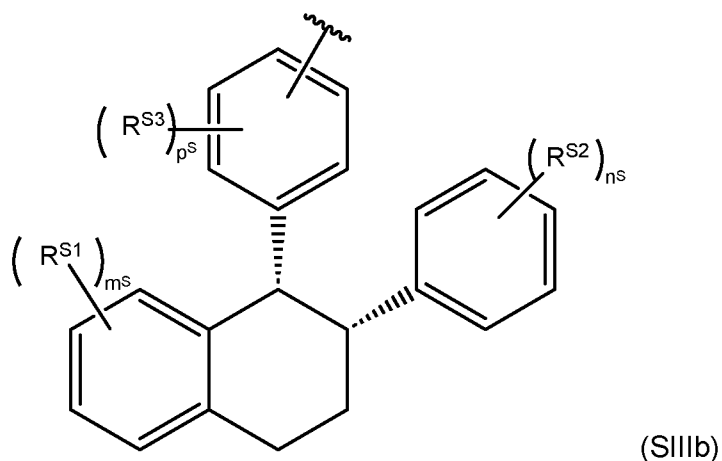
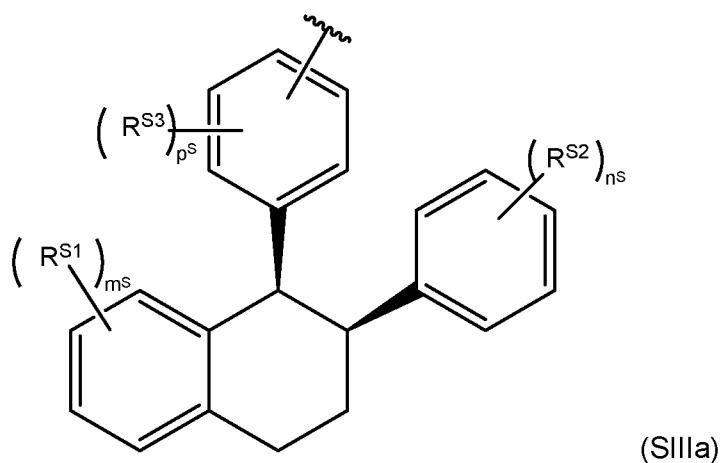
R^{T2} and $R^{T2'}$ are independently selected from H, halogen, -CN, C_{1-6} alkyl, $-OR^{Ta}$, $-C_{1-6}$ alkyl-OH, $-C_{1-6}$ alkyl- OR^{Ta} , $-C_{1-6}$ alkyl-SO₂- C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} cycloalkyl, 5- or 6-membered heterocycloalkyl, $-N(R^{Ta})_2$, $-C_{1-6}$ alkyl-NR^{Ta}- C_{1-6} alkyl, $-C_{1-6}$ alkyl-NH₂, $-C_{1-6}$ alkyl-NHSO₂- C_{1-6} alkyl, $-C_{1-6}$ alkyl-CN, -CO₂H, -COR^{Ta}, -CO₂R^{Ta}, -CON(R^{Ta})₂, $-C_{1-6}$ alkyl-CONH₂, -NR^{Ta}CO- C_{1-6} alkyl, -NR^{Ta}S(O)₂- C_{1-6} alkyl, -S(O)₂N(R^{Ta})₂;

R^{T3} is selected from halogen, -CN, C_{1-6} alkyl, CH₂OH, $-C_{1-6}$ alkyl- OR^{Ta} , $-C_{1-6}$ alkyl-SO₂- C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, C_{3-7} cyclohaloalkyl, 5- or 6-membered heterocycloalkyl, $-C_{1-6}$ alkyl-NR^{Ta}- C_{1-6} alkyl, $-C_{1-6}$ alkyl-NHSO₂- C_{1-6} alkyl, $-C_{1-6}$ alkyl-CN, -CO₂H, -CO- C_{1-6} alkyl, -CO₂- C_{1-6} alkyl, -CON(R^{Ta})₂, $-C_{1-6}$ alkyl-CONH₂, $-N(R^{Ta})_2$, -NR^{Ta}CO- C_{1-6} alkyl, -NR^{Ta}S(O)₂- C_{1-6} alkyl; and

q^T is 0, 1, 2 or 3;

wherein  indicates the point of attachment of the linker.

32. The bifunctional molecule of claim 31, wherein the TBL is of Formula SIIIa or Formula SIIIb:



wherein:

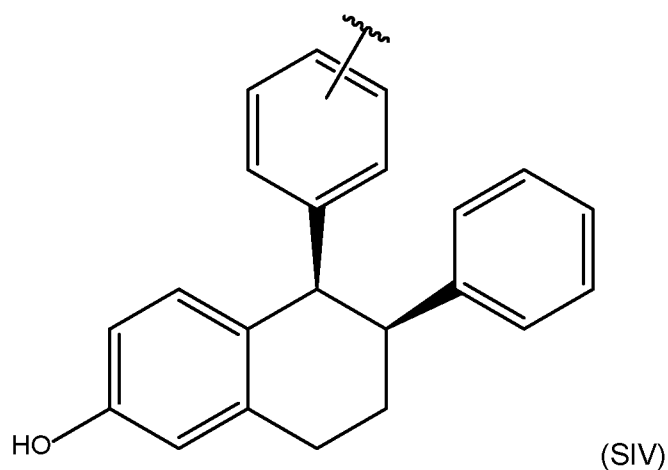
R^{S1} , R^{S2} , R^{S3} , m, n and p are as defined in Formula (SIII);

wherein  indicates the point of attachment of the linker.

33. The bifunctional molecule of claim 32, wherein:

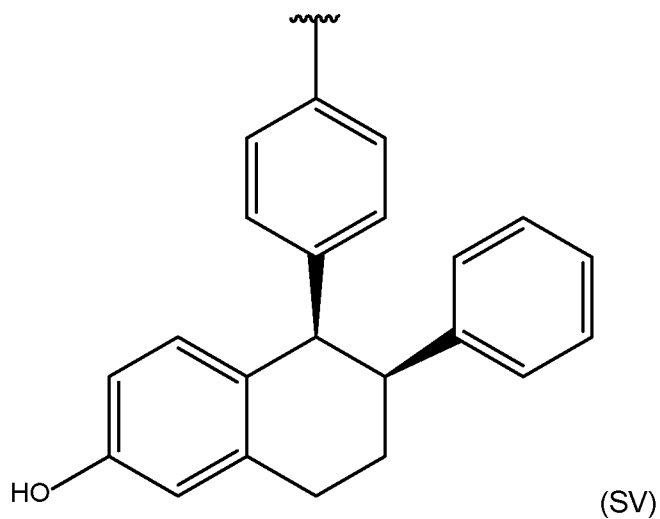
- a) R^{S1} is OH; and/or
- b) m^S is 1; and/or
- c) n^S is 0; and/or
- d) p^S is 0.

34. The bifunctional molecule of any one of claims 31 to 33, wherein TBL is of Formula SIV:



wherein  indicates the point of attachment of the linker.

35. The bifunctional molecule of claim 34, wherein TBL is of Formula SV:

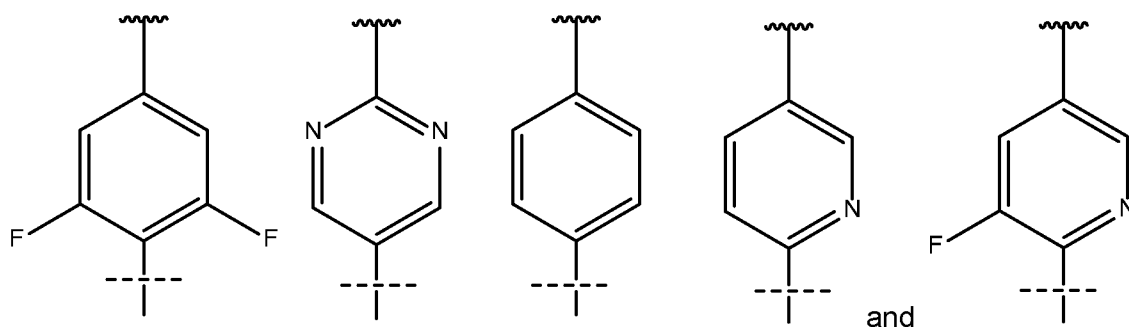


wherein  indicates the point of attachment of the linker.

36. The bifunctional molecule of claim 31, wherein when the TBL is of Formula TII:

- a) each X^T is N and each Y^T is CH; or
- b) each X^T is CH and each Y^T is CR^{Tc} .

37. The bifunctional molecule of claim 31, wherein ring G is selected from:

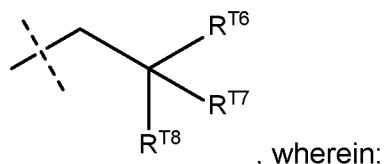


wherein  indicates the point of attachment of the linker; and

wherein  indicates the point of attachment to the remainder of the TBL structure.

38. The bifunctional molecule of any one of claims 31, 36 and 37, wherein R^{T2} is C_{1-6} alkyl and $R^{T2'}$ is H.

39. The bifunctional molecule of any one of claims 31 and 36 to 38, wherein R^{T1} is

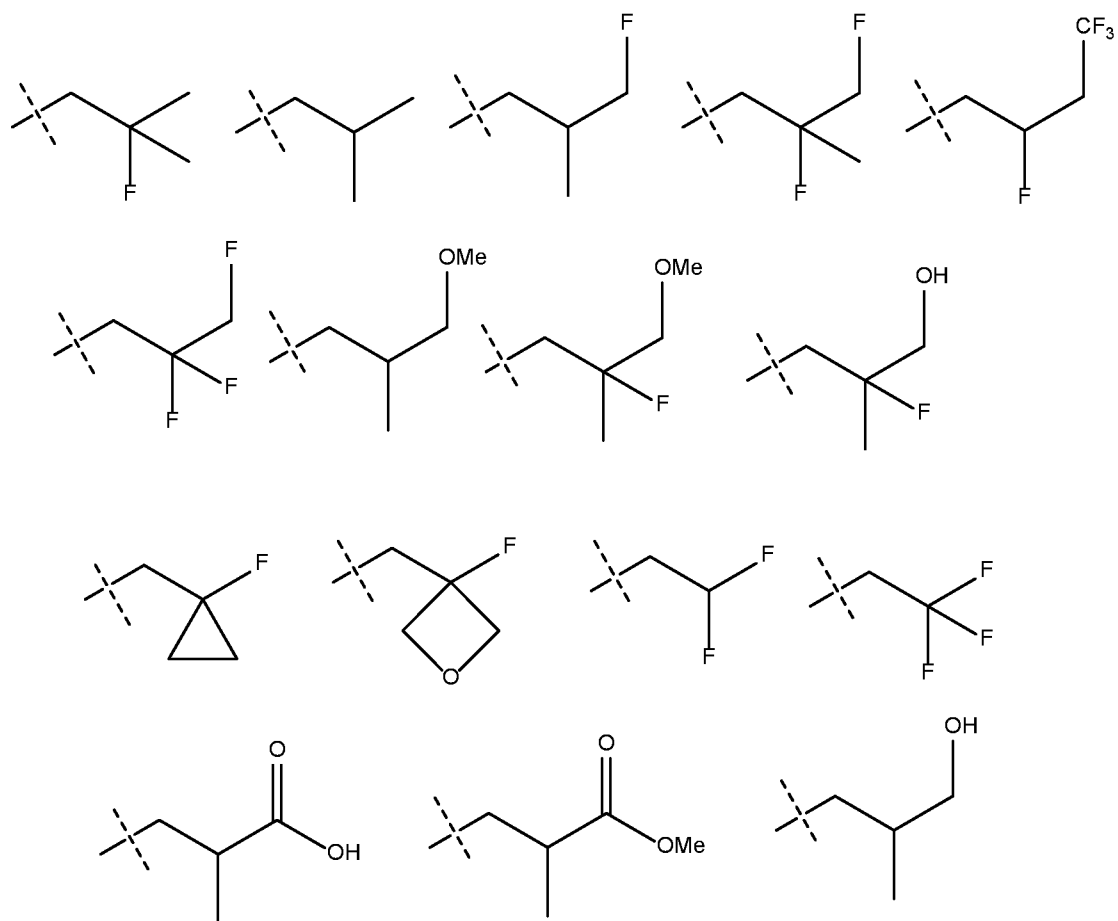


R^{T6} and R^{T7} are each independently selected from H, Me or F, or R^{T6} and R^{T7} taken together with the carbon atom to which they are attached form a cyclopropyl ring or an oxetanyl ring;

R^{T8} is selected from H, Me, F, CH_2F , CHF_2 , CF_3 , CN, CH_2CN , CH_2OMe , CH_2OH , CO_2H , CO_2Me or SO_2Me ; and

wherein  indicates the point of attachment to the remainder of the TBL structure.

40. The bifunctional molecule of claim 39, wherein, R^{T1} has a structure selected from:

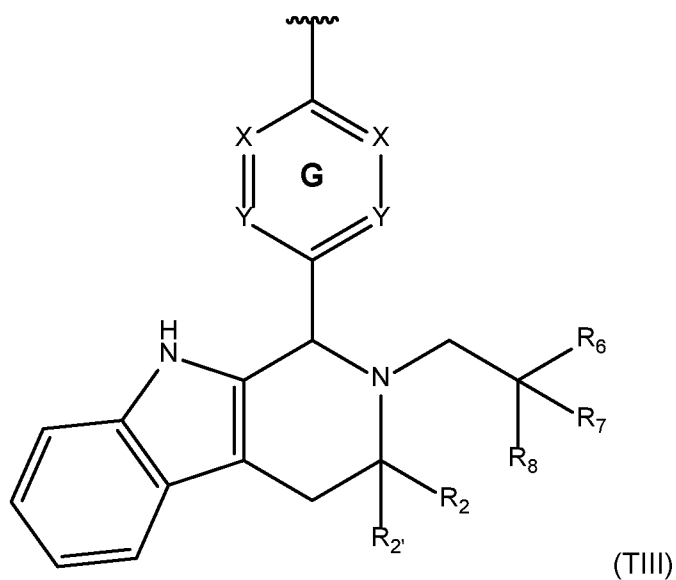


wherein  indicates the point of attachment to the remainder of the TBL structure.

41. The bifunctional molecule of claim 39 or claim 40, wherein:

- a) R^{T6} is Me; and/or
- b) R^{T7} is Me; and/or
- c) R^{T8} is F; and/or
- d) q^T is 0.

42. The bifunctional molecule of any one of claims 39 to 41, wherein the TBL is of Formula TIII:

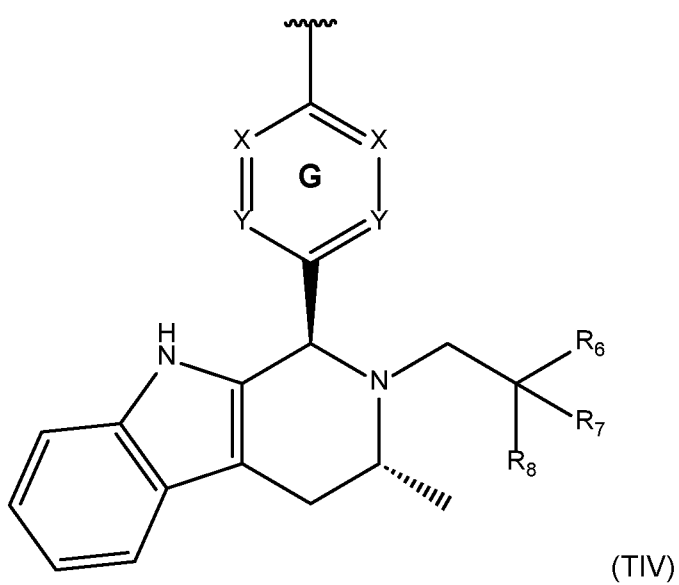


wherein:

Ring G, X^T , Y^T , R^{T2} , $R^{T2'}$, R^{T6} , R^{T7} and R^{T8} are as defined in Formula TII; and

wherein  indicates the point of attachment of the linker.

43. The bifunctional molecule of claim 42, wherein the TBL is of Formula TIV:

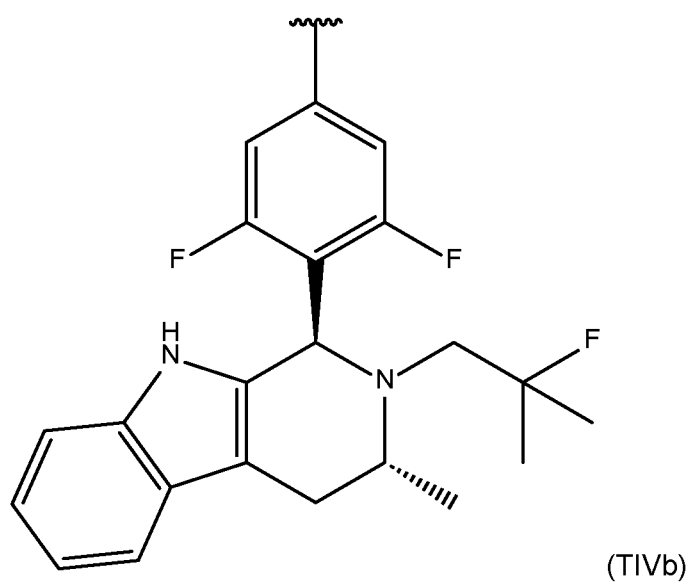
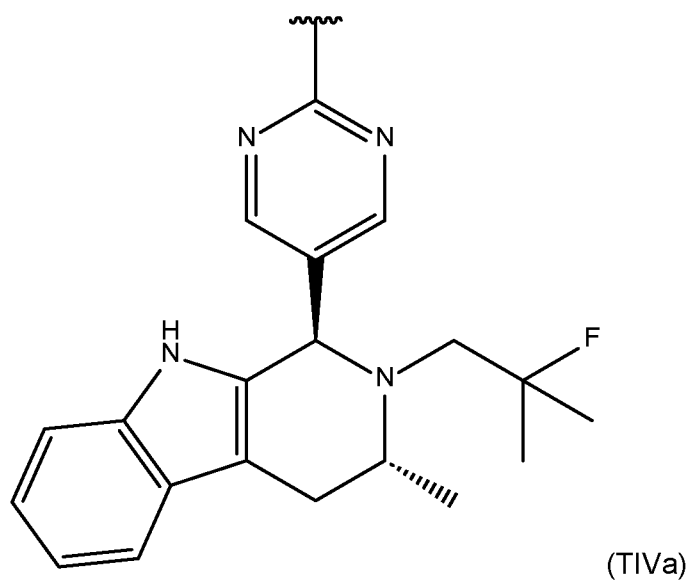


wherein:

Ring G, X^T , Y^T , R^{T6} , R^{T7} and R^{T8} are as defined in Formula TII or TIII; and

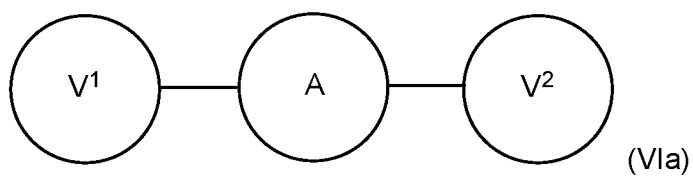
wherein  indicates the point of attachment of the linker.

44. The bifunctional molecule of claim 43, wherein the TBL is of Formula TIVa or TIVb:



wherein  indicates the point of attachment of the linker.

45. The bifunctional molecule according to any one of claims 1 to 30, wherein the TBL is of formula VIa:

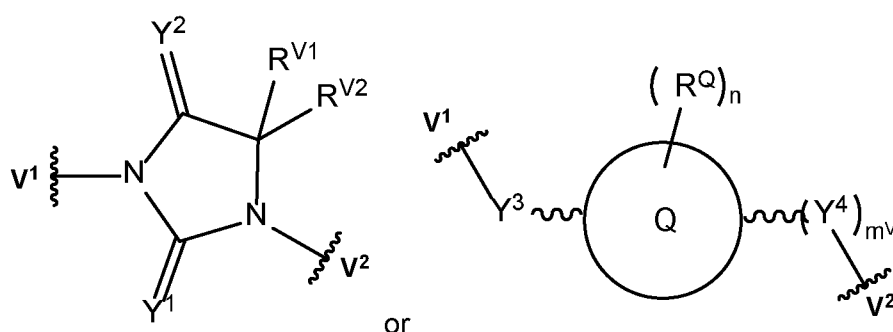


wherein:

V¹ is aryl or heteroaryl, wherein the aryl or heteroaryl is independently substituted by one or more R^{V1}, wherein each R^{V1} is independently selected from: halo; hydroxy; nitro; -CN; -C≡CH; C₁₋₆ alkyl optionally substituted by one or more halo; C₁₋₆ alkoxy optionally substituted by one or more halo, C₂₋₆ alkenyl, C₂₋₆ alkynyl;

V² is selected from: C₁₋₆ alkyl; C₁₋₈ cycloalkyl; heterocycloalkyl; aryl; or heteroaryl; each optionally substituted by 1, 2 or 3 R^{V2}, wherein each R^{V2} is independently selected from: halo, C₁₋₆ alkyl optionally substituted by one or more halo; OC₁₋₃ alkyl optionally substituted by one or more halo, OH, NR^{Y1}R^{Y2}, CN, C₂₋₄ alkenyl C₂₋₄ alkynyl;

A is selected from:



wherein indicates the point of attachment to ring V¹, and indicates the point of attachment to ring V²; and

wherein:

Y¹ and Y² are each independently selected from NR^{Y1}, O and S;

R^{V1}, R^{V2} are each independently selected from: H, C₁₋₆ alkyl optionally substituted by one or more halo; or R^{V1} and R^{V2} taken together with the atom to which they are attached, form a 3-7-membered cycloalkyl ring containing 0-2 heteroatoms selected from N, O and S;

Y³ is selected from NR^{Y1}, O and S;

Y⁴ is selected from a bond, NR^{Y2}, CR^{Y3}R^{Y4}, O and S; -NR^{Y2}C=O-, -C=ONR^{Y2}-; -NR^{Y2}C=S-, -C=SNR^{Y2}-; S=O; SO₂; and C=O;

Q is a 3- to 7-membered cycloalkyl ring, wherein the cycloalkyl ring contains 0-4 heteroatoms selected from N, O or S;

each R^Q is independently selected from C₁₋₆ alkyl optionally substituted by one or more halo; or two R^Q groups taken together with the atom to which they are attached, form a 3-7-membered cycloalkyl ring containing 0-2 heteroatoms selected from N, O and S;

R^{Y1} , R^{Y2} , R^{Y3} , R^{Y4} are each independently selected from: H, C_{1-6} alkyl optionally substituted by one or more halo;

n is 0, 1, 2, 3, 4, 5 or 6; and

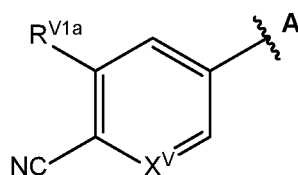
m is 0, 1, 2, 3, 4 or 5;

and

wherein the TBL is attached to the linker at any suitable position.

46. The bifunctional molecule of claim 45, wherein the TBL is attached to the linker via covalent coupling to V^2 .

47. The bifunctional molecule of claim 45 or claim 46, wherein V^1 is:



wherein  indicates the point of attachment to ring A; and

R^{V1a} is selected from: halo; C_{1-4} alkyl optionally substituted with halo; $-OC_{1-4}$ alkyl optionally substituted with halo;

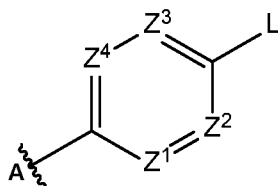
X^V is N, or CR^{V1b} , wherein R^{V1b} is selected from: H; halo; C_{1-4} alkyl optionally substituted with halo; $-OC_{1-4}$ alkyl optionally substituted with halo.

48. The bifunctional molecule of claim 47, wherein:

X^V is CH; and

R^{V1a} is selected from Cl and CF_3 .

49. The bifunctional molecule of any one of claims 45 to 48, wherein V^2 comprises:



wherein  indicates the point of attachment to ring A, and L indicates the point of attachment of the linker; and

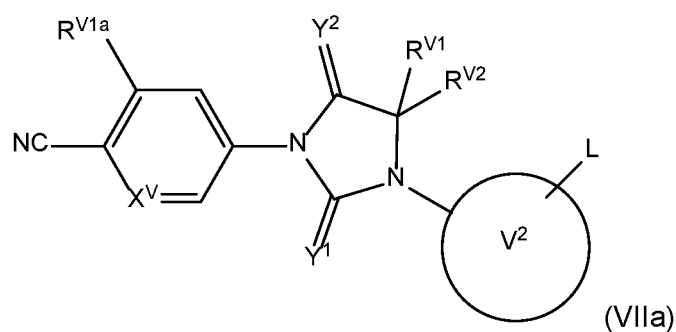
Z^1 , Z^2 , Z^3 and Z^4 are each independently selected from: N, or CR^{V2b} , wherein R^{V2b} is selected from: H; halo; C_{1-4} alkyl optionally substituted with halo; $-OC_{1-4}$ alkyl optionally substituted with halo.

50. The bifunctional molecule of claim 49, wherein:

Z^1 is N, or CH;

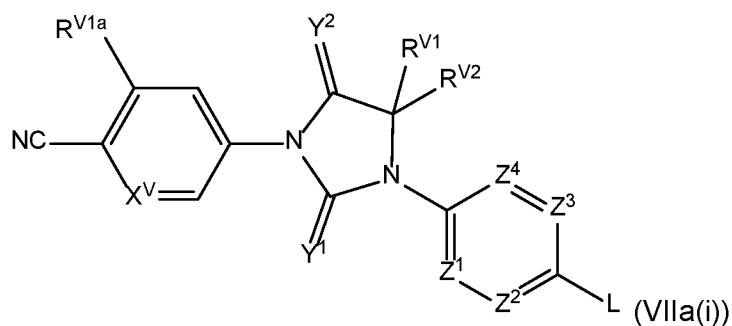
Z^2 , Z^3 and Z^4 are each CH.

51. The bifunctional molecule of any one of claims 45 to 50, wherein TBL is of Formula VIIa:



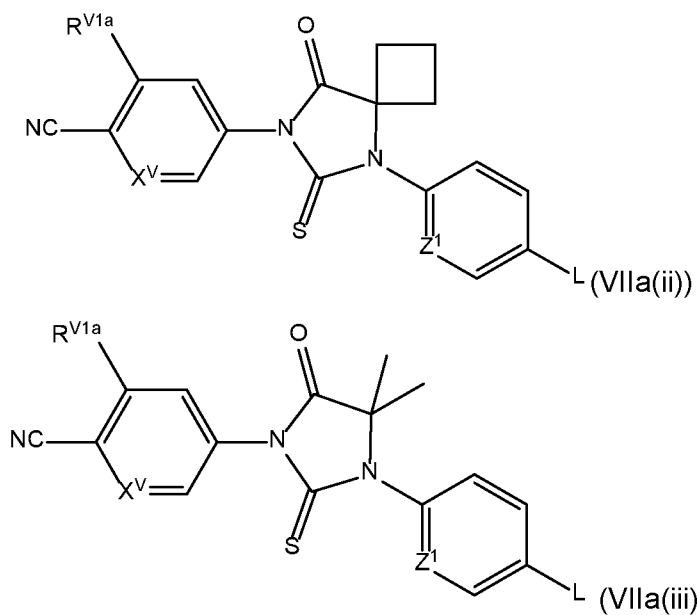
wherein V^2 , X^V , Y^1 , Y^2 , R^{V1} , R^{V2} , R^{V1a} and L are as defined for formula Via.

52. The bifunctional molecule of claim 51, wherein TBL is of Formula VIIa(i):



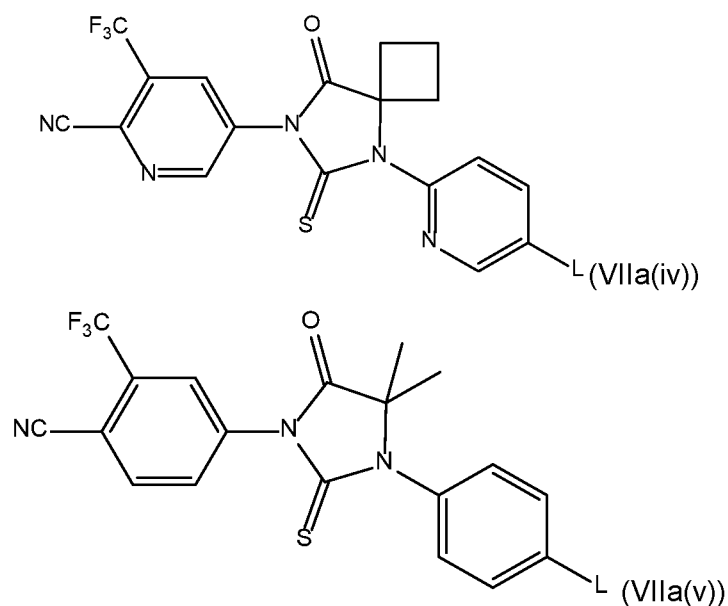
wherein X^V , Y^1 , Y^2 , R^{V1} , R^{V2} , R^{V1a} , Z^1 , Z^2 , Z^3 , Z^4 and L are as defined for formula Via.

53. The bifunctional molecule of claim 52, wherein TBL is of Formula VIIa(ii) or VIIa(iii):



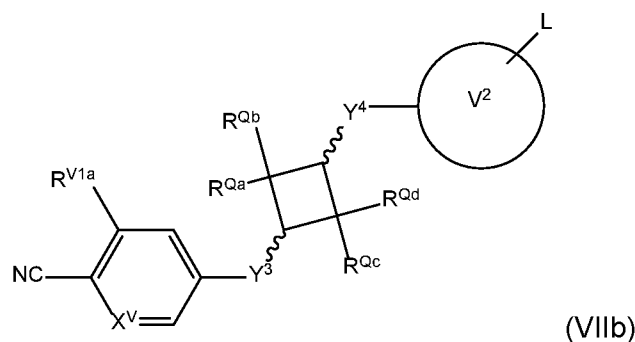
wherein X^V, R^{V1a}, Z¹, Z², Z³, Z⁴ and L are as defined for formula VIa.

54. The bifunctional molecule of claim 53, wherein TBL is of Formula VIIa(iv) or VIIa(v):



wherein L is as defined for formula VIa.

55. The bifunctional molecule of any one of claims 45 to 50, wherein TBL is of Formula VIIb:



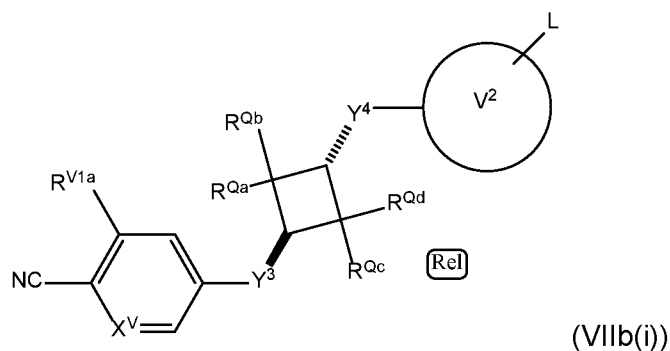
wherein V^2 , X^V , Y^3 , Y^4 , R^{V1a} and L are as defined for formula VIa; and

wherein:

R^{Qa} , R^{Qb} , R^{Qc} , R^{Qd} are each independently selected from C_{1-6} alkyl optionally substituted by one or more halo; or

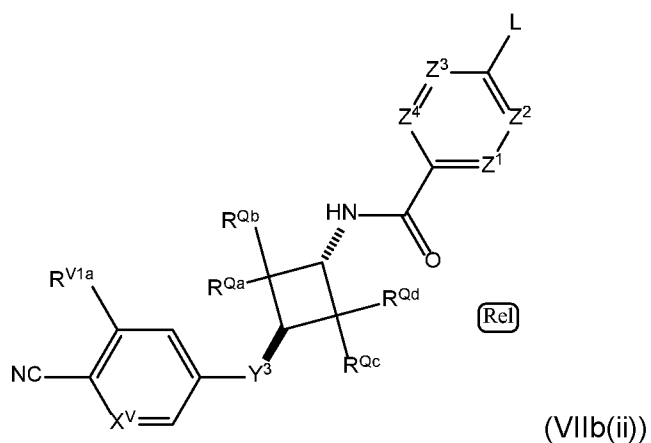
R^{Qa} and R^{Qb} , or R^{Qc} and R^{Qd} , taken together with the atom to which they are attached, form a 3-7-membered cycloalkyl ring containing 0-2 heteroatoms selected from N, O and S.

56. The bifunctional molecule of claim 55, wherein TBL is of Formula VIIb(i):



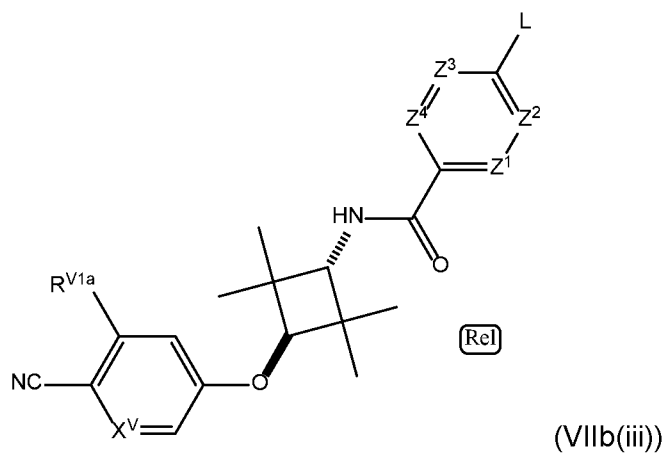
wherein X^V , Y^3 , R^{Qa} , R^{Qb} , R^{Qc} , R^{Qd} , R^{V1a} , Z^1 , Z^2 , Z^3 , Z^4 and L are as defined for formula VIIb.

57. The bifunctional molecule of claim 56, wherein TBL is of Formula VIIb(ii):



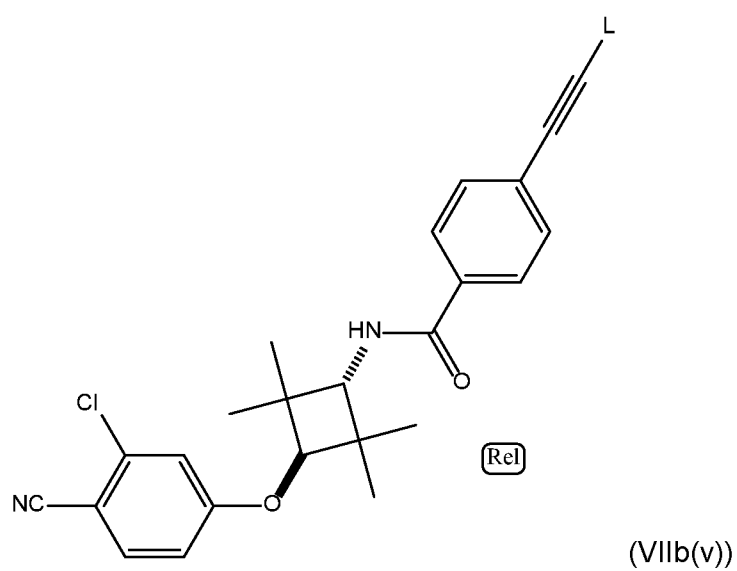
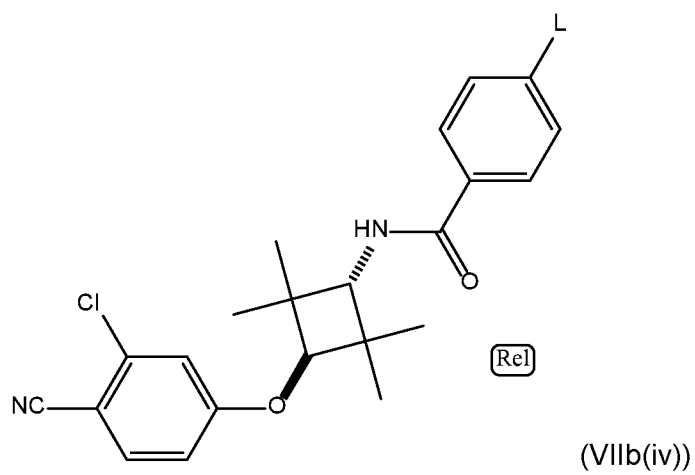
wherein X^V , Y^3 , R^{Qa} , R^{Qb} , R^{Qc} , R^{Qd} , R^{V1a} , Z^1 , Z^2 , Z^3 , Z^4 and L are as defined for formula VIIb.

58. The bifunctional molecule of claim 57, wherein TBL is of Formula VIIb(iii):



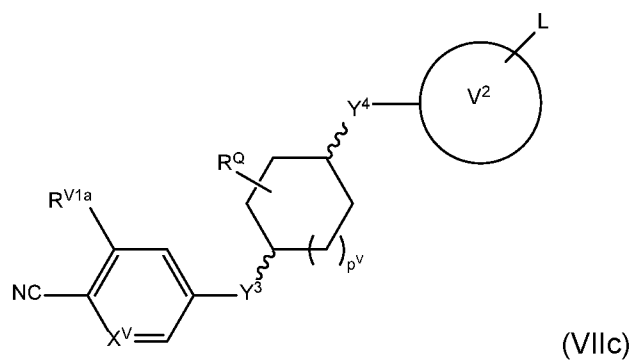
wherein X^V , Y^3 , R^{Qa} , R^{Qb} , R^{Qc} , R^{Qd} , R^{V1a} , Z^1 , Z^2 , Z^3 , Z^4 and L are as defined for formula VIIb.

59. The bifunctional molecule of claim 58, wherein TBL is of Formula VIIb(iv) or VIIb(v):



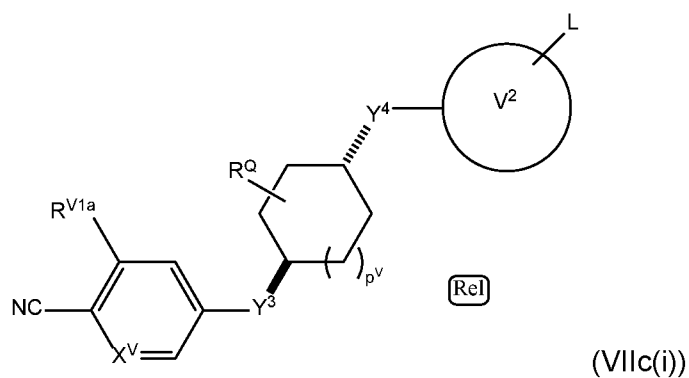
wherein L is as defined for formula VIIb.

60. The bifunctional molecule of any one of claims 45 to 59, wherein TBL is of Formula VIIc:



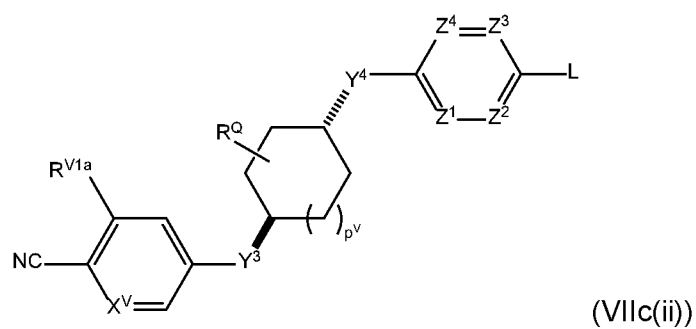
wherein X^V , V^2 , Y^3 , Y^4 , R^Q , R^{V1a} and L are as defined for formula VIIb; and p^V is 0, 1 or 2.

61. The bifunctional molecule of claim 60, wherein TBL is of Formula VIIc(i):



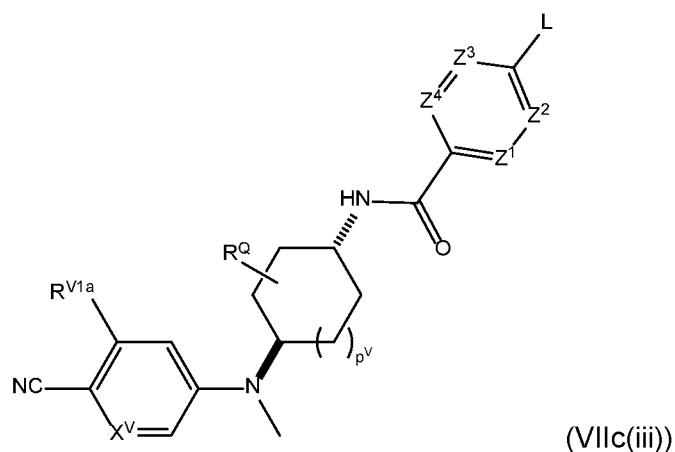
wherein X^V , V^2 , Y^3 , Y^4 , R^Q , R^{V1a} , p and L are as defined for formula VIIc.

62. The bifunctional molecule of claim 61, wherein TBL is of Formula VIIc(ii):



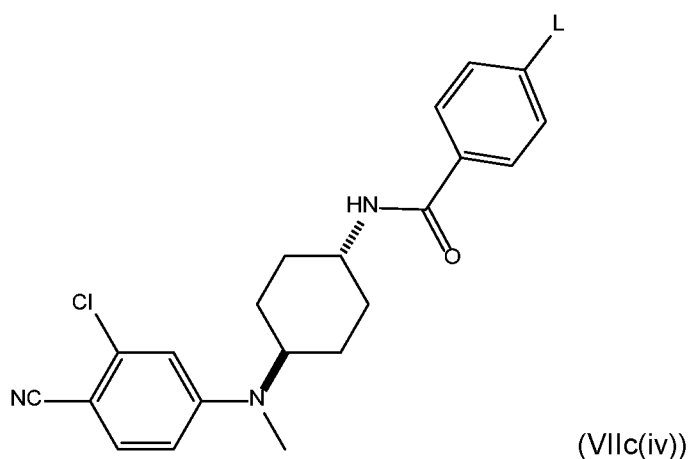
wherein X^V , Y^3 , Y^4 , R^Q , R^{V1a} , Z^1 , Z^2 , Z^3 , Z^4 , p^V and L are as defined for formula VIIc.

63. The bifunctional molecule of claim 62, wherein TBL is of Formula VIIc(iii):



wherein X^V , R^Q , R^{V1a} , Z^1 , Z^2 , Z^3 , Z^4 , p^V and L are as defined for formula VIIc.

64. The bifunctional molecule of claim 63, wherein TBL is of Formula VIIc(iv):



wherein L is as defined for formula VIIc.

65. The bifunctional molecule according to any one of claims 1 to 64, wherein the linker comprises 1 to 25 or 1 to 18 atoms in a single linear chain.

66. The bifunctional molecule according to any one of claims 1 to 65, wherein linker comprises 1 to 10 or 1 to 8 rotatable bonds.

67. The bifunctional molecule according to any one of claims 1 to 66, wherein the linker (L) is a covalent bond or the structure of the linker (L) is:



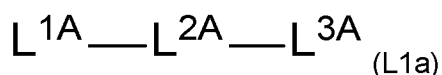
wherein each L_x represents a subunit of L that is independently selected from $CR^{L1}R^{L2}$, O , $C=O$, S , SO , SO_2 , NR^{L3} , $SONR^{L4}$, $SONR^{L5}C=O$, $CONR^{L6}$, $NR^{L7}CO$, $C(R^{L8})=C(R^{L9})$, $C\equiv C$, aryl,

substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl and substituted heterocycloalkyl groups;

wherein 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, halo, C_1 to C_6 alkyl, C_1 to C_6 haloalkyl, -OH, -O(C_1 to C_6 alkyl), -NH₂, -NH(C_1 to C_6 alkyl), -NO₂, -CN, -CONH₂, -CONH(C_1 to C_6 alkyl), -CON(C_1 to C_6 alkyl)₂, -SO₂(C_1 to C_6 alkyl), -CO₂(C_1 to C_6 alkyl), and -CO(C_1 to C_6 alkyl); and

q is an integer between 1 and 30.

68. The bifunctional molecule according to any one claims 1 to 67 wherein the linker (L) may be represented as shown in formula (L1a):



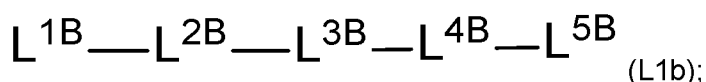
wherein L^{1A} is absent or is selected from C_1 - C_6 alkylene, C_1 - C_6 alkoxy) and C_1 - C_6 alkylamino;

L^{2A} is -NR^{L2A}C=O- or -C=ONR^{L2A}-; and

L^{3A} is selected from C_1 - C_3 alkylene, C_1 - C_6 alkoxy and C_1 - C_6 alkylamino;

wherein R^{L2A} is H or C_1 - C_6 alkyl;

or, the structure of the linker (L) may be represented as shown in formula (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}-;

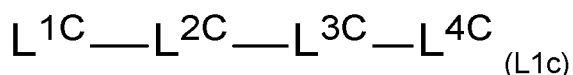
L^{3B} is selected from C_1 - C_{15} alkylene, -[(CH₂)₂O]₁₋₆(CH₂)₂-;

L^{4B} is -NR^{L2A}C=O- or -C=ONR^{L2A}- wherein R^{L2A} is H or C_1 - C_6 alkyl;

L^{5B} is selected from C_1 - C_3 alkylene, C_1 - C_6 alkoxy and C_1 - C_6 alkylamino;

wherein R^{L2A} is H or C_1 - C_6 alkyl;

or, the structure of the linker (L) may be represented as shown in formula (L1c):



wherein L^{1C} is an optionally substituted 4- to 7-membered monocyclic N-heterocycloalkyl, an optionally substituted 7- to 12-membered bicyclic N-heterocycloalkyl, or an optionally substituted 8- to 18-membered tricyclic N-heterocycloalkyl, each optionally containing one or two additional ring heteroatoms selected from N, O and S;

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

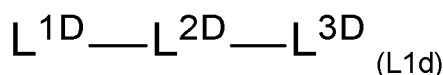
L^{4C} is selected from C_1 - C_3 alkylene, C_1 - C_6 alkoxy and C_1 - C_6 alkylamino;

wherein:

R^{L2A} is H or C_1 - C_6 alkyl; and

R^{L2B} is NR^{L2A} , or an N-linked optionally substituted 4- to 7-membered monocyclic N-heterocycloalkyl, an optionally substituted 7- to 12-membered bicyclic N-heterocycloalkyl, or an optionally substituted 8- to 18-membered tricyclic N-heterocycloalkyl, each optionally containing one or two additional ring heteroatoms selected from N, O and S;

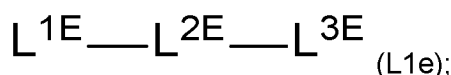
or, the structure of the linker (L) may be represented as shown in formula (L1d):



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 an optionally substituted 4- to 7-membered monocyclic N-heterocycloalkyl, an optionally substituted 7- to 12-membered bicyclic N-heterocycloalkyl, or an optionally substituted 8- to 18-membered tricyclic N-heterocycloalkyl, each optionally containing one or two additional ring heteroatoms selected from N, O and S; wherein R^{L2A} is H or C_1 - C_6 alkyl; and

L^{3D} is absent or is selected from C_1 - C_3 alkylene, $-O-$, $-N(C_1$ - C_3 alkyl)-, and CO;

or, the structure of the linker (L) may be represented as shown in formula (L1e):

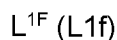


wherein L^{1E} is C_1 - C_3 alkylene or CO;

L^{2E} is an optionally substituted 4- to 7-membered monocyclic N-heterocycloalkyl, an optionally substituted 7- to 12-membered bicyclic N-heterocycloalkyl, each optionally containing one or two additional ring heteroatoms selected from N, O and S; and

L^{3E} is selected from C_1 - C_3 alkylene;

or, the linker (L) may be represented as shown in formula (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.

69. The bifunctional molecule according to any one of claims 1 to 68, wherein the bifunctional molecule has a structure as shown in Table 1.

70. A pharmaceutical composition comprising the bifunctional molecule according to any one of claims 1 to 69, together with a pharmaceutically acceptable carrier, optionally wherein the

bifunctional molecule is present in the composition as a pharmaceutically acceptable salt, solvate or derivative.

71. A bifunctional molecule according to any one of claims 1 to 69, or the pharmaceutical composition of claim 70, for use in medicine.

72. A bifunctional molecule according to any one of claims 1 to 69, or the pharmaceutical composition of claim 70, for use in 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 of the estrogen receptor or androgen receptor.

73. The bifunctional molecule or pharmaceutical composition for use of claim 71 or 72, for use in the treatment and/or prevention of cancer.

74. A method of treating and/or preventing any disease or condition which is associated with and/or is caused by an abnormal level of protein activity of the estrogen receptor or androgen receptor, the method comprising administering a therapeutically effective amount of a bifunctional molecule as defined in any one of claims 1 to 69, or the pharmaceutical composition of claim 70 to a subject in need thereof.

75. The method of claim 74, wherein the disease or condition is cancer.

76. 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 bifunctional molecule as defined in any one of claims 1 to 69 or the pharmaceutical composition of claim 70, wherein the target protein is selected from an: (i) estrogen receptor; and (ii) androgen receptor.

77. 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 bifunctional molecule as defined in any one of claims 1 to 69 or the pharmaceutical composition of claim 70, wherein the target protein is selected from an: (i) estrogen receptor; and (ii) androgen receptor.

78. Use of a moiety Z as defined in any one of claims 1 to 69 in a method of targeted protein degradation of a target protein selected from an: (i) estrogen receptor; and (ii) androgen receptor.

79. Use of a moiety Z as defined in any one of claims 1 to 69 in the manufacture of a bifunctional molecule suitable for targeted protein degradation of a target protein selected from an: (i) estrogen receptor; and (ii) androgen receptor.

80. A method of making a bifunctional molecule as defined in any one of claims 1 to 69.

81. A method of screening the bifunctional molecules according to any one of claims 1 to 69, comprising:

a. providing a bifunctional molecule comprising:

(i) a first ligand comprising a structure according to Z as defined in any one of claims 1 to 30;

(ii) a second ligand that binds to a target protein selected from an: (i) estrogen receptor; and (ii) androgen receptor; and

(iii) a linker that covalently attaches the first and second ligands;

b. contacting a cell with the bifunctional molecule;

c. detecting degradation of the target protein in the cell;

d. detecting degradation of the target protein in the cell in the absence of the bifunctional molecule; and

e. comparing the level of degradation of the target protein in the cell contacted with the bifunctional molecule to the level of degradation of the target protein in the absence of the bifunctional molecule;

wherein an increased level of degradation of the target protein in the cell contacted with the bifunctional molecule indicates that the bifunctional molecule has facilitated and/or promoted the degradation of the target protein,

optionally wherein detecting degradation of the target protein comprises detecting changes in the levels of the target protein in the cell.

82. The method of claim 81, wherein the second ligand is as defined in any one of claims 31 to 66.

83. The method of claim 80 or claim 81, wherein the linker is as defined in any one of claim 67 or claim 68.

84. A compound library comprising a plurality of bifunctional molecules according to any one of claims 1 to 69.

INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER

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ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61P C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2018/102725 A1 (ARVINAS INC [US]) 7 June 2018 (2018-06-07) claims 1, 24, 27, 30 page 495; compound 441 -----	1-84
X	WO 2018/071606 A1 (ARVINAS INC [US]) 19 April 2018 (2018-04-19) figure 3; compound 172 claims 1, 27, 31, 32 ----- ----- -/--	1-84



Further documents are listed in the continuation of Box C.



See patent family annex.

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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2023/051594

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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