

TETRACYCLIC COMPOUNDS FOR USE IN ANTIBODY-DRUG CONJUGATES FOR THE TREATMENT OF CANCER

Field of the Invention

The present invention relates to fused tetracyclic heteroaromatic compounds and
5 antibody-drug conjugates (ADCs) comprising the compounds. The present invention
also relates to processes for the preparation of the compounds and ADCs, and to
pharmaceutical compositions containing them and their use in therapy, particularly for
use in treating cancers.

10 Background of the Invention

Small molecules that interact with genomic DNA have a long history of use in cancer
chemotherapy (e.g. cisplatin family and anthracyclines).¹ Such molecules target DNA
indiscriminately and display broad toxicity in patients owing to their lack of molecular
and biological specificity. Despite adverse toxicity, these drugs are still widely
15 deployed in the clinic.²

G-quadruplexes (G4s) are four-stranded, non-canonical nucleic acid secondary
structures which can form in guanine-rich DNA and RNA sequences. In the human
genome, there are over 700,000 G4 forming sequences.³⁻⁵ These G4 motifs are
20 particularly enriched at repetitive elements of the genome, e.g. telomeres, and at
gene regulatory regions of protein-coding genes including many oncogenes.

Folded DNA and RNA G4s have been visualized in human cells and tissues,⁶⁻⁸ mapped
in human chromatin and the human transcriptome,⁹⁻¹² and overall been found to be
25 more abundant in cancer-like cells and tissues^{7,9}.

G4s have been implicated in several key genome functions such as transcription,
replication, translation, telomere maintenance and epigenetic regulation.¹³ Many G4s
are likely transient and readily resolved by helicases¹⁴. Unresolved DNA G4s can
30 impede DNA polymerases causing DNA damage and requiring homologous
recombination (HR) repair^{15,16}.

Some compounds, named G4 ligands (G4L), have been shown to interact with and
stabilise G4s in vitro and in human chromatin¹⁷⁻¹⁹. Given the involvement of G4s in
35 various pivotal cellular functions and the connection to cancer biology, G4Ls have been
explored as therapeutic agents and shown antiproliferative and chemosensitizing
effects against cancer cell lines and tumour models^{18,20-22}. In cancer cells, DNA G4
stabilization may interfere with replication and transcription, affect epigenetic

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modifications, promote DNA damage, affect the biogenesis and interactions of coding and non-coding RNA or impair telomerase and thereby inhibit tumour growth.^{18,23}

Different G4L chemotypes have been described to mediate genome-wide perturbations, target a subset of G4 topologies and particular G4s in certain oncogenes.¹⁸

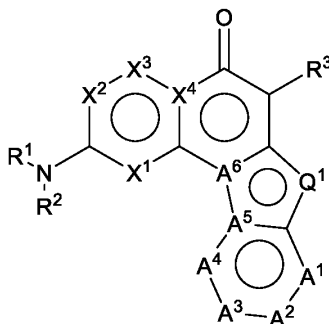
Cancer cells often display higher sensitivity to G4L treatment than non-cancerous cells in accordance with the higher occurrence of folded G4s in the chromatin of cancer cell lines and tissues^{9,22}. In addition, some G4Ls are synthetic lethal with loss of various cellular functions²⁴, in particular DNA damage repair²⁵⁻²⁸, suggesting a biomarker-driven therapeutic approach as well as combination treatment with other agents. Some G4Ls have shown activity in HR-deficient cells and tumour models that were resistant to PARP inhibitor treatment as well as gemcitabine-resistant pancreatic cancer cells, indicating that some G4Ls may be used to target difficult to treat certain tumours with acquired resistances.^{25,29,30}

The G4L CX-5461 entered clinical trials for solid tumours with HR-deficiency mutations (NCT02719977)²⁶. An observed reversion of BRCA2 and PALB2 confirmed the mechanism of action. The molecule was overall well tolerated, but displayed dose-limiting phototoxicity.²⁶ Similarly, photosensitivity had been observed in a previous clinical trial of CX-5461 in patients with hematologic malignancies.³¹

There is a need to provide compounds with improved pharmacological and/or physiological and/or physicochemical properties and/or those that provide a useful alternative to CX-5461.

Summary of the Invention

A first aspect of the invention provides a compound of Formula (I):



Formula (I)

wherein:

- R¹ and R² are each independently selected from hydrogen or a C₁-C₁₂ saturated or unsaturated hydrocarbyl group, wherein the hydrocarbyl group may be straight-chained or branched, or be or include one or more cyclic groups, wherein the hydrocarbyl group may optionally be substituted with one or more halo and/or -NO₂ groups, wherein the hydrocarbyl group may optionally include one or more heteroatoms each independently selected from N, O and S in its carbon skeleton, and wherein any -S- moiety in the hydrocarbyl group may optionally be substituted with one or two groups each independently selected from oxo (=O) and =NH to form a -SO-, -SO₂-, -S(=NH)- or -SO(=NH)- moiety;
- or R¹ and R² together with the nitrogen atom to which they are attached form a 3- to 12-membered cyclic group, wherein the cyclic group may optionally be substituted with one or more substituents each independently selected from a halo, oxo (=O), -OH, -SH, -NH₂, -SO₂H, -SO₃H, -SO₂NH₂, -NO₂, or a C₁-C₆ saturated or unsaturated hydrocarbyl group, wherein the hydrocarbyl group may be straight-chained or branched, or be or include a cyclic group, wherein the hydrocarbyl group may optionally be substituted with one or more halo and/or -NO₂ groups, wherein the hydrocarbyl group may optionally include one or more heteroatoms each independently selected from N, O and S in its carbon skeleton, and wherein any -S- moiety in the hydrocarbyl group may optionally be substituted with one or two groups each independently selected from oxo (=O) and =NH to form a -SO-, -SO₂-, -S(=NH)- or -SO(=NH)- moiety;
- R³ is a C₁-C₁₂ monovalent group, wherein the atom of R³ that is directly attached to the remainder of the compound of Formula (I) is a carbon atom, and wherein the C₁-C₁₂ monovalent group comprises:
- (i) a primary or a secondary amine, wherein the nitrogen atom of the primary or secondary amine is not directly attached to a sp² hybridised carbon atom; and/or
 - (ii) a -OH group, wherein the oxygen atom of the -OH group is not directly attached to a sp² hybridised carbon atom; and/or
 - (iii) a -SH group, wherein the sulphur atom of the -SH group is not directly attached to a sp² hybridised carbon atom;
- X¹ is N, C-H, C-Hal or C-R^{X1};
- X² is N;
- X³ is N, C-H, C-Hal or C-R^{X3}; and
- X⁴ is N or C;
- provided that no more than three of X¹, X², X³ and X⁴ are N;
- R^{X1} and R^{X3} are each independently selected from -OH, -SH, -NH₂, -SO₂H, -SO₃H, -SO₂NH₂, -NO₂, or a C₁-C₄ saturated or unsaturated hydrocarbyl group,

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wherein the hydrocarbyl group may be straight-chained or branched, or be or include a cyclic group, wherein the hydrocarbyl group may optionally be substituted with one or more halo and/or -NO₂ groups, wherein the hydrocarbyl group may optionally include one or more heteroatoms each independently selected from N, O and S in its carbon skeleton, and wherein any -S- moiety in the hydrocarbyl group may optionally be substituted with one or two groups each independently selected from oxo (=O) and =NH to form a -SO-, -SO₂-, -S(=NH)- or -SO(=NH)- moiety;

Q¹ is O, S, N, N-H, N-R^{Q1}, C-H, C-Hal, or C-R^{Q2};

R^{Q1} is selected from a C₁-C₄ saturated or unsaturated hydrocarbyl group,

wherein the hydrocarbyl group may be straight-chained or branched, or be or include a cyclic group, wherein the hydrocarbyl group may optionally be substituted with one or more halo and/or -NO₂ groups, wherein the hydrocarbyl group may optionally include one or more heteroatoms each independently selected from N, O and S in its carbon skeleton, and wherein any -S- moiety in the hydrocarbyl group may optionally be substituted with one or two groups each independently selected from oxo (=O) and =NH to form a -SO-, -SO₂-, -S(=NH)- or -SO(=NH)- moiety, provided that the atom of R^{Q1} that is directly attached to the nitrogen atom of N-R^{Q1} is a carbon atom;

R^{Q2} is selected from -OH, -SH, -NH₂, -SO₂H, -SO₃H, -SO₂NH₂, -NO₂, or a C₁-C₄ saturated or unsaturated hydrocarbyl group, wherein the hydrocarbyl group may be straight-chained or branched, or be or include a cyclic group, wherein the hydrocarbyl group may optionally be substituted with one or more halo and/or -NO₂ groups, wherein the hydrocarbyl group may optionally include one or more heteroatoms each independently selected from N, O and S in its carbon skeleton, and wherein any -S- moiety in the hydrocarbyl group may optionally be substituted with one or two groups each independently selected from oxo (=O) and =NH to form a -SO-, -SO₂-, -S(=NH)- or -SO(=NH)- moiety;

A¹ is N, C-H, C-Hal or C-R^{A1};

A² is N, C-H, C-Hal or C-R^{A2};

A³ is N, C-H, C-Hal or C-R^{A3};

A⁴ is N, C-H, C-Hal or C-R^{A4}; and

A⁵ is N or C;

provided that no more than three of A¹, A², A³, A⁴ and A⁵ are N;

R^{A1}, R^{A2}, R^{A3} and R^{A4} are each independently selected from -OH, -SH, -NH₂, -SO₂H, -SO₃H, -SO₂NH₂, -NO₂, or a C₁-C₄ saturated or unsaturated hydrocarbyl group, wherein the hydrocarbyl group may be straight-chained or branched, or be or include a cyclic group, wherein the hydrocarbyl group may optionally be substituted with one or more halo and/or -NO₂ groups, wherein the hydrocarbyl group may optionally include one or more heteroatoms each independently selected from N, O and S in its

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carbon skeleton, and wherein any -S- moiety in the hydrocarbyl group may optionally be substituted with one or two groups each independently selected from oxo (=O) and =NH to form a -SO-, -SO₂-, -S(=NH)- or -SO(=NH)- moiety;

A⁶ is N or C; and

5 each Hal is independently selected from a fluoro, chloro, bromo or iodo group.

As will be understood, and as indicated by the circles, each of the four rings in the fused tetracyclic ring system of Formula (I) is aromatic. In other words, X¹, X², X³, X⁴, A¹, A², A³, A⁴, A⁵, A⁶ and Q¹ are selected such that each ring of the fused tetracyclic
10 ring system of Formula (I) is aromatic.

In the context of the present specification, a "hydrocarbyl" substituent group or a hydrocarbyl moiety in a substituent group only includes carbon and hydrogen atoms but, unless stated otherwise, does not include any heteroatoms, such as N, O or S, in
15 its carbon skeleton. A hydrocarbyl group/moiety may be saturated or unsaturated (including aromatic), and may be straight-chained or branched, or be or include cyclic groups wherein, unless stated otherwise, the cyclic group does not include any heteroatoms, such as N, O or S, in its carbon skeleton. Examples of hydrocarbyl groups include alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl and aryl groups/moieties
20 and combinations of all of these groups/moieties. Typically a hydrocarbyl group is a C₁-C₂₀ hydrocarbyl group. More typically a hydrocarbyl group is a C₁-C₁₅ hydrocarbyl group. More typically a hydrocarbyl group is a C₁-C₁₀ hydrocarbyl group. A "hydrocarbylene" group is similarly defined as a divalent hydrocarbyl group.

25 An "alkyl" substituent group or an alkyl moiety in a substituent group may be linear (i.e. straight-chained) or branched. Examples of alkyl groups/moieties include methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, *t*-butyl and *n*-pentyl groups/moieties. Unless stated otherwise, the term "alkyl" does not include "cycloalkyl". Typically an alkyl group is a C₁-C₁₂ alkyl group. More typically an alkyl group is a C₁-C₆ alkyl group. An
30 "alkylene" group is similarly defined as a divalent alkyl group.

An "alkenyl" substituent group or an alkenyl moiety in a substituent group refers to an unsaturated alkyl group or moiety having one or more carbon-carbon double bonds. Examples of alkenyl groups/moieties include ethenyl, propenyl, 1-butenyl, 2-butenyl,
35 1-pentenyl, 1-hexenyl, 1,3-butadienyl, 1,3-pentadienyl, 1,4-pentadienyl and 1,4-hexadienyl groups/moieties. Unless stated otherwise, the term "alkenyl" does not include "cycloalkenyl". Typically an alkenyl group is a C₂-C₁₂ alkenyl group. More

typically an alkenyl group is a C₂-C₆ alkenyl group. An "alkenylene" group is similarly defined as a divalent alkenyl group.

5 An "alkynyl" substituent group or an alkynyl moiety in a substituent group refers to an unsaturated alkyl group or moiety having one or more carbon-carbon triple bonds. Examples of alkynyl groups/moieties include ethynyl, propargyl, but-1-ynyl and but-2-ynyl groups/moieties. Typically an alkynyl group is a C₂-C₁₂ alkynyl group. More typically an alkynyl group is a C₂-C₆ alkynyl group. An "alkynylene" group is similarly defined as a divalent alkynyl group.

10 A "cyclic" substituent group or a cyclic moiety in a substituent group refers to any hydrocarbyl ring, wherein the hydrocarbyl ring may be saturated or unsaturated (including aromatic) and may include one or more heteroatoms, e.g. N, O or S, in its carbon skeleton. Examples of cyclic groups include cycloalkyl, cycloalkenyl, 15 heterocyclic, aryl and heteroaryl groups as discussed below. A cyclic group may be monocyclic, bicyclic (e.g. bridged, fused or spiro), or polycyclic. Typically, a cyclic group is a 3- to 12-membered cyclic group, which means it contains from 3 to 12 ring atoms. More typically, a cyclic group is a 3- to 7-membered monocyclic group, which means it contains from 3 to 7 ring atoms.

20 For the avoidance of doubt, where it is stated that a bicyclic or polycyclic group is "saturated" it is to be understood that all of the ring systems within the bicyclic or polycyclic group (excluding any ring systems which are part of or formed by optional substituents) are saturated.

25 A "heterocyclic" substituent group or a heterocyclic moiety in a substituent group refers to a cyclic group or moiety including one or more carbon atoms and one or more (such as one, two, three or four) heteroatoms, e.g. N, O or S, in the ring structure. Examples of heterocyclic groups include heteroaryl groups as discussed 30 below and non-aromatic heterocyclic groups such as azetiny, azetidiny, oxetany, thietany, pyrrolidiny, tetrahydrofurany, tetrahydrothiopheny, pyrazolidiny, imidazolidiny, dioxolany, oxathiolany, piperidiny, tetrahydropyrany, thianyl, piperaziny, dioxany, morpholiny and thiomorpholiny groups.

35 A "cycloalkyl" substituent group or a cycloalkyl moiety in a substituent group refers to a saturated hydrocarbyl ring containing, for example, from 3 to 7 carbon atoms, examples of which include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. Unless

stated otherwise, a cycloalkyl substituent group or moiety may include monocyclic, bicyclic or polycyclic hydrocarbyl rings.

A "cycloalkenyl" substituent group or a cycloalkenyl moiety in a substituent group refers to a non-aromatic unsaturated hydrocarbyl ring having one or more carbon-carbon double bonds and containing, for example, from 3 to 7 carbon atoms, examples of which include cyclopent-1-en-1-yl, cyclohex-1-en-1-yl and cyclohex-1,3-dien-1-yl. Unless stated otherwise, a cycloalkenyl substituent group or moiety may include monocyclic, bicyclic or polycyclic hydrocarbyl rings.

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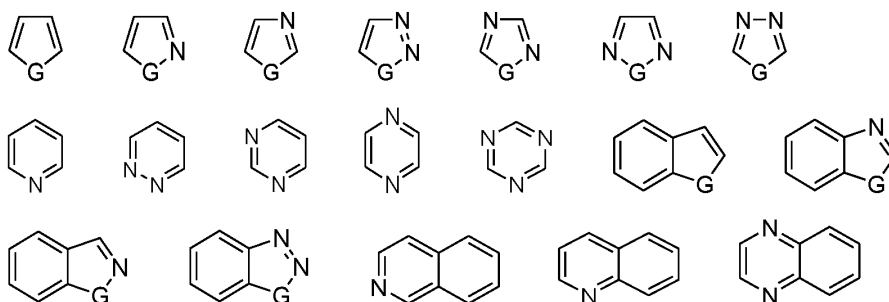
An "aryl" substituent group or an aryl moiety in a substituent group refers to an aromatic hydrocarbyl ring. The term "aryl" refers to monocyclic aromatic hydrocarbons and polycyclic fused ring aromatic hydrocarbons wherein all of the fused ring systems (excluding any ring systems which are part of or formed by optional substituents) are aromatic. Examples of aryl groups/moieties include phenyl, naphthyl, anthracenyl and phenanthrenyl. Unless stated otherwise, the term "aryl" does not include "heteroaryl".

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A "heteroaryl" substituent group or a heteroaryl moiety in a substituent group refers to an aromatic heterocyclic group or moiety. The term "heteroaryl" refers to monocyclic aromatic heterocycles and polycyclic fused ring aromatic heterocycles wherein all of the fused ring systems (excluding any ring systems which are part of or formed by optional substituents) are aromatic. Examples of heteroaryl groups/moieties include the following:

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wherein G = O, S or NH. Particular examples of 5- or 6-membered heteroaryl groups include furanyl, thiophenyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, furazanyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl groups.

30

Unless stated otherwise, where a cyclic group or moiety is stated to be aromatic, such as an aryl or a heteroaryl group, it is to be understood that each ring system within the group or moiety (excluding any ring systems which are part of or formed by

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optional substituents) is aromatic. Similarly, where a cyclic group or moiety is stated to be non-aromatic, such as a cycloalkyl, cycloalkenyl or non-aromatic heterocyclic group, it is to be understood that each ring system within the group or moiety (excluding any ring systems which are part of or formed by optional substituents) is non-aromatic.

For the purposes of the present specification, where a combination of moieties is referred to as one group, for example, arylalkyl, arylalkenyl, arylalkynyl, alkylaryl, alkenylaryl or alkynylaryl, the last mentioned moiety contains the atom by which the group is attached to the rest of the molecule. An example of an arylalkyl group is benzyl.

As will be appreciated, in an optionally substituted moiety:

- each hydrogen atom may optionally be replaced by any specified monovalent substituent;
- any two hydrogen atoms attached to the same carbon or nitrogen atom may optionally be replaced by any specified n-bonded substituent;
- any sulphur atom may optionally be substituted with one or two of any specified n-bonded substituents; and
- any two hydrogen atoms attached to the same or different atoms, within the same optionally substituted group or moiety, may optionally be replaced by any specified divalent bridging substituent.

Typically a substituted group comprises 1, 2, 3 or 4 substituents, more typically 1, 2 or 3 substituents, more typically 1 or 2 substituents, and more typically 1 substituent.

Unless stated otherwise, any divalent bridging substituent (e.g. -O-, -S-, -NH-, -CH₂-, -CH₂-CH₂-, etc.) of an optionally substituted group or moiety (e.g. R¹) must only be attached to the specified group or moiety and may not be attached to a second group or moiety (e.g. R²), even if the second group or moiety can itself be optionally substituted.

The term "halo" includes fluoro, chloro, bromo and iodo.

Unless stated otherwise, where a group is prefixed by the term "halo", such as a haloalkyl or halomethyl group, it is to be understood that the group in question is substituted with one or more halo groups independently selected from fluoro, chloro, bromo and iodo. Typically, the maximum number of halo substituents is limited only

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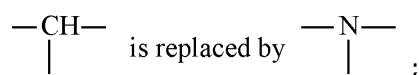
by the number of hydrogen atoms available for substitution on the corresponding group without the halo prefix. For example, a halomethyl group may contain one, two or three halo substituents. A haloethyl or halophenyl group may contain one, two, three, four or five halo substituents. Similarly, unless stated otherwise, where a group is prefixed by a specific halo group, it is to be understood that the group in question is substituted with one or more of the specific halo groups. For example, the term "fluoromethyl" refers to a methyl group substituted with one, two or three fluoro groups.

Similarly, unless stated otherwise, where a group is said to be "halo-substituted", it is to be understood that the group in question is substituted with one or more halo groups independently selected from fluoro, chloro, bromo and iodo. Typically, the maximum number of halo substituents is limited only by the number of hydrogen atoms available for substitution on the group said to be halo-substituted. For example, a halo-substituted methyl group may contain one, two or three halo substituents. A halo-substituted ethyl or halo-substituted phenyl group may contain one, two, three, four or five halo substituents.

Unless stated otherwise, any reference to an element is to be considered a reference to all isotopes of that element. Thus, for example, unless stated otherwise any reference to hydrogen is considered to encompass all isotopes of hydrogen including deuterium and tritium.

Unless stated otherwise, any reference to a compound or group is to be considered a reference to all tautomers of that compound or group.

Where reference is made to a hydrocarbyl or other group including one or more heteroatoms N, O or S in its carbon skeleton, or where reference is made to a carbon atom of a hydrocarbyl or other group being replaced by an N, O or S atom, what is intended is that:



–CH₂– is replaced by –NH–, –O– or –S–;

–CH₃ is replaced by –NH₂, –OH or –SH;

–CH= is replaced by –N=;

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CH₂= is replaced by NH=, O= or S=; or

CH≡ is replaced by N≡;

provided that the resultant group comprises at least one carbon atom. For example, methoxy, dimethylamino and aminoethyl groups are considered to be hydrocarbyl groups including one or more heteroatoms N, O or S in their carbon skeleton.

Typically, the compounds of the invention contain no more than one quaternary ammonium group. More typically, the compounds of the invention contain no quaternary ammonium groups.

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In the context of the present specification, unless otherwise stated, a C_x-C_y group is defined as a group containing from x to y carbon atoms. For example, a C₁-C₄ alkyl group is defined as an alkyl group containing from 1 to 4 carbon atoms. For the purposes of allocating x and y in a C_x-C_y group, optional substituents are not taken into account when calculating the total number of carbon atoms in the parent group substituted with the optional substituents. For the avoidance of doubt, replacement heteroatoms, e.g. N, O or S, are not to be counted as carbon atoms when calculating the number of carbon atoms in a C_x-C_y group. For example, a morpholinyl group is to be considered a C₄ heterocyclic group, not a C₆ heterocyclic group.

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For the purposes of the present specification, where it is stated that a first atom or group is "directly attached" to a second atom or group it is to be understood that the first atom or group is covalently bonded to the second atom or group with no intervening atom(s) or group(s) being present. So, for example, for the group -(C=O)N(CH₃)₂, the carbon atom of each methyl group is directly attached to the nitrogen atom and the carbon atom of the carbonyl group is directly attached to the nitrogen atom, but the carbon atom of the carbonyl group is not directly attached to the carbon atom of either methyl group.

30 As stated in accordance with the first aspect of the invention, R¹ and R² are each independently selected from hydrogen or a C₁-C₁₂ saturated or unsaturated hydrocarbyl group, wherein the hydrocarbyl group may be straight-chained or branched, or be or include one or more cyclic groups, wherein the hydrocarbyl group may optionally be substituted with one or more halo and/or -NO₂ groups, wherein the hydrocarbyl group may optionally include one or more heteroatoms each independently selected from N, O and S in its carbon skeleton, and wherein any -S- moiety in the hydrocarbyl group may optionally be substituted with one or two groups each independently selected from oxo (=O) and =NH to form a -SO-, -SO₂-, -S(=NH)-

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or -SO(=NH)- moiety, or R¹ and R² together with the nitrogen atom to which they are attached form a 3- to 12-membered cyclic group, wherein the cyclic group may optionally be substituted with one or more substituents each independently selected from a halo, oxo (=O), -OH, -SH, -NH₂, -SO₂H, -SO₃H, -SO₂NH₂, -NO₂, or a C₁-C₆ (e.g. C₁-C₄) saturated or unsaturated hydrocarbyl group, wherein the hydrocarbyl group may be straight-chained or branched, or be or include a cyclic group, wherein the hydrocarbyl group may optionally be substituted with one or more halo and/or -NO₂ groups, wherein the hydrocarbyl group may optionally include one or more heteroatoms each independently selected from N, O and S in its carbon skeleton, and wherein any -S- moiety in the hydrocarbyl group may optionally be substituted with one or two groups each independently selected from oxo (=O) and =NH to form a -SO-, -SO₂-, -S(=NH)- or -SO(=NH)- moiety.

In one embodiment of the first aspect of the invention, R¹ and R² are each independently selected hydrogen or a C₁-C₁₂ saturated or unsaturated hydrocarbyl group, wherein the hydrocarbyl group may be straight-chained or branched, or be or include one or more cyclic groups, wherein the hydrocarbyl group may optionally be substituted with one or more halo and/or -NO₂ groups, wherein the hydrocarbyl group may optionally include one or more heteroatoms each independently selected from N, O and S in its carbon skeleton, and wherein any -S- moiety in the hydrocarbyl group may optionally be substituted with one or two groups each independently selected from oxo (=O) and =NH to form a -SO-, -SO₂-, -S(=NH)- or -SO(=NH)- moiety.

Typically in such an embodiment, R¹ and R² are each independently selected from hydrogen or a C₁-C₈ saturated or unsaturated hydrocarbyl group, wherein the hydrocarbyl group may be straight-chained or branched, or be or include a single cyclic group, wherein the hydrocarbyl group may optionally be substituted with one or more halo and/or -NO₂ groups, and wherein the hydrocarbyl group may optionally include one, two, three or four heteroatoms each independently selected from N and O in its carbon skeleton. For example, R¹ may be a C₁-C₈ saturated or unsaturated hydrocarbyl group, wherein the hydrocarbyl group may be straight-chained or branched, or be or include a single cyclic group, wherein the hydrocarbyl group may optionally be substituted with one or more halo and/or -NO₂ groups, and wherein the hydrocarbyl group may optionally include one, two, three or four heteroatoms each independently selected from N and O in its carbon skeleton, and R² may be selected from hydrogen or a C₁-C₄ alkyl or C₁-C₄ haloalkyl group.

In one aspect of such an embodiment, R^1 and R^2 are each independently selected from hydrogen or a C_1 - C_8 saturated or unsaturated hydrocarbyl group, wherein the hydrocarbyl group may be straight-chained or branched, or be or include a single cyclic group, wherein the hydrocarbyl group may optionally be substituted with one or more halo and/or $-NO_2$ groups, and wherein the hydrocarbyl group may optionally include one, two or three heteroatoms each independently selected from N and O in its carbon skeleton. For example, R^1 may be a C_1 - C_8 saturated or unsaturated hydrocarbyl group, wherein the hydrocarbyl group may be straight-chained or branched, or be or include a single cyclic group, wherein the hydrocarbyl group may optionally be substituted with one or more halo and/or $-NO_2$ groups, and wherein the hydrocarbyl group may optionally include one, two or three heteroatoms each independently selected from N and O in its carbon skeleton, and R^2 may be selected from hydrogen or a C_1 - C_4 alkyl or C_1 - C_4 haloalkyl group.

In a further embodiment, R^1 is a C_1 - C_8 saturated hydrocarbyl group, wherein the hydrocarbyl group may be straight-chained or branched, or be or include a single cyclic group, wherein the hydrocarbyl group may optionally be substituted with one or more fluoro groups and/or a single oxo ($=O$) group, wherein the hydrocarbyl group optionally includes one or two heteroatoms each independently selected from N and O in its carbon skeleton, and R^2 is selected from hydrogen or a C_1 - C_3 alkyl or C_1 - C_3 fluoroalkyl group.

In one embodiment, R^1 is selected from a methyl, ethyl, isopropyl or cyclopropyl group, any of which may optionally be fluoro substituted, and R^2 is selected from hydrogen or a methyl or fluoromethyl group. For example, $-NR^1R^2$ may have the formula $-NMe_2$.

In another embodiment, R^1 is a C_2 - C_8 saturated hydrocarbyl group, wherein the hydrocarbyl group may be straight-chained or branched, or be or include a single cyclic group, wherein the hydrocarbyl group may optionally be substituted with one or more fluoro groups, wherein the hydrocarbyl group includes one or two heteroatoms each independently selected from N and O in its carbon skeleton, and R^2 is selected from hydrogen or a C_1 - C_3 alkyl or C_1 - C_3 fluoroalkyl group. For example, R^1 may be selected from a $-(C(R^{101})_2)_2-X^{10}-R^{102}$ or $-(C(R^{101})_2)_2-X^{10}-(C(R^{101})_2)_2-X^{11}-R^{102}$ group, and R^2 may be selected from hydrogen or a methyl or fluoromethyl group, wherein:

X^{10} is selected from O or NR^{103} ;

X^{11} is selected from O or NR^{104} ;

each R^{101} is hydrogen;

R¹⁰² is selected from a methyl, ethyl, isopropyl or cyclopropyl group, any of which may optionally be fluoro substituted;

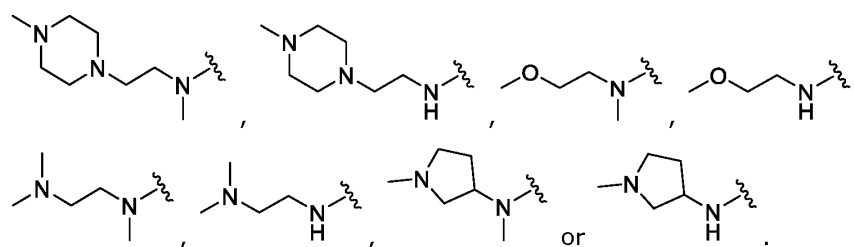
R¹⁰³ is selected from hydrogen or a methyl or fluoromethyl group; and

R¹⁰⁴ is selected from hydrogen or a methyl or fluoromethyl group; or

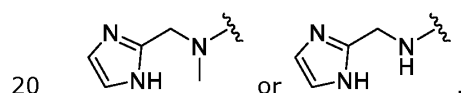
5 a single R¹⁰¹ and R¹⁰³, or a single R¹⁰¹ and R¹⁰⁴, or R¹⁰³ and R¹⁰⁴ together form a
-(CH₂)₂- group;

provided that any $-(C(R^{101})_2)_2-X^{10}-R^{102}$ or $-(C(R^{101})_2)_2-X^{10}-(C(R^{101})_2)_2-X^{11}-R^{102}$ group contains no more than 8 carbon atoms.

10 In one aspect of such an embodiment, -NR¹R² has a formula selected from:



15 In another embodiment, R¹ has the formula -L¹-R¹⁰, wherein L¹ is a C₁-C₂ alkylene or C₁-C₂ fluoroalkylene group, and R¹⁰ is a 5- or 6-membered heteroaryl group, such as an imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl or isothiazolyl group, and R² is selected from hydrogen or a C₁-C₃ alkyl or C₁-C₃ fluoroalkyl group. Typically in such an embodiment, R² is selected from hydrogen or a methyl or fluoromethyl group. In one aspect of such an embodiment, -NR¹R² has a formula selected from:



In one embodiment of the first aspect of the invention, R¹ and R² together with the nitrogen atom to which they are attached form a 3- to 12-membered cyclic group, wherein the cyclic group may optionally be substituted with one or more substituents each independently selected from a halo, oxo (=O), -OH, -SH, -NH₂, -SO₂H, -SO₃H, -SO₂NH₂, -NO₂, or a C₁-C₆ (e.g. C₁-C₄) saturated or unsaturated hydrocarbonyl group, wherein the hydrocarbonyl group may be straight-chained or branched, or be or include a cyclic group, wherein the hydrocarbonyl group may optionally be substituted with one or more halo and/or -NO₂ groups, wherein the hydrocarbonyl group may optionally include one or more heteroatoms each independently selected from N, O and S in its carbon skeleton, and wherein any -S- moiety in the hydrocarbonyl group may optionally be substituted with one or two groups each independently selected from oxo (=O) and =NH to form a -SO-, -SO₂-, -S(=NH)- or -SO(=NH)- moiety.

As will be understood, where R^1 and R^2 together with the nitrogen atom to which they are attached form a 3- to 12-membered cyclic group, the resultant cyclic group is a heterocyclic group.

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Typically in such an embodiment, R^1 and R^2 together with the nitrogen atom to which they are attached form a 4- to 7-membered monocyclic group or a 6- to 12-membered (e.g. 6- to 10-membered) bicyclic group, wherein the monocyclic or the bicyclic group may optionally be substituted with one or more substituents each independently selected from a halo, oxo ($=O$), $-OH$, $-NH_2$ or a C_1-C_6 saturated or unsaturated hydrocarbyl group, wherein the hydrocarbyl group may be straight-chained or branched, or be or include a cyclic group, wherein the hydrocarbyl group may optionally be substituted with one or more halo groups, and wherein the hydrocarbyl group may optionally include one or two heteroatoms each independently selected from N and O in its carbon skeleton. More typically in such an embodiment, R^1 and R^2 together with the nitrogen atom to which they are attached form a 4- to 7-membered monocyclic group or a 6- to 12-membered (e.g. 6- to 10-membered) bicyclic group, wherein the monocyclic or the bicyclic group may optionally be substituted with one or more substituents each independently selected from a halo, oxo ($=O$), $-OH$, $-NH_2$ or a C_1-C_4 saturated or unsaturated hydrocarbyl group, wherein the hydrocarbyl group may be straight-chained or branched, or be or include a cyclic group, wherein the hydrocarbyl group may optionally be substituted with one or more halo groups, and wherein the hydrocarbyl group may optionally include one or two heteroatoms each independently selected from N and O in its carbon skeleton.

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Where R^1 and R^2 together with the nitrogen atom to which they are attached form a 4- to 7-membered monocyclic group, typically the monocyclic group is a saturated monocyclic group.

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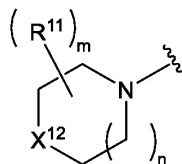
In one embodiment, R^1 and R^2 together with the nitrogen atom to which they are attached form a 6- or 7-membered saturated monocyclic group, wherein the saturated monocyclic group includes one further ring heteroatom selected from N and O in its carbon skeleton (such as a piperazinyl, morpholinyl, diazepanyl or oxazepanyl group), and wherein the saturated monocyclic group may optionally be substituted with one or more substituents each independently selected from a fluoro, oxo ($=O$), $-OH$, $-NH_2$, or a C_1-C_4 saturated hydrocarbyl group, wherein the saturated hydrocarbyl group may be straight-chained or branched, or be or include a cyclic group, wherein the saturated hydrocarbyl group may optionally be substituted with one or more fluoro groups

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- 15 -

and/or a single oxo (=O) group, and wherein the saturated hydrocarbyl group may optionally include a single heteroatom selected from N and O in its carbon skeleton.

For example, $-NR^1R^2$ may have the formula:



5

wherein:

n is 1 or 2;

m is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10;

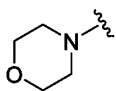
each R^{11} is independently selected from a fluoro, methyl or fluoromethyl group, provided that no more than four R^{11} are selected from a methyl or fluoromethyl group; X^{12} is O or NR^{12} ; and

R^{12} is hydrogen or a C_1 - C_4 saturated hydrocarbyl group, wherein the saturated hydrocarbyl group may be straight-chained or branched, or be or include a cyclic group, wherein the saturated hydrocarbyl group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group, and wherein the saturated hydrocarbyl group may optionally include a single heteroatom selected from N and O in its carbon skeleton.

Typically, m is 0.

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In one embodiment, X^{12} is O. For example, $-NR^1R^2$ may have the formula:



Typically, X^{12} is NR^{12} .

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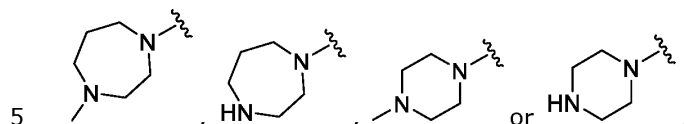
Typically, R^{12} is selected from hydrogen or a C_1 - C_4 alkyl, C_3 - C_4 cycloalkyl, C_1 - C_4 fluoroalkyl, C_3 - C_4 fluorocycloalkyl, cyclopropylmethyl, fluorocyclopropylmethyl or $-CO-R^{120}$ group, wherein R^{120} is selected from a C_1 - C_3 alkyl, C_1 - C_3 fluoroalkyl, cyclopropyl or fluorocyclopropyl group. More typically, R^{12} is selected from hydrogen or a C_1 - C_4 alkyl, C_3 - C_4 cycloalkyl, C_1 - C_4 fluoroalkyl, C_3 - C_4 fluorocycloalkyl, cyclopropylmethyl or fluorocyclopropylmethyl group. For example, R^{12} may be selected from hydrogen or a C_1 - C_4 alkyl, C_3 - C_4 cycloalkyl, C_1 - C_4 fluoroalkyl or C_3 - C_4 fluorocycloalkyl group. More typically still, R^{12} is selected from hydrogen or a C_1 - C_3

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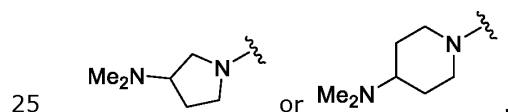
alkyl, C₁-C₃ fluoroalkyl, cyclopropyl or fluorocyclopropyl group. Yet more typically, R¹² is selected from hydrogen or a methyl or fluoromethyl group.

In one aspect of such an embodiment, -NR¹R² has a formula selected from:



In another embodiment, R¹ and R² together with the nitrogen atom to which they are attached form an azetidiny, pyrrolidinyl, piperidinyl or azepanyl group, wherein the azetidiny, pyrrolidinyl, piperidinyl or azepanyl group is substituted with an -NR¹³R¹⁴ group such that the nitrogen atom of the -NR¹³R¹⁴ group is not directly attached to a carbon atom that in turn is directly attached to the ring nitrogen atom of the azetidiny, pyrrolidinyl, piperidinyl or azepanyl group, wherein R¹³ and R¹⁴ are each independently selected from hydrogen or a methyl or fluoromethyl group, and wherein the azetidiny, pyrrolidinyl, piperidinyl or azepanyl group may optionally be further substituted with one or more fluoro groups and/or with one, two, three or four methyl or fluoromethyl groups. Typically in such an embodiment, R¹ and R² together with the nitrogen atom to which they are attached form a pyrrolidinyl or piperidinyl group, wherein the pyrrolidinyl or piperidinyl group is substituted with an -NR¹³R¹⁴ group such that the nitrogen atom of the -NR¹³R¹⁴ group is not directly attached to a carbon atom that in turn is directly attached to the ring nitrogen atom of the pyrrolidinyl or piperidinyl group, wherein R¹³ and R¹⁴ are each independently selected from hydrogen or a methyl or fluoromethyl group.

In one aspect of such an embodiment, -NR¹R² has the formula:



In yet another embodiment, R¹ and R² together with the nitrogen atom to which they are attached form a 6- to 12-membered (e.g. 6- to 10-membered) bicyclic group, wherein the bicyclic group may optionally be substituted with one or more substituents each independently selected from a halo, oxo (=O), -OH, -NH₂ or a C₁-C₄ saturated or unsaturated hydrocarbyl group, wherein the hydrocarbyl group may be straight-chained or branched, or be or include a cyclic group, wherein the hydrocarbyl group may optionally be substituted with one or more halo groups, and wherein the

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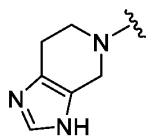
hydrocarbyl group may optionally include one or two heteroatoms each independently selected from N and O in its carbon skeleton.

Without wishing to be bound by theory, it is thought that the compounds of the invention where R^1 and R^2 together with the nitrogen atom to which they are attached form a bicyclic group offer particular steric and electronic properties that are advantageous to the pharmacological profile of the molecule.

Typically in such an embodiment, R^1 and R^2 together with the nitrogen atom to which they are attached form a 8- to 10-membered fused bicyclic group, such that the nitrogen atom of $-NR^1R^2$ is a ring atom of a first 5- or 6-membered ring of the fused bicyclic group, and the first 5- or 6-membered ring is fused to a second 5- or 6-membered ring of the fused bicyclic group. Typically, the first 5- or 6-membered ring is not aromatic, and the first 5- or 6-membered ring is optionally substituted with one or more substituents each independently selected from a fluoro, oxo ($=O$), $-OH$, $-NH_2$, or a C_1 - C_4 saturated hydrocarbyl group, wherein the saturated hydrocarbyl group may be straight-chained or branched, or be or include a cyclic group, wherein the saturated hydrocarbyl group may optionally be substituted with one or more fluoro groups and/or a single oxo ($=O$) group, and wherein the saturated hydrocarbyl group may optionally include a single heteroatom selected from N and O in its carbon skeleton.

In one embodiment, the second 5- or 6-membered ring is aromatic, and the second 5- or 6-membered ring is optionally substituted with one or more substituents each independently selected from a fluoro, chloro, bromo, $-OH$, $-NH_2$, or a C_1 - C_4 saturated hydrocarbyl group, wherein the saturated hydrocarbyl group may be straight-chained or branched, or be or include a cyclic group, wherein the saturated hydrocarbyl group may optionally be substituted with one or more fluoro groups and/or a single oxo ($=O$) group, and wherein the saturated hydrocarbyl group may optionally include a single heteroatom selected from N and O in its carbon skeleton.

In one aspect of such an embodiment, the first 5- or 6-membered ring is not aromatic and is unsubstituted, and the second 5- or 6-membered ring is an unsubstituted 5-membered heteroaryl ring comprising a NH group. In one aspect of such an embodiment, $-NR^1R^2$ has the formula:



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In another embodiment, the second 5- or 6-membered ring is not aromatic, and the second 5- or 6-membered ring is optionally substituted with one or more substituents each independently selected from a fluoro, oxo (=O), -OH, -NH₂, or a C₁-C₄ saturated hydrocarbyl group, wherein the saturated hydrocarbyl group may be straight-chained or branched, or be or include a cyclic group, wherein the saturated hydrocarbyl group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group, and wherein the saturated hydrocarbyl group may optionally include a single heteroatom selected from N and O in its carbon skeleton. Typically in such an embodiment, the first 5- or 6-membered ring is saturated and the second 5- or 6-membered ring is saturated. For example, R¹ and R² may together with the nitrogen atom to which they are attached form a 8- to 10-membered saturated fused bicyclic group, such that the nitrogen atom of -NR¹R² is a ring atom of a first 5- or 6-membered ring of the fused bicyclic group, wherein the first 5- or 6-membered ring is fused to a second 5- or 6-membered ring of the fused bicyclic group, and wherein the fused bicyclic group may optionally substituted with one or more substituents each independently selected from a fluoro, oxo (=O), -OH, -NH₂, or a C₁-C₄ saturated hydrocarbyl group, wherein the saturated hydrocarbyl group may be straight-chained or branched, or be or include a cyclic group, wherein the saturated hydrocarbyl group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group, and wherein the saturated hydrocarbyl group may optionally include a single heteroatom selected from N and O in its carbon skeleton.

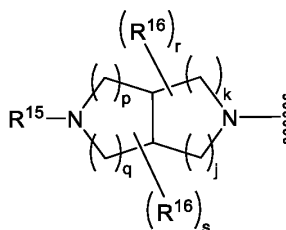
Typically in such an embodiment, the second 5- or 6-membered ring comprises at least one ring nitrogen atom. Typically, said ring nitrogen atom is not directly attached to a sp² hybridised carbon atom. Typically where the second 5- or 6-membered ring comprises at least one ring nitrogen atom, the first 5- or 6-membered ring is saturated and the second 5- or 6-membered ring is saturated. For example, R¹ and R² may together with the nitrogen atom to which they are attached form a 8- to 10-membered saturated fused bicyclic group, such that the nitrogen atom of -NR¹R² is a ring atom of a first 5- or 6-membered ring of the fused bicyclic group, wherein the first 5- or 6-membered ring is fused to a second 5- or 6-membered ring of the fused bicyclic group, wherein the second 5- or 6-membered ring comprises at least one ring nitrogen atom, and wherein the fused bicyclic group may optionally substituted with one or more substituents each independently selected from a fluoro, -OH, -NH₂, or a C₁-C₄ alkyl, C₃-C₄ cycloalkyl, C₁-C₄ fluoroalkyl, C₃-C₄ fluorocycloalkyl, cyclopropylmethyl, fluorocyclopropylmethyl or -CO-R¹²¹ group, wherein each R¹²¹ is independently selected from a C₁-C₃ alkyl, C₁-C₃ fluoroalkyl, cyclopropyl or

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fluorocyclopropyl group. More typically, where such a fused bicyclic group is substituted, it is substituted with one or more substituents each independently selected from a fluoro, -OH, -NH₂, or a C₁-C₄ alkyl, C₃-C₄ cycloalkyl, C₁-C₄ fluoroalkyl or C₃-C₄ fluorocycloalkyl group.

5

In one embodiment, -NR¹R² has the formula:



wherein:

- j is 0, 1, 2 or 3;
 10 k is 0, 1, 2 or 3;
 p is 0, 1, 2 or 3; and
 q is 0, 1, 2 or 3;

provided that:

- j + k = 2 or 3;
 15 p + q = 2 or 3;
 when j = 0, q is 1, 2 or 3;
 when k = 0, p is 1, 2 or 3;
 when p = 0, k is 1, 2 or 3; and
 when q = 0, j is 1, 2 or 3;

20 and wherein:

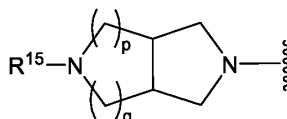
- r is 0, 1 or 2;
 s is 0, 1 or 2;
 R¹⁵ is hydrogen or a C₁-C₄ alkyl, C₃-C₄ cycloalkyl, C₁-C₄ fluoroalkyl, C₃-C₄
 fluorocycloalkyl, cyclopropylmethyl, fluorocyclopropylmethyl or -CO-R¹⁵⁰ group,
 25 wherein R¹⁵⁰ is selected from a C₁-C₃ alkyl, C₁-C₃ fluoroalkyl, cyclopropyl or
 fluorocyclopropyl group; and
 each R¹⁶ is independently selected from a methyl or fluoromethyl group.

Typically in such an embodiment, j is 1 or 2 and k is 1 or 2. More typically, j is 1 and k
 30 is 1.

Typically in such an embodiment, p is 0, 1 or 2 and q is 1 or 2. More typically, p is 1
 or 2 and q is 1 or 2.

Typically in such an embodiment, r is 0 and s is 0.

Thus, for example, $-NR^1R^2$ may have the formula:



5

wherein:

p is 1 or 2;

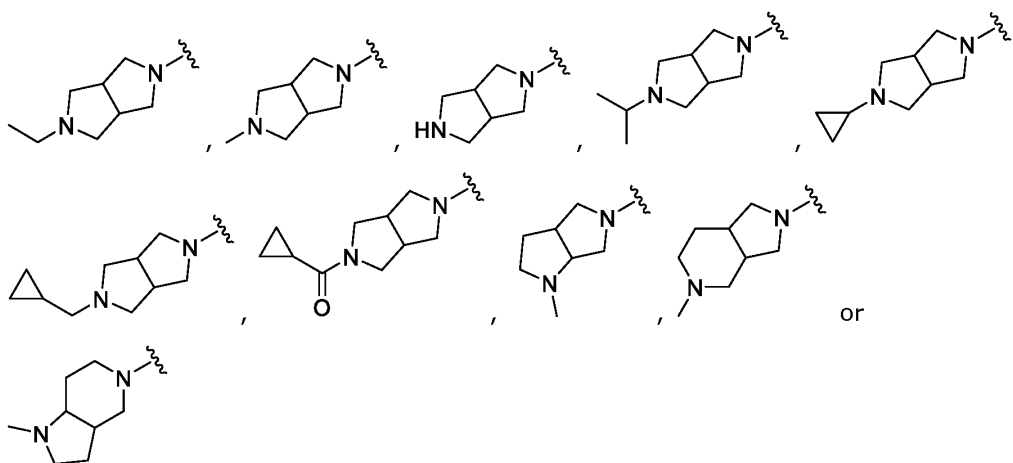
q is 1 or 2;

$p + q = 2$ or 3; and

10 R^{15} is hydrogen or a C_1 - C_4 alkyl, C_3 - C_4 cycloalkyl, C_1 - C_4 fluoroalkyl, C_3 - C_4 fluorocycloalkyl, cyclopropylmethyl, fluorocyclopropylmethyl or $-CO-R^{150}$ group, wherein R^{150} is selected from a C_1 - C_3 alkyl, C_1 - C_3 fluoroalkyl, cyclopropyl or fluorocyclopropyl group.

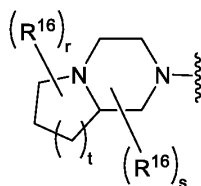
15 Typically in the above embodiments, R^{15} is hydrogen or a C_1 - C_4 alkyl, C_3 - C_4 cycloalkyl, C_1 - C_4 fluoroalkyl, C_3 - C_4 fluorocycloalkyl, cyclopropylmethyl or fluorocyclopropylmethyl group. More typically, R^{15} is hydrogen or a C_1 - C_3 alkyl, C_1 - C_3 fluoroalkyl, cyclopropyl or fluorocyclopropyl group.

20 For example, $-NR^1R^2$ may have a formula selected from:



25 In a further embodiment, $-NR^1R^2$ has the formula:

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wherein:

r is 0, 1 or 2;

s is 0, 1 or 2;

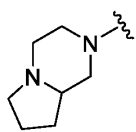
5 t is 1 or 2; and

each R^{16} is independently selected from a methyl or fluoromethyl group.

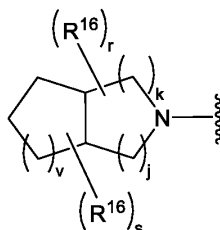
Typically in such an embodiment, r is 0 and s is 0.

10 Typically in such an embodiment, t is 1.

For example, $-NR^1R^2$ may have the formula:



15 In yet another embodiment, $-NR^1R^2$ has the formula:



wherein:

j is 0, 1, 2 or 3; and

k is 0, 1, 2 or 3;

20 provided that $j + k = 2$ or 3;

and wherein:

v is 1 or 2;

r is 0, 1 or 2;

s is 0, 1 or 2; and

25 each R^{16} is independently selected from a methyl or fluoromethyl group.

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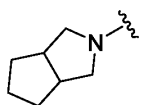
Typically in such an embodiment, j is 1 or 2 and k is 1 or 2. More typically, j is 1 and k is 1.

Typically in such an embodiment, v is 1.

5

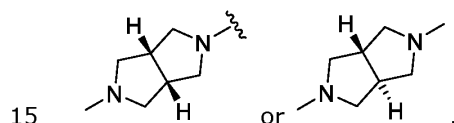
Typically in such an embodiment, r is 0 and s is 0.

For example, $-NR^1R^2$ may have the formula:



10

As will be understood, where a first 5- or 6-membered ring is fused to a second 5- or 6-membered ring across two sp^3 hybridised ring carbon atoms, e.g. across two ring carbon atoms in a saturated fused bicyclic ring system, the second ring may be fused *cis*- or *trans*- to the first ring. For example, $-NR^1R^2$ may have the formula:



15

In another embodiment, where R^1 and R^2 together with the nitrogen atom to which they are attached form a 6- to 12-membered bicyclic group, R^1 and R^2 together with the nitrogen atom to which they are attached form a 6- to 12-membered spiro bicyclic group, such that the nitrogen atom of $-NR^1R^2$ is a ring atom of a first 4- to 7-membered ring of the spiro bicyclic group, and the first 4 to 7-membered ring shares a spiro ring atom with a second 3- to 7-membered ring of the spiro bicyclic group. Typically, the 6- to 12-membered spiro bicyclic group is unsubstituted or substituted with one or more substituents each independently selected from a fluoro, oxo ($=O$), $-OH$, $-NH_2$, or a C_1 - C_4 saturated hydrocarbyl group, wherein the saturated hydrocarbyl group may be straight-chained or branched, or be or include a cyclic group, wherein the saturated hydrocarbyl group may optionally be substituted with one or more fluoro groups and/or a single oxo ($=O$) group, and wherein the saturated hydrocarbyl group may optionally include a single heteroatom selected from N and O in its carbon skeleton.

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Typically in such an embodiment, the first 4- to 7-membered ring is saturated and the second 3- to 7-membered ring is saturated. For example, R^1 and R^2 may together with the nitrogen atom to which they are attached form a 9- to 11-membered saturated

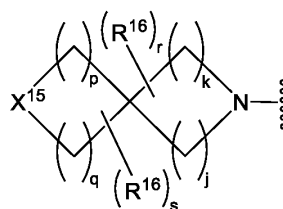
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spiro bicyclic group, such that the nitrogen atom of $-NR^1R^2$ is a ring atom of a first 5- or 6-membered ring of the spiro bicyclic group, and the first 5- or 6-membered ring shares a spiro ring atom with a second 5- or 6-membered ring of the spiro bicyclic group, and wherein the saturated spiro bicyclic group may optionally substituted with one or more substituents each independently selected from a fluoro, oxo ($=O$), $-OH$, $-NH_2$, or a C_1 - C_4 alkyl, C_3 - C_4 cycloalkyl, C_1 - C_4 fluoroalkyl, C_3 - C_4 fluorocycloalkyl, cyclopropylmethyl or fluorocyclopropylmethyl group.

Typically in such an embodiment, the second 3- to 7-membered ring is a 4- to 7-membered ring that comprises at least one ring nitrogen or ring oxygen atom. Typically, said ring nitrogen or ring oxygen atom is not directly attached to a sp^2 hybridised carbon atom. Typically where the second 4- to 7-membered ring comprises at least one ring nitrogen atom or at least one ring oxygen atom, the first 4- to 7-membered ring is saturated and the second 4- to 7-membered ring is saturated. For example, R^1 and R^2 may together with the nitrogen atom to which they are attached form a 9- to 11-membered saturated spiro bicyclic group, such that the nitrogen atom of $-NR^1R^2$ is a ring atom of a first 5- or 6-membered ring of the spiro bicyclic group, and the first 5- or 6-membered ring shares a spiro ring atom with a second 5- or 6-membered ring of the spiro bicyclic group, wherein the second 5- or 6-membered ring comprises at least one ring nitrogen atom or at least one ring oxygen atom, and wherein the saturated spiro bicyclic group may optionally substituted with one or more substituents each independently selected from a fluoro, oxo ($=O$), $-OH$, $-NH_2$, or a C_1 - C_4 alkyl, C_3 - C_4 cycloalkyl, C_1 - C_4 fluoroalkyl, C_3 - C_4 fluorocycloalkyl, cyclopropylmethyl or fluorocyclopropylmethyl group.

Typically, where the saturated spiro bicyclic group is substituted, it is substituted with one or more substituents each independently selected from a fluoro, oxo ($=O$), C_1 - C_4 alkyl, C_3 - C_4 cycloalkyl, C_1 - C_4 fluoroalkyl, C_3 - C_4 fluorocycloalkyl, cyclopropylmethyl or fluorocyclopropylmethyl group.

In one embodiment, $-NR^1R^2$ has the formula:



wherein:

X^{15} is O or NR^{15} ;

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j is 0, 1, 2, 3 or 4;
 k is 0, 1, 2, 3 or 4;
 p is 0, 1, 2, 3 or 4; and
 q is 0, 1, 2, 3 or 4;

5 provided that:

j + k = 3 or 4;
 p + q = 3 or 4;
 when j = 0, q is 1, 2, 3 or 4 and p is 1, 2, 3 or 4;
 when k = 0, q is 1, 2, 3 or 4 and p is 1, 2, 3 or 4;
 10 when p = 0, k is 1, 2, 3 or 4 and j is 1, 2, 3 or 4; and
 when q = 0, k is 1, 2, 3 or 4 and j is 1, 2, 3 or 4;

and wherein:

r is 0, 1 or 2;
 s is 0, 1 or 2;

15 R^{15} is hydrogen or a C_1 - C_4 alkyl, C_3 - C_4 cycloalkyl, C_1 - C_4 fluoroalkyl, C_3 - C_4 fluorocycloalkyl, cyclopropylmethyl, fluorocyclopropylmethyl or $-CO-R^{150}$ group, wherein R^{150} is selected from a C_1 - C_3 alkyl, C_1 - C_3 fluoroalkyl, cyclopropyl or fluorocyclopropyl group; and
 each R^{16} is independently selected from a methyl or fluoromethyl group.

20

Typically in such an embodiment, j is 1 or 2 and k is 1 or 2.

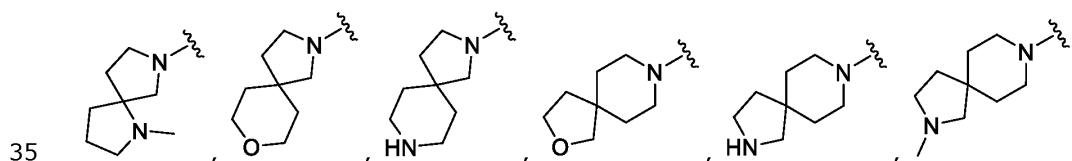
Typically in such an embodiment, p is 0, 1 or 2 and q is 1, 2 or 3. More typically, p is 0, 1 or 2 and q is 2 or 3.

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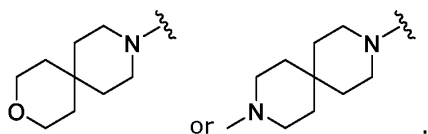
Typically in such an embodiment, r is 0 and s is 0.

Typically in such an embodiment, R^{15} is hydrogen or a C_1 - C_4 alkyl, C_3 - C_4 cycloalkyl, C_1 - C_4 fluoroalkyl, C_3 - C_4 fluorocycloalkyl, cyclopropylmethyl or fluorocyclopropylmethyl
 30 group. More typically, R^{15} is hydrogen or a C_1 - C_3 alkyl, C_1 - C_3 fluoroalkyl, cyclopropyl or fluorocyclopropyl group. More typically still, R^{15} is hydrogen or a methyl or fluoromethyl group.

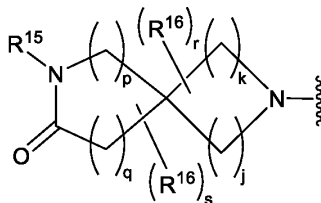
For example, $-NR^1R^2$ may have a formula selected from:



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In another embodiment, $-NR^1R^2$ has the formula:



5 wherein:

j is 0, 1, 2, 3 or 4;
 k is 0, 1, 2, 3 or 4;
 p is 0, 1, 2 or 3; and
 q is 0, 1, 2 or 3;

10 provided that:

j + k = 3 or 4;
 p + q = 2 or 3;
 when j = 0, p is 1, 2 or 3;
 when k = 0, p is 1, 2 or 3; and
 15 when p = 0, j is 1, 2, 3 or 4 and k is 1, 2, 3 or 4;

and wherein:

r is 0, 1 or 2;
 s is 0, 1 or 2;

20 R^{15} is hydrogen or a C_1 - C_4 alkyl, C_3 - C_4 cycloalkyl, C_1 - C_4 fluoroalkyl, C_3 - C_4 fluorocycloalkyl, cyclopropylmethyl or fluorocyclopropylmethyl group; and
 each R^{16} is independently selected from a methyl or fluoromethyl group.

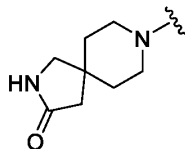
Typically in such an embodiment, j is 1 or 2 and k is 1 or 2.

25 Typically in such an embodiment, p is 1 or 2 and q is 1 or 2.

Typically in such an embodiment, r is 0 and s is 0.

30 Typically in such an embodiment, R^{15} is hydrogen or a C_1 - C_3 alkyl, C_1 - C_3 fluoroalkyl, cyclopropyl or fluorocyclopropyl group. More typically, R^{15} is hydrogen or a methyl or fluoromethyl group. More typically still, R^{15} is hydrogen.

For example, $-NR^1R^2$ may have the formula:



- 5 In a further embodiment, where R^1 and R^2 together with the nitrogen atom to which they are attached form a 6- to 12-membered bicyclic group, R^1 and R^2 together with the nitrogen atom to which they are attached form a 7- to 9-membered bridged bicyclic group. Typically, the 7- to 9-membered bridged bicyclic group is unsubstituted or substituted with one or more substituents each independently selected from a
 10 fluoro, oxo ($=O$), $-OH$, $-NH_2$, or a C_1 - C_4 saturated hydrocarbyl group, wherein the saturated hydrocarbyl group may be straight-chained or branched, or be or include a cyclic group, wherein the saturated hydrocarbyl group may optionally be substituted with one or more fluoro groups and/or a single oxo ($=O$) group, and wherein the saturated hydrocarbyl group may optionally include a single heteroatom selected from
 15 N and O in its carbon skeleton.

Typically in such an embodiment, the 7- to 9-membered bridged bicyclic group is saturated. For example, R^1 and R^2 may together with the nitrogen atom to which they are attached form a 7- or 8-membered saturated bridged bicyclic group, wherein the
 20 saturated bridged bicyclic group may optionally substituted with one or more substituents each independently selected from a fluoro, oxo ($=O$), $-OH$, $-NH_2$, or a C_1 - C_4 alkyl, C_3 - C_4 cycloalkyl, C_1 - C_4 fluoroalkyl, C_3 - C_4 fluorocycloalkyl, cyclopropylmethyl, fluorocyclopropylmethyl or $-CO-R^{121}$ group, wherein each R^{121} is independently selected from a C_1 - C_3 alkyl, C_1 - C_3 fluoroalkyl, cyclopropyl or fluorocyclopropyl group.

25 Typically in such an embodiment, the 7- to 9-membered bridged bicyclic group comprises a least one further ring nitrogen or ring oxygen atom. Typically, said further ring nitrogen or ring oxygen atom is not directly attached to a sp^2 hybridised carbon atom. Typically where the 7- to 9-membered bridged bicyclic group comprises a least
 30 one further ring nitrogen or ring oxygen atom, the 7- to 9-membered bridged bicyclic group is saturated. For example, R^1 and R^2 may together with the nitrogen atom to which they are attached form a 7- or 8-membered saturated bridged bicyclic group, wherein the saturated bridged bicyclic group contains one further ring nitrogen atom, and wherein the saturated bridged bicyclic group may optionally substituted with one
 35 or more substituents each independently selected from a fluoro, oxo ($=O$), $-OH$, $-NH_2$,

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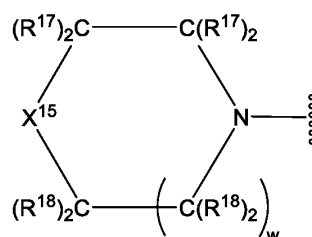
or a C₁-C₄ alkyl, C₃-C₄ cycloalkyl, C₁-C₄ fluoroalkyl, C₃-C₄ fluorocycloalkyl, cyclopropylmethyl, fluorocyclopropylmethyl or -CO-R¹²¹ group, wherein each R¹²¹ is independently selected from a C₁-C₃ alkyl, C₁-C₃ fluoroalkyl, cyclopropyl or fluorocyclopropyl group.

5

Typically, where the saturated bridged bicyclic group is substituted, it is substituted with one or more substituents each independently selected from a fluoro, oxo (=O), C₁-C₄ alkyl, C₃-C₄ cycloalkyl, C₁-C₄ fluoroalkyl, C₃-C₄ fluorocycloalkyl, cyclopropylmethyl or fluorocyclopropylmethyl group.

10

In one embodiment, -NR^{1R2} has the formula:



wherein:

w is 1 or 2;

15

X¹⁵ is O or NR¹⁵;

R¹⁵ is hydrogen or a C₁-C₄ alkyl, C₃-C₄ cycloalkyl, C₁-C₄ fluoroalkyl, C₃-C₄ fluorocycloalkyl, cyclopropylmethyl, fluorocyclopropylmethyl or -CO-R¹⁵⁰ group, wherein R¹⁵⁰ is selected from a C₁-C₃ alkyl, C₁-C₃ fluoroalkyl, cyclopropyl or fluorocyclopropyl group;

20

one R¹⁷ and one R¹⁸ together form a -CH₂- or -CH₂CH₂- group; and each remaining R¹⁷ and R¹⁸ is hydrogen.

Typically in such an embodiment, w is 1.

25

Typically in such an embodiment, X¹⁵ is NR¹⁵.

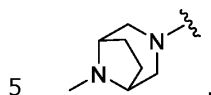
Typically in such an embodiment, R¹⁵ is hydrogen or a C₁-C₄ alkyl, C₃-C₄ cycloalkyl, C₁-C₄ fluoroalkyl, C₃-C₄ fluorocycloalkyl, cyclopropylmethyl or fluorocyclopropylmethyl group. More typically, R¹⁵ is hydrogen or a C₁-C₃ alkyl, C₁-C₃ fluoroalkyl, cyclopropyl or fluorocyclopropyl group. More typically still, R¹⁵ is hydrogen or a methyl or fluoromethyl group. Yet more typically, R¹⁵ is a methyl or fluoromethyl group.

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Typically in such an embodiment, one R^{17} and one R^{18} together form a $-CH_2CH_2-$ group.

For example, $-NR^1R^2$ may have the formula:



As stated in accordance with the first aspect of the invention, R^3 is a C_1 - C_{12} monovalent group, wherein the atom of R^3 that is directly attached to the remainder of the compound of Formula (I) is a carbon atom, and wherein the C_1 - C_{12} monovalent group comprises:

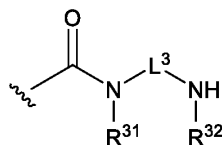
- (i) a primary or a secondary amine, wherein the nitrogen atom of the primary or secondary amine is not directly attached to a sp^2 hybridised carbon atom; and/or
- (ii) a $-OH$ group, wherein the oxygen atom of the $-OH$ group is not directly attached to a sp^2 hybridised carbon atom; and/or
- (iii) a $-SH$ group, wherein the sulphur atom of the $-SH$ group is not directly attached to a sp^2 hybridised carbon atom.

Typically, the carbon atom of R^3 that is directly attached to the remainder of the compound of Formula (I) is a sp^2 hybridised carbon atom. More typically, the carbon atom of R^3 that is directly attached to the remainder of the compound of Formula (I) is the carbon atom of a carbonyl group. More typically still, the carbon atom of R^3 that is directly attached to the remainder of the compound of Formula (I) is the carbon atom of an amide group.

In one embodiment of the first aspect of the invention, R^3 is a C_1 - C_{12} monovalent group, wherein the atom of R^3 that is directly attached to the remainder of the compound of Formula (I) is a carbon atom, and wherein the C_1 - C_{12} monovalent group comprises a primary or a secondary amine, wherein the nitrogen atom of the primary or secondary amine is not directly attached to a sp^2 hybridised carbon atom. Typically, where the C_1 - C_{12} monovalent group comprises a primary amine, the nitrogen atom of the primary amine is directly attached to a sp^3 hybridised carbon atom. Typically, where the C_1 - C_{12} monovalent group comprises a secondary amine, the nitrogen atom of the secondary amine is directly attached to two sp^3 hybridised carbon atoms.

In one embodiment, R^3 has the formula:

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wherein:

R³¹ is hydrogen or a C₁-C₆ saturated hydrocarbyl group, wherein the saturated hydrocarbyl group may be straight-chained or branched, or be or include a cyclic group, wherein the saturated hydrocarbyl group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group, and wherein the saturated hydrocarbyl group may optionally include one or two heteroatoms each independently selected from N and O in its carbon skeleton, provided that the atom of the hydrocarbyl group of R³¹ that is directly attached to the nitrogen atom of N-R³¹ is a carbon atom;

R³² is hydrogen or a C₁-C₆ saturated hydrocarbyl group, wherein the saturated hydrocarbyl group may be straight-chained or branched, or be or include a cyclic group, wherein the saturated hydrocarbyl group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group, and wherein the saturated hydrocarbyl group may optionally include one or two heteroatoms each independently selected from N and O in its carbon skeleton, provided that the atom of the hydrocarbyl group of R³² that is directly attached to the nitrogen atom of NH-R³² is a carbon atom that is not substituted with an oxo (=O) group;

or R³¹ and R³² together form a C₂-C₆ straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group and/or one, two, three or four groups R³³, provided that the carbon atom of the alkylene group that is directly attached to the nitrogen atom of NH-R³² is not substituted with an oxo (=O) group;

each R³³ is independently selected from a methyl or a fluoromethyl group;

L³ is a bond or a C₂-C₅ straight-chained alkylene group or a -CH₂CH₂-O-CH₂CH₂- or -CH₂CH₂-NH-CH₂CH₂- group, wherein the alkylene, the -CH₂CH₂-O-CH₂CH₂- or the -CH₂CH₂-NH-CH₂CH₂- group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group and/or one, two, three or four groups R^{L3}, provided that the carbon atom of the alkylene or the -CH₂CH₂-O-CH₂CH₂- or the -CH₂CH₂-NH-CH₂CH₂- group that is directly attached to the nitrogen atom of NH-R³² is not substituted with an oxo (=O) group;

each R^{L3} is independently selected from a methyl or a fluoromethyl group, or any two R^{L3} may together with the atom or atoms to which they are attached form a 3- to 7-membered cycloalkylene group or a 4- to 7-membered saturated heterocyclic

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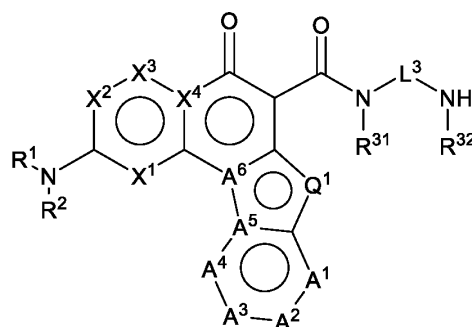
group, wherein the cycloalkylene group or the saturated heterocyclic group may optionally be fluoro substituted;

or any R^{L3} and R^{31} , or any R^{L3} and R^{32} , or any R^{L3} and any R^{33} , together form a C_1 - C_4 straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or a single oxo ($=O$) group and/or one, two, three or four groups R^{34} , provided that where any R^{L3} and R^{32} together form a C_1 - C_4 straight-chained alkylene group, the carbon atom of the alkylene group that is directly attached to the nitrogen atom of $NH-R^{32}$ is not substituted with an oxo ($=O$) group;

or any R^{L3} and any R^{33} together form a bond; and
each R^{34} is independently selected from a methyl or a fluoromethyl group;
provided that the group R^3 contains no more than 12 carbon atoms.

As will be understood, in such an embodiment, the compound is a compound of

Formula (II):



Formula (II)

wherein R^1 , R^2 , X^1 - X^4 , A^1 - A^6 , Q^1 , L^3 , R^{31} and R^{32} are as defined in accordance with Formula (I).

In one embodiment:

L^3 is a bond or a C_2 - C_4 straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or a single oxo ($=O$) group and/or one, two, three or four groups R^{L3} , provided that the carbon atom of the alkylene group that is directly attached to the nitrogen atom of $NH-R^{32}$ is not substituted with an oxo ($=O$) group; and

each R^{L3} is independently selected from a methyl or a fluoromethyl group, or any two R^{L3} may together with the atom or atoms to which they are attached form a 3- to 7-membered cycloalkylene group, wherein the cycloalkylene group may optionally be fluoro substituted;

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or any R^{L3} and R^{31} , or any R^{L3} and R^{32} , or any R^{L3} and any R^{33} , together form a C₁-C₄ straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group and/or one, two, three or four groups R^{34} , provided that where any R^{L3} and R^{32} together form a C₁-C₄ straight-chained alkylene group, the carbon atom of the alkylene group that is directly attached to the nitrogen atom of NH- R^{32} is not substituted with an oxo (=O) group;

or any R^{L3} and any R^{33} together form a bond.

Typically in the above embodiments, R^{31} is hydrogen.

In one embodiment, L^3 is not a bond. For example, L^3 may be a C₂-C₄ straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group and/or one, two, three or four groups R^{L3} , provided that the carbon atom of the alkylene group that is directly attached to the nitrogen atom of NH- R^{32} is not substituted with an oxo (=O) group, wherein:

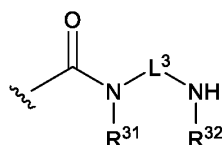
each R^{L3} is independently selected from a methyl or a fluoromethyl group, or any two R^{L3} may together with the atom or atoms to which they are attached form a 3- to 7-membered cycloalkylene group, wherein the cycloalkylene group may optionally be fluoro substituted;

or any R^{L3} and R^{31} , or any R^{L3} and R^{32} , or any R^{L3} and any R^{33} , together form a C₁-C₄ straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group and/or one, two, three or four groups R^{34} , provided that where any R^{L3} and R^{32} together form a C₁-C₄ straight-chained alkylene group, the carbon atom of the alkylene group that is directly attached to the nitrogen atom of NH- R^{32} is not substituted with an oxo (=O) group;

or any R^{L3} and any R^{33} together form a bond.

Typically where L^3 is not a bond, R^{31} is hydrogen.

In another embodiment, L^3 is not a bond and R^{31} is not hydrogen. Thus, there is provided an embodiment wherein R^3 has the formula:



wherein:

R³¹ is a C₁-C₆ saturated hydrocarbyl group, wherein the saturated hydrocarbyl group may be straight-chained or branched, or be or include a cyclic group, wherein the saturated hydrocarbyl group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group, and wherein the saturated hydrocarbyl group may optionally include one or two heteroatoms each independently selected from N and O in its carbon skeleton, provided that the atom of the hydrocarbyl group of R³¹ that is directly attached to the nitrogen atom of N-R³¹ is a carbon atom;

R³² is hydrogen or a C₁-C₆ saturated hydrocarbyl group, wherein the saturated hydrocarbyl group may be straight-chained or branched, or be or include a cyclic group, wherein the saturated hydrocarbyl group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group, and wherein the saturated hydrocarbyl group may optionally include one or two heteroatoms each independently selected from N and O in its carbon skeleton, provided that the atom of the hydrocarbyl group of R³² that is directly attached to the nitrogen atom of NH-R³² is a carbon atom that is not substituted with an oxo (=O) group;

or R³¹ and R³² together form a C₂-C₆ straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group and/or one, two, three or four groups R³³, provided that the carbon atom of the alkylene group that is directly attached to the nitrogen atom of NH-R³² is not substituted with an oxo (=O) group;

each R³³ is independently selected from a methyl or a fluoromethyl group;

L³ is a C₂-C₅ straight-chained alkylene group or a -CH₂CH₂-O-CH₂CH₂- or -CH₂CH₂-NH-CH₂CH₂- group, wherein the alkylene, the -CH₂CH₂-O-CH₂CH₂- or the -CH₂CH₂-NH-CH₂CH₂- group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group and/or one, two, three or four groups R^{L3}, provided that the carbon atom of the alkylene or the -CH₂CH₂-O-CH₂CH₂- or the -CH₂CH₂-NH-CH₂CH₂- group that is directly attached to the nitrogen atom of NH-R³² is not substituted with an oxo (=O) group;

each R^{L3} is independently selected from a methyl or a fluoromethyl group, or any two R^{L3} may together with the atom or atoms to which they are attached form a 3- to 7-membered cycloalkylene group or a 4- to 7-membered saturated heterocyclic group, wherein the cycloalkylene group or the saturated heterocyclic group may optionally be fluoro substituted;

or any R^{L3} and R³¹, or any R^{L3} and R³², or any R^{L3} and any R³³, together form a C₁-C₄ straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group and/or one, two, three or four groups R³⁴, provided that where any R^{L3} and R³² together form

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a C₁-C₄ straight-chained alkylene group, the carbon atom of the alkylene group that is directly attached to the nitrogen atom of NH-R³² is not substituted with an oxo (=O) group;

or any R^{L3} and any R³³ together form a bond; and

- 5 each R³⁴ is independently selected from a methyl or a fluoromethyl group; provided that the group R³ contains no more than 12 carbon atoms.

In one aspect of such an embodiment:

- 10 L³ is a C₂-C₄ straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group and/or one, two, three or four groups R^{L3}, provided that the carbon atom of the alkylene group that is directly attached to the nitrogen atom of NH-R³² is not substituted with an oxo (=O) group; and

- 15 each R^{L3} is independently selected from a methyl or a fluoromethyl group, or any two R^{L3} may together with the atom or atoms to which they are attached form a 3- to 7-membered cycloalkylene group, wherein the cycloalkylene group may optionally be fluoro substituted;

- 20 or any R^{L3} and R³¹, or any R^{L3} and R³², or any R^{L3} and any R³³, together form a C₁-C₄ straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group and/or one, two, three or four groups R³⁴, provided that where any R^{L3} and R³² together form a C₁-C₄ straight-chained alkylene group, the carbon atom of the alkylene group that is directly attached to the nitrogen atom of NH-R³² is not substituted with an oxo (=O) group;

- 25 or any R^{L3} and any R³³ together form a bond.

- 30 In one embodiment, R³¹ is hydrogen or a C₁-C₄ alkyl group, wherein the alkyl group may be straight-chained or branched, or be or include a cyclic group, wherein the alkyl group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group. Typically in such an embodiment, R³¹ is hydrogen or a C₁-C₄ alkyl group, wherein the alkyl group may be straight-chained or branched, or be or include a cyclic group, wherein the alkyl group may optionally be substituted with one or more fluoro groups. More typically in such an embodiment, R³¹ is hydrogen or a methyl or fluoromethyl group. More typically still, R³¹ is hydrogen.

- 35 In one embodiment, R³² is hydrogen or a C₁-C₄ alkyl group, wherein the alkyl group may be straight-chained or branched, or be or include a cyclic group, and wherein the alkyl group may optionally be substituted with one or more fluoro groups. Typically in

such an embodiment, R^{32} is hydrogen or a C_1 - C_3 alkyl, C_1 - C_3 fluoroalkyl, cyclopropyl or fluorocyclopropyl group.

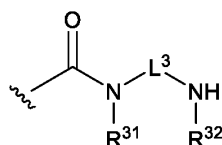
In another embodiment, R^{31} and R^{32} together form a C_2 - C_5 straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{33} . Typically in such an embodiment, R^{31} and R^{32} together form a C_3 - C_4 straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or a single group R^{33} .

10

In one embodiment, L^3 is a C_2 - C_5 straight-chained alkylene group or a $-\text{CH}_2\text{CH}_2\text{-O-CH}_2\text{CH}_2\text{-}$ or $-\text{CH}_2\text{CH}_2\text{-NH-CH}_2\text{CH}_2\text{-}$ group, wherein the alkylene, the $-\text{CH}_2\text{CH}_2\text{-O-CH}_2\text{CH}_2\text{-}$ or the $-\text{CH}_2\text{CH}_2\text{-NH-CH}_2\text{CH}_2\text{-}$ group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{L3} . Typically in such an embodiment, L^3 is a C_2 - C_4 or a C_2 - C_3 straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{L3} .

In one embodiment each R^{L3} is independently selected from a methyl or a fluoromethyl group, or any two R^{L3} together with the atom or atoms to which they are attached form a 5- or 6-membered cycloalkylene group, or any R^{L3} and R^{31} , or any R^{L3} and R^{32} , together form a C_2 - C_4 straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{34} , or any R^{L3} and any R^{33} together form a bond or a C_1 - C_2 straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{34} . Typically in such an embodiment, each R^{L3} is independently selected from a methyl or a fluoromethyl group, or any R^{L3} and R^{31} , or any R^{L3} and R^{32} , together form a C_2 - C_4 straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{34} , or any R^{L3} and any R^{33} together form a bond or a C_1 - C_2 straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{34} .

Thus, in one embodiment R^3 has the formula:



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wherein:

R³¹ is hydrogen or a C₁-C₄ alkyl group, wherein the alkyl group may be straight-chained or branched, or be or include a cyclic group, wherein the alkyl group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group;

R³² is hydrogen or a C₁-C₄ alkyl group, wherein the alkyl group may be straight-chained or branched, or be or include a cyclic group, and wherein the alkyl group may optionally be substituted with one or more fluoro groups;
or R³¹ and R³² together form a C₂-C₅ straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R³³;

each R³³ is independently selected from a methyl or a fluoromethyl group;
L³ is a C₂-C₅ straight-chained alkylene group or a -CH₂CH₂-O-CH₂CH₂- or -CH₂CH₂-NH-CH₂CH₂- group, wherein the alkylene, the -CH₂CH₂-O-CH₂CH₂- or the -CH₂CH₂-NH-CH₂CH₂- group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{L3};
each R^{L3} is independently selected from a methyl or a fluoromethyl group, or any two R^{L3} together with the atom or atoms to which they are attached form a 5- or 6-membered cycloalkylene group, or any R^{L3} and R³¹, or any R^{L3} and R³², together form a C₂-C₄ straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R³⁴, or any R^{L3} and any R³³ together form a bond or a C₁-C₂ straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R³⁴; and
each R³⁴ is independently selected from a methyl or a fluoromethyl group; provided that the group R³ contains no more than 12 carbon atoms.

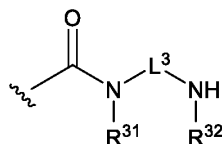
Typically in such an embodiment:

L³ is a C₂-C₄ or a C₂-C₃ straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{L3}; and
each R^{L3} is independently selected from a methyl or a fluoromethyl group, or any R^{L3} and R³¹, or any R^{L3} and R³², together form a C₂-C₄ straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R³⁴, or any R^{L3} and any R³³ together form a bond or a C₁-C₂ straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R³⁴.

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In one aspect of such an embodiment, R³¹ is hydrogen.

In another aspect of such an embodiment, R³¹ is not hydrogen. Thus, in one embodiment R³ has the formula:



5

wherein:

R³¹ is a C₁-C₄ alkyl group, wherein the alkyl group may be straight-chained or branched, or be or include a cyclic group, wherein the alkyl group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group;

10 R³² is hydrogen or a C₁-C₄ alkyl group, wherein the alkyl group may be straight-chained or branched, or be or include a cyclic group, and wherein the alkyl group may optionally be substituted with one or more fluoro groups;

or R³¹ and R³² together form a C₂-C₅ straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups

15 and/or one or two groups R³³;

each R³³ is independently selected from a methyl or a fluoromethyl group;

L³ is a C₂-C₅ straight-chained alkylene group or a -CH₂CH₂-O-CH₂CH₂- or -CH₂CH₂-NH-CH₂CH₂- group, wherein the alkylene, the -CH₂CH₂-O-CH₂CH₂- or the -CH₂CH₂-NH-CH₂CH₂- group may optionally be substituted with one or more fluoro

20 groups and/or one or two groups R^{L3};

each R^{L3} is independently selected from a methyl or a fluoromethyl group, or any two R^{L3} together with the atom or atoms to which they are attached form a 5- or 6-membered cycloalkylene group, or any R^{L3} and R³¹, or any R^{L3} and R³², together form a C₂-C₄ straight-chained alkylene group, wherein the alkylene group may

25 optionally be substituted with one or more fluoro groups and/or one or two groups R³⁴, or any R^{L3} and any R³³ together form a bond or a C₁-C₂ straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R³⁴; and

each R³⁴ is independently selected from a methyl or a fluoromethyl group;

30 provided that the group R³ contains no more than 12 carbon atoms.

Typically in such an aspect:

L³ is a C₂-C₄ or a C₂-C₃ straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{L3}; and

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- 37 -

each R^{L3} is independently selected from a methyl or a fluoromethyl group, or any R^{L3} and R^{31} , or any R^{L3} and R^{32} , together form a C_2 - C_4 straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{34} , or any R^{L3} and any R^{33} together form a bond or a C_1 - C_2 straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{34} .

In certain embodiments:

R^{31} is hydrogen or a C_1 - C_4 alkyl group, wherein the alkyl group may be straight-chained or branched, or be or include a cyclic group, wherein the alkyl group may optionally be substituted with one or more fluoro groups and/or a single oxo ($=O$) group;

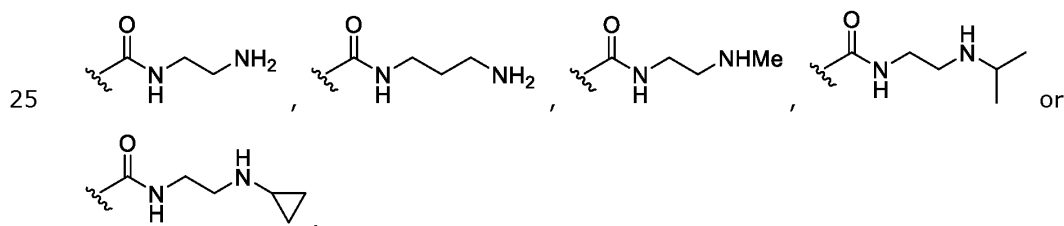
R^{32} is hydrogen or a C_1 - C_4 alkyl group, wherein the alkyl group may be straight-chained or branched, or be or include a cyclic group, and wherein the alkyl group may optionally be substituted with one or more fluoro groups;

L^3 is a C_2 - C_3 straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{L3} ; and

each R^{L3} is independently selected from a methyl or a fluoromethyl group; provided that the group R^3 contains no more than 12 carbon atoms.

Most typically in such embodiments, R^{31} is hydrogen.

For example, R^3 may have the formula:



In other embodiments:

R^{32} is hydrogen or a C_1 - C_4 alkyl group, wherein the alkyl group may be straight-chained or branched, or be or include a cyclic group, and wherein the alkyl group may optionally be substituted with one or more fluoro groups;

L^3 is a C_2 - C_3 straight-chained alkylene group, wherein the alkylene group is substituted with one group R^{L3} , and wherein the alkylene group may optionally be further substituted with one or more fluoro groups;

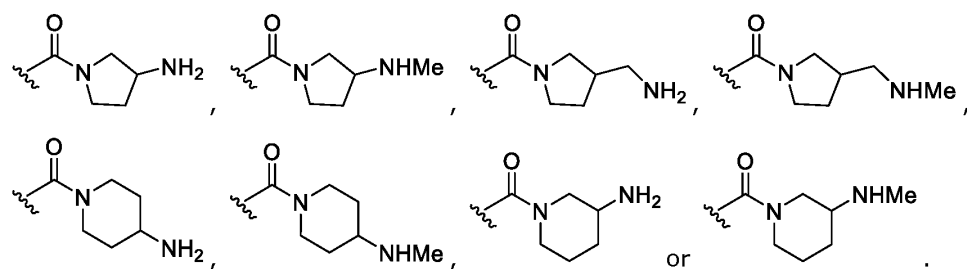
- 38 -

R^{L3} and R^{31} together form a C₂-C₄ straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{34} ; and

each R^{34} is independently selected from a methyl or a fluoromethyl group;

5 provided that the group R^3 contains no more than 12 carbon atoms.

For example, R^3 may have the formula:



10

In other embodiments:

R^{31} is hydrogen or a C₁-C₄ alkyl group, wherein the alkyl group may be straight-chained or branched, or be or include a cyclic group, wherein the alkyl group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group;

15

L^3 is a C₂-C₅ straight-chained alkylene group or a -CH₂CH₂-NH-CH₂CH₂- group, wherein the alkylene or the -CH₂CH₂-NH-CH₂CH₂- group is substituted with one or two groups R^{L3} , and wherein the alkylene or the -CH₂CH₂-NH-CH₂CH₂- group may optionally be further substituted with one or more fluoro groups;

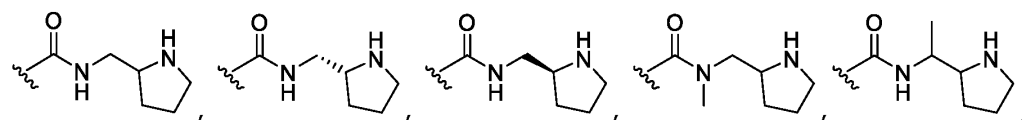
20 one R^{L3} and R^{32} together form a C₂-C₄ straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{34} ;

the second R^{L3} , if present, is selected from a methyl or a fluoromethyl group;

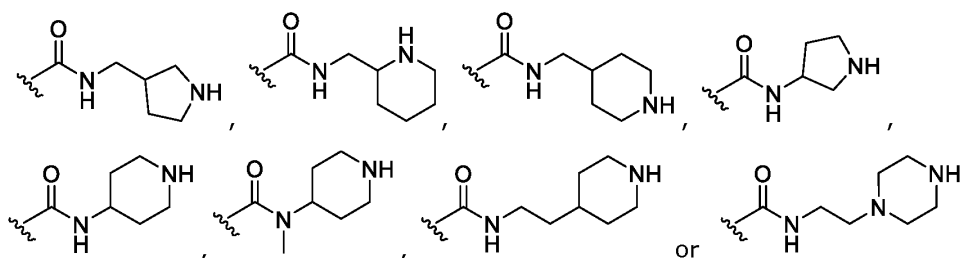
and

25 each R^{34} is independently selected from a methyl or a fluoromethyl group; provided that the group R^3 contains no more than 12 carbon atoms.

For example, R^3 may have the formula:



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Most typically in such embodiments, R^{31} is hydrogen.

5

In one aspect of such embodiments, L^3 is a C_2 - C_4 or a C_2 - C_3 straight-chained alkylene group, wherein the alkylene group is substituted with one group R^{L3} , and wherein the alkylene group may optionally be further substituted with one or more fluoro groups.

10 Most typically in such embodiments, the one R^{L3} and R^{32} together with the atoms of the L^3 -NH group to which they are attached together form a pyrrolidinyl or piperidinyl group. For instance, R^3 may have the formula $-CH_2-R^{30}$, wherein R^{30} is a pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-2-yl, piperidin-3-yl or piperidin-4-yl group.

15 In other embodiments:

R^{31} is hydrogen or a C_1 - C_4 alkyl group, wherein the alkyl group may be straight-chained or branched, or be or include a cyclic group, wherein the alkyl group may optionally be substituted with one or more fluoro groups and/or a single oxo ($=O$) group;

20 R^{32} is hydrogen or a C_1 - C_4 alkyl group, wherein the alkyl group may be straight-chained or branched, or be or include a cyclic group, and wherein the alkyl group may optionally be substituted with one or more fluoro groups;

L^3 is a C_2 - C_4 straight-chained alkylene group, wherein the alkylene group is substituted with two groups R^{L3} , and wherein the alkylene group may optionally be substituted with one or more fluoro groups; and

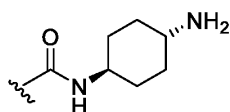
the two groups R^{L3} together with the atom or atoms to which they are attached form a 5- or 6-membered cycloalkylene group;

provided that the group R^3 contains no more than 12 carbon atoms.

30 Most typically in such embodiments, R^{31} is hydrogen.

For example, R^3 may have the formula:

- 40 -



In other embodiments:

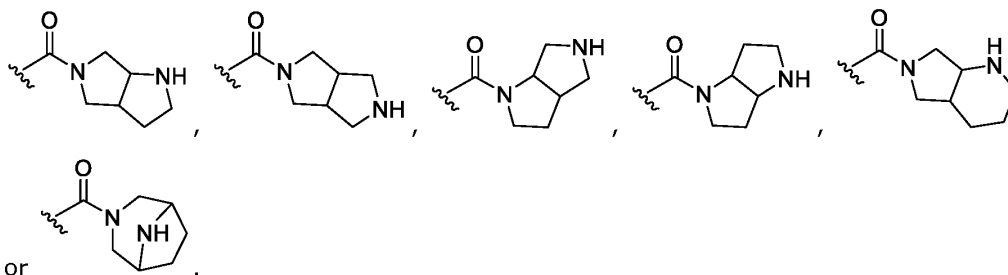
- 5 R^{31} and R^{32} together form a C_2 - C_5 straight-chained alkylene group, wherein the alkylene group is substituted with one group R^{33} , and wherein the alkylene group may optionally be substituted with one or more fluoro groups;

L^3 is a C_2 - C_3 straight-chained alkylene group, wherein the alkylene group is substituted with one group R^{L3} , and wherein the alkylene group may optionally be further substituted with one or more fluoro groups; and

- 10 R^{L3} and R^{33} together form a bond or a C_1 - C_2 straight-chained alkylene group, wherein the alkylene group may optionally be further substituted with one or more fluoro groups;

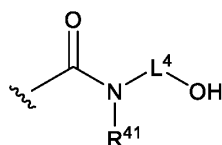
provided that the group R^3 contains no more than 12 carbon atoms.

- 15 For example, R^3 may have the formula:



- In another embodiment of the first aspect of the invention, R^3 is a C_1 - C_{12} monovalent group, wherein the atom of R^3 that is directly attached to the remainder of the compound of Formula (I) is a carbon atom, and wherein the C_1 - C_{12} monovalent group comprises a -OH group, wherein the oxygen atom of the -OH group is not directly attached to a sp^2 hybridised carbon atom. Typically, where the C_1 - C_{12} monovalent group comprises a -OH group, the oxygen atom of the -OH group is directly attached to a sp^3 hybridised carbon atom.
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For example, R^3 may have the formula:



wherein:

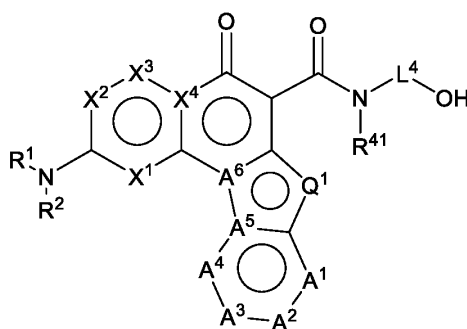
R^{41} is hydrogen or a C_1 - C_6 saturated hydrocarbyl group, wherein the saturated hydrocarbyl group may be straight-chained or branched, or be or include a cyclic group, wherein the saturated hydrocarbyl group may optionally be substituted with one or more fluoro groups and/or a single oxo ($=O$) group, and wherein the saturated hydrocarbyl group may optionally include one or two heteroatoms each independently selected from N and O in its carbon skeleton, provided that the atom of the hydrocarbyl group of R^{41} that is directly attached to the nitrogen atom of $N-R^{41}$ is a carbon atom;

L^4 is a C_2 - C_5 straight-chained alkylene group or a $-CH_2CH_2-O-CH_2CH_2-$ or $-CH_2CH_2-NH-CH_2CH_2-$ group, wherein the alkylene, the $-CH_2CH_2-O-CH_2CH_2-$ or the $-CH_2CH_2-NH-CH_2CH_2-$ group may optionally be substituted with one or more fluoro groups and/or a single oxo ($=O$) group and/or one, two, three or four groups R^{L4} , provided that the carbon atom of the alkylene or the $-CH_2CH_2-O-CH_2CH_2-$ or the $-CH_2CH_2-NH-CH_2CH_2-$ group that is directly attached to the oxygen atom of the $-OH$ group is not substituted with an oxo ($=O$) group;

each R^{L4} is independently selected from a methyl or a fluoromethyl group, or any two R^{L4} may together with the atom or atoms to which they are attached form a 3- to 7-membered cycloalkylene group or a 4- to 7-membered saturated heterocyclic group, wherein the cycloalkylene group or the saturated heterocyclic group may optionally be fluoro substituted;

or any R^{L4} and R^{41} may together form a C_1 - C_4 straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or a single oxo ($=O$) group and/or one, two, three or four groups R^{44} ; and each R^{44} is independently selected from a methyl or a fluoromethyl group; provided that the group R^3 contains no more than 12 carbon atoms.

As will be understood, in such an embodiment, the compound is a compound of Formula (III):



Formula (III)

wherein R^1 , R^2 , X^1 - X^4 , A^1 - A^6 , Q^1 , L^4 and R^{41} are as defined in accordance with Formula (I).

In one aspect of such an embodiment:

- 5 L^4 is a C_2 - C_4 straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or a single oxo ($=O$) group and/or one, two, three or four groups R^{L4} , provided that the carbon atom of the alkylene group that is directly attached to the oxygen atom of the $-OH$ group is not substituted with an oxo ($=O$) group; and
- 10 each R^{L4} is independently selected from a methyl or a fluoromethyl group, or any two R^{L4} may together with the atom or atoms to which they are attached form a 3- to 7-membered cycloalkylene group, wherein the cycloalkylene group may optionally be fluoro substituted;
- or any R^{L4} and R^{41} may together form a C_1 - C_4 straight-chained alkylene group,
- 15 wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or a single oxo ($=O$) group and/or one, two, three or four groups R^{44} .

In one aspect of such an embodiment, R^{41} is hydrogen.

- 20 In another aspect of such an embodiment, R^{41} is not hydrogen.

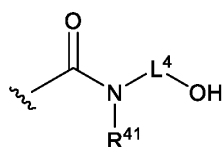
- In one embodiment, R^{41} is hydrogen or a C_1 - C_4 alkyl group, wherein the alkyl group may be straight-chained or branched, or be or include a cyclic group, wherein the alkyl group may optionally be substituted with one or more fluoro groups and/or a single
- 25 oxo ($=O$) group. Typically in such an embodiment, R^{41} is hydrogen or a C_1 - C_4 alkyl group, wherein the alkyl group may be straight-chained or branched, or be or include a cyclic group, wherein the alkyl group may optionally be substituted with one or more fluoro groups. More typically in such an embodiment, R^{41} is hydrogen or a methyl or fluoromethyl group. More typically still, R^{41} is hydrogen.

- 30 In one embodiment, L^4 is a C_2 - C_5 straight-chained alkylene group or a $-CH_2CH_2-O-CH_2CH_2-$ or $-CH_2CH_2-NH-CH_2CH_2-$ group, wherein the alkylene, the $-CH_2CH_2-O-CH_2CH_2-$ or the $-CH_2CH_2-NH-CH_2CH_2-$ group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{L4} . Typically in such an
- 35 embodiment, L^4 is a C_2 - C_3 straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{L4} .

In one embodiment each R^{L4} is independently selected from a methyl or a fluoromethyl group, or any two R^{L4} together with the atom or atoms to which they are attached form a 5- or 6-membered cycloalkylene group, or any R^{L4} and R^{41} may together form a C₂-C₄ straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{44} . Typically in such an embodiment, each R^{L4} is independently selected from a methyl or a fluoromethyl group, or any R^{L4} and R^{41} may together form a C₂-C₄ straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{44} .

10

Thus, in one embodiment R^3 has the formula:



wherein:

R^{41} is hydrogen or a C₁-C₄ alkyl group, wherein the alkyl group may be straight-chained or branched, or be or include a cyclic group, wherein the alkyl group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group;

L^4 is a C₂-C₅ straight-chained alkylene group or a -CH₂CH₂-O-CH₂CH₂- or -CH₂CH₂-NH-CH₂CH₂- group, wherein the alkylene, the -CH₂CH₂-O-CH₂CH₂- or the -CH₂CH₂-NH-CH₂CH₂- group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{L4} ;

each R^{L4} is independently selected from a methyl or a fluoromethyl group, or any two R^{L4} together with the atom or atoms to which they are attached form a 5- or 6-membered cycloalkylene group, or any R^{L4} and R^{41} may together form a C₂-C₄ straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{44} ; and

each R^{44} is independently selected from a methyl or a fluoromethyl group; provided that the group R^3 contains no more than 12 carbon atoms.

Typically in such an embodiment:

L^4 is a C₂-C₃ straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{L4} ; and

each R^{L4} is independently selected from a methyl or a fluoromethyl group, or any R^{L4} and R^{41} may together form a C₂-C₄ straight-chained alkylene group, wherein

- 44 -

the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{44} .

Typically in such an embodiment, R^{41} is hydrogen.

5

In one aspect of such an embodiment, R^{41} is not hydrogen.

In certain embodiments:

10 R^{41} is hydrogen or a C_1 - C_4 alkyl group, wherein the alkyl group may be straight-chained or branched, or be or include a cyclic group, wherein the alkyl group may optionally be substituted with one or more fluoro groups and/or a single oxo ($=O$) group;

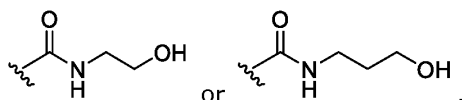
15 L^4 is a C_2 - C_3 straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{L4} ; and

each R^{L4} is independently selected from a methyl or a fluoromethyl group; provided that the group R^3 contains no more than 12 carbon atoms.

Typically in such embodiments, R^{41} is hydrogen.

20

For example, R^3 may have the formula:



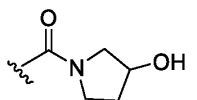
In other embodiments:

25 L^4 is a C_2 - C_3 straight-chained alkylene group, wherein the alkylene group is substituted with one group R^{L4} , and wherein the alkylene group may optionally be further substituted with one or more fluoro groups;

30 R^{L4} and R^{41} together form a C_2 - C_4 straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{44} ; and

each R^{44} is independently selected from a methyl or a fluoromethyl group; provided that the group R^3 contains no more than 12 carbon atoms.

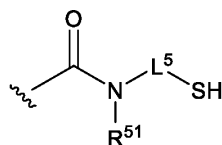
For example, R^3 may have the formula:



In another embodiment of the first aspect of the invention, R^3 is a C_1 - C_{12} monovalent group, wherein the atom of R^3 that is directly attached to the remainder of the compound of Formula (I) is a carbon atom, and wherein the C_1 - C_{12} monovalent group comprises a -SH group, wherein the sulphur atom of the -SH group is not directly attached to a sp^2 hybridised carbon atom. Typically, where the C_1 - C_{12} monovalent group comprises a -SH group, the sulphur atom of the -SH group is directly attached to a sp^3 hybridised carbon atom.

10

For example, R^3 may have the formula:



wherein:

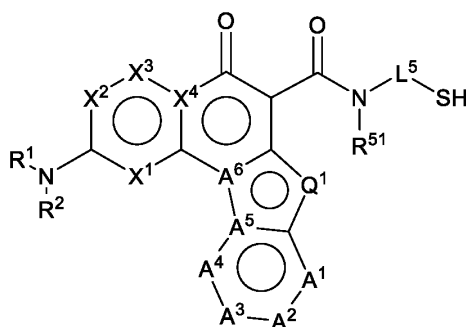
R^{51} is hydrogen or a C_1 - C_6 saturated hydrocarbyl group, wherein the saturated hydrocarbyl group may be straight-chained or branched, or be or include a cyclic group, wherein the saturated hydrocarbyl group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group, and wherein the saturated hydrocarbyl group may optionally include one or two heteroatoms each independently selected from N and O in its carbon skeleton, provided that the atom of the hydrocarbyl group of R^{51} that is directly attached to the nitrogen atom of $N-R^{51}$ is a carbon atom;

L^5 is a C_2 - C_5 straight-chained alkylene group or a $-CH_2CH_2-O-CH_2CH_2-$ or $-CH_2CH_2-NH-CH_2CH_2-$ group, wherein the alkylene, the $-CH_2CH_2-O-CH_2CH_2-$ or the $-CH_2CH_2-NH-CH_2CH_2-$ group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group and/or one, two, three or four groups R^{L5} , provided that the carbon atom of the alkylene or the $-CH_2CH_2-O-CH_2CH_2-$ or the $-CH_2CH_2-NH-CH_2CH_2-$ group that is directly attached to the sulphur atom of the -SH group is not substituted with an oxo (=O) group;

each R^{L5} is independently selected from a methyl or a fluoromethyl group, or any two R^{L5} may together with the atom or atoms to which they are attached form a 3- to 7-membered cycloalkylene group or a 4- to 7-membered saturated heterocyclic group, wherein the cycloalkylene group or the saturated heterocyclic group may optionally be fluoro substituted;

or any R^{L5} and R^{S1} may together form a C₁-C₄ straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group and/or one, two, three or four groups R^{S4}; and each R^{S4} is independently selected from a methyl or a fluoromethyl group; provided that the group R³ contains no more than 12 carbon atoms.

As will be understood, in such an embodiment, the compound is a compound of Formula (IV):



Formula (IV)

wherein R¹, R², X¹-X⁴, A¹-A⁶, Q¹, L⁵ and R⁵¹ are as defined in accordance with Formula (I).

In one aspect of such an embodiment:

15 L⁵ is a C₂-C₄ straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group and/or one, two, three or four groups R^{L5}, provided that the carbon atom of the alkylene group that is directly attached to the sulphur atom of the -SH group is not substituted with an oxo (=O) group; and

20 each R^{L5} is independently selected from a methyl or a fluoromethyl group, or any two R^{L5} may together with the atom or atoms to which they are attached form a 3- to 7-membered cycloalkylene group, wherein the cycloalkylene group may optionally be fluoro substituted;

or any R¹⁵ and R⁵¹ may together form a C₁-C₄ straight-chained alkylene group,
25 wherein the alkylene group may optionally be substituted with one or more fluoro
groups and/or a single oxo (=O) group and/or one, two, three or four groups R⁵⁴.

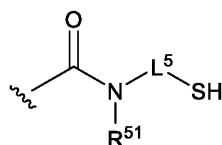
Typically in such an embodiment, R⁵¹ is hydrogen.

30 In another aspect of such an embodiment, R^{51} is not hydrogen.

- In one embodiment, R^{51} is hydrogen or a C_1 - C_4 alkyl group, wherein the alkyl group may be straight-chained or branched, or be or include a cyclic group, wherein the alkyl group may optionally be substituted with one or more fluoro groups and/or a single oxo ($=O$) group. Typically in such an embodiment, R^{51} is hydrogen or a C_1 - C_4 alkyl group, wherein the alkyl group may be straight-chained or branched, or be or include a cyclic group, wherein the alkyl group may optionally be substituted with one or more fluoro groups. More typically in such an embodiment, R^{51} is hydrogen or a methyl or fluoromethyl group. More typically still, R^{51} is hydrogen.
- 5 In one embodiment, L^5 is a C_2 - C_5 straight-chained alkylene group or a $-CH_2CH_2-O-CH_2CH_2-$ or $-CH_2CH_2-NH-CH_2CH_2-$ group, wherein the alkylene, the $-CH_2CH_2-O-CH_2CH_2-$ or the $-CH_2CH_2-NH-CH_2CH_2-$ group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{L5} . Typically in such an embodiment, L^5 is a C_2 - C_3 straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{L5} .
- 10
15

- In one embodiment each R^{L5} is independently selected from a methyl or a fluoromethyl group, or any two R^{L5} together with the atom or atoms to which they are attached form a 5- or 6-membered cycloalkylene group, or any R^{L5} and R^{51} may together form a C_2 - C_4 straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{54} . Typically in such an embodiment, each R^{L5} is independently selected from a methyl or a fluoromethyl group, or any R^{L5} and R^{51} may together form a C_2 - C_4 straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{54} .
- 20
25

Thus, in one embodiment R^3 has the formula:



- 30 wherein:

R^{51} is hydrogen or a C_1 - C_4 alkyl group, wherein the alkyl group may be straight-chained or branched, or be or include a cyclic group, wherein the alkyl group may optionally be substituted with one or more fluoro groups and/or a single oxo ($=O$) group;

L⁵ is a C₂-C₅ straight-chained alkylene group or a -CH₂CH₂-O-CH₂CH₂- or -CH₂CH₂-NH-CH₂CH₂- group, wherein the alkylene, the -CH₂CH₂-O-CH₂CH₂- or the -CH₂CH₂-NH-CH₂CH₂- group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{L5};

- 5 each R^{L5} is independently selected from a methyl or a fluoromethyl group, or any two R^{L5} together with the atom or atoms to which they are attached form a 5- or 6-membered cycloalkylene group, or any R^{L5} and R⁵¹ may together form a C₂-C₄ straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R⁵⁴; and
- 10 each R⁵⁴ is independently selected from a methyl or a fluoromethyl group; provided that the group R³ contains no more than 12 carbon atoms.

Typically in such an embodiment:

- L⁵ is a C₂-C₃ straight-chained alkylene group, wherein the alkylene group may
- 15 optionally be substituted with one or more fluoro groups and/or one or two groups R^{L5}; and
- each R^{L5} is independently selected from a methyl or a fluoromethyl group, or any R^{L5} and R⁵¹ may together form a C₂-C₄ straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups
- 20 and/or one or two groups R⁵⁴.

Typically in such an embodiment, R⁵¹ is hydrogen.

In one aspect of such an embodiment, R⁵¹ is not hydrogen.

- 25 In certain embodiments:

R⁵¹ is hydrogen or a C₁-C₄ alkyl group, wherein the alkyl group may be straight-chained or branched, or be or include a cyclic group, wherein the alkyl group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O)

30 group;

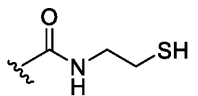
L⁵ is a C₂-C₃ straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{L5}; and

- each R^{L5} is independently selected from a methyl or a fluoromethyl group;
- 35 provided that the group R³ contains no more than 12 carbon atoms.

Typically in such embodiments, R⁵¹ is hydrogen.

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For example, R³ may have the formula:



As stated in accordance with the first aspect of the invention:

5 X¹ is N, C-H, C-Hal or C-R^{X1};

X² is N;

X³ is N, C-H, C-Hal or C-R^{X3}; and

X⁴ is N or C;

provided that no more than three of X¹, X², X³ and X⁴ are N; and

10 R^{X1} and R^{X3} are each independently selected from -OH, -SH, -NH₂, -SO₂H, -SO₃H, -SO₂NH₂, -NO₂, or a C₁-C₄ saturated or unsaturated hydrocarbyl group, wherein the hydrocarbyl group may be straight-chained or branched, or be or include a cyclic group, wherein the hydrocarbyl group may optionally be substituted with one or more halo and/or -NO₂ groups, wherein the hydrocarbyl group may optionally
15 include one or more heteroatoms each independently selected from N, O and S in its carbon skeleton, and wherein any -S- moiety in the hydrocarbyl group may optionally be substituted with one or two groups each independently selected from oxo (=O) and =NH to form a -SO-, -SO₂-, -S(=NH)- or -SO(=NH)- moiety.

20 Typically, when X⁴ is N, A⁶ is C.

Typically, when X⁴ is C, A⁶ is N.

Typically, no more than two of X¹, X², X³ and X⁴ are N.

25

In one embodiment of the first aspect of the invention:

X¹ is N, C-H, C-Hal or C-R^{X1};

X² is N;

X³ is N, C-H, C-Hal or C-R^{X3}; and

30 X⁴ is C;

provided that no more than two of X¹, X² and X³ are N.

More typically:

X¹ is N, C-H, C-Hal or C-R^{X1};

35 X² is N;

X³ is C-H, C-Hal or C-R^{X3}; and

- 50 -

X⁴ is C.

- In one embodiment of the first aspect of the invention, R^{X1} and R^{X3} are each independently selected from -OH, -SH, -NH₂, -SO₂H, -SO₃H, -SO₂NH₂ or a C₁-C₄ saturated or unsaturated hydrocarbyl group, wherein the hydrocarbyl group may be straight-chained or branched, or be or include a cyclic group, wherein the hydrocarbyl group may optionally be substituted with one or more halo groups, and wherein the hydrocarbyl group may optionally include one or two heteroatoms each independently selected from N and O in its carbon skeleton. More typically, R^{X1} and R^{X3} are each independently selected from a C₁-C₄ saturated hydrocarbyl group, wherein the hydrocarbyl group may be straight-chained or branched, or be or include a cyclic group, wherein the hydrocarbyl group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group, and wherein the hydrocarbyl group may optionally include a single heteroatom selected from N and O in its carbon skeleton. More typically still, R^{X1} and R^{X3} are each independently selected from a methyl, fluoromethyl, methoxy or fluoromethoxy group. Yet more typically, R^{X1} and R^{X3} are each independently selected from a methyl or fluoromethyl group.

In a further embodiment:

- X¹ is N, C-H or C-Hal;
X² is N;
X³ is N, C-H or C-Hal; and
X⁴ is N or C;
provided that no more than three of X¹, X², X³ and X⁴ are N. Typically in such an embodiment, no more than two of X¹, X², X³ and X⁴ are N.

Typically in such an embodiment:

- X¹ is N, C-H or C-Hal;
X² is N;
X³ is N, C-H or C-Hal; and
X⁴ is C;
provided that no more than two of X¹, X² and X³ are N.

More typically in such an embodiment:

- X¹ is N, C-H or C-Hal;
X² is N;
X³ is C-H or C-Hal; and
X⁴ is C.

Yet more typically:

- 5 X¹ is N or C-H;
 X² is N;
 X³ is C-H; and
 X⁴ is C.

In one embodiment:

- 10 X¹ is N;
 X² is N;
 X³ is C-H, C-Hal or C-R^{X3}; and
 X⁴ is C.

Typically in such an embodiment, X³ is C-H or C-Hal. More typically, X³ is C-H.

- 15 As stated in accordance with the first aspect of the invention:

- Q¹ is O, S, N, N-H, N-R^{Q1}, C-H, C-Hal, or C-R^{Q2};
 R^{Q1} is selected from a C₁-C₄ saturated or unsaturated hydrocarbyl group,
wherein the hydrocarbyl group may be straight-chained or branched, or be or include
a cyclic group, wherein the hydrocarbyl group may optionally be substituted with one
20 or more halo and/or -NO₂ groups, wherein the hydrocarbyl group may optionally
include one or more heteroatoms each independently selected from N, O and S in its
carbon skeleton, and wherein any -S- moiety in the hydrocarbyl group may optionally
be substituted with one or two groups each independently selected from oxo (=O) and
=NH to form a -SO-, -SO₂-, -S(=NH)- or -SO(=NH)- moiety, provided that the atom of
25 R^{Q1} that is directly attached to the nitrogen atom of N-R^{Q1} is a carbon atom; and
 R^{Q2} is selected from -OH, -SH, -NH₂, -SO₂H, -SO₃H, -SO₂NH₂, -NO₂, or a C₁-C₄
saturated or unsaturated hydrocarbyl group, wherein the hydrocarbyl group may be
straight-chained or branched, or be or include a cyclic group, wherein the hydrocarbyl
group may optionally be substituted with one or more halo and/or -NO₂ groups,
30 wherein the hydrocarbyl group may optionally include one or more heteroatoms each
independently selected from N, O and S in its carbon skeleton, and wherein any -S-
moiety in the hydrocarbyl group may optionally be substituted with one or two groups
each independently selected from oxo (=O) and =NH to form a -SO-, -SO₂-, -S(=NH)-
or -SO(=NH)- moiety.

35

In one embodiment of the first aspect of the invention, R^{Q1} and R^{Q2} are each
independently selected from a C₁-C₄ alkyl, C₃-C₄ cycloalkyl, C₁-C₄ fluoroalkyl, C₃-C₄
fluorocycloalkyl, cyclopropylmethyl, fluorocyclopropylmethyl or -CO-R^{Q3} group,

- 52 -

wherein R^{Q3} is selected from a C_1 - C_3 alkyl, C_1 - C_3 fluoroalkyl, cyclopropyl or fluorocyclopropyl group. More typically, R^{Q1} and R^{Q2} are each independently selected from a C_1 - C_4 alkyl, C_3 - C_4 cycloalkyl, C_1 - C_4 fluoroalkyl, C_3 - C_4 fluorocycloalkyl, cyclopropylmethyl or fluorocyclopropylmethyl group. More typically still, R^{Q1} and R^{Q2} are each independently selected from a C_1 - C_3 alkyl, C_1 - C_3 fluoroalkyl, cyclopropyl or fluorocyclopropyl group. Yet more typically, R^{Q1} and R^{Q2} are each independently selected from a methyl or fluoromethyl group.

Typically, Q^1 is O, S, N-H, N- R^{Q1} , C-H, C-Hal, or C- R^{Q2} . More typically, Q^1 is O, S, N-H or N- R^{Q1} . For example, Q^1 may be O, S, N-H or N- R^{Q1} , wherein R^{Q1} is selected from a C_1 - C_4 alkyl, C_3 - C_4 cycloalkyl, C_1 - C_4 fluoroalkyl, C_3 - C_4 fluorocycloalkyl, cyclopropylmethyl, fluorocyclopropylmethyl or -CO- R^{Q3} group, wherein R^{Q3} is selected from a C_1 - C_3 alkyl, C_1 - C_3 fluoroalkyl, cyclopropyl or fluorocyclopropyl group.

More typically still, Q^1 is S, N-H or N- R^{Q1} . Typically in such an embodiment, R^{Q1} is a methyl or fluoromethyl group.

In one embodiment, Q^1 is S.

In another embodiment, Q^1 is O.

In yet another embodiment, Q^1 is N-H or N- R^{Q1} , wherein R^{Q1} is a methyl or fluoromethyl group. Typically in such an embodiment, Q^1 is N-H.

As stated in accordance with the first aspect of the invention:

A^1 is N, C-H, C-Hal or C- R^{A1} ;

A^2 is N, C-H, C-Hal or C- R^{A2} ;

A^3 is N, C-H, C-Hal or C- R^{A3} ;

A^4 is N, C-H, C-Hal or C- R^{A4} ; and

A^5 is N or C;

provided that no more than three of A^1 , A^2 , A^3 , A^4 and A^5 are N; and

R^{A1} , R^{A2} , R^{A3} and R^{A4} are each independently selected from -OH, -SH, -NH₂, -SO₂H, -SO₃H, -SO₂NH₂, -NO₂, or a C_1 - C_4 saturated or unsaturated hydrocarbyl group, wherein the hydrocarbyl group may be straight-chained or branched, or be or include a cyclic group, wherein the hydrocarbyl group may optionally be substituted with one or more halo and/or -NO₂ groups, wherein the hydrocarbyl group may optionally include one or more heteroatoms each independently selected from N, O and S in its carbon skeleton, and wherein any -S- moiety in the hydrocarbyl group may optionally

- 53 -

be substituted with one or two groups each independently selected from oxo (=O) and =NH to form a -SO-, -SO₂-, -S(=NH)- or -SO(=NH)- moiety.

Typically, no more than two of A¹, A², A³, A⁴ and A⁵ are N. More typically, no more
 5 than one of A¹, A², A³, A⁴ and A⁵ is N.

Typically, when A⁵ is N, X⁴ is N, A⁶ is C and Q¹ is N, C-H, C-Hal, or C-R^{Q2}. More typically, when A⁵ is N, X⁴ is N, A⁶ is C and Q¹ is C-H, C-Hal, or C-R^{Q2}.

10 Typically, where Q¹ is O, S, N-H or N-R^{Q1}, A⁵ is C.

In one embodiment,

A¹ is N, C-H, C-Hal or C-R^{A1};
 A² is N, C-H, C-Hal or C-R^{A2};
 15 A³ is N, C-H, C-Hal or C-R^{A3};
 A⁴ is N, C-H, C-Hal or C-R^{A4}; and
 A⁵ is C;
 provided that no more than two of A¹, A², A³ and A⁴ are N.

20 Typically in such an embodiment, no more than one of A¹, A², A³ and A⁴ is N.
 Typically, where one of A¹, A², A³ and A⁴ is N, A² is N or A³ is N. More typically, A³ is N.

In a further embodiment,

A¹ is C-H C-Hal or C-R^{A1};
 25 A² is C-H, C-Hal or C-R^{A2};
 A³ is C-H, C-Hal or C-R^{A3};
 A⁴ is C-H, C-Hal or C-R^{A4}; and
 A⁵ is C.

30 Typically in the above embodiments, no more than two of A¹, A², A³ and A⁴ are C-R^{A1}, C-R^{A2}, C-R^{A3} or C-R^{A4}. More typically, no more than one of A¹, A², A³ and A⁴ is C-R^{A1}, C-R^{A2}, C-R^{A3} or C-R^{A4}.

In one embodiment, R^{A1}, R^{A2}, R^{A3} and R^{A4} are each independently selected from -OH,
 35 -SH, -NH₂, -SO₂H, -SO₃H, -SO₂NH₂ or a C₁-C₄ saturated or unsaturated hydrocarbyl group, wherein the hydrocarbyl group may be straight-chained or branched, or be or include a cyclic group, wherein the hydrocarbyl group may optionally be substituted with one or more halo groups, and wherein the hydrocarbyl group may optionally

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include one or two heteroatoms each independently selected from N and O in its carbon skeleton. More typically, R^{A1} , R^{A2} , R^{A3} and R^{A4} are each independently selected from a C_1 - C_4 saturated hydrocarbyl group, wherein the hydrocarbyl group may be straight-chained or branched, or be or include a cyclic group, wherein the hydrocarbyl group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group, and wherein the hydrocarbyl group may optionally include a single heteroatom selected from N and O in its carbon skeleton. More typically still, R^{A1} , R^{A2} , R^{A3} and R^{A4} are each independently selected from a methyl, fluoromethyl, methoxy or fluoromethoxy group. Yet more typically, R^{A1} , R^{A2} , R^{A3} and R^{A4} are each independently selected from a methyl or fluoromethyl group.

In another embodiment,

A^1 is N, C-H or C-Hal;
 A^2 is N, C-H or C-Hal;
15 A^3 is N, C-H or C-Hal;
 A^4 is N, C-H or C-Hal; and
 A^5 is C;
provided that no more than two of A^1 , A^2 , A^3 and A^4 are N.

20 Typically in such an embodiment, no more than one of A^1 , A^2 , A^3 and A^4 is N.
Typically, where one of A^1 , A^2 , A^3 and A^4 is N, A^2 is N or A^3 is N. More typically, A^3 is N.

In a further embodiment,

A^1 is C-H or C-Hal;
25 A^2 is C-H or C-Hal;
 A^3 is C-H or C-Hal;
 A^4 is C-H or C-Hal; and
 A^5 is C.

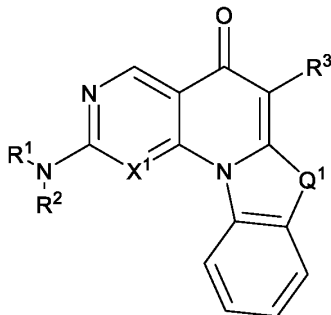
30 Most typically, A^1 is C-H, A^2 is C-H, A^3 is C-H, A^4 is C-H and A^5 is C.

As stated in accordance with the first aspect of the invention, A^6 is N or C. Typically, A^6 is N.

35 As stated in accordance with the first aspect of the invention, each Hal is independently selected from a fluoro, chloro, bromo or iodo group. Typically, each Hal is independently selected from a fluoro, chloro or bromo group.

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In one embodiment of the first aspect of the invention, the compound is a compound of Formula (V):

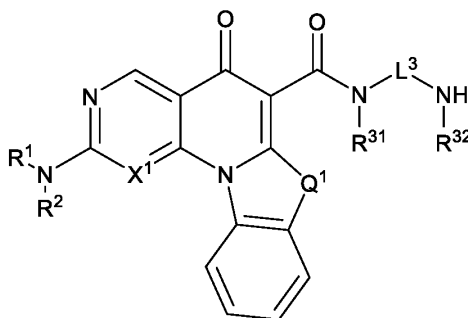


5

Formula (V)

wherein R¹, R², R³, X¹ and Q¹ are as defined in accordance with Formula (I).

In another embodiment of the first aspect of the invention, the compound is a compound of Formula (VI):

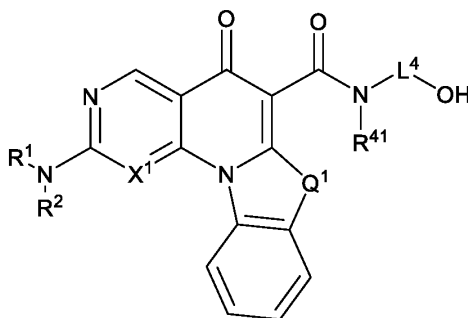


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Formula (VI)

wherein R¹, R², X¹, Q¹, L³, R³¹ and R³² are as defined in accordance with Formula (I).

In a further embodiment of the first aspect of the invention, the compound is a compound of Formula (VII):

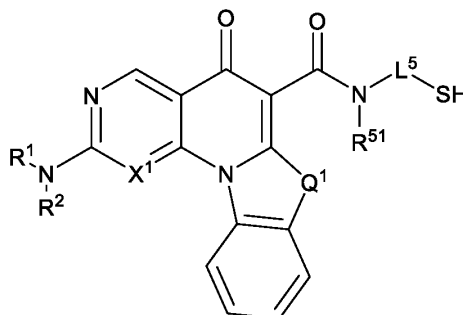


Formula (VII)

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wherein R^1 , R^2 , X^1 , Q^1 , L^4 and R^{41} are as defined in accordance with Formula (I).

In yet another embodiment of the first aspect of the invention, the compound is a compound of Formula (VIII):



Formula (VIII)

wherein R^1 , R^2 , X^1 , Q^1 , L^5 and R^{51} are as defined in accordance with Formula (I).

As will be understood, insofar as practical, embodiments directed to one substituent or moiety (such as a given R or X group) may be read in conjunction with embodiments directed to a different substituent or moiety.

For example, in a first exemplary embodiment, there is provided a compound of Formula (I) as defined above, wherein:

R^1 is a C_1 - C_8 saturated hydrocarbyl group, wherein the hydrocarbyl group may be straight-chained or branched, or be or include a single cyclic group, wherein the hydrocarbyl group may optionally be substituted with one or more fluoro groups and/or a single oxo ($=O$) group, wherein the hydrocarbyl group optionally includes one or two heteroatoms each independently selected from N and O in its carbon skeleton; and

R^2 is selected from hydrogen or a C_1 - C_3 alkyl or C_1 - C_3 fluoroalkyl group; or

R^1 and R^2 together with the nitrogen atom to which they are attached form a 4- to 7-membered monocyclic group or a 6- to 12-membered bicyclic group, wherein the monocyclic or the bicyclic group may optionally be substituted with one or more substituents each independently selected from a halo, oxo ($=O$), $-OH$, $-NH_2$ or a C_1 - C_6 saturated or unsaturated hydrocarbyl group, wherein the hydrocarbyl group may be straight-chained or branched, or be or include a cyclic group, wherein the hydrocarbyl group may optionally be substituted with one or more halo groups, and wherein the hydrocarbyl group may optionally include one or two heteroatoms each independently selected from N and O in its carbon skeleton;

R³ is a C₁-C₁₂ monovalent group, wherein the atom of R³ that is directly attached to the remainder of the compound of Formula (I) is a sp² hybridised carbon atom, and wherein the C₁-C₁₂ monovalent group comprises a primary or a secondary amine, wherein the nitrogen atom of the primary or secondary amine is not directly attached to a sp² hybridised carbon atom; or

R³ is a C₁-C₁₂ monovalent group, wherein the atom of R³ that is directly attached to the remainder of the compound of Formula (I) is a sp² hybridised carbon atom, and wherein the C₁-C₁₂ monovalent group comprises a -OH group, wherein the oxygen atom of the -OH group is not directly attached to a sp² hybridised carbon atom; or

R³ is a C₁-C₁₂ monovalent group, wherein the atom of R³ that is directly attached to the remainder of the compound of Formula (I) is a sp² hybridised carbon atom, and wherein the C₁-C₁₂ monovalent group comprises a -SH group, wherein the sulphur atom of the -SH group is not directly attached to a sp² hybridised carbon atom;

X¹ is N, C-H, C-Hal or C-R^{X1};

X² is N;

X³ is C-H, C-Hal or C-R^{X1};

X⁴ is C;

R^{X1} and R^{X3} are each independently selected from a C₁-C₄ saturated hydrocarbyl group, wherein the hydrocarbyl group may be straight-chained or branched, or be or include a cyclic group, wherein the hydrocarbyl group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group, and wherein the hydrocarbyl group may optionally include a single heteroatom selected from N and O in its carbon skeleton;

Q¹ is O, S, N-H or N-R^{Q1};

R^{Q1} is selected from a C₁-C₄ alkyl, C₃-C₄ cycloalkyl, C₁-C₄ fluoroalkyl, C₃-C₄ fluorocycloalkyl, cyclopropylmethyl, fluorocyclopropylmethyl or -CO-R^{Q3} group;

R^{Q3} is selected from a C₁-C₃ alkyl, C₁-C₃ fluoroalkyl, cyclopropyl or fluorocyclopropyl group;

A¹ is N, C-H, C-Hal or C-R^{A1};

A² is N, C-H, C-Hal or C-R^{A2};

A³ is N, C-H, C-Hal or C-R^{A3};

A⁴ is N, C-H, C-Hal or C-R^{A4};

A⁵ is C; and

R^{A1}, R^{A2}, R^{A3} and R^{A4} are each independently selected from a C₁-C₄ saturated hydrocarbyl group, wherein the hydrocarbyl group may be straight-chained or branched, or be or include a cyclic group, wherein the hydrocarbyl group may

optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group, and wherein the hydrocarbyl group may optionally include a single heteroatom selected from N and O in its carbon skeleton;

provided that no more than one of A¹, A², A³ and A⁴ is N; and

- 5 provided that no more than two of A¹, A², A³ and A⁴ are C-R^{A1}, C-R^{A2}, C-R^{A3} or C-R^{A4};

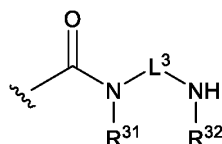
A⁶ is N; and

each Hal is independently selected from a fluoro, chloro or bromo group.

- 10 Typically in accordance with the first exemplary embodiment, the carbon atom of R³ that is directly attached to the remainder of the compound of Formula (I) is the carbon atom of an amide group.

More typically in accordance with the first exemplary embodiment:

- 15 (i) R³ has the formula:



wherein:

- R³¹ is hydrogen or a C₁-C₆ saturated hydrocarbyl group, wherein the saturated hydrocarbyl group may be straight-chained or branched, or be or include a cyclic group, wherein the saturated hydrocarbyl group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group, and wherein the saturated hydrocarbyl group may optionally include one or two heteroatoms each independently selected from N and O in its carbon skeleton, provided that the atom of the hydrocarbyl group of R³¹ that is directly attached to the nitrogen atom of N-R³¹ is a carbon atom;
- 20
25

- R³² is hydrogen or a C₁-C₆ saturated hydrocarbyl group, wherein the saturated hydrocarbyl group may be straight-chained or branched, or be or include a cyclic group, wherein the saturated hydrocarbyl group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group, and wherein the saturated hydrocarbyl group may optionally include one or two heteroatoms each independently selected from N and O in its carbon skeleton, provided that the atom of the hydrocarbyl group of R³² that is directly attached to the nitrogen atom of NH-R³² is a carbon atom that is not substituted with an oxo (=O) group;
- 30

- or R³¹ and R³² together form a C₂-C₆ straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups
- 35

and/or a single oxo (=O) group and/or one, two, three or four groups R^{33} , provided that the carbon atom of the alkylene group that is directly attached to the nitrogen atom of $NH-R^{32}$ is not substituted with an oxo (=O) group;

each R^{33} is independently selected from a methyl or a fluoromethyl group;

- 5 L^3 is a bond or a C_2 - C_5 straight-chained alkylene group or a $-CH_2CH_2-O-CH_2CH_2-$ or $-CH_2CH_2-NH-CH_2CH_2-$ group, wherein the alkylene, the $-CH_2CH_2-O-CH_2CH_2-$ or the $-CH_2CH_2-NH-CH_2CH_2-$ group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group and/or one, two, three or four groups R^{L3} , provided that the carbon atom of the alkylene or the
- 10 $-CH_2CH_2-O-CH_2CH_2-$ or the $-CH_2CH_2-NH-CH_2CH_2-$ group that is directly attached to the nitrogen atom of $NH-R^{32}$ is not substituted with an oxo (=O) group;

each R^{L3} is independently selected from a methyl or a fluoromethyl group, or any two R^{L3} may together with the atom or atoms to which they are attached form a 3- to 7-membered cycloalkylene group or a 4- to 7-membered saturated heterocyclic group, wherein the cycloalkylene group or the saturated heterocyclic group may

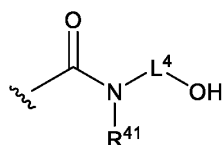
15 optionally be fluoro substituted;

or any R^{L3} and R^{31} , or any R^{L3} and R^{32} , or any R^{L3} and any R^{33} , together form a C_1 - C_4 straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group and/or

20 one, two, three or four groups R^{34} , provided that where any R^{L3} and R^{32} together form a C_1 - C_4 straight-chained alkylene group, the carbon atom of the alkylene group that is directly attached to the nitrogen atom of $NH-R^{32}$ is not substituted with an oxo (=O) group;

or any R^{L3} and any R^{33} together form a bond; and

- 25 each R^{34} is independently selected from a methyl or a fluoromethyl group; or
- (ii) R^3 has the formula:



wherein:

- R^{41} is hydrogen or a C_1 - C_6 saturated hydrocarbyl group, wherein the saturated
- 30 hydrocarbyl group may be straight-chained or branched, or be or include a cyclic group, wherein the saturated hydrocarbyl group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group, and wherein the saturated hydrocarbyl group may optionally include one or two heteroatoms each independently selected from N and O in its carbon skeleton, provided that the atom of the

- 60 -

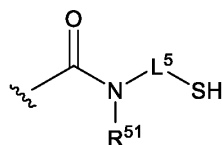
hydrocarbyl group of R^{41} that is directly attached to the nitrogen atom of $N-R^{41}$ is a carbon atom;

L^4 is a C_2 - C_5 straight-chained alkylene group or a $-CH_2CH_2-O-CH_2CH_2-$ or $-CH_2CH_2-NH-CH_2CH_2-$ group, wherein the alkylene, the $-CH_2CH_2-O-CH_2CH_2-$ or the $-CH_2CH_2-NH-CH_2CH_2-$ group may optionally be substituted with one or more fluoro groups and/or a single oxo ($=O$) group and/or one, two, three or four groups R^{L4} , provided that the carbon atom of the alkylene, the $-CH_2CH_2-O-CH_2CH_2-$ or the $-CH_2CH_2-NH-CH_2CH_2-$ group that is directly attached to the oxygen atom of the $-OH$ group is not substituted with an oxo ($=O$) group;

each R^{L4} is independently selected from a methyl or a fluoromethyl group, or any two R^{L4} may together with the atom or atoms to which they are attached form a 3- to 7-membered cycloalkylene group or a 4- to 7-membered saturated heterocyclic group, wherein the cycloalkylene group or the saturated heterocyclic group may optionally be fluoro substituted;

or any R^{L4} and R^{41} may together form a C_1 - C_4 straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or a single oxo ($=O$) group and/or one, two, three or four groups R^{44} ; and each R^{44} is independently selected from a methyl or a fluoromethyl group; or

(iii) R^3 has the formula:



wherein:

R^{51} is hydrogen or a C_1 - C_6 saturated hydrocarbyl group, wherein the saturated hydrocarbyl group may be straight-chained or branched, or be or include a cyclic group, wherein the saturated hydrocarbyl group may optionally be substituted with one or more fluoro groups and/or a single oxo ($=O$) group, and wherein the saturated hydrocarbyl group may optionally include one or two heteroatoms each independently selected from N and O in its carbon skeleton, provided that the atom of the hydrocarbyl group of R^{51} that is directly attached to the nitrogen atom of $N-R^{51}$ is a carbon atom;

L^5 is a C_2 - C_5 straight-chained alkylene group or a $-CH_2CH_2-O-CH_2CH_2-$ or $-CH_2CH_2-NH-CH_2CH_2-$ group, wherein the alkylene, the $-CH_2CH_2-O-CH_2CH_2-$ or the $-CH_2CH_2-NH-CH_2CH_2-$ group may optionally be substituted with one or more fluoro groups and/or a single oxo ($=O$) group and/or one, two, three or four groups R^{L5} , provided that the carbon atom of the alkylene or the $-CH_2CH_2-O-CH_2CH_2-$ or the

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-CH₂CH₂-NH-CH₂CH₂- group that is directly attached to the sulphur atom of the -SH group is not substituted with an oxo (=O) group;

each R^{L5} is independently selected from a methyl or a fluoromethyl group, or any two R^{L5} may together with the atom or atoms to which they are attached form a
 5 3- to 7-membered cycloalkylene group or a 4- to 7-membered saturated heterocyclic group, wherein the cycloalkylene group or the saturated heterocyclic group may optionally be fluoro substituted;

or any R^{L5} and R⁵¹ may together form a C₁-C₄ straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro
 10 groups and/or a single oxo (=O) group and/or one, two, three or four groups R⁵⁴; and each R⁵⁴ is independently selected from a methyl or a fluoromethyl group; provided that in each of options (i), (ii) and (iii) the group R³ contains no more than 12 carbon atoms.

15 Typically in accordance with the first exemplary embodiment, Q¹ is S or N-H.

In a second exemplary embodiment, there is provided a compound of Formula (VI) as defined above, wherein:

X¹ is N or C-H;
 20 Q¹ is O, S, N-H or N-R^{Q1};
 R^{Q1} is a methyl or fluoromethyl group;
 R¹ is selected from a methyl, ethyl, isopropyl or cyclopropyl group, any of which may optionally be fluoro substituted; or
 R¹ has the formula -L¹-R¹⁰, wherein L¹ is a C₁-C₂ alkylene or C₁-C₂
 25 fluoroalkylene group, and R¹⁰ is a 5- or 6-membered heteroaryl group; or
 R¹ is selected from a -(C(R¹⁰¹)₂)₂-X¹⁰-R¹⁰² or
 -(C(R¹⁰¹)₂)₂-X¹⁰-(C(R¹⁰¹)₂)₂-X¹¹-R¹⁰² group;
 X¹⁰ is selected from O or NR¹⁰³;
 X¹¹ is selected from O or NR¹⁰⁴;
 30 each R¹⁰¹ is hydrogen;
 R¹⁰² is selected from a methyl, ethyl, isopropyl or cyclopropyl group, any of which may optionally be fluoro substituted;
 R¹⁰³ is selected from hydrogen or a methyl or fluoromethyl group; and
 R¹⁰⁴ is selected from hydrogen or a methyl or fluoromethyl group; or
 35 a single R¹⁰¹ and R¹⁰³, or a single R¹⁰¹ and R¹⁰⁴, or R¹⁰³ and R¹⁰⁴ together form a -(CH₂)₂- group;
 provided that any -(C(R¹⁰¹)₂)₂-X¹⁰-R¹⁰² or -(C(R¹⁰¹)₂)₂-X¹⁰-(C(R¹⁰¹)₂)₂-X¹¹-R¹⁰² group contains no more than 8 carbon atoms;

R^2 is selected from hydrogen or a methyl or fluoromethyl group;

R^{31} is hydrogen or a C_1 - C_4 alkyl group, wherein the alkyl group may be straight-chained or branched, or be or include a cyclic group, wherein the alkyl group may optionally be substituted with one or more fluoro groups and/or a single oxo ($=O$) group;

R^{32} is hydrogen or a C_1 - C_4 alkyl group, wherein the alkyl group may be straight-chained or branched, or be or include a cyclic group, and wherein the alkyl group may optionally be substituted with one or more fluoro groups;

or R^{31} and R^{32} together form a C_2 - C_5 straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{33} ;

each R^{33} is independently selected from a methyl or a fluoromethyl group;

L^3 is a C_2 - C_5 straight-chained alkylene group or a $-CH_2CH_2-O-CH_2CH_2-$ or $-CH_2CH_2-NH-CH_2CH_2-$ group, wherein the alkylene, the $-CH_2CH_2-O-CH_2CH_2-$ or the $-CH_2CH_2-NH-CH_2CH_2-$ group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{L3} ; and

each R^{L3} is independently selected from a methyl or a fluoromethyl group;

or any two R^{L3} together with the atom or atoms to which they are attached form a 5- or 6-membered cycloalkylene group;

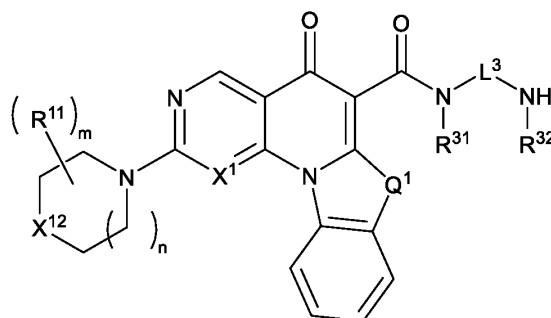
or any R^{L3} and R^{31} , or any R^{L3} and R^{32} , together form a C_2 - C_4 straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{34} ;

or any R^{L3} and any R^{33} together form a bond or a C_1 - C_2 straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{34} ; and

each R^{34} is independently selected from a methyl or a fluoromethyl group;

provided that the group $-CO-N(R^{31})-L^3-NHR^{32}$ contains no more than 12 carbon atoms.

In a third exemplary embodiment, there is provided a compound of Formula (VIa):



Formula (VIa)

wherein:

- X^1 is N or C-H;
- Q^1 is O, S, N-H or N- R^{Q1} ;
- 5 R^{Q1} is a methyl or fluoromethyl group;
- n is 1 or 2;
- m is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10;
- each R^{11} is independently selected from a fluoro, methyl or fluoromethyl group, provided that no more than four R^{11} are selected from a methyl or fluoromethyl group;
- 10 X^{12} is O or NR^{12} ;
- R^{12} is selected from hydrogen or a C_1 - C_4 alkyl, C_3 - C_4 cycloalkyl, C_1 - C_4 fluoroalkyl, C_3 - C_4 fluorocycloalkyl, cyclopropylmethyl, fluorocyclopropylmethyl or -CO- R^{120} group;
- R^{120} is selected from a C_1 - C_3 alkyl, C_1 - C_3 fluoroalkyl, cyclopropyl or
- 15 fluorocyclopropyl group;
- R^{31} is hydrogen or a C_1 - C_4 alkyl group, wherein the alkyl group may be straight-chained or branched, or be or include a cyclic group, wherein the alkyl group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group;
- 20 R^{32} is hydrogen or a C_1 - C_4 alkyl group, wherein the alkyl group may be straight-chained or branched, or be or include a cyclic group, and wherein the alkyl group may optionally be substituted with one or more fluoro groups;
- or R^{31} and R^{32} together form a C_2 - C_5 straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups
- 25 and/or one or two groups R^{33} ;
- each R^{33} is independently selected from a methyl or a fluoromethyl group;
- L^3 is a C_2 - C_5 straight-chained alkylene group or a -CH₂CH₂-O-CH₂CH₂- or -CH₂CH₂-NH-CH₂CH₂- group, wherein the alkylene, the -CH₂CH₂-O-CH₂CH₂- or the -CH₂CH₂-NH-CH₂CH₂- group may optionally be substituted with one or more fluoro
- 30 groups and/or one or two groups R^{L3} ; and
- each R^{L3} is independently selected from a methyl or a fluoromethyl group;
- or any two R^{L3} together with the atom or atoms to which they are attached form a 5- or 6-membered cycloalkylene group;
- or any R^{L3} and R^{31} , or any R^{L3} and R^{32} , together form a C_2 - C_4 straight-chained
- 35 alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{34} ;

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or any R^{L3} and any R^{33} together form a bond or a C_1 - C_2 straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{34} ; and

each R^{34} is independently selected from a methyl or a fluoromethyl group;

- 5 provided that the group $-CO-N(R^{31})-L^3-NHR^{32}$ contains no more than 12 carbon atoms.

In a fourth exemplary embodiment, there is provided a compound of Formula (VI) as defined above, wherein:

- 10 X^1 is N or C-H;

Q^1 is O, S, N-H or N- R^{Q1} ;

R^{Q1} is a methyl or fluoromethyl group;

- R^1 and R^2 together with the nitrogen atom to which they are attached form a pyrrolidinyl or piperidinyl group, wherein the pyrrolidinyl or piperidinyl group is substituted with an $-NR^{13}R^{14}$ group such that the nitrogen atom of the $-NR^{13}R^{14}$ group is not directly attached to a carbon atom that in turn is directly attached to the ring nitrogen atom of the pyrrolidinyl or piperidinyl group;

R^{13} and R^{14} are each independently selected from hydrogen or a methyl or fluoromethyl group;

- 20 R^{31} is hydrogen or a C_1 - C_4 alkyl group, wherein the alkyl group may be straight-chained or branched, or be or include a cyclic group, wherein the alkyl group may optionally be substituted with one or more fluoro groups and/or a single oxo ($=O$) group;

- R^{32} is hydrogen or a C_1 - C_4 alkyl group, wherein the alkyl group may be straight-chained or branched, or be or include a cyclic group, and wherein the alkyl group may optionally be substituted with one or more fluoro groups;

or R^{31} and R^{32} together form a C_2 - C_5 straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{33} ;

- 30 each R^{33} is independently selected from a methyl or a fluoromethyl group;

L^3 is a C_2 - C_5 straight-chained alkylene group or a $-CH_2CH_2-O-CH_2CH_2-$ or $-CH_2CH_2-NH-CH_2CH_2-$ group, wherein the alkylene, the $-CH_2CH_2-O-CH_2CH_2-$ or the $-CH_2CH_2-NH-CH_2CH_2-$ group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{L3} ; and

- 35 each R^{L3} is independently selected from a methyl or a fluoromethyl group; or any two R^{L3} together with the atom or atoms to which they are attached form a 5- or 6-membered cycloalkylene group;

or any R^{L3} and R^{31} , or any R^{L3} and R^{32} , together form a C_2 - C_4 straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{34} ;

5 or any R^{L3} and any R^{33} together form a bond or a C_1 - C_2 straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{34} ; and

each R^{34} is independently selected from a methyl or a fluoromethyl group;

provided that the group $-CO-N(R^{31})-L^3-NHR^{32}$ contains no more than 12 carbon atoms.

10

In a fifth exemplary embodiment, there is provided a compound of Formula (VI) as defined above, wherein:

X^1 is N or C-H;

Q^1 is O, S, N-H or N- R^{Q1} ;

15 R^{Q1} is a methyl or fluoromethyl group;

R^1 and R^2 together with the nitrogen atom to which they are attached form a 8- or 9-membered fused bicyclic group, such that the nitrogen atom of $-NR^1R^2$ is a ring atom of a first 5- or 6-membered ring of the fused bicyclic group, and the first 5- or 6-membered ring is fused to a second 5-membered ring of the fused bicyclic group, wherein the first 5- or 6-membered ring is not aromatic and is unsubstituted, and the second 5-membered ring is an unsubstituted 5-membered heteroaryl ring comprising a NH group;

20 R^{31} is hydrogen or a C_1 - C_4 alkyl group, wherein the alkyl group may be straight-chained or branched, or be or include a cyclic group, wherein the alkyl group may optionally be substituted with one or more fluoro groups and/or a single oxo ($=O$) group;

R^{32} is hydrogen or a C_1 - C_4 alkyl group, wherein the alkyl group may be straight-chained or branched, or be or include a cyclic group, and wherein the alkyl group may optionally be substituted with one or more fluoro groups;

30 or R^{31} and R^{32} together form a C_2 - C_5 straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{33} ;

each R^{33} is independently selected from a methyl or a fluoromethyl group;

35 L^3 is a C_2 - C_5 straight-chained alkylene group or a $-CH_2CH_2-O-CH_2CH_2-$ or $-CH_2CH_2-NH-CH_2CH_2-$ group, wherein the alkylene, the $-CH_2CH_2-O-CH_2CH_2-$ or the $-CH_2CH_2-NH-CH_2CH_2-$ group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{L3} ; and

each R^{L3} is independently selected from a methyl or a fluoromethyl group;

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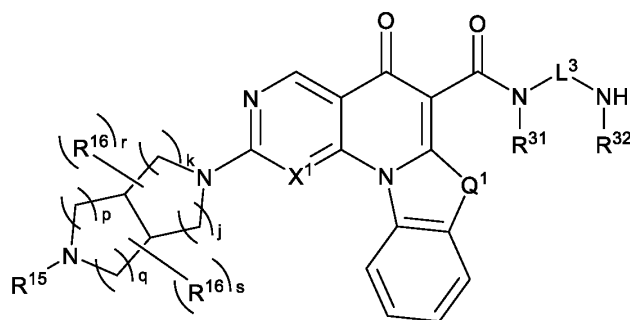
or any two R^{L3} together with the atom or atoms to which they are attached form a 5- or 6-membered cycloalkylene group;

or any R^{L3} and R^{31} , or any R^{L3} and R^{32} , together form a C_2 - C_4 straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or
5 more fluoro groups and/or one or two groups R^{34} ;

or any R^{L3} and any R^{33} together form a bond or a C_1 - C_2 straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{34} ; and

each R^{34} is independently selected from a methyl or a fluoromethyl group;
10 provided that the group $-CO-N(R^{31})-L^3-NHR^{32}$ contains no more than 12 carbon atoms.

In a sixth exemplary embodiment, there is provided a compound of Formula (VIb):



Formula (VIb)

wherein:

X^1 is N or C-H;

Q^1 is O, S, N-H or N- R^{Q1} ;

R^{Q1} is a methyl or fluoromethyl group;

20 j is 0, 1, 2 or 3;

k is 0, 1, 2 or 3;

p is 0, 1, 2 or 3; and

q is 0, 1, 2 or 3;

provided that:

25 $j + k = 2$ or 3;

$p + q = 2$ or 3;

when $j = 0$, q is 1, 2 or 3;

when $k = 0$, p is 1, 2 or 3;

when $p = 0$, k is 1, 2 or 3; and

30 when $q = 0$, j is 1, 2 or 3;

and wherein:

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r is 0, 1 or 2;

s is 0, 1 or 2;

R¹⁵ is hydrogen or a C₁-C₄ alkyl, C₃-C₄ cycloalkyl, C₁-C₄ fluoroalkyl, C₃-C₄ fluorocycloalkyl, cyclopropylmethyl, fluorocyclopropylmethyl or -CO-R¹⁵⁰ group;

5 R¹⁵⁰ is selected from a C₁-C₃ alkyl, C₁-C₃ fluoroalkyl, cyclopropyl or fluorocyclopropyl group;

each R¹⁶ is independently selected from a methyl or fluoromethyl group;

10 R³¹ is hydrogen or a C₁-C₄ alkyl group, wherein the alkyl group may be straight-chained or branched, or be or include a cyclic group, wherein the alkyl group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group;

R³² is hydrogen or a C₁-C₄ alkyl group, wherein the alkyl group may be straight-chained or branched, or be or include a cyclic group, and wherein the alkyl group may optionally be substituted with one or more fluoro groups;

15 or R³¹ and R³² together form a C₂-C₅ straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R³³;

each R³³ is independently selected from a methyl or a fluoromethyl group;

20 L³ is a C₂-C₅ straight-chained alkylene group or a -CH₂CH₂-O-CH₂CH₂- or -CH₂CH₂-NH-CH₂CH₂- group, wherein the alkylene, the -CH₂CH₂-O-CH₂CH₂- or the -CH₂CH₂-NH-CH₂CH₂- group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{L3}; and

each R^{L3} is independently selected from a methyl or a fluoromethyl group;

25 or any two R^{L3} together with the atom or atoms to which they are attached form a 5- or 6-membered cycloalkylene group;

or any R^{L3} and R³¹, or any R^{L3} and R³², together form a C₂-C₄ straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R³⁴;

30 or any R^{L3} and any R³³ together form a bond or a C₁-C₂ straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R³⁴; and

each R³⁴ is independently selected from a methyl or a fluoromethyl group; provided that the group -CO-N(R³¹)-L³-NHR³² contains no more than 12 carbon atoms.

35

Typically in accordance with the sixth exemplary embodiment:

j is 1;

k is 1;

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p is 1 or 2;

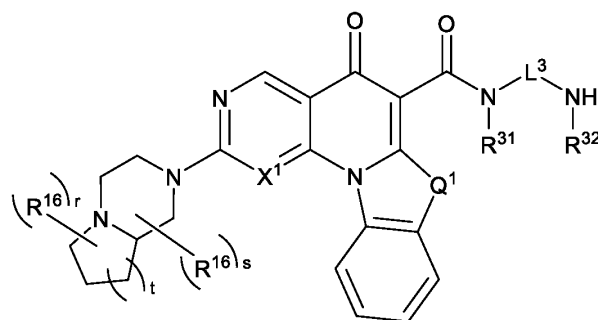
q is 1 or 2;

r is 0; and

s is 0.

5

In a seventh exemplary embodiment, there is provided a compound of Formula (VIc):



Formula (VIc)

wherein:

10 X¹ is N or C-H;

Q¹ is O, S, N-H or N-R^{Q1};

R^{Q1} is a methyl or fluoromethyl group;

r is 0, 1 or 2;

s is 0, 1 or 2;

15 t is 1 or 2;

each R¹⁶ is independently selected from a methyl or fluoromethyl group;

R³¹ is hydrogen or a C₁-C₄ alkyl group, wherein the alkyl group may be straight-chained or branched, or be or include a cyclic group, wherein the alkyl group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group;

R³² is hydrogen or a C₁-C₄ alkyl group, wherein the alkyl group may be straight-chained or branched, or be or include a cyclic group, and wherein the alkyl group may optionally be substituted with one or more fluoro groups;

or R³¹ and R³² together form a C₂-C₅ straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R³³;

each R³³ is independently selected from a methyl or a fluoromethyl group;

L³ is a C₂-C₅ straight-chained alkylene group or a -CH₂CH₂-O-CH₂CH₂- or -CH₂CH₂-NH-CH₂CH₂- group, wherein the alkylene, the -CH₂CH₂-O-CH₂CH₂- or the -CH₂CH₂-NH-CH₂CH₂- group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{L3}; and

30

each R^{L3} is independently selected from a methyl or a fluoromethyl group;

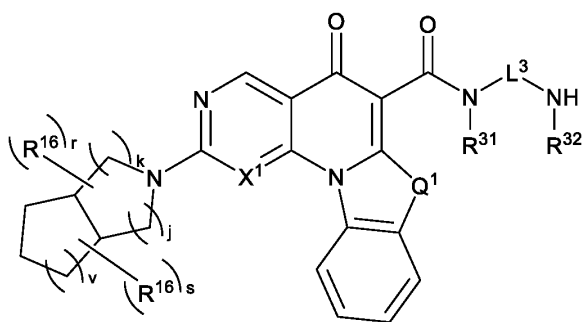
or any two R^{L3} together with the atom or atoms to which they are attached form a 5- or 6-membered cycloalkylene group;

or any R^{L3} and R³¹, or any R^{L3} and R³², together form a C₂-C₄ straight-chained
5 alkylene group, wherein the alkylene group may optionally be substituted with one or
more fluoro groups and/or one or two groups R³⁴;

or any R^{L3} and any R³³ together form a bond or a C₁-C₂ straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R³⁴; and

10 each R³⁴ is independently selected from a methyl or a fluoromethyl group;
provided that the group -CO-N(R³¹)-L³-NHR³² contains no more than 12 carbon
atoms.

In an eighth exemplary embodiment, there is provided a compound of Formula (VIId):



Formula (VId)

wherein:

X¹ is N or C-H;

Q¹ is O, S, N-H or N-R^{Q1};

20 R^{Q1} is a methyl or fluoromethyl group;

j is 0, 1, 2 or 3; and

k is 0, 1, 2 or 3;

provided that $j + k = 2$ or 3 ;

and wherein:

25 v is 1 or 2;

r is 0, 1 or 2;

s is 0, 1 or 2;

each R¹⁶ is independently selected from a methyl or fluoromethyl group;

R³¹ is hydrogen or a C₁-C₄ alkyl group, wherein the alkyl group may be
30 straight-chained or branched, or be or include a cyclic group, wherein the alkyl group

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may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group;

R^{32} is hydrogen or a C_1 - C_4 alkyl group, wherein the alkyl group may be straight-chained or branched, or be or include a cyclic group, and wherein the alkyl group may optionally be substituted with one or more fluoro groups;

or R^{31} and R^{32} together form a C_2 - C_5 straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{33} ;

each R^{33} is independently selected from a methyl or a fluoromethyl group;

L^3 is a C_2 - C_5 straight-chained alkylene group or a $-CH_2CH_2-O-CH_2CH_2-$ or $-CH_2CH_2-NH-CH_2CH_2-$ group, wherein the alkylene, the $-CH_2CH_2-O-CH_2CH_2-$ or the $-CH_2CH_2-NH-CH_2CH_2-$ group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{L3} ; and

each R^{L3} is independently selected from a methyl or a fluoromethyl group;

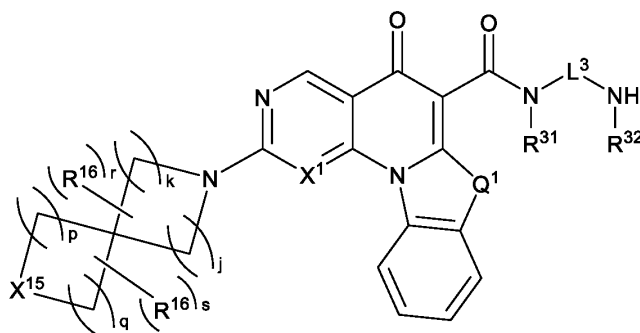
or any two R^{L3} together with the atom or atoms to which they are attached form a 5- or 6-membered cycloalkylene group;

or any R^{L3} and R^{31} , or any R^{L3} and R^{32} , together form a C_2 - C_4 straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{34} ;

or any R^{L3} and any R^{33} together form a bond or a C_1 - C_2 straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{34} ; and

each R^{34} is independently selected from a methyl or a fluoromethyl group; provided that the group $-CO-N(R^{31})-L^3-NHR^{32}$ contains no more than 12 carbon atoms.

In a ninth exemplary embodiment, there is provided a compound of Formula (VIe):



Formula (VIe)

wherein:

X^1 is N or C-H;

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Q^1 is O, S, N-H or N- R^{Q1} ;

R^{Q1} is a methyl or fluoromethyl group;

X^{15} is O or NR^{15} ;

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

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

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

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

provided that:

j + k = 3 or 4;

10 p + q = 3 or 4;

when j = 0, q is 1, 2, 3 or 4 and p is 1, 2, 3 or 4;

when k = 0, q is 1, 2, 3 or 4 and p is 1, 2, 3 or 4;

when p = 0, k is 1, 2, 3 or 4 and j is 1, 2, 3 or 4; and

when q = 0, k is 1, 2, 3 or 4 and j is 1, 2, 3 or 4;

15 and wherein:

r is 0, 1 or 2;

s is 0, 1 or 2;

R^{15} is hydrogen or a C_1 - C_4 alkyl, C_3 - C_4 cycloalkyl, C_1 - C_4 fluoroalkyl, C_3 - C_4 fluorocycloalkyl, cyclopropylmethyl, fluorocyclopropylmethyl or $-CO-R^{150}$ group;

20 R^{150} is selected from a C_1 - C_3 alkyl, C_1 - C_3 fluoroalkyl, cyclopropyl or fluorocyclopropyl group;

each R^{16} is independently selected from a methyl or fluoromethyl group;

R^{31} is hydrogen or a C_1 - C_4 alkyl group, wherein the alkyl group may be straight-chained or branched, or be or include a cyclic group, wherein the alkyl group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group;

R^{32} is hydrogen or a C_1 - C_4 alkyl group, wherein the alkyl group may be straight-chained or branched, or be or include a cyclic group, and wherein the alkyl group may optionally be substituted with one or more fluoro groups;

30 or R^{31} and R^{32} together form a C_2 - C_5 straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{33} ;

each R^{33} is independently selected from a methyl or a fluoromethyl group;

35 L^3 is a C_2 - C_5 straight-chained alkylene group or a $-CH_2CH_2-O-CH_2CH_2-$ or $-CH_2CH_2-NH-CH_2CH_2-$ group, wherein the alkylene, the $-CH_2CH_2-O-CH_2CH_2-$ or the $-CH_2CH_2-NH-CH_2CH_2-$ group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{L3} ; and

each R^{L3} is independently selected from a methyl or a fluoromethyl group;

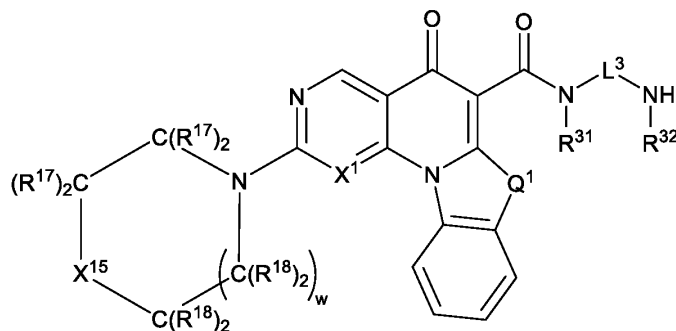
or any two R^{L3} together with the atom or atoms to which they are attached form a 5- or 6-membered cycloalkylene group;

or any R^{L3} and R³¹, or any R^{L3} and R³², together form a C₂-C₄ straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or 5 more fluoro groups and/or one or two groups R³⁴;

or any R^{L3} and any R³³ together form a bond or a C₁-C₂ straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R³⁴; and

each R^{34} is independently selected from a methyl or a fluoromethyl group;
10 provided that the group $-\text{CO}-\text{N}(\text{R}^{31})-\text{L}^3-\text{NHR}^{32}$ contains no more than 12 carbon atoms.

In a tenth exemplary embodiment, there is provided a compound of Formula (VI_f):



Formula (VI f)

wherein:

X¹ is N or C-H;

Q¹ is O, S, N-H or N-R^{Q1};

R^{Q1} is a methyl or fluoromethyl group;

20 w is 1 or 2;

X^{15} is 0 or NR^{15} ;

R¹⁵ is hydrogen or a C₁-C₄ alkyl, C₃-C₄ cycloalkyl, C₁-C₄ fluoroalkyl, C₃-C₄ fluorocycloalkyl, cyclopropylmethyl, fluorocyclopropylmethyl or -CO-R¹⁵⁰ group;

R¹⁵⁰ is selected from a C₁-C₃ alkyl, C₁-C₃ fluoroalkyl, cyclopropyl or

25 fluorocyclopropyl group;

one R¹⁷ and one R¹⁸ together form a -CH₂- or -CH₂CH₂- group;

each remaining R¹⁷ and R¹⁸ is hydrogen;

R³¹ is hydrogen or a C₁-C₄ alkyl group, wherein the alkyl group may be straight-chained or branched, or be or include a cyclic group, wherein the alkyl group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group;

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R³² is hydrogen or a C₁-C₄ alkyl group, wherein the alkyl group may be straight-chained or branched, or be or include a cyclic group, and wherein the alkyl group may optionally be substituted with one or more fluoro groups;

5 or R³¹ and R³² together form a C₂-C₅ straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R³³;

each R³³ is independently selected from a methyl or a fluoromethyl group;

10 L³ is a C₂-C₅ straight-chained alkylene group or a -CH₂CH₂-O-CH₂CH₂- or -CH₂CH₂-NH-CH₂CH₂- group, wherein the alkylene, the -CH₂CH₂-O-CH₂CH₂- or the -CH₂CH₂-NH-CH₂CH₂- group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{L3}; and

each R^{L3} is independently selected from a methyl or a fluoromethyl group;

or any two R^{L3} together with the atom or atoms to which they are attached form a 5- or 6-membered cycloalkylene group;

15 or any R^{L3} and R³¹, or any R^{L3} and R³², together form a C₂-C₄ straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R³⁴;

or any R^{L3} and any R³³ together form a bond or a C₁-C₂ straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or 20 more fluoro groups and/or one or two groups R³⁴; and

each R³⁴ is independently selected from a methyl or a fluoromethyl group; provided that the group -CO-N(R³¹)-L³-NHR³² contains no more than 12 carbon atoms.

Typically in accordance with any of the second to the tenth exemplary embodiments, 25 Q¹ is S or N-H.

In one aspect of any of the second to the tenth exemplary embodiments:

30 R³¹ is hydrogen or a C₁-C₄ alkyl group, wherein the alkyl group may be straight-chained or branched, or be or include a cyclic group, wherein the alkyl group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group;

R³² is hydrogen or a C₁-C₄ alkyl group, wherein the alkyl group may be straight-chained or branched, or be or include a cyclic group, and wherein the alkyl group may optionally be substituted with one or more fluoro groups;

35 L³ is a C₂-C₃ straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{L3}; and

each R^{L3} is independently selected from a methyl or a fluoromethyl group;

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provided that the group R^3 contains no more than 12 carbon atoms.

Typically in such an aspect, R^{31} is hydrogen.

- 5 For example, there may be provided a compound of Formula (VIb) of the sixth exemplary embodiment wherein:

Q^1 is S or N-H;

R^{31} is hydrogen;

- R^{32} is hydrogen or a C_1 - C_4 alkyl group, wherein the alkyl group may be
10 straight-chained or branched, or be or include a cyclic group, and wherein the alkyl group may optionally be substituted with one or more fluoro groups;
 L^3 is a C_2 - C_3 straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{L3} ; and
15 each R^{L3} is independently selected from a methyl or a fluoromethyl group.

In another aspect of any of the second to the tenth exemplary embodiments:

- R^{31} is hydrogen or a C_1 - C_4 alkyl group, wherein the alkyl group may be straight-chained or branched, or be or include a cyclic group, wherein the alkyl group
20 may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group;

- L^3 is a C_2 - C_5 straight-chained alkylene group or a $-CH_2CH_2-NH-CH_2CH_2-$ group, wherein the alkylene or the $-CH_2CH_2-NH-CH_2CH_2-$ group is substituted with one or two groups R^{L3} , and wherein the alkylene or the $-CH_2CH_2-NH-CH_2CH_2-$ group may
25 optionally be further substituted with one or more fluoro groups;

one R^{L3} and R^{32} together form a C_2 - C_4 straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{34} ;

- the second R^{L3} , if present, is selected from a methyl or a fluoromethyl group;
30 and
each R^{34} is independently selected from a methyl or a fluoromethyl group;
provided that the group R^3 contains no more than 12 carbon atoms.

Typically in such an aspect, R^{31} is hydrogen.

- 35 For example, there may be provided a compound of Formula (VIb) of the sixth exemplary embodiment wherein:

Q^1 is S or N-H;

R³¹ is hydrogen;

L³ is a C₂-C₅ straight-chained alkylene group or a -CH₂CH₂-NH-CH₂CH₂- group, wherein the alkylene or the -CH₂CH₂-NH-CH₂CH₂- group is substituted with one or two groups R^{L3}, and wherein the alkylene or the -CH₂CH₂-NH-CH₂CH₂- group may

5 optionally be further substituted with one or more fluoro groups;

one R^{L3} and R³² together form a C₂-C₄ straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R³⁴;

the second R^{L3}, if present, is selected from a methyl or a fluoromethyl group;

10 and

each R³⁴ is independently selected from a methyl or a fluoromethyl group; provided that the group R³ contains no more than 12 carbon atoms.

Typically in such an example:

15 L³ is a C₂-C₅ straight-chained alkylene group, wherein the alkylene group is substituted with one or two groups R^{L3}, and wherein the alkylene group may optionally be further substituted with one or more fluoro groups; and

the one R^{L3} and R³² together with the atoms of the L³-NH group to which they are attached form a pyrrolidinyl or piperidinyl group.

20

In yet another aspect of any of the second to the tenth exemplary embodiments:

R³¹ is hydrogen or a C₁-C₄ alkyl group, wherein the alkyl group may be straight-chained or branched, or be or include a cyclic group, wherein the alkyl group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group;

25

R³² is hydrogen or a C₁-C₄ alkyl group, wherein the alkyl group may be straight-chained or branched, or be or include a cyclic group, and wherein the alkyl group may optionally be substituted with one or more fluoro groups;

L³ is a C₂-C₄ straight-chained alkylene group, wherein the alkylene group is substituted with two groups R^{L3}, and wherein the alkylene group may optionally be substituted with one or more fluoro groups; and

30

the two groups R^{L3} together with the atom or atoms to which they are attached form a 5- or 6-membered cycloalkylene group;

provided that the group R³ contains no more than 12 carbon atoms.

35

Typically in such an aspect, R³¹ is hydrogen.

For example, there may be provided a compound of Formula (VIb) of the sixth exemplary embodiment wherein:

Q^1 is S or N-H;

R^{31} is hydrogen;

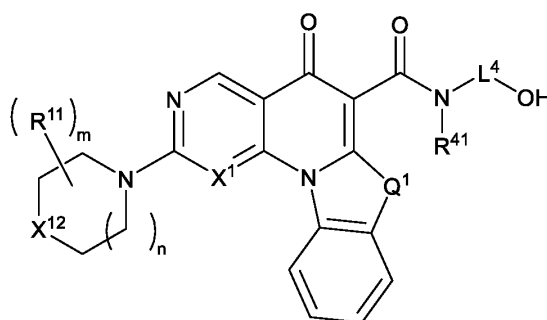
- 5 R^{32} is hydrogen or a C_1 - C_4 alkyl group, wherein the alkyl group may be straight-chained or branched, or be or include a cyclic group, and wherein the alkyl group may optionally be substituted with one or more fluoro groups;

- L^3 is a C_2 - C_4 straight-chained alkylene group, wherein the alkylene group is substituted with two groups R^{L3} , and wherein the alkylene group may optionally be
10 substituted with one or more fluoro groups; and

the two groups R^{L3} together with the atom or atoms to which they are attached form a 5- or 6-membered cycloalkylene group;

provided that the group R^3 contains no more than 12 carbon atoms.

- 15 In an eleventh exemplary embodiment, there is provided a compound of Formula (VIIa):



Formula (VIIa)

wherein:

- 20 X^1 is N or C-H;
 Q^1 is O, S, N-H or N- R^{Q1} ;
 R^{Q1} is a methyl or fluoromethyl group;
 n is 1 or 2;
 m is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10;
 25 each R^{11} is independently selected from a fluoro, methyl or fluoromethyl group, provided that no more than four R^{11} are selected from a methyl or fluoromethyl group;
 X^{12} is O or NR^{12} ;
 R^{12} is selected from hydrogen or a C_1 - C_4 alkyl, C_3 - C_4 cycloalkyl, C_1 - C_4 fluoroalkyl, C_3 - C_4 fluorocycloalkyl, cyclopropylmethyl, fluorocyclopropylmethyl or
 30 $-CO-R^{120}$ group;

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R¹²⁰ is selected from a C₁-C₃ alkyl, C₁-C₃ fluoroalkyl, cyclopropyl or fluorocyclopropyl group;

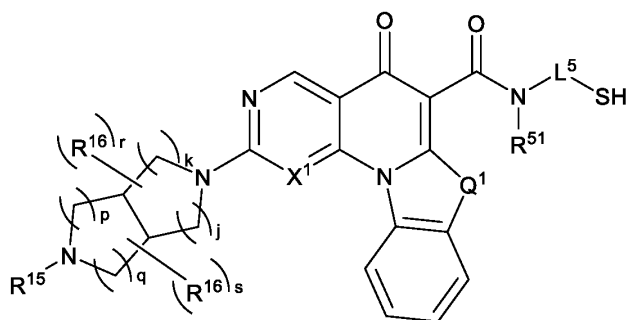
R⁴¹ is hydrogen or a C₁-C₄ alkyl group, wherein the alkyl group may be straight-chained or branched, or be or include a cyclic group, wherein the alkyl group
5 may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group;

L⁴ is a C₂-C₅ straight-chained alkylene group or a -CH₂CH₂-O-CH₂CH₂- or -CH₂CH₂-NH-CH₂CH₂- group, wherein the alkylene, the -CH₂CH₂-O-CH₂CH₂- or the -CH₂CH₂-NH-CH₂CH₂- group may optionally be substituted with one or more fluoro
10 groups and/or one or two groups R^{L4};

each R^{L4} is independently selected from a methyl or a fluoromethyl group, or any two R^{L4} together with the atom or atoms to which they are attached form a 5- or 6-membered cycloalkylene group, or any R^{L4} and R⁴¹ may together form a C₂-C₄ straight-chained alkylene group, wherein the alkylene group may optionally be
15 substituted with one or more fluoro groups and/or one or two groups R⁴⁴; and

each R⁴⁴ is independently selected from a methyl or a fluoromethyl group;
provided that the group -CO-N(R⁴¹)-L⁴-OH contains no more than 12 carbon atoms.

20 In a twelfth exemplary embodiment, there is provided a compound of Formula (VIIIa):



Formula (VIIIa)

wherein:

- X¹ is N or C-H;
25 Q¹ is O, S, N-H or N-R^{Q1};
R^{Q1} is a methyl or fluoromethyl group;
j is 0, 1, 2 or 3;
k is 0, 1, 2 or 3;
p is 0, 1, 2 or 3; and
30 q is 0, 1, 2 or 3;

provided that:

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$j + k = 2$ or 3 ;
 $p + q = 2$ or 3 ;
 when $j = 0$, q is $1, 2$ or 3 ;
 when $k = 0$, p is $1, 2$ or 3 ;
 when $p = 0$, k is $1, 2$ or 3 ; and
 when $q = 0$, j is $1, 2$ or 3 ;

and wherein:

r is $0, 1$ or 2 ;
 s is $0, 1$ or 2 ;

- R^{15} is hydrogen or a C_1 - C_4 alkyl, C_3 - C_4 cycloalkyl, C_1 - C_4 fluoroalkyl, C_3 - C_4 fluorocycloalkyl, cyclopropylmethyl, fluorocyclopropylmethyl or $-CO-R^{150}$ group;
 R^{150} is selected from a C_1 - C_3 alkyl, C_1 - C_3 fluoroalkyl, cyclopropyl or fluorocyclopropyl group;
 each R^{16} is independently selected from a methyl or fluoromethyl group;
- R^{51} is hydrogen or a C_1 - C_4 alkyl group, wherein the alkyl group may be straight-chained or branched, or be or include a cyclic group, wherein the alkyl group may optionally be substituted with one or more fluoro groups and/or a single oxo ($=O$) group;
- L^5 is a C_2 - C_5 straight-chained alkylene group or a $-CH_2CH_2-O-CH_2CH_2-$ or $-CH_2CH_2-NH-CH_2CH_2-$ group, wherein the alkylene, the $-CH_2CH_2-O-CH_2CH_2-$ or the $-CH_2CH_2-NH-CH_2CH_2-$ group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{L5} ;
 each R^{L5} is independently selected from a methyl or a fluoromethyl group, or any two R^{L5} together with the atom or atoms to which they are attached form a 5- or 6-membered cycloalkylene group, or any R^{L5} and R^{51} may together form a C_2 - C_4 straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{54} ; and
 each R^{54} is independently selected from a methyl or a fluoromethyl group;
 provided that the group $-CO-N(R^{51})-L^5-SH$ contains no more than 12 carbon atoms.

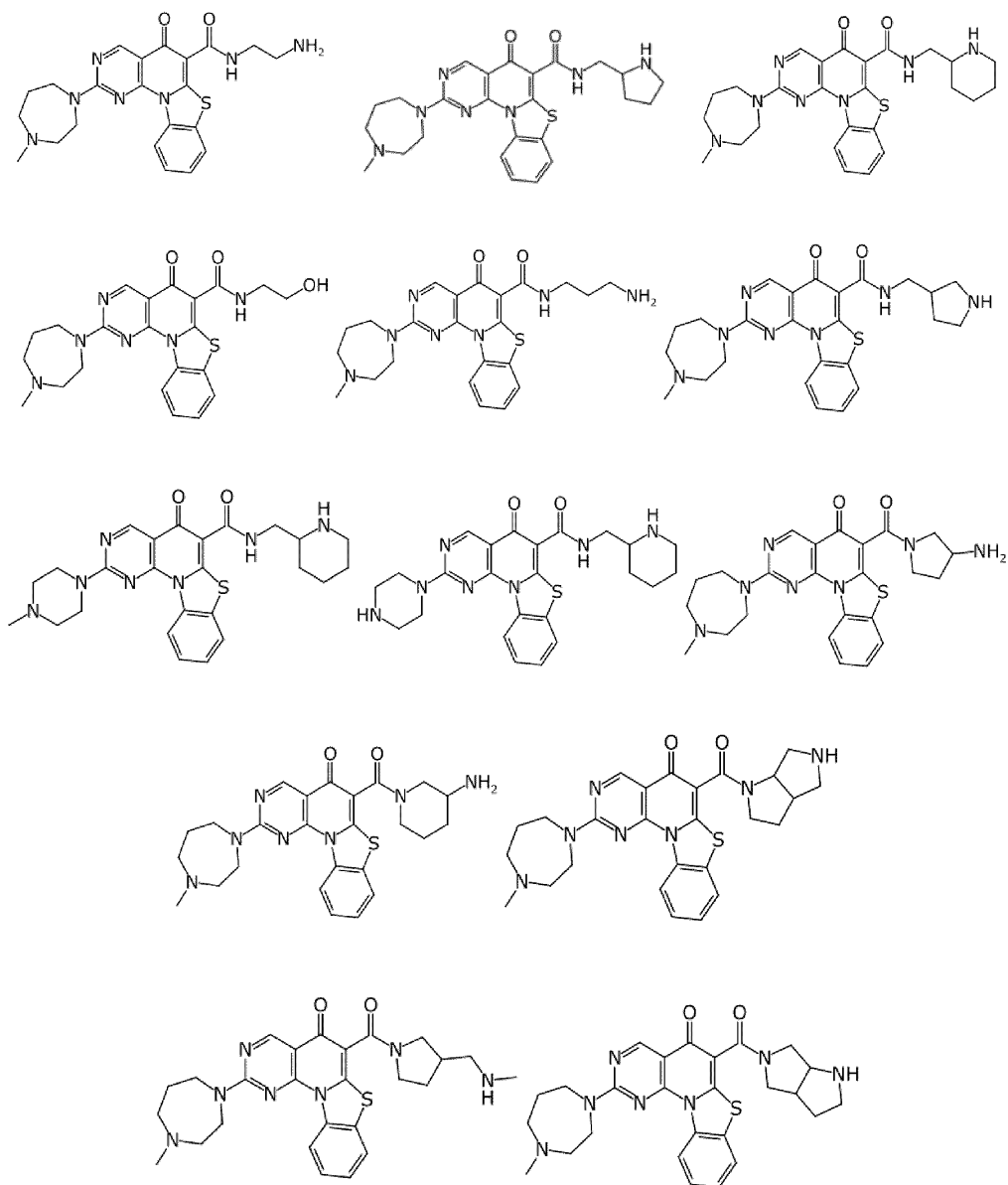
Typically in accordance with the eleventh or twelfth exemplary embodiments, Q^1 is S or N-H.

- In one aspect of any of the above embodiments, the compound of the first aspect of the invention has a molecular weight of from 300 to 1000 Da. Typically, the compound of the first aspect of the invention has a molecular weight of from 350 to 750 Da.

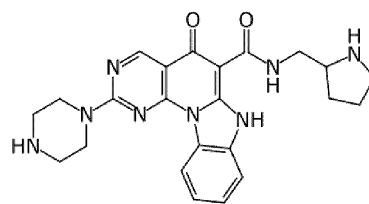
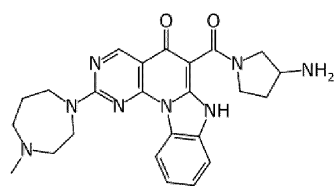
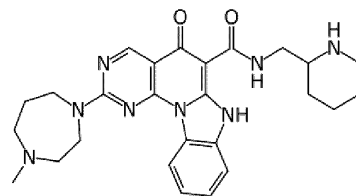
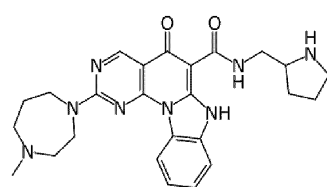
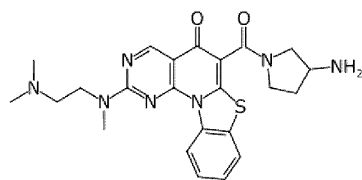
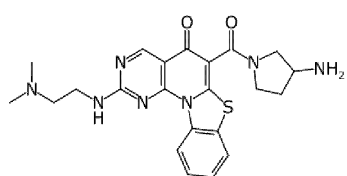
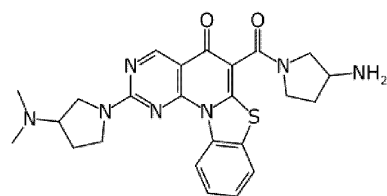
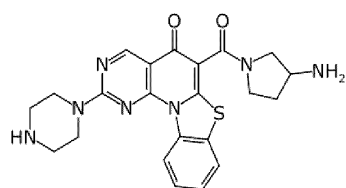
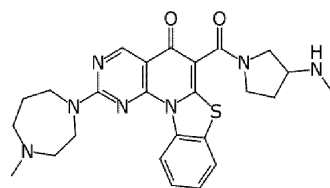
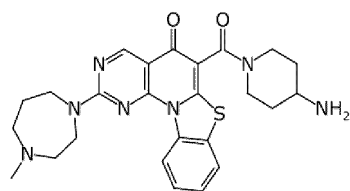
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More typically, the compound of the first aspect of the invention has a molecular weight of from 400 to 600 Da.

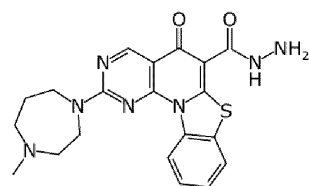
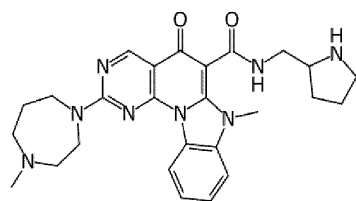
A second aspect of the invention provides a compound selected from the group
5 consisting of:



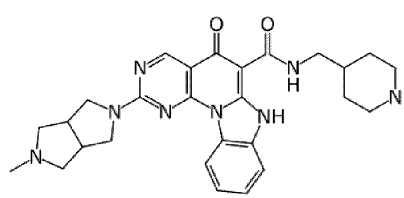
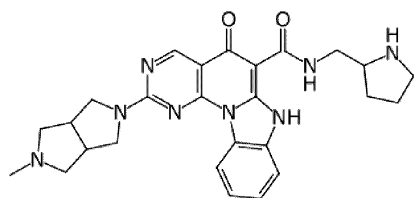
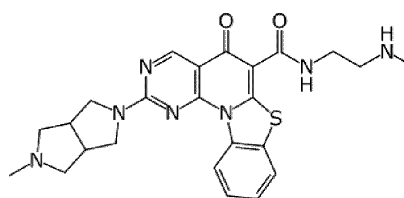
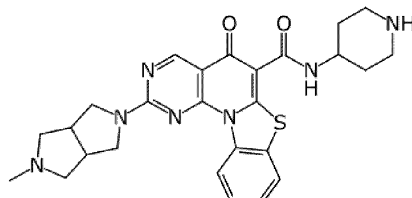
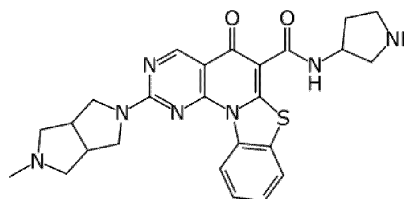
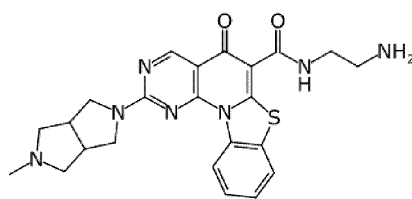
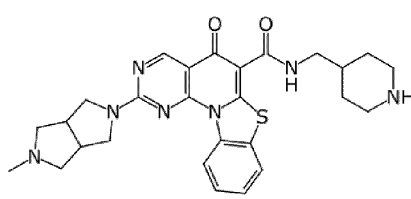
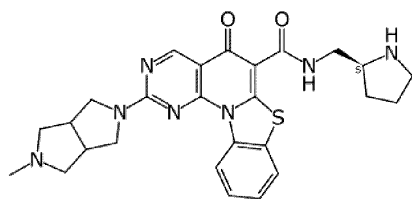
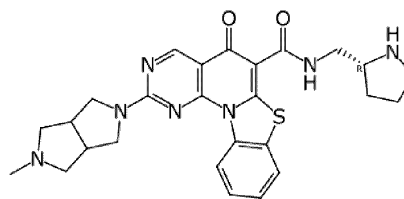
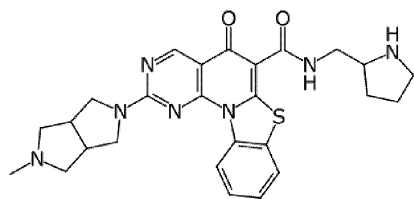
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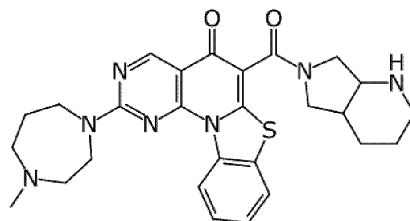
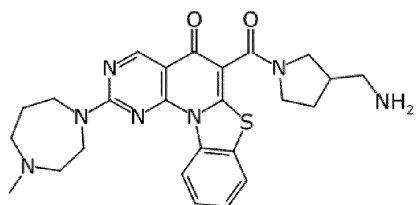
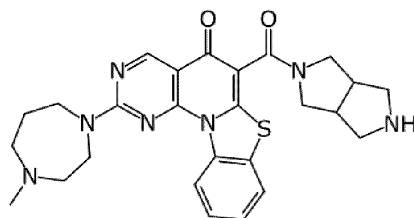
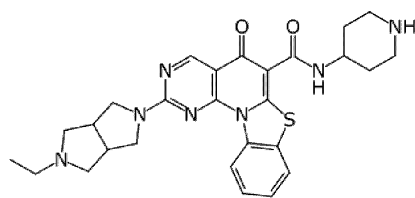
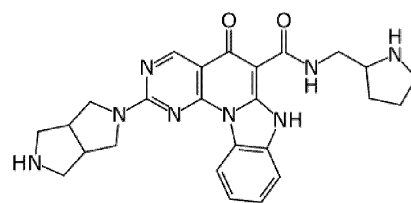
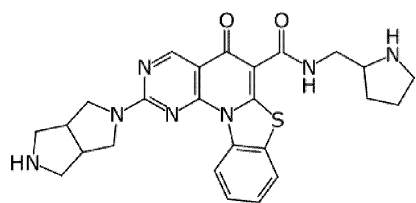
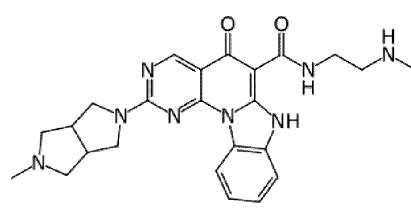
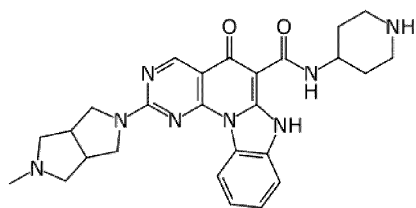
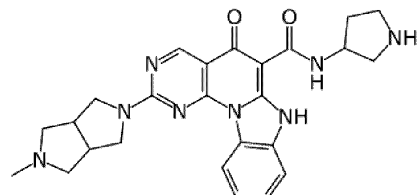
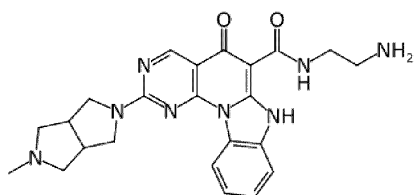
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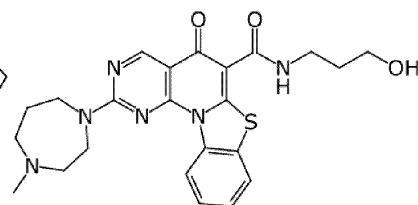
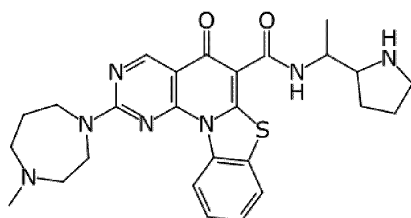
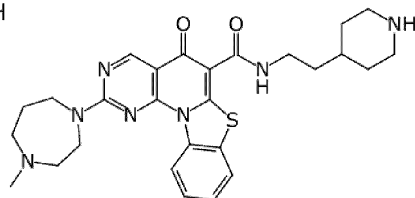
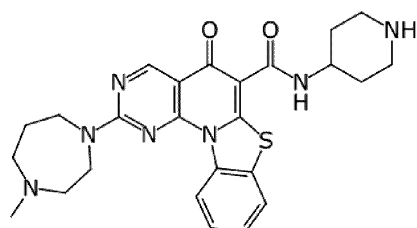
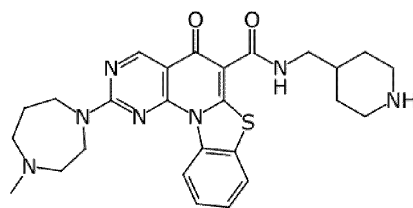
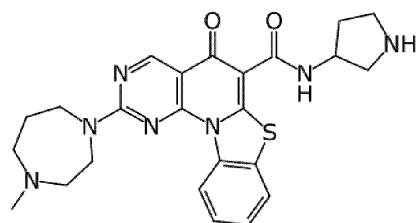
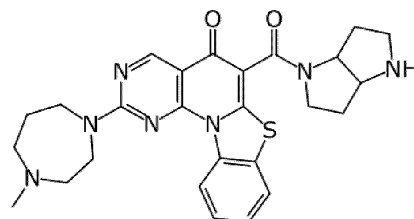
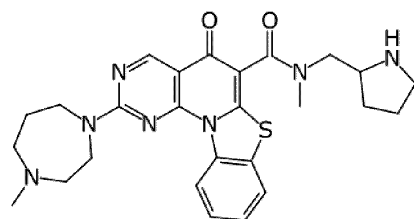
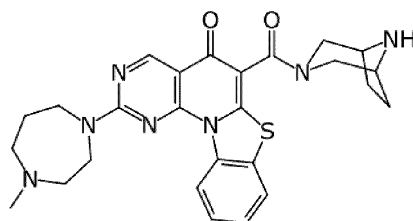
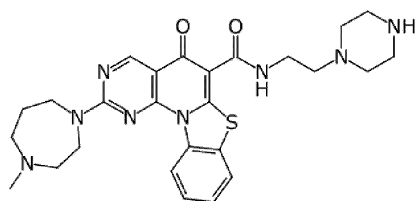
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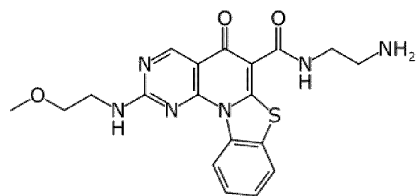
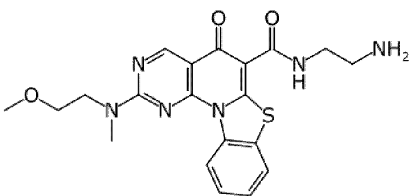
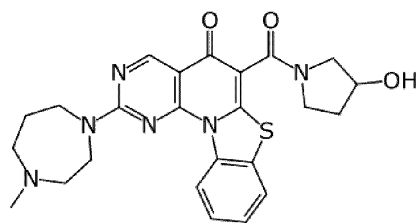
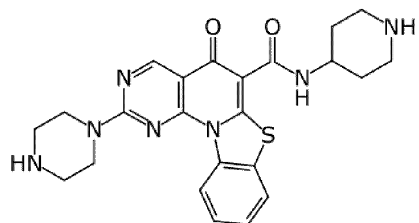
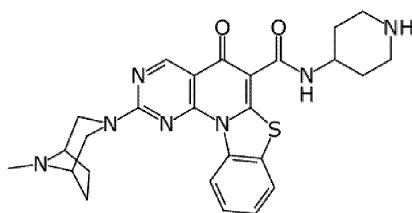
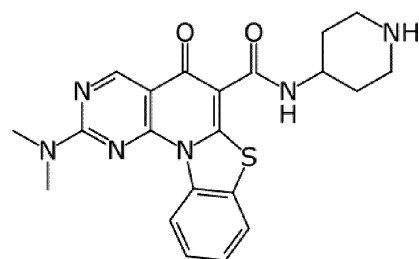
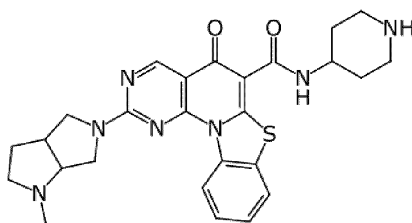
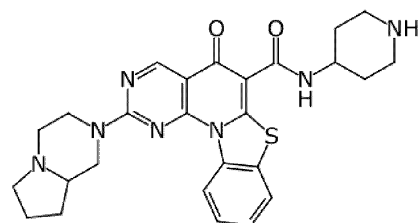
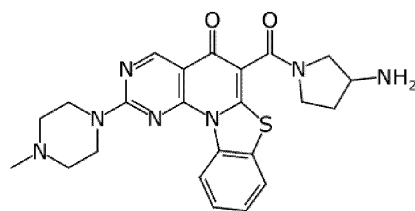
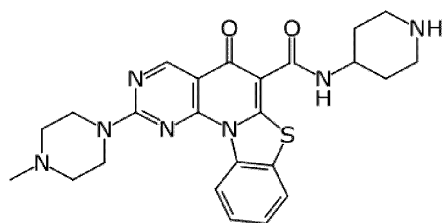
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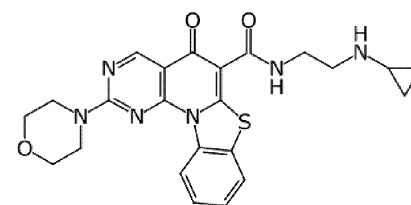
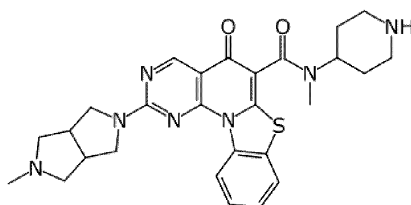
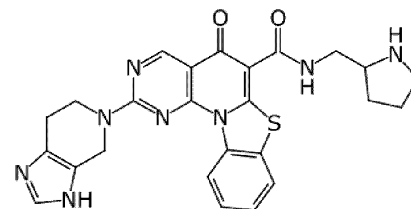
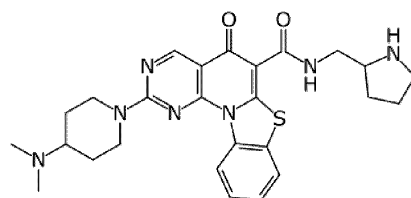
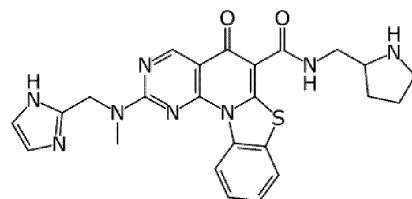
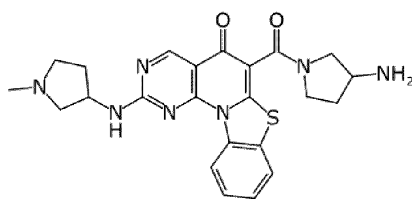
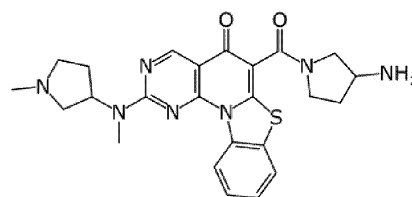
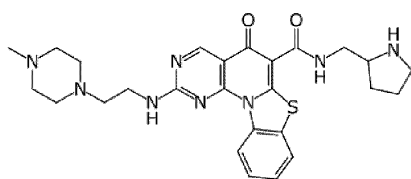
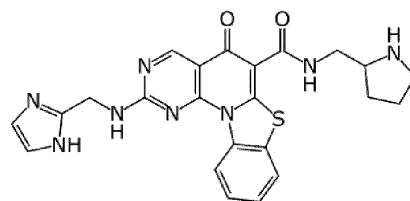
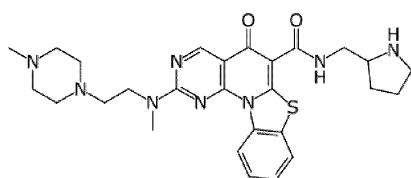


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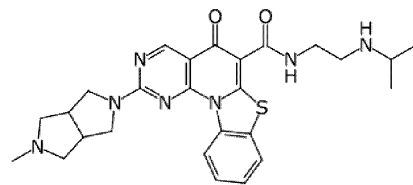
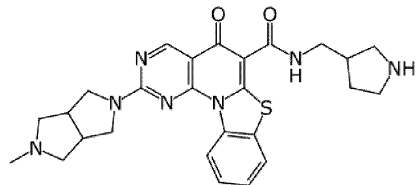
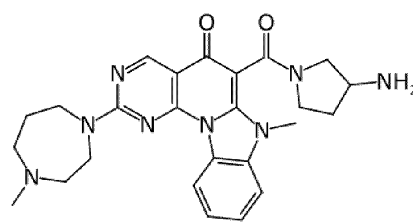
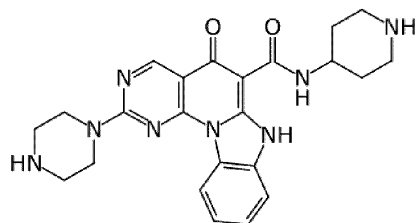
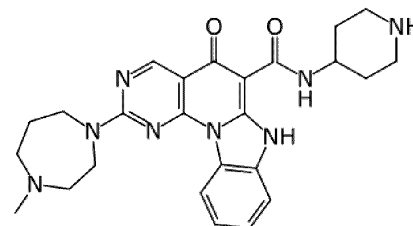
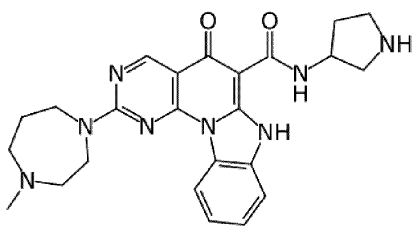
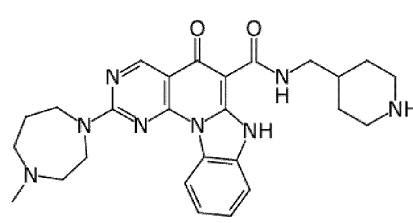
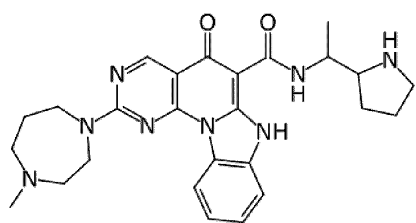
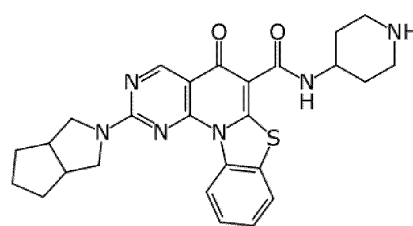
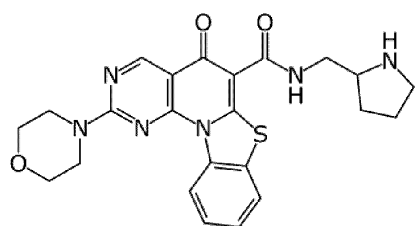


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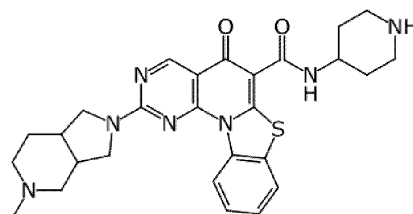
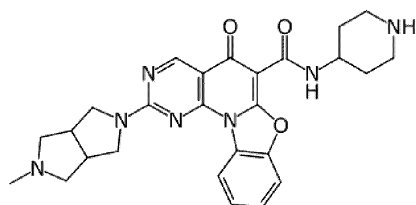
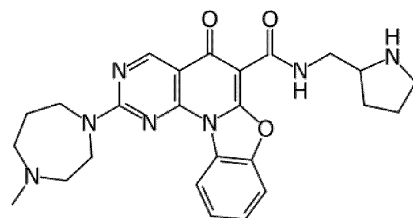
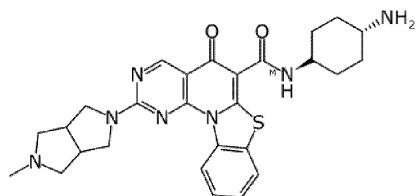
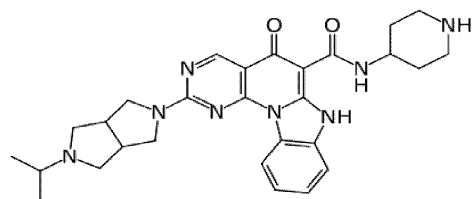
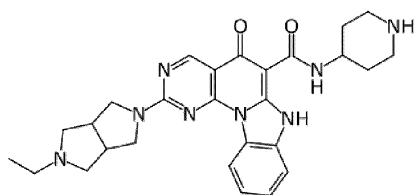
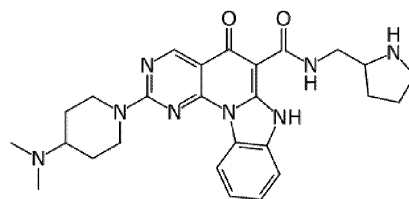
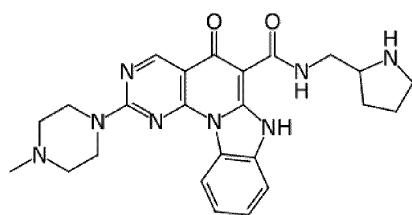
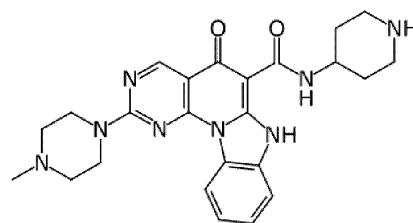
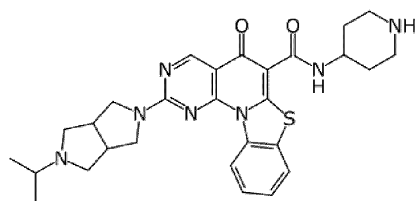




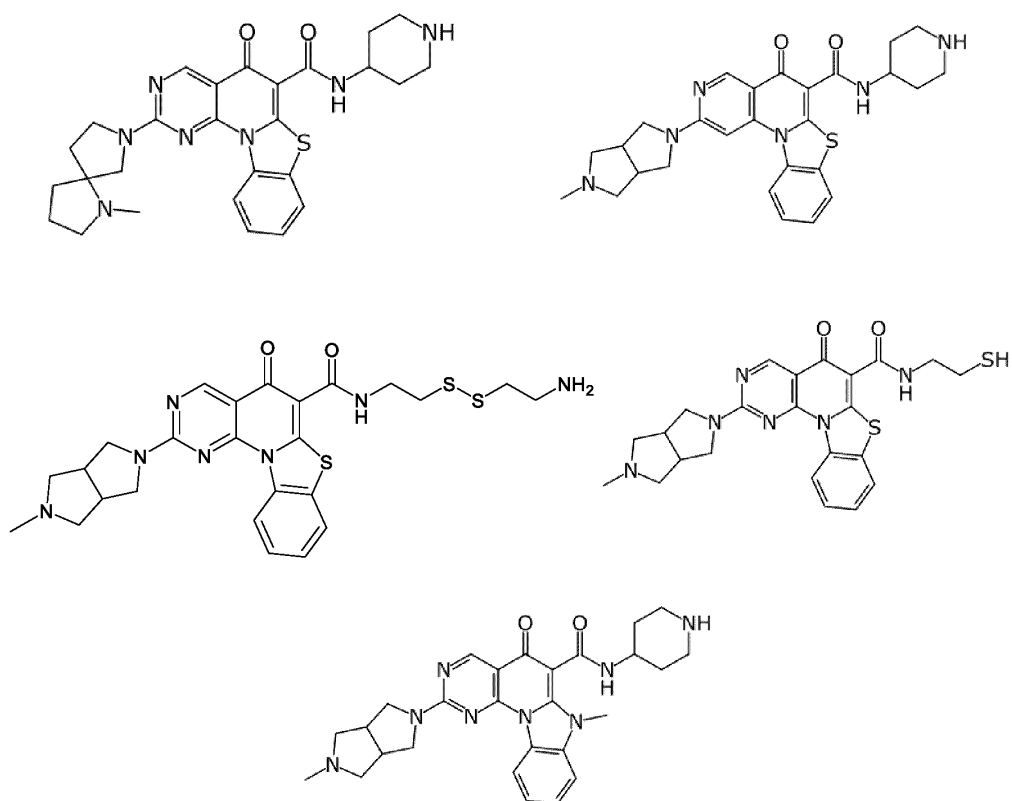
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or a pharmaceutically acceptable salt and/or solvate and/or prodrug of the selected
 5 compound.

A third aspect of the invention provides a pharmaceutically acceptable salt and/or
 solvate and/or prodrug of any compound of the first or second aspect of the invention.

10 In one embodiment, the third aspect of the invention provides a pharmaceutically
 acceptable salt and/or solvate of any compound of the first or second aspect of the
 invention. For example, the third aspect of the invention may provide (i) a
 pharmaceutically acceptable salt of any compound of the first or second aspect of the
 invention, or (ii) a pharmaceutically acceptable solvate of any compound of the first or
 15 second aspect of the invention, or (iii) a pharmaceutically acceptable solvate of a
 pharmaceutically acceptable salt of any compound of the first or second aspect of the
 invention.

The compounds of the present invention can be used both, in their free base form and
 20 their acid addition salt form. For the purposes of this invention, a "salt" of a compound
 of the present invention includes an acid addition salt. Acid addition salts are

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preferably pharmaceutically acceptable, non-toxic addition salts with suitable acids, including but not limited to inorganic acids such as hydrohalogenic acids (for example, hydrofluoric, hydrochloric, hydrobromic or hydroiodic acid) or other inorganic acids (for example, nitric, perchloric, sulfuric or phosphoric acid); or organic acids such as
5 organic carboxylic acids (for example, propionic, butyric, glycolic, lactic, mandelic, citric, acetic, trifluoroacetic, benzoic, salicylic, succinic, malic or hydroxysuccinic, tartaric, fumaric, maleic, hydroxymaleic, mucic or galactaric, gluconic, pantothenic or pamoic acid), organic sulfonic acids (for example, methanesulfonic, trifluoromethanesulfonic, ethanesulfonic, 2-hydroxyethanesulfonic, benzenesulfonic,
10 toluene-p-sulfonic, naphthalene-2-sulfonic or camphorsulfonic acid) or amino acids (for example, ornithinic, glutamic or aspartic acid). The acid addition salt may be a mono-, di-, tri- or multi-acid addition salt. A preferred salt is a hydrohalogenic, sulfuric, phosphoric or organic acid addition salt. A preferred salt is a hydrochloric acid addition salt.

15

Where a compound of the invention includes a quaternary ammonium group, typically the compound is used in its salt form. The counter ion to the quaternary ammonium group may be any pharmaceutically acceptable, non-toxic counter ion. Examples of suitable counter ions include the conjugate bases of the protic acids discussed above
20 in relation to acid addition salts.

The compounds of the present invention can also be used both, in their free acid form and their salt form. For the purposes of this invention, a "salt" of a compound of the present invention includes one formed between a protic acid functionality (such as a
25 carboxylic acid group) of a compound of the present invention and a suitable cation. Suitable cations include, but are not limited to lithium, sodium, potassium, magnesium, calcium and ammonium. The salt may be a mono-, di-, tri- or multi-salt. Preferably the salt is a mono- or di-lithium, sodium, potassium, magnesium, calcium or ammonium salt. More preferably the salt is a mono-sodium salt or a mono-
30 potassium salt.

Preferably any salt is a pharmaceutically acceptable non-toxic salt. However, in addition to pharmaceutically acceptable salts, other salts are included in the present invention, since they have potential to serve as intermediates in the purification or
35 preparation of other, for example, pharmaceutically acceptable salts, or are useful for identification, characterisation or purification of the free acid or base.

The compounds and/or salts of the present invention may be anhydrous or in the form of a hydrate (e.g. a hemihydrate, monohydrate, dihydrate or trihydrate) or other solvate. Such other solvates may be formed with common organic solvents, including but not limited to, alcoholic solvents e.g. methanol, ethanol or isopropanol.

5

In one embodiment, the third aspect of the invention provides a prodrug of any compound of the first or second aspect of the invention. Similarly, the third aspect of the invention may provide a pharmaceutically acceptable salt and/or solvate of such a prodrug. For example, the third aspect of the invention may provide (i) a
10 pharmaceutically acceptable salt of a prodrug, or (ii) a pharmaceutically acceptable solvate of a prodrug, or (iii) a pharmaceutically acceptable solvate of a pharmaceutically acceptable salt of a prodrug.

In some embodiments of the present invention, therapeutically inactive prodrugs are
15 provided. Prodrugs are compounds which, when administered to a subject such as a human, are converted in whole or in part to a compound of the invention. In most embodiments, the prodrugs are pharmacologically inert chemical derivatives that can be converted *in vivo* to the active drug molecules to exert a therapeutic effect. Any of the compounds described herein can be administered as a prodrug to increase the
20 activity, bioavailability, or stability of the compound or to otherwise alter the properties of the compound. Typical examples of prodrugs include compounds that have biologically labile protecting groups on a functional moiety of the active compound. Prodrugs include, but are not limited to, compounds that can be oxidized, reduced, aminated, deaminated, hydroxylated, dehydroxylated, hydrolyzed,
25 dehydrolyzed, alkylated, dealkylated, acylated, deacylated, phosphorylated, and/or dephosphorylated to produce the active compound. The present invention also encompasses salts and solvates of such prodrugs as described above.

The compounds, salts, solvates and prodrugs of the present invention may be
30 obtained in all grades of purity, for example via conventional techniques such as recrystallisation and/or column chromatography.

For example, the compounds, salts, solvates and prodrugs of the present invention may be at least 90% pure, at least 95% pure, at least 99% pure, at least 99.5% pure
35 or at least 99.9% pure, as measured by HPLC.

Alternately, the compounds, salts, solvates and prodrugs of the present invention may be at least 90% pure, at least 95% pure, at least 99% pure, at least 99.5% pure or at least 99.9% pure, as measured by LCMS.

- 5 Alternately still, the compounds, salts, solvates and prodrugs of the present invention may be at least 90% pure, at least 95% pure, at least 99% pure, at least 99.5% pure or at least 99.9% pure, as measured by ¹H NMR.

- 10 The compounds, salts, solvates and prodrugs of the present invention may contain at least one chiral centre. The compounds, salts, solvates and prodrugs may therefore exist in at least two isomeric forms. The present invention encompasses racemic mixtures of the compounds, salts, solvates and prodrugs of the present invention as well as enantiomerically enriched and substantially enantiomerically pure isomers. For the purposes of this invention, a "substantially enantiomerically pure" isomer of a
15 compound comprises less than 5% of other isomers of the same compound, more typically less than 2%, and most typically less than 0.5% by weight.

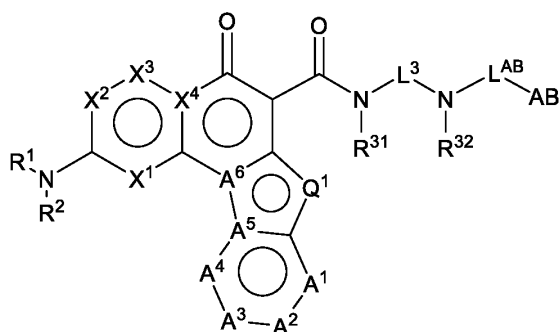
- The compounds, salts, solvates and prodrugs of the present invention may contain any stable isotope including, but not limited to ¹²C, ¹³C, ¹H, ²H (D), ¹⁴N, ¹⁵N, ¹⁶O, ¹⁷O,
20 ¹⁸O, ¹⁹F and ¹²⁷I, and any radioisotope including, but not limited to ¹¹C, ¹⁴C, ³H (T), ¹³N, ¹⁵O, ¹⁸F, ¹²³I, ¹²⁴I, ¹²⁵I and ¹³¹I.

- The compounds, salts, solvates and prodrugs of the present invention may be in any polymorphic or amorphous form.
25

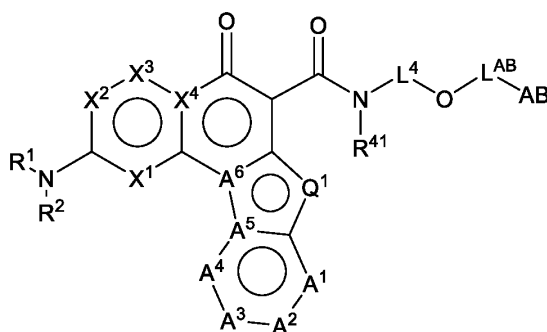
- A fourth aspect of the invention provides an antibody-drug conjugate comprising a compound of the first or second aspect of the invention, or a pharmaceutically acceptable salt and/or solvate and/or prodrug of the third aspect of the invention. For the avoidance of doubt, it will be understood that the compound, salt, solvate or
30 prodrug needs to lose at least one atom such as a hydrogen atom in order to form the link to the antibody.

- The compound, salt, solvate or prodrug of the present invention comprises a primary or a secondary amine, a -OH group, or a -SH group, each of which can be used to link
35 the compound, salt, solvate or prodrug to an antibody, with the loss of a hydrogen atom from the amine, -OH or -SH group. For example, the antibody-drug conjugate can have the Formula (IIA), (IIIA) or (IVA):

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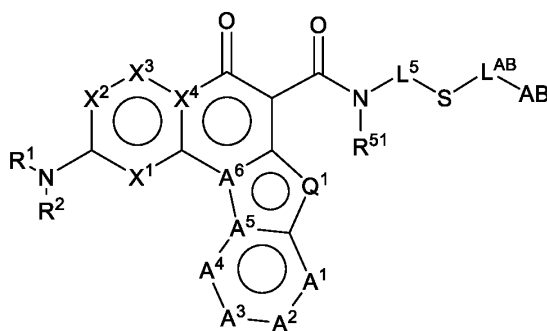


Formula (IIA)



Formula (IIIA)

5



Formula (IVA)

- 10 wherein L^{AB} is a linker, AB is an antibody, and X^1 - X^4 , A^1 - A^6 , Q^1 , R^{31} , R^{32} , L^3 , R^{41} , L^4 , R^{51} and L^5 are as defined in accordance with Formula (I).

Typical antibodies that may be used to prepare the antibody-drug conjugate of the fourth aspect of the invention are:

- 15
- Cetuximab
 - Trastuzumab
 - Brentuximab

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- ado-Trastuzumab
- Polatuzumab
- Inotuzumab
- Gemtuzumab
- 5 • Sacituzumab
- Enfortumab
- Loncastuximab
- fam-Trastuzumab
- Tisotumab
- 10 • Belantamab
- Mirvetuximab
- Amivantamab

Thus, where the antibody-drug conjugate has the Formula (IIA), (IIIA) or (IVA), the
 15 antibody AB may be selected from any of the above.

The linker L^{AB} is typically a C₂₀-C₁₀₀ saturated or unsaturated hydrocarbylene group, wherein the hydrocarbylene group may be straight-chained or branched, or be or include one or more cyclic groups, wherein the hydrocarbylene group may optionally
 20 be substituted with one or more halo and/or -NO₂ groups, wherein the hydrocarbylene group may optionally include one or more heteroatoms each independently selected from N, O and S in its carbon skeleton, and wherein any -S- moiety in the hydrocarbylene group may optionally be substituted with one or two groups each independently selected from oxo (=O) and =NH to form a -SO-, -SO₂-, -S(=NH)- or
 25 -SO(=NH)- moiety.

More typically, the linker L^{AB} is a C₃₀-C₇₀ or C₄₀-C₆₀ partially unsaturated hydrocarbylene group, wherein the hydrocarbylene group may be straight-chained or branched, or be or include one, two, three, four, five or six cyclic groups, wherein the
 30 hydrocarbylene group may optionally be substituted with one or more halo groups, wherein the hydrocarbylene group includes from 10 to 30 oxygen atoms, from 5 to 15 nitrogen atoms and from 0 to 5 sulphur atoms in its carbon skeleton, wherein any -S- moiety in the hydrocarbylene group may optionally be substituted with one or two groups each independently selected from oxo (=O) and =NH to form a -SO-, -SO₂-,
 35 -S(=NH)- or -SO(=NH)- moiety.

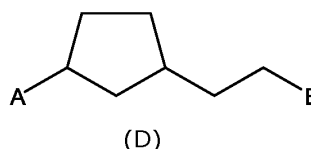
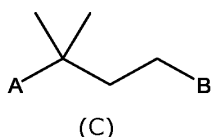
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Typically, the linker L^{AB} comprises a maleimide moiety, one or more PEG spacers, optionally a BCN moiety, a valine-citrulline (Val-Cit) dipeptide, and a para-aminobenzyl (PAB) spacer.

- 5 Typically, the hydrocarbylene group of linker L^{AB} has a chain length of from 20 to 80 atoms. More typically, the hydrocarbylene group has a chain length of from 30 to 70 atoms, or from 40 to 60 atoms.

As will be understood, the "chain length" of a hydrocarbylene group refers to the
10 number of atoms of the hydrocarbylene group that are bonded to each other in a continuous chain between the two points of attachment of the hydrocarbylene group to the remainder of the molecule, as measured by the shortest route. By way of example, structure (C) has a chain length between A and B of 3 atoms, whereas structure (D) has a chain length between A and B of 5 atoms:

15



Typical linkers that may be used to link a compound of the first or second aspect of
20 the invention, or a pharmaceutically acceptable salt and/or solvate and/or prodrug of the third aspect of the invention, to an antibody to prepare the antibody-drug conjugate of the fourth aspect of the invention are:

- maleimide-valine-citrulline-PABC, including those comprising PEG and/or a BCN-derived moiety
- 25 • thioether
- hydrazone and disulfide
- CL2a linker
- maleimide-valine-alanine-PABC
- maleimide tetrapeptide linker (GGFG)
- 30 • Maleidocaproic linker
- Sulfo-SPDB disulfide

Thus, where the antibody-drug conjugate has the Formula (IIA), (IIIA) or (IVA), the linker L^{AB} may be selected from any of the above.

35

In one embodiment of the fourth aspect of the invention, the antibody-drug conjugate is selected from:

- Cetuximab-mal-PEG6-vc-N-(2-aminoethyl)-4-(4-methyl-1,4-diazepan-1-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0²,7.0¹²,¹⁷]-heptadeca-2,4,6,9,12,14,16-heptaene-9-carboxamide;
- Cetuximab-mal-PEG6-vc-4-(4-methyl-1,4-diazepan-1-yl)-8-oxo-N-[(pyrrolidin-2-yl)methyl]-11-thia-1,3,5-triazatetracyclo[8.7.0.0²,7.0¹²,¹⁷]-heptadeca-2,4,6,9,12,14,16-heptaene-9-carboxamide;
- Trastuzumab-mal-PEG6-vc-N-(2-aminoethyl)-4-(4-methyl-1,4-diazepan-1-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0²,7.0¹²,¹⁷]-heptadeca-2,4,6,9,12,14,16-heptaene-9-carboxamide;
- Sacituzumab-mal-PEG6-vc-N-(2-aminoethyl)-4-(4-methyl-1,4-diazepan-1-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0²,7.0¹²,¹⁷]-heptadeca-2,4,6,9,12,14,16-heptaene-9-carboxamide;
- Cetuximab-mal-PEG6-vc-4-(2-methyl-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl)-8-oxo-N-pyrrolidin-3-yl-1,3,5,11-tetrazatetracyclo[8.7.0.0²,7.0¹²,17]-heptadeca-2,4,6,9,12(17),13,15-heptaene-9-carboxamide;
- Cetuximab-mal-PEG6-vc-4-(2-methyl-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl)-8-oxo-N-(4-piperidyl)-1,3,5,11-tetrazatetracyclo[8.7.0.0²,7.0¹²,¹⁷]-heptadeca-2,4,6,9,12(17),13,15-heptaene-9-carboxamide;
- Cetuximab-mal-PEG6-vc-N-(2-aminoethyl)-4-(2-methyl-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0²,7.0¹²,¹⁷]-heptadeca-2,4,6,9,12(17),13,15-heptaene-9-carboxamide;
- Cetuximab-mal-PEG6-vc-4-(2-methyl-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl)-8-oxo-N-(4-piperidyl)-11-thia-1,3,5-triazatetracyclo[8.7.0.0²,7.0¹²,¹⁷]-heptadeca-2,4,6,9,12(17),13,15-heptaene-9-carboxamide;
- Amivantamab-mal-PEG8-vc-4-2-(5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-oxo-N-(pyrrolidin-2-ylmethyl)-5H-benzo[4',5']thiazolo-[3',2':1,6]pyrido[2,3-d]-pyrimidine-6-carboxamide;
- Cetuximab-mal-PEG8-vc-N-(aminomethyl)-4-(2-methyl-1,3,3a,4,6,6a-hexahydropyrrolo-[3,4-c]pyrrol-5-yl)-8-oxo-1,3,5,11-tetrazatetracyclo[8.7.0.0²,7.0¹²,17]-heptadeca-2,4,6,9,12(17),13,15-heptaene-9-carboxamide;

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- Cetuximab-mal-PEG8-vc-2-(4-methyl-1,4-diazepan-1-yl)-5-oxo-N-(piperidin-4-yl)-5,7-dihydrobenzo[4',5']imidazo[1',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamide;

or a pharmaceutically acceptable salt and/or solvate thereof.

5

A fifth aspect of the invention provides a pharmaceutical composition comprising a compound of the first or second aspect of the invention, or a pharmaceutically acceptable salt and/or solvate and/or prodrug of the third aspect of the invention, or an antibody-drug conjugate of the fourth aspect of the invention, and a

10 pharmaceutically acceptable excipient.

Conventional procedures for the selection and preparation of suitable pharmaceutical formulations are described in, for example, "Aulton's Pharmaceuticals - The Design and Manufacture of Medicines", M. E. Aulton and K. M. G. Taylor, Churchill Livingstone

15 Elsevier, 4th Ed., 2013.

Pharmaceutically acceptable excipients including adjuvants, diluents or carriers that may be used in the pharmaceutical compositions of the invention are those conventionally employed in the field of pharmaceutical formulation, and include, but are not limited to, sugars, sugar alcohols, starches, ion exchangers, alumina, aluminium stearate, lecithin, serum proteins such as human serum albumin, buffer substances such as phosphates, glycerine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinylpyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

30 A sixth aspect of the invention provides a compound of the first or second aspect of the invention, or a pharmaceutically acceptable salt and/or solvate and/or prodrug of the third aspect of the invention, or an antibody-drug conjugate of the fourth aspect of the invention, or a pharmaceutical composition of the fifth aspect of the invention, for use in medicine, and/or for use in the treatment or prevention of a disease, disorder
35 or condition. Typically, the use comprises the administration of the compound, salt, solvate, prodrug, antibody-drug conjugate or pharmaceutical composition to a subject.

The term "treatment" as used herein refers equally to curative therapy, and ameliorating or palliative therapy. The term includes obtaining beneficial or desired physiological results, which may or may not be established clinically. Beneficial or desired clinical results include, but are not limited to, the alleviation of symptoms, the prevention of symptoms, the diminishment of extent of disease, the stabilisation (i.e., not worsening) of a condition, the delay or slowing of progression/worsening of a condition/symptom, the amelioration or palliation of a condition/symptom, and remission (whether partial or total), whether detectable or undetectable. The term "palliation", and variations thereof, as used herein, means that the extent and/or undesirable manifestations of a physiological condition or symptom are lessened and/or time course of the progression is slowed or lengthened, as compared to not administering a compound, salt, solvate, prodrug, antibody-drug conjugate or pharmaceutical composition of the present invention. The term "prevention" as used herein in relation to a disease, disorder or condition, relates to prophylactic or preventative therapy, as well as therapy to reduce the risk of developing the disease, disorder or condition. The term "prevention" includes both the avoidance of occurrence of the disease, disorder or condition, and the delay in onset of the disease, disorder or condition. Any statistically significant ($p \leq 0.05$) avoidance of occurrence, delay in onset or reduction in risk as measured by a controlled clinical trial may be deemed a prevention of the disease, disorder or condition. Subjects amenable to prevention include those at heightened risk of a disease, disorder or condition as identified by genetic or biochemical markers. Typically, the genetic or biochemical markers are appropriate to the disease, disorder or condition under consideration.

A seventh aspect of the invention provides the use of a compound of the first or second aspect of the invention, or a pharmaceutically acceptable salt and/or solvate and/or prodrug of the third aspect of the invention, or an antibody-drug conjugate of the fourth aspect of the invention, in the manufacture of a medicament for the treatment or prevention of a disease, disorder or condition. Typically, the treatment or prevention comprises the administration of the compound, salt, solvate, prodrug, antibody-drug conjugate or medicament to a subject.

An eighth aspect of the invention provides a method of treatment or prevention of a disease, disorder or condition, the method comprising the step of administering an effective amount of a compound of the first or second aspect of the invention, or a pharmaceutically acceptable salt and/or solvate and/or prodrug of the third aspect of the invention, or an antibody-drug conjugate of the fourth aspect of the invention, or a pharmaceutical composition of the fifth aspect of the invention, to thereby treat or

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prevent the disease, disorder or condition. Typically, the administration is to a subject in need thereof.

5 A ninth aspect of the invention provides a compound of the first or second aspect of the invention, or a pharmaceutically acceptable salt and/or solvate and/or prodrug of the third aspect of the invention, or an antibody-drug conjugate of the fourth aspect of the invention, or a pharmaceutical composition of the fifth aspect of the invention, for use in the treatment or prevention of a cancer. Typically, the use comprises the administration of the compound, salt, solvate, prodrug, antibody-drug conjugate or
10 pharmaceutical composition to a subject.

A tenth aspect of the invention provides the use of a compound of the first or second aspect of the invention, or a pharmaceutically acceptable salt and/or solvate and/or prodrug of the third aspect of the invention, or an antibody-drug conjugate of the
15 fourth aspect of the invention, in the manufacture of a medicament for the treatment or prevention of a cancer. Typically, the treatment or prevention comprises the administration of the compound, salt, solvate, prodrug, antibody-drug conjugate or medicament to a subject.

20 An eleventh aspect of the invention provides a method of treatment or prevention of a cancer, the method comprising the step of administering an effective amount of a compound of the first or second aspect of the invention, or a pharmaceutically acceptable salt and/or solvate and/or prodrug of the third aspect of the invention, or an antibody-drug conjugate of the fourth aspect of the invention, or a pharmaceutical
25 composition of the fifth aspect of the invention, to thereby treat or prevent the cancer. Typically, the administration is to a subject in need thereof.

The compound of the first or second aspect of the invention, or the pharmaceutically acceptable salt and/or solvate and/or prodrug of the third aspect of the invention, or the
30 the antibody-drug conjugate of the fourth aspect of the invention, or the pharmaceutical composition of the fifth aspect of the invention can be combined with other therapeutic agents and treatments, for example, to exploit synergies and enhance the cytotoxic activity in cancer treatment. For example, the compound, salt, solvate, prodrug, antibody-drug conjugate or pharmaceutical composition can used in
35 combination with X-ray radiation; DNA alkylating agents like cisplatin; NU7441, an inhibitor of DNA repair regulating kinase DNA-PK; MK1775, an inhibitor of the cell cycle regulator WEE1 kinase; Pimozide, an inhibitor of the deubiquitinylation enzyme USP1; NSC697923, an inhibitor of ubiquitin conjugating enzyme UBE2N; APR-246, a

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P53 activator; PARP inhibitors; topoisomerase 1 knockdown; HDAC inhibitors; lysosome inhibitors; and immunomodulators.

5 Unless stated otherwise, in any of the sixth to eleventh aspects of the invention, the subject may be any human or other animal. Typically, the subject is a mammal, more typically a human or a domesticated mammal such as a cow, pig, lamb, sheep, goat, horse, cat, dog, rabbit, mouse etc. Most typically, the subject is a human.

10 Any of the medicaments employed in the present invention can be administered by oral, parenteral (including intravenous, subcutaneous, intramuscular, intradermal, intratracheal, intraperitoneal, intraarticular, intracranial and epidural), airway (aerosol), rectal, vaginal, ocular or topical (including transdermal, buccal, mucosal, sublingual and topical ocular) administration.

15 Typically, the mode of administration selected is that most appropriate to the disorder, disease or condition to be treated or prevented.

For oral administration, the compounds, salts, solvates, prodrugs or antibody-drug conjugates of the present invention will generally be provided in the form of tablets, capsules, hard or soft gelatine capsules, caplets, troches or lozenges, as a powder or granules, or as an aqueous solution, suspension or dispersion.

20

Tablets for oral use may include the active ingredient mixed with pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavouring agents, colouring agents and preservatives. Suitable inert diluents include sodium and calcium carbonate, sodium and calcium phosphate, and lactose. Corn starch and alginic acid are suitable disintegrating agents. Binding agents may include starch and gelatine. The lubricating agent, if present, may be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a material, such as glyceryl monostearate or glyceryl distearate, to delay absorption in the gastrointestinal tract. Tablets may also be effervescent and/or dissolving tablets.

25

30

Capsules for oral use include hard gelatine capsules in which the active ingredient is mixed with a solid diluent, and soft gelatine capsules wherein the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin or olive oil.

35

Powders or granules for oral use may be provided in sachets or tubs. Aqueous solutions, suspensions or dispersions may be prepared by the addition of water to powders, granules or tablets.

- 5 Any form suitable for oral administration may optionally include sweetening agents such as sugar, flavouring agents, colouring agents and/or preservatives.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising, for example, cocoa butter or a salicylate.

10

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

- 15 For parenteral use, the compounds, salts, solvates, prodrugs or antibody-drug conjugates of the present invention will generally be provided in a sterile aqueous solution or suspension, buffered to an appropriate pH and isotonicity. Suitable aqueous vehicles include Ringer's solution and isotonic sodium chloride or glucose. Aqueous suspensions according to the invention may include suspending agents such
20 as cellulose derivatives, sodium alginate, polyvinylpyrrolidone and gum tragacanth, and a wetting agent such as lecithin. Suitable preservatives for aqueous suspensions include ethyl and n-propyl p-hydroxybenzoate. The compounds of the invention may also be presented as liposome formulations.

- 25 For ocular administration, the compounds, salts, solvates, prodrugs or antibody-drug conjugates of the invention will generally be provided in a form suitable for topical administration, e.g. as eye drops. Suitable forms may include ophthalmic solutions, gel-forming solutions, sterile powders for reconstitution, ophthalmic suspensions, ophthalmic ointments, ophthalmic emulsions, ophthalmic gels and ocular inserts.
30 Alternatively, the compounds, salts, solvates or prodrugs of the invention may be provided in a form suitable for other types of ocular administration, for example as intraocular preparations (including as irrigating solutions, as intraocular, intravitreal or juxtasclear injection formulations, or as intravitreal implants), as packs or corneal shields, as intracameral, subconjunctival or retrobulbar injection formulations, or as
35 iontophoresis formulations.

For transdermal and other topical administration, the compounds, salts, solvates, prodrugs or antibody-drug conjugates of the invention will generally be provided in the

form of ointments, cataplasms (poultices), pastes, powders, dressings, creams, plasters or patches.

Suitable suspensions and solutions can be used in inhalers for airway (aerosol) administration.

The dose of the compounds, salts, solvates, prodrugs or antibody-drug conjugates of the present invention will, of course, vary with the disease, disorder or condition to be treated or prevented. In general, a suitable dose will be in the range of 0.01 to 500 mg per kilogram body weight of the recipient per day. The desired dose may be presented at an appropriate interval such as once every other day, once a day, twice a day, three times a day or four times a day. The desired dose may be administered in unit dosage form, for example, containing 1 mg to 50 g of active ingredient per unit dosage form.

All citations are incorporated herein by reference in their entirety.

For the avoidance of doubt, insofar as is practicable any embodiment of a given aspect of the present invention may occur in combination with any other embodiment of the same aspect of the present invention. In addition, insofar as is practicable it is to be understood that any preferred, typical or optional embodiment of any aspect of the present invention should also be considered as a preferred, typical or optional embodiment of any other aspect of the present invention.

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- 25

Examples – Compound Synthesis

All solvents, reagents and compounds were purchased and used without further purification unless stated otherwise.

30

NMR:

¹H NMR, ¹³C NMR spectra and 2D NMR spectra were recorded on a Bruker Avance Neo 400 MHz NMR spectrometer at 25°C in CDCl₃/MeOD/ DMSO-*d*₆/DMSO-*d*₆+D₂O, respectively, residual undeuterated solvent as internal reference. Chemical shifts (δ) are expressed in ppm and coupling constants (J) are given in Hz.

35

LCMS method:

All final compounds were purified to $\geq 95\%$ purity as determined Shimadzu LC-20AD XR&MS 2020 with UV detection at 220 nm using the following method: Halo C18 column (5.0 μm , 3.0 mm $\times$ 30 mm), eluting with binary solvent systems A and B using a 5–95% B over 3.0 minutes gradient elution [A, H_2O with 0.04% TFA; B, CH_3CN with 0.02% TFA]; flow rate 1.0 mL/min. Mass spectral data were recorded on an Shimadzu LC-20AD XR&MS 2020 with UV detection, ESI.

Preparative HPLC method:

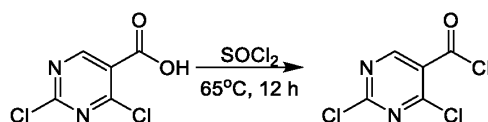
TFA as buffer: Preparative reversed-phase high pressure liquid chromatography (RP-HPLC) was performed using a Gilson 281 Semi-preparative HPLC system and Phenomenex Luna C18 column (5 μm , 100 mm $\times$ 40 mm), eluting with binary solvent systems A and B using a gradient elution [A, H_2O with 0.1% TFA; B, CH_3CN] with UV detection at 220 nm.

HCl as buffer: Preparative reversed-phase high pressure liquid chromatography (RP-HPLC) was performed using a Gilson 281 Semi-preparative HPLC system and Phenomenex Luna C18 column (5 μm , 100 mm $\times$ 40 mm), eluting with binary solvent systems A and B using a gradient elution [A, H_2O with 0.04% HCl; B, CH_3CN] with UV detection at 220 nm.

NH_4HCO_3 as buffer: Preparative reversed-phase high pressure liquid chromatography (RP-HPLC) was performed using a Gilson 281 Semi-preparative HPLC system and Waters Xbridge Prep OBD C18 (10 μm , 150 mm $\times$ 40 mm), eluting with binary solvent systems A and B using a gradient elution [A, H_2O with 10mM NH_4HCO_3 ; B, CH_3CN] with UV detection at 220 nm.

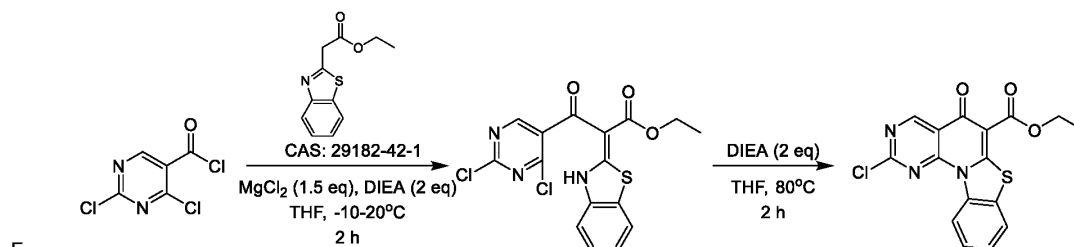
Synthetic Route 1

Example 1: N-(2-aminoethyl)-4-(4-methyl-1,4-diazepan-1-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12,14,16-heptaene-9-carboxamide



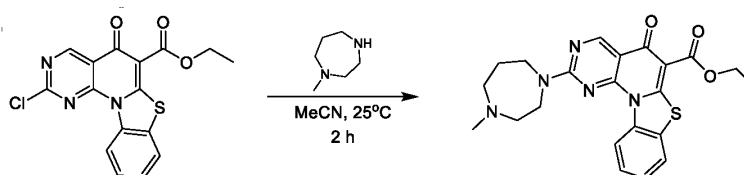
2,4-Dichloropyrimidine-5-carbonyl chloride: A mixture of acid (1.00 g, 5.18 mmol, 1 eq) in SOCl_2 (10.00 mL) was stirred at 65°C for 12 h. TLC showed the

reaction was completed. The mixture was concentrated in vacuum to give the desired product (1.00 g, 4.73 mmol, 91.28% yield) as a yellow solid. The crude product was used in the next step without further purification.



Ethyl 4-chloro-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]-

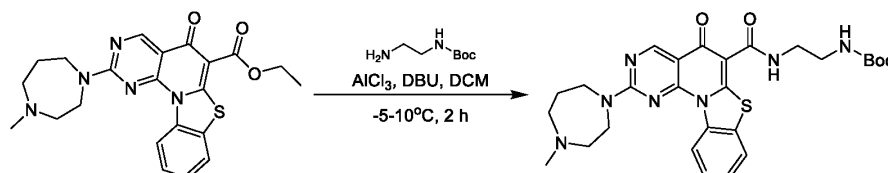
heptadeca-2(7),3,5,9,12,14,16-heptaene-9-carboxylate: To a mixture of acid chloride (0.5 g, 2.26 mmol, 1 eq) and MgCl₂ (322.71 mg, 3.39 mmol, 139.10 μL, 1.5 eq) in MeCN (10.00 mL) was added benzothiazole (621.09 mg, 2.94 mmol, 1.3 eq) and TEA (457.30 mg, 4.52 mmol, 629.02 μL, 2 eq) at -10°C under N₂. The mixture was stirred at 20°C for 2 h, then to the mixture was added DIEA (457.30 mg, 4.52 mmol, 629.02 μL, 2 eq) and the reaction heated to 25°C and stirred for 10 h. LCMS showed the reaction was completed. The mixture was concentrated and the residue was triturated with MeCN (10 mL). The mixture was filtered and the solid was collected to give the desired product (0.22 g, 0.611 mmol, 27.06% yield) as yellow solid. The crude product was used in the next step without further purification. ¹H NMR (400 MHz, CDCl₃) δ = 9.63 (s, 1H), 9.37 (br d, J= 8.3 Hz, 1H), 7.75 (br d, J= 7.6 Hz, 1H), 7.64 - 7.56 (m, 1H), 7.54 - 7.45 (m, 1H), 4.50 (q, J= 7.0 Hz, 2H), 1.49 (br t, J= 7.0 Hz, 3H).



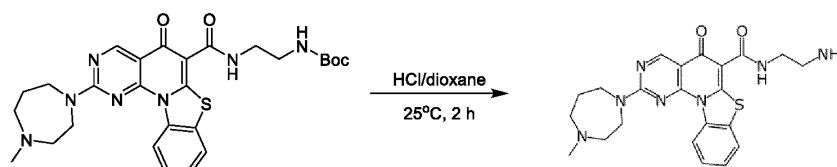
Ethyl 4-(4-methyl-1,4-diazepan-1-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]-

heptadeca-2(7),3,5,9,12,14,16-heptaene-9-carboxylate: To a mixture of ester (0.17 g, 472.51 μmol, 1 eq) in MeCN (5.00 mL) was added 1-methyl-1,4-diazepane (107.91 mg, 0.946 mmol, 2 eq) at 25°C under N₂. The mixture was stirred at 25°C for 12 h. LCMS showed the reaction was completed. The mixture was concentrated in vacuum. The residue was triturated with MeCN (20 mL) for 10 min. Then the mixture was filtered and the solid was collected to afford the desired

product (0.14 g, 319.99 μmol , 67.72% yield) as yellow solid. **LCMS** (ESI+): m/z 438.4 (M+H)⁺, Rt: 0.466 min



- 5 **tert-Butyl N-(2-{[4-(4-methyl-1,4-diazepan-1-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0²,7.0¹²,17]heptadeca-2,4,6,9,12,14,16-heptaen-9-yl]formamido}ethyl)carbamate:** To a solution of ethyl 4-(4-methyl-1,4-diazepan-1-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0²,7.0¹²,17]heptadeca-2,4,6,9,12,14,16-heptaene-9-carboxylate (0.5 g, 1.14 mmol, 1 eq) in DCM (5 mL)
 10 was added tert-butyl N-(2-aminoethyl)carbamate (366.19 mg, 2.29 mmol, 360.42 μL , 2 eq), the mixture was cooled at -5°C and added DBU (521.95 mg, 3.43 mmol, 516.78 μL , 3 eq) dropwise and AlCl₃ (243.81 mg, 1.83 mmol, 99.92 μL , 1.6 eq) in portions. The reaction was stirred at 25°C for 2 h. The reaction mixture was poured into 50% of NaOH aqueous solution (2 mL). The aqueous phase was extracted with
 15 dichloromethane (5 mL*2). The combined organic phases were concentrated in vacuum to give the title compound (500 mg, 842.91 μmol , 73.76% yield, 93% purity) as yellow solid. **LCMS** (ESI+): m/z 552.4 (M+H)⁺, Rt: 0.377 min.



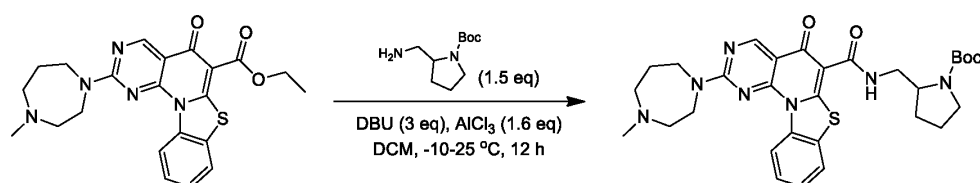
- 20 **N-(2-aminoethyl)-4-(4-methyl-1,4-diazepan-1-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0²,7.0¹²,17]heptadeca-2,4,6,9,12,14,16-heptaene-9-carboxamide:** The solution of tert-butyl N-(2-{[4-(4-methyl-1,4-diazepan-1-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0²,7.0¹²,17]heptadeca-2,4,6,9,12,14,16-heptaen-9-yl]formamido}ethyl)carbamate (0.5 g, 907.98 μmol , 1 eq) in HCl/dioxane (4 M, 4.54 mL, 20 eq) was stirred at 25°C for 2 h. The mixture was concentrated in
 25 vacuum to give crude product, which was purified by prep-HPLC (column: Phenomenex luna C18 100*40mm*5 μm ; mobile phase: [H₂O(0.04% HCl)-MeCN]; gradient: 5%-35% B over 8.0 min) to give the title compound (**Example 1**, 230 mg, 467.07 μmol , 51.44% yield, 98.90% purity, HCl) as yellow solid. **LCMS** (ESI+): m/z 452.3 (M+H)⁺, Rt: 1.235 min. **¹H NMR** (400 MHz, DMSO-d₆) δ = 11.48 - 11.26 (m,

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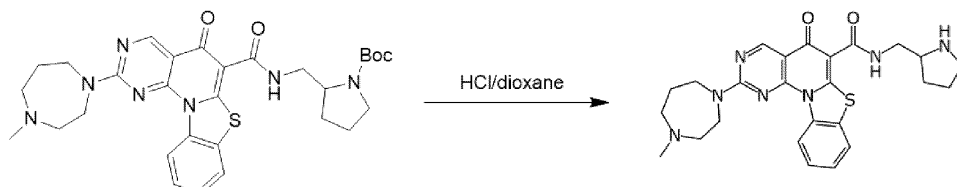
1H), 10.31 (br t, $J = 5.8$ Hz, 1H), 9.26 (d, $J = 8.6$ Hz, 2H), 8.10 - 8.01 (m, 3H), 7.70 - 7.47 (m, 2H), 4.65 (br dd, $J = 4.6, 15.6$ Hz, 1H), 4.32 (br dd, $J = 3.3, 16.0$ Hz, 1H), 4.18 - 3.96 (m, 2H), 3.90 - 3.78 (m, 1H), 3.63 (br s, 2H), 3.55 - 3.38 (m, 2H), 3.30 - 3.21 (m, 1H), 3.08 - 2.97 (m, 2H), 2.78 (d, $J = 4.6$ Hz, 3H), 2.48 - 2.41 (m, 1H),
 5 2.38 - 2.20 (m, 1H).

Example 2: 4-(4-methyl-1,4-diazepan-1-yl)-8-oxo-N-[(pyrrolidin-2-yl)-methyl]-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12,14,16-heptaene-9-carboxamide

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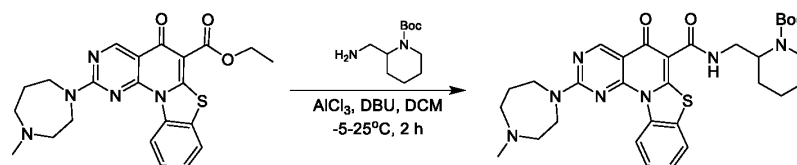
tert-Butyl 2-({[4-(4-methyl-1,4-diazepan-1-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12,14,16-heptaen-9-yl]formamido}methyl)pyrrolidine-1-carboxylate: To a solution of N-(2-aminoethyl)-4-(4-methyl-1,4-diazepan-1-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo-
 15 [8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12,14,16-heptaene-9-carboxamide (0.1 g, 228.56 μ mol, 1 eq) in DCM (1.00 mL) was added tert-butyl 2-(aminomethyl)-pyrrolidine-1-carboxylate (68.66 mg, 342.85 μ mol, 1.5 eq). The mixture was cooled to -10°C, then DBU (104.39 mg, 685.69 μ mol, 103.35 μ L, 3 eq) and AlCl₃ (48.76 mg, 365.70 μ mol, 19.98 μ L, 1.6 eq) was added to the above mixture at -10°C. The mixture
 20 was stirred at -10 °C for 12 h. The mixture was poured into 50% NaOH solution (5 mL) very slowly under N₂, then the mixture was filtered with diatomaceous earth. The aqueous phase was extracted with dichloromethane (10 mL*3) to give the title compound (0.1 g, 150.41 μ mol, 65.81% yield, 89% purity) as yellow solid. **LCMS**
 25 (ESI+): m/z 592.4 (M+H)⁺, Rt: 0.427 min.



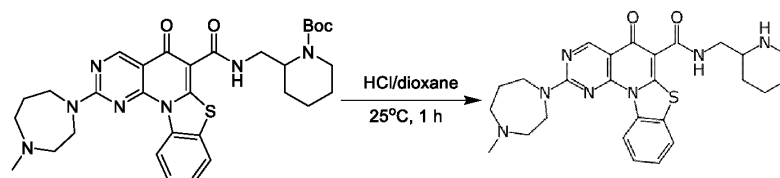
4-(4-methyl-1,4-diazepan-1-yl)-8-oxo-N-[(pyrrolidin-2-yl)methyl]-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12,14,16-heptaene-9-carboxamide: The solution of tert-butyl 2-({[4-(4-methyl-1,4-

diazepan-1-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0²,7.0¹²,¹⁷]heptadeca-2,4,6,9,12,14,16-heptaen-9-yl]formamido}methyl)pyrrolidine-1-carboxylate (0.1 g, 152.10 μ mol, 1 eq) in HCl/dioxane (4 M, 38.02 μ L, 1 eq) was stirred at 25°C for 2 h. The mixture was concentrated in vacuum. The crude product was purified by prep-HPLC (column: Phenomenex luna C18 100*40mm*5 μ m; mobile phase: [H₂O(0.04% HCl)-MeCN];gradient:1%-25% B over 8.0 min) to give the title compound (**Example 2**, 52.0 mg, 102.28 μ mol, 67.25% yield, 96.7% purity) as yellow solid. **LCMS** (ESI+): m/z 492.4(M+H) +, Rt: 1.301 min. **¹H NMR** (400 MHz, DMSO-d₆) δ = 9.15 - 8.99 (m, 1H), 8.90 (br d, J = 8.5 Hz, 1H), 7.96 - 7.83 (m, 1H), 7.60 - 7.41 (m, 2H), 4.54 (br d, J = 14.1 Hz, 1H), 4.14 (br d, J = 13.5 Hz, 1H), 3.98 (br d, J = 5.6 Hz, 1H), 3.78 - 3.48 (m, 5H), 3.45 (br d, J = 11.6 Hz, 1H), 3.32 - 3.10 (m, 4H), 2.81 (s, 3H), 2.33 (br s, 1H), 2.22 (br s, 1H), 2.17 - 2.04 (m, 1H), 2.03 - 1.82 (m, 2H), 1.69 (br dd, J = 8.3, 12.5 Hz, 1H).

Example 3: 4-(4-Methyl-1,4-diazepan-1-yl)-8-oxo-N-[(piperidin-2-yl)-methyl]-11-thia-1,3,5-triazatetracyclo[8.7.0.0²,7.0¹²,¹⁷]heptadeca-2,4,6,9,12,14,16-heptaene-9-carboxamide

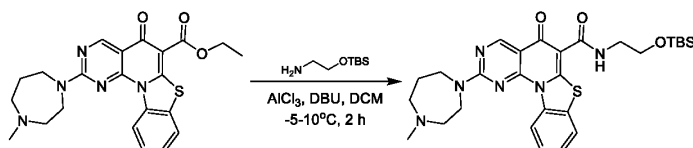


tert-Butyl 2-({[4-(4-methyl-1,4-diazepan-1-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0²,7.0¹²,¹⁷]heptadeca-2,4,6,9,12,14,16-heptaen-9-yl]formamido}methyl)piperidine-1-carboxylate: To a solution of N-(2-aminoethyl)-4-(4-methyl-1,4-diazepan-1-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0²,7.0¹²,¹⁷]heptadeca-2,4,6,9,12,14,16-heptaene-9-carboxamide (150 mg, 342.85 μ mol, 1 eq) in Dichloromethane (2 mL) was added tert-butyl 2-(aminomethyl)piperidine-1-carboxylate (146.95 mg, 685.69 μ mol, 19.59 μ L, 2 eq), DBU (156.58 mg, 1.03 mmol, 155.03 μ L, 3 eq) at -5°C. Then to the reaction was added AlCl₃ (73.14 mg, 548.55 μ mol, 29.98 μ L, 1.6 eq) slowly at -5°C. The reaction was warmed to 25°C and stirred for 2 h. LCMS showed ~60% of the desired MS. The reaction was quenched by addition of 50% of NaOH aqueous solution (1 mL) slowly. The reaction mixture was filtered. The filtrate was concentrated in vacuum to give a residue. The crude product was purified by prep-TLC (DCM: MeOH=10:1, R_f =0.46) to give the title compound (120 mg, 198.10 μ mol, 57.78% yield, 70% purity) as a white solid. **LCMS:** (Rt=0.685, M+H=606.4).



4-(4-Methyl-1,4-diazepan-1-yl)-8-oxo-N-[(piperidin-2-yl)methyl]-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12,14,16-heptaene-9-carboxamide: The solution of tert-Butyl 2-({[4-(4-methyl-1,4-diazepan-1-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12,14,16-heptaen-9-yl]formamido}methyl)piperidine-1-carboxylate (120 mg, 198.10 μ mol, 1 eq) in HCl/dioxane (1 mL) was stirred at 25°C for 1 h. LCMS showed 81% of the desired MS. The mixture was concentrated in vacuum to give a residue. The crude product was purified by prep-HPLC (column: Phenomenex luna C18 100*40mm*5 μ m; mobile phase: [H₂O(0.1% TFA)-MeCN];gradient:1%-30% B over 10.0 min) to give the title compound (**Example 3**, 20.7 mg, 33.41 μ mol, 16.86% yield, TFA) as a white solid. **LCMS** (Rt = 1.415 min, M+H=506). **¹H NMR** (400 MHz, DMSO-D₂O-d₆) δ = 10.46 (t, J = 6.3 Hz, 1H), 9.42 - 9.20 (m, 2H), 8.14 - 8.05 (m, 1H), 7.73 - 7.63 (m, 1H), 7.62 - 7.48 (m, 1H), 4.75 - 4.28 (m, 1H), 4.14 - 3.90 (m, 3H), 3.73 - 3.53 (m, 3H), 3.44 (s, 3H), 3.26 (br d, J = 12.1 Hz, 3H), 2.98 - 2.80 (m, 3H), 2.47 - 2.32 (m, 1H), 2.29 - 2.17 (m, 1H), 1.94 - 1.85 (m, 1H), 1.84 - 1.70 (m, 2H), 1.65 - 1.39 (m, 3H).

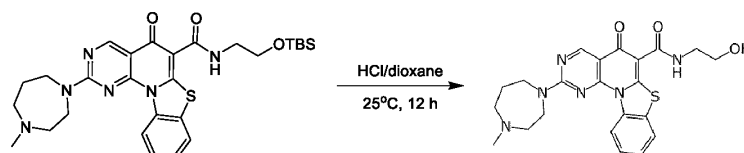
Example 4: N-(2-hydroxyethyl)-4-(4-methyl-1,4-diazepan-1-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12,14,16-heptaene-9-carboxamide



N-{2-[(tert-Butyldimethylsilyl)oxy]ethyl}-4-(4-methyl-1,4-diazepan-1-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12,14,16-heptaene-9-carboxamide: To a mixture of N-(2-aminoethyl)-4-(4-methyl-1,4-diazepan-1-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12,14,16-heptaene-9-carboxamide (0.3 g, 685.69 μ mol, 1 eq) and 2-[tert-butyl(dimethyl)silyl]oxyethanamine (240.46 mg, 1.37 mmol, 2 eq) in DCM (10.00 mL) was added DBU (313.17 mg, 2.06 mmol, 310.07 μ L, 3 eq) and AlCl₃ (146.29 mg, 1.10 mmol, 59.95 μ L, 1.6 eq) in portions at 0°C. Then the reaction was

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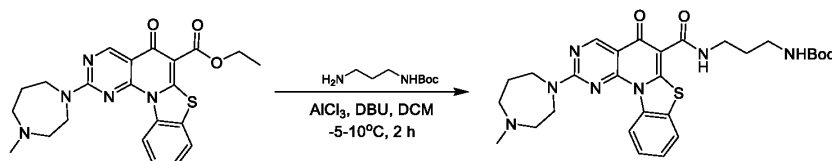
stirred at 0°C for 2 h. LCMS showed the reaction was completed. The mixture was quenched with 50% of NaOH aqueous solution (5.00 mL) at 0°C for 10 min. Then the mixture was filtered and the filtrate was concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Ethyl acetate: Methanol=1/0, 1/5) to afford the title compound (0.25 g, 441.08 μmol, 64.33% yield) as yellow solid. **¹H NMR** (400 MHz, CDCl₃) δ = 10.46 (br s, 1H), 9.47 - 9.30 (m, 2H), 7.73 (br d, J = 7.5 Hz, 1H), 7.53 - 7.39 (m, 2H), 4.23 - 4.16 (m, 1H), 4.07 (br dd, J = 5.9, 8.4 Hz, 1H), 3.99 (t, J = 6.3 Hz, 1H), 3.83 (t, J = 5.9 Hz, 2H), 3.68 - 3.58 (m, 2H), 3.32 (br t, J = 5.5 Hz, 4H), 2.94 - 2.88 (m, 1H), 2.78 - 2.74 (m, 1H), 2.64 (td, J = 5.4, 10.5 Hz, 2H), 2.23 - 2.00 (m, 2H), 0.92 (s, 9H), 0.13 - 0.05 (m, 6H).



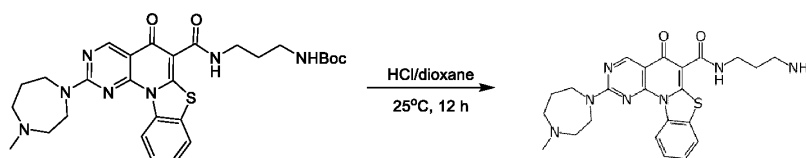
N-(2-hydroxyethyl)-4-(4-methyl-1,4-diazepan-1-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12,14,16-heptaene-9-carboxamide: A mixture of N-{2-[(tert-butyldimethylsilyl)oxy]ethyl}-4-(4-methyl-1,4-diazepan-1-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12,14,16-heptaene-9-carboxamide (0.2 g, 352.87 μmol, 1 eq) in HCl/dioxane (4 M, 5.00 mL, 56.68 eq) was stirred at 25°C for 2 h. LCMS showed the reaction was completed. The mixture was filtered and the filtrate was concentrated in vacuum. The mixture was purified by prep-HPLC (column: Phenomenex luna C18 100*40mm*5 μm; mobile phase: [H₂O(0.04% HCl)-MeCN]; gradient: 1%-30% B over 8.0 min) to give the title compound (**Example 4**, 40.3 mg, 89.06 μmol, 25.24% yield) as a yellow solid. **LCMS** (ESI⁺): m/z 453.3 (M+H)⁺, Rt: 1.381 min. **¹H NMR** (400 MHz, DMSO-d₆+D₂O) δ = 10.95 - 10.74 (m, 1H), 10.29 (t, J = 5.4 Hz, 1H), 9.27 - 9.03 (m, 2H), 8.03 - 7.94 (m, 1H), 7.67 - 7.39 (m, 2H), 4.70 - 4.26 (m, 1H), 4.22 - 3.77 (m, 4H), 3.72 - 3.51 (m, 5H), 3.30 - 3.14 (m, 3H), 2.80 (d, J = 4.6 Hz, 3H), 2.43 - 2.16 (m, 2H).

Example 5: N-(3-aminopropyl)-4-(4-methyl-1,4-diazepan-1-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12,14,16-heptaene-9-carboxamide

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tert-Butyl N-(3-{[4-(4-methyl-1,4-diazepan-1-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0²,7.0¹²,1⁷]heptadeca-2,4,6,9,12,14,16-heptaen-9-yl]formamido}propyl)carbamate: To a solution of N-(2-aminoethyl)-4-(4-methyl-1,4-diazepan-1-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0²,7.0¹²,1⁷]heptadeca-2,4,6,9,12,14,16-heptaene-9-carboxamide (200 mg, 457.13 μ mol, 1 eq) in dichloromethane (3 mL) was added tert-butyl N-(3-aminopropyl)carbamate (159.30 mg, 914.26 μ mol, 159.62 μ L, 2 eq) and DBU (208.77 mg, 1.37 mmol, 206.71 μ L, 3 eq) at -5°C. Then to the reaction was added AlCl₃ (97.53 mg, 731.41 μ mol, 39.97 μ L, 1.6 eq) slowly at -5°C. The reaction was warmed to 10°C and stirred for 2 h. LCMS showed ~80% of the desired MS. The reaction was quenched by addition of 50% of NaOH aqueous solution (5 mL) slowly over 1 min under N₂. The reaction mixture was filtered. The filter cake was triturated with 2-methoxy-2-methylpropane (20 mL) at 25°C for 20 min. After filtration, the filter cake was collected and dried to give the title compound (180 mg, 318.20 μ mol, 69.61% yield) as a white solid. The crude product was used in the next step directly. **LCMS:** (Rt=0.381min, M+H=566.3).

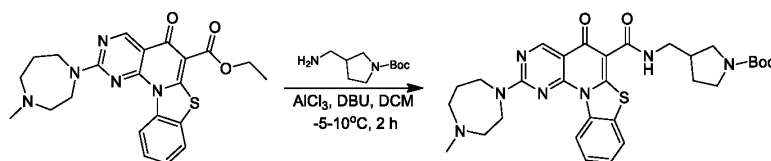


N-(3-aminopropyl)-4-(4-methyl-1,4-diazepan-1-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0²,7.0¹²,1⁷]heptadeca-2,4,6,9,12,14,16-heptaene-9-carboxamide: The solution of tert-Butyl N-(3-{[4-(4-methyl-1,4-diazepan-1-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0²,7.0¹²,1⁷]heptadeca-2,4,6,9,12,14,16-heptaen-9-yl]formamido}propyl)carbamate (180 mg, 318.20 μ mol, 1 eq) in HCl/dioxane (6 mL) was stirred at 25°C for 1 h. LCMS showed 90% of the desired MS. The reaction was concentrated in vacuum to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 100*40mm*5 μ m; mobile phase: [H₂O(0.1% TFA)-MeCN]; gradient:1%-35% B over 7.0 min) to give the title compound (**Example 5**, 65.7 mg, 141.12 μ mol, 44.35% yield, TFA) as a yellow solid. **LCMS:** (Rt=1.348 min, M+H=466.2). **¹H NMR** (400 MHz, DMSO-d₆): δ = 10.40 - 10.19 (m, 2H), 9.32 - 9.04 (m, 2H), 8.08 - 7.97 (m, 1H), 7.86 (br s, 2H), 7.66 - 7.47 (m, 2H),

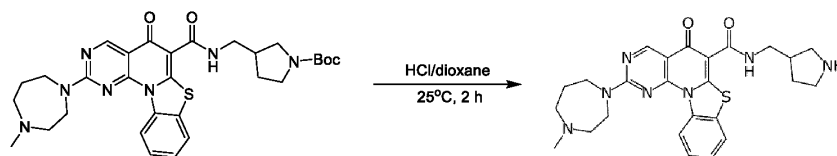
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4.68 - 4.23 (m, 1H), 4.16 - 3.82 (m, 3H), 3.74 - 3.55 (m, 1H), 3.49 - 3.40 (m, 3H), 3.29 (br s, 2H), 2.85 (s, 5H), 2.36 (br s, 1H), 2.23 (br s, 1H), 1.95 - 1.76 (m, 2H).

Example 6: 4-(4-Methyl-1,4-diazepan-1-yl)-8-oxo-N-[(pyrrolidin-3-yl)methyl]-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12,14,16-heptaene-9-carboxamide



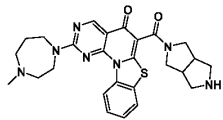
tert-Butyl 3-({[4-(4-methyl-1,4-diazepan-1-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12,14,16-heptaene-9-yl]formamido}methyl)pyrrolidine-1-carboxylate: To a solution of N-(2-aminoethyl)-4-(4-methyl-1,4-diazepan-1-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12,14,16-heptaene-9-carboxamide (0.3 g, 685.69 μ mol, 1 eq) in DCM (5 mL) was added tert-butyl 3-(aminomethyl)pyrrolidine-1-carboxylate (274.66 mg, 1.37 mmol, 2 eq), DBU (313.17 mg, 2.06 mmol, 310.07 μ L, 3 eq) and AlCl_3 (146.29 mg, 1.10 mmol, 59.95 μ L, 1.6 eq) under N_2 protection at -10°C . The mixture was stirred at -5°C for 2 h. LCMS showed R1 was consumed, 16.18% of P1 ($R_t = 0.406$, $M+H = 592.6$). The reaction mixture was quenched by addition of 50% of NaOH aqueous solution (2 mL) at 25°C , and then extracted with DCM (5 mL *3). The combined organic layers were washed with saturated brine (1 mL * 3), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The crude product was triturated with methyl tert-butyl ether (5 mL) at 25°C for 5 min. After filtration, the filter cake was collected to give the title compound (0.2 g, 338.00 μ mol, 49.29% yield) as yellow solid. **LCMS** (ESI+): m/z 592.6 ($M+H$)⁺, R_t : 0.406 min.

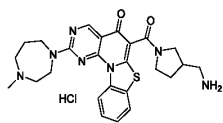
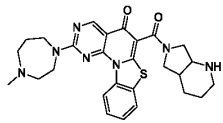


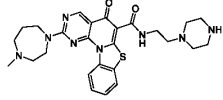
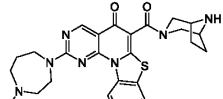
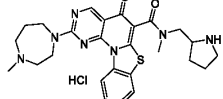
4-(4-Methyl-1,4-diazepan-1-yl)-8-oxo-N-[(pyrrolidin-3-yl)methyl]-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12,14,16-heptaene-9-carboxamide: The solution of tert-butyl 3-({[4-(4-methyl-1,4-diazepan-1-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-

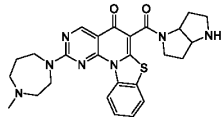
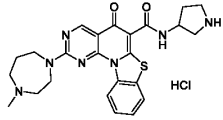
- 2,4,6,9,12,14,16-heptaen-9-yl]formamido}methyl)pyrrolidine-1-carboxylate (0.2 g, 338.00 μmol , 1 eq) in HCl/dioxane (3 mL) was stirred at 25°C for 2 h. LCMS showed R1 was consumed, 26% of P1 (R_t = 0.278, $M+H$ = 492.2) was generated. The reaction mixture was concentrated. The crude product was purified by prep-HPLC (column: Phenomenex luna C18 100*40mm*5 μm ; mobile phase: [H_2O (0.04% HCl)-MeCN]; gradient:1%-25% B over 8.0 min) to give the title compound (**Example 6**, 81.5 mg, 165.78 μmol , 49.05% yield) as yellow solid. **LCMS** (ESI+): m/z 492.3 ($M+H$)⁺, R_t : 1.311 min. **¹H NMR** (400 MHz, DMSO- d_6) δ = 11.44 - 11.00 (m, 1H), 10.36 (br t, J = 5.8 Hz, 1H), 9.27 - 9.21 (m, 2H), 8.02 (dd, J = 3.3, 7.4 Hz, 1H), 7.76 - 7.42 (m, 2H), 4.72 - 4.26 (m, 1H), 4.23 - 3.76 (m, 4H), 3.73 - 3.37 (m, 5H), 3.31 - 3.09 (m, 5H), 2.97 - 2.85 (m, 1H), 2.79 (br d, J = 3.5 Hz, 3H), 2.62 - 2.52 (m, 2H), 2.41 - 2.16 (m, 1H), 2.12 - 1.99 (m, 1H), 1.76 - 1.62 (m, 1H).

- The following examples were synthesised according to the method outlined in Synthetic Route 1 using commercially available starting materials:

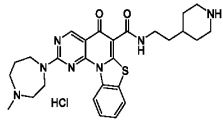
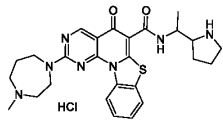
Name	Structure	Example	Yield	Analytical Data
2-(4-methyl-1,4-diazepan-1-yl)-6-(octahydropyrrolo[3,4-c]pyrrole-2-carbonyl)-5H-benzo[4',5']thiazolo[3',2':1,6]pyrido[2,3-d]pyrimidin-5-one		41	59%	LCMS (ESI+): m/z 504.2 ($M+H$) ⁺ , R_t : 1.164 min. ¹H NMR (400 MHz, DMSO- d_6 +D ₂ O) δ = 9.19 - 8.93 (m, 2H), 7.88 (dd, J = 7.8, 15.8 Hz, 1H), 7.65 - 7.34 (m, 2H), 4.69 - 4.22 (m, 1H), 4.17 - 4.00 (m, 1H), 3.99 - 3.85 (m, 2H), 3.84 - 3.74 (m, 2H), 3.67 - 3.59 (m, 2H), 3.57 - 3.45 (m, 2H), 3.36 (br d, J = 8.4 Hz, 2H), 3.32 - 3.13 (m, 2H), 3.12 - 2.87 (m, 4H), 2.80 (s, 3H), 2.48 - 2.10 (m, 2H)

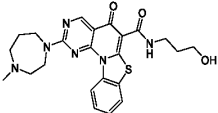
Name	Structure	Example	Yield	Analytical Data
6-(3-(aminomethyl)pyrrolidine-1-carbonyl)-2-(4-methyl-1,4-diazepan-1-yl)-5H-benzo[4',5']thiazolo[3',2':1,6]pyrido[2,3-d]pyrimidin-5-one		42	38%	LCMS (ESI+): m/z 492.4 (M+H) ⁺ , Rt: 1.157 min. ¹H NMR (400 MHz, DMSO-d ₆ + D ₂ O) δ = 9.25 - 9.02 (m, 2H), 7.93 - 7.84 (m, 1H), 7.65 - 7.54 (m, 1H), 7.47 (q, J = 7.1 Hz, 1H), 4.67 - 4.21 (m, 1H), 4.10 - 3.95 (m, 2H), 3.84 - 3.63 (m, 2H), 3.56 - 3.38 (m, 4H), 3.32 - 3.14 (m, 3H), 2.98 - 2.87 (m, 1H), 2.84 - 2.73 (m, 4H), 2.46 - 2.28 (m, 2H), 2.20 (br s, 1H), 2.14 - 1.97 (m, 1H), 1.78 - 1.57 (m, 1H)
2-(4-methyl-1,4-diazepan-1-yl)-6-(octahydro-1H-pyrrolo[3,4-b]pyridine-6-carbonyl)-5H-benzo[4',5']thiazolo[3',2':1,6]pyrido[2,3-d]pyrimidin-5-one		43	13%	LCMS (ESI+): Rt: 1.234 min, m/z 518.3 (M+H) ⁺ . ¹H NMR (400 MHz, DMSO-d ₆ + D ₂ O) δ = 9.37 - 9.08 (m, 2H), 7.99 (dt, J = 2.8, 7.7 Hz, 1H), 7.70 - 7.57 (m, 1H), 7.55 - 7.46 (m, 1H), 4.73 - 4.28 (m, 1H), 4.26 - 3.87 (m, 4H), 3.85 - 3.57 (m, 4H), 3.56 - 3.48 (m, 2H), 3.34 - 3.05 (m, 3H), 2.96 - 2.75 (m, 4H), 2.69 - 2.57 (m, 1H), 2.45 - 2.16 (m, 2H), 1.80 - 1.48 (m, 4H).

Name	Structure	Example	Yield	Analytical Data
2-(4-methyl-1,4-diazepan-1-yl)-5-oxo-N-(2-(piperazin-1-yl)ethyl)-5H-benzo[4',5']thiazolo[3',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamide		44	11%	LCMS (ESI+): m/z 521.4 (M+H) ⁺ , Rt: 1.620 min. ¹H NMR (400 MHz, DMSO-d ₆ +D ₂ O) δ = 9.23 - 8.95 (m, 2H), 7.99 - 7.89 (m, 1H), 7.64 - 7.44 (m, 2H), 4.64 - 4.14 (m, 1H), 4.01 (br d, J = 4.8 Hz, 1H), 3.73 (br d, J = 5.8 Hz, 4H), 3.57 - 3.37 (m, 10H), 3.35 - 3.20 (m, 4H), 2.81 (s, 3H), 2.34 (br s, 1H), 2.22 (br s, 1H).
6-((1R,5S)-3,8-diazabicyclo[3.2.1]octane-3-carbonyl)-2-(4-methyl-1,4-diazepan-1-yl)-5H-benzo[4',5']thiazolo[3',2':1,6]pyrido[2,3-d]pyrimidin-5-one		45	67%	LCMS (ESI+): m/z 504.3 (M+H) ⁺ , Rt: 1.182 min. ¹H NMR (400 MHz, DMSO-d ₆ +D ₂ O) δ = 9.23 - 9.04 (m, 2H), 7.99 - 7.90 (m, 1H), 7.67 - 7.55 (m, 1H), 7.52 - 7.42 (m, 1H), 4.70 - 4.24 (m, 2H), 4.16 - 4.08 (m, 1H), 4.06 - 3.90 (m, 2H), 3.90 - 3.75 (m, 2H), 3.69 - 3.65 (m, 1H), 3.61 (br s, 2H), 3.57 - 3.41 (m, 2H), 3.29 - 3.18 (m, 2H), 2.81 (s, 3H), 2.46 - 2.15 (m, 2H), 1.99 (br d, J = 4.5 Hz, 1H), 1.93 - 1.71 (m, 3H).
N-methyl-2-(4-methyl-1,4-diazepan-1-yl)-5-oxo-N-(pyrrolidin-		46	55%	LCMS (ESI+): m/z 506.3 (M+H) ⁺ , Rt: 1.231 min. ¹H NMR (400 MHz, DMSO-d ₆ +D ₂ O) δ = 9.33 - 9.05 (m, 2H), 7.96 (br s, 1H),

Name	Structure	Example	Yield	Analytical Data
2-ylmethyl)- 5H- benzo[4',5']th iazolo[3',2':1, 6]pyrido[2,3- d]pyrimidine- 6- carboxamide				7.63 (br d, J = 4.3 Hz, 1H), 7.50 (br s, 1H), 4.69 - 4.26 (m, 1H), 4.15 - 3.88 (m, 3H), 3.79 (br s, 2H), 3.69 - 3.62 (m, 1H), 3.57 - 3.40 (m, 2H), 3.37 - 3.14 (m, 4H), 3.11 - 2.93 (m, 3H), 2.82 (s, 3H), 2.36 (br s, 1H), 2.27 - 1.89 (m, 3H), 1.86 - 1.34 (m, 2H).
2-(4-methyl- 1,4-diazepan- 1-yl)-6- (octahydropyr rolo[3,2- b]pyrrole-1- carbonyl)-5H- benzo[4', 5']thiazolo[3', 2':1,6]pyrido[2,3- d]pyrimidin- 5-one		47	9%	LCMS (ESI+): m/z 504.3 (M+H) ⁺ , Rt: 1.206 min. ¹H NMR (400 MHz, DMSO- d ₆ +D ₂ O) δ = 9.30 - 9.09 (m, 2H), 7.94 (br d, J = 7.6 Hz, 1H), 7.63 - 7.53 (m, 1H), 7.49 - 7.41 (m, 1H), 4.71 - 4.25 (m, 1H), 4.07 (br d, J = 4.4 Hz, 1H), 4.02 - 3.87 (m, 3H), 3.81 - 3.65 (m, 1H), 3.54 - 3.37 (m, 2H), 2.88 - 2.79 (m, 2H), 2.77 - 2.62 (m, 2H), 2.58 - 2.52 (m, 2H), 2.28 (d, J = 8.5 Hz, 3H), 2.13 - 2.04 (m, 1H), 2.03 - 1.96 (m, 1H), 1.95 - 1.88 (m, 1H), 1.86 - 1.71 (m, 2H), 1.71 - 1.56 (m, 1H).
2-(4-methyl- 1,4-diazepan- 1-yl)-5-oxo- N-(pyrrolidin- 3-yl)-5H- benzo [4',5']		48	23%	LCMS (ESI+): m/z 478.3 (M+H) ⁺ , Rt: 1.316 min. ¹H NMR (400 MHz, DMSO- d ₆ +D ₂ O) δ = 9.00 (d, J = 16.4 Hz, 1H), 8.84 (br d, J = 8.1 Hz, 1H), 7.85 (br d, J

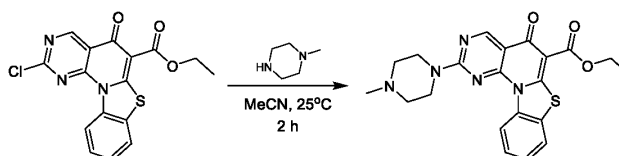
Name	Structure	Example	Yield	Analytical Data
thiazolo [3',2':1,6] pyrido[2,3- d]pyrimidine- 6- carboxamide				= 8.9 Hz, 1H), 7.50 - 7.34 (m, 2H), 4.58 - 4.50 (m, 1H), 4.13 - 3.97 (m, 1H), 3.96 - 3.71 (m, 3H), 3.68 - 3.62 (m, 1H), 3.52 (br s, 2H), 3.41 - 3.18 (m, 4H), 3.12 (dt, $J = 5.6$, 11.5 Hz, 1H), 2.82 (br s, 3H), 2.46 - 2.14 (m, 3H), 1.96 (td, $J = 6.8$, 13.4 Hz, 1H).
2-(4-methyl- 1,4-diazepan- 1-yl)-5-oxo- N-(piperidin- 4-ylmethyl)- 5H- benzo[4',5']th- iazolo[3',2':1, 6]pyrido[2,3- d]pyrimidine- 6- carboxamide		49	47%	LCMS (ESI+): m/z 506.3 (M+H) ⁺ , Rt: 1.358 min. ¹H NMR (400 MHz, DMSO-d ₆ +D ₂ O) $\delta = 9.08 - 8.82$ (m, 2H), 7.91 - 7.80 (m, 1H), 7.56 - 7.33 (m, 2H), 4.59 - 4.09 (m, 1H), 4.06 - 3.79 (m, 3H), 3.77 - 3.60 (m, 2H), 3.55 - 3.38 (m, 1H), 3.34 - 3.19 (m, 5H), 2.96 - 2.77 (m, 5H), 2.45 - 2.13 (m, 2H), 1.84 (br d, $J = 13.1$ Hz, 3H), 1.50 - 1.33 (m, 2H).
2-(4-methyl- 1,4-diazepan- 1-yl)-5-oxo- N-(piperidin- 4-yl)-5H- benzo[4',5']th- iazolo[3',2':1, 6]pyrido[2,3- d]pyrimidine- 6- carboxamide		50	39%	LCMS (ESI+): m/z 492.4 (M+H) ⁺ , Rt: 1.332 min. ¹H NMR (400 MHz, DMSO-d ₆ +D ₂ O) $\delta = 9.23 - 8.93$ (m, 2H), 8.01 - 7.86 (m, 1H), 7.65 - 7.41 (m, 2H), 4.61 - 4.15 (m, 1H), 4.09 - 3.95 (m, 2H), 3.92 - 3.85 (m, 1H), 3.80 - 3.73 (m, 1H), 3.71 - 3.38 (m, 2H), 3.36 - 3.14 (m, 4H), 3.06 (br t, $J = 11.5$ Hz, 2H),

Name	Structure	Example	Yield	Analytical Data
				2.81 (s, 3H), 2.33 (br s, 1H), 2.21 (br s, 1H), 2.12 (br dd, $J = 1.6, 9.2$ Hz, 2H), 1.79 - 1.62 (m, 2H).
2-(4-methyl-1,4-diazepan-1-yl)-5-oxo-N-(2-(piperidin-4-yl)ethyl)-5H-benzo [4',5']thiazolo [3',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamide		51	66%	LCMS (ESI+): m/z 520.2 (M+H) ⁺ , Rt: 1.344 min. ¹H NMR (400 MHz, DMSO- d_6 +D ₂ O) $\delta = 8.92$ (br d, $J = 17.0$ Hz, 1H), 8.85 - 8.68 (m, 1H), 7.80 (br d, $J = 6.0$ Hz, 1H), 7.48 - 7.25 (m, 2H), 4.60 - 3.98 (m, 2H), 3.89 - 3.80 (m, 2H), 3.69 - 3.51 (m, 2H), 3.50 - 3.36 (m, 1H), 3.27 (br d, $J = 13.0$ Hz, 5H), 2.90 - 2.75 (m, 5H), 2.36 (br d, $J = 5.3$ Hz, 2H), 1.88 (br d, $J = 12.6$ Hz, 2H), 1.63 (br s, 1H), 1.54 - 1.33 (m, 4H).
2-(4-methyl-1,4-diazepan-1-yl)-5-oxo-N-(1-(pyrrolidin-2-yl)ethyl)-5H-benzo[4',5']thiazolo[3',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamide		52	36%	LCMS (ESI+): m/z 504.3 (M+H) ⁺ , Rt: 1.357 min. ¹H NMR (400 MHz, DMSO- d_6) $\delta = 11.53$ (br d, $J = 17.3$ Hz, 1H), 10.57 - 10.38 (m, 1H), 9.96 - 9.61 (m, 1H), 9.32 - 9.05 (m, 2H), 8.68 (br s, 1H), 8.04 (br d, $J = 7.6$ Hz, 1H), 7.72 - 7.47 (m, 2H), 4.71 - 4.43 (m, 1H), 4.38 - 4.24 (m, 1H), 4.20 - 3.96 (m, 2H), 3.91 - 3.78 (m, 1H), 3.70 - 3.57 (m, 2H), 3.55 - 3.40 (m, 1H), 3.34 - 3.08 (m, 4H),

Name	Structure	Example	Yield	Analytical Data
				2.77 (br d, J = 4.5 Hz, 3H), 2.69 - 2.55 (m, 1H), 2.39 - 2.17 (m, 1H), 2.15 - 2.04 (m, 1H), 2.02 - 1.81 (m, 2H), 1.79 - 1.66 (m, 1H), 1.38 - 1.26 (m, 3H).
N-(3-hydroxypropyl)-2-(4-methyl-1,4-diazepan-1-yl)-5-oxo-5H-benzo[4',5']thiazolo[3',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamide		53	31%	LCMS (ESI+): m/z 467.3 (M+H) ⁺ , Rt: 1.380 min. ¹H NMR (400 MHz, DMSO-d ₆ +D ₂ O) δ = 9.21 - 8.98 (m, 2H), 7.96 - 7.90 (m, 1H), 7.60 - 7.42 (m, 2H), 4.62 - 4.18 (m, 1H), 4.04 - 3.82 (m, 3H), 3.69 - 3.63 (m, 1H), 3.54 - 3.45 (m, 3H), 3.38 (br t, J = 6.8 Hz, 2H), 3.32 - 3.18 (m, 2H), 2.83 (s, 3H), 2.33 (br d, J = 1.6 Hz, 1H), 1.77 - 1.47 (m, 3H).

Synthetic Route 2

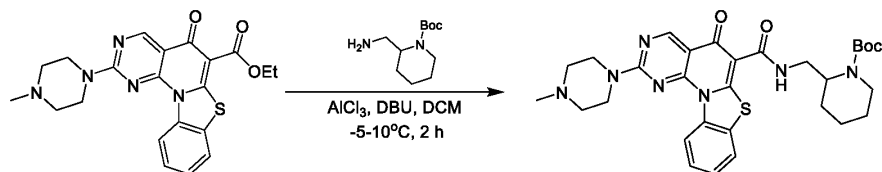
5 **Example 7: 4-(4-Methylpiperazin-1-yl)-8-oxo-N-[(piperidin-2-yl)methyl]-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12,14,16-heptaene-9-carboxamide**



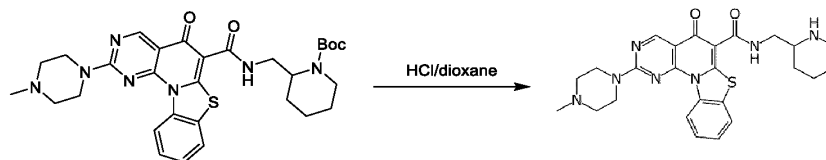
10 **Ethyl 4-(4-methylpiperazin-1-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12,14,16-heptaene-9-carboxylate:** To a solution of ethyl 4-chloro-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2(7),3,5,9,12,14,16-heptaene-9-carboxylate (3 g, 8.34 mmol, 1 eq) in MeCN (30 mL) was added 1-methylpiperazine (1.25 g, 12.51 mmol, 2.08 mL, 1.5 eq) and the mixture was stirred at 25°C for 2 h. LCMS showed 93% of desired MS, Rt =

- 120 -

0.323min, Ms+H = 424. The mixture was concentrated in vacuum to give crude product. The crude product was triturated with MeCN (20 mL) for 30 min. The mixture was filtered to give the filter cake. The filter cake was collected and dried to give the title compound (2.3 g, 5.43 mmol, 65.15% yield, 90% purity) as yellow solid. **LCMS** (ESI+): m/z 424.3 (M+H)⁺, Rt: 0.323 min.



tert-Butyl 2-({[4-(4-methylpiperazin-1-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0²,7.0¹²,17]heptadeca-2,4,6,9,12,14,16-heptaen-9-yl]formamido}methyl)piperidine-1-carboxylate: To a mixture of ethyl 4-(4-methylpiperazin-1-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0²,7.0¹²,17]-heptadeca-2,4,6,9,12,14,16-heptaene-9-carboxylate (0.3 g, 708.40 μmol, 1 eq) in DCM (10.00 mL) was added DBU (323.54 mg, 2.13 mmol, 320.34 μL, 3 eq) and AlCl₃ (151.13 mg, 1.13 mmol, 61.94 μL, 1.6 eq) in portion at 0°C. Then the reaction was stirred at 10°C for 2 h. LCMS showed the reaction was completed. The mixture was quenched with 50% of NaOH aqueous solution (3.00 mL) at 0°C for 10 min. Then the mixture was filtered and the filtrate was concentrated in vacuum. The crude product was triturated with MeOH (5.00 mL) at 0°C for 10 min, then the mixture was filtered and the solid was collected to give the title compound (0.25 g, 422.50 μmol, 59.64% yield) as a yellow solid. **¹H NMR** (400 MHz, CDCl₃). δ = 10.35 (br t, J = 5.4 Hz, 1H), 9.44 - 9.28 (m, 2H), 7.74 (d, J = 7.5 Hz, 1H), 7.59 - 7.37 (m, 2H), 4.53 (br s, 1H), 4.09 (br s, 4H), 3.83 - 3.70 (m, 1H), 3.67 - 3.58 (m, 1H), 3.54 - 3.35 (m, 1H), 3.03 - 2.86 (m, 1H), 2.60 (br s, 3H), 2.40 (s, 3H), 1.87 - 1.54 (m, 7H), 1.42 (s, 9H).



4-(4-Methylpiperazin-1-yl)-8-oxo-N-[(piperidin-2-yl)methyl]-11-thia-1,3,5-triazatetracyclo[8.7.0.0²,7.0¹²,17]heptadeca-2,4,6,9,12,14,16-heptaene-9-carboxamide: A mixture of tert-butyl 2-({[4-(4-methylpiperazin-1-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0²,7.0¹²,17]heptadeca-2,4,6,9,12,14,16-heptaen-9-yl]formamido}methyl)piperidine-1-carboxylate (0.2 g, 338.00 μmol, 1 eq) in

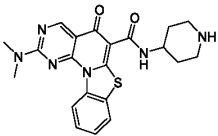
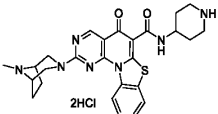
- HCl/dioxane (4 M, 4.00 mL, 47.34 eq) was stirred at 25°C for 2 h. LCMS showed the reaction was completed. The mixture was filtered and the filtrate was concentrated in vacuum. The crude product was triturated with MeCN (5.00 mL) at 0°C for 10 min to give the title compound (**Example 7**, 120.3 mg, 244.71 μ mol, 72.40% yield) as a yellow solid. **LCMS** (ESI+): m/z 492.4 (M+H)⁺, Rt: 1.301 min **¹H NMR** (400 MHz, DMSO-*d*₆+D₂O) δ = 10.40 (br t, *J* = 5.9 Hz, 1H), 9.35 (s, 1H), 9.24 (br d, *J* = 8.5 Hz, 1H), 8.04 (br d, *J* = 7.6 Hz, 1H), 7.67 (br t, *J* = 7.8 Hz, 1H), 7.60 - 7.49 (m, 1H), 5.14 - 4.55 (m, 2H), 3.67 - 3.51 (m, 6H), 3.32 - 3.11 (m, 4H), 2.94 - 2.79 (m, 4H), 1.88 (br d, *J* = 8.4 Hz, 1H), 1.74 (br d, *J* = 18.4 Hz, 2H), 1.63 - 1.40 (m, 3H).

10

The following examples were synthesised according to the method outlined in Synthetic Route 2 using commercially available starting materials:

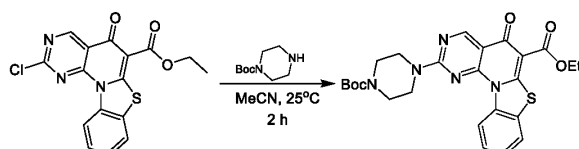
Name	Structure	Example	Yield	Analytical Data
4-(4-methylpiperazin-1-yl)-8-oxo-N-(4-piperidyl)-11-thia-1,3,5-triazatetracyclo[8.7.0.0 ^{2,7} .0 ^{12,17}]heptadecan-2,4,6,9,12(17),13,15-heptaene-9-carboxamide		54	13%	HCl salt LCMS (ESI+): m/z 478.1 (M+H) ⁺ , Rt: 1.586 min. ¹H NMR (400 MHz, DMSO- <i>d</i> ₆ +D ₂ O) δ 9.20 (s, 1H), 9.03 (br d, <i>J</i> = 8.3 Hz, 1H), 7.92 (br d, <i>J</i> = 7.5 Hz, 1H), 7.60 - 7.46 (m, 2H), 5.13 - 4.42 (m, 2H), 4.02 (br s, 1H), 3.77 - 3.41 (m, 4H), 3.30 (br d, <i>J</i> = 12.8 Hz, 2H), 3.25 - 3.17 (m, 1H), 3.15 - 2.93 (m, 3H), 2.87 (s, 3H), 2.12 (br d, <i>J</i> = 11.9 Hz, 2H), 1.78 - 1.64 (m, 2H).
6-(3-aminopyrrolidin-1-carbonyl)-2-(4-methylpiperazin-1-yl)-5H-benzo[4',5']th		55	45%	LCMS (ESI+): m/z 464.3 (M+H) ⁺ , Rt: 1.103 min. ¹H NMR (400 MHz, DMSO- <i>d</i> ₆ +D ₂ O) δ 9.24 (s, 1H), 9.18 (d, <i>J</i> = 8.5 Hz, 1H), 7.95 (dd, <i>J</i> = 2.5, 7.8 Hz, 1H), 7.63 (t, <i>J</i> = 7.9 Hz, 1H), 7.54 - 7.45 (m, 1H),

Name	Structure	Example	Yield	Analytical Data
iazolo[3',2':1,6]pyrido[2,3-d]pyrimidin-5-one				5.11 - 4.54 (m, 2H), 3.91 - 3.82 (m, 1H), 3.77 - 3.71 (m, 2H), 3.68 - 3.46 (m, 6H), 3.35 - 3.04 (m, 2H), 2.86 (s, 3H), 2.34 - 2.13 (m, 1H), 2.05 - 1.81 (m, 1H).
2-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-5-oxo-N-(piperidin-4-yl)-5H-benzo[4',5']thiazolo[3',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamide		56	62%	LCMS (ESI+): m/z 504.1 (M+H) ⁺ , Rt: 2.659 min. ¹H NMR (400 MHz, DMSO- <i>d</i> ₆ + D ₂ O) δ 9.29 - 9.14 (m, 1H), 9.08 (br d, <i>J</i> = 7.3 Hz, 1H), 7.97 (br d, <i>J</i> = 7.6 Hz, 1H), 7.65 - 7.44 (m, 2H), 4.17 - 3.97 (m, 3H), 3.95 - 3.81 (m, 2H), 3.69 - 3.51 (m, 2H), 3.30 (br d, <i>J</i> = 12.8 Hz, 4H), 3.06 (br t, <i>J</i> = 11.1 Hz, 3H), 2.34 - 1.97 (m, 5H), 1.94 - 1.82 (m, 1H), 1.77 - 1.65 (m, 2H).
2-(1-methylhexahydropyrrolo[3,4-b]pyrrol-5(1H)-yl)-5-oxo-N-(piperidin-4-yl)-5H-benzo[4',5']thiazolo[3',2':1,6]pyrido[2,3-d]pyrimidine-6-		57	40%	LCMS (ESI+): m/z 504.1 (M+H) ⁺ , Rt: 1.725 min. ¹H NMR (400 MHz, DMSO- <i>d</i> ₆ + D ₂ O) 9.41 (br dd, <i>J</i> = 1.1, 6.4 Hz, 1H), 9.29 (s, 1H), 8.04 (br d, <i>J</i> = 7.3 Hz, 1H), 7.75 - 7.62 (m, 1H), 7.60 - 7.49 (m, 1H), 4.44 - 4.16 (m, 2H), 4.16 - 3.90 (m, 3H), 3.75 - 3.68 (m, 2H), 3.29 (br d, <i>J</i> = 13.6 Hz, 3H), 3.15 - 3.01 (m, 3H), 2.95 (br d, <i>J</i> = 13.9

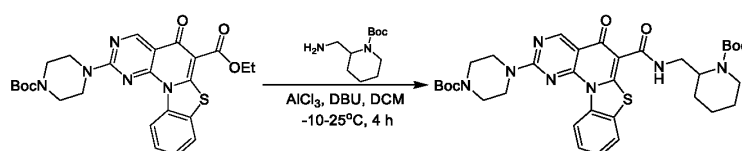
Name	Structure	Example	Yield	Analytical Data
carboxamide				Hz, 3H), 2.11 (br dd, J = 1.7, 10.2 Hz, 2H), 2.02 - 1.89 (m, 1H), 1.76 - 1.65 (m, 2H), 1.54 - 1.43 (m, 1H).
2-(dimethylamino)-5-oxo-N-(piperidin-4-yl)-5H-benzo[4',5']thiazolo[3',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamide		58	57%	LCMS (ESI+): m/z 423.2 (M+H) ⁺ , Rt: 1.670min. ¹H NMR (400 MHz, DMSO-d ₆ + D ₂ O) δ 9.26 (d, J = 8.4 Hz, 1H), 9.14 (s, 1H), 7.99 (dd, J = 0.9, 7.7 Hz, 1H), 7.58 - 7.52 (m, 1H), 7.51 - 7.46 (m, 1H), 4.14 - 4.05 (m, 1H), 3.36 - 3.24 (m, 8H), 3.13 - 3.03 (m, 2H), 2.15 - 2.06 (m, 2H), 1.77 - 1.65 (m, 2H).
2-((1R,5S)-8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)-5-oxo-N-(piperidin-4-yl)-5H-benzo[4',5']thiazolo[3',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamide		59	58%	LCMS (ESI+): m/z 504.4 (M+H) ⁺ , Rt: 1.281 min. ¹H NMR (400 MHz, DMSO-d ₆ + D ₂ O) δ 9.15 (s, 1H), 8.96 (br d, J = 8.3 Hz, 1H), 7.87 (br d, J = 7.4 Hz, 1H), 7.54 - 7.44 (m, 2H), 4.77 (br d, J = 11.8 Hz, 1H), 4.50 - 4.34 (m, 1H), 4.06 - 3.90 (m, 2H), 3.74 - 3.48 (m, 2H), 3.30 (br d, J = 12.6 Hz, 2H), 3.14 - 2.92 (m, 3H), 2.78 (s, 3H), 2.23 (br s, 2H), 2.10 (br s, 2H), 1.91 - 1.82 (m, 2H), 1.69 (br d, J = 11.0 Hz, 2H).

Synthetic Route 3

Example 8: 8-Oxo-4-(piperazin-1-yl)-N-[(piperidin-2-yl)methyl]-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12,14,16-heptaene-9-carboxamide



Ethyl 4-{4-[(tert-butoxy)carbonyl]piperazin-1-yl}-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12,14,16-heptaene-9-carboxylate: To a solution of ethyl 4-chloro-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2(7),3,5,9,12,14,16-heptaene-9-carboxylate (2 g, 5.56 mmol, 1 eq) in MeCN (20 mL) was added tert-butyl piperazine-1-carboxylate (1.55 g, 8.34 mmol, 1.5 eq) and the mixture was stirred at 25°C for 2 h. LCMS showed that 91% of desired MS (Rt= 0.589min, M+H=510) was detected. The mixture was concentrated in vacuum to give a residue. The crude product was triturated with MTBE (20 mL) for 30 min and after filtration the filter cake was collected to give the title compound (2 g, 3.53 mmol, 63.54% yield, 90% purity) as yellow solid. **LCMS** (ESI⁺): m/z 510.3 (M+H)⁺, Rt: 0.589 min.

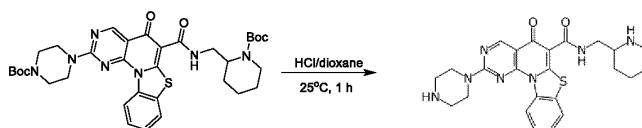


tert-Butyl 4-{9-[(1-[(tert-butoxy)carbonyl]piperidin-2-yl)methyl]-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12,14,16-heptaen-4-yl}piperazine-1-carboxylate: To a solution of ethyl 4-{4-[(tert-butoxy)carbonyl]piperazin-1-yl}-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12,14,16-heptaene-9-carboxylate (0.3 g, 588.72 μmol, 1 eq) in DCM (3 mL) was added tert-butyl 2-(aminomethyl)piperidine-1-carboxylate (189.25 mg, 883.09 μmol, 25.23 μL, 1.5 eq), the mixture was cool at -10°C, was added DBU (268.88 mg, 1.77 mmol, 266.21 μL, 3 eq) dropwise then AlCl₃ (125.60 mg, 941.96 μmol, 51.48 μL, 1.6 eq) was added in portions, the reaction was stirred for 4 h at 25°C. LCMS showed 85% of desired MS (Rt=0.711min, M+H=678). The reaction was quenched by 50% of NaOH solution (2 mL) slowly and filtered. The mixture was extracted with Dichloromethane (3*5 mL).

The combined organic phases were dried over anhydrous Na₂SO₄, concentrated in vacuum to give the title compound (0.2 g, 265.56 μmol, 45.11% yield, 90% purity) as yellow solid. The crude product was used for next step directly without purification.

LCMS (ESI+): m/z 678.5 (M+H)⁺, Rt: 0.713 min.

5



8-Oxo-4-(piperazin-1-yl)-N-[(piperidin-2-yl)methyl]-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12,14,16-heptaene-9-carboxamide: The solution of tert-butyl 4-{9-[(1-[(tert-butoxy)carbonyl]piperidin-2-yl)methyl]carbamoyl}-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]-

10 heptadeca-2,4,6,9,12,14,16-heptaen-4-yl}piperazine-1-carboxylate (0.2 g, 295.07 μmol, 1 eq) in HCl/dioxane (5 mL) was stirred for 1 h at 25°C. LCMS showed 90% of desired MS, Rt= 0.280min, M+H=478. The reaction was concentrated in vacuum to give a residue. The crude product was purified by prep-HPLC (column: Phenomenex luna C18 100*40mm*5 μm; mobile phase: [H₂O(0.04% HCl)-MeCN];gradient:1%-
15 30% B over 8.0 min) to give the title compound (**Example 8**, 0.12 g, 228.75 μmol, 77.53% yield, 97.99% purity, HCl) as yellow solid. **LCMS** of product (ESI+): m/z 478.3 (M+H)⁺, Rt: 1.709 min. **¹H NMR** (400 MHz, DMSO-d₆) δ = 10.37 (br t, J = 6.1 Hz, 1H), 9.29 (s, 1H), 9.19 (d, J = 8.5 Hz, 1H), 8.00 (d, J = 7.4 Hz, 1H), 7.68 - 7.60 (m, 1H), 7.57 - 7.50 (m, 1H), 4.18 (br s, 4H), 3.65 - 3.52 (m, 2H), 3.43 - 3.16 (m,
20 6H), 2.90 - 2.77 (m, 1H), 1.93 - 1.69 (m, 3H), 1.64 - 1.39 (m, 3H).

The following examples were synthesised according to the method outlined in Synthetic Route 3 using commercially available starting materials:

Name	Structure	Example	Yield	Analytical Data
5-oxo-2-(piperazin-1-yl)-N-(piperidin-4-yl)-5H-benzo[4',5']thiazolo[3',2':1,6]pyrido[2,3-d]pyrimidine-6-		60	32%	LCMS (ESI+): m/z 464.2 (M+H) ⁺ , Rt: 1.239 min. ¹H NMR (400 MHz, D ₂ O) δ = 8.79 (s, 1H), 8.12 (br d, J = 8.4 Hz, 1H), 7.57 (d, J = 7.8 Hz, 1H), 7.33 (t, J = 7.5 Hz, 1H), 7.16 (br t, J = 7.8 Hz, 1H), 4.23 - 3.94

Name	Structure	Example	Yield	Analytical Data
carboxamide				(m, 2H), 3.93 - 3.64 (m, 3H), 3.54 - 3.43 (m, 2H), 3.38 (br s, 4H), 3.27 - 3.12 (m, 2H), 2.27 - 2.14 (m, 2H), 1.88 - 1.73 (m, 2H).

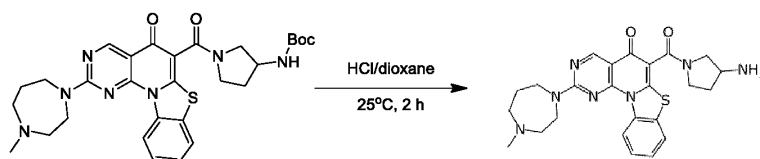
Synthetic Route 4

Example 9: 9-(3-aminopyrrolidine-1-carbonyl)-4-(4-methyl-1,4-diazepan-1-yl)-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12,14,16-heptaen-8-one



tert-Butyl N-{1-[4-(4-methyl-1,4-diazepan-1-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12,14,16-heptaene-9-carbonyl]pyrrolidin-3-yl}carbamate: To a solution of N-(2-aminoethyl)-4-(4-methyl-1,4-diazepan-1-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12,14,16-heptaene-9-carboxamide (0.1 g, 228.56 μmol, 1 eq) in DCM (2 mL) was added tert-butyl N-pyrrolidin-3-yl carbamate (85.14 mg, 457.13 μmol, 2 eq), DBU (104.39 mg, 685.69 μmol, 103.36 μL, 3 eq) and AlCl₃ (48.76 mg, 365.70 μmol, 19.98 μL, 1.6 eq) under N₂ protection at -5°C. The mixture was stirred for 2 h at 10°C. The reaction mixture was quenched by addition of 50% NaOH (aq) 1 mL at 25°C, and then extracted with DCM (2 mL*3). The combined organic layers were washed with saturated brine (3 mL*3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the title compound (0.1 g, 173.10 μmol, 75.73% yield) as yellow solid, which was used in the next step directly without purification. **LCMS** (ESI+): m/z 578.5 (M+H) +, Rt: 0.326 min.

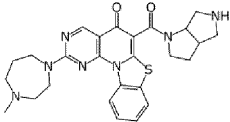
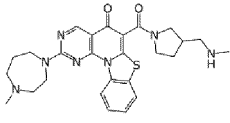
- 127 -

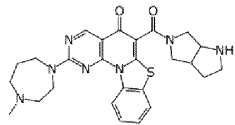
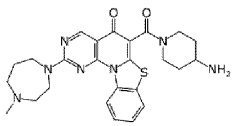


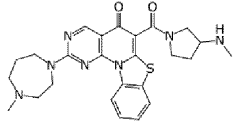
- 9-(3-aminopyrrolidine-1-carbonyl)-4-(4-methyl-1,4-diazepan-1-yl)-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12,14,16-heptaen-8-one:** The mixture of tert-butyl N-{1-[4-(4-methyl-1,4-diazepan-1-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12,14,16-heptaene-9-carbonyl]pyrrolidin-3-yl}carbamate (0.1 g, 173.10 μ mol, 1 eq) in HCl/dioxane (1 mL) was stirred at 25°C for 2 h. The reaction mixture was concentrated in vacuum. The crude product was purified by prep-HPLC (column: Phenomenex luna C18 100*40mm*5 μ m; mobile phase: [H₂O(0.04% HCl)-MeCN]; gradient:1%-25% B over 8.0 min) to give the title compound (**Example 9**, 44.5 mg, 93.18 μ mol, 53.83% yield) as an off-yellow solid. **LCMS** (ESI+): m/z 478.4 (M+H)⁺, Rt: 0.231 min. **¹H NMR** (400 MHz, DMSO-d₆) δ = 11.17 - 10.92 (m, 1H), 9.32 - 9.05 (m, 2H), 8.32 (br s, 2H), 8.07 - 7.92 (m, 1H), 7.71 - 7.56 (m, 1H), 7.50 (q, J = 6.8 Hz, 1H), 4.72 - 4.29 (m, 1H), 4.27 - 4.06 (m, 1H), 3.96 - 3.82 (m, 2H), 3.74 (br d, J = 8.4 Hz, 2H), 3.66 - 3.47 (m, 4H), 3.25 (br d, J = 3.8 Hz, 3H), 2.78 (br d, J = 3.6 Hz, 3H), 2.27 (br s, 3H), 2.09 - 1.86 (m, 1H).

The following examples were synthesised according to the method outlined in Synthetic Route 4 using commercially available starting materials:

Name	Structure	Example	Yield	Analytical Data
9-(3-aminopiperidine-1-carbonyl)-4-(4-methyl-1,4-diazepan-1-yl)-11-thia-1,3,5-triazatetracyclo[8.7.0.0 ^{2,7} .0 ^{12,17}]heptadeca-2,4,6,9,12,14,		10	34%	LCMS (ESI+): m/z 492.3 (M+H) ⁺ , Rt: 1.201min. ¹H NMR (400 MHz, DMSO + D ₂ O-d ₆) δ = 9.32 - 9.04 (m, 2H), 7.94 (br d, J = 7.5 Hz, 1H), 7.68 - 7.58 (m, 1H), 7.54 - 7.45 (m, 1H), 4.70 - 4.46 (m, 1H), 4.40 - 4.14 (m, 1H), 4.10 - 3.88 (m, 3H), 3.81 - 3.74 (m, 1H), 3.58 - 3.43 (m, 2H), 3.31 - 2.95 (m, 5H), 2.82 (s, 3H), 2.41 - 2.33 (m,

Name	Structure	Example	Yield	Analytical Data
16-heptaen-8-one				¹ H), 2.28 - 2.16 (m, 1H), 2.08 - 1.97 (m, 1H), 1.92 - 1.66 (m, 1H), 1.62 - 1.41 (m, 2H)
4-(4-methyl-1,4-diazepan-1-yl)-9-{octahydropyrrolo[2,3-c]pyrrole-1-carbonyl}-11-thia-1,3,5-triazatetracyclo[8.7.0.0 ^{2,7} .0 ^{12,17}]heptadeca-2,4,6,9,12,14,16-heptaen-8-one		11	44%	LCMS (ESI+): m/z 504.3 (M+H) ⁺ , Rt: 1.231 min. ¹H NMR (400 MHz, DMSO-d ₆) δ = 11.41 - 11.12 (m, 1H), 9.52 (br d, J = 1.0 Hz, 2H), 9.30 - 9.05 (m, 2H), 7.97 (br t, J = 6.6 Hz, 1H), 7.71 - 7.55 (m, 1H), 7.48 (q, J = 7.3 Hz, 1H), 4.65 (br d, J = 8.5 Hz, 2H), 4.26 - 3.74 (m, 4H), 3.70 - 3.62 (m, 2H), 3.54 - 3.33 (m, 3H), 3.28 - 2.86 (m, 5H), 2.78 (br d, J = 4.3 Hz, 3H), 2.65 - 2.51 (m, 1H), 2.39 - 2.15 (m, 1H), 2.06 - 1.79 (m, 2H)
4-(4-methyl-1,4-diazepan-1-yl)-9-{3-[(methylamino)methyl]pyrrolidine-1-carbonyl}-11-thia-1,3,5-triazatetracyclo[8.7.0.0 ^{2,7} .0 ^{12,17}]heptadeca-2(7),3,5,9,12,		12	25%	LCMS (ESI+): m/z 506.4 (M+H) ⁺ , Rt: 0.273 min. ¹H NMR (400 MHz, DMSO-d ₆) δ = 11.43 - 11.19 (m, 1H), 9.27 - 9.07 (m, 2H), 9.04 - 8.83 (m, 1H), 8.02 - 7.91 (m, 1H), 7.68 - 7.55 (m, 1H), 7.48 (q, J = 7.3 Hz, 1H), 4.73 - 4.32 (m, 1H), 4.25 - 3.86 (m, 3H), 3.83 - 3.73 (m, 1H), 3.54 -

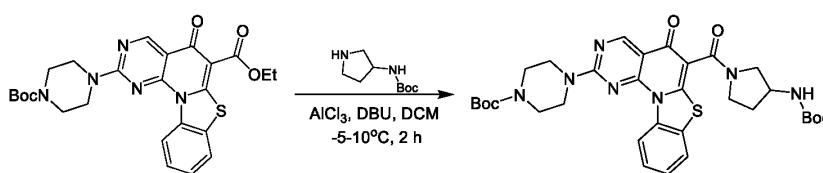
Name	Structure	Example	Yield	Analytical Data
14,16-heptaen-8-one				3.39 (m, 3H), 3.37 - 3.13 (m, 3H), 3.01 (br s, 1H), 2.89 (br s, 1H), 2.77 (br d, J = 3.4 Hz, 3H), 2.66 - 2.52 (m, 3H), 2.47 (br s, 2H), 2.39 - 1.98 (m, 2H), 1.81 - 1.61 (m, 1H)
4-(4-methyl-1,4-diazepan-1-yl)-9-{octahydropyrrolo[3,4-b]pyrrole-5-carbonyl}-11-thia-1,3,5-triazatetracyclo[8.7.0.0 ^{2,7} .0 ^{12,17}]heptadeca-2(7),3,5,9,12,14,16-heptaen-8-one		13	59%	LCMS (ESI+): m/z 504.3 (M+H) ⁺ , Rt: 1.524 min. ¹H NMR (400 MHz, DMSO-d ₆) δ = 11.40 (br d, J = 1.3 Hz, 1H), 10.04 - 9.81 (m, 1H), 9.54 - 9.24 (m, 1H), 9.21 - 8.98 (m, 2H), 7.98 - 7.87 (m, 1H), 7.70 - 7.70 (m, 1H), 7.66 - 7.49 (m, 1H), 7.49 - 7.38 (m, 1H), 4.63 (br d, J = 15.4 Hz, 1H), 4.30 (br s, 1H), 4.23 - 3.98 (m, 3H), 3.81 - 3.57 (m, 4H), 3.56 - 3.34 (m, 2H), 3.32 - 2.94 (m, 5H), 2.77 (br s, 3H), 2.65 - 2.53 (m, 1H), 2.38 - 1.94 (m, 2H), 1.93 - 1.73 (m, 1H).
9-(4-Aminopiperidine-1-carbonyl)-4-(4-methyl-1,4-diazepan-1-yl)-11-thia-		14	37%	LCMS (ESI+): m/z 492.3 (M+H) ⁺ , Rt: 0.262 min. ¹H NMR (400 MHz, MeOD) δ = 9.37 - 9.15 (m, 2H), 7.83 - 7.75 (m, 1H), 7.66 - 7.56 (m, 1H), 7.53 - 7.42 (m,

Name	Structure	Example	Yield	Analytical Data
1,3,5-triazatetracyclo[8.7.0.0 ^{2,7} .0 ^{12,17}]heptadeca-2(7),3,5,9,12,14,16-heptaen-8-one				1H), 4.85 - 4.74 (m, 1H), 4.45 - 4.21 (m, 3H), 4.20 - 3.91 (m, 3H), 3.85 - 3.58 (m, 2H), 3.52 - 3.34 (m, 3H), 3.18 - 3.07 (m, 2H), 3.04 - 2.95 (m, 3H), 2.50 (br s, 2H), 2.09 (br d, J = 12.0 Hz, 2H), 1.82 - 1.61 (m, 2H).
4-(4-methyl-1,4-diazepan-1-yl)-9-[3-(methylamino)pyrrolidine-1-carbonyl]-11-thia-1,3,5-triazatetracyclo[8.7.0.0 ^{2,7} .0 ^{12,17}]heptadeca-2(7),3,5,9,12,14,16-heptaen-8-one		15	29%	LCMS (ESI+): Rt: 1.181 min, m/z 492.2 (M+H). ¹H NMR (400 MHz, DMSO-d ₆) δ = 11.36 - 11.10 (m, 1H), 9.60 - 9.27 (m, 2H), 9.26 - 9.05 (m, 2H), 8.01 - 7.93 (m, 1H), 7.67 - 7.55 (m, 1H), 7.48 (q, J = 7.4 Hz, 1H), 4.72 - 4.31 (m, 1H), 4.27 - 3.97 (m, 2H), 3.95 - 3.76 (m, 3H), 3.74 - 3.64 (m, 2H), 3.63 - 3.53 (m, 2H), 3.32 - 3.13 (m, 2H), 2.77 (d, J = 4.8 Hz, 3H), 2.60 (br t, J = 5.1 Hz, 1H), 2.50 (br s, 3H), 2.49 - 2.42 (m, 1H), 2.39 - 2.19 (m, 2H), 2.18 - 1.96 (m, 1H).

Name	Structure	Example	Yield	Analytical Data
6-(3-hydroxypyrrolidine-1-carbonyl)-2-(4-methyl-1,4-diazepan-1-yl)-5H-benzo[4',5']thiazolo[3',2':1,6]pyrido[2,3-d]pyrimidin-5-one		61	26%	LCMS (ESI+): m/z 479.3 (M+H) ⁺ , Rt: 1.652 min. ¹H NMR (400 MHz, DMSO-d ₆ +D ₂ O) δ = 9.26 - 9.04 (m, 2H), 7.90 (br d, J = 5.0 Hz, 1H), 7.65 - 7.54 (m, 1H), 7.51 - 7.41 (m, 1H), 4.70 - 4.15 (m, 2H), 4.10 - 3.87 (m, 3H), 3.65 - 3.50 (m, 4H), 3.44 - 3.23 (m, 3H), 3.19 - 3.09 (m, 1H), 2.82 (s, 3H), 2.35 - 2.14 (m, 2H), 2.03 - 1.70 (m, 2H).

Synthetic Route 5

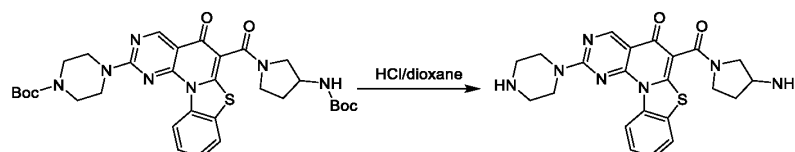
Example 16: 9-(3-Aminopyrrolidine-1-carbonyl)-4-(piperazin-1-yl)-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2(7),3,5,9,12,14,16-heptaen-8-one



tert-Butyl 4-[9-(3-[(tert-butoxy)carbonyl]amino)pyrrolidine-1-carbonyl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2(7),3,5,9,12,14,16-heptaen-4-yl]piperazine-1-carboxylate: To a mixture of ethyl 4-[4-[(tert-butoxy)carbonyl]piperazin-1-yl]-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12,14,16-heptaene-9-carboxylate (0.3 g, 588.72 μmol, 1 eq) and tert-butyl N-pyrrolidin-3-ylcarbamate (219.30 mg, 1.18 mmol, 2 eq) in DCM (10 mL) was added DBU (268.88 mg, 1.77 mmol, 266.22 μL, 3 eq) and AlCl₃ (125.60 mg, 941.96 μmol, 51.48 μL, 1.6 eq) in portions at -5°C. Then the reaction was warmed to 10°C and stirred for 2 h. LCMS

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showed the reaction was completed. The mixture was quenched with 50% of NaOH (aq) (3 mL) at 0°C for 10 min. Then the mixture was filtered and the filtrate was concentrated in vacuum. The crude product was triturated with MeOH (5 mL) at 0°C for 10 min to give the title compound (0.15 g, 230.85 μmol, 39.21% yield) as a yellow solid. **LCMS** (ESI+): Rt: 0.568 min, m/z 650.3 (M+H)⁺.

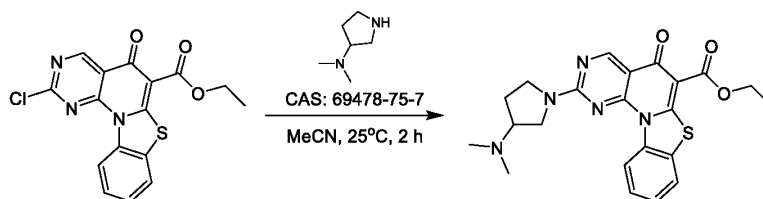


9-(3-Aminopyrrolidine-1-carbonyl)-4-(piperazin-1-yl)-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2(7),3,5,9,12,14,16-heptaen-8-one: A mixture of tert-butyl 4-[9-(3-[[[(tert-butoxy)carbonyl]amino}pyrrolidine-1-carbonyl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2(7),3,5,9,12,14,16-heptaen-4-yl]piperazine-1-carboxylate (0.15 g, 230.85 μmol, 1 eq) in HCl/dioxane (4 M, 5 mL, 86.63 eq) was stirred at 25°C for 2 h. LCMS showed the reaction was completed. The mixture was filtered and the filtrate was concentrated in vacuum. The residue was purified by prep-HPLC (column: Phenomenex luna C18 100*40mm*5 μm; mobile phase: [H₂O(0.04% HCl)-MeCN]; gradient: 1%-15% B over 8.0 min) to give the title compound (**Example 16**, 22.3 mg, 49.61 μmol, 21.49% yield) as a yellow solid. **LCMS** (ESI+): m/z 450.2 (M+H)⁺, Rt: 1.078 min **¹H NMR** (400 MHz, DMSO-d₆) δ = 9.28 - 9.15 (m, 2H), 7.99 (br dd, J = 4.3, 6.8 Hz, 1H), 7.63 (br t, J = 7.9 Hz, 1H), 7.54 - 7.48 (m, 1H), 4.18 (br s, 4H), 3.91 - 3.83 (m, 1H), 3.77 - 3.68 (m, 1H), 3.63 - 3.53 (m, 2H), 3.31 (br s, 4H), 3.17 (br d, J = 7.5 Hz, 1H), 2.31 - 2.09 (m, 1H), 2.05 - 1.84 (m, 1H).

Synthetic Route 6

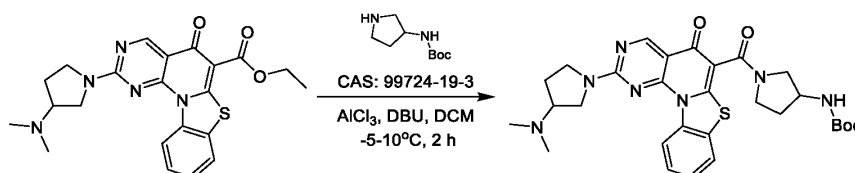
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Example 17: 9-(3-Aminopyrrolidine-1-carbonyl)-4-[3-(dimethylamino)-pyrrolidin-1-yl]-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2(7),3,5,9,12,14,16-heptaen-8-one

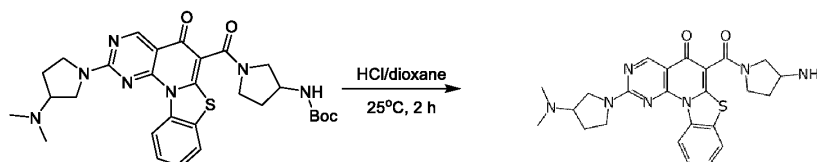


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Ethyl 4-[3-(dimethylamino)pyrrolidin-1-yl]-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2(7),3,5,9,12,14,16-heptaene-9-carboxylate: To the solution of ethyl 4-chloro-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2(7),3,5,9,12,14,16-heptaene-9-carboxylate (0.5 g, 1.39 mmol, 1 eq) in MeCN (5 mL) was added N,N-dimethylpyrrolidin-3-amine (317.38 mg, 2.78 mmol, 2 eq). The mixture was stirred at 25°C for 2 h. The reaction mixture was concentrated. The crude product was triturated with methyl tert-butyl ether (30 mL) for 30 min. After being filtered, the filter cake was collected and dried to give the title compound (400 mg, 914.26 μmol, 65.79% yield) as a white solid. The crude product was used for next step directly. **LCMS** (ESI⁺): m/z 438.1 (M+H)⁺, Rt: 0.339 min.

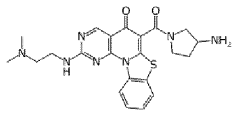


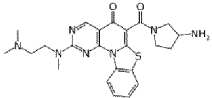
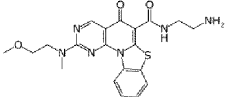
tert-Butyl N-(1-{4-[3-(dimethylamino)pyrrolidin-1-yl]-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2(7),3,5,9,12,14,16-heptaene-9-carboxyl}pyrrolidin-3-yl)carbamate: To a solution of ethyl 4-[3-(dimethylamino)pyrrolidin-1-yl]-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2(7),3,5,9,12,14,16-heptaene-9-carboxylate (350 mg, 799.97 μmol, 1 eq) and tert-butyl N-pyrrolidin-3-ylcarbamate (297.99 mg, 1.60 mmol, 2 eq) in DCM (5 mL) was added DBU (365.36 mg, 2.40 mmol, 361.74 μL, 3 eq) and AlCl₃ (213.34 mg, 1.60 mmol, 87.43 μL, 2 eq) at -5°C. The mixture was warmed to 10°C and stirred for 2 h. The reaction mixture was quenched by NaOH (50%, 5 mL) at 25°C and filtered. The filtrate mixture was extracted with ethyl acetate 30 mL (10 mL * 3). The combined organic layers were washed with saturated brine (30 mL), dried over NaSO₄, filtered and concentrated under reduced pressure to give the title compound (100 mg, 173.10 μmol, 21.64% yield) as a white solid. **LCMS** (ESI⁺): m/z 578.6 (M+H)⁺, Rt: 0.346 min.

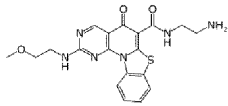
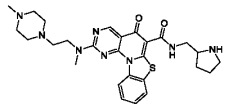
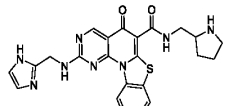


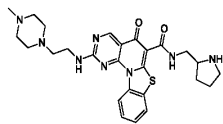
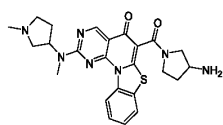
9-(3-Aminopyrrolidine-1-carbonyl)-4-[3-(dimethylamino)pyrrolidin-1-yl]-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2(7),3,5,9,12,14,16-

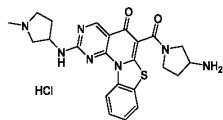
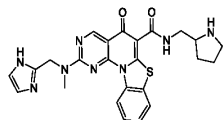
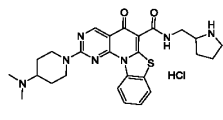
- heptaen-8-one:** The solution of tert-butyl N-(1-{4-[3-(dimethylamino)pyrrolidin-1-yl]-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0²,7.0^{12,17}]heptadeca-2(7),3,5,9,12,14,16-heptaene-9-carbonyl}pyrrolidin-3-yl)carbamate (100 mg, 173.10 µmol, 1 eq) in HCl/dioxane (3 mL) was stirred at 25 °C for 2 h. The reaction was
- 5 concentrated in vacuum. The residue was purified by prep-HPLC (column: Phenomenex luna C18 100*40mm*5 µm; mobile phase: [H₂O(0.04% HCl)-MeCN]; gradient:1%-25% B over 8.0 min) to give the title compound (**Example 17**, 25 mg, 52.35 µmol, 30.24% yield) as a yellow solid. **LCMS** (ESI+): m/z 478.3 (M+H)⁺, Rt: 1.142 min. **¹H NMR** (400 MHz, DMSO-d₆) δ = 11.57 - 11.19 (m, 1H), 9.35 (br d, J =
- 10 8.3 Hz, 1H), 9.28 - 9.17 (m, 1H), 8.39 - 8.13 (m, 3H), 7.98 (t, J = 7.0 Hz, 1H), 7.70 - 7.55 (m, 1H), 7.53 - 7.45 (m, 1H), 4.26 - 4.17 (m, 1H), 4.13 - 3.95 (m, 2H), 3.91 - 3.84 (m, 1H), 3.82 - 3.68 (m, 3H), 3.66 - 3.53 (m, 3H), 2.95 - 2.75 (m, 6H), 2.53 (br d, J = 5.9 Hz, 1H), 2.47 (br s, 1H), 2.31 - 2.11 (m, 1H), 2.06 - 1.86 (m, 1H).
- 15 *The following examples were synthesised according to the method outlined in Synthetic Route 6 using commercially available starting materials:*

Name	Structure	Example	Yield	Analytical Data
9-(3-aminopyrrolidine-1-carbonyl)-4-{[2-(dimethylamino)ethyl]amino}-11-thia-1,3,5-triazatetracyclo[8.7.0.0 ² ,7.0 ^{12,17}]heptadeca-2(7),3,5,9,12,14,16-heptaen-8-one		18	29%	LCMS (ESI+): m/z 452.2 (M+H) ⁺ , Rt: 1.102 min. ¹H NMR (400 MHz, DMSO-d ₆) δ = 10.61 - 9.97 (m, 1H), 9.33 - 8.93 (m, 1H), 8.83 (br d, J = 11.8 Hz, 1H), 8.50 - 8.25 (m, 1H), 8.11 - 7.93 (m, 3H), 7.65 - 7.32 (m, 1H), 7.16 (br t, J = 7.8 Hz, 1H), 3.64 - 3.48 (m, 3H), 3.40 (br d, J = 7.8 Hz, 2H), 3.25 - 3.19 (m, 2H), 3.13 - 2.96 (m, 2H), 2.21 - 2.09 (m, 6H), 1.96 - 1.76 (m, 1H), 1.72 - 1.53 (m, 1H).

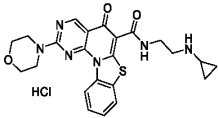
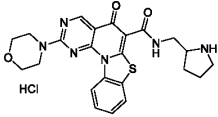
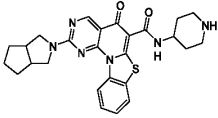
Name	Structure	Example	Yield	Analytical Data
9-(3-aminopyrrolidine-1-carbonyl)-4-{[2-(dimethylamino)ethyl](methyl)amino}-11-thia-1,3,5-triazatetracyclo[8.7.0.0 ^{2,7} .0 ^{12,17}]heptadeca-2(7),3,5,9,12,14,16-heptaen-8-one		19	25%	LCMS (ESI+): m/z 466.3 (M+H) ⁺ , Rt: 1.187 min. ¹H NMR (400 MHz, DMSO-d ₆) δ = 11.27 – 10.08 (m, 1H), 9.39 – 9.09 (m, 2H), 8.56 – 8.22 (m, 3H), 7.98 (t, J = 7.0 Hz, 1H), 7.77 – 7.55 (m, 1H), 7.49 (br t, J = 7.2 Hz, 1H), 4.21 (br s, 2H), 3.87 (br d, J = 8.4 Hz, 1H), 3.80 – 3.67 (m, 2H), 3.63 – 3.48 (m, 5H), 3.42 (br d, J = 4.6 Hz, 2H), 2.85 (br s, 6H), 2.31 – 2.10 (m, 1H), 2.07 – 1.88 (m, 1H).
N-(2-aminoethyl)-4-[(2-methoxyethyl)(methyl)amino]-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0 ^{2,7} .0 ^{12,17}]heptadeca-2(7),3,5,9,12(17),13,15-heptaene-9-carboxamide		62	57%	LCMS (ESI+): m/z 427.3 (M+H) ⁺ , Rt: 1.626 min. ¹H NMR (400 MHz, DMSO-d ₆ + D ₂ O) δ = 9.37 – 9.17 (m, 2H), 8.03 – 7.95 (m, 1H), 7.63 – 7.48 (m, 2H), 3.99 (br t, J = 5.3 Hz, 1H), 3.92 (br t, J = 5.6 Hz, 1H), 3.79 – 3.70 (m, 1H), 3.66 – 3.57 (m, 3H), 3.34 (d, J = 3.9 Hz, 3H), 3.29 (d, J = 10.0 Hz, 3H), 3.02 (br t, J = 6.1 Hz, 2H).

Name	Structure	Example	Yield	Analytical Data
N-(2-aminoethyl)-4-[(2-methoxyethyl)amino]-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0 ^{2,7} .0 ^{12,17}]heptadeca-2(7),3,5,9,12(17),13,15-heptaene-9-carboxamide		63	77%	TFA salt LCMS (ESI+): m/z 413.1 (M+H) ⁺ , Rt: 0.324 min. ¹H NMR (400 MHz, DMSO-d ₆) δ = 10.47 - 10.36 (m, 1H), 9.79 - 9.43 (m, 1H), 9.23 (d, J = 18.8 Hz, 1H), 8.80 - 8.63 (m, 1H), 8.10 - 7.99 (m, 1H), 7.81 (br s, 3H), 7.65 - 7.48 (m, 2H), 3.73 - 3.65 (m, 3H), 3.64 - 3.54 (m, 3H), 3.31 (br s, 3H), 3.03 (br t, J = 5.8 Hz, 2H).
2-(methyl(2-(4-methylpiperazin-1-yl)ethyl)amino)-5-oxo-N-(pyrrolidin-2-ylmethyl)-5H-benzo[4',5']thiazolo[3',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamide		64	83%	LCMS (ESI+): Rt: 1.367 min, m/z 535.4 (M+H) ⁺ . ¹H NMR (400 MHz, DMSO-d ₆ +D ₂ O) δ = 9.51 - 9.17 (m, 2H), 8.07 (br d, J = 7.9 Hz, 1H), 7.77 - 7.62 (m, 1H), 7.58 - 7.49 (m, 1H), 4.28 - 4.03 (m, 2H), 3.83 - 3.50 (m, 7H), 3.40 - 3.39 (m, 3H), 3.38 - 3.09 (m, 8H), 2.82 (br s, 3H), 2.18 - 2.03 (m, 1H), 2.00 - 1.82 (m, 2H), 1.73 - 1.61 (m, 1H)
2-(((1H-imidazol-2-yl)methyl)amino)-5-oxo-N-(pyrrolidin-2-ylmethyl)-5H-benzo[4',5']thiazolo		65	28%	LCMS (ESI+): m/z 475.2 (M+H) ⁺ , Rt: 1.254 min. ¹H NMR (400 MHz, DMSO-d ₆ +D ₂ O) δ = 10.46 (td, J = 5.7, 11.2 Hz, 1H), 9.78 - 8.55 (m, 2H), 8.07 - 7.93 (m, 1H), 7.66 - 7.39 (m, 4H), 5.07 - 4.92 (m, 2H),

Name	Structure	Example	Yield	Analytical Data
[3',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamide				3.69 - 3.55 (m, 3H), 3.25 - 3.09 (m, 2H), 2.14 - 2.03 (m, 1H), 2.01 - 1.81 (m, 2H), 1.73 - 1.61 (m, 1H).
2-((2-(4-methylpiperazin-1-yl)ethyl)amino)-5-oxo-N-(pyrrolidin-2-ylmethyl)-5H-benzo[4',5']thiazolo[3',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamide		66	52%	LCMS (ESI+): Rt: 1.291 min, m/z 521.4 (M+H)+. ¹H NMR (400 MHz, DMSO-d ₆ +D ₂ O) δ = 9.71 - 9.29 (m, 1H), 9.28 - 9.19 (m, 1H), 8.01 (d, J = 7.0 Hz, 1H), 7.75 - 7.48 (m, 2H), 4.05 - 3.79 (m, 4H), 3.78 - 3.65 (m, 4H), 3.64 - 3.56 (m, 4H), 3.50 (br s, 3H), 3.28 - 3.09 (m, 2H), 2.87 (s, 3H), 2.14 - 2.05 (m, 1H), 2.02 - 1.82 (m, 2H), 1.75 - 1.62 (m, 1H)
6-(3-aminopyrrolidin-1-carbonyl)-2-(methyl(1-methylpyrrolidin-3-yl)amino)-5H-benzo[4',5']thiazolo[3',2':1,6]pyrido[2,3-d]pyrimidin-5-one		67	19%	LCMS (ESI+): m/z 478.4 (M+H)+, Rt: 1.228 min. ¹H NMR (400 MHz, DMSO-d ₆) δ = 9.28 (d, J = 2.3 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.60 (br s, 1H), 7.54 - 7.43 (m, 1H), 5.95 - 5.43 (m, 1H), 3.92 - 3.79 (m, 1H), 3.74 - 3.47 (m, 3H), 3.40 (br dd, J = 5.6, 12.7 Hz, 1H), 3.36 (s, 3H), 3.28 - 3.12 (m, 1H), 2.93 - 2.75 (m, 3H), 2.68 - 2.53 (m, 1H), 2.45 (s, 3H), 2.38 - 1.97 (m, 3H), 1.90 - 1.70 (m, 1H).

Name	Structure	Example	Yield	Analytical Data
6-(3-aminopyrrolidine-1-carbonyl)-2-((1-methylpyrrolidin-3-yl)amino)-5H-benzo[4',5']thiazolo[3',2':1,6]pyrido[2,3-d]pyrimidin-5-one		68	18%	LCMS (ESI+): m/z 464.3 (M+H) ⁺ , Rt: 1.133 min. ¹H NMR (400 MHz, DMSO-d ₆ + D ₂ O) δ = 9.63 - 9.25 (m, 1H), 9.22 - 9.12 (m, 1H), 7.97 (br s, 1H), 7.75 - 7.45 (m, 2H), 4.91 - 4.69 (m, 1H), 4.10 - 3.84 (m, 2H), 3.79 - 3.67 (m, 3H), 3.52 - 3.43 (m, 2H), 3.35 - 3.04 (m, 2H), 2.90 (br d, J = 14.0 Hz, 3H), 2.35 - 1.81 (m, 4H).
2-(((1H-imidazol-2-yl)methyl)(methyl)amino)-5-oxo-N-(pyrrolidin-2-ylmethyl)-5H-benzo[4',5']thiazolo[3',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamide		69	27%	LCMS (ESI+): Rt: 1.327 min, m/z 489.3 (M+H) ⁺ . ¹H NMR (400 MHz, DMSO-d ₆ + D ₂ O) δ = 9.51 - 9.39 (m, 1H), 9.31 - 8.52 (m, 1H), 8.12 - 7.98 (m, 1H), 7.72 - 7.44 (m, 4H), 5.47 - 5.26 (m, 2H), 3.77 - 3.60 (m, 3H), 3.53 (s, 3H), 3.26 - 3.11 (m, 2H), 2.15 - 2.03 (m, 1H), 2.00 - 1.84 (m, 2H), 1.76 - 1.61 (m, 1H).
2-(4-(dimethylamino)piperidin-1-yl)-5-oxo-N-(pyrrolidin-2-ylmethyl)-5H-benzo[4',5']thiazolo[3',2':1,6]pyrido[2,3-d]pyrimidine-		70	25%	LCMS (ESI+): m/z 506.3 (M+H) ⁺ , Rt: 1.366 min. ¹H NMR (400 MHz, DMSO-d ₆ + D ₂ O) δ = 9.02 (s, 1H), 8.88 (br d, J = 7.0 Hz, 1H), 7.83 (br dd, J = 2.9, 5.8 Hz, 1H), 7.47 - 7.42 (m, 2H), 4.93 (br s, 1H), 4.54 (br s, 1H), 3.76 - 3.66 (m, 1H), 3.65 - 3.58

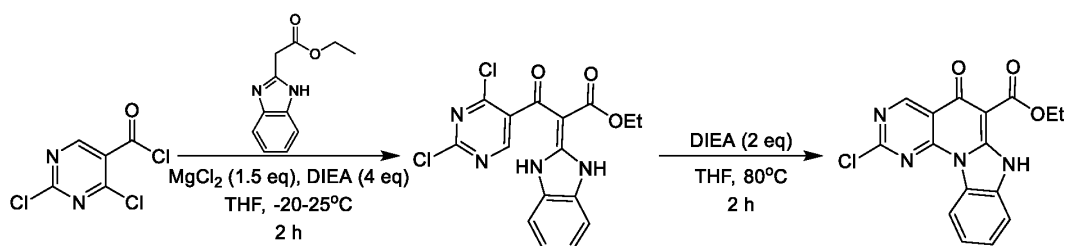
Name	Structure	Example	Yield	Analytical Data
6-carboxamide				(m, 1H), 3.58 - 3.47 (m, 2H), 3.28 - 3.03 (m, 4H), 2.77 (s, 6H), 2.23 (br s, 2H), 2.10 (dt, J = 7.4, 12.4 Hz, 1H), 2.03 - 1.82 (m, 2H), 1.76 - 1.55 (m, 3H).
2-(6,7-dihydro-3H-imidazo[4,5-c]pyridin-5(4H)-yl)-5-oxo-N-(pyrrolidin-2-ylmethyl)-5H-benzo[4',5']thiazolo[3',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamide		71	63%	LCMS (ESI+): Rt: 1.367 min, m/z 501.3 (M+H)+. ¹H NMR (400 MHz, DMSO-d ₆ +D ₂ O) δ = 9.12 - 9.01 (m, 1H), 8.97 - 8.65 (m, 2H), 7.86 - 7.65 (m, 1H), 7.57 - 7.24 (m, 2H), 5.07 - 4.59 (m, 2H), 4.34 - 4.01 (m, 2H), 3.79 - 3.68 (m, 1H), 3.60 (br s, 2H), 3.34 - 3.10 (m, 2H), 2.89 (br s, 2H), 2.20 - 1.85 (m, 3H), 1.78 - 1.61 (m, 1H).
N-methyl-4-(2-methyl-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl)-8-oxo-N-(4-piperidyl)-11-thia-1,3,5-triazatetracyclo[8.7.0.0.2,7.0.12,17]heptadeca-2,4,6,9,12(17),13,15-		72	43%	LCMS ((ESI+): Rt: 1.397 min, m/z 518.3 (M+H)+ ¹H NMR (400 MHz, DMSO-d ₆ +D ₂ O) δ = 9.32 (br d, J = 8.6 Hz, 1H), 9.16 (s, 1H), 7.91 (br d, J = 7.3 Hz, 1H), 7.60 (t, J = 7.8 Hz, 1H), 7.51 - 7.43 (m, 1H), 4.61 - 3.96 (m, 2H), 3.93 - 3.79 (m, 4H), 3.68 - 3.57 (m, 1H), 3.50 - 3.16 (m, 6H), 3.10 - 3.01 (m, 2H), 2.91 - 2.84 (m, 4H), 2.82 - 2.75 (m, 2H), 2.05 - 1.80 (m, 4H).

Name	Structure	Example	Yield	Analytical Data
heptaene-9-carboxamide				
N-(2-(cyclopropylamino)ethyl)-2-morpholino-5-oxo-5H-benzo[4',5']thiazolo[3',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamide		73	36%	LCMS (ESI+): m/z 465.3 (M+H) ⁺ , Rt: 1.645 min. ¹H NMR (400 MHz, DMSO-d ₆ +D ₂ O) δ = 9.08 (s, 1H), 9.01 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 7.5 Hz, 1H), 7.54 - 7.40 (m, 2H), 3.95 - 3.84 (m, 3H), 3.80 - 3.70 (m, 5H), 3.64 (br t, J = 6.1 Hz, 2H), 3.22 (br t, J = 6.2 Hz, 2H), 2.79 - 2.70 (m, 1H), 0.86 - 0.75 (m, 4H).
2-morpholino-5-oxo-N-(pyrrolidin-2-ylmethyl)-5H-benzo[4',5']thiazolo[3',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamide		74	20%	LCMS (ESI+): m/z 465.3 (M+H) ⁺ , Rt: 1.634 min. ¹H NMR (400 MHz, DMSO-d ₆ +D ₂ O) δ = 10.47 (br t, J = 5.4 Hz, 1H), 9.27 - 9.19 (m, 2H), 7.98 (d, J = 7.8 Hz, 1H), 7.66 - 7.58 (m, 1H), 7.55 - 7.45 (m, 1H), 3.93 (br s, 4H), 3.76 (br d, J = 9.4 Hz, 4H), 3.70 - 3.63 (m, 2H), 3.61 - 3.52 (m, 1H), 3.26 - 3.09 (m, 2H), 2.15 - 2.04 (m, 1H), 2.01 - 1.83 (m, 2H), 1.75 - 1.59 (m, 1H).
2-(hexahydrocyclopenta[c]pyrrol-2(1H)-yl)-5-oxo-N-(piperidin-4-yl)-5H-		75	34%	LCMS (ESI+): m/z 489.3 (M+H) ⁺ , Rt: 2.023 min. ¹H NMR (400 MHz, D ₂ O) δ = 8.08 (br s, 1H), 7.67 - 7.46 (m, 1H), 7.30 - 6.97 (m, 2H), 6.68 (br s, 1H), 3.81 (br s, 1H), 3.48 (br d,

Name	Structure	Example	Yield	Analytical Data
benzo[4', 5']thiazolo [3', 2':1, 6]pyrido[2, 3-d]pyrimidine-6-carboxamide				J = 9.5 Hz, 3H), 3.19 (br t, J = 11.5 Hz, 2H), 2.99 (br d, J = 1.3 Hz, 1H), 2.88 - 2.41 (m, 4H), 2.17 (br d, J = 11.9 Hz, 2H), 1.94 - 1.63 (m, 6H), 1.54 - 1.31 (m, 2H).

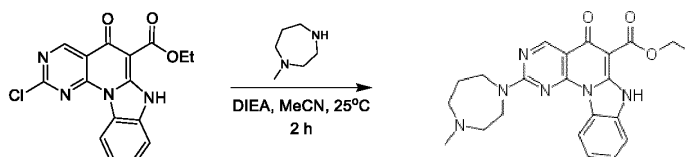
Synthetic Route 7

Example 20: 4-(4-Methyl-1,4-diazepan-1-yl)-8-oxo-N-[(pyrrolidin-2-yl)-
methyl]-1,3,5,11-tetraazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-
2(7),3,5,9,12,14,16-heptaene-9-carboxamide

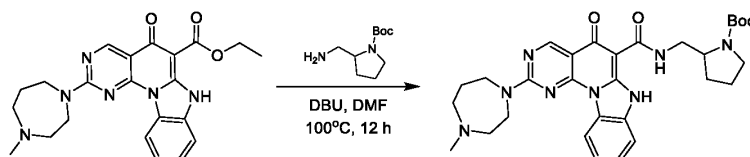


Ethyl 4-chloro-8-oxo-1,3,5,11-tetraazatetracyclo[8.7.0.0.2^{7,0}1¹²,1⁷]-heptadeca-2(7),3,5,9,12,14,16-heptaene-9-carboxylate: To a solution of ethyl 2-(1H-benzimidazol-2-yl) acetate (1.56 g, 7.69 mmol, 1 eq) in THF (15 mL) was added MgCl₂ (1.09 g, 11.54 mmol, 470.32 μL, 1.5 eq) at 25°C. Then to the mixture was added a solution of 2,4-dichloropyrimidine-5-carbonyl chloride (2.1 g, 10.0 mmol, 1.3 eq) in THF (10 mL) dropwise at -20°C. Then to the mixture was added DIEA (3.96 g, 80.58 mmol, 5.32 mL, 4 eq) at -20°C. The mixture was stirred at 25°C for 2 h. LCMS showed the starting materials to be consumed and 60% of product generated. The mixture was concentrated in vacuum. The crude product was triturated with water (50 mL) for 30 min. After filtered, the filter cake was triturated with MeCN (50 mL *2) for 30 min. After filtration, the filter cake was collected to give the title compound (3.5 g, 6.13 mmol, 93.56% yield, 60% purity) as yellow solid. LCMS (ESI+): m/z 342.9 (M+H)⁺, Rt: 0.419 min.

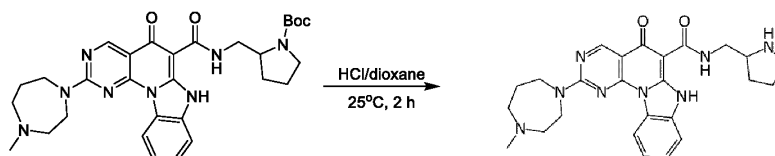
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- Ethyl 4-(4-methyl-1,4-diazepan-1-yl)-8-oxo-1,3,5,11-tetraazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2(7),3,5,9,12,14,16-heptaene-9-carboxylate:** To a solution of ethyl 4-chloro-8-oxo-1,3,5,11-tetraazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]-heptadeca-2(7),3,5,9,12,14,16-heptaene-9-carboxylate (1.5 g, 4.38 mmol, 1 eq) in MeCN (20 mL) was added 1-methyl-1,4-diazepane (999.50 mg, 8.75 mmol, 1.09 mL, 2 eq) and DIEA (1.70 g, 13.13 mmol, 2.29 mL, 3 eq). The mixture was stirred at 25°C for 2 h. LCMS showed the starting material to be consumed and 40% of product was generated. The mixture was concentrated in vacuum. The residue was purified by prep-HPLC (column: Phenomenex luna C18 100*40mm*5 um; mobile phase: [H₂O(0.04% HCl)-MeCN]; gradient: 1%-35% B over 10.0 min) to give the title compound (1.2 g, 2.86 mmol, 65.21% yield, 90% purity) as yellow solid. **LCMS** (ESI⁺): m/z 421.3 (M+H)⁺, Rt: 1.393 min.



- tert-Butyl 2-({[4-(4-methyl-1,4-diazepan-1-yl)-8-oxo-1,3,5,11-tetraazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12,14,16-heptaen-9-yl]formamido}methyl)pyrrolidine-1-carboxylate:** To a solution of ethyl 4-(4-methyl-1,4-diazepan-1-yl)-8-oxo-1,3,5,11-tetraazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]-heptadeca-2(7),3,5,9,12,14,16-heptaene-9-carboxylate (300 mg, 713.50 μmol, 1 eq) in DMF (5 mL) was added tert-butyl 2-(aminomethyl)pyrrolidine-1-carboxylate (285.79 mg, 1.43 mmol, 2 eq) and DBU (325.86 mg, 2.14 mmol, 322.63 μL, 3 eq). The mixture was stirred at 100°C for 12 h. The reaction was poured into water (50 mL). The mixture was extracted with ethyl acetate (3*5 mL). The combined organic phases were washed with saturated brine (50 mL), dried over anhydrous Na₂SO₄, concentrated in vacuum to give the title compound (300 mg, 469.83 μmol, 65.85% yield, 90% purity) as yellow solid, which was used in the next step directly without purification. **LCMS** (ESI⁺): m/z 575.3 (M+H)⁺, Rt: 0.386 min.



4-(4-Methyl-1,4-diazepan-1-yl)-8-oxo-N-[(pyrrolidin-2-yl)methyl]-1,3,5,11-tetraazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2(7),3,5,9,12,14,16-

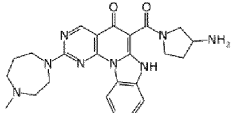
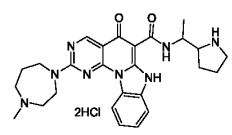
heptaene-9-carboxamide: A solution of tert-butyl 2-({[4-(4-methyl-1,4-diazepan-1-yl)-8-oxo-1,3,5,11-tetraazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-

- 5 2,4,6,9,12,14,16-heptaen-9-yl]formamido}methyl)pyrrolidine-1-carboxylate (300 mg, 522.04 μ mol, 1 eq) in HCl/dioxane (5 mL) was stirred at 25°C for 2 h. The mixture was concentrated in vacuum. The residue was purified by prep-HPLC (column: Phenomenex luna C18 100*40mm*5 μ m; mobile phase: [H₂O (0.04% HCl)-MeCN]; gradient: 1%-25% B over 8.0 min) to give the title compound (**Example 20**, 121.2
- 10 mg, 255.40 μ mol, 48.92% yield) as yellow solid. **LCMS** (ESI+): m/z 475.4 (M+H)⁺, Rt: 1.273 min. **¹H NMR** (400 MHz, DMSO-d₆) δ = 12.97 (br s, 1H), 11.27 - 11.02 (m, 1H), 10.53 (br t, J = 5.3 Hz, 1H), 9.58 (br d, J = 1.5 Hz, 1H), 9.17 (dd, J = 1.7, 9.4 Hz, 1H), 9.00 (br s, 1H), 8.67 - 8.48 (m, 1H), 7.79 (d, J = 7.9 Hz, 1H), 7.53 - 7.36 (m, 2H), 4.70 - 4.36 (m, 1H), 4.21 - 3.86 (m, 3H), 3.85 - 3.59 (m, 5H), 3.29 - 3.12
- 15 (m, 4H), 2.78 (br d, J = 2.8 Hz, 3H), 2.37 - 2.17 (m, 1H), 2.14 - 2.02 (m, 1H), 2.02 - 1.83 (m, 2H), 1.80 - 1.67 (m, 1H).

The following examples were synthesised according to the method outlined in Synthetic Route 7 using commercially available starting materials:

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Name	Structure	Example	Yield	Analytical Data
4-(4-methyl-1,4-diazepan-1-yl)-8-oxo-N-[(piperidin-2-yl)methyl]-1,3,5,11-tetraazatetracyclo[8.7.0.0 ^{2,7} .0 ^{12,17}]heptadeca-2(7),3,5,9,12,14,16-heptaene-		21	11%	LCMS (ESI+): m/z 489.4 (M+H) ⁺ , Rt: 1.295 min. ¹H NMR (400 MHz, DMSO-d ₆) δ = 9.19 (d, J = 9.0 Hz, 1H), 8.71 - 8.49 (m, 1H), 7.78 (br d, J = 7.9 Hz, 1H), 7.53 - 7.38 (m, 2H), 4.65 - 4.32 (m, 1H), 4.17 - 3.97 (m, 3H), 3.93 - 3.83 (m, 2H), 3.55 (br s, 2H), 3.25 (br d, J = 11.0 Hz, 4H), 2.91 - 2.76

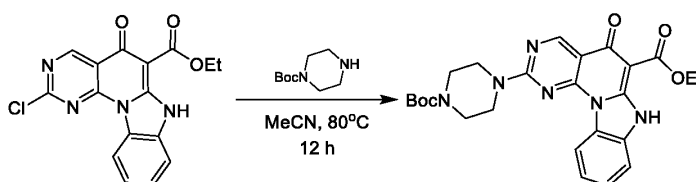
Name	Structure	Example	Yield	Analytical Data
9-carboxamide				(m, 4H), 2.42 - 2.18 (m, 2H), 1.95 - 1.68 (m, 3H), 1.66 - 1.37 (m, 3H)
9-(3-aminopyrrolidine-1-carbonyl)-4-(4-methyl-1,4-diazepan-1-yl)-1,3,5,11-tetraazatetracyclo[8.7.0.0 ^{2,7} .0 ^{12,17}]heptadeca-2(7),3,5,9,12,14,16-heptaen-8-one		22	25%	LCMS (ESI+): m/z 461.2 (M+H) ⁺ , Rt: 0.243 min. ¹H NMR (400 MHz, DMSO-d ₆) δ = 9.00 (br s, 1H), 8.51 (br dd, J = 7.3, 19.7 Hz, 1H), 7.51 - 7.35 (m, 1H), 7.27 (br t, J = 7.3 Hz, 1H), 7.20 - 7.11 (m, 1H), 4.00 (br s, 2H), 3.93 (br t, J = 6.1 Hz, 2H), 3.78 - 3.71 (m, 2H), 3.54 (br s, 2H), 3.47 - 3.37 (m, 2H), 2.82 (br s, 1H), 2.65 (br d, J = 3.6 Hz, 1H), 2.57 - 2.53 (m, 1H), 2.28 (br d, J = 4.9 Hz, 3H), 2.17 - 1.97 (m, 2H), 1.95 - 1.73 (m, 2H)
2-(4-methyl-1,4-diazepan-1-yl)-5-oxo-N-(1-(pyrrolidin-2-yl)ethyl)-5,7-dihydrobenzo[4',5']imidazo[1',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamide		76	24%	LCMS (ESI+): m/z 489.2 (M+H) ⁺ , Rt: 1.320 min. ¹H NMR (400 MHz, DMSO-d ₆ +D ₂ O) δ = 9.21 (d, J = 8.2 Hz, 1H), 8.76 - 8.52 (m, 1H), 7.83 - 7.73 (m, 1H), 7.56 - 7.39 (m, 2H), 4.66 - 4.21 (m, 2H), 4.13 - 4.02 (m, 1H), 4.00 - 3.77 (m, 2H), 3.71 - 3.62 (m, 2H), 3.47 - 3.41 (m, 1H), 3.34 - 3.11 (m, 4H), 2.83 (br s, 3H), 2.36 (br d, J = 2.1 Hz, 1H), 2.22 (br d, J = 2.9 Hz,

Name	Structure	Example	Yield	Analytical Data
				1H), 2.17 - 2.04 (m, 1H), 2.03 - 1.81 (m, 2H), 1.81 - 1.67 (m, 1H), 1.30 (br d, J = 6.7 Hz, 3H).
2-(4-methyl-1,4-diazepan-1-yl)-5-oxo-N-(piperidin-4-ylmethyl)-5,7-dihydrobenzo[4',5']imidazo[1',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamide		77	45%	LCMS (ESI+): m/z 489.4 (M+H)+, Rt: 1.280 min. ¹H NMR (400 MHz, DMSO-d ₆ + D ₂ O) δ = 9.16 (d, J = 10.0 Hz, 1H), 8.69 - 8.47 (m, 1H), 7.75 (br d, J = 7.8 Hz, 1H), 7.54 - 7.37 (m, 2H), 4.64 - 4.30 (m, 1H), 4.14 - 3.93 (m, 2H), 3.90 (br d, J = 9.9 Hz, 1H), 3.64 (br s, 1H), 3.53 - 3.42 (m, 1H), 3.39 - 3.10 (m, 6H), 2.93 - 2.75 (m, 5H), 2.40 - 2.16 (m, 2H), 1.92 - 1.76 (m, 3H), 1.50 - 1.31 (m, 2H).
2-(4-methyl-1,4-diazepan-1-yl)-5-oxo-N-(pyrrolidin-3-yl)-5,7-dihydrobenzo[4',5']imidazo[1',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamide		78	30%	LCMS (ESI+): m/z 461.2 (M+H)+, Rt: 1.226 min. ¹H NMR (400 MHz, DMSO-d ₆ + D ₂ O) δ = 9.08 - 8.98 (m, 1H), 8.50 - 8.32 (m, 1H), 7.71 (br dd, J = 5.0, 7.4 Hz, 1H), 7.49 - 7.29 (m, 2H), 4.61 - 4.21 (m, 2H), 4.03 - 3.77 (m, 3H), 3.63 (br s, 1H), 3.57 - 3.42 (m, 2H), 3.39 - 3.20 (m, 4H), 3.16 - 3.00 (m, 1H), 2.80 (s, 3H), 2.36 - 2.24 (m, 2H), 1.96 (br dd, J = 5.7, 12.2 Hz, 1H), 1.68 - 1.41 (m, 1H).

Name	Structure	Example	Yield	Analytical Data
2-(4-methyl-1,4-diazepan-1-yl)-5-oxo-N-(piperidin-4-yl)-5,7-dihydrobenzo[4',5']imidazo[1',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamide		79	53%	LCMS (ESI+): Rt: 1.245 min, m/z 475.3 (M+H)+. ¹H NMR (400 MHz, DMSO-d ₆ +D ₂ O) δ = 9.08 (d, J = 18.3 Hz, 1H), 8.53 - 8.37 (m, 1H), 7.74 (dd, J = 5.0, 7.6 Hz, 1H), 7.50 - 7.29 (m, 2H), 4.67 - 4.29 (m, 1H), 4.14 - 3.97 (m, 2H), 3.92 - 3.74 (m, 2H), 3.69 - 3.48 (m, 2H), 3.33 - 3.17 (m, 4H), 3.15 - 3.02 (m, 2H), 2.79 (s, 3H), 2.49 (br s, 1H), 2.41 - 2.29 (m, 1H), 2.22 - 2.05 (m, 2H), 1.85 - 1.66 (m, 2H).

Synthetic Route 8

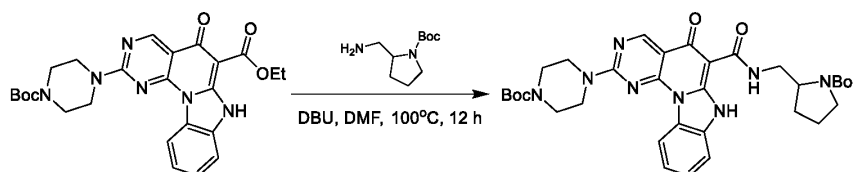
Example 23: 8-Oxo-4-(piperazin-1-yl)-N-[(pyrrolidin-2-yl)methyl]-1,3,5,11-tetraazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2(7),3,5,9,12,14,16-heptaene-9-carboxamide



Ethyl 4-{4-[(tert-butoxy)carbonyl]piperazin-1-yl}-8-oxo-1,3,5,11-tetraazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2(7),3,5,9,12,14,16-heptaene-9-carboxylate: To a solution of ethyl 4-chloro-8-oxo-1,3,5,11-tetraazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2(7),3,5,9,12,14,16-heptaene-9-carboxylate (3 g, 8.77 mmol, 1 eq) in MeCN (40 mL) was added tert-butyl piperazine-1-carboxylate (3.26 g, 17.54 mmol, 2 eq). The mixture was stirred at 80°C for 12 hr. The mixture was concentrated *in vacuo*. The residue was purified by prep-HPLC (column: Phenomenex luna C18 (250*70mm, 15 μm); mobile phase: [H₂O(0.04%

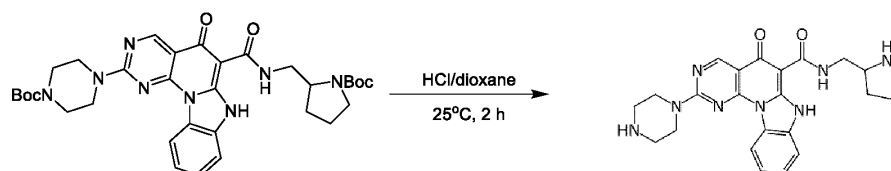
- 147 -

HCl)-MeCN]; gradient: 40%-80% B over 18.0 min) to give the title compound (800 mg, 1.62 mmol, 13.92% yield) as yellow solid. **LCMS** (ESI+): m/z 493.2 (M+H)⁺, Rt: 0.488 min.



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tert-Butyl 4-((tert-butoxycarbonyl)piperazin-1-yl)-8-oxo-1,3,5,11-tetraazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2(7),3,5,9,12,14,16-heptaene-9-carboxylate: To a solution of ethyl 4-((tert-butoxycarbonyl)piperazin-1-yl)-8-oxo-1,3,5,11-tetraazatetracyclo-
 10 [8.7.0.0^{2,7}.0^{12,17}]heptadeca-2(7),3,5,9,12,14,16-heptaene-9-carboxylate (500 mg, 1.02 mmol, 1 eq) in DMF (5 mL) was added DBU (463.65 mg, 3.06 mmol, 459.05 μ L, 3 eq) and tert-butyl 2-(aminomethyl)pyrrolidine-1-carboxylate (406.65 mg, 2.04 μ mol, 2 eq). The mixture was stirred at 100°C for 12 hr. LCMS showed R1 was consumed and 60% of P1 was generated. The reaction was poured into ice-water
 15 (w/w = 1/1) (50 mL). The mixture was filtered to give the filter cake. The filter cake was collected and dried to give the title compound crude which was used in the next step directly without purification (200 mg, 309.44 μ mol, 30.46% yield) as yellow solid. **LCMS** (ESI+): m/z 647.4 (M+H)⁺, Rt: 0.667 min.



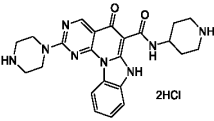
8-Oxo-4-(piperazin-1-yl)-N-((pyrrolidin-2-yl)methyl)-1,3,5,11-tetraazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2(7),3,5,9,12,14,16-heptaene-9-carboxamide: A solution of tert-butyl 4-((tert-butoxycarbonyl)piperazin-1-yl)-8-oxo-1,3,5,11-tetraazatetracyclo-
 20 [8.7.0.0^{2,7}.0^{12,17}]heptadeca-2(7),3,5,9,12,14,16-heptaene-9-carboxylate (200 mg, 309.25 μ mol, 1 eq) in HCl/dioxane (3 mL) was stirred at 25°C for 2 hr. The mixture was filtered to give the filter cake. The filter cake was purified by prep-HPLC (column: Phenomenex luna C18 100*40mm*5 μ m; mobile phase: [H₂O (0.04% HCl)-MeCN]; gradient: 1%-30% B over 8.0 min) to give the title compound
 25 (**Example 23**, 165.4 mg, 370.67 μ mol, 94.44% yield) as brown solid. **LCMS** (ESI+):

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m/z 447.1 (M+H)⁺, Rt: 0.271 min. **¹H NMR** (400 MHz, DMSO-d₆) δ = 12.87 (br s, 1H), 10.56 - 10.34 (m, 1H), 9.89 - 9.61 (m, 3H), 9.16 (br d, J = 4.3 Hz, 1H), 9.10 (s, 1H), 8.48 (br d, J = 8.0 Hz, 1H), 7.72 (d, J = 7.9 Hz, 1H), 7.48 - 7.41 (m, 1H), 7.39 - 7.32 (m, 1H), 4.17 (br s, 4H), 3.76 (td, J = 6.3, 12.9 Hz, 1H), 3.72 - 3.59 (m, 2H),
 5 3.29 (br s, 3H), 3.27 - 3.14 (m, 3H), 2.14 - 2.03 (m, 1H), 2.03 - 1.93 (m, 1H), 1.93 - 1.83 (m, 1H), 1.80 - 1.68 (m, 1H).

The following examples were synthesised according to the method outlined in Synthetic Route 8 using commercially available starting materials:

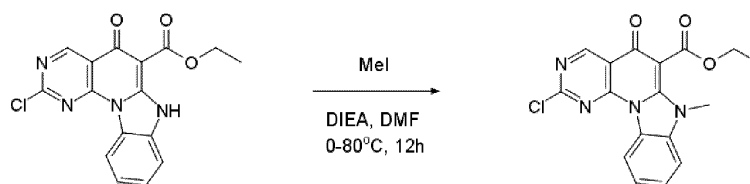
10

Name	Structure	Example	Yield	Analytical Data
5-oxo-2-(piperazin-1-yl)-N-(piperidin-4-yl)-5, 7-dihydrobenzo [4', 5'] I midazo [1', 2':1, 6] pyrido[2,3-d]pyrimidine-6-carboxamide		80	43%	LCMS (ESI ⁺): m/z 447.3 (M+H) ⁺ , Rt: 1.215 min. ¹H NMR (400 MHz, DMSO-d ₆ +D ₂ O) δ = 9.20 (s, 1H), 8.64 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 7.9 Hz, 1H), 7.53 - 7.37 (m, 2H), 4.24 - 4.16 (m, 4H), 4.15 - 4.07 (m, 1H), 3.36 - 3.21 (m, 6H), 3.14 - 3.03 (m, 2H), 2.13 (br dd, J = 3.1, 13.6 Hz, 2H), 1.79 - 1.62 (m, 2H).

Synthetic Route 9

15 **Example 24: 11-methyl-4-(4-methyl-1,4-diazepan-1-yl)-8-oxo-N-[(pyrrolidin-2-yl)methyl]-1,3,5,11-tetraazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2(7),3,5,9,12,14,16-heptaene-9-carboxamide**

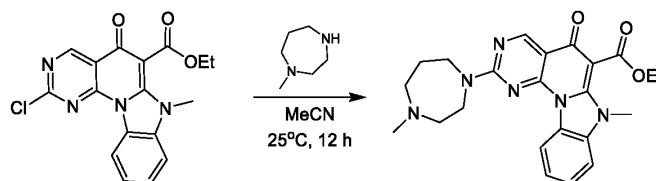
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Ethyl 4-chloro-11-methyl-8-oxo-1,3,5,11-tetraazatetracyclo-

[8.7.0.0^{2,7.0^{12,17}}]heptadeca-2(7),3,5,9,12,14,16-heptaene-9-carboxylate:

To a solution of ethyl 4-chloro-8-oxo-1,3,5,11-tetraazatetracyclo[8.7.0.0^{2,7.0^{12,17}}]-heptadeca-2(7),3,5,9,12,14,16-heptaene-9-carboxylate (3.0 g, 8.77 mmol, 1 eq) in DMF (30 mL) was added DIEA (3.4 g, 26.31 mmol, 4.58 mL, 3 eq). Then the mixture was cooled to 0°C and CH₃I (1.86 g, 13.16 mmol, 817.8 µL, 1.5 eq) was added. The mixture was stirred at 80°C for 12 h. LCMS showed all of the starting material was consumed and 40% of product was generated. The reaction was quenched by addition of 150 mL of water and stirred for 20 min. Solid was precipitated out. The mixture was filtered to give the filter cake. The filter cake was collected and dried to give the title compound (3.0 g, 8.43 mmol, 96.15% yield, 60% purity) as yellow solid. The crude product was used for next step directly without further purification. **LCMS** (ESI⁺): m/z 357.0 (M+H)⁺, Rt: 0.444 min.



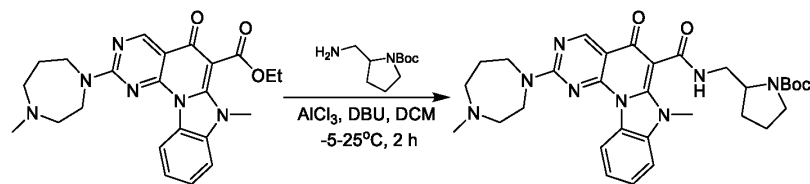
Ethyl 11-methyl-4-(4-methyl-1,4-diazepan-1-yl)-8-oxo-1,3,5,11-

tetraazatetracyclo[8.7.0.0^{2,7.0^{12,17}}]heptadeca-2(7),3,5,9,12,14,16-

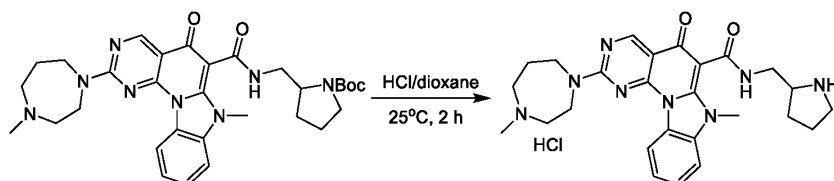
heptaene-9-carboxylate:

To a solution of ethyl 4-chloro-11-methyl-8-oxo-1,3,5,11-tetraazatetracyclo[8.7.0.0^{2,7.0^{12,17}}]heptadeca-2(7),3,5,9,12,14,16-heptaene-9-carboxylate (3.4 g, 9.53 mmol, 1 eq) in MeCN (35 mL) was added 1-methyl-1,4-diazepane (2.18 g, 19.06 mmol, 2.37 mL, 2 eq) and DIEA (3.70 g, 28.59 mmol, 4.98 mL, 3 eq). The mixture was stirred at 25°C for 12 h. LCMS showed material was consumed and 30% of product was generated. The mixture was concentrated in vacuum. The residue was purified by prep-HPLC (column: Phenomenex luna C18 (250*70mm, 15 µm); mobile phase: [H₂O (0.04% HCl)-MeCN]; gradient: 20%-50% B over 18.0 min) to give the title (600 mg, 1.38 mmol, 14.49% yield) as yellow solid. **LCMS** (ESI⁺): m/z 435.2 (M+H)⁺, Rt: 0.323 min.

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{1-[(tert-Butoxy)carbonyl]pyrrolidin-2-yl}methyl 11-methyl-4-(4-methyl-1,4-diazepan-1-yl)-8-oxo-1,3,5,11-tetraazatetracyclo[8.7.0.0²,7.0¹²,17]-heptadeca-2(7),3,5,9,12,14,16-heptaene-9-carboxylate: To a solution of ethyl 11-methyl-4-(4-methyl-1,4-diazepan-1-yl)-8-oxo-1,3,5,11-tetraazatetracyclo-
 5 [8.7.0.0²,7.0¹²,17]heptadeca-2(7),3,5,9,12,14,16-heptaene-9-carboxylate (300 mg, 690.46 μ mol, 1 eq) in DCM (2 mL) was added tert-butyl 2-(aminomethyl)pyrrolidine-1-carboxylate (276.57 mg, 1.38 mmol, 2 eq), DBU (315.35 mg, 2.07 mmol, 312.23 μ L, 3 eq) and AlCl₃ (138.10 mg, 1.04 mmol, 56.60 μ L, 1.5 eq) at -5°C. Then the
 10 mixture was stirred at 25°C for 2 h. LCMS showed material was consumed and 40% of product was generated. The reaction was quenched by addition of 10 mL of 50% of NaOH (aq) under N₂. The aqueous phase was extracted with DCM (2 mL*3). The combined organic phases were washed with saturated brine (30 mL), dried over anhydrous Na₂SO₄, concentrated in vacuum to give the title compound (120 mg,
 15 203.84 μ mol, 29.52% yield). The crude product was used in the next step directly without further purification. **LCMS** (ESI⁺): m/z 589.3 (M+H)⁺, Rt: 0.373 min.



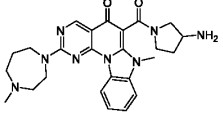
11-methyl-4-(4-methyl-1,4-diazepan-1-yl)-8-oxo-N-[(pyrrolidin-2-yl)methyl]-1,3,5,11-tetraazatetracyclo[8.7.0.0²,7.0¹²,17]heptadeca-2(7),3,5,9,12,14,16-heptaene-9-carboxamide: A solution of {1-[(tert-butoxy)-carbonyl]pyrrolidin-2-yl}methyl 11-methyl-4-(4-methyl-1,4-diazepan-1-yl)-8-oxo-1,3,5,11-tetraazatetracyclo[8.7.0.0²,7.0¹²,17]heptadeca-2(7),3,5,9,12,14,16-
 20 heptaene-9-carboxylate (120 mg, 203.97 μ mol, 1 eq) in HCl/dioxane (2 mL) was stirred at 25°C for 2 h. LCMS showed material was consumed and 60% of product was generated. The mixture was concentrated in vacuum. The residue was purified by prep-HPLC (column: Phenomenex luna C18 100*40mm*5 μ m; mobile phase: [H₂O (0.04% HCl)-MeCN];gradient:1%-30% B over 7.0 min) to give the title compound
 25 **(Example 24, 86.4 mg, 176.84 μ mol, 69.40% yield)** as yellow solid. **LCMS** (ESI⁺):
 30 m/z 489.4 (M+H)⁺, Rt: 1.226 min. **¹H NMR** (400 MHz, DMSO-d₆) δ = 11.27 (br d, J = 2.5 Hz, 1H), 9.71 (br d, J = 1.6 Hz, 1H), 9.38 (br s, 1H), 9.17 - 9.01 (m, 2H), 8.69 -

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8.46 (m, 1H), 7.64 (d, J = 7.9 Hz, 1H), 7.55 - 7.37 (m, 2H), 4.63 - 4.35 (m, 1H), 4.11 - 3.99 (m, 1H), 3.95 - 3.73 (m, 3H), 3.70 - 3.58 (m, 5H), 3.56 - 3.34 (m, 2H), 3.30 - 3.09 (m, 4H), 2.78 (br s, 3H), 2.49 - 2.40 (m, 1H), 2.39 - 2.16 (m, 1H), 2.15 - 2.05 (m, 1H), 2.05 - 1.94 (m, 1H), 1.94 - 1.83 (m, 1H), 1.83 - 1.68 (m, 1H).

5

The following examples were synthesised according to the method outlined in Synthetic Route 9 using commercially available starting materials:

Name	Structure	Example	Yield	Analytical Data
6-(3-aminopyrrolidine-1-carbonyl)-7-methyl-2-(4-methyl-1,4-diazepan-1-yl)benzo [4',5']imidazo[1',2':1,6]pyrido[2,3-d]pyrimidin-5(7H)-one		81	61%	LCMS (ESI+): m/z 475.3 (M+H) ⁺ , Rt: 5.016 min. ¹H NMR (400 MHz, DMSO-d ₆ + D ₂ O) δ = 9.14 - 8.96 (m, 1H), 8.66 - 8.37 (m, 1H), 7.62 - 7.31 (m, 3H), 4.71 - 4.28 (m, 1H), 4.20 - 4.04 (m, 1H), 4.02 - 3.87 (m, 2H), 3.86 - 3.72 (m, 3H), 3.64 (br s, 1H), 3.60 - 3.45 (m, 6H), 3.43 - 3.16 (m, 2H), 2.91 - 2.77 (m, 3H), 2.41 - 2.16 (m, 3H), 2.12 - 1.91 (m, 1H).

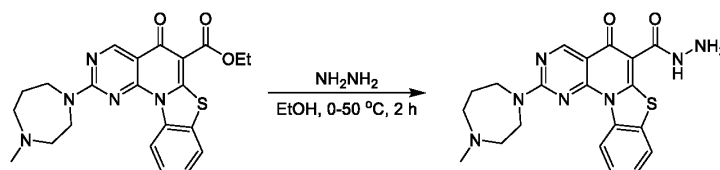
10

Synthetic Route 10

Example 25: 4-(4-Methyl-1,4-diazepan-1-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2(7),3,5,9,12,14,16-heptaene-9-carbohydrazide

15

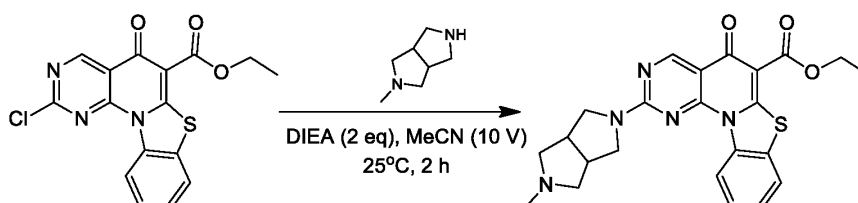
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To a solution of ethyl 4-(4-methyl-1,4-diazepan-1-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0²,7.0¹²,17]heptadeca-2(7),3,5,9,12,14,16-heptaene-9-carboxylate (5 g, 11.43 mmol, 1 eq) in EtOH (50 mL) was added hydrazine (732.45 mg, 22.86 mmol, 2 eq) at 0 °C under N₂. The reaction was heated to 50 °C and stirred for 2 h. The mixture was quenched by H₂O (50 mL) at 0 °C before being extracted with dichloromethane (50 mL x 3). The combined organics were washed with saturated brine solution (50 mL x 2), dried over anhydrous sodium sulfate and concentrated in vacuum to give the title compound (2.8 g, 6.61 mmol, 57.85% yield) as a yellow solid. **LCMS** (ESI⁺): m/z 424.2 (M+H)⁺, Rt: 0.275 min.

Synthetic Route 11

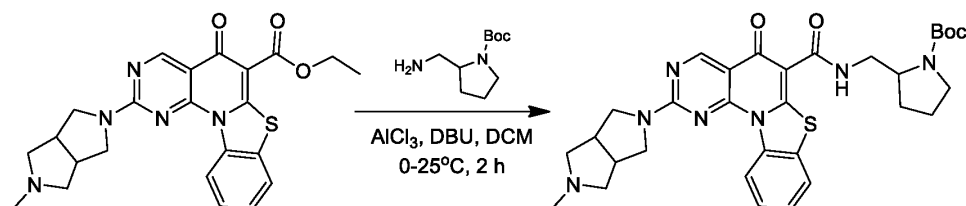
Example 26: 2-(5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-oxo-N-(pyrrolidin-2-ylmethyl)-5H-benzo[4',5']thiazolo[3',2':1,6]pyrido[2,3-d]-pyrimidine-6-carboxamide



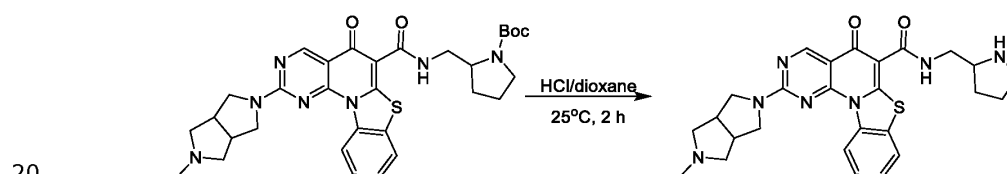
Ethyl 4-{5-methyl-octahydropyrrolo[3,4-c]pyrrol-2-yl}-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0²,7.0¹²,17]heptadeca-2(7),3,5,9,12,14,16-heptaene-9-carboxylate: To a mixture of ethyl 4-chloro-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0²,7.0¹²,17]heptadeca-2(7),3,5,9,12,14,16-heptaene-9-carboxylate (2 g, 5.56 mmol, 1 eq) in MeCN (20 mL) was added 5-methyl-2,3,3a,4,6,6a-hexahydro-1H-pyrrolo[3,4-c]pyrrole (1.40 g, 11.12 mmol, 2 eq) and DIEA (2.16 g, 16.68 mmol, 2.90 mL, 3 eq). The mixture was stirred at 25°C for 2 h and then concentrated *in vacuo*. The mixture was triturated with MeCN (20 mL) for 5 min. After filtration, the filter cake was triturated with methyl tert-butyl ether (20 mL) for 5 min before the filter cake was collected to give the title compound (2 g, 4.00 mmol, 72.03% yield, 90% purity) as a yellow solid. **LCMS** (ESI⁺): Rt: 0.356 min, m/z 450.2 (M+H)⁺.

30

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***Tert*-butyl 2-((2-(5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-oxo-5H-benzo[4',5']thiazolo[3',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamido)-methyl)pyrrolidine-1-carboxylate:** To a solution of ethyl 4-((5-methylhexahydropyrrolo[3,4-c]pyrrol-2-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2(7),3,5,9,12,14,16-heptaene-9-carboxylate (0.3 g, 667.37 μ mol, 1 *eq*) in DCM (3 mL) was added *tert*-butyl 2-(aminomethyl)pyrrolidine-1-carboxylate (267.32 mg, 1.33 mmol, 2 *eq*). DBU (304.79 mg, 2.00 mmol, 301.78 μ L, 3 *eq*) was added dropwise at -10°C and the mixture was stirred for 20 min. AlCl₃ (142.38 mg, 1.07 mmol, 58.35 μ L, 1.6 *eq*) was added in portions and the reaction mixture was stirred at 25°C for 2 h. The reaction was quenched by 2M NaOH (sat aq, 1 mL) and extracted with dichloromethane (3 x 2 mL). The combined organic phases were washed with saturated brine (3 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to give a residue. The crude product was purified by prep-HPLC (column: Phenomenex luna C18 100*40mm*5 μ m; mobile phase: [H₂O(0.04% HCl)-ACN];gradient:20%-55% B over 8.0 min) to give the title compound (0.2 g, 298.14 μ mol, 44.67% yield, 90% purity) as a yellow solid. **LCMS** (ESI⁺): Rt: 0.429 min, m/z 604.4 (M+H)⁺.



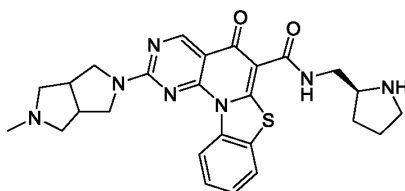
2-((5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-oxo-N-(pyrrolidin-2-ylmethyl)-5H-benzo[4',5']thiazolo[3',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamide: A mixture of *tert*-butyl 2-((2-(5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-oxo-5H-benzo[4',5']thiazolo[3',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamido) methyl)pyrrolidine-1-carboxylate (0.2 g, 414.09 μ mol, 1 *eq*) in HCl/dioxane (5 mL) was stirred at 25°C for 2 h. The mixture was concentrated *in vacuo* to give a residue which was purified by prep-HPLC (column: Phenomenex luna C18 100*40mm*5 μ m; mobile phase: [H₂O(0.04% HCl)-CAN];gradient:1%-30% B over 8.0 min) to give the title compound (**Example 26**, 0.05 g, 89.80 μ mol, 21.69% yield, 97% purity, HCl salt) as a yellow solid. **LCMS** (ESI⁺): Rt: 1.321 min, m/z 504.2 (M+H)⁺. **¹H NMR** (400 MHz, DMSO-d₆ + D₂O) δ = 9.07 (br s, 2H), 7.87 (br d, *J* = 6.3

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Hz, 1H), 7.48 (br s, 2H), 3.95 - 3.73 (m, 4H), 3.73 - 3.51 (m, 5H), 3.48 - 3.29 (m, 2H), 3.29 - 3.12 (m, 3H), 3.10 - 2.95 (m, 1H), 2.84 (br d, $J = 12.8$ Hz, 3H), 2.10 (br d, $J = 6.9$ Hz, 1H), 2.01 - 1.83 (m, 2H), 1.76 - 1.59 (m, 1H).

5 Example 26 was separated into isomer 1 (Example 26A) and isomer 2 (Example 26B):

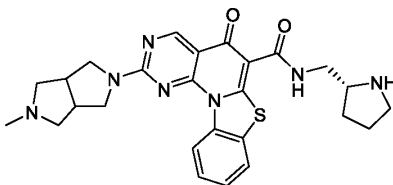
Example 26A: 4-(2-methyl-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl)-8-oxo-N-[[2-(2S)-pyrrolidin-2-yl]methyl]-11-thia-1,3,5-triazatetracyclo-[8.7.0.0.2,7.0]heptadeca-2,4,6,9,12(17),13,15-heptaene-9-carboxamide



Yield: 29%

LCMS (ESI+): m/z 504.3 (M+H)⁺, Rt: 1.926 min. **¹H NMR** (400 MHz, DMSO- d_6 +D₂O) δ = 9.49 - 8.75 (m, 2H), 7.89 (br d, $J = 6.8$ Hz, 1H), 7.48 (br d, $J = 6.6$ Hz, 2H), 3.93 - 3.92 (m, 1H), 3.92 - 3.72 (m, 4H), 3.70 - 3.51 (m, 4H), 3.47 - 3.32 (m, 2H), 3.28 - 3.13 (m, 3H), 3.10 - 2.97 (m, 1H), 2.85 (br d, $J = 13.1$ Hz, 3H), 2.10 (br d, $J = 6.0$ Hz, 1H), 2.02 - 1.86 (m, 2H), 1.75 - 1.62 (m, 1H).

Example 26B: 4-(2-methyl-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl)-8-oxo-N-[[2-(2R)-pyrrolidin-2-yl]methyl]-11-thia-1,3,5-triazatetracyclo-[8.7.0.0.2,7.0]heptadeca-2,4,6,9,12(17),13,15-heptaene-9-carboxamide



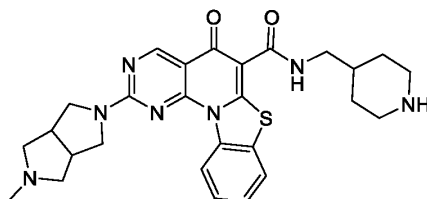
Yield: 38%

LCMS (ESI+): m/z 504.3 (M+H)⁺, Rt: 2.014 min. **¹H NMR** (400 MHz, DMSO- d_6 +D₂O) δ = 8.75 (br s, 1H), 8.61 (br s, 1H), 7.65 (br d, $J = 6.6$ Hz, 1H), 7.43 - 7.22 (m, 2H), 3.90 (br s, 1H), 3.84 - 3.73 (m, 1H), 3.71 - 3.54 (m, 4H), 3.53 - 3.40 (m, 4H), 3.36 (br dd, $J = 2.4, 4.4$ Hz, 1H), 3.22 (br s, 3H), 2.99 (br s, 1H), 2.92 - 2.78 (m, 3H), 2.19 - 2.07 (m, 1H), 2.04 - 1.86 (m, 2H), 1.75 - 1.62 (m, 1H).

30

The following examples 27-31 were synthesised according to the method outlined in Synthetic Route 11 using commercially available starting materials:

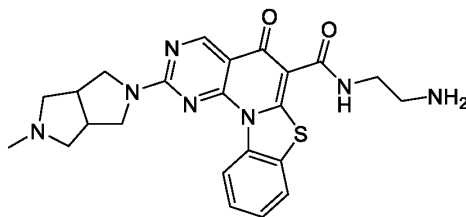
Example 27: 4-(2-methyl-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl)-8-oxo-N-(4-piperidylmethyl)-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]-heptadeca-2,4,6,9,12(17),13,15-heptaene-9-carboxamide



Yield: 45%

LCMS (ESI+): m/z 518.3 (M+H)⁺, Rt: 1.933 min. **¹H NMR** (400 MHz, DMSO-d₆ + D₂O) δ = 9.39 (dd, J = 4.3, 8.2 Hz, 1H), 9.26 (s, 1H), 8.01 (d, J = 7.6 Hz, 1H), 7.65 - 7.58 (m, 1H), 7.57 - 7.49 (m, 1H), 4.10 - 3.97 (m, 1H), 3.96 - 3.87 (m, 2H), 3.96 - 3.77 (m, 2H), 3.74 - 3.68 (m, 1H), 3.49 - 3.41 (m, 1H), 3.38 (br d, J = 8.0 Hz, 1H), 3.34 - 3.21 (m, 5H), 3.14 - 2.98 (m, 1H), 2.94 - 2.79 (m, 5H), 1.85 (br d, J = 11.6 Hz, 3H), 1.48 - 1.33 (m, 2H).

Example 28: N-(2-aminoethyl)-4-(2-methyl-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]-heptadeca-2,4,6,9,12(17),13,15-heptaene-9-carboxamide

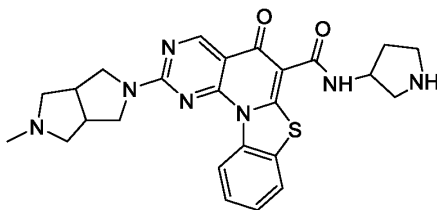


Yield: 30%

LCMS (ESI+): m/z 464.3 (M+H)⁺, Rt: 1.766 min. **¹H NMR** (400 MHz, DMSO-d₆ + D₂O) δ = 9.21 - 9.04 (m, 2H), 7.88 (br d, J = 7.1 Hz, 1H), 7.58 - 7.44 (m, 2H), 3.96 - 3.75 (m, 4H), 3.71 - 3.65 (m, 1H), 3.63 - 3.52 (m, 3H), 3.45 - 3.22 (m, 3H), 3.03 (br t, J = 5.9 Hz, 3H), 2.84 (br d, J = 12.9 Hz, 3H).

Example 29: 4-(2-methyl-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl)-8-oxo-N-pyrrolidin-3-yl-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]-heptadeca-2,4,6,9,12(17),13,15-heptaene-9-carboxamide

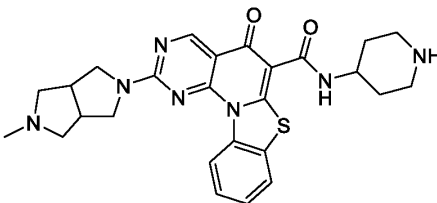
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Yield: 11%

LCMS (ESI+): m/z 490.3 (M+H)⁺, Rt: 1.867 min. **¹H NMR** (400 MHz, D₂O) δ = 8.65 (br d, *J* = 12.3 Hz, 1H), 8.46 - 8.28 (m, 1H), 7.64 (br d, *J* = 6.0 Hz, 1H), 7.37 (br t, *J* = 7.3 Hz, 1H), 7.28 - 7.20 (m, 1H), 4.51 - 4.39 (m, 1H), 4.12 - 3.99 (m, 1H), 3.95 - 3.58 (m, 4H), 3.57 - 3.48 (m, 4H), 3.47 - 3.23 (m, 4H), 3.19 - 3.08 (m, 1H), 3.05 - 2.93 (m, 3H), 2.60 - 2.42 (m, 1H), 2.15 - 2.02 (m, 1H).

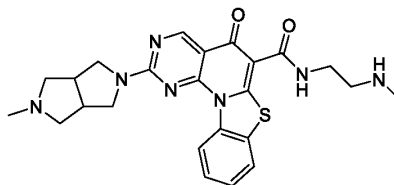
Example 30: 4-(2-methyl-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl)-8-oxo-N-(4-piperidyl)-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]-heptadeca-2,4,6,9,12(17),13,15-heptaene-9-carboxamide



Yield: 17.46%

LCMS (ESI+): m/z 504.3 (M+H)⁺, Rt: 1.844 min. **¹H NMR** (400 MHz, D₂O) δ = 8.75 (br s, 1H), 8.55 - 8.34 (m, 1H), 7.77 - 7.55 (m, 1H), 7.42 (br t, *J* = 7.4 Hz, 1H), 7.30 (br d, *J* = 8.1 Hz, 1H), 4.10 - 3.94 (m, 2H), 3.91 - 3.78 (m, 1H), 3.70 (br d, *J* = 3.0 Hz, 1H), 3.52 (br d, *J* = 5.5 Hz, 6H), 3.43 - 3.36 (m, 1H), 3.33 - 3.07 (m, 4H), 2.99 (br d, *J* = 17.8 Hz, 3H), 2.35 - 2.18 (m, 2H), 1.95 - 1.76 (m, 2H).

Example 31: N-(2-(methylamino)ethyl)-2-(5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-oxo-5H-benzo[4',5']thiazolo[3',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamide



Yield: 71%. Isolated as HCl salt.

LCMS (ESI+): m/z 478.2 (M+H)⁺, Rt: 1.272 min. **¹H NMR** (400 MHz, DMSO-d₆) δ = 11.37 (br s, 1H), 10.32 (t, J = 5.8 Hz, 1H), 9.23 (t, J = 7.0 Hz, 1H), 9.16 (d, J = 9.4 Hz, 1H), 9.00 - 8.87 (m, 2H), 7.99 (dd, J = 1.2, 7.7 Hz, 1H), 7.58 - 7.46 (m, 2H), 4.08 - 3.94 (m, 1H), 3.92 - 3.77 (m, 4H), 3.73 - 3.60 (m, 3H), 3.45 - 3.23 (m, 3H),
 5 3.17 - 2.98 (m, 3H), 2.84 (dd, J = 4.8, 9.8 Hz, 3H), 2.60 (t, J = 5.2 Hz, 3H).

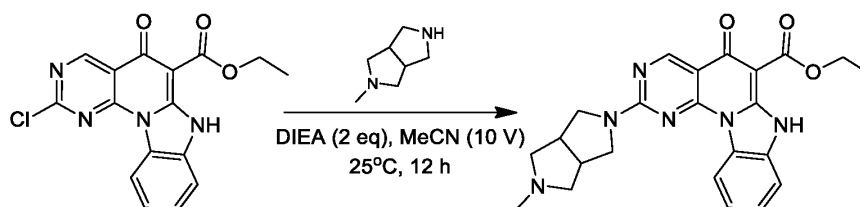
The following examples were synthesised according to the method outlined in Synthetic Route 11 using commercially available starting materials:

Name	Structure	Example	Yield	Analytical Data
2-(5-methylhexahydro-pyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-oxo-N-(pyrrolidin-3-ylmethyl)-5H-benzo[4',5']thiazolo[3',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamide		82	48%	LCMS (ESI+): m/z 504.1 (M+H) ⁺ , Rt: 2.718 min. ¹H NMR (400 MHz, D ₂ O) δ 8.58 (br s, 1H), 8.29 (br s, 1H), 7.59 (br s, 1H), 7.40 - 7.29 (m, 1H), 7.18 (br s, 1H), 4.09 (br d, J = 2.0 Hz, 1H), 3.92 - 3.68 (m, 3H), 3.67 - 3.29 (m, 11H), 3.16 (br s, 1H), 3.04 (br d, J = 16.4 Hz, 3H), 2.66 (br d, J = 2.8 Hz, 1H), 2.28 (br d, J = 1.3 Hz, 1H), 1.97 - 1.72 (m, 1H).
N-(2-(isopropylamino)ethyl)-2-(5-methylhexahydro-pyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-oxo-5H-benzo[4',5']thiazolo[3',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamide		83	7%	LCMS (ESI+): m/z 506.2 (M+H) ⁺ , Rt: 1.352 min. ¹H NMR (400 MHz, DMSO + D ₂ O-d ₆) δ = 10.38 (t, J = 6.0 Hz, 1H), 9.41 (d, J = 8.6 Hz, 1H), 9.27 (s, 1H), 8.01 (d, J = 7.5 Hz, 1H), 7.68 -

Name	Structure	Example	Yield	Analytical Data
2,3-d]pyrimidine-6-carboxamide				7.59 (m, 1H), 7.58 - 7.50 (m, 1H), 4.09 - 3.85 (m, 4H), 3.72 - 3.55 (m, 4H), 3.46 - 3.20 (m, 4H), 3.11 (br t, J = 6.3 Hz, 2H), 3.08 - 2.96 (m, 1H), 2.85 (br d, J = 10.1 Hz, 3H), 1.21 (d, J = 6.5 Hz, 6H)

Synthetic Route 12

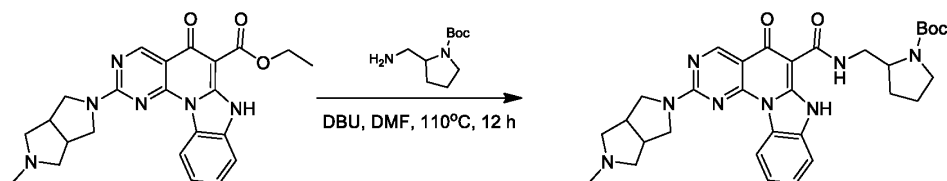
Example 32: 2-(5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-oxo-N-(pyrrolidin-2-ylmethyl)-5,7-dihydrobenzo[4',5']imidazo[1',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamide



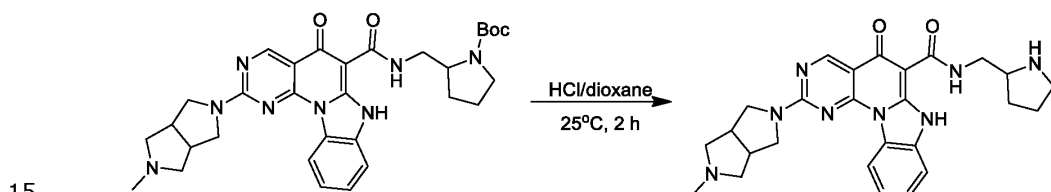
Ethyl 2-(5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-oxo-5,7-dihydrobenzo[4',5']imidazo[1',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxylate:

To a mixture of ethyl 4-chloro-8-oxo-1,3,5,11-tetraazatetracyclo[8.7.0.0.2,7.0.12,17]-heptadeca-2(7),3,5,9,12,14,16-heptaene-9-carboxylate (1.5 g, 4.38 mmol, 1 eq) in MeCN (15 mL) was added 5-methyl-2,3,3a,4,6,6a-hexahydro-1H-pyrrolo[3,4-c]pyrrole (1.1 g, 8.75 mmol, 2 eq) and DIEA (1.51 g, 13.13 mmol, 3 eq). The mixture was stirred at 25°C for 12 h. The mixture was concentrated *in vacuo* and triturated with MeCN (15 mL) for 5 min. The residue was collected by filtration and the filter cake was triturated with methyl tert-butyl ether (15 mL) for 5 min. After filtration, the filter cake was collected to give the title compound (1.1 g, 2.54 mmol, 58.12% yield) as a yellow solid. **LCMS** (ESI⁺): m/z 433.1 (M+H)⁺, Rt: 0.319 min.

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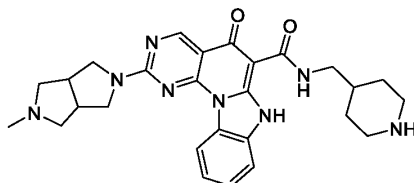
tert-butyl 2-((2-(5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-oxo-5,7-dihydrobenzo[4',5']imidazo[1',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamido)methyl)pyrrolidine-1-carboxylate: To a mixture of ethyl 2-(5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-oxo-5,7-dihydrobenzo[4',5']imidazo[1',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxylate (0.3 g, 693.68 μ mol, 1 eq) in DMF (3 mL) was added *tert*-butyl 2-(aminomethyl)pyrrolidine-1-carboxylate (277.86 mg, 1.39 mmol, 2 eq) and DBU (316.81 mg, 2.08 mmol, 313.67 μ L, 3 eq). The mixture was heated to 110°C and stirred for 12 h. The reaction was poured into water (30 mL) and stirred for 5 min. The solid was collected by filtration to give the title compound (0.2 g, 340.90 μ mol, 49.14% yield) as a yellow solid. The crude product was used in the next step directly without purification. **LCMS** (ESI+): m/z 587.5 (M+H)⁺, Rt: 0.409 min.



2-((2-(5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-oxo-5,7-dihydrobenzo[4',5']imidazo[1',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamido)methyl)pyrrolidine-1-carboxamide: A mixture of *tert*-butyl 2-((2-(5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-oxo-5,7-dihydrobenzo[4',5']imidazo[1',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamido)methyl)pyrrolidine-1-carboxylate (0.2 g, 340.90 μ mol, 1 eq) in HCl/dioxane (2 mL) was stirred at 25°C for 2 h. The mixture was concentrated *in vacuo*. The crude product was purified by prep-HPLC (column: Phenomenex luna C18 100*40mm*5 μ m; mobile phase: [H₂O(0.04% HCl)-ACN]; gradient: 1%-25% B over 8.0 min) to give the title compound (**Example 32**, 93.2 mg, 174.02 μ mol, 51.05% yield, 97.66% purity, HCl salt) as a yellow solid. **LCMS** (ESI+): Rt: 1.257 min, m/z 487.3 (M+H)⁺. **¹H NMR** (400 MHz, DMSO-d₆ + D₂O) δ = 9.17 (d, J = 1.6 Hz, 1H), 8.72 (br d, J = 8.1 Hz, 1H), 7.79 (d, J = 7.9 Hz, 1H), 7.51 - 7.45 (m, 1H), 7.44 - 7.37 (m, 1H), 4.12 - 3.99 (m, 1H), 3.96 - 3.73 (m, 5H), 3.72 - 3.55 (m, 3H), 3.34 (br d, J = 11.0 Hz, 2H), 3.30 - 3.14 (m, 3H), 3.12 - 2.95 (m, 1H), 2.85 (br d, J = 8.3 Hz, 3H), 2.13 - 2.03 (m, 1H), 2.02 - 1.83 (m, 2H), 1.80 - 1.67 (m, 1H).

The following examples 33-37 were synthesised according to the method outlined in Synthetic Route 12 using commercially available starting materials:

Example 33: 4-(2-methyl-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl)-8-oxo-N-(4-piperidylmethyl)-1,3,5,11-tetrazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]-heptadeca-2,4,6,9,12(17),13,15-heptaene-9-carboxamide

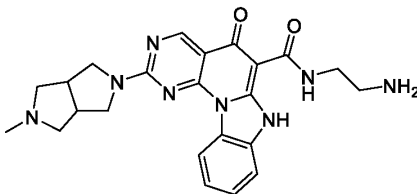


Yield: 54%. Isolated as HCl salt.

LCMS (ESI⁺): m/z 501.3 (M+H)⁺, Rt: 1.794 min. **¹H NMR** (400 MHz, DMSO-*d*₆) δ = 9.11 (s, 1H), 8.66 (br d, *J* = 8.1 Hz, 1H), 7.74 (d, *J* = 7.9 Hz, 1H), 7.52 - 7.42 (m, 1H), 7.41 - 7.33 (m, 1H), 4.09 - 3.93 (m, 1H), 3.92 - 3.84 (m, 2H), 3.79 (br d, *J* = 18.8 Hz, 2H), 3.70 - 3.52 (m, 2H), 3.51 - 3.34 (m, 2H), 3.33 - 3.25 (m, 4H), 3.25 - 3.15 (m, 1H), 3.09 - 2.95 (m, 1H), 2.88 (br d, *J* = 3.5 Hz, 1H), 2.84 (br d, *J* = 8.8 Hz, 3H), 1.91 - 1.77 (m, 3H), 1.50 - 1.35 (m, 2H).

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Example 34: N-(aminomethyl)-4-(2-methyl-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl)-8-oxo-1,3,5,11-tetrazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]-heptadeca-2,4,6,9,12(17),13,15-heptaene-9-carboxamide



20 Yield: 38%. Isolated as HCl salt.

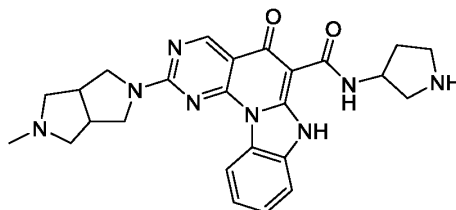
LCMS (ESI⁺): m/z 447.3 (M+H)⁺, Rt: 1.523 min. **¹H NMR** (400 MHz, DMSO-*d*₆) δ = 12.99 - 12.76 (m, 1H), 11.51 - 11.29 (m, 1H), 10.37 (br d, *J* = 2.1 Hz, 1H), 9.07 (d, *J* = 6.5 Hz, 1H), 8.59 (d, *J* = 8.1 Hz, 1H), 8.20 (br s, 3H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.50 - 7.39 (m, 1H), 7.38 - 7.29 (m, 1H), 4.06 - 3.96 (m, 1H), 3.91 - 3.77 (m, 4H), 3.68 - 3.54 (m, 3H), 3.44 - 3.29 (m, 2H), 3.25 (br s, 1H), 3.11 - 2.95 (m, 3H), 2.82 (t, *J* = 4.4 Hz, 3H).

25

Example 35: 4-(2-methyl-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl)-8-oxo-N-pyrrolidin-3-yl-1,3,5,11-tetrazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]-heptadeca-2,4,6,9,12(17),13,15-heptaene-9-carboxamide

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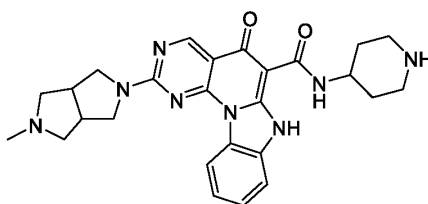


Yield: 58%. Isolated as HCl salt.

LCMS (ESI⁺): m/z 473.3 (M+H)⁺, Rt: 1.758 min. **¹H NMR** (400 MHz, DMSO-*d*₆) δ = 12.87 (br s, 1H), 11.59 - 11.27 (m, 1H), 10.52 (br d, *J* = 5.8 Hz, 1H), 9.69 (br d, *J* = 3.4 Hz, 1H), 9.60 - 9.46 (m, 1H), 9.03 (d, *J* = 3.9 Hz, 1H), 8.53 (dd, *J* = 3.9, 7.9 Hz, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.43 (t, *J* = 7.7 Hz, 1H), 7.36 - 7.28 (m, 1H), 4.65 - 4.52 (m, 1H), 4.03 - 3.90 (m, 1H), 3.89 - 3.74 (m, 4H), 3.70 - 3.49 (m, 2H), 3.41 - 3.20 (m, 5H), 3.16 - 2.96 (m, 2H), 2.86 - 2.77 (m, 3H), 2.37 - 2.25 (m, 1H), 1.96 (br dd, *J* = 5.8, 12.4 Hz, 1H).

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Example 36: 4-(2-methyl-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl)-8-oxo-N-(4-piperidyl)-1,3,5,11-tetrazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12(17),13,15-heptaene-9-carboxamide



15 Yield: 62.50%. Isolated as HCl salt.

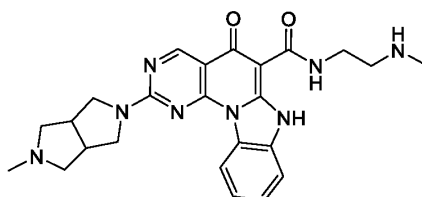
LCMS (ESI⁺): m/z 487.3 (M+H)⁺, Rt: 1.812 min. **¹H NMR** (400 MHz, DMSO-*d*₆) δ = 12.91 (br s, 1H), 11.45 - 11.11 (m, 1H), 10.46 (br d, *J* = 5.0 Hz, 1H), 9.23 - 9.09 (m, 2H), 9.08 (d, *J* = 3.3 Hz, 1H), 8.60 (t, *J* = 8.5 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.52 - 7.41 (m, 1H), 7.38 - 7.28 (m, 1H), 4.11 (br d, *J* = 6.8 Hz, 1H), 4.04 - 3.95 (m, 1H), 3.90 - 3.76 (m, 4H), 3.69 - 3.53 (m, 1H), 3.36 (br dd, *J* = 8.2, 18.2 Hz, 2H), 3.25 (br s, 3H), 3.12 - 2.96 (m, 3H), 2.82 (t, *J* = 4.1 Hz, 3H), 2.13 (br d, *J* = 4.8 Hz, 2H), 1.77 (br d, *J* = 10.6 Hz, 2H).

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Example 37: N-(2-(methylamino)ethyl)-2-(5-methylhexahydropyrrolo[3,4-c]-pyrrol-2(1H)-yl)-5-oxo-5,7-dihydrobenzo[4',5']imidazo[1',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamide

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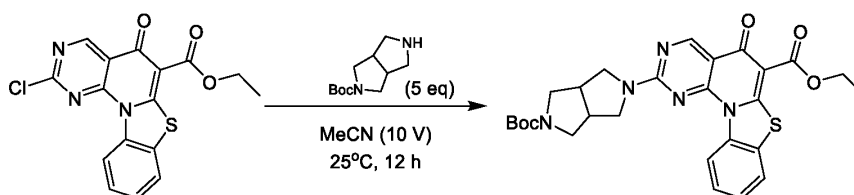


Yield: 36%. Isolated as HCl salt.

LCMS (ESI+): m/z 461.2 ($M+H$)⁺, Rt: 1.719 min. **¹H NMR** (400 MHz, DMSO- d_6) δ 13.07 - 12.79 (m, 1H), 11.35 - 11.07 (m, 1H), 10.54 - 10.28 (m, 1H), 9.28 - 9.05 (m, 1H), 9.00 - 8.79 (m, 2H), 8.77 - 8.67 (m, 1H), 7.80 (br d, J = 8.0 Hz, 1H), 7.57 - 7.29 (m, 2H), 3.81 - 3.75 (m, 2H), 3.74 - 3.61 (m, 4H), 3.53 - 3.23 (m, 4H), 3.20 - 2.91 (m, 4H), 2.82 (br d, J = 4.9 Hz, 3H), 2.59 (br d, J = 4.6 Hz, 3H).

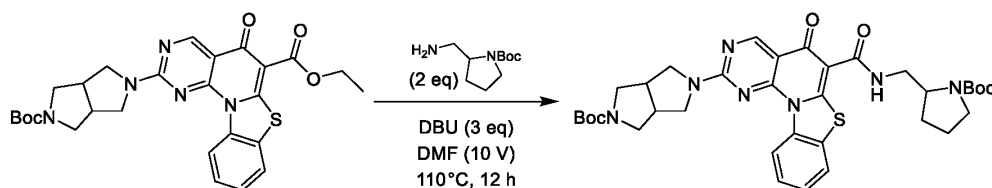
Synthetic Route 13

Example 38: 4-(2,3,3a,4,6,6a-hexahydro-1H-pyrrolo[3,4-c]pyrrol-5-yl)-8-oxo-N-(pyrrolidin-2-ylmethyl)-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12(17),13,15-heptaene-9-carboxamide



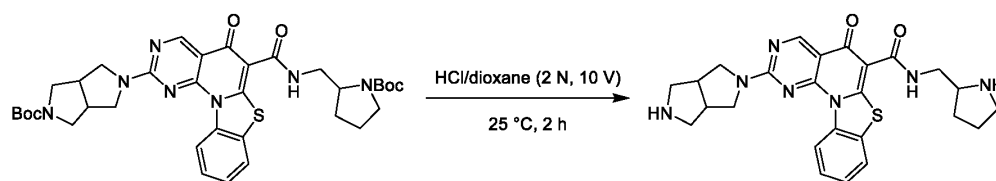
Ethyl 4-(5-*tert*-butoxycarbonyl-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-2-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12(17),13,15-heptaene-9-carboxylate: To a solution of ethyl 4-chloro-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2(7),3,5,9,12,14,16-heptaene-9-carboxylate (0.5 g, 1.39 mmol, 1 eq) in ACN (5 mL) was added *tert*-butyl 2,3,3a,4,6,6a-hexahydro-1H-pyrrolo[3,4-c]pyrrole-5-carboxylate (1.48 g, 6.94 mmol, 5 eq). The mixture was stirred at 25°C for 12 hrs. The reaction mixture was concentrated under vacuum and the crude product was triturated with ACN (5 mL) at 25°C for 2 hrs to give the title compound (0.6 g, 1.08 mmol, 77.87% yield, 88.9% purity) as a yellow solid. **LCMS** (ESI+): m/z 536.3 ($M+H$)⁺, Rt: 0.553 min. **¹H NMR** (400 MHz, DMSO- d_6) δ = 9.48 - 9.35 (m, 1H), 9.14 (s, 1H), 8.04 (d, J = 8.3 Hz, 1H), 7.71 - 7.58 (m, 1H), 7.51 (t, J = 7.3 Hz, 1H), 4.33 (q, J = 7.2 Hz, 2H), 4.07 - 3.89 (m, 2H), 3.60 - 3.54 (m, 2H), 3.12 - 3.08 (m, 2H), 3.03 (br s, 2H), 2.65 (br s, 2H), 1.39 (br s, 9H), 1.32 (t, J = 7.1 Hz, 3H).

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***Tert*-butyl 2-[9-[(1-*tert*-butoxycarbonylpyrrolidin-2-yl)methylcarbamoyl]-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12(17),13,15-heptaen-4-yl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-**

- c]pyrrole-5-carboxylate:** To a solution of ethyl 4-(5-*tert*-butoxycarbonyl-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-2-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12(17),13,15-heptaene-9-carboxylate (0.15 g, 280.06 μ mol, 1 eq) in DMF (1.5 mL) was added DBU (127.9 mg, 840.16 μ mol, 3 eq) and *tert*-butyl 2-(aminomethyl)pyrrolidine-1-carboxylate (112.18 mg, 560.1 μ mol, 2 eq). The mixture was stirred at 110°C for 12 hrs. The resulting product was filtered to give the title compound (0.15 g, 184.83 μ mol, 66.00% yield, 67% purity) as a yellow solid which was directly used in the next step without purification. **LCMS** (ESI+): m/z 690.3 (M+H)⁺, Rt: 0.645 min.



- 4-(2,3,3a,4,6,6a-hexahydro-1H-pyrrolo[3,4-c]pyrrol-5-yl)-8-oxo-N-(pyrrolidin-2-ylmethyl)-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]-heptadeca-2,4,6,9,12(17),13,15-heptaene-9-carboxamide:** To a solution of *tert*-butyl 2-[9-[(1-*tert*-butoxycarbonylpyrrolidin-2-yl)methylcarbamoyl]-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12(17),13,15-heptaen-4-yl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrole-5-carboxylate (0.15 g, 217.44 μ mol, 1 eq) in HCl/dioxane (2 N, 1.5 mL) was stirred at 25°C for 2 hrs. The reaction mixture was concentrated under vacuum and the residue was purified by prep-HPLC (HCl condition, column: CD02-Waters Xbridge BEH C18 150*25*10 μ m; mobile phase: [water(0.015% HCl)-ACN]; gradient: 1%-27% B over 10 min) to give the title compound (**Example 38**, 30 mg, 65.73 μ mol, 30.23% yield, 97.52% purity, HCl salt) as a yellow solid. **LCMS** (ESI+): m/z 490.2 (M+H)⁺, Rt: 1.922 min. **¹H NMR** (400 MHz, DMSO- d_6) δ = 10.52 - 10.43 (m, 1H), 9.71 - 9.58 (m, 1H), 9.50 (br d, J = 2.0 Hz, 1H), 9.45 - 9.30 (m, 2H), 9.25 (s, 1H), 8.97 - 8.85 (m, 1H), 8.04 (br d, J = 7.4 Hz, 1H), 7.63 - 7.50 (m, 2H), 3.98 (br dd, J = 6.9, 11.8 Hz, 2H), 3.87 - 3.76 (m, 2H),

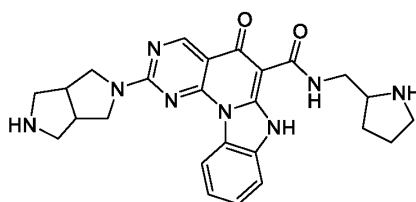
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3.73 - 3.59 (m, 3H), 3.54 - 3.45 (m, 2H), 3.29 (br s, 2H), 3.25 - 3.12 (m, 4H), 2.15 - 2.05 (m, 1H), 2.01 - 1.93 (m, 1H), 1.91 - 1.83 (m, 1H), 1.75 - 1.65 (m, 1H).

The following example 39 was synthesised according to the method outlined in

5 Synthetic Route 13 using commercially available starting materials:

Example 39: 4-(2,3,3a,4,6,6a-hexahydro-1H-pyrrolo[3,4-c]pyrrol-5-yl)-8-oxo-N-(pyrrolidin-2-ylmethyl)-1,3,5,11-tetrazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12(17),13,15-heptaene-9-carboxamide



10

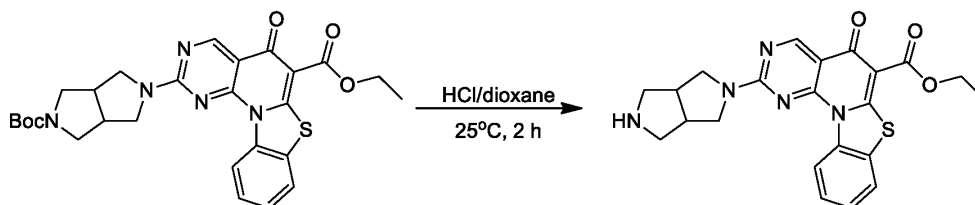
Yield: 32%

LCMS (ESI⁺): m/z 473.3 (M+H)⁺, Rt: 1.765 min. **¹H NMR** (400 MHz, DMSO-d₆) δ = 12.96 - 12.85 (m, 1H), 10.54 (br t, J = 5.7 Hz, 1H), 9.61 (br s, 3H), 9.12 (s, 1H), 9.03 (br d, J = 4.1 Hz, 1H), 8.66 (d, J = 7.9 Hz, 1H), 7.77 (d, J = 7.9 Hz, 1H), 7.51 - 7.42 (m, 1H), 7.41 - 7.33 (m, 1H), 4.02 - 3.88 (m, 2H), 3.82 - 3.68 (m, 4H), 3.64 (br d, J = 5.9 Hz, 1H), 3.47 (br d, J = 4.9 Hz, 2H), 3.33 - 3.12 (m, 6H), 2.12 - 2.03 (m, 1H), 2.01 - 1.94 (m, 1H), 1.88 (td, J = 7.6, 12.7 Hz, 1H), 1.76 - 1.64 (m, 1H).

15

Synthetic Route 14

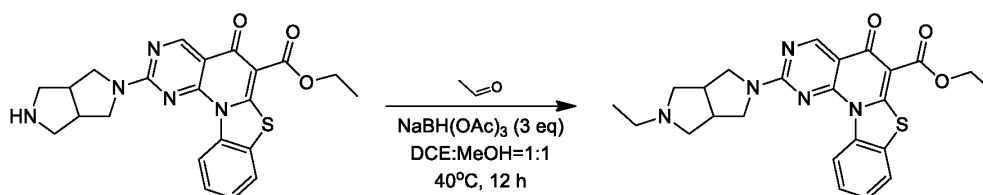
20 **Example 40: 2-(5-ethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-oxo-N-(piperidin-4-yl)-5H-benzo[4',5']thiazolo[3',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamide**



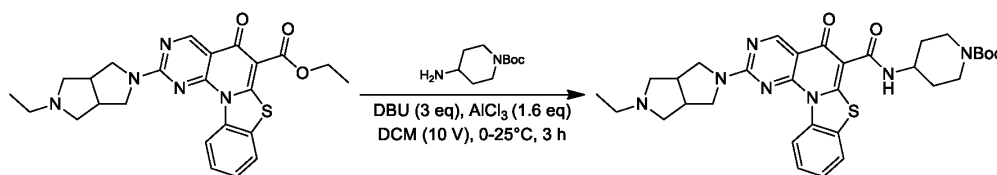
25 **Ethyl 2-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-oxo-5H-benzo[4',5']thiazolo[3',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxylate:** A mixture of ethyl 4-(5-tert-butoxycarbonyl-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-2-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12(17),13,15-heptaene-

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9-carboxylate (1 g, 1.87 mmol, 1 eq) in HCl/dioxane (10 mL) was stirred at 25°C for 2 h. LCMS showed material was consumed, 88% of product was generated. The mixture was concentrated *in vacuo* to give ethyl 2-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-oxo-5H-benzo[4',5']thiazolo[3',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxylate (0.8 g, 1.84 mmol, 98.39% yield) as a yellow solid. The crude product was used in the next step without purification. **LCMS** (ESI⁺): Rt: 0.338 min, m/z 436.2 (M+H)⁺.



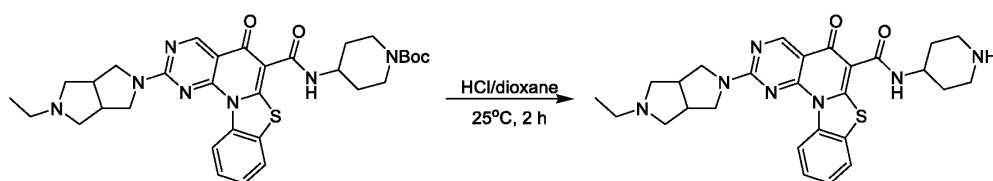
Ethyl 2-(5-ethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-oxo-5H-benzo[4',5']thiazolo[3',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxylate: To a mixture of ethyl 2-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-oxo-5H-benzo[4',5']thiazolo[3',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxylate (0.3 g, 688.87 μmol, 1 eq) in DCE (1.5 mL) and MeOH (1.5 mL) was added acetaldehyde (5 M, 688.87 μL, 5 eq) and NaBH(OAc)₃ (438.00 mg, 2.07 mmol, 3 eq). The mixture was heated to 40°C and stirred for 12 h. The mixture was concentrated *in vacuo* and the crude product was purified by prep-HPLC (column: Phenomenex Luna C18 100*30mm*5μm; mobile phase: [H₂O(0.1% TFA)-ACN]; gradient:10%-40% B over 9.0 min) to give the title compound (0.25 g, 539.31 μmol, 78.29% yield) as a yellow solid. **LCMS** (ESI⁺): Rt: 1.163 min, m/z 464.3 (M+H)⁺.



Tert-butyl 4-(2-(5-ethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-oxo-5H-benzo[4',5']thiazolo[3',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamido)-piperidine-1-carboxylate: To a mixture of ethyl 2-(5-ethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-oxo-5H-benzo[4',5']thiazolo[3',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxylate (0.2 g, 431.45 μmol, 1 eq) in DCM (2 mL) was added *tert*-butyl 4-aminopiperidine-1-carboxylate (172.82 mg, 862.90 μmol, 2 eq), DBU (197.05 mg, 1.29 mmol, 195.10 μL, 3 eq) and AlCl₃ (92.05 mg, 690.32 μmol, 37.72 μL, 1.6 eq) at 0°C. The mixture was stirred at 25°C for 3 h. The reaction mixture was quenched by

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the addition of NH₄Cl (sat aq, 2 mL) at 25°C, and then extracted with DCM (3 x 5 mL). The combined organic layers were washed with saturated brine (2 x 2 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the title compound (0.1 g, 161.88 μmol, 37.52% yield) as a yellow solid. **LCMS** (ESI+): Rt: 0.436 min, m/z 618.3 (M+H)⁺.



2-(5-ethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-oxo-N-(piperidin-4-yl)-5H-benzo [4',5'] thiazolo[3',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamide: A mixture of *tert*-butyl 4-(2-(5-ethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-oxo-5H-benzo[4',5']thiazolo[3',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamido)piperidine-1-carboxylate (0.1 g, 161.88 μmol, 1 eq) in HCl/dioxane (1 mL) was stirred at 25°C for 2 h. The mixture was concentrated *in vacuo* and the crude product was purified by prep-HPLC (column: Phenomenex luna C18 100*40mm*5 μm; mobile phase: [H₂O (0.04% HCl)-ACN]; gradient:1%-35% B over 8.0 min) to give the title compound (**Example 40**, 45 mg, 78.97 μmol, 48.78% yield, 97.24% purity, HCl salt) as a yellow solid. **LCMS** (ESI+): Rt: 1.328 min, m/z 518.3 (M+H)⁺. **¹H NMR** (400 MHz, DMSO-d₆) δ = 10.78 - 10.51 (m, 1H), 10.49 - 10.41 (m, 1H), 9.51 - 9.40 (m, 1H), 9.30 (s, 1H), 8.85 - 8.56 (m, 2H), 8.13 - 8.01 (m, 1H), 7.69 - 7.49 (m, 2H), 4.19 - 4.03 (m, 2H), 4.01 - 3.79 (m, 4H), 3.76 - 3.60 (m, 1H), 3.28 - 3.16 (m, 5H), 3.15 - 2.94 (m, 4H), 2.10 (br d, J = 12.5 Hz, 2H), 1.75 - 1.65 (m, 2H), 1.61 - 1.46 (m, 1H), 1.25 (q, J = 7.0 Hz, 3H).

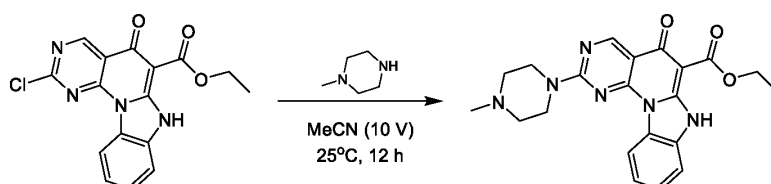
The following example was synthesised according to the method outlined in Synthetic Route 14 using commercially available starting materials:

Name	Structure	Ex.	Yield	Analytical Data
2-(5-isopropylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-		84	61%	LCMS (ESI+): m/z 532.3 (M+H) ⁺ , Rt: 1.334 min. ¹H NMR (400 MHz, MeOD-d ₄) δ = 8.93 (s, 1H), 8.72 (br

Name	Structure	Ex.	Yield	Analytical Data
oxo-N-(piperidin-4-yl)-5H-benzo[4',5']thiazolo[3',2':1,6]pyridino[2,3-d]pyrimidine-6-carboxamide				dd, $J = 8.3, 19.3$ Hz, 1H), 7.78 (d, $J = 7.9$ Hz, 1H), 7.53 - 7.33 (m, 2H), 4.14 - 3.94 (m, 3H), 3.81 - 3.49 (m, 9H), 3.42 (br s, 1H), 3.20 (br s, 3H), 2.42 - 2.21 (m, 2H), 2.01 - 1.80 (m, 2H), 1.43 (br t, $J = 7.5$ Hz, 6H).

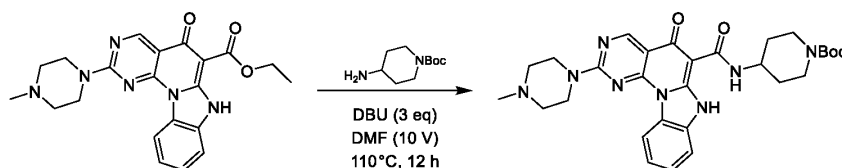
Synthetic Route 15

Example 85: 2-(4-methylpiperazin-1-yl)-5-oxo-N-(piperidin-4-yl)-5,7-dihydrobenzo[4',5']imidazo [1',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamide



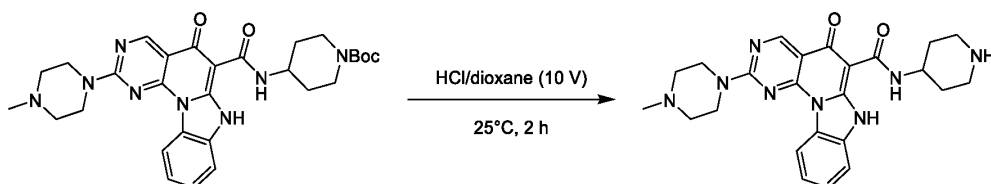
Ethyl 2-(4-methylpiperazin-1-yl)-5-oxo-5,7-dihydrobenzo[4',5']imidazo-[1',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxylate: To a solution of ethyl 4-chloro-8-oxo-1,3,5,11-tetraazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12(17),13,15-heptaene-9-carboxylate (1 g, 2.92 mmol, 1 eq) in ACN (15 mL) was added 1-methylpiperazine (1.46 g, 14.5 mmol, 1.62 mL, 5 eq) and the reaction was stirred at 25°C for 12 hrs. The mixture was concentrated under reduced pressure to give a residue. The crude product was triturated with ACN (15 mL) at 25°C for 20 min to give the title compound (0.9 g, 2.04 mmol, 69.8% yield, 92% purity) as a yellow solid. **LCMS** (ESI+): m/z 407.3 (M+H)⁺, Rt: 1.024 min. **¹H NMR** (400 MHz, DMSO-*d*₆) δ 12.75 - 12.00 (m, 1H), 8.99 (br s, 1H), 8.53 (br d, $J = 7.8$ Hz, 1H), 7.69 (br d, $J = 4.9$ Hz, 1H), 7.37 (br dd, $J = 7.5, 13.5$ Hz, 2H), 4.30 (br d, $J = 6.8$ Hz, 2H), 3.92 (br s, 4H), 2.46 (br s, 4H), 2.25 (br s, 3H), 1.32 (br t, $J = 6.5$ Hz, 3H).

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Tert-butyl 4-(2-(4-methylpiperazin-1-yl)-5-oxo-5,7-dihydrobenzo[4',5']imidazo[1',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamido)piperidine-1-carboxylate : To a solution of ethyl 2-(4-methylpiperazin-1-yl)-5-oxo-5,7-

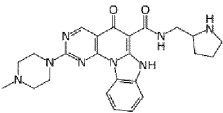
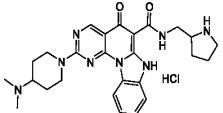
- 5 dihydrobenzo[4',5']imidazo[1',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxylate (200 mg, 452 μmol , 1 eq) and tert-butyl 4-aminopiperidine-1-carboxylate (181.34 mg, 905.43 μmol , 2 eq) in DMF (2 mL) was added DBU (137 mg, 905 μmol , 136 μL , 2 eq). The mixture was stirred at 110°C for 12 hrs and concentrated *in vacuo*. The residue was purified by prep-HPLC (HCl condition, Column: CD06-Waters Xbidge C18 150*40*10 μm ; mobile phase: [water (0.05% HCl)-ACN]; gradient: 0%-27% B over 11 min) to give the title compound (140 mg, 234 μmol , 51.8% yield, 94% purity) as a white solid. **LCMS** (ESI+): m/z 561.3 ($M+H$)⁺, Rt: 3.064 min. **¹H NMR** (400 MHz, DMSO- d_6) δ 13.06 (s, 1H), 10.41 (d, J = 7.4 Hz, 1H), 10.26 - 9.92 (m, 1H), 9.23 (s, 1H), 8.66 (d, J = 8.1 Hz, 1H), 7.80 (d, J = 7.6 Hz, 1H), 7.53 - 7.46 (m, 1H), 7.45 - 7.37 (m, 1H), 5.11 - 4.69 (m, 2H), 4.11 - 3.98 (m, 1H), 3.85 - 3.74 (m, 2H), 3.66 - 3.45 (m, 3H), 3.22 (br d, J = 4.0 Hz, 2H), 3.13 - 3.05 (m, 2H), 2.88 (br s, 3H), 1.93 (br dd, J = 3.8, 9.1 Hz, 2H), 1.47 - 1.35 (m, 11H).



- 20 **2-(4-methylpiperazin-1-yl)-5-oxo-N-(piperidin-4-yl)-5,7-dihydrobenzo[4',5']imidazo[1',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamide**: To tert-butyl 4-(2-(4-methylpiperazin-1-yl)-5-oxo-5,7-dihydrobenzo[4',5']imidazo[1',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamido)piperidine-1-carboxylate (140 mg, 234 μmol , 1 eq) was added HCl/dioxane (2 N, 2 mL). The mixture was stirred at 25°C for 2 hrs. The mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (HCl condition, Column: CD06-Waters Xbidge C18 150*40*10 μm ; mobile phase: [water(0.05% HCl)-ACN]; gradient: 0%-27% B over 11 min) to give the title compound (56 mg, 121 μmol , 51.7% yield, 99.7% purity, HCl salt) as a yellow solid. **LCMS** (ESI+): m/z 461.1 ($M+H$)⁺, Rt: 1.432 min. **¹H NMR** (400 MHz, DMSO- d_6 +D₂O) δ 9.18 (s, 1H), 8.59 (d, J = 8.1 Hz, 1H), 7.76 (d, J = 7.9 Hz, 1H), 7.53 - 7.36 (m, 2H), 5.06 - 4.67 (m, 2H), 4.16 - 4.04 (m, 1H), 3.69 - 3.57 (m, 4H), 3.32 - 3.25 (m,

2H), 3.18 (br s, 2H), 3.08 (br t, $J = 10.7$ Hz, 2H), 2.87 (s, 3H), 2.20 - 2.08 (m, 2H), 1.71 (q, $J = 10.1$ Hz, 2H).

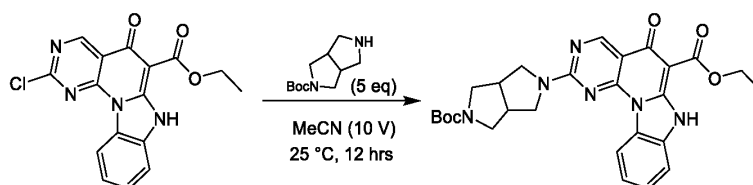
The following examples were synthesised according to the method outlined in
 5 Synthetic Route 15 using commercially available starting materials:

Name	Structure	Ex.	Yield	Analytical Data
4-(4-methylpiperazin-1-yl)-8-oxo-N-[(pyrrolidin-2-yl)methyl]-1,3,5,11-tetraazatetracyclo[8.7.0.0.2,7.0 ^{12,17}]heptadeca-2(7),3,5,9,12(17),13,15-heptaene-9-carboxamide		86	100%	LCMS (ESI ⁺): m/z 461.2 (M+H) ⁺ , Rt: 0.273 min. ¹H NMR (400 MHz, DMSO- d_6) δ = 12.88 (br s, 1H), 11.69 (br d, $J = 1.1$ Hz, 1H), 10.45 (br t, $J = 5.6$ Hz, 1H), 9.81 (br d, $J = 4.8$ Hz, 1H), 9.17 (br d, $J = 5.0$ Hz, 1H), 9.11 (s, 1H), 8.48 (br d, $J = 8.0$ Hz, 1H), 7.73 (d, $J = 7.9$ Hz, 1H), 7.49 - 7.41 (m, 1H), 7.40 - 7.32 (m, 1H), 5.10 - 4.56 (m, 2H), 3.82 - 3.53 (m, 7H), 3.30 - 3.09 (m, 4H), 2.84 (br d, $J = 4.3$ Hz, 3H), 2.13 - 2.03 (m, 1H), 1.98 (dt, $J = 6.1, 12.1$ Hz, 1H), 1.93 - 1.83 (m, 1H), 1.80 - 1.68 (m, 1H)
2-(4-(dimethylamino)piperidin-1-yl)-5-oxo-N-(pyrrolidin-2-ylmethyl)-5,7-dihydrobenzo[4',5']imidazo[1',2':1,6]pyridine-2,3-dipyrimidine -		87	25%	LCMS (ESI ⁺): m/z 489.4 (M+H) ⁺ , Rt: 1.313 min. ¹H NMR (400 MHz, DMSO- d_6 +D ₂ O) δ = 9.14 (s, 1H), 8.59 (d, $J = 7.9$ Hz, 1H), 7.75 (d, $J = 7.5$ Hz, 1H), 7.50 - 7.39 (m, 2H), 5.13 - 4.77 (m, 2H), 3.79 - 3.70 (m, 2H), 3.62 - 3.51 (m, 2H), 3.27 - 3.10 (m, 4H), 2.76 (s, 6H), 2.24 (br d, $J = 3.0$ Hz, 2H), 2.13 - 2.03

Name	Structure	Ex.	Yield	Analytical Data
6-carboxamide				(m, 1H), 2.02 - 1.85 (m, 2H), 1.76 - 1.60 (m, 3H).

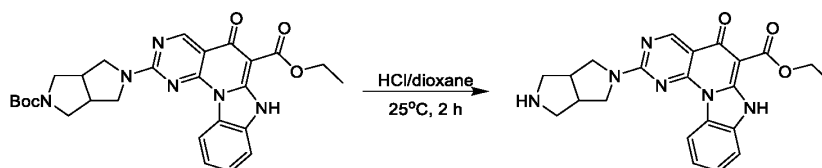
Synthetic Route 16

Example 88: 2-(5-Ethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-oxo-N-(piperidin-4-yl)-5,7-dihydrobenzo[4',5']imidazo[1',2':1,6]pyrido[2,3-d]-pyrimidine-6-carboxamide

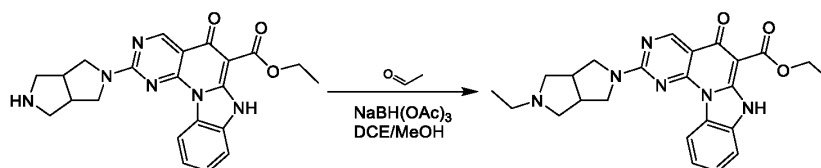


Ethyl 4-(5-tert-butoxycarbonyl-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-2-yl)-8-oxo-1,3,5,11-tetraazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12(17),13,15-heptaene-9-carboxylate: To a solution of ethyl 4-chloro-8-oxo-1,3,5,11-tetraazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12(17),13,15-heptaene-9-carboxylate (500 mg, 1.46 mmol, 1 eq) in ACN (5 mL) was added tert-butyl 2,3,3a,4,6,6a-hexahydro-1H-pyrrolo[3,4-c]pyrrole-5-carboxylate (1.55 g, 7.29 mmol, 5 eq). The mixture was stirred at 25°C for 12 hrs. The reaction mixture was concentrated under reduced pressure and the crude product was triturated with ACN (2 mL) at 25°C for 30 min to give the title compound (500 mg, 838.86 μmol, 57.5% yield, 87% purity) as a yellow solid. **LCMS** (ESI+): m/z 519.2 (M+H)⁺, Rt: 0.468 min. **¹H NMR** (400 MHz, DMSO-d₆) δ = 9.14 - 8.38 (m, 2H), 7.77 - 7.55 (m, 1H), 7.49 - 7.12 (m, 2H), 4.51 - 4.22 (m, 2H), 4.02 - 3.88 (m, 1H), 3.58 (br dd, J = 4.6, 14.6 Hz, 3H), 3.46 - 3.42 (m, 2H), 3.11 (br d, J = 10.1 Hz, 2H), 2.82 - 2.76 (m, 2H), 1.42 - 1.38 (m, 12H).

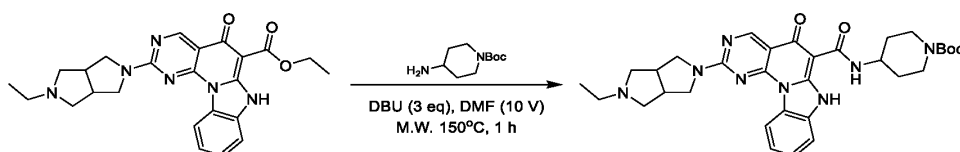
- 171 -



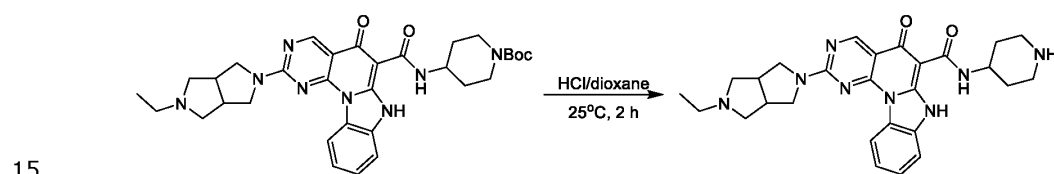
Ethyl 2-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-oxo-5,7-dihydrobenzo[4',5']imidazo[1',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxylate: To ethyl 2-(5-(tert-butoxycarbonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-oxo-5,7-dihydrobenzo[4',5']imidazo[1',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxylate (2.5 g, 4.82 mmol, 1 eq) was added HCl/dioxane (10 mL) and the reaction was stirred at 25°C for 2 h. The mixture was concentrated *in vacuo* and the crude product was triturated with ACN (30 mL) for 30 min. After filtration, the filter cake was collected to give the title compound (1.8 g, 4.04 mmol, 83.87% yield, 94% purity) as a yellow solid. **LCMS** (ESI+): m/z 419.2 ($M+H$)⁺, Rt: 0.301 min.



Ethyl 2-(5-ethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-oxo-5,7-dihydrobenzo[4',5']imidazo[1',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxylate: To a solution of ethyl 2-(5-hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-oxo-5,7-dihydrobenzo[4',5']imidazo[1',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxylate (0.5 g, 1.19 mmol, 1 eq) in DCE (3 mL) and MeOH (3 mL) was added acetaldehyde (5 M, 2.39 mL, 10 eq). The mixture was stirred at 40°C for 2 h, then NaBH(OAc)₃ (759.74 mg, 3.58 mmol, 3 eq) was added, and the reaction was stirred at 40°C for 12 h. The mixture was extracted with dichloromethane (3 x 3 mL) and the combined organic phases were washed with saturated brine (3 mL), before being dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The crude product was triturated with ACN (10 mL) for 30 min and collected by filtration to give the title compound (0.4 g, 788.35 μmol, 65.98% yield, 88% purity) as a yellow solid. **LCMS** (ESI+): m/z 447.3 ($M+H$)⁺, Rt: 0.347 min.

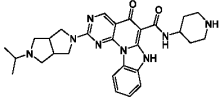


tert-Butyl 4-(2-(5-ethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-oxo-5,7-dihydrobenzo [4',5']imidazo[1',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamido)piperidine-1-carboxylate: Ethyl 2-(5-ethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-oxo-5,7-dihydrobenzo [4',5'] imidazo [1',2':1,6]pyrido[2,3-d]-pyrimidine-6-carboxylate (0.17 g, 380.74 μ mol, 1 eq), tert-butyl 4-aminopiperidine-1-carboxylate (114.38 mg, 571.11 μ mol, 1.5 eq) and DBU (173.89 mg, 1.14 mmol, 172.16 μ L, 3 eq) were taken up into a microwave tube in DMF (2 mL). The sealed tube was heated to 150°C and stirred for 1 h under microwave irradiation. The mixture was extracted with dichloromethane (3 x 5 mL) and the combined organic phases were washed with saturated brine (5 mL), before being dried over anhydrous Na₂SO₄, and concentrated *in vacuo* to give the title compound (0.1 g, 101.55 μ mol, 26.67% yield, 61% purity) as a yellow solid. The crude product was used in the next step directly without purification. **LCMS** (ESI+): m/z 601.4 (M+H)⁺, Rt: 0.403 min.



2-(5-ethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-oxo-N-(piperidin-4-yl)-5,7-dihydrobenzo[4',5']imidazo[1',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamide: To tert-butyl 4-(2-(5-ethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-oxo-5,7-dihydrobenzo[4',5']imidazo[1',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamido)piperidine-1-carboxylate (0.1 g, 166.47 μ mol, 1 eq) was added HCl/dioxane (2 mL) and the reaction was stirred at 25°C for 2 h. The mixture was concentrated *in vacuo* and the crude product was purified by prep-HPLC (column: Phenomenex luna C18 100*40mm*5 μ m; mobile phase: [H₂O(0.04% HCl)-ACN]; gradient: 1%-30% B over 8.0 min) to give the title compound (0.038 g, 74.03 μ mol, 44.47% yield, 97.53% purity) as a yellow solid. **LCMS** (ESI+): m/z 501.3 (M+H)⁺, Rt: 1.286 min. **¹H NMR** (400 MHz, DMSO-d₆+D₂O) δ = 9.13 (d, *J* = 2.4 Hz, 1H), 8.76 - 8.66 (m, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.53 - 7.36 (m, 2H), 4.09 (br s, 2H), 3.91 (br s, 4H), 3.73 - 3.53 (m, 2H), 3.46 - 3.34 (m, 2H), 3.30 - 3.18 (m, 4H), 3.07 (br t, *J* = 10.8 Hz, 2H), 3.01 - 2.89 (m, 1H), 2.13 (br d, *J* = 12.0 Hz, 2H), 1.76 - 1.63 (m, 2H), 1.27 - 1.16 (m, 3H).

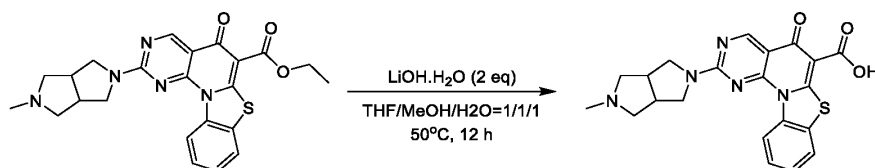
The following examples were synthesised according to the method outlined in Synthetic Route 16 using commercially available starting materials:

Name	Structure	Example	Yield	Analytical Data
2- (5-isopropylhexahydropyrrolo[3, 4-c]pyrrol- 2(1H)-yl)- 5- oxo- N-(piperidin- 4-yl)- 5, 7-dihydrobenzo[4', 5']imidazo[1',2': 1,6]pyrido[2,3-d]pyrimidine-6-carboxamide		89	29%	LCMS (ESI+): m/z 515.3 (M+H) ⁺ , Rt: 1.322 min. ¹H NMR (400 MHz, DMSO-d ₆ +D ₂ O) δ = 9.16 (d, J = 1.5 Hz, 1H), 8.74 (dd, J = 4.7, 7.8 Hz, 1H), 7.78 (d, J = 7.8 Hz, 1H), 7.52 - 7.38 (m, 2H), 4.17 - 3.98 (m, 2H), 3.96 - 3.75 (m, 4H), 3.71 - 3.55 (m, 1H), 3.43 - 3.36 (m, 2H), 3.34 - 3.16 (m, 4H), 3.08 (br t, J = 10.8 Hz, 3H), 2.12 (br d, J = 10.7 Hz, 2H), 1.70 (q, J = 10.1 Hz, 2H), 1.29 (t, J = 5.8 Hz, 6H).

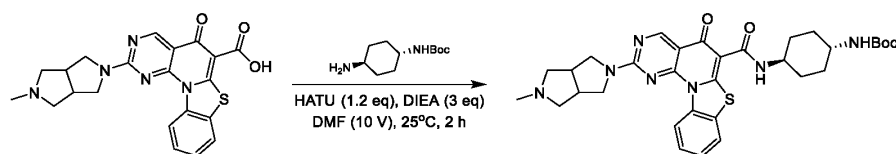
Synthetic Route 17

- 5 **Example 90: N-((1r,4r)-4-aminocyclohexyl)-2-(5-methylhexa hydropyrrolo [3,4-c]pyrrol-2(1H)-yl)-5-oxo-5H-benzo[4',5']thiazolo [3',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamide**

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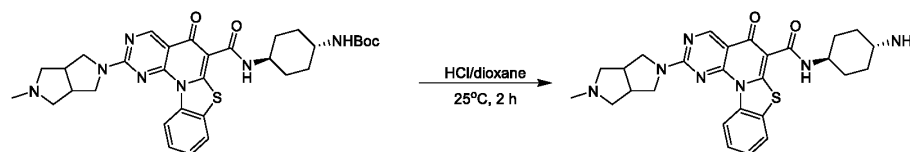


2-(5-Methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-oxo-5H-benzo[4',5']-thiazolo[3',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxylic acid: To a solution of ethyl 2-(5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-oxo-5H-benzo[4',5']-thiazolo[3',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxylate (300 mg, 667.37 μmol , 1 *eq*) in THF (1 mL), MeOH (1 mL) and H₂O (1 mL) was added LiOH.H₂O (42.01 mg, 1.00 mmol, 2 *eq*). The mixture was stirred at 50°C for 12 h. The mixture was filtered and the filter cake was collected. The filter cake was triturated with MeOH (5 mL), filtered, and the product was collected to give the title compound (320 mg, 607.40 μmol , 91.01% yield, 80% purity) as a yellow solid. **LCMS** (ESI⁺): *m/z* 422.1 (M+H)⁺, Rt: 0.345 min.



tert-Butyl ((1r,4r)-4-(2-(5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-oxo-5H-benzo [4',5']thiazolo[3',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamido)cyclohexyl)carbamate: To a solution of 2-(5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-oxo-5H-benzo[4',5']thiazolo [3',2':1,6]-pyrido[2,3-d]pyrimidine-6-carboxylic acid (320 mg, 759.24 μmol , 1 *eq*) in DMF (5 mL) was added HATU (433.03 mg, 1.14 mmol, 1.2 *eq*) and DIEA (294.37 mg, 2.28 mmol, 396.73 μL , 3 *eq*). The mixture was stirred at 25°C for 0.5 h. tert-Butyl N-(4-aminocyclohexyl)carbamate (325.42 mg, 1.52 mmol, 2 *eq*) was added and the mixture stirred at 25°C for 2 h. The mixture was poured into H₂O (3 mL) and extracted with DCM (3 x 5 mL). The combined organic phases were washed with saturated brine (10 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The crude product was triturated with MeOH (5 mL) and collected by filtration to give the title compound (300 mg, 485.63 μmol , 63.96% yield) as a yellow solid. **LCMS** (ESI⁺): *m/z* 618.4 (M+H)⁺, Rt: 0.436 min.

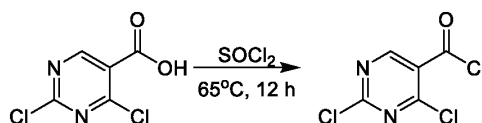
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- N-((1*r*,4*r*)-4-aminocyclohexyl)-2-(5-methylhexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)-5-oxo-5*H*-benzo[4',5']thiazolo[3',2':1,6]pyrido[2,3-*d*]pyrimidine-6-carboxamide:** A solution of tert-butyl ((1*r*,4*r*)-4-(2-(5-methylhexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)-5-oxo-5*H*-benzo[4',5'] thiazolo[3',2':1,6]pyrido[2,3-*d*]pyrimidine-6-carboxamido)cyclohexyl)carbamate (300 mg, 485.63 μ mol, 1 *eq*) in HCl/dioxane (3 mL) was stirred at 25°C for 2 h. The mixture was concentrated *in vacuo* and the crude product was triturated with ACN (5 mL). The product was collected by filtration and purified by prep-HPLC (column: Phenomenex luna C18 100*40mm*5 μ m; mobile phase: [H₂O(0.04% HCl)-ACN]; gradient: 1%-30% B over 8.0 min) to give the title compound (20 mg, 36.32 μ mol, 56.09% yield, 94.0% purity) as a yellow solid. **LCMS** (ESI⁺): *m/z* 518.2 (M+H)⁺, *R_t*: 1.356 min. **¹H NMR** (400 MHz, DMSO-*d*₆+D₂O) δ = 9.41 - 9.33 (m, 1H), 9.23 (d, *J* = 1.0 Hz, 1H), 8.00 (br d, *J* = 7.6 Hz, 1H), 7.65 - 7.47 (m, 2H), 4.07 - 3.96 (m, 1H), 3.95 - 3.63 (m, 6H), 3.44 - 3.18 (m, 3H), 3.13 - 2.98 (m, 2H), 2.85 (d, *J* = 10.6 Hz, 3H), 2.01 (br s, 4H), 1.54 - 1.31 (m, 4H).

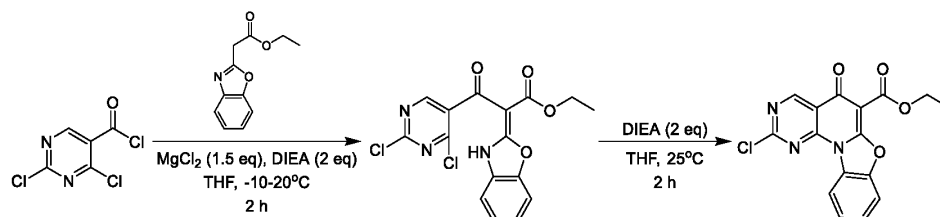
Synthetic Route 18

- Example 91: 2-(4-methyl-1,4-diazepan-1-yl)-5-oxo-N-(pyrrolidin-2-ylmethyl)-5*H*-benzo[4',5']oxazolo[3',2':1,6]pyrido[2,3-*d*]pyrimidine-6-carboxamide**



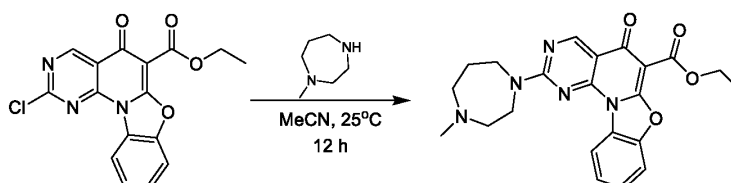
- 2,4-Dichloropyrimidine-5-carbonyl chloride:** A mixture of acid (1.00 g, 5.18 mmol, 1 *eq*) in SOCl₂ (10.00 mL) was stirred at 65°C for 12 h. TLC showed the reaction was completed. The mixture was concentrated *in vacuo* to give the desired product (1.00 g, 4.73 mmol, 91.28% yield) as a yellow solid. The crude product was used in the next step without further purification.

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Ethyl 2-chloro-5-oxo-5H-benzo[4',5']oxazolo[3',2':1,6]pyrido[2,3-d]-pyrimidine-6-carboxylate:

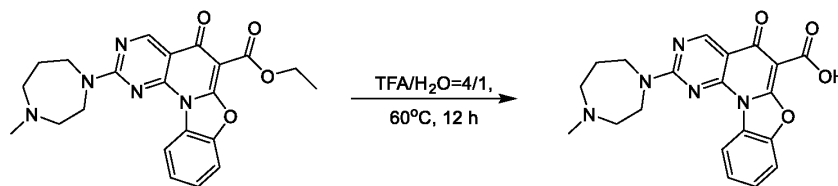
To a solution of ethyl 2-(benzo[d]oxazol-2-yl)acetate (1.42 g, 6.91 mmol, 1 eq) in THF (20 mL) was added MgCl₂ (987.21 mg, 10.37 mmol, 425.52 μL, 1.5 eq) at 25 °C. Then to the mixture was added 2,4-dichloropyrimidine-5-carbonyl chloride (2.0 g, 9.52 mmol, 83.06% yield, 75% purity) with THF (20 mL) dropwise at -10°C. Then to the mixture was added DIEA (2.68 g, 20.74 mmol, 3.61 mL, 3 eq) dropwise at -25°C. The mixture was stirred at 25°C for 2 h. LCMS showed material consumed and 60% of product generated. The mixture was concentrated *in vacuo*. The residue was triturated with water (50 mL) for 30 min. After filtration, the filter cake was collected to give crude product. Then the crude product was triturated with ACN (50 mL) for 30 min. After filtration, the filter cake was collected to give ethyl 2-chloro-5-oxo-5H-benzo[4',5']oxazolo[3',2':1,6]pyrido[2,3-d]-pyrimidine-6-carboxylate (1.8 g, 5.24 mmol, 84.18% yield) as yellow solid. **LCMS** (ESI+): m/z 343.9 (M+H)⁺, Rt: 0.442 min.



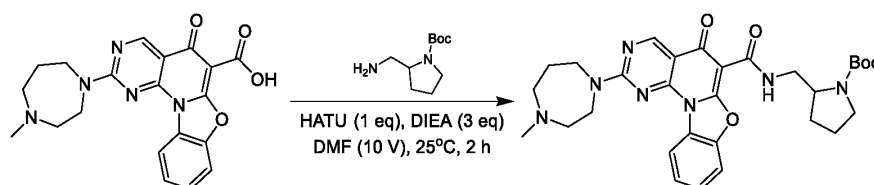
Ethyl 2-(4-methyl-1,4-diazepan-1-yl)-5-oxo-5H-benzo[4',5']oxazolo[3',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxylate:

To a solution of ethyl 2-chloro-5-oxo-5H-benzo[4',5']oxazolo[3',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxylate (1.8 g, 5.24 mmol, 1 eq) in ACN (20 mL) was added 1-methyl-1,4-diazepane (1.20 g, 10.48 mmol, 1.45 mL, 2 eq). The mixture was stirred at 25°C for 12 hr. The mixture was concentrated *in vacuo* and the residue was purified by prep-HPLC (column: Phenomenex luna C18 100*40mm*5 μm; mobile phase: [H₂O(0.04% HCl)-ACN]; gradient: 1%-30% B over 8.0 min) to give the title compound (0.8 g, 1.90 mmol, 36.2% yield) as a yellow solid. **LCMS** (ESI+): m/z 422.1 (M+H)⁺, Rt: 0.319 min.

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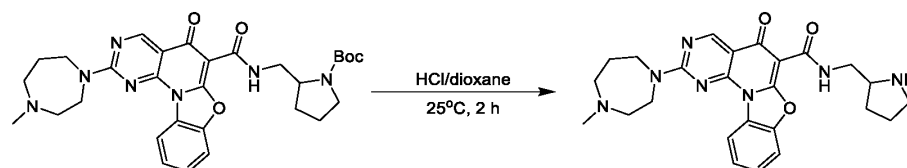
- 2-(4-Methyl-1,4-diazepan-1-yl)-5-oxo-5H-benzo[4',5']oxazolo[3',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxylic acid:** A solution of ethyl 2-(4-methyl-1,4-diazepan-1-yl)-5-oxo-5H-benzo[4',5']oxazolo[3',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxylate (500 mg, 1.19 mmol, 1 eq) in TFA (2 mL) and H₂O (6 mL) was stirred at 60°C for 12 hr. The mixture was filtered and the filter cake was purified by prep-HPLC (column: Phenomenex luna C18 100*40mm*5 μm; mobile phase: [H₂O(0.04% HCl)-ACN]; gradient: 1%-25% B over 8.0 min) to give the title compound (200 mg, 508.39 μmol, 42.85% yield) as white solid. **LCMS** (ESI⁺): m/z 394.2 (M+H)⁺, Rt: 1.324 min.
- ¹H NMR** (400 MHz, DMSO-d₆+D₂O) δ = 9.33 (d, J = 9.1 Hz, 1H), 8.61 - 8.44 (m, 1H), 8.02 - 7.96 (m, 1H), 7.64 (dd, J = 3.1, 5.6 Hz, 2H), 4.73 - 4.32 (m, 1H), 4.20 - 3.88 (m, 3H), 3.85 - 3.62 (m, 1H), 3.47 (br s, 1H), 3.41 - 3.18 (m, 2H), 2.82 (br s, 3H), 2.40 - 2.30 (m, 1H), 2.24 (br d, J = 4.5 Hz, 1H).



- tert-Butyl 2-((2-(4-methyl-1,4-diazepan-1-yl)-5-oxo-5H-benzo[4',5']oxazolo[3',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamido)methyl)pyrrolidine-1-carboxylate:** To a solution of 2-(4-methyl-1,4-diazepan-1-yl)-5-oxo-5H-benzo[4',5']oxazolo[3',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxylic acid (120 mg, 305.04 μmol, 1 eq) in DMF (1 mL) was added HATU (115.98 mg, 305.04 μmol, 1 eq) and DIEA (118.27 mg, 915.11 μmol, 159.39 μL, 3 eq). The mixture was stirred at 25°C for 30 min. Then the mixture was added tert-butyl 2-(aminomethyl)pyrrolidine-1-carboxylate (73.31 mg, 366.04 μmol, 1.2 eq). The mixture was stirred at 25°C for 2 h. The reaction was then poured into ice-water (w/w = 1/1) (10 mL) and extracted with DCM (3 x 1 mL). The combined organic phases were washed with saturated brine (5 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to give the title compound (80 mg, 138.97 μmol, 45.56% yield) as a yellow solid. The crude product was used in the next step directly without purification. **LCMS** (ESI⁺): m/z 576.3 (M+H)⁺, Rt: 0.383 min.

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2-(4-Methyl-1,4-diazepan-1-yl)-5-oxo-N-(pyrrolidin-2-ylmethyl)-5H-benzo [4',5']oxazolo[3',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamide: A solution of tert-butyl 2-((2-(4-methyl-1,4-diazepan-1-yl)-5-oxo-5H-benzo[4',5']oxazolo[3',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamido)methyl)pyrrolidine-1-carboxylate (80 mg, 138.97 μ mol, 1 eq) in HCl/dioxane (2 mL) was stirred at 25°C for 2 hr. The mixture was concentrated *in vacuo* and the residue was purified by prep-HPLC (column: Phenomenex luna C18 100*40mm*5 μ m; mobile phase: [H₂O(0.04% HCl)-ACN]; gradient: 1%-20% B over 8.0 min) to give the title compound (32.1 mg, 67.50 μ mol, 48.57% yield) as a yellow solid. **LCMS** (ESI+): m/z 476.4 (M+H)⁺, Rt: 1.211 min. **¹H NMR** (400 MHz, DMSO-d₆+D₂O) δ = 9.23 (d, J = 8.4 Hz, 1H), 8.56 - 8.39 (m, 1H), 7.88 - 7.80 (m, 1H), 7.62 - 7.52 (m, 2H), 4.69 - 4.35 (m, 1H), 4.18 - 3.98 (m, 2H), 3.97 - 3.79 (m, 2H), 3.73 - 3.59 (m, 3H), 3.46 - 3.36 (m, 1H), 3.31 - 3.11 (m, 4H), 2.81 (s, 3H), 2.45 - 2.17 (m, 2H), 2.12 - 2.02 (m, 1H), 2.01 - 1.83 (m, 2H), 1.77 - 1.63 (m, 1H).

The following example was synthesised according to the method outlined in Synthetic Route 18 using commercially available starting materials:

Name	Structure	Example	Yield	Analytical Data
4-(2-methyl-1,3,3a, 4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl)-8-oxo-N-(4-piperidyl)-11-oxa-1,3,5-triazatetracyclo[8.7.0.02,7.012,17]heptadeca-2,4,6,9,12(17),13,15-heptaene-9-carboxamide		92	69%	LCMS (ESI+): Rt: 1.718 min, m/z 488.3 (M+H) ⁺ . ¹H NMR (400 MHz, DMSO-d ₆ +D ₂ O) δ = 9.19 (s, 1H), 8.57 (d, J = 3.9 Hz, 1H), 7.86 - 7.79 (m, 1H), 7.57 (d, J = 3.4 Hz, 2H), 4.11 - 3.99 (m, 2H), 3.96 - 3.79 (m, 4H), 3.50 - 3.18 (m, 6H), 3.12 - 3.01 (m, 3H), 2.86

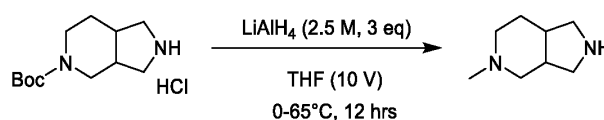
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				(d, J = 10.0 Hz, 3H), 2.14 - 2.07 (m, 2H), 1.74 - 1.64 (m, 2H)
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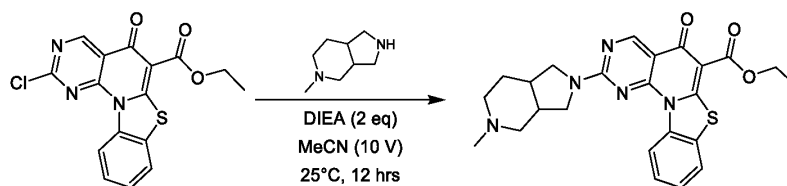
Synthetic Route 19

Example 93: 4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-8-oxo-N-(4-piperidyl)-11-thia-1,3,5-triazatetracyclo

5 **[8.7.0.02,7.012,17]heptadeca-2,4,6,9,12(17),13,15-heptaene-9-carboxamide**



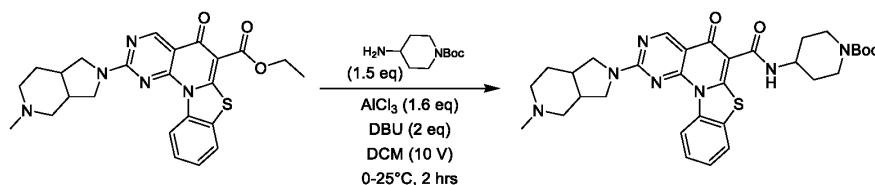
5-methyl-1,2,3,3a,4,6,7,7a-octahydropyrrolo[3,4-c]pyridine: To a solution of tert-butyl 1,2,3,3a,4,6,7,7a-octahydropyrrolo[3,4-c]pyridine-5-carboxylate (900 mg, 3.42 mmol, 1 eq, HCl) in THF (9 mL) was added LiAlH₄ (2.5 M, 4.11 mL, 3 eq) at 0°C. The mixture was stirred at 65 °C for 12 hrs. The mixture was cooled to 0°C and quenched with Na₂SO₄·10H₂O (5 g). The resulting slurry was filtered and the filtrate was concentrated under reduced pressure to give the title compound (450 mg, 3.11 mmol, 90.79% yield, 96.90% purity) as a colorless oil which was directly used in the next step without purification. **LCMS** (ESI⁺): m/z 141.2 (M+H)⁺, Rt: 0.096 min.



Ethyl 4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12(17),13,15-heptaene-9-carboxylate: To a solution of ethyl 4-chloro-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12(17),13,15-heptaene-9-carboxylate (500 mg, 1.39 mmol, 1 eq) in ACN (5 mL) was added DIEA (359.22 mg, 2.78 mmol, 484.12 μL, 2 eq) and 5-methyl-1,2,3,3a,4,6,7,7a-octahydropyrrolo[3,4-c]pyridine (292.31 mg, 2.08 mmol, 1.5 eq). The mixture was stirred at 25 °C for 12 hrs. The reaction mixture was concentrated under reduced pressure and the crude product was triturated with ACN (10 mL) at 25 °C for 30 min

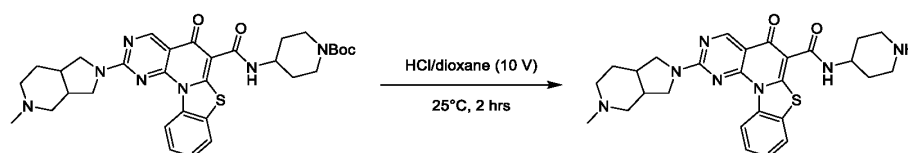
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to give the title compound (600 mg, 1.18 mmol, 84.62% yield, 90.85% purity) as a faint yellow solid. **LCMS** (ESI+): m/z 464.2. $(M+H)^+$, R_t : 0.339min.



- 5 **tert-Butyl 4-[[4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0.2,7.0.12,17]heptadeca-2,4,6,9,12(17),13,15-heptaene-9-carboxylate]amino]piperidine-1-carboxylate:** To a solution of ethyl 4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0.2,7.0.12,17] heptadeca-
- 10 2,4,6,9,12(17),13,15-heptaene-9-carboxylate (300 mg, 647.18 μ mol, 1 eq) and tert-butyl 4-aminopiperidine-1-carboxylate (194.42 mg, 970.77 μ mol, 1.5 eq) in DCM (3 mL) was added $AlCl_3$ (138.07 mg, 1.04 mmol, 56.59 μ L, 1.6 eq) and DBU (197.05 mg, 1.29 mmol, 195.10 μ L, 2 eq) at 0 °C. The mixture was stirred at 25 °C for 2 hrs. The reaction mixture was quenched by the addition of saturated ammonium chloride
- 15 solution (10 mL) at 0°C, and then extracted with DCM (3 x 5 mL). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give the title compound (200 mg, 323.75 μ mol, 50.02% yield) as a brown solid which was directly used in the next step without purification. **LCMS** (ESI+): m/z 618.3. $(M+H)^+$, R_t : 0.418 min.

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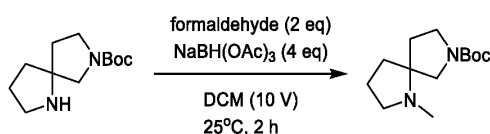
- 4-(5-Methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-8-oxo-N-(4-piperidyl)-11-thia-1,3,5-triazatetracyclo[8.7.0.0.2,7.0.12,17]heptadeca-2,4,6,9,12(17),13,15-heptaene-9-carboxamide:** A solution of tert-butyl 4-[[4-(5-
- 25 methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0.2,7.0.12,17]heptadeca-2,4,6,9,12(17),13,15-heptaene-9-carboxylate]amino]piperidine-1-carboxylate (200.00 mg, 323.75 μ mol, 1 eq) in HCl/dioxane (2 N, 2 mL) was stirred at 25 °C for 2 hrs. The reaction mixture was concentrated under reduced pressure and the residue was purified by prep-HPLC (HCl

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condition, column: CD24-XPT C18 150*25*7 μm ; mobile phase: [water (0.05% HCl)-ACN]; gradient: 0%-25% B over 11 min) to give the title compound (15 mg, 24.44 μmol , 7.55% yield, 96.21% purity, 2HCl) as a yellow solid. **LCMS** (ESI+): m/z 518.2. (M+1)⁺, Rt: 2.059 min. **¹H NMR** (400 MHz, DMSO- d_6 +D $_2$ O) δ 9.20 - 8.70 (m, 2H), 7.91 - 7.71 (m, 1H), 7.53 - 7.27 (m, 2H), 3.95 - 3.69 (m, 2H), 3.67 - 3.45 (m, 3H), 3.44 - 3.18 (m, 5H), 3.16 - 2.96 (m, 3H), 2.77 (br d, J = 18.0 Hz, 5H), 2.18 - 1.95 (m, 3H), 1.82 - 1.55 (m, 3H).

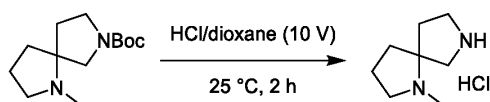
Synthetic Route 20

- 10 **Example 94: 4-(1-methyl-1,7-diazaspiro[4.4]nonan-7-yl)-8-oxo-N-(4-piperidyl)-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12(17),13,15-heptaene-9-carboxamide**



- 15 **tert-Butyl 1-methyl-1,7-diazaspiro[4.4]nonane-7-carboxylate:** To a solution of tert-butyl 1,7-diazaspiro[4.4]nonane-7-carboxylate (1.5 g, 6.63 mmol, 1 eq) in DCM (15 mL) was added NaBH(OAc)₃ (5.62 g, 26.51 mmol, 4 eq) and formaldehyde (1.08 g, 13.26 mmol, 986.91 μL , 37% purity, 2 eq). The mixture was stirred at 25 °C for 2 hrs. The reaction mixture was quenched by the addition of saturated NaHCO₃ to pH = 7~8, and then extracted with DCM (3 x 50 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the title compound (1.3 g, 5.35 mmol, 80.79% yield, 100% purity) as a colorless oil which was directly used in the next step without purification. **LCMS** (ESI+): m/z 241.1 (M+H)⁺, Rt: 0.362 min.

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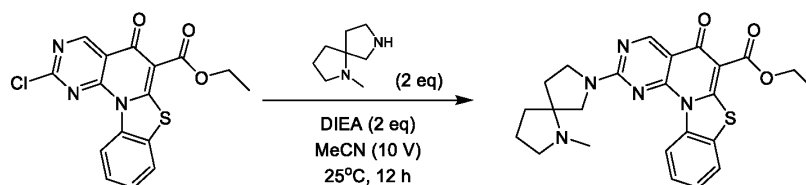


- 1-Methyl-1,7-diazaspiro[4.4]nonane:** To a solution of tert-butyl 1-methyl-1,7-diazaspiro[4.4]nonane-7-carboxylate (1.3 g, 5.41 mmol, 1 eq) was added HCl/dioxane (2 N, 13 mL). The mixture was stirred at 25 °C for 2 hr. The reaction mixture was concentrated under reduced pressure to give the title compound (1 g, 4.60 mmol,

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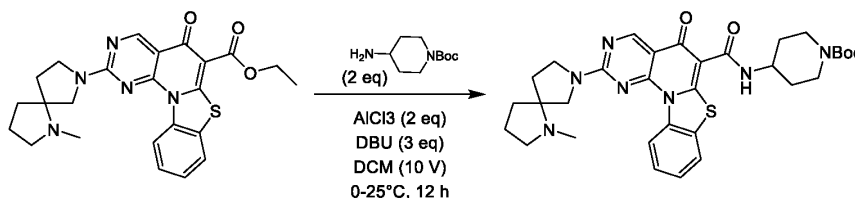
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85.00% yield, 98.95% purity, 2HCl) as a grey solid which was used directly in the next step without purification. **LCMS** (ESI+): m/z 141. $(M+H)^+$, Rt: 0.074 min.



- 5 **Ethyl 4-(1-methyl-1,7-diazaspiro[4.4]nonan-7-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12(17),13,15-heptaene-9-carboxylate:** To a solution of ethyl 4-chloro-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12(17),13,15-heptaene-9-carboxylate (500 mg, 1.39 mmol, 1 eq) in ACN (5 mL) was added DIEA (359.22 mg, 2.78 mmol, 484.12 μ L, 2 eq) and 1-methyl-1,7-diazaspiro[4.4]nonane (592.43 mg, 2.78 mmol, 2 eq, 2HCl). The mixture was stirred at 25 °C for 12 hrs. The reaction mixture was concentrated under reduced pressure and the crude product was triturated with ACN (10 mL) at 25 °C for 30 min to give the title compound (500 mg, 1.00 mmol, 72.18% yield, 93.94% purity) as a yellow solid. **LCMS** (ESI+): m/z 464.1. $(M+H)^+$, Rt: 0.336 min.

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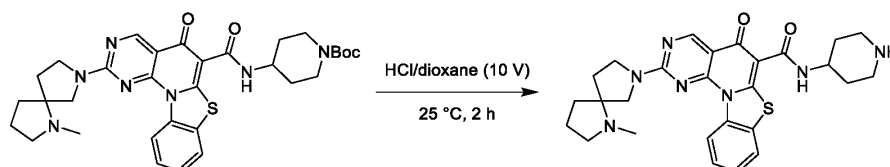


- tert-butyl 4-[[4-(1-methyl-1,7-diazaspiro[4.4]nonan-7-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12(17),13,15-heptaene-9-carbonyl]amino]piperidine-1-carboxylate:** To a solution of ethyl 4-(1-methyl-1,7-diazaspiro[4.4]nonan-7-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12(17),13,15-heptaene-9-carboxylate (300 mg, 647.18 μ mol, 1 eq) and tert-butyl 4-aminopiperidine-1-carboxylate (259.23 mg, 1.29 mmol, 2 eq) in DCM (3 mL) was added $AlCl_3$ (172.59 mg, 1.29 mmol, 70.73 μ L, 2 eq) and DBU (295.57 mg, 1.94 mmol, 292.65 μ L, 3 eq) at 0 °C. The mixture was stirred at 25 °C for 2 hrs. The reaction mixture was quenched by addition NH_4Cl (aq) (10 mL) at 25°C, and then extracted with DCM mL (3 x 10 mL). The combined organic layers were washed with saturated brine (3 x 5 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (HCl

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condition, column: CD24-XPT C18 150*25*7 μm ; mobile phase: [water (0.05% HCl)-ACN]; gradient: 23%-53% B over 10 min to give the title compound (90 mg, 145.69 μmol , 22.51% yield, 97.43% purity) as a white solid. **LCMS** (ESI⁺): m/z 518.2. (M-99)⁺, Rt: 0.278 min.

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4-(1-methyl-1,7-diazaspiro[4.4]nonan-7-yl)-8-oxo-N-(4-piperidyl)-11-thia-1,3,5-triazatetracyclo[8.7.0.0.2,7.0.12,17]heptadeca-2,4,6,9,12(17),13,15-heptaene-9-carboxamide: A solution of tert-butyl 4-[[4-(1-methyl-1,7-diazaspiro-

10 [4.4]nonan-7-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0.2,7.0.12,17]heptadeca-2,4,6,9,12(17),13,15-heptaene-9-carbonyl]amino]piperidine-1-carboxylate (90 mg, 145.69 μmol , 1 eq) in HCl/dioxane (2 N, 1 mL) was stirred at 25 °C for 2 hrs. The reaction mixture was concentrated under reduced pressure to remove solvent. The crude product was triturated with ACN (2 mL) at 25 °C for 30 min to give the title

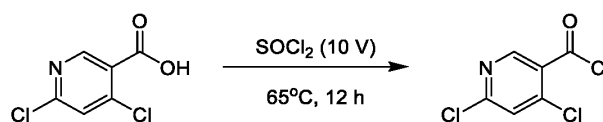
15 compound (35 mg, 62.35 μmol , 42.80% yield, 98.71% purity, HCl salt) as a yellow solid. **LCMS** (ESI⁺): m/z 518.2. (M+1)⁺, Rt: 2.003 min. **¹H NMR** (400 MHz, D₂O) δ 8.36 (br s, 1H), 7.72 (br s, 1H), 7.41 - 7.23 (m, 1H), 7.09 (br t, J = 6.6 Hz, 1H), 6.99 - 6.74 (m, 1H), 3.94 - 3.52 (m, 4H), 3.48 - 3.31 (m, 3H), 3.14 (br t, J = 10.9 Hz, 4H), 2.90 (br s, 3H), 2.50 - 2.04 (m, 8H), 1.70 (br s, 2H)

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Synthetic Route 21

Example 95: 2-(2-Methyl-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl)-5-oxo-N-(4-piperidyl)-[1,3]benzothiazolo[3,2-a][1,6]naphthyridine-6-carboxamide

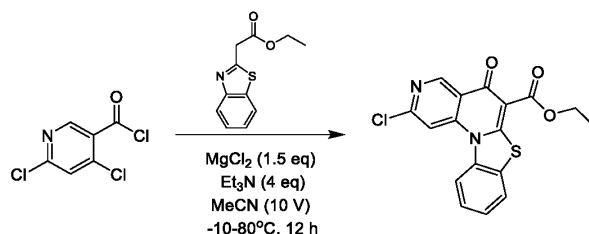
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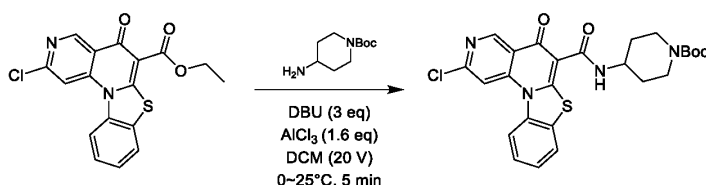
4,6-Dichloropyridine-3-carbonyl chloride: To 4,6-dichloropyridine-3-carboxylic acid (10 g, 52.0 mmol, 1 eq) was added SOCl₂ (100 mL). The mixture was stirred at 65 °C for 12 hrs. The mixture was concentrated under reduced pressure to give the

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title compound (10 g, 46.4 mmol, 89.4% yield, 98% purity) as a yellow solid which was used directly in the next step without purification. **LCMS** (ESI+): m/z 206.0 ($M-4$)⁺, R_t : 1.313 min.



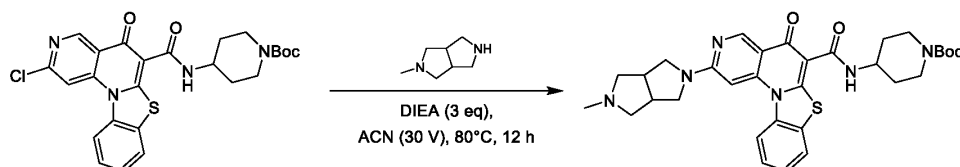
- 5 **Ethyl 2-chloro-5-oxo-[1,3]benzothiazolo[3,2-a][1,6]naphthyridine-6-carboxylate:** To a solution of ethyl 2-(1,3-benzothiazol-2-yl)acetate (5 g, 22.6 mmol, 1 eq) and $MgCl_2$ (3.23 g, 33.8 mmol, 1.39 mL, 1.5 eq) in ACN (50 mL) was added 4,6-dichloropyridine-3-carbonyl chloride (6.18 g, 29.3 mmol, 1.3 eq) and TEA (9.14 g, 90.2 mmol, 4 eq) slowly at $-10^\circ C$. The mixture was stirred at $80^\circ C$ for 12 hrs. The mixture was concentrated under reduced pressure and the crude product was trituated with water (50 mL) and then ACN (50 mL) at $25^\circ C$ for 2 hrs to give the title compound (8 g, 19.8 mmol, 87.7% yield, 98% purity) as a light yellow solid. **LCMS** (ESI+): m/z 359.0 ($M+H$)⁺, R_t : 0.394 min. **1H NMR** (400 MHz, $DMSO-d_6$) δ 9.30 - 9.16 (m, 1H), 8.59 - 8.43 (m, 2H), 8.14 (br d, $J = 8.0$ Hz, 1H), 7.72 - 7.48 (m, 2H), 4.35 (q, $J = 7.1$ Hz, 2H), 1.33 (br t, $J = 7.1$ Hz, 3H).



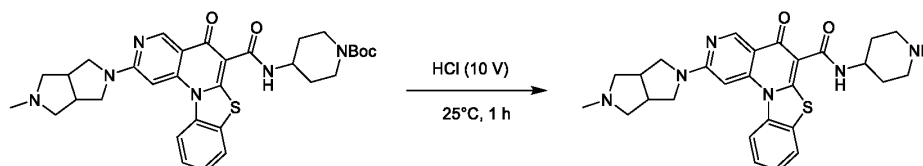
- 20 **tert-Butyl 4-[(2-chloro-5-oxo-[1,3]benzothiazolo[3,2-a][1,6]naphthyridine-6-carbonyl)amino]piperidine-1-carboxylate:** To a solution of ethyl 2-chloro-5-oxo-[1,3]benzothiazolo[3,2-a][1,6]naphthyridine-6-carboxylate (300 mg, 836.12 μ mol, 1 eq) and tert-butyl 4-aminopiperidine-1-carboxylate (251.18 mg, 1.25 mmol, 1.5 eq) in DCM (6 mL) was added DBU (381.86 mg, 2.51 mmol, 378.08 μ L, 3 eq) and $AlCl_3$ (178.38 mg, 1.34 mmol, 73.11 μ L, 1.6 eq) at $0^\circ C$. The mixture was stirred at $25^\circ C$ for 5 min. The reaction mixture was quenched by addition NH_4Cl (aq) 50 mL at $25^\circ C$, and then extracted with DCM mL (3 x 5 mL). The combined organic layers were washed with saturated brine (3 x 2 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude product was trituated with MeCN at $25^\circ C$ for 15

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min and collected by filtration to give the title compound (198 mg, 385.96 μ mol, 46.16% yield) as a yellow solid. **LCMS** (ESI⁺): m/z 513.1 (M+H)⁺, Rt: 0.630 min.



- 5 **tert-Butyl 4-[(2-(2-methyl-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl)-5-oxo-[1,3]benzothiazolo[3,2-a][1,6]naphthyridine-6-carbonyl)amino]piperidine-1-carboxylate:** To a solution of tert-butyl 4-[(2-chloro-5-oxo-[1,3]-benzothiazolo[3,2-a][1,6]naphthyridine-6-carbonyl)amino] piperidine-1-carboxylate (177 mg, 345.02 μ mol, 1 eq) in MeCN (5 mL) was added DIEA (133.78 mg, 1.04 mmol, 180.29 μ L, 3 eq) and 5-methyl-2,3,3a,4,6,6a-hexahydro-1H-pyrrolo[3,4-c]-pyrrole (52.25 mg, 414.03 μ mol, 1.2 eq). The mixture was stirred at 80°C for 12 h. The reaction mixture was concentrated under reduced pressure to remove solvent. The crude product was triturated with MeCN at 25°C for 15 min to give the title compound (157 mg, 260.47 μ mol, 75.49% yield) as a yellow solid. **LCMS** (ESI⁺): m/z 603.6 (M+H)⁺, Rt: 0.465 min.



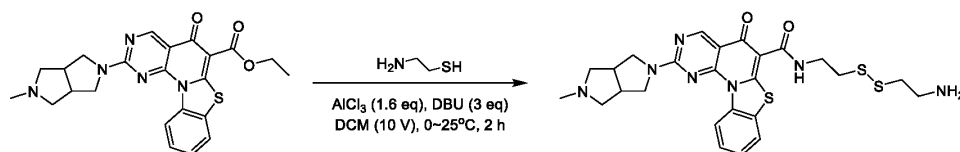
- 20 **2-(2-Methyl-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl)-5-oxo-N-(4-piperidyl)-[1,3]benzothiazolo[3,2-a][1,6]naphthyridine-6-carboxamide:** A solution of tert-butyl 4-[(2-(2-methyl-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl)-5-oxo-[1,3]benzothiazolo[3,2-a][1,6]naphthyridine-6-carbonyl)amino]piperidine-1-carboxylate (156 mg, 258.82 μ mol, 1 eq) in HCl (2 mL) was stirred at 25°C for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by prep-HPLC (HCl condition: column: CD24-WePure Biotech XPT C18 25 150*25*7 μ m; mobile phase: [H₂O (0.05% HCl)-ACN]; gradient: 0%-27% B over 10.0 min) to give the title compound (50.3 mg, 87.07 μ mol, 33.64% yield, 99.63% purity, 2HCl) as a yellow solid. **LCMS** (ESI⁺): m/z 503.2 (M+H)⁺, Rt: 1.844 min. **¹H NMR** (400 MHz, DMSO-d₆ + D₂O) δ = 9.06 (s, 1H), 8.42 (d, J = 8.4 Hz, 1H), 8.01 (d, J = 7.8 Hz, 1H), 7.71 - 7.41 (m, 2H), 7.14 (br d, J = 9.1 Hz, 1H), 4.12 - 4.00 (m, 2H),

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3.88 - 3.78 (m, 2H), 3.71 - 3.56 (m, 3H), 3.44 - 3.14 (m, 5H), 3.10 - 2.91 (m, 3H), 2.83 (br d, $J = 12.3$ Hz, 3H), 2.20 - 1.99 (m, 2H), 1.78 - 1.57 (m, 2H).

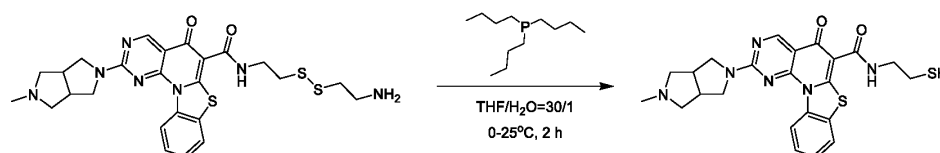
Synthetic Route 22

- 5 **Example 96: N-(2-((2-aminoethyl)disulfaneyl)ethyl)-2-(5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-oxo-5H-benzo[4',5']thiazolo[3',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamide**



- To a solution of ethyl 2-(5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-oxo-5H-benzo[4',5']thiazolo[3',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxylate (500 mg, 1.11 mmol, 1 eq) in DCM (5 mL) was added 2-aminoethanethiol (858.11 mg, 11.12 mmol, 10 eq), DBU (508.00 mg, 3.34 mmol, 502.97 μ L, 3 eq) and AlCl_3 (222.47 mg, 1.67 mmol, 91.18 μ L, 1.6 eq) at 0°C under N_2 . The mixture was stirred at 25°C for 2 h. The reaction was quenched by addition of 15 mL of 15% of NaOH (sat aq) and the aqueous phase was extracted with DCM (3 x 5 mL). The combined organic phases were washed with saturated brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100*30mm*5 μ m; mobile phase: $[\text{H}_2\text{O}(0.1\% \text{ TFA})\text{-ACN}]$; gradient: 5%-40% B over 8.0 min) to give the title compound (180 mg, 323.89 μ mol, 29.12% yield) as a yellow solid. **LCMS** (ESI⁺): m/z 556.2 (M+H)⁺, Rt: 0.337 min.

- Example 97: N-(2-Mercaptoethyl)-2-(5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-oxo-5H-benzo[4',5']thiazolo[3',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamide**



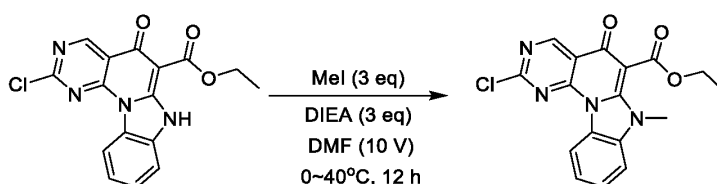
To a solution of N-(2-((2-aminoethyl)disulfaneyl)ethyl)-2-(5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-oxo-5H-benzo[4',5']thiazolo[3',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamide (80 mg, 143.95 μ mol, 1 eq) in THF (1 mL) and H_2O (0.03 mL) was added tributylphosphane (58.25 mg, 287.91 μ mol, 71.03 μ L, 2 eq) at 0°C.

The mixture was stirred at 25°C for 2 h. The mixture was concentrated *in vacuo* and the residue was purified by prep-HPLC (column: Phenomenex luna C18 100*40mm*5 um; mobile phase: [H₂O(0.1% TFA)-ACN]; gradient: 15%-40% B over 10.0 min) to give the title compound (8 mg, 16.20 μmol, 11.25% yield, 97.32% purity) as a white solid.

5 **LCMS** (ESI⁺): *m/z* 481.0 (M+H)⁺, *Rt*: 1.509 min. **¹H NMR** (400 MHz, DMSO-*d*₆+D₂O) δ = 10.26 (br s, 1H), 9.03 - 8.78 (m, 2H), 7.80 - 7.61 (m, 1H), 7.46 - 7.23 (m, 2H), 3.96 - 3.75 (m, 3H), 3.59 - 3.48 (m, 4H), 3.44 - 3.14 (m, 4H), 3.10 - 2.93 (m, 3H), 2.85 (br s, 3H).

10 **Synthetic Route 23**

Example 98: 7-methyl-2-(5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-oxo-N-(piperidin-4-yl)-5,7-dihydrobenzo[4',5']imidazo[1',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamide

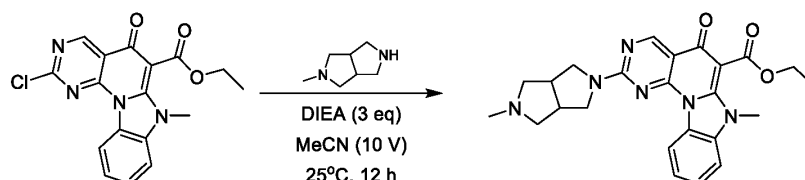


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Ethyl 2-chloro-7-methyl-5-oxo-5,7-dihydrobenzo[4',5']imidazo[1',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxylate:

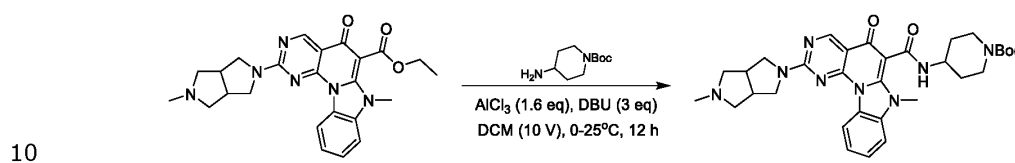
To a solution of ethyl 2-chloro-5-oxo-5,7-dihydrobenzo[4',5']imidazo[1',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxylate (2 g, 5.84 mmol, 1 eq) in DMF (20 mL) was added DIEA (2.26 g, 17.51 mmol, 3.05 mL, 3 eq) and MeI (2.48 g, 17.51 mmol, 1.09 mL, 3 eq) at 0°C under N₂. The reaction was heated to 40°C and stirred for 12 h. After cooling to 25°C, the reaction was quenched with NH₄Cl (aq, 20 mL) and the solid collected by filtration. The crude product was triturated with ACN (15 mL) for 10 min and collected by filtration to give the title compound (1 g, 2.80 mmol, 48.03% yield) as a yellow solid. **LCMS** (ESI⁺): *m/z* 357.0 (M+H)⁺, *Rt*: 1.459 min.

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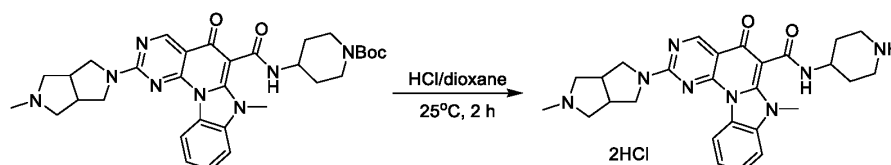
Ethyl 7-methyl-2-(5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-oxo-5,7-dihydrobenzo[4',5']imidazo[1',2':1,6]pyrido[2,3-d]pyrimidine-6-

carboxylate: To a solution of ethyl 2-chloro-7-methyl-5-oxo-5,7-dihydrobenzo[4',5']-imidazo[1',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxylate (1 g, 2.80 mmol, 1 eq) in ACN (10 mL) was added 5-methyl-2,3,3a,4,6,6a-hexahydro-1H-pyrrolo[3,4-c]pyrrole (424.48 mg, 3.36 mmol, 1.2 eq) and DIEA (1.09 g, 8.41 mmol, 1.46 mL, 3 eq) at 25°C. The reaction was stirred at 25°C for 12 h. The reaction was filtered and the filter cake was collected. The crude product was triturated with ACN (15 mL) for 10 min and the solid collected by filtration to give the title compound (1 g, 2.24 mmol, 79.90% yield) as a yellow solid. **LCMS** (ESI⁺): m/z 447.2 (M+H)⁺, Rt: 0.359 min.



tert-Butyl 4-(7-methyl-2-(5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-oxo-5,7-dihydrobenzo[4',5']imidazo[1',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamido)piperidine-1-carboxylate: To a solution of ethyl 7-methyl-2-(5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-oxo-5,7-dihydrobenzo[4',5']-imidazo[1',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxylate (300 mg, 671.89 μmol, 1 eq) in DCM (3 mL) was added tert-butyl 4-aminopiperidine-1-carboxylate (161.48 mg, 806.27 μmol, 1.2 eq), DBU (306.87 mg, 2.02 mmol, 303.83 μL, 3 eq) and AlCl₃ (143.34 mg, 1.08 mmol, 58.75 μL, 1.6 eq) at 0°C under N₂. The reaction was warmed to 25 °C and stirred for 12 h. The reaction was quenched with 15% NaOH (aq, 3 mL), extracted with DCM (3 x 3 mL), washed with saturated brine solution (2 x 3 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was triturated with ACN (3 mL) for 10 min and the solid collected by filtration to give the title compound (200 mg, 332.94 μmol, 49.55% yield) as a yellow solid. **LCMS** (ESI⁺): m/z 601.4(M+H)⁺, Rt: 0.410 min.

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7-methyl-2-(5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-oxo-N-(piperidin-4-yl)-5,7-dihydrobenzo[4',5']imidazo[1',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamide: A solution of tert-butyl 4-(7-methyl-2-(5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-oxo-5,7-dihydrobenzo[4',5']-imidazo[1',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamido)piperidine-1-carboxylate (190 mg, 316.29 μmol, 1 eq) in HCl/dioxane (2 mL) was stirred at 25°C for 2 h. The reaction

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was concentrated *in vacuo* and the crude product was purified by prep-HPLC (column: Phenomenex luna C18 100*40mm*5 µm; mobile phase: [H₂O(0.04% HCl)-ACN]; gradient: 1%-35% B over 8.0 min) to give the title compound (87.5 mg, 162.93 µmol, 51.51% yield, HCl) as a yellow solid. **LCMS** (ESI+): m/z 501.4 (M+H)⁺, Rt: 1.159 min. **¹H NMR** (400 MHz, DMSO+D₂O-d₆) δ = 9.07 - 8.88 (m, 1H), 8.64 - 8.36 (m, 1H), 7.52 - 7.28 (m, 3H), 4.12 - 4.00 (m, 1H), 3.94 - 3.79 (m, 5H), 3.55 (s, 1H), 3.48 (br s, 2H), 3.45 - 3.26 (m, 5H), 3.25 - 3.16 (m, 1H), 3.15 - 2.99 (m, 3H), 2.89 (s, 3H), 2.07 (br d, J = 1.3 Hz, 2H), 1.78 - 1.63 (m, 2H).

10 Examples – Antibody-Drug Conjugate Synthesis

General experimental

All reagents were purchased from Aldrich, MedChemExpress or ChemCruz and were used as received. All reactions were monitored by Liquid chromatography - mass spectrometry (LC-MS) on a Waters Xevo G2-S QToF. Flash chromatographic purifications were carried out using CombiFlash Rf (Teledyne Isco) with a Interchim column (PF-15C18HP-F0025), with H₂O-Acetonitrile gradient. ¹H NMR spectra were recorded at ambient temperature using an internal deuterium lock on Bruker DPX (400 MHz; ¹H DUL probe) and Bruker Avance III HD (400 MHz; Smart probe). Excess solvents were removed either by rotary evaporation on Buchi Rotavapor R-114 or Genevac EZ-2 Elite.

Bioconjugation

Small molecules, drugs and fluorophores were removed from antibodies/bioconjugates *via* Zeba™ Spin Desalting Columns and Plates, 7K and 40K MWCO, 0.5 mL–5 mL, unless otherwise stated. Equivalents of drugs added to antibodies/bioconjugates are reported as 1:1 antibody:drug (*i.e.* not accounting number of available cysteine residues for reaction). UV-vis spectra were recorded over a range of 220 – 650 nm on a Thermo Scientific™ NanoDrop™ One Microvolume UV-vis spectrophotometer and was used to determine concentration of bioconjugates, and FAR (Fluorophore-to-Antibody Ratio). Sample buffer was used as blank for baseline correction. Final ADC formulations were stored in PBS, pH 7.4, at 4°C. The estimated concentration of Cetuximab conjugates was determined spectrophotometrically at 280 nm by using a molar extinction coefficient, ε, of 210.000 M⁻¹cm⁻¹. Correction factor (CF) for small molecules was calculated. Determination of molecule over antibody ratio, *r*, follows the formula below:

$$r = \frac{A_{\lambda} / \epsilon_{\lambda}}{(A_{280} - \sum_{\lambda} CF_{\lambda} \times A_{\lambda}) / \epsilon_{280}}$$

SDS-PAGE gels

SDS-PAGE was carried out on pre-cast Bio-Rad 4-15 % GTX mini-Protean acrylamide gels run over 40 min at fixed current of 40 mA. Gels were either visualised under UV light in a SynGene[®] G:BOX (*e.g.* for visualisation of fluorescent species). Alternatively, this gels were washed in H₂O and stained in InstantBlue[®] Gel Stain for 1 h and visualised under white light. Samples (7 µL at ~5 µM construct) were mixed with 6x loading buffer (3 µL) and heated at 75 °C for 4 min.

10 Ellman's assay

The Ellman's assay involved combining 2 µL of a 1 mM solution of 5,5'-dithio-bis-(2-nitrobenzoic acid) (Ellman's reagent) in PBS with a bioconjugate sample at a known concentration, in PBS (8 µL). After incubating the solution at 21 °C for 2 minutes, the absorption was recorded at both 280 nm (to determine protein concentration) and 412 nm (for 2-nitro-5-thiobenzoic acid). A reference blank was created using a 1 mM solution of Ellman's reagent in PBS (1 µL), diluted in PBS (4 µL) to serve as a baseline correction. Each sample in PBS was analysed with and without Ellman's reagent, both under identical concentration conditions. The sulfhydryl per protein ratio (SPR) was calculated as follows with $\epsilon_{412} = 14150 \text{ M}^{-1} \text{ cm}^{-1}$:

$$20 \quad \text{SPR} = \frac{A_{412}/\epsilon_{412}}{A_{280}/\epsilon_{280}}$$

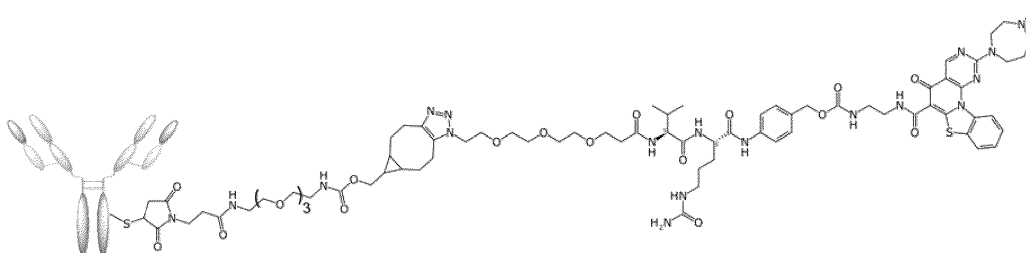
Protein LC-MS

Antibodies and their respective conjugates were prepared for analysis by removal of small molecules + buffer exchange into miliQ H₂O on ZebaSpin[™] columns, and were submitted with a concentration of 10-15 µM (1.0 mg×mL⁻¹) for analysis on the Xevo QTOF LC-MS system. 4-10 µL of each sample was injected and separation was achieved using mobile phase A (95% water, 5% MeCN, 0.1% formic acid) and B (5% water, 95% MeCN, 0.1% formic acid) using a gradient elution. Typical conditions were capillary voltage 1.6-2.2 kV, cone voltage 160– 190 V, Trap 40–50 V, Transfer 140 V with backing pressure 3–4 mbar and source temperature of 20 °C. Data acquisition and processing were performed using MassLynx 4.1. The raw data was converted to zero charge mass spectra using a maximum entropy deconvolution algorithm, over the full peak regions as identified *via* the LC trace. All full antibody samples were deglycosylated with PNGase F enzyme treatment prior to LC-MS analysis. A 2-step protocol was utilised for Cetuximab antibody and respective conjugates to efficiently remove Fab and Fc region N-glycans.

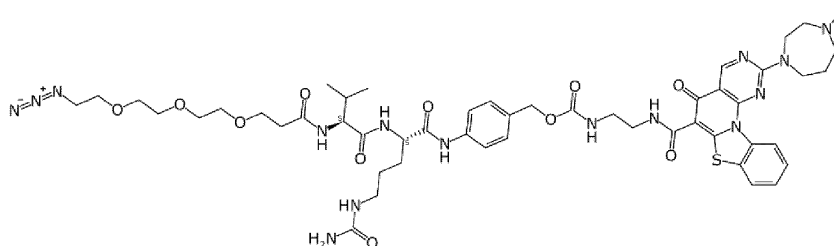
ADC Synthetic Route 1

Example ADC-1: Cetuximab-mal-PEG6-vc-N-(2-aminoethyl)-4-(4-methyl-1,4-diazepan-1-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]-

5 **heptadeca-2,4,6,9,12,14,16-heptaene-9-carboxamide**



Intermediate 1:



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To a solution of Azido-PEG3-Val-Cit-PAB-PNP (20 mg, 0.026 mmol) in DMF (5 mL), N-(2-aminoethyl)-4-(4-methyl-1,4-diazepan-1-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo-
[8.7.0.0²,7.0¹²,1⁷]heptadeca-2,4,6,9,12,14,16-heptaene-9-carboxamide (0.028 mmol
1 eq.) and DIPEA (0.028 mmol, 1.1 eq.) were added, under inert atmosphere (argon)
and the reaction was stirred at 21 °C for 16 h. After consumption of starting material,
solvents were removed in vacuo and crude product was purified via RP flash
chromatography to yield intermediate 1. **LCMS** (ESI+): m/z 1087 (M+H) +, Rt: 2.14
min.

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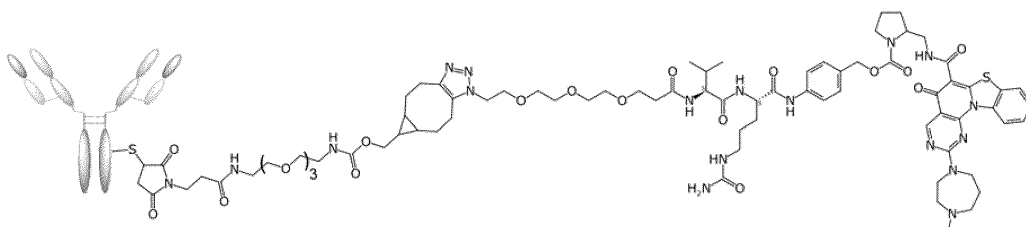
To a solution of native Cetuximab (CTX) (500 μ L, 20 μ M, 1 eq.) in PBS EDTA (0.5 mM EDTA, pH 7.4) was added TCEP (10 μ L, 20 mM in PBS pH = 7.4, 20 eq.) and the reaction mixture incubated at 21 $^{\circ}$ C for 16 h. The excess reagents were then removed by repeated diafiltration (5x) into fresh buffer using VivaSpin sample concentrators (GE Healthcare, 30,000 MWCO). Analysis by SDS-PAGE, LC-MS and UV-

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Vis revealed >95% conversion to reduced CTX which was used as is in the next step.
Observed mass (deglycosylated): LC = 23425 Da, HC = 46851 Da.

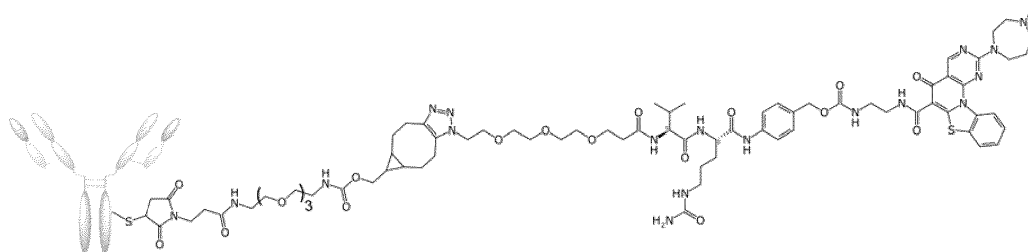
- To a solution of reduced CTX (3000 μ L, 22 μ M, 1 eq.) in PBS EDTA (0.5 mm EDTA, pH 7.4) was added BCN-PEG3-Mal (endo) (80 μ L, 20 mM in PBS pH = 7.4, 24 eq.) and the reaction mixture incubated at 21 °C for 16 h. The excess reagents were then removed by SEC Zebaspin™ column, and simultaneously buffer was exchanged to PBS, pH 7.4. Following this, analysis by SDS-PAGE, LC-MS and UV/Vis (Ellman's assay) revealed >90% conversion to CTX-mal-BCN. Calculated SPR~0.
- To a solution of CTX-mal-PEG3-BCN (500 μ L, 20 μ M, 1 eq.) in PBS (pH 7.4) was added Intermediate 1 (10 μ L, 20 mM in PBS pH = 7.4, 20 eq.) and the reaction mixture incubated at 21 °C for 16 h. The excess reagents were then removed by SEC Zebaspin™ column, and simultaneously buffer was exchanged to PBS, pH 7.4. Following this, analysis by SDS-PAGE, UV/Vis and LC-MS revealed >90% conversion to afford the title compound (**Example ADC-1**), DAR > 6. Expected mass: LC = 25032 Da (LC + 1d), HC = 51669 Da (HC + 3d). (calculated from reduced CTX LC/MS) Observed mass: LC = 25032 Da (LC + 1d) , HC = 50063 (LC + 2d) Da.

- Example ADC-2: Cetuximab-mal-PEG6-vc-4-(4-methyl-1,4-diazepan-1-yl)-8-oxo-N-[(pyrrolidin-2-yl)methyl]-11-thia-1,3,5-triazatetracyclo-[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12,14,16-heptaene-9-carboxamide**



- Example ADC-2 was synthesised according to the method outlined in ADC Synthetic Route 1 using 4-(4-methyl-1,4-diazepan-1-yl)-8-oxo-N-[(pyrrolidin-2-yl)methyl]-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12,14,16-heptaene-9-carboxamide. Analysis by SDS-PAGE, UV/Vis and LC/MS revealed >90% conversion, DAR > 6. Expected mass: LC = 25072 Da (LC + 1d), HC = 51789 Da (HC + 3d), observed mass for lightest peaks only: LC = 25072 Da (LC + 1d) , HC = 50341 (LC + ~2d) Da.

Example ADC-3: Trastuzumab-mal-PEG6-vc-N-(2-aminoethyl)-4-(4-methyl-1,4-diazepan-1-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]-heptadeca-2,4,6,9,12,14,16-heptaene-9-carboxamide

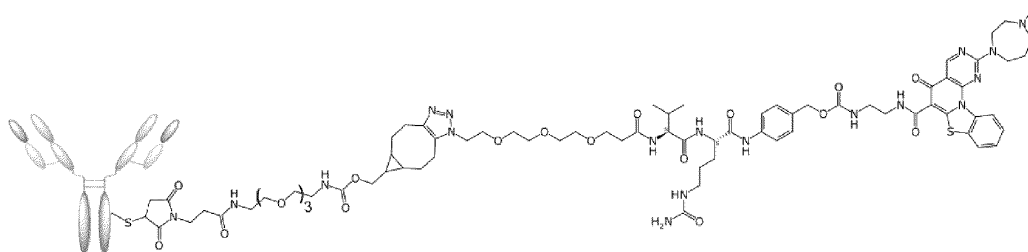


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To a solution of native Trastuzumab (TRAZ) (500 μ L, 20 μ M, 1 eq.) in PBS EDTA (0.5 mM EDTA, pH 7.4) was added TCEP (10 μ L, 20 mM in PBS pH = 7.4, 20 eq.) and the reaction mixture incubated at 21 $^{\circ}$ C for 16 h. The excess reagents were then removed by repeated diafiltration (5x) into fresh buffer using VivaSpin sample concentrators (GE Healthcare, 30,000 MWCO). After this, to reduced Traz (300 μ L, 22 μ M, 1 eq.) in PBS EDTA (0.5 mM EDTA, pH 7.4), was added BCN-PEG3-Mal (endo) (8 μ L, 20 mM in PBS pH = 7.4, 24 eq.) and the reaction mixture incubated at 21 $^{\circ}$ C for 16 h. The excess reagents were then removed by SEC ZebaspinTM column, and simultaneously buffer was exchanged to PBS, pH 7.4, to yield Traz-mal-BCN. Traz-mal-PEG3-BCN (50 μ L, 20 μ M, 1 eq.) was conjugated with Alexa FluorTM 488 azide (1 μ L, 20 mM in DMSO, 20 eq.) to generate Traz-mal-488, to confirm presence and reactivity of strained alkyne handles. Excess fluorophore was removed by SEC ZebaspinTM column, and simultaneously buffer was exchanged to PBS, pH 7.4. Fluorescent conjugate SDS-PAGE was visualised under UV light and FAR analysed *via* UV/Vis. Calculated FAR = 6.6.

Following this, to a solution of Traz-mal-PEG3-BCN (200 μ L, 20 μ M, 1 eq.) was added Intermediate 1 (12 μ L, 20 mM in PBS pH = 7.4, 20 eq.) and the reaction mixture incubated at 21 $^{\circ}$ C for 16 h. The excess reagents were then removed by SEC ZebaspinTM column, and simultaneously buffer was exchanged to PBS, pH 7.4. Following this, analysis by SDS-PAGE and UV/Vis revealed >95% conversion to give the title compound, DAR > 6. Expected mass: LC = 25044 Da (LC + 1d), HC = 53977 Da (HC + 3d). (calculated from SCT MW) Observed mass: LC = 25048 Da (LC + 1d) Da, HC = 53980 Da (HC + 2d).

Example ADC-4: Sacituzumab-mal-PEG6-vc-N-(2-aminoethyl)-4-(4-methyl-1,4-diazepan-1-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]-heptadeca-2,4,6,9,12,14,16-heptaene-9-carboxamide



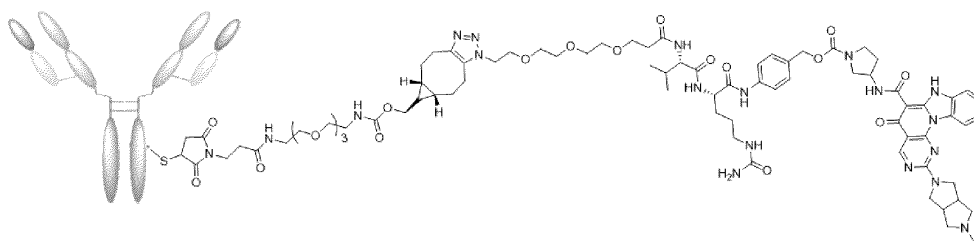
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- To a solution of native Sacituzumab (SCT) (500 μ L, 20 μ M, 1 eq.) in PBS EDTA (0.5 mm EDTA, pH 7.4) was added TCEP (10 μ L, 20 mM in PBS pH = 7.4, 20 eq.) and the reaction mixture incubated at 21 $^{\circ}$ C for 16 h. The excess reagents were then removed by repeated diafiltration (5x) into fresh buffer using VivaSpin sample
- 10 concentrators (GE Healthcare, 30,000 MWCO). After this, to reduced SCT (300 μ L, 22 μ M, 1 eq.) in PBS EDTA (0.5 mm EDTA, pH 7.4), was added BCN-PEG3-Mal (endo) (8 μ L, 20 mM in PBS pH = 7.4, 24 eq.) and the reaction mixture incubated at 21 $^{\circ}$ C for 16 h. The excess reagents were then removed by SEC ZebaspinTM column, and simultaneously buffer was exchanged to PBS, pH 7.4, to yield SCT-mal-PEG3-BCN.
- 15 SCT-mal-PEG3-BCN (50 μ L, 20 μ M, 1 eq.) was conjugated with Alexa FluorTM 488 azide (1 μ L, 20 mM in DMSO, 20 eq.) to confirm presence and reactivity of strained alkyne handles. Excess fluorophore was removed by SEC ZebaspinTM column, and simultaneously buffer was exchanged to PBS, pH 7.4. Fluorescent conjugate was visualised under UV light and FAR analysed *via* UV/Vis. Calculated FAR = 6.0.
- 20 Following this, to a solution of SCT-mal-PEG3-BCN (200 μ L, 20 μ M, 1 eq.) was added Intermediate 1 (12 μ L, 20 mM in PBS pH = 7.4, 20 eq.) and the reaction mixture incubated at 21 $^{\circ}$ C for 16 h. The excess reagents were then removed by SEC ZebaspinTM column, and simultaneously buffer was exchanged to PBS, pH 7.4. Following this, analysis by SDS-PAGE, UV/Vis revealed >95% conversion to afford the
- 25 title compound, DAR > 6. Expected mass: LC = 24946 Da (LC + 1d), HC = 50501 Da (HC + 3d). Observed mass: LC = 24944 (LC + 1d) Da, HC = 48894 Da (HC + 2d).

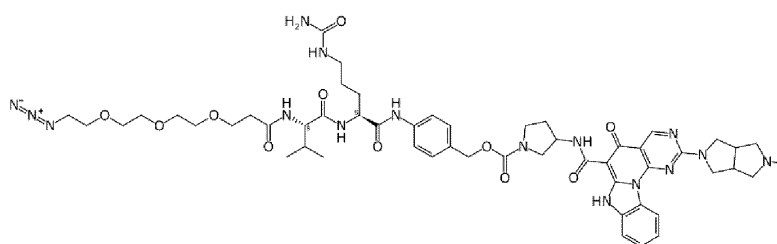
ADC Synthetic Route 2

- 30 **Example ADC-5: Cetuximab-mal-PEG6-vc-4-(2-methyl-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl)-8-oxo-N-pyrrolidin-3-yl-1,3,5,11-**

tetrazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12(17),13,15-heptaene-9-carboxamide



Intermediate 2:



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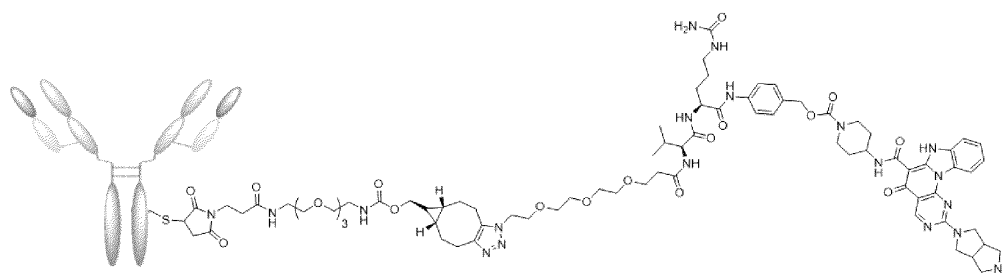
To a solution of Azido-PEG3-Val-Cit-PAB-PNP (20 mg, 0.026 mmol) in DMF (5 mL), 4-(2-methyl-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl)-8-oxo-N-pyrrolidin-3-yl-1,3,5,11-tetrazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12(17),13,15-heptaene-9-carboxamide (0.028 mmol, 1 eq.) and DIPEA (0.028 mmol, 1.1 eq.) were added under inert atmosphere (argon) and the reaction was stirred at 21°C for 16 h. After consumption of starting material, the solvents were removed *in vacuo* and the crude product was purified via RP flash chromatography (5-90% MeCN : H₂O) to yield **intermediate 2**. **LCMS** (ESI⁺): m/z 1107 Da (M+H)⁺, Rt: 2.37 min.

15 To a solution of native Cetuximab (CTX) (800 µL, 28 µM, 1 eq.) in PBS EDTA (0.5 mM EDTA, pH 7.4) was added TCEP (112 µL, 20 mM in PBS pH = 7.4, 100 eq.) and the reaction mixture incubated at 21 °C for 16 h. The excess reagents were then removed by repeated diafiltration (5x) into fresh buffer using VivaSpin sample concentrators (GE Healthcare, 30,000 MWCO). Following this, analysis by SDS-PAGE and UV-Vis revealed >95% conversion to reduced CTX.

25 To a solution of reduced CTX (700 µL, 28 µM, 1 eq.) in PBS EDTA (0.5 mM EDTA, pH 7.4) was added BCN-PEG3-Mal (endo) (98 µL, 20 mM in phosphate-buffered saline (PBS) pH = 7.4, 100 eq.) and the reaction mixture incubated at 21 °C for 16 h. The excess reagents were then removed by repeated diafiltration (5x) into fresh buffer using VivaSpin sample concentrators (GE Healthcare, 30,000 MWCO) and simultaneously buffer was exchanged to PBS, pH 7.4. Following this, analysis by SDS-PAGE and UV/Vis revealed >90% conversion to CTX-mal-PEG3-BCN.

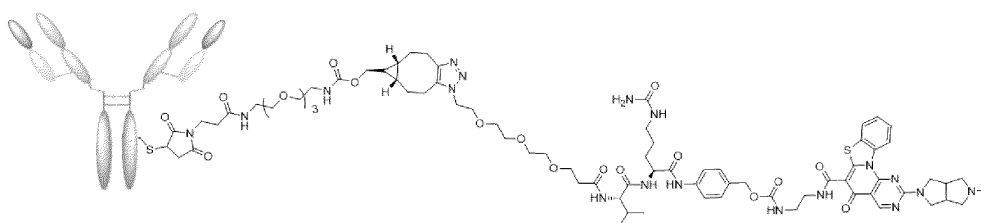
To a solution of CTX-mal-PEG3-BCN (200 μ L, 20 μ M, 1 eq.) in PBS (pH 7.4) was added **intermediate 2** (17 μ L, 10 mM in PBS pH = 7.4, 40 eq.) and the reaction mixture incubated at 21 °C for 16 h. The excess reagents were then removed by SEC
 5 Zebaspin™ column, and simultaneously buffer was exchanged to PBS, pH 7.4. Following this, analysis by SDS-PAGE and UV/Vis revealed >90% conversion to give the title compound (**Example ADC-5**) with estimated DAR=6.8.

Example ADC-6: Cetuximab-mal-PEG6-vc-4-(2-methyl-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl)-8-oxo-N-(4-piperidyl)-1,3,5,11-tetrazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12(17),13,15-heptaene-9-carboxamide
 10



Example ADC-6 was synthesised according to the method outlined in ADC Synthetic
 15 Route 2 using 4-(2-methyl-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl)-8-oxo-N-(4-piperidyl)-1,3,5,11-tetrazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12(17),13,15-heptaene-9-carboxamide. Analysis by SDS-PAGE and UV/Vis revealed >90% conversion to the title compound with an estimated DAR=6.8.

Example ADC-7: Cetuximab-mal-PEG6-vc-N-(2-aminoethyl)-4-(2-methyl-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12(17),13,15-heptaene-9-carboxamide
 20

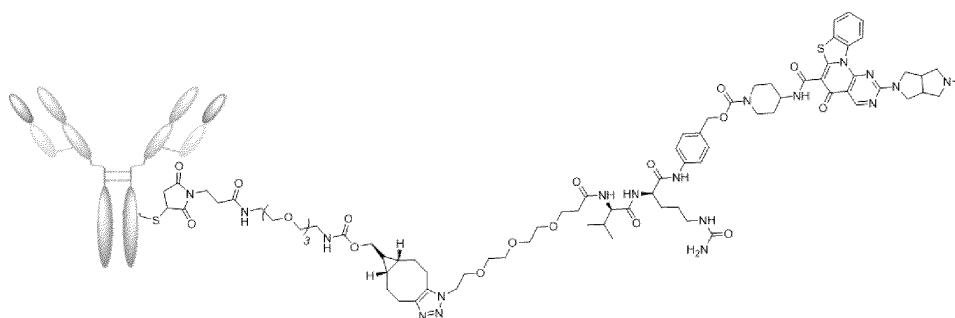


Example ADC-7 was synthesised according to the method outlined in ADC Synthetic
 25 Route 2 using N-(2-aminoethyl)-4-(2-methyl-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl)-8-oxo-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-

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2,4,6,9,12(17),13,15-heptaene-9-carboxamide. Analysis by SDS-PAGE and UV/Vis revealed >90% conversion to the title compound with an estimated DAR=6.8.

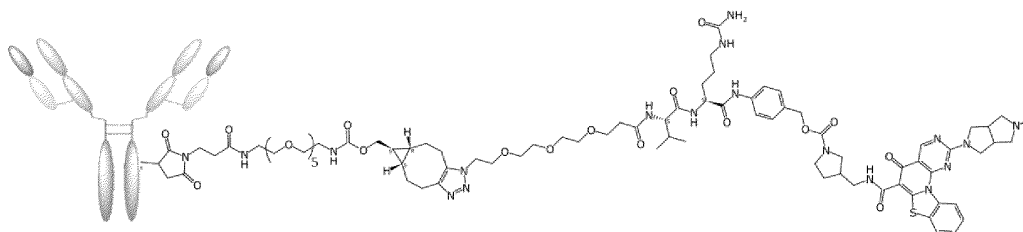
Example ADC-8: Cetuximab-mal-PEG6-vc-4-(2-methyl-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl)-8-oxo-N-(4-piperidyl)-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12(17),13,15-heptaene-9-carboxamide



Example ADC-8 was synthesised according to the method outlined in ADC Synthetic Route 2 using 4-(2-methyl-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl)-8-oxo-N-(4-piperidyl)-11-thia-1,3,5-triazatetracyclo[8.7.0.0^{2,7}.0^{12,17}]heptadeca-2,4,6,9,12(17),13,15-heptaene-9-carboxamide. Analysis by SDS-PAGE and UV/Vis revealed >90% conversion to the title compound with an estimated DAR=6.8.

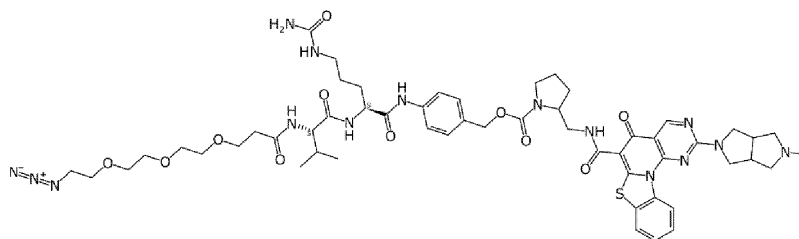
ADC Synthetic Route 3

Example ADC-9: Amivantamab-mal-PEG8-vc-4-2-(5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-oxo-N-(pyrrolidin-2-ylmethyl)-5H-benzo[4',5']-thiazolo[3',2':1,6]pyrido[2,3-d]-pyrimidine-6-carboxamide



Intermediate 3:

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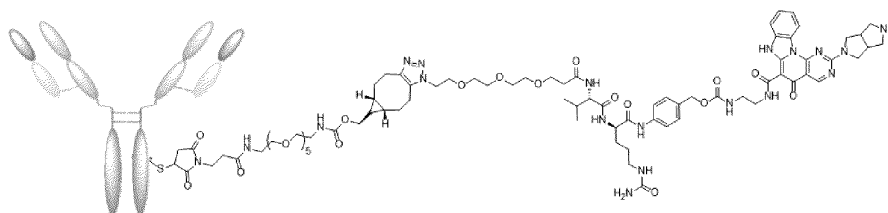


To a solution of Azido-PEG3-Val-Cit-PAB-PNP (20 mg, 0.026 mmol) in DMF (5 mL) was added 2-(5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-5-oxo-N-(pyrrolidin-2-ylmethyl)-5H-benzo[4',5']thiazolo[3',2':1,6]pyrido[2,3-d]-pyrimidine-6-carboxamide (0.028 mmol 1 eq.) and DIPEA (0.028 mmol, 1.1 eq.) under inert atmosphere (argon) and the reaction was stirred at 21 °C for 16 h. After consumption of starting material, solvents were removed *in vacuo* and the crude product was purified via reversed-phase flash chromatography to yield intermediate 3. **LCMS** (ESI+): *m/z* 1139.41 (M+H)⁺, Rt: 2.46 min.

To a solution of reduced Amivantamab (700 μL, 28 μM, 1 eq.) in PBS EDTA (0.5 mM EDTA, pH 7.4) was added BCN-PEG5-Mal (endo) (78 μL, 20 mM in PBS, pH = 7.4, 80 eq.) and the reaction mixture was incubated at 21 °C for 16 h. The excess reagents were then removed by repeated diafiltration (5x) into fresh buffer using VivaSpin sample concentrators (GE Healthcare, 30,000 MWCO) and, simultaneously, buffer was exchanged to PBS, pH 7.4. Following this, analysis by SDS-PAGE and UV/Vis revealed >90% conversion to Amivantamab-Mal-PEG5-BCN.

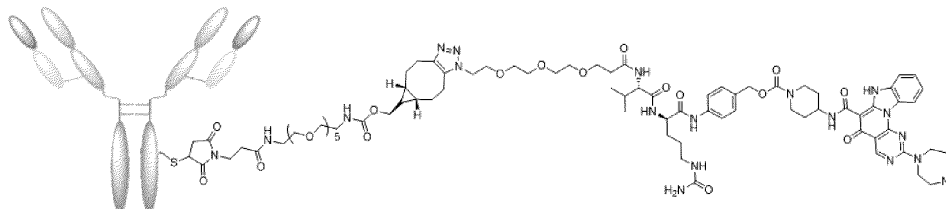
To a solution of Amivantamab-Mal-PEG5-BCN (200 μL, 20 μM, 1 eq.) in PBS (pH 7.4) was added **intermediate 3** (17 μL, 10 mM in PBS pH = 7.4, 40 eq.) and the reaction mixture incubated at 21 °C for 16 h. The excess reagents were then removed by SEC Zebaspin™ column, and simultaneously buffer was exchanged to PBS, pH 7.4. Following this, analysis by SDS-PAGE and UV/Vis revealed >90% conversion to the title compound. Estimated DAR=7.

Example ADC-10: Cetuximab-mal-PEG8-vc-N-(aminomethyl)-4-(2-methyl-1,3,3a,4,6,6a-hexahydropyrrolo-[3,4-c]pyrrol-5-yl)-8-oxo-1,3,5,11-tetrazatetracyclo[8.7.0.02,7.012,17]-heptadeca-2,4,6,9,12(17),13,15-heptaene-9-carboxamide



Example ADC-10 was synthesised according to the method outlined in ADC Synthetic
 5 Route 3 using N-(aminomethyl)-4-(2-methyl-1,3,3a,4,6,6a-hexahydropyrrolo-[3,4-
 c]pyrrol-5-yl)-8-oxo-1,3,5,11-tetrazatetracyclo[8.7.0.02,7.012,17]-heptadeca-
 2,4,6,9,12(17),13,15-heptaene-9-carboxamide. Analysis by SDS-PAGE and UV/Vis
 revealed >90% conversion to the title compound. Estimated DAR=7.

10 **Example ADC-11: Cetuximab-mal-PEG8-vc-2-(4-methyl-1,4-diazepan-1-yl)-5-
 oxo-N-(piperidin-4-yl)-5,7-dihydrobenzo[4',5']imidazo[1',2':1,6]pyrido[2,3-
 d]pyrimidine-6-carboxamide**



15

Example ADC-11 was synthesised according to the method outlined in ADC Synthetic
 Route 3 using 2-(4-methyl-1,4-diazepan-1-yl)-5-oxo-N-(piperidin-4-yl)-5,7-
 dihydrobenzo[4',5']imidazo[1',2':1,6]pyrido[2,3-d]pyrimidine-6-carboxamide. Analysis
 20 by SDS-PAGE and UV/Vis revealed >90% conversion to IFX-769, Estimated DAR=7.

Examples – Biological Activity

Cell culture studies

25 The antiproliferative effects of the present compounds and ADCs may be tested using
 a cell viability assay following protocols described below.

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Cell culture. Human colorectal adenocarcinoma HCT116 cells (CCL-247, ATCC), HCT116 BRCA2^{-/-} knockout cells (clone 42, Cancer Research UK) as well as colorectal adenocarcinoma DLD-1 cells (CCL-221, Horizon Discovery) and DLD-1 BRCA2^{-/-} knockout cells (HD 105-007, Horizon Discovery) were cultured in RPMI1640, GlutaMAX™ (Gibco) supplemented with 10% heat inactivated fetal bovine serum (ThermoFisher Scientific) at 37 °C in a humidified 5% CO₂ atmosphere.

Cell Titer Glo assays. Antiproliferative effects of compound and ADCs were tested using a CellTiter-Glo® 2.0 cell viability assay (Promega), which determines the number of viable cells in culture by quantifying ATP of metabolically active cells. Cells (500/well) were seeded on 384-well flat bottom plates in 25µL of culture medium containing compounds or ADCs at various concentrations. After incubation for 96 hours under normal growth condition, 25 µL of Cell Titer Glo reagent were added to each well, mixed and incubated for 10 min. End-point luminescence was then measured using a PHERAstar Plus (BMG Labtech) and normalized in relation to the average survival of samples treated only with DMSO (100% viability) and wells with no cells added (0% viability). Dose-dependent cell viability was fit using a four-parameter logistic curve in CDD Vault (Collaborative Drug). The 50% inhibitory concentrations (IC₅₀) were determined from three replicates.

FRET-melting assay

FRET DNA melting assays were performed as previously described (DECIAN et al., 2007) using 100 nM oligonucleotides and 1 µM compounds. Dual-labelled DNA oligonucleotides (Sigma-Aldrich) had the donor fluorophore 6-carboxyfluorescein (FAM) and acceptor fluorophore 6-carboxytetramethylrhodamine (TAMRA).

G4 hTelo: [FAM]GGGTTAGGGTTAGGGTTAGGG[TAMRA]

FRET probes were dissolved as a 100 µM stock in nuclease-free water and diluted to 200 nM (2× final concentration) in assay buffer (Li cacodylate 10 mM, pH 7.4, KCl 10 mM, and LiCl 90 mM) and then annealed by heating to 95 °C for 5 min, followed by gradually cooling to 20 °C. Compounds were prepared as 10 mM stock solutions in DMSO and diluted to 2 µM (2× concentration) in assay buffer (Li cacodylate 10 mM, pH 7.4, KCl 10 mM, and LiCl 90 mM).

Next, 15 µL of annealed oligonucleotides were mixed with 15 µL compound solution in 384-well plates (Bio-Rad, HSP3805), sealed and gently shaken for 10min. The FAM signal was recorded using a CFX Opus 384 Real-Time PCR System (Bio-Rad).

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Fluorescence readings were taken at intervals of 0.5 °C in the range 25–95 °C, with a constant temperature being maintained for 10 s prior to each reading. Melting temperatures were determined using CFX Maestro (Bio-Rad) as the first derivative of the relative fluorescence over time. Relative stabilisation (ΔT_m) was calculated compared to a control as mean of four replicates.

BALB/3T3 clone A31 Phototoxicity Assay

Day 0: Once the cells become >70% confluent in the flask (approx. 3 days), the media will be aspirated and the cell monolayers will be rinsed with 10 mL DPBS. After aspirating the rinse buffer, trypsin will be added to cover the cell monolayer, tilting once or twice. Cell media will be added and pipetted up and down several times to mix and dissociate cell clumps until cells will be separated. Cells will be counted, and 150000 cells/mL of suspension will be prepared. Assay plates will be seeded with BALB/3T3 clone A31 cells in DMEM media, 15000 cells/well in the 96-well plate, 100 µL/well. Incubate the cells overnight at 37 °C, 10% CO₂, relative humidity >90%.

Day 1:

- 1) After allowing for cell attachment overnight, wash the cell with 100 µL HBSS once and is replaced with HBSS.
- 2) Set the Pico8 digital dispenser to add the test and control articles to the cell assay plates. The top concentration of the working concentration of test article will be started from 100 µM, 3-fold dilution, 8 concentrations. The control article Chlorpromazine will be started from 100 µM, 3-fold dilution, 8 concentrations. The solubility of the compounds and cell status will be observed after the compounds were added into the cell media.
- 3) The plate 1 and 2 will be incubated in the RT for 1h. Then the plate 2 will be incubated in the dark for 1h. Meanwhile plate 1 will be exposed to about 2.4 J/cm² of UVA irradiation for 40min. After that the test solution will be removed from the plates; the wells will be washed with 150 µL HBSS once and replaced the fresh culture medium. Incubate the cells overnight at 37 °C, 10% CO₂, relative humidity >90%.

Day 2:

- 1) Remove the medium, then wash the cells with 100 µL of the pre-warmed HBSS and cultured with 100 µL 50µg/mL Neutral Red (NR) Medium and the cells will be returned to the incubator at 37 °C for an additional 3 hours.
- 2) Following the 3-hour uptake of the Neutral Red (NR), the medium will be discarded, the wells will be washed with HBSS, and 150 µL extraction buffer (1.0% Glacial Acetic Acid, 50% Ethanol, 49% dH₂O) will be added to each well.

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- 3) Shake the microplate gently on a microplate shaker for 2 min and incubated for 15 min in the dark until Neutral Red (NR) have been extracted from the cells and have formed a homogeneous solution. Measure the optical density of the Neutral Red (NR) extract at 540 nm in a spectrophotometer. Save data in an appropriate electronic file format for subsequent analysis.

For data analysis, raw data will be exported to Excel for calculation as the equation below.

1. Inhibition% = $(1 - (\text{Sample} / \text{DMSO control})) \times 100$
2. The IC₅₀ value will be determined from the concentration-response curve with Nonlinear Regression using Sigmoidal dose-response (variable slope) meanwhile transforming X values using $X = \text{Log}(X)$ by XL-fit software (Supplier: ID Business Solutions Ltd., Software version: XL fit 5.5.0.5).
3. A Photo-Irritation-Factor (PIF) will be calculated using the following formula:
$$\text{PIF} = \text{IC}_{50} (-\text{irradiation}) / \text{IC}_{50} (+\text{irradiation}).$$

Liver Microsome Metabolic Stability Assay (NADPH):

- Test compounds are incubated at 37°C with liver microsomes (pooled from multiple donors) at 1.0 µM in the presence of NADPH (~1.0 mM) at 0.5 mg/ml microsomal protein. Positive controls include testosterone (3A4 substrate), propafenone (2D6) and diclofenac (2C9). They will be incubated with microsomes in the presence of NADPH. Time samples (0, 5, 15, 30, 45 and 60 minutes) will be removed, immediately mixed with cold acetonitrile containing internal standard (IS). Test compounds incubated with microsomes without NADPH for 60 min are also included. Single point for each test condition (n=1). Samples are analyzed by LC/MS/MS; disappearance of test compound will be assessed based on peak area ratios of analyte/IS (no standard curve).

Liver Hepatocyte Assay (NADPH):

- Test compounds are incubated at 37°C with cryopreserved liver hepatocytes (pooled from multiple donors) at 0.5×10^6 cells per mL. The reaction samples will be removed at multiple time points (0, 15, 30, 60, and 90 minutes), and medium control samples without cells at 0 and 90 minutes will be incubated. All samples will be immediately mixed with cold organic solution containing internal standard (IS) to stop the reaction. Samples will be analyzed by LC/MS/MS, and the disappearance of test compound will be assessed based on peak area ratios of analyte/IS (no standard curve).

Protein Binding Assay:

The test compounds or positive control warfarin will be spiked into frozen plasma (commercial vendors, pooled from multiple individuals) at the final concentration of 2 μ M. An aliquot of 150 μ L of the compound-spiked plasma sample will be added to one side of the chamber in a 96-well equilibrium dialysis plate (HTD dialysis) and an equal volume of dialysis buffer (100 mM sodium phosphate and 150 mM NaCl, 7.4 ± 0.1) will be added to the other side of the chamber. An aliquot of plasma sample will be harvested before the incubation and used as T0 samples for recovery calculation. Triplicate incubations will be performed. The plate will then be incubated in a humidified incubator with 5% CO₂ at 37°C for 4 hours. After incubation, 50 μ L samples will be taken from the plasma side as well as the buffer side. The plasma sample will be mixed with an equal volume of blank buffer; buffer samples will be mixed with an equal volume of blank plasma. The matrix-matched samples will be quenched with stop solution containing internal standard (IS). Samples are analyzed by LC-MS/MS. Test compound concentrations in plasma and buffer samples will be determined based on peak area ratio of analyte to IS without a standard curve.

HCT116 - UVA phototoxicity assay

The cell line HCT116 (ATCC, cat no. CCL-247) is passaged in RPMI-1640, supplemented with 10% heat Inactivated FBS, in 5% CO₂ at 37°C, to a confluence of 70-90%. Media is aspirated, and the cell monolayer washed with 10 mL DPBS. After aspiration of DPBS, cells are detached using trypsin (5 minutes) before media is added to neutralize the trypsin. Cells are mixed in equal volumes of trypan blue (10 μ L:10 μ L) and viable cells counted. Cells (500/well) were seeded on 384-well flat bottom plates in 25 μ L of culture medium containing compounds. Plates were incubated for 30 minutes at 37°C, 5% CO₂. Following incubation one replicate plate is irradiated (lid off) with 125 mJ/cm² UVA light for 5 minutes using a Stratalinker crosslinker CL-1000, fitted with UVA (365 nm) bulbs. Following irradiation all plates are incubated for a further 96 hours at 37°C, 5% CO₂.

After incubation for 96 hours under normal growth condition, 25 μ L of Cell Titer Glo reagent were added to each well and agitated at 600 rpm for 2 minutes on a plate shaker, plates are further incubated for 10 min at room temperature. End-point luminescence was then measured using a PHERAstar Plus (BMG Labtech) and normalized in relation to the average survival of samples treated only with DMSO (100% viability) and wells with no cells added (0% viability). Dose-dependent cell viability was fit using a four-parameter logistic curve in CDD Vault (Collaborative Drug). The 50% inhibitory concentrations (IC₅₀) were determined from three

replicates. Ratios of IC50s between unirradiated and irradiated replicate plates were determined and used to determine phototoxicity of compounds.

Cell Titre Glow Data IC50 values:

Example	DLD-1	DLD-1 BRCA2^{-/-}	HCT116	HCT116 BRCA2^{-/-}
1	++	++++	+++	++++
2	++++	+++++	++++	+++++
3	++++	++++	+++	+++++
4	+++	++++	+++	+++++
5	+	+++	+	++++
6	+++	+++	+++	+++++
7	++++	+++++	+++	+++++
8	+++	+++	+++	+++++
9	+	+++	++	++++
10	+++	+++	+++	++++
11	+	+++	++	+++
12	+++	++++	+++	+++++
13	+	+++	++	++++
14	+	++	+	+++
15	+++	+++	+++	++++
16	+	++	+	+++
17	+	+++	++++	++++
19	+	+	+	++
20	+++	+++	+++	++++
21	+++	++++	+++	+++++
23	++	+++	+++	++++
24	+	+	+	++++
25	+	+++	+++	++++
26	++++	++++	++++	++++
26A	+++++	++++	+++++	+++++
26B	++++	++++	++++	+++++
27	+++	+++++	++++	++++
28	++++	+++++	++++	+++++
29	++++	+++++	++++	++++
30	++++	+++++	++++	+++++
31	++++	++++	++++	++++

Example	DLD-1	DLD-1 BRCA2 ^{-/-}	HCT116	HCT116 BRCA2 ^{-/-}
32	+++	+++++	++++	+++++
33	+++	+++	++++	++++
34	+++	++++	++++	++++
35	++++	+++++	+++++	+++++
36	++++	+++++	+++++	+++++
37	++++	++++	++++	++++
38	++	++	++	+++
39	++	++	++	++
40	++++	++++	++++	++++
41	+	+++	+	+++
42	+	++	+	+++
43	++	+++	+++	++++
44	+++	+++	+++	+++++
45	++	+++	++	+++++
46	+	++	++	++++
47	+	+++	++	++++
48	+++	++++	++++	+++++
49	+++	+++	+++	++++
50	++++	++++	++++	+++++
51	++	+++	+++	+++++
52	++++	++++	++++	+++++
53	++++	++++	++++	+++++
54	+++	++++	++++	+++++
55	+	+	+	+++
56	+++	++++	+++	++++
57	+++	++++	++++	+++++
58	++	+++	++	++++
59	++++	+++++	++++	+++++
60	++++	++++	+++++	+++++
61	+	+++	+	+++
62	++	++	++	+++
63	+	+	++	+++
64	++	+++	++	+++
65	+	+	+	+++
66	+	+	+	+++

Example	DLD-1	DLD-1 BRCA2 ^{-/-}	HCT116	HCT116 BRCA2 ^{-/-}
67	+	+	+	+++
68	+	+	+	+
69	+	++	+	+++
70	+++	++++	++++	+++++
71	+	+	+	++
72	+++	++++	++++	+++++
73	+++	+++++	+++	+++++
74	+++	+++++	++++	+++++
75	+	+	++	++
76	+++	+++	+++	++++
77	+	+++	++	++++
78	+++	++++	+++	+++++
79	+++	+++	++++	+++++
80	+++	++++	++++	+++++
81	+	+	+	+
82	+++	++++	++++	+++++
83	++++	+++++	++++	+++++
84	+++++	+++++	+++++	+++++
85	+++	++++	+++	+++++
86	+++	+++	+++	++++
87	++	+++	+++	++++
88	+++	++++	++++	+++++
89	++++	++++	+++++	+++++
90	+++++	+++++	+++++	+++++
91	+	++	+	+++
92	++++	+++++	+++++	+++++
93	+++++	+++++	+++++	+++++
94	++++	++++	++++	+++++
95	+++	++++	++++	+++++
97	++	++++	+++	++++
98	++	+++	++++	++++
ADC-1	-	-	+	+++
ADC-2	-	-	+	+++
ADC-3	-	-	++	+++
ADC-4	-	-	+	++++

Example	DLD-1	DLD-1 BRCA2 ^{-/-}	HCT116	HCT116 BRCA2 ^{-/-}
ADC-5	-	-	+	+++
ADC-6	-	-	+	++
ADC-7	-	-	+	+
ADC-8	-	-	++	+++
ADC-9	-	-	+++	++++
ADC-10	-	-	+++	+++
ADC-11	-	-	+++	++++

IC₅₀ < 20 nM = '+++++', 20-<100 nM = '++++', 100-<500 nM = '+++', 500-<1 μM = '++', 1-10 μM = '+'

FRET-melting (Thermal shift ΔT_m [°C]):

5

Example	ΔT _m	Example	ΔT _m	Example	ΔT _m
1	27	16	6	38	33
2	29	17	7	40	36
3	26	18	3	48	32
4	16	19	5	51	34
5	28	20	22	52	24
6	30	21	21	53	20
7	21	22	2	60	31
8	28	23	22	69	19
9	5	24	12	71	33
10	6	25	17	73	14
11	10	26	32	76	19
12	7	29	32	80	23
13	14	32	27	85	23
14	7	33	30	91	18
15	7	36	31	97	26

Select Human PPB data:

Example	% Bound	Example	% Bound
CX5461	+	10	+++++
1	+++	20	+++
2	++	21	+++
3	++++	<u>27</u>	+++

Example	% Bound	Example	% Bound
4	++	28	+++
9	++++	34	+++

>95% bound = '+', >75-95% bound = '++', >50-75% bound = '+++', >25-50% bound = '++++', ≤25% bound = '+++++'

Select Human microsomes data:

Example	mL/min/kg	Example	mL/min/kg
1	+	9	++
2	++	10	+
3	++	20	+
4	+	21	+

5 mL/min/kg < 10 = '++', 10-20 = '+'

Select Human hepatocyte data:

Example	CL _{int} (hep) (μL/min/10 ⁶ cells)
30	++
35	++

μL/min/10⁶ cells < 10 = '++++', 10-50 = '++', >50 '+'

10 **Select 3T3 Phototoxicity data:**

Example	PIF	Example	PIF
1	+++	15	+++
2	+++	16	+++
9	+++	20	+++
10	+++	22	+++
13	+++	24	+++
14	+++	CX5461	+

PIF < 5 = '++++', 5-<10 = '++', ≥10 = '++++'

HCT116 - UVA phototoxicity assay

Example	PIF	Example	PIF
2	+++	34	+++
9	+++	60	+++
20	+++	73	+++
26	+++	90	+++
32	+++	92	+++

Example	PIF	Example	PIF
33	+++	CX5461	+

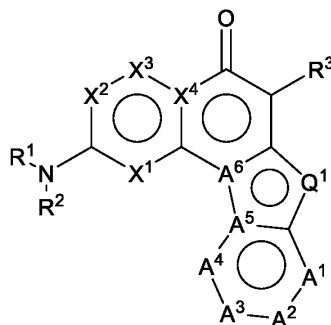
PIF < 5 = '++++', 5-<10 = '+++', ≥10 = '+'

It will be understood that the present invention has been described above by way of example only. The examples are not intended to limit the scope of the invention.

- 5 Various modifications and embodiments can be made without departing from the scope and spirit of the invention, which is defined by the following claims only.

Claims

1. A compound of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt and/or solvate and/or prodrug thereof;
wherein:

R¹ and R² are each independently selected from hydrogen or a C₁-C₁₂ saturated or unsaturated hydrocarbyl group, wherein the hydrocarbyl group may be straight-chained or branched, or be or include one or more cyclic groups, wherein the hydrocarbyl group may optionally be substituted with one or more halo and/or -NO₂ groups, wherein the hydrocarbyl group may optionally include one or more heteroatoms each independently selected from N, O and S in its carbon skeleton, and wherein any -S- moiety in the hydrocarbyl group may optionally be substituted with one or two groups each independently selected from oxo (=O) and =NH to form a -SO-, -SO₂-, -S(=NH)- or -SO(=NH)- moiety;

or R¹ and R² together with the nitrogen atom to which they are attached form a 3- to 12-membered cyclic group, wherein the cyclic group may optionally be substituted with one or more substituents each independently selected from a halo, oxo (=O), -OH, -SH, -NH₂, -SO₂H, -SO₃H, -SO₂NH₂, -NO₂, or a C₁-C₆ saturated or unsaturated hydrocarbyl group, wherein the hydrocarbyl group may be straight-chained or branched, or be or include a cyclic group, wherein the hydrocarbyl group may optionally be substituted with one or more halo and/or -NO₂ groups, wherein the hydrocarbyl group may optionally include one or more heteroatoms each independently selected from N, O and S in its carbon skeleton, and wherein any -S- moiety in the hydrocarbyl group may optionally be substituted with one or two groups each independently selected from oxo (=O) and =NH to form a -SO-, -SO₂-, -S(=NH)- or -SO(=NH)- moiety;

R³ is a C₁-C₁₂ monovalent group, wherein the atom of R³ that is directly attached to the remainder of the compound of Formula (I) is a carbon atom, and wherein the C₁-C₁₂ monovalent group comprises:

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- (i) a primary or a secondary amine, wherein the nitrogen atom of the primary or secondary amine is not directly attached to a sp^2 hybridised carbon atom; and/or
- (ii) a -OH group, wherein the oxygen atom of the -OH group is not directly attached to a sp^2 hybridised carbon atom; and/or
- (iii) a -SH group, wherein the sulphur atom of the -SH group is not directly attached to a sp^2 hybridised carbon atom;

X^1 is N, C-H, C-Hal or C- R^{X^1} ;

X^2 is N;

X^3 is N, C-H, C-Hal or C- R^{X^3} ; and

X^4 is N or C;

provided that no more than three of X^1 , X^2 , X^3 and X^4 are N;

R^{X^1} and R^{X^3} are each independently selected from -OH, -SH, -NH₂, -SO₂H, -SO₃H, -SO₂NH₂, -NO₂, or a C₁-C₄ saturated or unsaturated hydrocarbyl group, wherein the hydrocarbyl group may be straight-chained or branched, or be or include a cyclic group, wherein the hydrocarbyl group may optionally be substituted with one or more halo and/or -NO₂ groups, wherein the hydrocarbyl group may optionally include one or more heteroatoms each independently selected from N, O and S in its carbon skeleton, and wherein any -S- moiety in the hydrocarbyl group may optionally be substituted with one or two groups each independently selected from oxo (=O) and =NH to form a -SO-, -SO₂-, -S(=NH)- or -SO(=NH)- moiety;

Q^1 is O, S, N, N-H, N- R^{Q^1} , C-H, C-Hal, or C- R^{Q^2} ;

R^{Q^1} is selected from a C₁-C₄ saturated or unsaturated hydrocarbyl group, wherein the hydrocarbyl group may be straight-chained or branched, or be or include a cyclic group, wherein the hydrocarbyl group may optionally be substituted with one or more halo and/or -NO₂ groups, wherein the hydrocarbyl group may optionally include one or more heteroatoms each independently selected from N, O and S in its carbon skeleton, and wherein any -S- moiety in the hydrocarbyl group may optionally be substituted with one or two groups each independently selected from oxo (=O) and =NH to form a -SO-, -SO₂-, -S(=NH)- or -SO(=NH)- moiety, provided that the atom of R^{Q^1} that is directly attached to the nitrogen atom of N- R^{Q^1} is a carbon atom;

R^{Q^2} is selected from -OH, -SH, -NH₂, -SO₂H, -SO₃H, -SO₂NH₂, -NO₂, or a C₁-C₄ saturated or unsaturated hydrocarbyl group, wherein the hydrocarbyl group may be straight-chained or branched, or be or include a cyclic group, wherein the hydrocarbyl group may optionally be substituted with one or more halo and/or -NO₂ groups, wherein the hydrocarbyl group may optionally include one or more heteroatoms each independently selected from N, O and S in its carbon skeleton, and wherein any -S- moiety in the hydrocarbyl group may optionally be substituted with one or two groups

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each independently selected from oxo (=O) and =NH to form a -SO-, -SO₂-, -S(=NH)- or -SO(=NH)- moiety;

A¹ is N, C-H, C-Hal or C-R^{A1};

A² is N, C-H, C-Hal or C-R^{A2};

A³ is N, C-H, C-Hal or C-R^{A3};

A⁴ is N, C-H, C-Hal or C-R^{A4}; and

A⁵ is N or C;

provided that no more than three of A¹, A², A³, A⁴ and A⁵ are N;

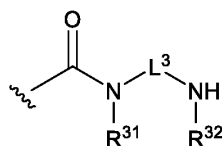
R^{A1}, R^{A2}, R^{A3} and R^{A4} are each independently selected from -OH, -SH, -NH₂, -SO₂H, -SO₃H, -SO₂NH₂, -NO₂, or a C₁-C₄ saturated or unsaturated hydrocarbyl group, wherein the hydrocarbyl group may be straight-chained or branched, or be or include a cyclic group, wherein the hydrocarbyl group may optionally be substituted with one or more halo and/or -NO₂ groups, wherein the hydrocarbyl group may optionally include one or more heteroatoms each independently selected from N, O and S in its carbon skeleton, and wherein any -S- moiety in the hydrocarbyl group may optionally be substituted with one or two groups each independently selected from oxo (=O) and =NH to form a -SO-, -SO₂-, -S(=NH)- or -SO(=NH)- moiety;

A⁶ is N or C; and

each Hal is independently selected from a fluoro, chloro, bromo or iodo group.

2. A compound as claimed in claim 1, or a pharmaceutically acceptable salt and/or solvate and/or prodrug thereof, wherein R³ is a C₁-C₁₂ monovalent group, wherein the atom of R³ that is directly attached to the remainder of the compound of Formula (I) is a sp² hybridised carbon atom, and wherein the C₁-C₁₂ monovalent group comprises a primary or a secondary amine, wherein the nitrogen atom of the primary or secondary amine is not directly attached to a sp² hybridised carbon atom.

3. A compound as claimed in claim 2, or a pharmaceutically acceptable salt and/or solvate and/or prodrug thereof, wherein R³ has the formula:



wherein:

R³¹ is hydrogen or a C₁-C₆ saturated hydrocarbyl group, wherein the saturated hydrocarbyl group may be straight-chained or branched, or be or include a cyclic group, wherein the saturated hydrocarbyl group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group, and wherein the saturated

hydrocarbyl group may optionally include one or two heteroatoms each independently selected from N and O in its carbon skeleton, provided that the atom of the hydrocarbyl group of R^{31} that is directly attached to the nitrogen atom of $N-R^{31}$ is a carbon atom;

R^{32} is hydrogen or a C_1 - C_6 saturated hydrocarbyl group, wherein the saturated hydrocarbyl group may be straight-chained or branched, or be or include a cyclic group, wherein the saturated hydrocarbyl group may optionally be substituted with one or more fluoro groups and/or a single oxo ($=O$) group, and wherein the saturated hydrocarbyl group may optionally include one or two heteroatoms each independently selected from N and O in its carbon skeleton, provided that the atom of the hydrocarbyl group of R^{32} that is directly attached to the nitrogen atom of $NH-R^{32}$ is a carbon atom that is not substituted with an oxo ($=O$) group;

or R^{31} and R^{32} together form a C_2 - C_6 straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or a single oxo ($=O$) group and/or one, two, three or four groups R^{33} , provided that the carbon atom of the alkylene group that is directly attached to the nitrogen atom of $NH-R^{32}$ is not substituted with an oxo ($=O$) group;

each R^{33} is independently selected from a methyl or a fluoromethyl group;

L^3 is a bond or a C_2 - C_5 straight-chained alkylene group or a $-CH_2CH_2-O-CH_2CH_2-$ or $-CH_2CH_2-NH-CH_2CH_2-$ group, wherein the alkylene, the $-CH_2CH_2-O-CH_2CH_2-$ or the $-CH_2CH_2-NH-CH_2CH_2-$ group may optionally be substituted with one or more fluoro groups and/or a single oxo ($=O$) group and/or one, two, three or four groups R^{L3} , provided that the carbon atom of the alkylene or the $-CH_2CH_2-O-CH_2CH_2-$ or the $-CH_2CH_2-NH-CH_2CH_2-$ group that is directly attached to the nitrogen atom of $NH-R^{32}$ is not substituted with an oxo ($=O$) group;

each R^{L3} is independently selected from a methyl or a fluoromethyl group, or any two R^{L3} may together with the atom or atoms to which they are attached form a 3- to 7-membered cycloalkylene group or a 4- to 7-membered saturated heterocyclic group, wherein the cycloalkylene group or the saturated heterocyclic group may optionally be fluoro substituted;

or any R^{L3} and R^{31} , or any R^{L3} and R^{32} , or any R^{L3} and any R^{33} , together form a C_1 - C_4 straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or a single oxo ($=O$) group and/or one, two, three or four groups R^{34} , provided that where any R^{L3} and R^{32} together form a C_1 - C_4 straight-chained alkylene group, the carbon atom of the alkylene group that is directly attached to the nitrogen atom of $NH-R^{32}$ is not substituted with an oxo ($=O$) group;

or any R^{L3} and any R^{33} together form a bond; and

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each R³⁴ is independently selected from a methyl or a fluoromethyl group;
provided that the group R³ contains no more than 12 carbon atoms.

4. A compound as claimed in claim 3, or a pharmaceutically acceptable salt and/or solvate and/or prodrug thereof, wherein:

R³¹ is hydrogen or a C₁-C₄ alkyl group, wherein the alkyl group may be straight-chained or branched, or be or include a cyclic group, wherein the alkyl group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group;

R³² is hydrogen or a C₁-C₄ alkyl group, wherein the alkyl group may be straight-chained or branched, or be or include a cyclic group, and wherein the alkyl group may optionally be substituted with one or more fluoro groups;

or R³¹ and R³² together form a C₂-C₅ straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R³³;

each R³³ is independently selected from a methyl or a fluoromethyl group;

L³ is a C₂-C₅ straight-chained alkylene group or a -CH₂CH₂-O-CH₂CH₂- or -CH₂CH₂-NH-CH₂CH₂- group, wherein the alkylene, the -CH₂CH₂-O-CH₂CH₂- or the -CH₂CH₂-NH-CH₂CH₂- group may optionally be substituted with one or more fluoro groups and/or one or two groups R^{L3};

each R^{L3} is independently selected from a methyl or a fluoromethyl group, or any two R^{L3} together with the atom or atoms to which they are attached form a 5- or 6-membered cycloalkylene group, or any R^{L3} and R³¹, or any R^{L3} and R³², together form a C₂-C₄ straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R³⁴, or any R^{L3} and any R³³ together form a bond or a C₁-C₂ straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or one or two groups R³⁴; and

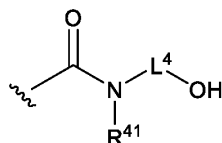
each R³⁴ is independently selected from a methyl or a fluoromethyl group;
provided that the group R³ contains no more than 12 carbon atoms.

5. A compound as claimed in claim 3 or claim 4, or a pharmaceutically acceptable salt and/or solvate and/or prodrug thereof, wherein L³ is not a bond and R³¹ is not hydrogen.

6. A compound as claimed in claim 1, or a pharmaceutically acceptable salt and/or solvate and/or prodrug thereof, wherein R³ is a C₁-C₁₂ monovalent group, wherein the atom of R³ that is directly attached to the remainder of the compound of Formula (I) is

a sp^2 hybridised carbon atom, and wherein the C_1 - C_{12} monovalent group comprises a -OH group, wherein the oxygen atom of the -OH group is not directly attached to a sp^2 hybridised carbon atom.

7. A compound as claimed in claim 6, or a pharmaceutically acceptable salt and/or solvate and/or prodrug thereof, wherein R^3 has the formula:



wherein:

R^{41} is hydrogen or a C_1 - C_6 saturated hydrocarbyl group, wherein the saturated hydrocarbyl group may be straight-chained or branched, or be or include a cyclic group, wherein the saturated hydrocarbyl group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group, and wherein the saturated hydrocarbyl group may optionally include one or two heteroatoms each independently selected from N and O in its carbon skeleton, provided that the atom of the hydrocarbyl group of R^{41} that is directly attached to the nitrogen atom of N - R^{41} is a carbon atom;

L^4 is a C_2 - C_5 straight-chained alkylene group or a $-\text{CH}_2\text{CH}_2\text{-O-CH}_2\text{CH}_2\text{-}$ or $-\text{CH}_2\text{CH}_2\text{-NH-CH}_2\text{CH}_2\text{-}$ group, wherein the alkylene, the $-\text{CH}_2\text{CH}_2\text{-O-CH}_2\text{CH}_2\text{-}$ or the $-\text{CH}_2\text{CH}_2\text{-NH-CH}_2\text{CH}_2\text{-}$ group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group and/or one, two, three or four groups R^{L4} , provided that the carbon atom of the alkylene, the $-\text{CH}_2\text{CH}_2\text{-O-CH}_2\text{CH}_2\text{-}$ or the $-\text{CH}_2\text{CH}_2\text{-NH-CH}_2\text{CH}_2\text{-}$ group that is directly attached to the oxygen atom of the -OH group is not substituted with an oxo (=O) group;

each R^{L4} is independently selected from a methyl or a fluoromethyl group, or any two R^{L4} may together with the atom or atoms to which they are attached form a 3- to 7-membered cycloalkylene group or a 4- to 7-membered saturated heterocyclic group, wherein the cycloalkylene group or the saturated heterocyclic group may optionally be fluoro substituted;

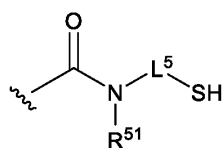
or any R^{L4} and R^{41} may together form a C_1 - C_4 straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group and/or one, two, three or four groups R^{44} ; and each R^{44} is independently selected from a methyl or a fluoromethyl group; provided that the group R^3 contains no more than 12 carbon atoms.

8. A compound as claimed in claim 1, or a pharmaceutically acceptable salt and/or solvate and/or prodrug thereof, wherein R^3 is a C_1 - C_{12} monovalent group, wherein the

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atom of R^3 that is directly attached to the remainder of the compound of Formula (I) is a sp^2 hybridised carbon atom, and wherein the C_1 - C_{12} monovalent group comprises a -SH group, wherein the sulphur atom of the -SH group is not directly attached to a sp^2 hybridised carbon atom.

9. A compound as claimed in claim 8, or a pharmaceutically acceptable salt and/or solvate and/or prodrug thereof, wherein R^3 has the formula:



wherein:

R^{51} is hydrogen or a C_1 - C_6 saturated hydrocarbyl group, wherein the saturated hydrocarbyl group may be straight-chained or branched, or be or include a cyclic group, wherein the saturated hydrocarbyl group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group, and wherein the saturated hydrocarbyl group may optionally include one or two heteroatoms each independently selected from N and O in its carbon skeleton, provided that the atom of the hydrocarbyl group of R^{51} that is directly attached to the nitrogen atom of N - R^{51} is a carbon atom;

L^5 is a C_2 - C_5 straight-chained alkylene group or a $-\text{CH}_2\text{CH}_2\text{-O-CH}_2\text{CH}_2\text{-}$ or $-\text{CH}_2\text{CH}_2\text{-NH-CH}_2\text{CH}_2\text{-}$ group, wherein the alkylene, the $-\text{CH}_2\text{CH}_2\text{-O-CH}_2\text{CH}_2\text{-}$ or the $-\text{CH}_2\text{CH}_2\text{-NH-CH}_2\text{CH}_2\text{-}$ group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group and/or one, two, three or four groups R^{L5} , provided that the carbon atom of the alkylene or the $-\text{CH}_2\text{CH}_2\text{-O-CH}_2\text{CH}_2\text{-}$ or the $-\text{CH}_2\text{CH}_2\text{-NH-CH}_2\text{CH}_2\text{-}$ group that is directly attached to the sulphur atom of the -SH group is not substituted with an oxo (=O) group;

each R^{L5} is independently selected from a methyl or a fluoromethyl group, or any two R^{L5} may together with the atom or atoms to which they are attached form a 3- to 7-membered cycloalkylene group or a 4- to 7-membered saturated heterocyclic group, wherein the cycloalkylene group or the saturated heterocyclic group may optionally be fluoro substituted;

or any R^{L5} and R^{51} may together form a C_1 - C_4 straight-chained alkylene group, wherein the alkylene group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group and/or one, two, three or four groups R^{54} ; and

each R^{54} is independently selected from a methyl or a fluoromethyl group;

provided that the group R^3 contains no more than 12 carbon atoms.

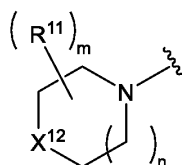
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10. A compound as claimed in any one of claims 1 to 9, or a pharmaceutically acceptable salt and/or solvate and/or prodrug thereof, wherein R^1 is a C_1 - C_8 saturated hydrocarbyl group, wherein the hydrocarbyl group may be straight-chained or branched, or be or include a single cyclic group, wherein the hydrocarbyl group may optionally be substituted with one or more fluoro groups and/or a single oxo ($=O$) group, wherein the hydrocarbyl group optionally includes one or two heteroatoms each independently selected from N and O in its carbon skeleton, and R^2 is selected from hydrogen or a C_1 - C_3 alkyl or C_1 - C_3 fluoroalkyl group.

11. A compound as claimed in any one of claims 1 to 9, or a pharmaceutically acceptable salt and/or solvate and/or prodrug thereof, wherein R^1 has the formula $-L^1-R^{10}$, wherein L^1 is a C_1 - C_2 alkylene or C_1 - C_2 fluoroalkylene group, and R^{10} is a 5- or 6-membered heteroaryl group, such as an imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl or isothiazolyl group, and R^2 is selected from hydrogen or a C_1 - C_3 alkyl or C_1 - C_3 fluoroalkyl group.

12. A compound as claimed in any one of claims 1 to 9, or a pharmaceutically acceptable salt and/or solvate and/or prodrug thereof, wherein R^1 and R^2 together with the nitrogen atom to which they are attached form a 4- to 7-membered monocyclic group or a 6- to 12-membered bicyclic group, wherein the monocyclic or the bicyclic group may optionally be substituted with one or more substituents each independently selected from a halo, oxo ($=O$), $-OH$, $-NH_2$ or a C_1 - C_6 saturated or unsaturated hydrocarbyl group, wherein the hydrocarbyl group may be straight-chained or branched, or be or include a cyclic group, wherein the hydrocarbyl group may optionally be substituted with one or more halo groups, and wherein the hydrocarbyl group may optionally include one or two heteroatoms each independently selected from N and O in its carbon skeleton.

13. A compound as claimed in claim 12, or a pharmaceutically acceptable salt and/or solvate and/or prodrug thereof, wherein $-NR^1R^2$ has the formula:



wherein:

n is 1 or 2;

m is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10;

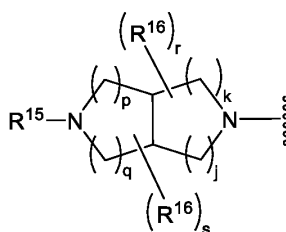
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each R^{11} is independently selected from a fluoro, methyl or fluoromethyl group, provided that no more than four R^{11} are selected from a methyl or fluoromethyl group;

X^{12} is O or NR^{12} ; and

R^{12} is hydrogen or a C_1 - C_4 saturated hydrocarbyl group, wherein the saturated hydrocarbyl group may be straight-chained or branched, or be or include a cyclic group, wherein the saturated hydrocarbyl group may optionally be substituted with one or more fluoro groups and/or a single oxo ($=O$) group, and wherein the saturated hydrocarbyl group may optionally include a single heteroatom selected from N and O in its carbon skeleton.

14. A compound as claimed in claim 12, or a pharmaceutically acceptable salt and/or solvate and/or prodrug thereof, wherein $-NR^1R^2$ has the formula:



wherein:

j is 0, 1, 2 or 3;

k is 0, 1, 2 or 3;

p is 0, 1, 2 or 3; and

q is 0, 1, 2 or 3;

provided that:

$j + k = 2$ or 3;

$p + q = 2$ or 3;

when $j = 0$, q is 1, 2 or 3;

when $k = 0$, p is 1, 2 or 3;

when $p = 0$, k is 1, 2 or 3; and

when $q = 0$, j is 1, 2 or 3;

and wherein:

r is 0, 1 or 2;

s is 0, 1 or 2;

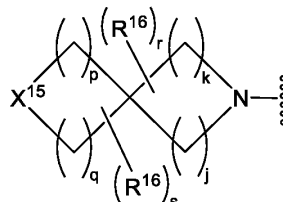
R^{15} is hydrogen or a C_1 - C_4 alkyl, C_3 - C_4 cycloalkyl, C_1 - C_4 fluoroalkyl, C_3 - C_4 fluorocycloalkyl, cyclopropylmethyl, fluorocyclopropylmethyl or $-CO-R^{150}$ group;

R^{150} is selected from a C_1 - C_3 alkyl, C_1 - C_3 fluoroalkyl, cyclopropyl or fluorocyclopropyl group; and

each R^{16} is independently selected from a methyl or fluoromethyl group.

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15. A compound as claimed in claim 12, or a pharmaceutically acceptable salt and/or solvate and/or prodrug thereof, wherein $-NR^1R^2$ has the formula:



wherein:

X^{15} is O or NR^{15} ;

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

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

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

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

provided that:

$j + k = 3$ or 4;

$p + q = 3$ or 4;

when $j = 0$, q is 1, 2, 3 or 4 and p is 1, 2, 3 or 4;

when $k = 0$, q is 1, 2, 3 or 4 and p is 1, 2, 3 or 4;

when $p = 0$, k is 1, 2, 3 or 4 and j is 1, 2, 3 or 4; and

when $q = 0$, k is 1, 2, 3 or 4 and j is 1, 2, 3 or 4;

and wherein:

r is 0, 1 or 2;

s is 0, 1 or 2;

R^{15} is hydrogen or a C_1 - C_4 alkyl, C_3 - C_4 cycloalkyl, C_1 - C_4 fluoroalkyl, C_3 - C_4 fluorocycloalkyl, cyclopropylmethyl, fluorocyclopropylmethyl or $-CO-R^{150}$ group;

R^{150} is selected from a C_1 - C_3 alkyl, C_1 - C_3 fluoroalkyl, cyclopropyl or fluorocyclopropyl group; and

each R^{16} is independently selected from a methyl or fluoromethyl group.

16. A compound as claimed in any one of claims 1 to 15, or a pharmaceutically acceptable salt and/or solvate and/or prodrug thereof, wherein:

X^1 is N, C-H, C-Hal or $C-R^{X1}$;

X^2 is N;

X^3 is C-H, C-Hal or $C-R^{X1}$;

X^4 is C; and

R^{X1} and R^{X3} are each independently selected from a C_1 - C_4 saturated hydrocarbyl group, wherein the hydrocarbyl group may be straight-chained or branched, or be or

include a cyclic group, wherein the hydrocarbonyl group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group, and wherein the hydrocarbonyl group may optionally include a single heteroatom selected from N and O in its carbon skeleton.

17. A compound as claimed in any one of claims 1 to 16, or a pharmaceutically acceptable salt and/or solvate and/or prodrug thereof, wherein Q^1 is O, S, N-H or N- R^{Q1} , wherein R^{Q1} is selected from a C_1 - C_4 alkyl, C_3 - C_4 cycloalkyl, C_1 - C_4 fluoroalkyl, C_3 - C_4 fluorocycloalkyl, cyclopropylmethyl, fluorocyclopropylmethyl or -CO- R^{Q3} group, wherein R^{Q3} is selected from a C_1 - C_3 alkyl, C_1 - C_3 fluoroalkyl, cyclopropyl or fluorocyclopropyl group.

18. A compound as claimed in any one of claims 1 to 17, or a pharmaceutically acceptable salt and/or solvate and/or prodrug thereof, wherein:

A^1 is N, C-H, C-Hal or C- R^{A1} ;

A^2 is N, C-H, C-Hal or C- R^{A2} ;

A^3 is N, C-H, C-Hal or C- R^{A3} ;

A^4 is N, C-H, C-Hal or C- R^{A4} ;

A^5 is C; and

R^{A1} , R^{A2} , R^{A3} and R^{A4} are each independently selected from a C_1 - C_4 saturated hydrocarbonyl group, wherein the hydrocarbonyl group may be straight-chained or branched, or be or include a cyclic group, wherein the hydrocarbonyl group may optionally be substituted with one or more fluoro groups and/or a single oxo (=O) group, and wherein the hydrocarbonyl group may optionally include a single heteroatom selected from N and O in its carbon skeleton;

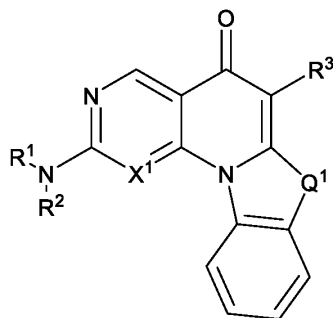
provided that no more than one of A^1 , A^2 , A^3 and A^4 is N; and

provided that no more than two of A^1 , A^2 , A^3 and A^4 are C- R^{A1} , C- R^{A2} , C- R^{A3} or C- R^{A4} .

19. A compound as claimed in any one of claims 1 to 18, or a pharmaceutically acceptable salt and/or solvate and/or prodrug thereof, wherein A^6 is N.

20. A compound as claimed in any one of claims 1 to 19, or a pharmaceutically acceptable salt and/or solvate and/or prodrug thereof, wherein each Hal is independently selected from a fluoro, chloro or bromo group.

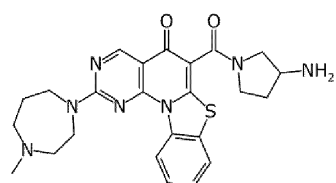
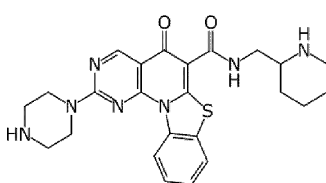
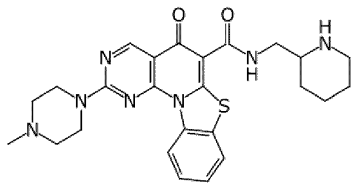
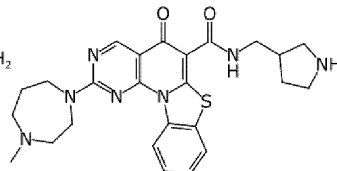
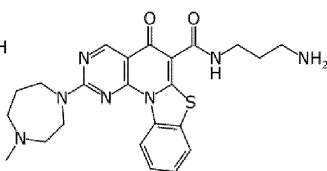
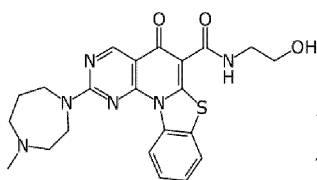
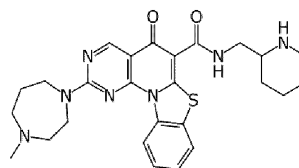
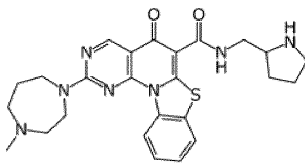
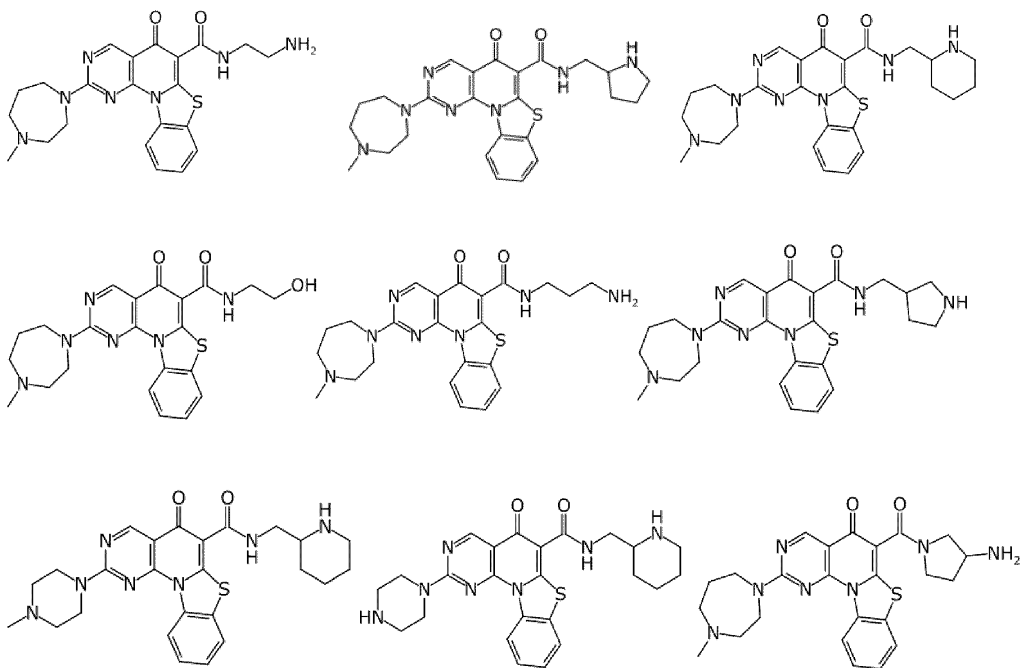
21. A compound as claimed in any one of claims 1 to 19, or a pharmaceutically acceptable salt and/or solvate and/or prodrug thereof, wherein the compound is a compound of Formula (V):

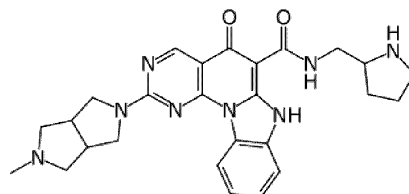
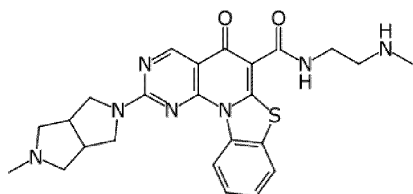
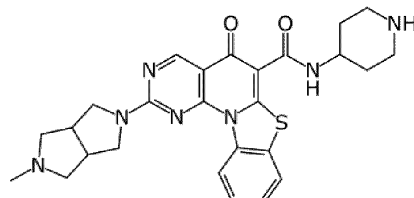
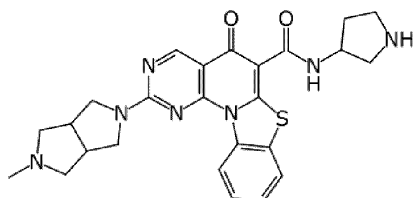
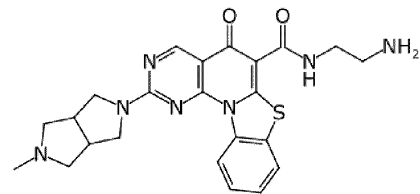
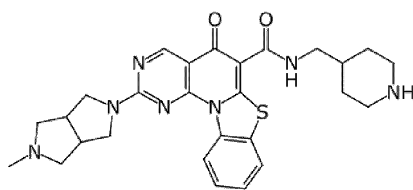
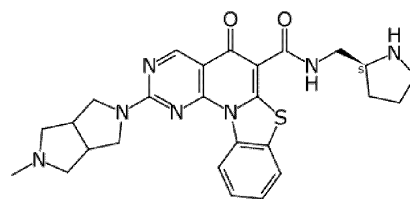
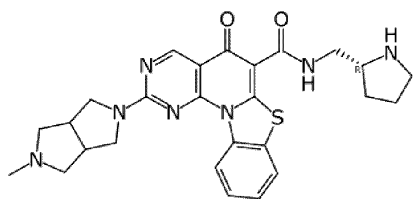
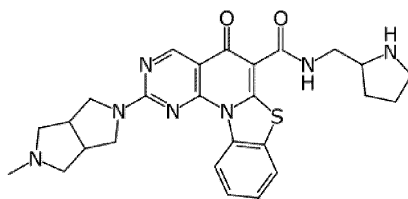
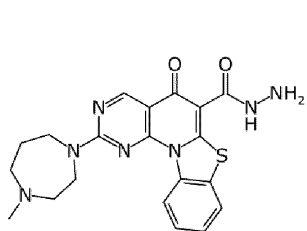


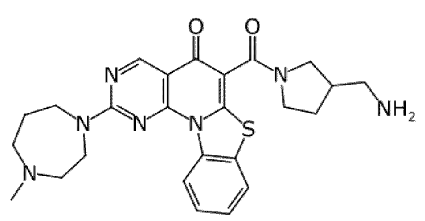
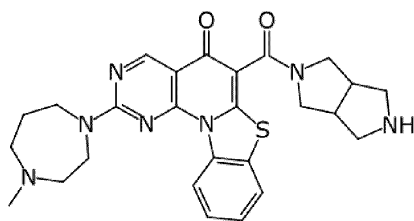
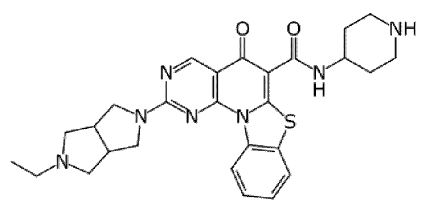
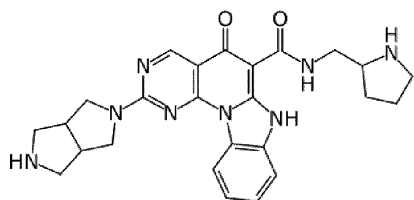
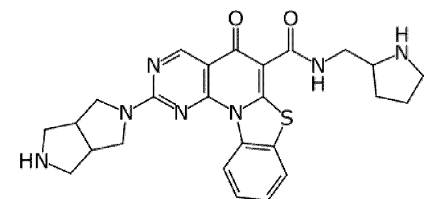
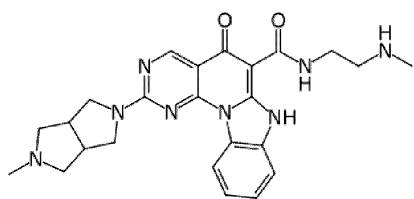
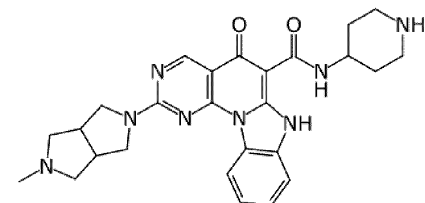
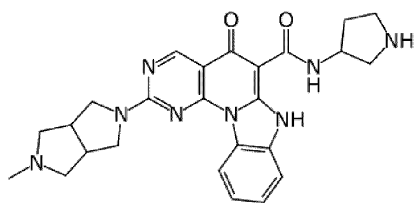
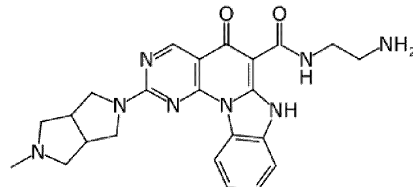
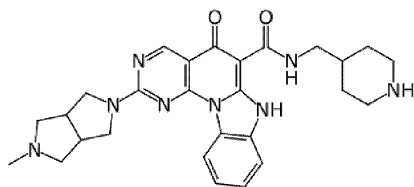
Formula (V)

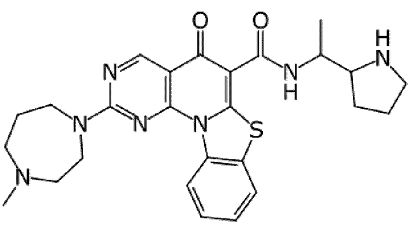
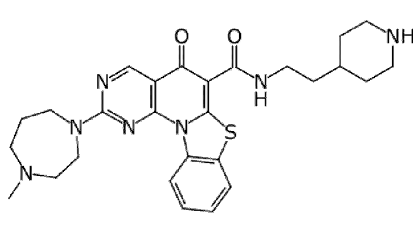
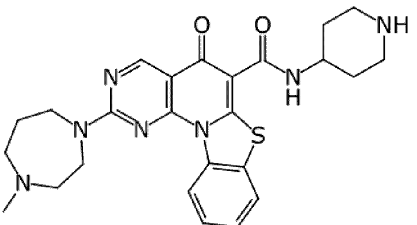
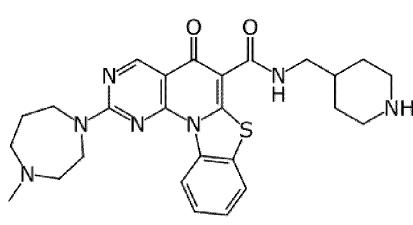
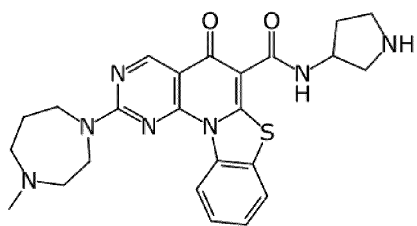
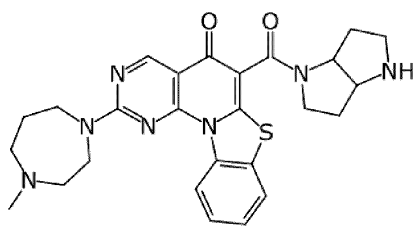
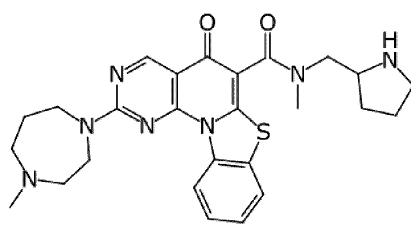
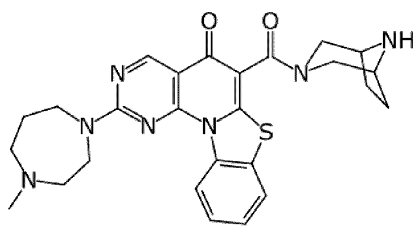
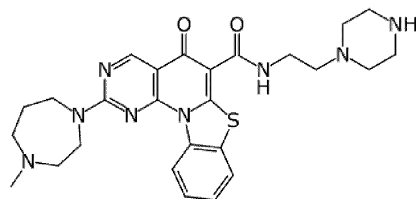
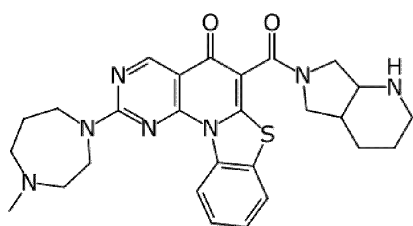
wherein R¹, R², R³, X¹ and Q¹ are as defined in accordance with any preceding claim.

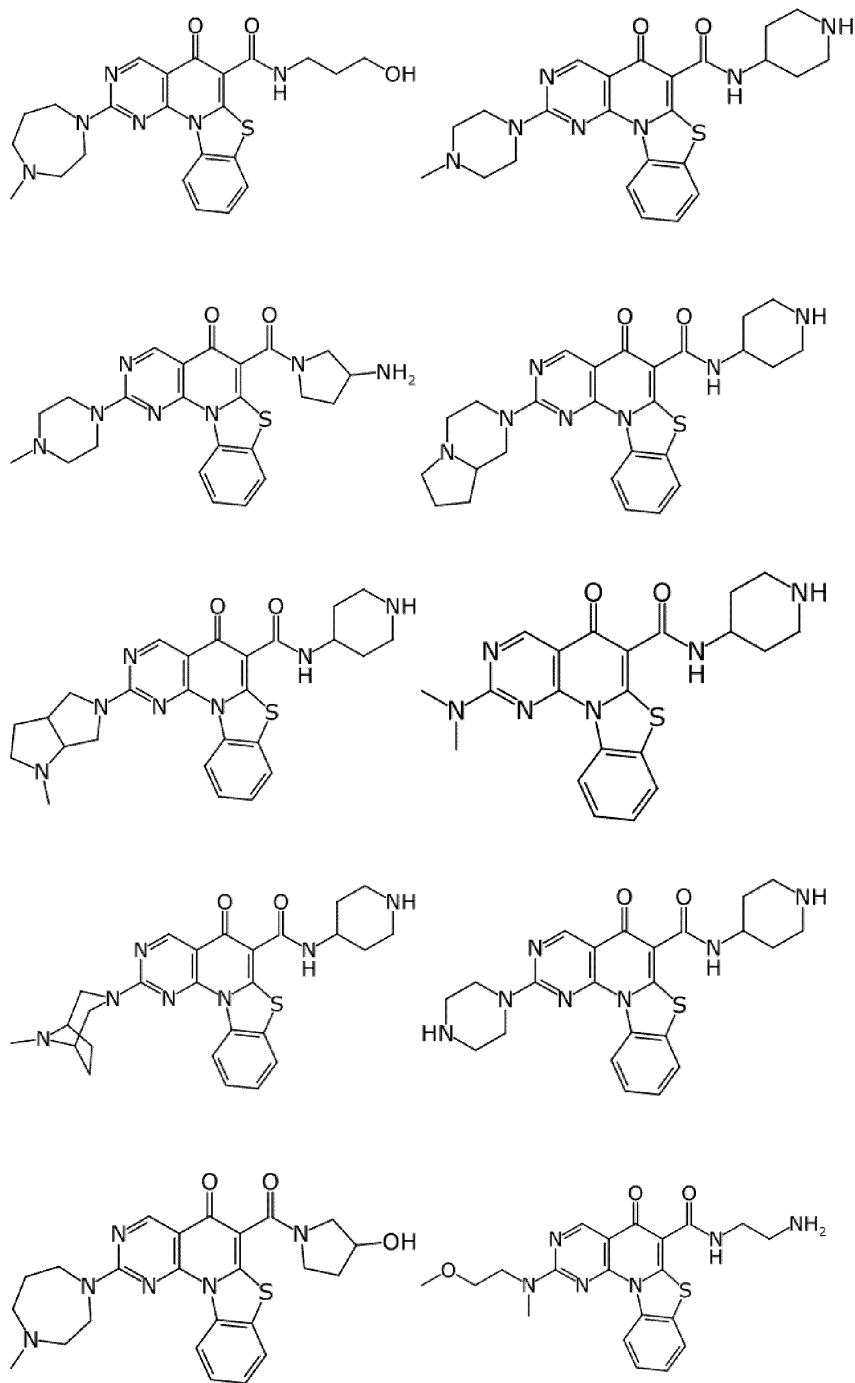
22. A compound selected from the group consisting of:

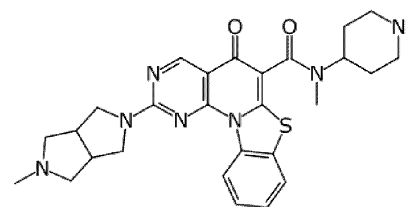
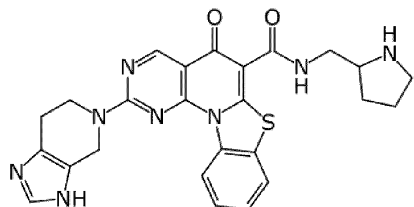
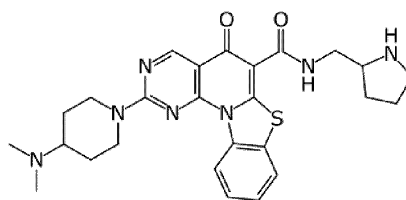
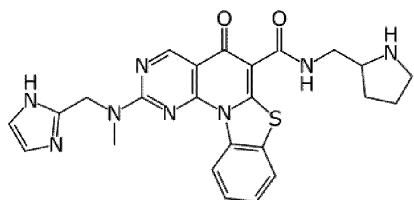
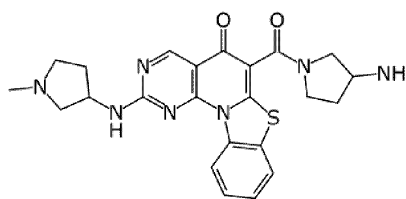
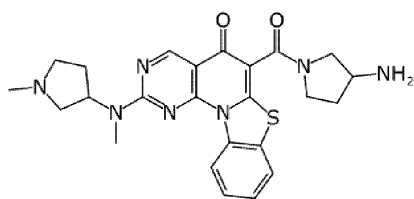
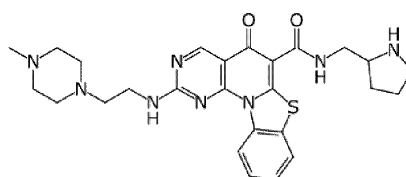
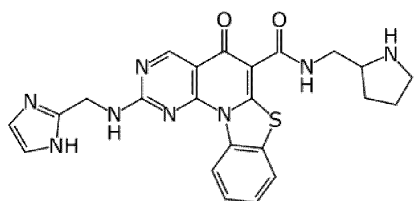
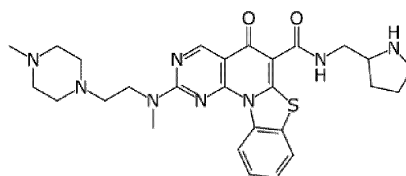
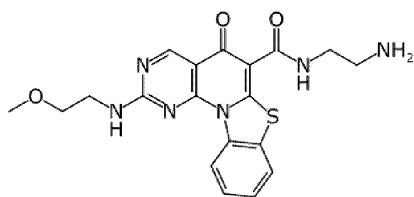


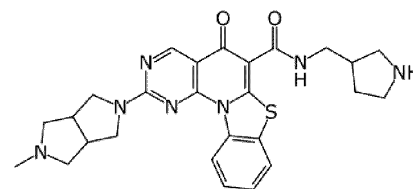
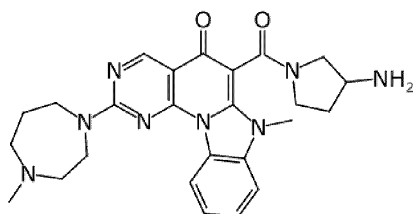
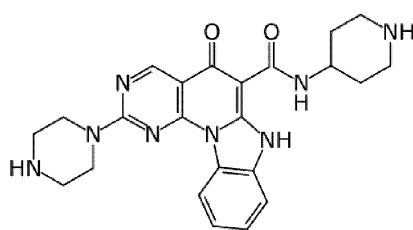
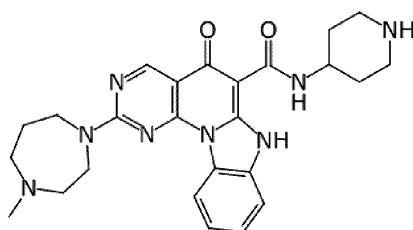
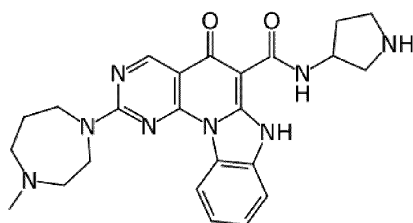
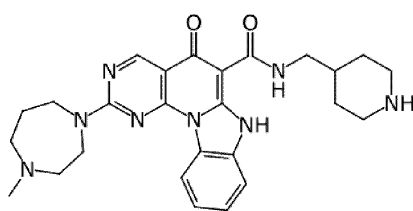
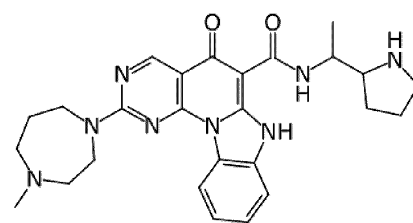
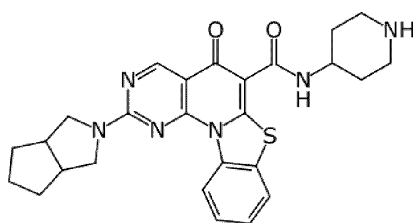
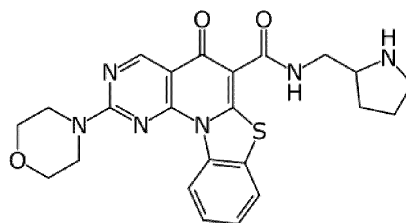
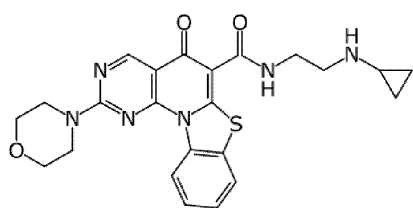


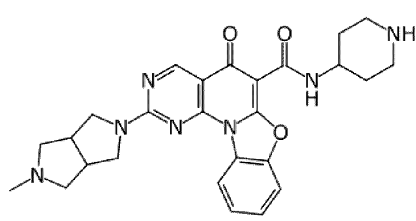
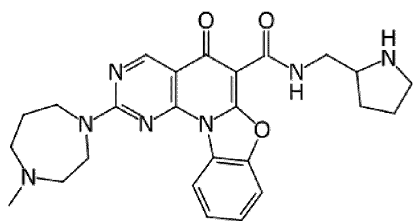
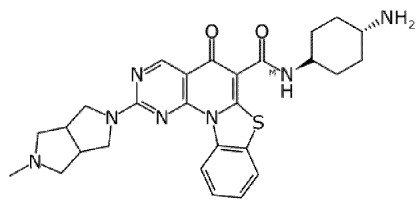
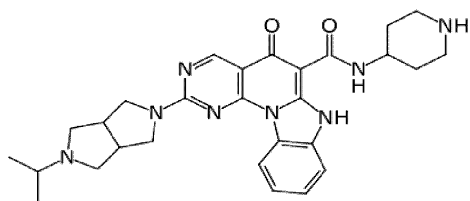
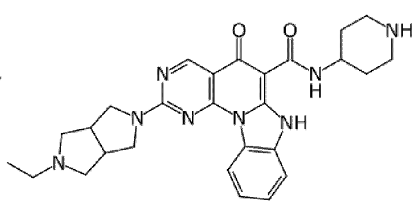
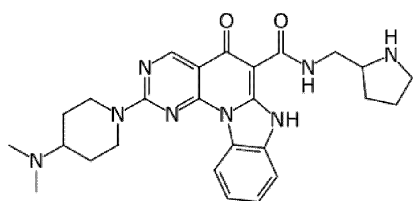
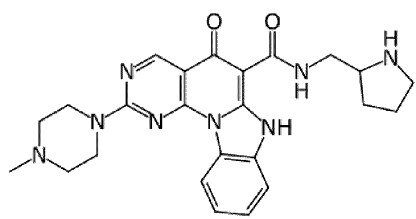
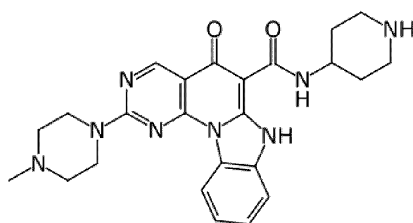
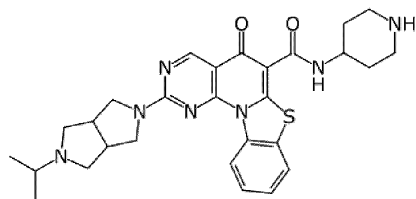
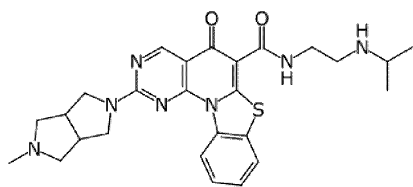




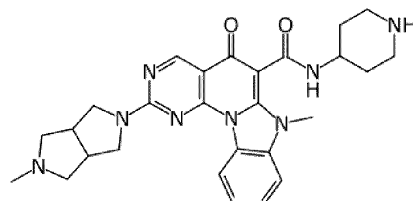
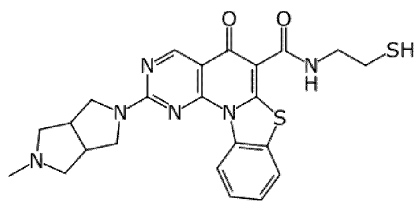
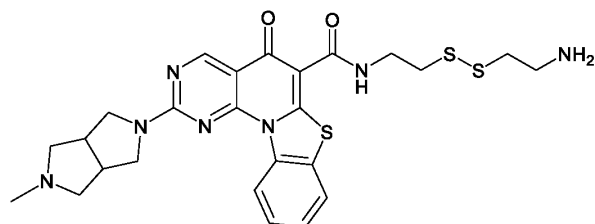
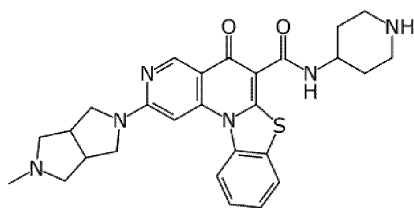
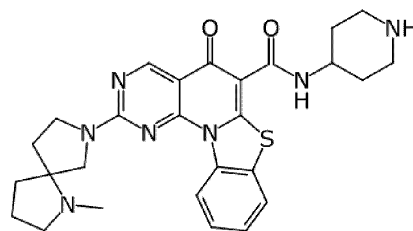
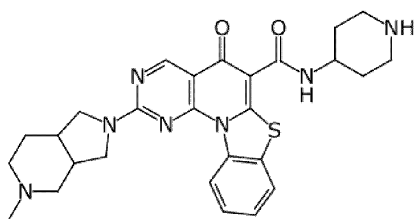








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or a pharmaceutically acceptable salt and/or solvate and/or prodrug of the selected compound.

23. An antibody-drug conjugate comprising a compound, or a pharmaceutically acceptable salt and/or solvate and/or prodrug thereof, as claimed in any one of claims 1 to 22.

24. A pharmaceutical composition comprising a compound, or a pharmaceutically acceptable salt and/or solvate and/or prodrug thereof, as claimed in any one of claims 1 to 22, or an antibody-drug conjugate as claimed in claim 23, and a pharmaceutically acceptable excipient.

25. A compound, or a pharmaceutically acceptable salt and/or solvate and/or prodrug thereof, as claimed in any one of claims 1 to 22, or an antibody-drug conjugate as claimed in claim 23, or a pharmaceutical composition as claimed in claim 24, for use in medicine.

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26. A compound, or a pharmaceutically acceptable salt and/or solvate and/or prodrug thereof, as claimed in any one of claims 1 to 22, or an antibody-drug conjugate as claimed in claim 23, or a pharmaceutical composition as claimed in claim 24, for use in treating cancer.