PCSK9 Inhibitors and Methods of Use Thereof

This application claims priority from European Patent Application No. 24164964.9, filed March 20, 2024, the disclosure of which is incorporated by reference herein in its entirety.

The present disclosure relates to compounds which inhibit PCSK9 and their use in methods of treatment.

Background

PCSK9, also referred to as "proprotein convertase subtilisin/kexin 9", is a member of the secretory proprotein convertase family and plays an important role in cholesterol metabolism. PCSK9 increases the levels of circulating LDL cholesterol (LDL-C) via the enhanced degradation of the LDLRs independently of its catalytic activity. Secreted PCSK9 binds to the Epidermal Growth Factor domain A (EGFA) of the LDL receptor (LDLR) at the cell surface and the PCSK9/LDLR complex is internalized into endosomal/lysosomal compartments. The enhanced binding affinity of PCSK9 to the LDLR at the acidic pH of late endosomes/lysosomes reduces LDLR receptor recycling and instead targets LDLR for lysosomal degradation. Genetic association studies have demonstrated that loss-of-function mutations in PCSK9 are associated with low plasma LDL-C levels and a reduction in the incidence of adverse cardiovascular events.

For cardiovascular disease, few options exist for inhibiting PCSK9. Statins actually upregulate PCSK9 in HepG2 cells and in human primary hepatocytes through the increased expression of SREBP-2, a transcription factor that upregulates both the LDLR and PCSK9 genes. Since an elevated level of PCSK9 decreases the abundance of LDLR on the cell surface, increasing doses of statins have failed to achieve proportional LDL-C lowering effects.

Two monoclonal antibodies (mAbs) that bind selectively to extracellular PCSK9 and prevent its interaction with the LDLR, alirocumab and evolocumab, have recently received FDA approval for lowering LDL-C levels. In clinical trials, alirocumab showed an about 50% decrease in LDL levels compared to placebo (Elbitar 2016). Patients taking evolocumab showed an about 60-75% decrease in LDL levels. The potency of these drugs demonstrates the potential for inhibitors of PCSK9 to be effective treatments for those with hypercholesterolemia and other cardiovascular diseases. However, both antibody drugs require intravenous administration and can cause allergic reactions or other deleterious immune responses in the body.

Cardiovascular diseases often require management over a person's lifetime, unlike an infection that could be episodic. Thus, ease of dosing and administration become important factors for

patient compliance with maintenance drug treatments. There is a need for PCSK9 inhibitors with increased efficacy and greater ease of administration, which can be achieved with small molecule PCSK9 inhibitors.

WO 2020/150473 A2 relates to heteroaryl compounds and pharmaceutical preparations thereof. It also relates to methods of treating or preventing cardiovascular diseases, and methods of treating sepsis or septic shock, using the described novel heterocyclic compounds.

WO 2020/15474 A1 relates to an inhibitor pharmacophore of PCSK9 and heteroaryl compounds that bind the PCSK9 protein.

WO 2023/084449 A1 relates to diaminocyclopentylpyridine derivatives as modulators of PCKS9.

Summary

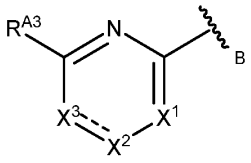
A first aspect there is provided a compound of Formula (I)

A-B-C (I)

or a pharmaceutically acceptable salt and tautomeric forms or stereoisomers thereof,

wherein A is of one of the following formulae:

(A1a)



wherein the wavy line indicates the point of attachment to B;

X^1 is N or C-R^{A1};
X^2 is N or C-R^{A4};
X^3 is N-($C_{1\text{-}6}$ hydrocarbon) or C-R^{A2};

R^{A1} is selected from the group consisting of:
(i) H;
(ii) halo;

(iii) CN;
(iv) C_{1-6} hydrocarbon, optionally substituted by one or more OH, CN, C_{1-6} alkyl acyl, C_{1-6} alkoxy or one or more halo groups;
(v) C_{1-6} alkoxy, optionally substituted by OH, one or more halo groups, or C_{1-6} alkyl amido;
(vi) C_{1-6} alkyl ester;
(vii) C_{1-6} alkyl acyl; and
(viii) OH;

R^{A2} is selected from the group consisting of:
(i) H;
(ii) halo;
(iii) CN;
(iv) C_{1-6} hydrocarbon, optionally substituted by OH, CN, C_{1-6} alkyl acyl, C_{1-6} alkoxy or one or more halo groups;
(v) C_{1-6} alkoxy, optionally substituted by OH, C_{1-6} alkyl amido, or one or more halo groups;
(vi) C_{1-6} acylamido (wherein the acyl is optionally substituted by H or methyl);
(vii) C_{1-6} thioalkyl;
(viii) C_{1-6} alkyl ester;
(ix) C_{1-6} alkyl acyl;
(x) C_{4-5} heterocyclyl;
(xi) C_5 heteroaryl;
(xii) C_{1-6} alkyl amido, optionally substituted by C_{1-3} alkyl amido, CN, OH, C_{2-3} alkynyl, C_{4-6} heterocyclyl, C_{1-3} alkyl wherein the C_{1-3} alkyl is optionally substituted with one or more halo or OH groups;
(xiii) OH; and
(xiv) C_{1-6} alkylamino;

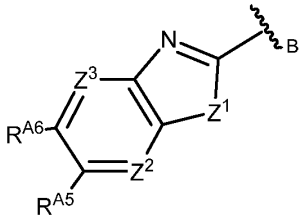
R^{A3} is selected from the group consisting of:
(i) H;
(ii) halo;
(iii) CN;
(iv) C_{1-6} hydrocarbon which is optionally substituted by OH, CN, C_{1-6} thioalkyl, C_{1-6} alkoxy, C_{1-6} alkyl acyl, C_{1-6} acyloxy, carboxy, C_{1-6} alkyl ester, C_{1-6} alkylamino, $-C(=O)NH_2$, C_{1-6} alkyl amido, C_{1-6} alkyl acylamido, C_{1-6} alkyl sulfinyl, C_{1-6} alkyl sulfonyl or one or more halo groups;
(v) OH;
(vi) C_{1-6} alkoxy, optionally substituted by OH, NH_2, C_4 heterocyclyl or one or more halo groups;
(vii) C_{1-6} acyloxy;

(viii) C_4 heterocycyl;
(ix) NH_2;
(x) C_{1-6} alkylamino, optionally substituted by CN, OH, or C_4 heterocyclyl;
(xi) C_{1-6} dialkylamino, optionally substituted by -NH_2;
(xii) C_{1-6} acylamido (where acyl substituent is H or Me);
(xiii) carbaimidoyl or methyl-carbaimidoyl;
(xiv) carboxyamino;
(xv) C_{1-6} thioalkyl, optionally substituted by OH or NH_2;
(xvi) C_{1-6} alkyl sulfinyl;
(xvii) C_{1-6} alkyl sulfonyl, optionally substituted by one or more halo groups;
(xviii) C_{1-6} sulfonimodyl;
(xix) C_{1-6} alkyl phosphinyl;
(xx) carboxy;
(xxi) C(=O)NH_2;
(xxii) C_{1-6} alkyl ester;
(xxiii) C_{1-6} alkyl acyl, optionally substituted by one or more halo groups; and
(xxiv) C_{1-6} alkyl amido;

or wherein R^{A3} and R^{A2} together with the carbon atoms to which they are bound form:
(i) an optionally substituted C_{5-7} heterocycle ring;
(ii) an optionally substituted C_{5-7} heteroaromatic ring;
(iii) an optionally substituted C_6 carboaromatic ring; or
(iv) an optionally substituted C_{5-7} carbocyclic ring
wherein, when present, the one, two three or four optional substituents are independently selected from C_{1-6}alkyl, halo, C_{1-6} alkoxy, NH_2, C_{1-6}alkylamino, OH, and CN;

R^{A4} is selected from the group consisting of:
(i) H;
(ii) halo;
(iii) CN;
(iv) C_{1-6} hydrocarbon, optionally substituted by one or more OH, CN, C_{1-6} alkyl acyl, C_{1-6} alkoxy or one or more halo groups;
(v) C_{1-6} alkoxy, optionally substituted by OH, one or more halo groups, C_{1-6} alkyl amido;
(vi) C_{1-6} alkyl ester;
(vii) C_{1-6} alkyl acyl;
(viii) OH; and
(ix) oxo;

(A2a)



wherein the wavy line indicates the point of attachment to B;

Z^1 is selected from O, S or NH;

Z^2 is either N or C-H

Z^3 is either N or C-R^{A7};

wherein if Z^1 is NH and Z^2 is C-H then Z^3 is C-R^{A7};

when Z^1 is NH, R^{A5} is Z^4 and R^{A6} is Z^5;

when Z^2 is N and Z^1 is O or S, R^{A5} is Z^4 and R^{A6} is Z^5;

when Z^2 is CH and Z^1 is S, R^{A5} is Z^4 and R^{A6} is Z^5;

when Z^2 is CH and Z^1 is O, R^{A5} is Z^5 and R^{A6} is Z^4;

Z^4 is selected from the group consisting of:

(i) H;

(ii) halo;

(iii) CN;

(iv) C_1 alkyl optionally substituted by one or more OH, CN, or one or more halo groups; and

(v) C_1 alkoxy, optionally substituted by one or more halo groups;

Z^5 is selected from the group consisting of:

(i) H;

(ii) halo;

(iii) CN;

(iv) $C_{1\text{-}6}$ hydrocarbon, optionally substituted by OH, CN, $C_{1\text{-}6}$ alkyl acyl, $C_{1\text{-}6}$ alkoxy or one or more halo groups;

(v) $C_{1\text{-}6}$ alkoxy, optionally substituted by $C_{1\text{-}6}$ alkyl amido, $C_{1\text{-}6}$ alkyl phosphonyl, or one or more halo groups;

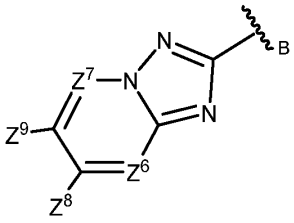
(vi) $C_{1\text{-}6}$ alkylamino

(vii) $C_{1\text{-}6}$ thioalkyl,

(viii) C_{1-6} alkyl phosphinyl; and
(ix) C_{1-6} alkyl phosphonyl;

R^{A7} is selected from the group consisting of:
(i) H;
(ii) halo;
(iii) CN;
(iv) C_{1-6} hydrocarbon, optionally substituted by OH, CN, C_{1-6} thioalkyl, C_{1-6} alkoxy, C_{1-6} alkyl acyl, C_{1-6} acyloxy, C(=O)OH, C_{1-6} alkyl ester, C_{1-6} alkylamino, -C(=O)NH_2, C_{1-6} alkyl amido, C_{1-6} acylamido, C_{1-6} alkyl sulfinyl, C_{1-6} alkyl sulfonyl or one or more halo groups;
(v) C_{1-6} alkoxy, optionally substituted by NH_2, C_4 heterocyclyl and one or more halo groups;
(vi) C_4 heterocycyl;
(vii) C_{1-6} alkylamino, optionally substituted by CN, OH, C_4 heterocyclyl;
(viii) C_{1-6} dialkylamino, optionally substituted by -NH_2; and
(ix) C_{1-6} thioalkyl, optionally substituted by OH or -NH_2;

(A2b)



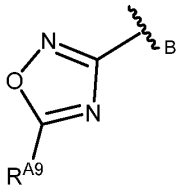
wherein the wavy line indicates the point of attachment to B;
Z^6 is either N or C-H
Z^7 is either N or C-R^{A8}

Z^8 and Z^9 are independently selected from the group consisting of:
(i) H;
(ii) halo;
(iii) CN;
(iv) C_{1-6} hydrocarbon, optionally substituted by OH, CN, C_{1-6} alkyl acyl, C_{1-6} alkoxy or one or more halo groups;
(v) C_{1-6} alkoxy, optionally substituted by C_{1-6} alkyl amido, C_{1-6} alkyl phosphonyl, or one or more halo groups;
(vi) C_{1-6} alkylamino;
(vii) C_{1-6} thioalkyl;

(viii) C_{1-6} alkyl phosphinyl; and
(ix) C_{1-6} alkyl phosphonyl;

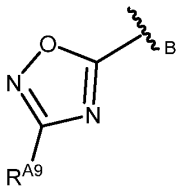
R^{A8} is selected from the group consisting of:
(i) H;
(ii) halo;
(iii) CN;
(iv) C_{1-6} hydrocarbon, optionally substituted by OH, CN, C_{1-6} thioalkyl, C_{1-6} alkoxy, C_{1-6} alkyl acyl, C_{1-6} acyloxy, C(=O)OH, C_{1-6} alkyl ester, C_{1-6} alkylamino, -C(=O)NH_2, C_{1-6} alkyl amido, C_{1-6} acylamido, C_{1-6} alkyl sulfinyl, C_{1-6} alkyl sulfonyl or one or more halo groups;
(v) C_{1-6} alkoxy, optionally substituted by NH_2, C_4 heterocyclyl, or one or more halo groups;
(vi) C_4 heterocycyl;
(vii) C_{1-6} alkylamino, optionally substituted by CN, OH, or C_4 heterocyclyl;
(viii) C_{1-6} dialkylamino, optionally substituted by -NH_2; and
(ix) C_{1-6} thioalkyl, optionally substituted by OH or -NH_2;

(A3a)



; or

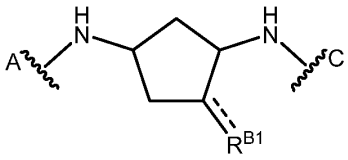
(A3b)



wherein the wavy line indicates the point of attachment to B;

where R^{A9} is selected from H, methyl, ethyl, n-propyl, *i*-propyl, cyclopropyl, 1-methylcyclopropyl and 2-methylcyclopropyl;

wherein B is of formula:
(B-1)

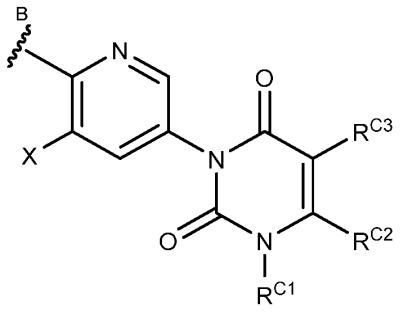


wherein the wavy lines indicate the points of attachment to A and C;

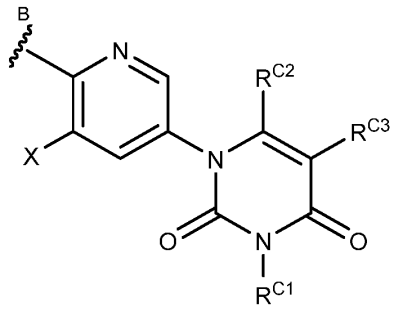
R^{B1} is -H, -OH, =$CHCH_2$-OH, -C_{1-4} alkyoxy, or -C_{1-4} alkyl which -C_{1-4} alkyl is optionally substituted by OH or OMe;

wherein C is of formula

(C-1a) or (C-1b):



(C-1a)



(C-1b);

X is hydrogen or fluorine;

one of R^{C2} and R^{C3} is hydrogen and the other is C_{1-3} alkoxy;

or R^{C2} and R^{C3} together represent a fused benzene ring or C_{5-6} heteroaromatic ring, which rings are optionally substituted by one or more R^{C4} groups;

R^{C1} is selected from:

(i) H;

(ii) C_{1-6} alkyl optionally substituted by one or more halo groups;

(iv) C_{5-6} heterocyclyl or C_{5-6} heteroaryl with an optional methyl substituent;

(x) phenyl optionally substituted by one or more halo atoms;

R^{C4} is selected from:

(i) C_{1-6} alkyl optionally substituted by one or more halo groups;

(ii) C_{1-6} alkoxy optionally substituted by one or more halo groups;

(iii) C_{5-6} heterocyclyl or C_{5-6} heteroaryl with an optional methyl substituent;

(iv) di-C_{1-6} alkyl amido;

(v) C_{1-6} acylamido;

(vi) halo; and

(vii) CN.

A second aspect provides a pharmaceutical composition comprising the compound of the first aspect and a pharmaceutically acceptable diluent, carrier or excipient.

The third aspect provides the compound of the first aspect for use in a method of therapy. The third aspect also provides the use of a compound of the first aspect in the manufacture of a medicament for treating a cardiovascular disease. The third aspect also provides a compound of the first aspect for use in the treatment of a cardiovascular disease. The third aspect also provides a method of treating a cardiovascular disease comprising administering a therapeutically effective amount of a compound of the first aspect or a composition according to the second aspect to a patient in need thereof.

This disclosure includes the combination of the aspects and preferred features described except where such a combination is clearly impermissible or expressly avoided.

Description of the Figures

Figure 1 shows the structure of the Mouse GalNAc ASO for in the vivo experiments of Assay 6.

Detailed Description

Aspects and embodiments will now be discussed. Further aspects and embodiments will be apparent to those skilled in the art. All documents mentioned in this text are incorporated herein by reference.

Compounds of Formula (I) and its use in the treatment of cardiovascular diseases are described herein. The compounds disclosed herein are PCSK9 inhibitors. The compounds may have higher inhibition of PCSK9, lower hERG activity, improved secondary pharmacology profile including GSK3β and/or other kinases, good stability, and/or improved activity in the treatment of cardiovascular diseases. The compounds may have an improved secondary pharmacology profile or an improved off-target profile.

Definitions

Substituents

The phrase “optionally substituted” as used herein, pertains to a parent group which may be unsubstituted or which may be substituted.

Unless otherwise specified, the term "substituted" as used herein, pertains to a parent group which bears one or more substituents. The term "substituent" is used herein in the conventional sense and refers to a chemical moiety which is covalently attached to, or if appropriate, fused to, a parent group. A wide variety of substituents are well known, and methods for their formation and introduction into a variety of parent groups are also well known.

Examples of substituents are described in more detail below.

Unless otherwise stated, halo is selected from chloro (Cl), fluoro (F), bromo (Br) and iodo (I).

Cyano (nitrile, carbonitrile): -CN.

Hydroxy: -OH.

Oxo: =O (oxygen double bonded to the rest of the molecule).

C_{1-6} hydrocarbon: The term "C_{1-6} hydrocarbon" as used herein pertains to a monovalent moiety obtained by removing a hydrogen atom from a carbon atom of a hydrocarbon compound having from 1 to 6 carbon atoms, which may be aliphatic or alicyclic, which may be saturated or unsaturated (e.g. partially unsaturated, fully unsaturated) and may also be branched. Thus, the term "hydrocarbon" includes the terms alkyl, alkenyl, alkynyl, cycloalkyl, etc., discussed below.

C_{1-6} alkyl: The term "C_{1-6} alkyl" as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a carbon atom of a hydrocarbon compound having from 1 to 6 carbon atoms, which are saturated and may also be branched. The term "C_{1-4} alkyl" as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a carbon atom of a hydrocarbon compound having from 1 to 4 carbon atoms, which are saturated.

Examples of saturated alkyl groups include, but are not limited to, methyl (C_1), ethyl (C_2), propyl (C_3), butyl (C_4), pentyl (C_5) and hexyl (C_6).

Examples of saturated linear alkyl groups include, but are not limited to, methyl (C_1), ethyl (C_2), n-propyl (C_3), n-butyl (C_4), n-pentyl (amyl) (C_5) and n-hexyl (C_6).

Examples of saturated branched alkyl groups include isopropyl (C_3), iso-butyl (C_4), sec-butyl (C_4), tert-butyl (C_4), iso-pentyl (C_5), and neopentyl (C_5).

C_{2-6} Alkenyl: The term "C_{2-6} alkenyl" as used herein, pertains to a hydrocarbon group having one or more carbon-carbon double bonds.

Examples of unsaturated alkenyl groups include, but are not limited to, ethenyl (vinyl, -$CH=CH_2$), 1-propenyl (-$CH=CH-CH_3$), 2-propenyl (allyl, $CHCH=CH_2$), iso-propenyl (1-methylvinyl, $C(CH_3)=CH_2$), butenyl (C_4), pentenyl (C_5), and hexenyl (C_6).

C_{2-6} alkynyl: The term "C_{2-6} alkynyl" as used herein, pertains to a hydrocarbon group having one or more carbon-carbon triple bonds.

Examples of unsaturated alkynyl groups include, but are not limited to, ethynyl (-C≡CH) and 2-propynyl (propargyl, $-CH_2C{\equiv}CH$).

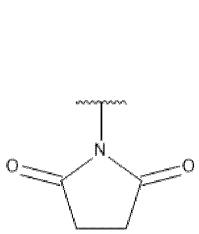
C_{1-6} alkoxy: The term C_{1-6} alkoxy as used herein, pertains to an OR group, wherein R is an C_{1-6} hydrocarbon group. Examples of C_{1-6} alkoxy groups include, but are not limited to, OMe, OEt (ethoxy), -O(nPr) (n-propoxy), -O(iPr) (iso-propoxy), O(nBu) (n-butoxy), O(sBu) (sec-butoxy), O(iBu) (iso-butoxy), and O(tBu) (tert-butoxy).

C_{1-6} acyloxy: The term C_{1-6} acyloxy (reverse ester) as used herein, pertains to an OC(=O)R, wherein R is a C_{1-6} hydrocarbon group. Examples of acyloxy groups include, but are not limited to, $OC(=O)CH_3$ (acetoxy), $OC(=O)CH_2CH_3$, or $OC(=O)C(CH_3)_3$.

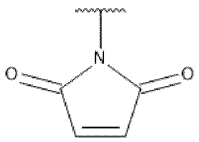
Amino: NR^1R^2, wherein R^1 and R^2 are independently amino substituents, for example, hydrogen, a C_{1-6} hydrocarbon group (also referred to as C_{1-6} alkylamino or C_{1-6} dialkylamino, where both groups are a C_{1-6} hydrocarbon group), or, in the case of a "cyclic" amino group, R^1 and R^2, taken together with the nitrogen atom to which they are attached, form a heterocyclic ring having from 4 to 6 ring atoms. Amino groups may be primary ($-NH_2$), secondary ($-NHR^1$), or tertiary ($-NR^1R^2$), and in cationic form, may be quaternary ($-^+NR^1R^2R^3$). Examples of amino groups include, but are not limited to NH_2, $NHCH_3$, $NHCH(CH_3)_2$, $N(CH_3)_2$, $N(CH_2CH_3)_2$, and NHPh. Examples of cyclic amino groups include, but are not limited to, aziridino, azetidino, pyrrolidino, piperidino, piperazino, morpholino, and thiomorpholino.

C_{1-6} acylamido: Acylamido (acylamino): $NR^1C(=O)R^2$, wherein R^1 is an amide substituent, for example, hydrogen or a C_{1-6} hydrocarbon group, and R^2 is an acyl substituent, for example, a C_{1-6} hydrocarbon group. Examples of acylamide groups include, but are not limited to, $NHC(=O)CH_3$ and $NHC(=O)CH_2CH_3$. In some embodiments R^1 and R^2 may together form a cyclic or bicyclic structure and form a cyclic acylamido group. Examples of such groups include

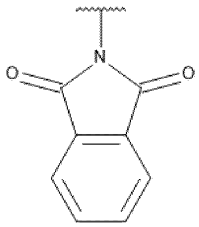
succinimidyl, maleimidyl, phthalimidyl, 2-oxo-3*H*-benzimidazol-1-yl, 3-methyl-2-oxo-benzimidazol-1-yl, 1-methyl-2-oxoimidazo[4,5-*b*]pyridin-3-yl, 2,5-dioxoimidazolidin-1-yl and 2,4-dioxoimidazolidin-1-yl:



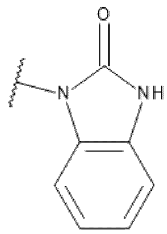
succinimidyl



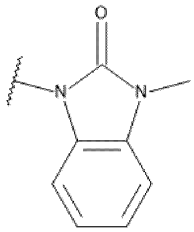
maleimidyl



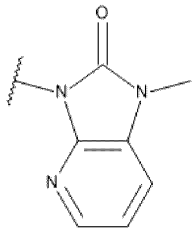
phthalimidyl



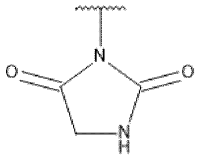
(2-oxo-3H-benzimidazol-1-yl)



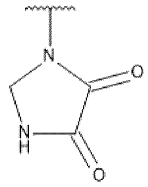
(3-methyl-2-oxo-benzimidazol-1-yl)



(1-methyl-2-oxo-imidazo[4,5-b]pyridin-3-yl)



(2,5-dioxoimidazolidin-1-yl)



(4,5-dioxoimidazolidin-1-yl)

Carbaimidoyl: -C(=NH)NH_2.

Methyl-carbaimidoyl: -C(=N-CH_3)NH_2.

Carboxyamino: -N(H)(C(=O)OH).

C_{1-6} thioalkyl: The term C_{1-6} thioalkyl as used herein, pertains to an SR, wherein R is a C_{1-6} hydrocarbon group. Examples of C_{1-6} alkylthio groups include, but are not limited to, SCH_3 and SCH_2CH_3.

C_{1-6} alkyl sulfinyl: The term C_{1-6} alkyl sulfinyl pertains to a sulfine (sulfinyl, sulfoxide) which has the structure S(=O)R-, wherein R is a C_{1-6} hydrocarbon group. Examples of C_{1-6} alkyl sulfinyl groups include, but are not limited to, $S(=O)CH_3$ and $S(=O)CH_2CH_3$.

C_{1-6} alkyl sulfonyl: The term C_{1-6} alkyl sulfonyl as used herein pertains to an $-S(=O)_2R$, group wherein R is a C_{1-6} hydrocarbon group, including, for example, a fluorinated or perfluorinated C_{1-6} alkyl group. Examples of C_{1-6} alkyl sulfonyl groups include, but are not limited to, $-S(=O)_2CH_3$ (methanesulfonyl, mesyl), $-S(=O)_2CF_3$ (triflyl), $-S(=O)_2CH_2CH_3$ (esyl), $-S(=O)_2C_4F_9$ (nonaflyl) and $-S(=O)_2CH_2CF_3$ (tresyl).

C_{1-6} sulfonimodyl: The term C_{1-6} sulfonimodyl is also referred to as Sulfonamido (sulfinamoyl; sulfonic acid amide; sulfonamide or di-C_{1-6} alkyl sulfonamido) and has the structure $S(=O)_2NR^1R^2$, wherein R^1 and R^2 are independently amino substituents, as defined for amino groups. Examples of sulfonamido groups include, but are not limited to, $-S(=O)_2NH_2$, $-S(=O)_2NH(CH_3)$, $-S(=O)_2N(CH_3)_2$, $-S(=O)_2NH(CH_2CH_3)$ and $-S(=O)_2N(CH_2CH_3)_2$.

Sulfonamino: $NR^1S(=O)_2R$, wherein R^1 is an amino substituent, as defined for amino groups, and R is a sulfonamino substituent, for example, a C_{1-6} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-6} alkyl group. Examples of sulfonamino groups include, but are not limited to, $NHS(=O)_2CH_3$ and $N(CH_3)S(=O)_2C_6H_5$.

C_{1-6} alkyl phosphinyl: The term C_{1-6} alkyl phosphinyl (phosphine oxide) has the structure $-P(=O)R_2$, wherein each R is independently a C_{1-6} hydrocarbon group. Examples of C_{1-6} alkyl phosphinyl groups include, but are not limited to, $P(=O)Me_2$, $P(=O)(CH_2CH_3)_2$ and $P(=O)(tBu)_2$. Wherein each R group can be the same or different groups.

C_{1-6} alkyl phosphonyl: The term C_{1-6} alkyl phosphonyl has the structure $-P(=O)_2R$, wherein R is a C_{1-6} hydrocarbon group. Examples of C_{1-6} alkyl phosphonyl groups include, but are not limited to, $P(=O)_2(CH_3)$, $P(=O)_2(CH_2CH_3)$ and $P(=O)_2(tBu)$.

Carboxy (carboxylic acid): $-C(=O)OH$.

C_{1-6} alkyl ester: The term C_{1-6} alkyl ester (carboxylate, carboxylic acid ester, oxycarbonyl) has the structure $C(=O)OR$, wherein R is a C_{1-6} hydrocarbon group. Examples of ester groups include, but are not limited to, $C(=O)OCH_3$, $C(=O)OCH_2CH_3$ and $C(=O)OC(CH_3)_3$.

C_{1-6} alkyl acyl: The term C_{1-6} alkyl acyl also known as Acyl (keto) has the structure $C(=O)R$, wherein R is a C_{1-6} hydrocarbon group. Examples of C_{1-6} alkyl acyl groups include, but are not limited to, $C(=O)CH_3$ (acetyl), $C(=O)CH_2CH_3$ (propionyl) or $C(=O)C(CH_3)_3$ (tert-butyryl).

C_{1-6} alkyl amido: The term C_{1-6} alkyl amido (also referred to as carbamoyl, carbamyl, aminocarbonyl, carboxamide) has the structure $C(=O)NR^1R^2$, wherein R^1 and R^2 are independently amino substituents, as defined for amino groups for example, hydrogen, a C_{1-6} hydrocarbon group (also referred to as C_{1-6} alkyl amido or C_{1-6} dialkyl amido), or, in the case of a "cyclic" amido group, R^1 and R^2, taken together with the nitrogen atom to which they are attached, form a heterocyclic ring having from 4 to 6 ring atoms. Examples of amido groups include, but are not limited to, $C(=O)NH_2$, $C(=O)NHCH_3$, $C(=O)N(CH_3)_2$, $C(=O)NHCH_2CH_3$, and $C(=O)N(CH_2CH_3)_2$, as well as amido groups in which R^1 and R^2, together with the nitrogen atom to which they are attached, form a heterocyclic structure as in, for example, piperidinocarbonyl, morpholinocarbonyl, thiomorpholinocarbonyl, and piperazinocarbonyl.

C_{3-12} cycloalkyl: The term "C_{3-12} cycloalkyl" as used herein, pertains to an alkyl group which is also a cyclyl group; that is, a monovalent moiety obtained by removing a hydrogen atom from an alicyclic ring atom of a cyclic hydrocarbon (carbocyclic) compound, which moiety has from 3 to 7 carbon atoms, including from 3 to 7 ring atoms. The carbocyclic ring may be saturated or unsaturated and may be bridged or unbridged. The ring may be a fused ring or a single ring.

Examples of cycloalkyl groups include, but are not limited to, those derived from:

saturated monocyclic hydrocarbon compounds:

cyclopropane (C_3), cyclobutane (C_4), cyclopentane (C_5), cyclohexane (C_6), cycloheptane (C_7), methylcyclopropane (C_4), dimethylcyclopropane (C_5), methylcyclobutane (C_5), dimethylcyclobutane (C_6), methylcyclopentane (C_6), dimethylcyclopentane (C_7) and methylcyclohexane (C_7);

unsaturated monocyclic hydrocarbon compounds:

cyclopropene (C_3), cyclobutene (C_4), cyclopentene (C_5), cyclohexene (C_6), methylcyclopropene (C_4), dimethylcyclopropene (C_5), methylcyclobutene (C_5), dimethylcyclobutene (C_6), methylcyclopentene (C_6), dimethylcyclopentene (C_7) and methylcyclohexene (C_7); and

saturated polycyclic hydrocarbon compounds:

norcarane (C_7), norpinane (C_7), norbornane (C_7).

C_{3-10} heterocyclyl: The term "C_{3-10} heterocyclyl" as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a ring atom of a heterocyclic compound, which moiety has from 3 to 10 ring atoms, of which from 1 to 5 are ring heteroatoms. In certain embodiments, each ring has from 3 to 7 ring atoms, of which from 1 to 4 are ring heteroatoms. The ring may be saturated or unsaturated, and may be bridged or unbridged. The ring may be a

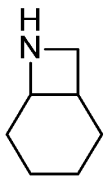
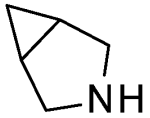
fused ring or a single ring. For the avoidance of doubt, substituents on the heterocyclyl ring may be linked via either a carbon atom or a heteroatom.

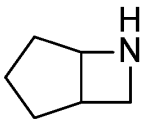
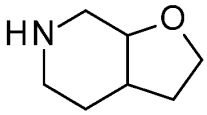
In this context the term 'heteroatom' means O, S, N, Si or B (Boron). More commonly in a pharmaceutical context, the term 'heteroatom' means O, S or N.

In this context, the prefixes (e.g. C_{3-10} C_{3-7}, C_{5-6}, etc.) denote the number of ring atoms, or range of number of ring atoms, whether carbon atoms or heteroatoms. For example, the term "C_{5-6} heterocyclyl", as used herein, pertains to a heterocyclyl group having 5 or 6 ring atoms.

Examples of monocyclic heterocyclyl groups include, but are not limited to, those derived from:
N_1: aziridine (C_3), azetidine (C_4), pyrrolidine (tetrahydropyrrole) (C_5), pyrroline (e.g. 2,5-dihydro-1*H*-pyrrole) (C_5), 2*H*-pyrrole or 3*H*-pyrrole, isoazole (C_5), piperidine (C_6), dihydropyridine (C_6), tetrahydropyridine (C_6), azepine (C_7);
O_1: oxirane (C_3), oxetane (C_4), oxolane (tetrahydrofuran) (C_5), oxole (dihydrofuran) (C_5), oxane (tetrahydropyran) (C_6), dihydropyran (C_6), pyran (C_6), oxepin (C_7);
S_1: thiirane (C_3), thietane (C_4), thiolane (tetrahydrothiophene) (C_5), thiane (tetrahydrothiopyran) (C_6), thiepane (C_7);
O_2: dioxolane (C_5), dioxane (C_6), and dioxepane (C_7);
O_3: trioxane (C_6);
N_2: imidazolidine (C_5), pyrazolidine (diazolidine) (C_5), imidazoline (C_5), pyrazoline (dihydropyrazole) (C_5), piperazine (C_6);
N_1O_1: tetrahydrooxazole (C_5), dihydrooxazole (C_5), tetrahydroisoxazole (C_5), dihydroisoxazole (C_5), morpholine (C_6), tetrahydrooxazine (C_6), dihydrooxazine (C_6), oxazine (C_6);
N_1S_1: thiazoline (C_5), thiazolidine (C_5), thiomorpholine (C_6);
N_2O_1: oxadiazine (C_6);
O_1S_1: oxathiole (C_5) and oxathiane (thioxane) (C_6); and,
$N_1O_1S_1$: oxathiazine (C_6).

Examples of bicyclic heterocyclyl groups include, but are not limited to those derived from:

Compound	Structure	Compound	Structure
7-azabicyclo[4.2.0]octane (N_1) C_8		3-azabicyclo[3.1.0]hexane (N_1) C_6	

6-azabicyclo[3.2.0]heptane (N_1) C_7		2,3,3a,4,5,6,7,7a-octahydrofuro[2,3-c]pyridine (N_1O_1) C_9	

C_{6-10} carboaryl: The term "C_{6-10} carboaryl", as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from an aromatic ring atom of an aromatic compound, which moiety has from 6 to 10 ring atoms and the ring atoms are all carbon atoms, as in "carboaryl groups". The ring may be a fused ring or a single ring. Examples of carboaryl groups include, but are not limited to, those derived from benzene (i.e. phenyl) (C_6), naphthalene (C_{10}) and azulene (C_{10}).

In this context, the prefixes (e.g. C_{5-7}, C_{5-6}, C_{5-10}, etc.) denote the number of ring atoms, or range of number of ring atoms. For example, the term "C_{5-6} aryl" as used herein, pertains to an aryl group having 5 or 6 ring atoms.

Examples of carboaryl groups which comprise fused rings, at least one of which is an aromatic ring, include, but are not limited to, groups derived from indane (e.g. 2,3-dihydro-1H-indene) (C_9), indene (C_9), isoindene (C_9) and tetraline (1,2,3,4-tetrahydronaphthalene) (C_{10}).

C_{5-10} heteroaryl: The term "C_{5-10} heteroaryl", as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from an aromatic ring atom of an aromatic compound, which moiety has from 5 to 10 ring atoms of which from 1 to 5 are ring heteroatoms. In certain embodiments, each ring has from 5 to 7 ring atoms, of which from 1 to 4 are ring heteroatoms. For the avoidance of doubt, substituents on the heteroaryl ring may be linked via either a carbon atom or a heteroatom. The ring may be a fused ring or a single ring.

In this context the term 'heteroatom' means O, S, N, Si or B (Boron). More commonly in a pharmaceutical context, the term 'heteroatom' means O, S or N.

Examples of monocyclic heteroaryl groups include, but are not limited to, those derived from:
N_1: pyrrole (azole) (C_5), pyridine (azine) (C_6);
O_1: furan (oxole) (C_5);
S_1: thiophene (thiole) (C_5);
N_1O_1: oxazole (C_5), isoxazole (C_5), isoxazine (C_6);
N_2O_1: oxadiazole (furazan) (C_5);
N_3O_1: oxatriazole (C_5);

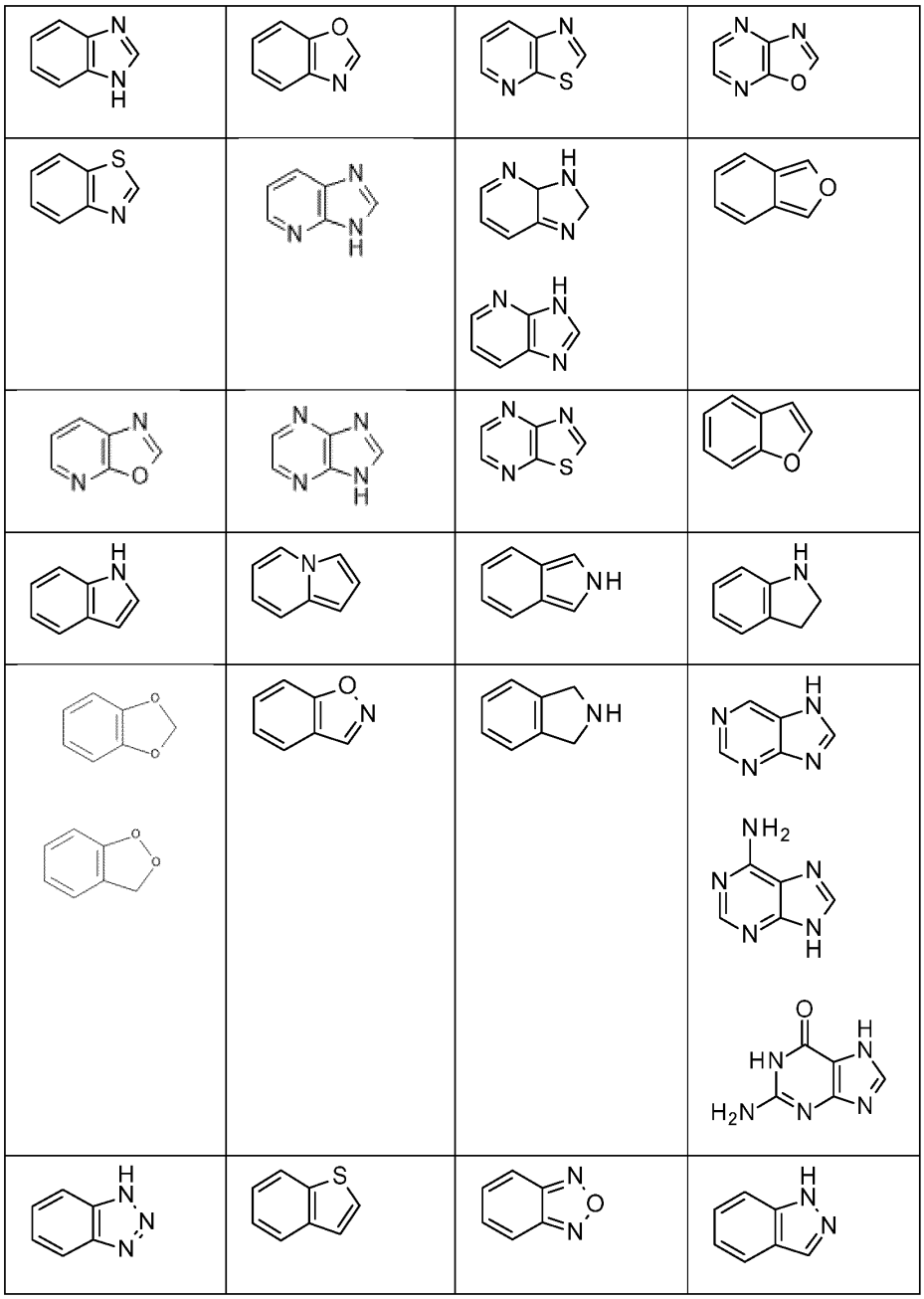
N_1S_1: thiazole (C_5), isothiazole (C_5);

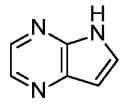
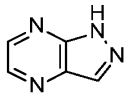
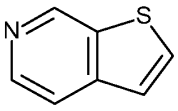
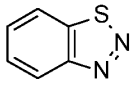
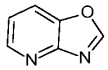
N_2: 1*H*-imidazole (1,3-diazole) (C_5), 1*H*-pyrazole (1,2-diazole) (C_5), pyridazine (1,2-diazine) (C_6), pyrimidine (1,3-diazine) (C_6) (e.g., cytosine, thymine, uracil), pyrazine (1,4-diazine) (C_6);

N_3: triazole (C_5), triazine (C_6); and,

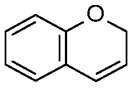
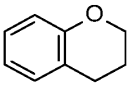
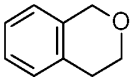
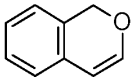
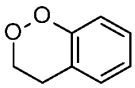
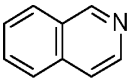
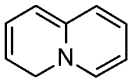
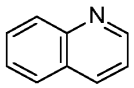
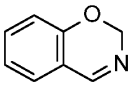
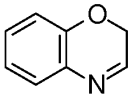
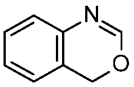
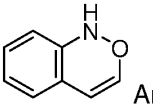
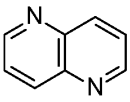
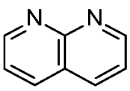
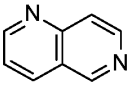
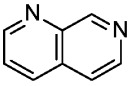
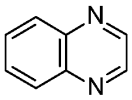
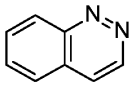
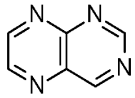
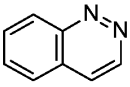
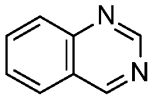
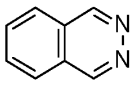
N_4: tetrazole (C_5).

Examples of heteroaryl which comprise fused rings, include, but are not limited to C_9 heteroaryl (with 2 fused rings) derived from:

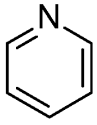
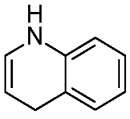


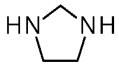
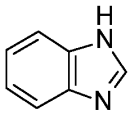
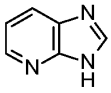
			
			

Examples of heteroaryl which comprise fused rings, include, but are not limited to C_{10} heteroaryl (with 2 fused rings) derived from:

			
			
    And isomers thereof	    And isomers thereof		
			

Examples of heteroaryl or heterocyclic compounds include but are not limited to those derived from:

Pyridyl (pyridine)		Dihydroquinolinyl (dihydroquinoline)	

Imidazolidinyl (imidazolidine)		Benzimidazolyl (benzimidazole)	
Imidazopyridinyl (Imidazopyridine)			

Spiro C_{6-12} carbocyclyl: The term Spiro C_{6-12} carbocyclyl as used herein pertains to a moiety that has at least two molecular rings with only one common atom. The simplest spiro compounds are bicyclic (having just two rings), or have a bicyclic portion as part of the larger ring system, in either case with the two rings connected through the defining single common atom. Spiro C_{6-12} carbocyclyl pertains to a cyclyl group; that is, a monovalent moiety obtained by removing a hydrogen atom from an alicyclic ring atom of a cyclic hydrocarbon (carbocyclic) compound, which moiety has from 6 to 12 carbon atoms, including from 3 to 7 ring atoms wherein the rings share a common atom.

Spiro C_{6-12} heterocyclyl: The term Spiro C_{6-12} heterocyclyl as used herein pertains to a moiety that has at least two molecular rings with only one common atom. The simplest spiro compounds are bicyclic (having just two rings), or have a bicyclic portion as part of the larger ring system, in either case with the two rings connected through the defining single common atom. The spiro C_{6-12} heterocyclyl moiety pertains to a monovalent moiety obtained by removing a hydrogen atom from a ring atom of a heterocyclic compound, which moiety has from 8 to 12 ring atoms of which from 1 to 3 are ring heteroatoms wherein the rings share a common atom. In certain embodiments, each ring has from 9 to 11 ring atoms, of which from 1 to 2 are ring heteroatoms. For the avoidance of doubt, substituents on the heteroaryl ring may be linked via either a carbon atom or a heteroatom.

For the avoidance of doubt, where multiple substituents are independently selected from a given group, the selected substituents may comprise the same substituents or different substituents from within the given group.

Pharmaceutically acceptable salt

The term “pharmaceutically acceptable” is used to specify that an object (for example a salt, dosage form or excipient) is suitable for use in patients. An example list of pharmaceutically acceptable salts can be found in the *Handbook of Pharmaceutical Salts: Properties*, *Selection and Use*, P. H. Stahl and C. G. Wermuth, editors, Weinheim/Zürich: Wiley-VCH/VHCA, 2002.

A suitable pharmaceutically acceptable salt of a compound of Formula (I) is, for example, an acid addition salt. An acid addition salt of a compound of Formula (I) may be formed by bringing the compound into contact with a suitable inorganic or organic acid under conditions known to the skilled person. An acid addition salt may for example be formed using an inorganic acid selected from the group consisting of hydrochloric acid, hydrobromic acid, sulphuric acid and phosphoric acid. An acid addition salt may also be formed using an organic acid selected from the group consisting of trifluoroacetic acid, citric acid, maleic acid, oxalic acid, acetic acid, formic acid, benzoic acid, fumaric acid, succinic acid, tartaric acid, lactic acid, pyruvic acid, methanesulfonic acid, benzenesulfonic acid and *para*-toluenesulfonic acid.

Another suitable pharmaceutically acceptable salt of a compound of Formula (I) is, for example, a base addition salt. A base addition salt of a compound of Formula (I) may be formed by bringing the compound into contact with a suitable inorganic or organic base under conditions known to the skilled person. A base addition salt may for example be formed using an inorganic base selected from the group consisting of lithium hydroxide, sodium hydroxide, potassium hydroxide, magnesium hydroxide and calcium hydroxide. A base addition salt may also be formed using an organic base selected from the group consisting of L-arginine, choline, L-lysine, t-butylamine, ethylenediamine, ammonia, dimethylaminoethanol, N-methylglucamine, tromethamine and hydroxyethylmorpholine.

Therefore, in one embodiment there is provided a compound of Formula (I) or a pharmaceutically acceptable salt thereof, where the pharmaceutically acceptable salt is a hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, trifluoroacetic acid, citric acid, maleic acid, oxalic acid, acetic acid, formic acid, benzoic acid, fumaric acid, succinic acid, tartaric acid, lactic acid, pyruvic acid, methanesulfonic acid, benzenesulfonic acid or *para*-toluenesulfonic acid salt.

Therefore, in another embodiment there is provided a compound of Formula (I) or a pharmaceutically acceptable salt thereof, where the pharmaceutically acceptable salt is a lithium salt, sodium salt, potassium salt, magnesium salt, calcium salt, L-arginine salt, choline salt, L-lysine salt, t-butylamine salt, ethylenediamine salt, ammonia salt, dimethylaminoethanol salt, N-methylglucamine salt, tromethamine salt or hydroxyethylmorpholine salt.

Other forms

Compounds and salts described in this specification may exist in solvated forms and unsolvated forms. For example, a solvated form may be a hydrated form, such as a hemihydrate, a monohydrate, a dihydrate, a trihydrate or an alternative quantity thereof. The compounds of

Formula (I) encompass all such solvated and unsolvated forms of compounds of Formula (I), particularly to the extent that such forms possess PCSK9 inhibitory activity, as for example measured using the tests described herein.

Compounds and salts described in this specification include one or more chiral (i.e. asymmetric) centres. To the extent a structure or chemical name in this specification does not indicate the chirality, the structure or name is intended to encompass any single stereoisomer (i.e. any single chiral isomer) corresponding to that structure or name, as well as any mixture of stereoisomers (e.g. a racemate). In some embodiments, a single stereoisomer is obtained by isolating it from a mixture of isomers (e.g. a racemate) using, for example, chiral chromatographic separation. In other embodiments, a single stereoisomer is obtained through direct synthesis from, for example, a chiral starting material.

A particular enantiomer of a compound described herein may be more active than other enantiomers of the same compound.

According to one embodiment there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, which is a single enantiomer being in an enantiomeric excess (%ee) of ≥ 95, ≥ 98% or ≥ 99%. Conveniently, the single enantiomer is present in an enantiomeric excess (%ee) of ≥ 99%.

According to another embodiment there is provided a pharmaceutical composition, which comprises a compound of Formula (I), which is a single enantiomer being in an enantiomeric excess (%ee) of ≥ 95, ≥ 98% or ≥ 99% or a pharmaceutically acceptable salt thereof, in association with one or more pharmaceutically acceptable excipients. Conveniently, the single enantiomer is present in an enantiomeric excess (%ee) of ≥ 99%.

Isotopes

Atoms of the compounds and salts described in this specification may exist as their isotopes. The compound of Formula (I) encompasses all compounds of Formula (I) where an atom is replaced by one or more of its isotopes (for example a compound of Formula (I) where one or more carbon atom is an ^{11}C or ^{13}C carbon isotope, or where one or more hydrogen atoms is a ^{2}H or ^{3}H isotope).

Tautomers

Compounds and salts described in this specification may exist as a mixture of tautomers. “Tautomers” are structural isomers that exist in equilibrium resulting from the migration of a

hydrogen atom. The compound of Formula (I) includes all tautomers of compounds of Formula (I) particularly to the extent that such tautomers possess PCSK9 inhibitory activity.

Therapy, prophylaxis and related terms

The term “therapy” is intended to have its normal meaning of dealing with a disease in order to entirely or partially relieve one, some or all of its symptoms, or to correct or compensate for the underlying pathology. The term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be interpreted in a corresponding manner.

The term “prophylaxis” is intended to have its normal meaning and includes primary prophylaxis to prevent the development of the disease and secondary prophylaxis whereby the disease has already developed and the patient is temporarily or permanently protected against exacerbation or worsening of the disease or the development of new symptoms associated with the disease.

The term “treatment” is used synonymously with “therapy”. Similarly the term “treat” can be regarded as “applying therapy” where “therapy” is as defined herein.

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

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

Pharmaceutical compositions

The compounds of Formula (I), and pharmaceutically acceptable salts thereof, may be administered as pharmaceutical compositions, comprising one or more pharmaceutically acceptable excipients.

Therefore, in one embodiment there is provided a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

The excipient(s) selected for inclusion in a particular composition will depend on factors such as the mode of administration and the form of the composition provided. Suitable pharmaceutically acceptable excipients are well known to persons skilled in the art and are described, for example, in the *Handbook of Pharmaceutical Excipients*, Sixth edition, Pharmaceutical Press, edited by Rowe, Ray C; Sheskey, Paul J; Quinn, Marian. Pharmaceutically acceptable excipients may function as, for example, adjuvants, diluents, carriers, stabilisers, flavourings, colorants, fillers, binders, disintegrants, lubricants, glidants, thickening agents and coating agents. As persons skilled in the art will appreciate, certain pharmaceutically acceptable excipients may serve more than one function and may serve alternative functions depending on how much of the excipient is present in the composition and what other excipients are present in the composition.

The pharmaceutical compositions may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous or intramuscular dosing), or as a suppository for rectal dosing. The compositions may be obtained by conventional procedures well known in the art. Compositions intended for oral use may contain additional components, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

Suitable daily doses of the compounds disclosed herein, or a pharmaceutically acceptable salt thereof, in therapeutic treatment of humans are about 0.0001-100 mg/kg body weight. Pharmaceutical formulations as described herein may be formulated by methods known to those skilled in the art to provide doses of the active compound in the range of 0.1 mg to 1000 mg. The daily dose will necessarily be varied depending upon the host treated, the particular route of administration, any therapies being co-administered, and the severity of the illness being treated. Accordingly, the practitioner who is treating any particular patient may determine the optimum dosage.

The pharmaceutical compositions described herein comprise compounds of Formula (I), or a pharmaceutically acceptable salt thereof, and are therefore expected to be useful in therapy.

As such, in one embodiment there is provided a pharmaceutical composition for use in therapy, comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

In one embodiment there is provided a pharmaceutical composition for use in the treatment of a disease in which inhibition of PCSK9 is beneficial, comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient. In one embodiment there is provided a pharmaceutical composition for use in the treatment of a cardiovascular disease, comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient. In one embodiment there is provided a pharmaceutical composition for use in the treatment of a cardiovascular disease in which inhibition of PCSK9 is beneficial, comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

Methods of Use

The compounds described herein may be used in a method of therapy. Also provided is a method of treatment, comprising administering to a subject in need of treatment a therapeutically effective amount of a compound of Formula (I). The term “therapeutically effective amount” is an amount sufficient to show benefit to a patient. Such benefit may be at least amelioration of at least one symptom. The actual amount administered, and rate and time-course of administration, will depend on the nature and severity of what is being treated. Prescription of treatment, e.g. decisions on dosage, is within the responsibility of general practitioners and other medical doctors.

A compound may be administered alone or in combination with other treatments, either simultaneously or sequentially dependent upon the condition to be treated.

In one embodiment there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising the compound of Formula (I) for use in therapy. In one embodiment there is provided the use of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising the compound of Formula (I) for the manufacture of a medicament. In another embodiment there is provided a method of treatment comprising administering to a subject the compound of

Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising the compound of Formula (I).

The compounds described herein are PCSK9 inhibitors. The PCSK9 gene was identified using genetic mapping techniques on DNA from subjects with autosomal dominant hypercholesterolemia (Abifadel 2003). The encoded protein is a serine protease that is mostly expressed in the liver, gut, kidney, and nervous system and circulates in plasma. While not wishing to be bound by any particular theory, studies on mutations in the gene indicated that its putative role was in reducing LDLR at the cell surface independently of its catalytic activity (Abifadel 2010). Binding of PCSK9 to the LDLR results in their lysosomal degradation. This enhanced LDLR degradation results in increases in the amount of circulating low-density lipoprotein (LDL). PCSK9 is upregulated by statins, SREBP-1a and SREBP-2, LXR agonist, and insulin, but downregulated by dietary cholesterol, glucagon, ethinylestradiol, chenodeoxycholic acid and the bile acid-activated farnesoid X receptor (FXR) (Maxwell 2003; Persson 2009; Langhi 2008). Since an elevated level of PCSK9 decreases the abundance of LDLR on the cell surface, increasing doses of statins fail to achieve proportional LDL-C lowering results. Thus, disclosed herein are methods for treating a wide range of cardiovascular diseases and conditions that benefit from inhibiting PCSK9 thereby lowering LDL-C.

In certain embodiments, the method of inhibiting PCSK9 occurs in a subject in need thereof, thereby treating a disease or disorder mediated by PCSK9. Also, disclosed herein are methods of treating or preventing a disease or a disorder mediated by PCSK9 comprising administering a compound of Formula (I) or a pharmaceutically acceptable salt thereof. In certain embodiments, disclosed herein are methods of treating a disease or a disorder mediated by PCSK9 comprising administering a compound of Formula (I) or a pharmaceutically acceptable salt thereof. In certain embodiments, disclosed herein are methods of preventing a disease or a disorder mediated by PCSK9 comprising administering a compound of Formula (I) or a pharmaceutically acceptable salt thereof. The prevention of cardiovascular events through the inhibition of PCSK9 has been described, e.g., in Robinson 2015.

In some embodiments there is provided a method of treating a cardiovascular disease comprising administering to a subject a compound of Formula (I), or a pharmaceutical composition comprising a compound of Formula (I). In some embodiments there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula (I) for use in the treatment of a cardiovascular disease. In some embodiments there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a

compound of Formula (I) for the manufacture of a medicament for the treatment of a cardiovascular disease.

Exemplary cardiovascular diseases and conditions include, but are not limited to, dyslipidemia, hypercholesterolemia, hypertriglyceridemia, hyperlipidemia, hypoalphalipoproteinemia, metabolic syndrome, diabetic complications, atherosclerosis, stroke, vascular dementia, chronic kidney disease, coronary heart disease, coronary artery disease, retinopathy, inflammation, thrombosis, peripheral vascular disease, heart failure or congestive heart failure. In certain embodiments, exemplary cardiovascular diseases and conditions include, but are not limited to, hypercholesterolemia, hyperlipidemia, hyperlipoproteinemia, hypertriglyceridemia, dyslipidemia, dyslipoproteinemia, atherosclerosis, hepatic steatosis, metabolic syndrome and coronary artery disease. In certain embodiments, the disease is hypercholesterolemia, such as familial hypercholesterolemia or autosomal dominant hypercholesterolemia. In certain embodiments, the disease is hyperlipidemia. In certain embodiments, the disease is coronary artery disease.

In certain embodiments, the disclosed methods of treatment can decrease high levels of circulating serum cholesterol, such as LDL-C and VLDL-Cholesterol. In addition, the disclosed methods are useful for decreasing circulating serum triglycerides, circulating serum lipoprotein A, circulating serum LDL-C and atherogenic lipoproteins. In certain embodiments, the diseases or conditions treated with the disclosed compounds and compositions include atherosclerosis and atherosclerotic plaque formation. Subjects having a gain-of-function mutation in the PCSK9 gene also benefit with treatment with the disclosed compounds and compositions counteracting the mutation through their inhibition of PCSK9.

In some embodiments there is provided a method of treating a kidney disease comprising administering to a subject a compound of Formula (I), or a pharmaceutical composition comprising a compound of Formula (I). In some embodiments there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula (I) for use in the treatment of a kidney disease. In some embodiments there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula (I) for the manufacture of a medicament for the treatment of a kidney disease. In some embodiments the kidney disease is a chronic kidney disease.

Combination treatments

Disclosed compounds and compositions may be conjointly administered with other therapeutic agents, such as other agents suitable for the treatment of high levels of LDL-C and triglycerides. In certain embodiments, conjointly administering one or more additional therapeutic agents with

a compound described herein provides a synergistic effect. In certain embodiments, conjointly administering one or more additional therapeutic agents provides an additive effect.

In some embodiments in which a combination therapy is used, the amount of the compound or salt described in this specification and the amount of the other pharmaceutically active agent(s) are, when combined, therapeutically effective to treat a targeted disorder in the animal patient. In this context, the combined amounts are "therapeutically effective amounts" if they are, when combined, sufficient to reduce or completely alleviate symptoms or other detrimental effects of the disorder; cure the disorder; reverse, completely stop, or slow the progress of the disorder; or reduce the risk of the disorder getting worse. Typically, such amounts may be determined by one skilled in the art by, for example, starting with the dosage range described in this specification for the compound or salt and an approved or otherwise published dosage range(s) of the other pharmaceutically active compound(s).

A pharmaceutical composition of the specification may comprise one or more further active ingredients, as appropriate, examples of combinations of a compound of the specification (or a pharmaceutically acceptable salt thereof) and one or more additional active ingredients are described herein.

The specification further relates to a combination therapy wherein a compound of the specification, or a pharmaceutically acceptable salt thereof, and a second active ingredient are administered concurrently, sequentially or in admixture, for the treatment of one or more of the conditions listed above. Such a combination may be used in combination with one or more further active ingredients.

In one aspect there is provided a combination (for example, for use as a medicament for the treatment of one of the diseases or conditions listed herein, such as a cardiovascular disease) comprising a compound of the specification, or a pharmaceutically acceptable salt thereof, and at least one active ingredient selected from:

i) a statin;
ii) a cholesterol absorption inhibitor;
iii) a SGLT2 inhibitor;
iv) a P2Y12 inhibitor;
v) an ATP-citrate lyase inhibitor; and
vi) anti-hypertensive drugs.

In a further aspect of the present specification there is provided a pharmaceutical composition (for example, for use as a medicament for the treatment of one of the diseases or conditions listed herein, such as a cardiovascular disease) comprising a compound of the specification, or a pharmaceutically acceptable salt thereof, and at least one active ingredient selected from:

i) a statin;
ii) a cholesterol absorption inhibitor;
iii) a SGLT2 inhibitor;
iv) a P2Y12 inhibitor;
v) an ATP-citrate lyase inhibitor; and
vi) anti-hypertensive drugs.

In another embodiment there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and at least one additional active ingredient selected from a statin, wherein the statin is selected from Atorvastatin, Fluvastatin, Lovastatin, Mevastatin, Pitavastatin, Pravastatin, Rosuvastatin and Simvastatin. In another aspect the statin is Rosuvastatin (Crestor).

In another embodiment there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and at least one additional active ingredient selected from a cholesterol absorption inhibitor, wherein the cholesterol absorption inhibitor is selected from Ezetimibe (Ezetrol).

In another embodiment there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and at least one additional active ingredient selected from a SGLT2 inhibitor, wherein the SGLT2 inhibitor is selected from Canagliflozin, Dapagliflozin, Empagliflozin, Ertugliflozin, Ipragliflozin, Luseogliflozin, Remogliflozin etabonate, Sergliflozin etabonate, Sotagliflozin or Tofogliflozin. In some aspects the SGLT2 inhibitor is selected from Dapagliflozin (Farxiga or Forxiga).

In another embodiment there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and at least one additional active ingredient selected from a P2Y12 inhibitor, wherein the P2Y12 inhibitor is selected from Brilinta (Ticagrelor) and Clopidogrel (Plavix).

In another embodiment there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and at least one additional active ingredient selected from an ATP-citrate lyase inhibitor, wherein the ATP-citrate lyase inhibitor is Bempedoic acid (Nexletol).

In another embodiment there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and at least one additional active ingredient selected from Ezetimibe, Rosuvastatin, Dapagliflozin and Ticagrelor. In one embodiment there is one additional active ingredient. In another embodiment there are two additional active ingredients. In one embodiment the additional active ingredient is Ezetimibe, Rosuvastatin, Dapagliflozin or Ticagrelor. In another embodiment the additional two active ingredients are Ezetimibe and Rosuvastatin or Dapagliflozin and Rosuvastatin.

In another embodiment there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and at least one additional active ingredient selected from anti-hypertensive drugs. In some aspects, the antihypertensive drug is selected from Valsartan (Diovan), Metoprolol (Lopressor), HCTZ (Hydrochlorothiazide), Olmesartan (Benicar), Lisinopril (Prinivil, Zestril), Amlodipine besylate (Norvasc), Candesartan, or a calcium channel blocker or a combination thereof. In another aspect there is provided the compound of Formula (I) or a pharmaceutically acceptable salt thereof in combination with:

i) Valsartan;
ii) Metoprolol;
iii) Valsartan and HCTZ;
iv) Olmesartan;
v) Olmesartan and HCTZ;
vi) Lisinopril;
vii) Amlodipine;
viii) Candesartan;
ix) a calcium channel blocker; or
x) HCTZ.

In one embodiment there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and at least one additional active ingredient for use in the simultaneous, separate or sequential treatment of a cardiovascular disease. In one embodiment there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in the treatment of a cardiovascular disease, where the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered simultaneously, separately or sequentially with at least one an additional active substance selected from Ezetimibe, Rosuvastatin, Dapagliflozin and Ticagrelor.

In another embodiment there is provided a method of treating a cardiovascular disease in a subject, which comprises administering to said subject a compound of Formula (I) or a pharmaceutically acceptable salt thereof, and simultaneously, separately or sequentially administering at least one additional active substance, wherein the at least one additional active substance is selected from Ezetimibe, Rosuvastatin, Dapagliflozin and Ticagrelor.

In one embodiment there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof for use in the treatment of a cardiovascular disease in a subject, wherein said treatment comprises the separate, sequential or simultaneous administration of i) said compound of Formula (I) or a pharmaceutically acceptable salt thereof, and ii) at least one additional active ingredient to said subject.

In one embodiment there is provided a method of treatment of a cardiovascular disease, comprising administering to a subject in need thereof, a first amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof and a second amount of at least one additional active ingredient, wherein the first amount and the second amount together comprise a therapeutically effective amount.

In one embodiment there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of a cardiovascular disease wherein said treatment comprises the separate, sequential or simultaneous administration of i) said medicament comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof and ii) at least one additional active ingredient to said subject.

In the above embodiments, the at least one additional active ingredient may be selected from (a) a statin or pharmaceutically acceptable salt thereof, (b) ezetimibe or a pharmaceutically acceptable salt thereof, and/or (c) bempedoic acid or a pharmaceutically acceptable salt thereof.

Thus, in some embodiments the at least one additional active ingredient is a statin or pharmaceutically acceptable salt thereof. In some embodiments the at least one additional active ingredient is ezetimibe or a pharmaceutically acceptable salt thereof. In some embodiments the at least one additional active ingredient is bempedoic acid or a pharmaceutically acceptable salt thereof. In some embodiments the at least one additional active ingredient is a statin or pharmaceutically acceptable salt thereof and ezetimibe or a pharmaceutically acceptable salt thereof.

Statins

Statins include atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, velostatin, compactin, dihydrocompactin, dalvastatin, fluindostatin, rosuvastatin, and simvastatin; and pharmaceutically acceptable salts thereof.

US4231938 discloses certain compounds isolated after cultivation of a microorganism belonging to the genus Aspergillus, such as lovastatin. Also, US4444784 discloses synthetic derivatives of the aforementioned compounds, such as simvastatin. Also, US4739073 discloses certain substituted indoles, such as fluvastatin. Also, US4346227 discloses ML-236B derivatives, such as pravastatin. Also, EP0491226A and US5502199 disclose certain pyridyldihydroxyheptenoic acids, such as cerivastatin. In addition, US5273995 discloses certain 6-[2-(substituted-pyrrol-1-yl)alkyl]pyran-2-ones such as atorvastatin and any pharmaceutically acceptable form thereof (i.e. LIPITOR®). Atorvastatin calcium (i.e., atorvastatin hemicalcium), disclosed in US5273995 is currently sold as Lipitor®. US RE37,314 E discloses rosuvastatin and rosuvastatin calcium. EP0304063 and US5011930 disclose pitivastatin. US3983140 discloses mevastatin. US4448784 and US4450171 disclose velostatin. US4804770 discloses compactin. EP0738510A2 discloses dalvastatin. EP0363934A1 discloses fluindostatin. US4450171 discloses dihydrocompactin.

In some embodiments, the statin is selected from atorvastatin, rosuvastatin, lovastatin, pravastatin, simvastatin and fluvastatin; and pharmaceutically acceptable salts thereof.

In some embodiments, the statin is rosuvastatin or a pharmaceutically acceptable salt thereof. In some of these embodiments, the statin is rosuvastatin or rosuvastatin calcium.

<u>Dosing levels</u>

In some embodiments, the statin dosing regimen is a moderate-intensity dosing according to the ACC (American College of Cardiology)/AHA (American Heart Association) (Grundy 2018).

This moderate-intensity dosing may be:

	Dosing regimen
Atorvastatin	10 to 20 mg once daily
Fluvastatin	40 mg twice daily; or 80 mg once daily
Lovastatin	40 to 80 mg once daily
Pitavastatin	1 to 4 mg once daily
Pravastatin	40 to 80 mg once daily

Rosuvastatin	5 to 10 mg once daily
Simvastatin	20 to 40 mg once daily

The rosuvastatin may be dosed as rosuvastatin calcium, where the dose given is calculated as rosuvastatin in its free form.

The atorvastatin may be dosed as atorvastatin calcium or atorvastatin calcium trihydrate, where the dose given is calculated as atorvastatin in its free form.

The pravastatin may be dosed as pravastatin calcium, where the dose given is calculated as pravastatin in its free form.

The pitavastatin may be dosed as pitavastatin calcium, where the dose given is calculated as pitavastatin in its free form.

In some embodiments, the statin dosing regimen is a high-intensity dosing according to the ACC (American College of Cardiology)/AHA (American Heart Association) (Grundy 2018).

This high-intensity dosing may be:

	Dosing regimen
Atorvastatin	40 to 80 mg once daily
Rosuvastatin	20 to 40 mg once daily

As above, the rosuvastatin may be dosed as rosuvastatin calcium, where the dose given is calculated as rosuvastatin in its free form.

As above, the atorvastatin may be dosed as atorvastatin calcium or atorvastatin calcium trihydrate, where the dose given is calculated as atorvastatin in its free form.

In some embodiments, the statin dosing regimen is one appropriate to patients from, for example, Japan:

	Dosing regimen
Atorvastatin	10 to 40 mg once daily
Fluvastatin	60 mg once daily
Pitavastatin	1 to 4 mg once daily
Rosuvastatin	2.5 to 20 mg once daily
Simvastatin	10 to 20 mg once daily

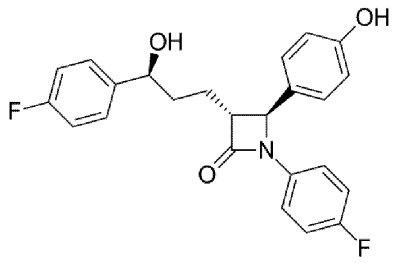
As above, the rosuvastatin may be dosed as rosuvastatin calcium, where the dose given is calculated as rosuvastatin in its free form.

As above, the atorvastatin may be dosed as atorvastatin calcium or atorvastatin calcium trihydrate, where the dose given is calculated as atorvastatin in its free form.

As above, the pitavastatin may be dosed as pitavastatin calcium, where the dose given is calculated as pitavastatin in its free form.

Ezetimibe

Ezetimibe refers to a compound with the chemical name (3*R*,4*S*)-1-(4-fluorophenyl)-3-[(3*S*)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)azetidin-2-one and the structure shown below:



Ezetimibe inhibits the absorption of cholesterol from the small intestine and decreases the amount of cholesterol normally available to liver cells. The lower levels of cholesterol in the liver cells leads them to absorb more cholesterol from circulation and thus lowering the levels of circulating cholesterol. It blocks the critical mediator of cholesterol absorption, the Niemann-Pick C1-like 1 (NPC1L1) protein on the gastrointestinal tract epithelial cells, as well as in hepatocytes; it blocks aminopeptidase N and interrupts a caveolin 1-annexin A2 complex involved in trafficking cholesterol (Phan 2012).

Awad 2018 reported that ezetimibe reduces plasma LDL-C levels by up to 20% when used alone, and that it lowered plasma levels of lipoprotein(a) by about 7%.

In some embodiments, ezetimibe is administered in a dose of 5 to 15 mg per day. The daily dose may be up to 10 mg, 11 mg, 12 mg, 13 mg, 14 mg or 15 mg. The daily dose may be at least 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, or 10 mg.

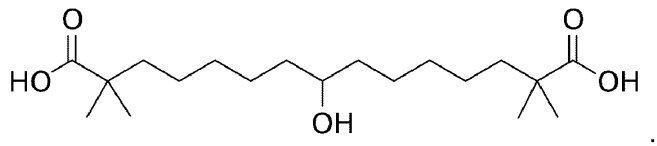
In some embodiments, ezetimibe is administered in a dose of 10 mg per day.

In some embodiments, ezetimibe is administered as a free base, i.e. not in salt form.

In some embodiments, ezetimibe is administered as a pharmaceutically acceptable salt thereof, where the dosage is that of ezetimibe not in a salt form. Unless otherwise stated, any reference in this disclosure to an amount of ezetimibe, or pharmaceutically acceptable salt thereof, is based on the ezetimibe free base equivalent weight. For example, "wt%" refers to weight % based on ezetimibe free base equivalent weight.

Bempedoic acid

Bempedoic acid refers to a compound also known as 8-hydroxy-2,2,14,14-tetramethylpentadecanedioic acid and the structure shown below:



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Bempedoic acid targets the cholesterol biosynthesis pathway in the liver. Bempedoic acid inhibits ATP-citrate lyase (ACL), two steps upstream of HMG CoA reductase. Bempedoic acid is converted to active coenzyme A form by enzymes found only in the liver and not in muscles (Agarwala and Goldberg 2020)

Bempedoic acid has been approved for use in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or, alone or in combination with other lipid-lowering therapies in patients who are statin intolerant, or for whom a statin is contraindicated.

In some embodiments, bempedoic acid is administered in a dose of 150 to 200 mg per day. The daily dose may be up to 180 mg, 185 mg, 190 mg, 195 mg, or 200 mg. The daily dose may be at least 150 mg, 155 mg, 160 mg, 165 mg, 170 mg, 175 mg or 180 mg.

In some embodiments, bempedoic acid is administered in a dose of 180 mg per day.

In some embodiments, bempedoic acid is administered as a free acid, i.e. not in salt form.

In some embodiments, bempedoic acid is administered as a pharmaceutically acceptable salt thereof, where the dosage is that of bempedoic acid not in a salt form. Unless otherwise stated, any reference in this disclosure to an amount of bempedoic acid, or pharmaceutically

acceptable salt thereof, is based on the bempedoic acid free acid equivalent weight. For example, “wt%” refers to weight % based on bempedoic acid free acid equivalent weight.

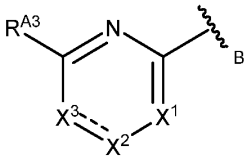
Salts of bempedoic acid are described in WO 2020/257573.

Further Embodiments

The following embodiments may apply to all aspects as described above or may relate to a single aspect. The embodiments may be combined together in any combination.

(A1a)

In some embodiments, A is (A1a).



(A1a)

In some embodiments X^1 is N or C-R^{A1}.

In some embodiments X^2 is N or C-R^{A4}.

In some embodiments X^3 is N-(C_{1-6} hydrocarbon) or C-R^{A2}.

In some embodiments of formula A1a, at least one of X^1, X^2 and X^3 is N.

In some embodiments of formula A1a, X^1 is N, X^2 is N and X^3 is C-R^{A2}.

In some embodiments of formula A1a, X^1 is N, X^2 is C-R^{A4} and X^3 is C-R^{A2}.

In some embodiments of formula A1a, X^1 is C-R^{A1}, X^2 is N and X^3 is C-R^{A2}.

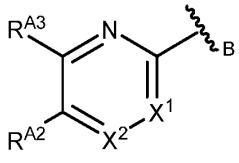
In some embodiments of formula A1a, X^1 is C-R^{A1}, X^2 is C-R^{A4} and X^3 is C-R^{A2}.

In some embodiments of formula A1a, X^1 is C-R^{A1}, X^2 is C-R^{A4}, and X^3 is N-(C_{1-6} hydrocarbon).

In some embodiments of formula A1a, X^1 is N, X^2 is C-R^{A4}, and X^3 is N-(C_{1-6} hydrocarbon).

In some embodiments, X^2 is C-R^{A4}.

In some embodiments A is of formula (A1):



(A1).

R^{A1}

In some embodiments R^{A1} is selected from the group consisting of:
(i) H
(ii) halo;
(iii) CN;
(iv) C_{1-6} hydrocarbon, optionally substituted by one or more OH, CN, C_{1-6} alkyl acyl, C_{1-6} alkoxy or one or more halo groups;
(v) C_{1-6} alkoxy, optionally substituted by OH, one or more halo groups, C_{1-6} alkyl amido;
(vi) C_{1-6} alkyl ester;
(vii) C_{1-6} alkyl acyl; and
(viii) OH.

In some embodiments R^{A1} is selected from the group consisting of:
(i) H
(ii) halo;
(iii) CN;
(iv) C_{1-6} hydrocarbon, optionally substituted by one or more OH, CN, C_{1-6} alkyl acyl, C_{1-6} alkoxy or one or more halo groups; and
(v) C_{1-6} alkoxy, optionally substituted by OH, halo or C_{1-6} alkyl amido.

In some embodiments R^{A1} is selected from the group consisting of:
(i) H
(ii) halo;
(iii) CN;
(iv) C_{1-6} hydrocarbon, optionally substituted by one or more OH, CN, C_{1-6} alkyl acyl, C_{1-6} alkoxy or one or more halo groups;
(v) C_{1-6} alkoxy, optionally substituted by OH, one or more halo groups or C_{1-6} alkyl amido; and
(vi) OH.

When R^{A1} is an optionally substituted C_{1-6} hydrocarbon it is an optionally substituted C_{1-6} alkyl. In some embodiments it is optionally substituted methyl or optionally substituted ethyl. In further embodiments, it is optionally substituted methyl. In further embodiments, it is unsubstituted methyl.

When R^{A1} is optionally substituted C_{1-6} alkyl, in some embodiments the optional substituents are selected from OH, CN, or one or more halo groups. In further embodiments the optional substituents are selected from OH, F and Br.

When R^{A1} is optionally substituted C_{1-6} alkoxy, in some embodiments it is optionally substituted OMe or ethoxy. In some embodiments R^{A1} is unsubstituted OMe.

When R^{A1} is optionally substituted C_{1-6} alkoxy, in some embodiments the optional substituents are selected from C_{1-6} alkyl amido or one or more halo groups. In another embodiment the optional substituents are selected from one, two or three F atoms.

When R^{A1} is halo, in some embodiments it is F, Br or Cl. In other embodiments it is Br or Cl.

In some embodiments R^{A1} is H.
In some embodiments R^{A1} is OH.
In some embodiments R^{A1} is CN.
In some embodiments R^{A1} is methyl.
In some embodiments R^{A1} is $-OCF_2H$.

In some embodiments R^{A1} is selected from H, Br, Cl, CN, OMe, ethoxy, methyl or ethyl. In further embodiments R^{A1} is selected from H, $-OCF_2H$, Br and Cl. In further embodiments R^{A1} is selected from H, Br or Cl. In other embodiments R^{A1} is H or $-OCF_2H$.

In some embodiments R^{A1} is selected from the group consisting of H, OH, Br, Cl, CN, $-OCF_2H$, OMe, ethoxy, methyl and ethyl. In some embodiments R^{A1} is selected from the group consisting of H, Br, Cl, CN, $-OCF_2H$, OMe, ethoxy, methyl and ethyl. In some embodiments R^{A1} is selected from the group consisting of H, OH, $-OCF_2H$, Br and Cl. In some embodiments R^{A1} is selected from the group consisting of H, $-OCF_2H$, Br and Cl.
In some embodiments R^{A1} is H.

In some embodiments R^{A1} is OH or H.

R^{A2}

In some embodiments R^{A2} is selected from the group consisting of:
(i) H;
(ii) halo;
(iii) CN;
(iv) C_{1-6} hydrocarbon, optionally substituted by OH, CN, C_{1-6} alkyl acyl, C_{1-6} alkoxy or one or more halo groups;
(v) C_{1-6} alkoxy, optionally substituted by OH, alkyl amido, or one or more halo groups;
(vi) C_{1-6} acylamido (where acyl substituent is H or Me);

(vii) C_{1-6} thioalkyl;
(viii) C_{1-6} alkyl ester;
(ix) C_{1-6} alkyl acyl;
(x) C_{4-5} heterocyclyl;
(xi) C_5 heteroaryl;
(xii) C_{1-6} alkyl amido optionally substituted by C_{1-3} alkyl amido, CN, OH, C_{2-3} alkynyl, C_{4-6} heterocyclyl, C_{1-3} alkyl which alkyl is optionally substituted with one or more halo or OH groups;
(xiii) OH; and
(xiv) C_{1-6} alkylamino.

In some embodiments R^{A2} is selected from the group consisting of:
(i) H;
(ii) halo;
(iii) CN;
(iv) C_{1-6} hydrocarbon, optionally substituted by OH, CN, C_{1-6} alkyl acyl, C_{1-6} alkoxy or one or more halo groups;
(v) C_{1-6} alkoxy, optionally substituted by OH, alkyl amido, or one or more halo groups;
(vi) C_{1-6} acylamido (where acyl substituent is H or Me);
(vii) C_{1-6} thioalkyl;
(viii) C_{1-6} alkyl ester;
(ix) C_{1-6} alkyl acyl;
(x) C_{4-5} heterocyclyl;
(xi) C_5 heteroaryl;
(xii) C_{1-6} alkyl amido optionally substituted by C_{1-3} alkyl amido, CN, C_{2-3} alkynyl, C_{4-6} heterocyclyl, C_{1-3} alkyl which alkyl is optionally substituted with one or more halo or OH groups; and
(xiii) OH.

In some embodiments R^{A2} is selected from the group consisting of:
(i) H;
(ii) halo;
(iii) CN;
(iv) C_{1-6} hydrocarbon, optionally substituted by OH, CN, C_{1-6} acyl, C_{1-6} alkoxy or one or more halo groups;
(v) OH;
(vi) C_{1-6} alkoxy, optionally substituted by OH, C_{1-6} alkyl amido, or one or more halo groups;
(vii) C_{1-6} alkyl ester;
(viii) C_{1-6} alkyl acyl;

(ix) C_{1-6} alkyl amido optionally substituted by C_{1-3} alkyl amido, CN, C_{2-3} alkynyl, C_{4-6} heterocyclyl, or C_{1-3} alkyl which alkyl is optionally substituted with one or more halo or OH groups; and
(x) C_{1-6} alkylamino.

In further embodiments R^{A2} is selected from the group consisting of:
(i) H;
(ii) halo;
(iii) CN;
(iv) C_{1-6} hydrocarbon, optionally substituted by OH, CN, C_{1-6} acyl, C_{1-6} alkoxy or one or more halo groups;
(v) OH;
(vi) C_{1-6} alkoxy, optionally substituted by OH, C_{1-6} alkyl amido, or one or more halo groups;
(vii) C_{1-6} alkyl ester;
(viii) C_{1-6} alkyl acyl; and
(ix) C_{1-6} alkyl amido optionally substituted by C_{1-3} alkyl amido, CN, C_{2-3} alkynyl, C_{4-6} heterocyclyl, or C_{1-3} alkyl which alkyl is optionally substituted with one or more halo or OH groups.

In further embodiments R^{A2} is selected from the group consisting of:
(i) H;
(ii) halo;
(iii) CN;
(iv) C_{1-6} hydrocarbon, optionally substituted by OH, CN, C_{1-6} alkyl acyl, C_{1-6} alkoxy or one or more halo groups;
(v) C_{1-6} alkoxy, optionally substituted by OH, C_{1-6} alkyl amido, or one or more halo groups;
(vi) C_{1-6} thioalkyl;
(viii) C_{1-6} alkyl ester; and
(ix) C_{1-6} alkyl amido optionally substituted by C_{1-3} alkyl amido, CN, C_{2-3} alkynyl, C_{4-6} heterocyclyl, or C_{1-3} alkyl which alkyl is optionally substituted with one or more halo or OH groups.

In further embodiments R^{A2} is selected from the group consisting of:
(i) H;
(ii) halo;
(iii) C_{1-6} alkyl ester;
(iv) C_{1-6} hydrocarbon;
(v) C_{1-6} alkyl amido optionally substituted by C_{1-3} alkyl amido, C_{2-3} alkynyl, C_{4-6} heterocyclyl, or C_{1-3} alkyl which alkyl is optionally substituted with one or more halo or OH groups;
(vi) C_{1-6} thioalkyl;

(vii)C_{1-6} alkyl acyl;
(viii) C_5 heteroaryl; or
(ix) C_{1-6} alkylamino.

When R^{A2} is halo, in some embodiments it is Br or Cl. In further embodiments it is Cl.

In some embodiments R^{A2} is selected from CN, Cl, OMe, methyl, cyclopropyl, 1-methylcyclopropyl, $-OCHF_2$, $-OCF_3$ and optionally substituted C_{1-6} alkylamido.

In some embodiments R^{A2} is selected from Cl, methyl, $-CF_3$, cyclopropyl, 1-methylcyclopropyl, $-OCHF_2$ and $-OCF_3$.

In some embodiments R^{A2} is selected from C_{1-6} alkyl ester,

In some embodiments R^{A2} is CN.
In some embodiments R^{A2} is H.
In some embodiments R^{A2} is OH.
In some embodiments R^{A2} is $-C(=O)CH_3$.
In some embodiments R^{A2} is $-OCHF_2$.
In some embodiments R^{A2} is cyclopropyl.
In some embodiments R^{A2} is Cl.
In some embodiments R^{A2} is methyl.
In some embodiments R^{A2} is $-CF_3$.
In some embodiments R^{A2} is S-ethyl.
In some embodiments R^{A2} is a pyrazole.
In some embodiments R^{A2} is $N(CH_3)_2$.
In some embodiments R^{A2} is $C(=O)NH(CH_2C(=O)NH_2$, $C(=O)NHCH_2C{\equiv}CH$, C(=O)NH(oxetane), $C(=O)NH(CH_2CHF_2)$, $C(=O)NH(CH_2CH_3)$, $C(=O)NH_2$, $C(=O)NH(CH_2)$, $C(=O)N(CH_3)_2$, $C(=O)N(CH_3)(CH_2CH_2OH)$, $C(=O)N(CH_3)(CH_2C{\equiv}CH$ or $C(=O)NH(CH_2CH_2OH)$.
In some embodiments R^{A2} is $-S-CH_3$.
In some embodiments R^{A2} is $-S-CH_2CH_3$.
In some embodiments R^{A2} is $-S-CH_2-C(=O)-O-CH_3$.
In some embodiments R^{A2} is $C(=O)NH(CH)_3$.

When R^{A2} is an optionally substituted C_{1-6} hydrocarbon it is an optionally substituted C_{1-6} alkyl. In some embodiments it is optionally substituted methyl, optionally substituted ethyl or optionally

substituted cyclopropyl. In further embodiments, it is optionally substituted methyl. In further embodiments, it is unsubstituted methyl. In other embodiments it is unsubstituted cyclopropyl.

When R^{A2} is optionally substituted C_{1-6} alkyl, in some embodiments the optional substituents are selected from OH, CN, or one or more halo groups. In further embodiments the optional substituents are selected from OH, F and Br.

When R^{A2} is optionally substituted C_{1-6} alkoxy, in some embodiments it is optionally substituted OMe or ethoxy.

When R^{A2} is optionally substituted C_{1-6} alkoxy, in some embodiments the optional substituents are selected from alkyl amido or one or more halo groups. In another embodiment the optional substituents are selected from one or more F. In another embodiment where R^{A2} is optionally substituted C_{1-6} alkoxy it is difluoromethoxy (-$OCHF_2$).

When R^{A2} is C_{1-6} alkyl ester, in some embodiments it is -$C(=O)OCH_2CH_3$.

When R^{A2} is C_{1-6} alkyl amido, in some embodiments the optional substituents are selected from one or more methyl groups, an oxetane ring, a C_2 alkylamido, ethyl which ethyl is optionally substituted by OH or one or more halo groups. In other embodiments when R^{A2} is C_{1-6} alkyl amido it is $C(=O)NHCH_2C(=O)NH_2$, $C(=O)NHCH_2CHCH$, -C(=O)NH-oxetane, $C(=O)NHCH_2CHF_2$, $C(=O)NHCH_2CH_2OH$, $C(=O)NHCH_2CH_3$, $C(=O)NH_2$, $C(=O)NHCH_3$, and $C(=O)N(CH_3)_2$. When R^{A2} is C_{1-6} alkyl amido, in some embodiments the optional substituent is OH.

When R^{A2} is C_{1-6} alkylamino in some embodiments it is $NHCH_3$, $NHCH(CH_3)_2$, $N(CH_2CH_3)_2$, or $N(CH_3)_2$. In some embodiments when R^{A2} is C_{1-6} alkylamino it is $N(CH_3)_2$.

In other embodiments R^{A2} is selected from -$OCHF_2$, Cl, -OMe, methyl, $C(=O)CH_3$, CN, -CH_2OH, H and cyclopropyl. In further embodiments R^{A2} is selected from methyl, -$OCHF_2$, Cl, -CH_2OH, H, CN, -$C(=O)CH_3$ and -OMe.

In further embodiments R^{A2} is selected from methyl, -$OCHF_2$, Cl and cyclopropyl.

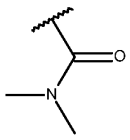
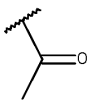
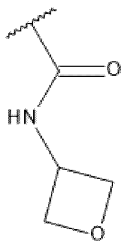
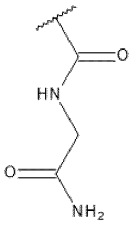
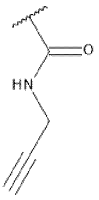
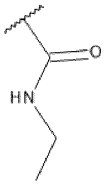
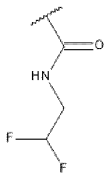
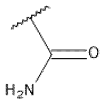
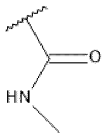
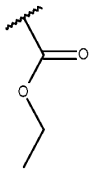
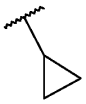
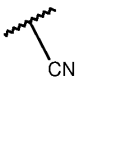
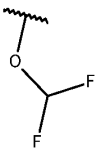
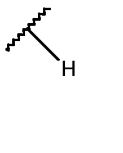
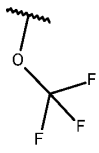
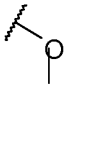
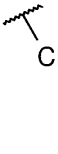
In further embodiments R^{A2} is selected from H, -COOH, -CH_2OH, methyl, CN, cyclopropyl, -$C(=O)CH_3$, -$OCHF_2$, Cl, -$C(=O)OCH_2CH_3$, -$C(=O)NH_2$, -$C(=O)NHCH_3$, -$C(=O)N(CH_3)_2$, -

C(=O)NHCH$_2$C(=O)NH$_2$, -C(=O)NHCH$_2$CHCH, -C(=O)NH-oxetane, -C(=O)NHCH$_2$CHF$_2$, -C(=O)NHCH$_2$CH$_2$OH, and -C(=O)NHCH$_2$CH$_3$.

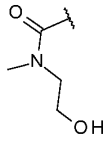
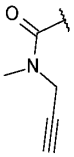
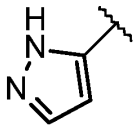
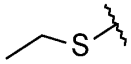
In some embodiments R^{A2} is selected from the group consisting of -CN, methyl, Cl, -C(=O)CH$_3$, -C(=O)OCH$_2$CH$_3$, cyclopropyl, -C(=O)NHCH$_2$C(=O)NH$_2$, -C(=O)NHCH$_2$CHCH, -C(=O)NH-oxetane, -C(=O)NHCH$_2$CHF$_2$, -C(=O)NHCH$_2$CH$_2$OH, -C(=O)NHCH$_2$CH$_3$, -C(=O)NH$_2$, -C(=O)NHCH$_3$, -C(=O)N(CH$_3$)$_2$, -OCHF$_2$, H, -OMe, and -OCF$_3$.

In some embodiments R^{A2} is selected from C(=O)OCH$_2$CH$_3$, cyclopropyl, methyl, C(=O)NH(CH$_2$C(=O)NH$_2$, C(=O)NHCH$_2$C≡CH, C(=O)NH(oxetane), C(=O)NH(CH$_2$CHF$_2$), C(=O)NH(CH$_2$CH$_3$), C(=O)NH$_2$, C(=O)NH(CH$_3$), C(=O)N(CH$_3$)$_2$, H, C(=O)N(CH$_3$)(CH$_2$CH$_2$OH), C(=O)N(CH$_3$)(CH$_2$C≡CH, Cl, N(CH$_3$)$_2$, pyrazole, S-ethyl, C(=O)CH$_3$, and C(=O)NH(CH$_2$CH$_2$OH).

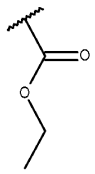
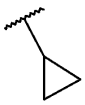
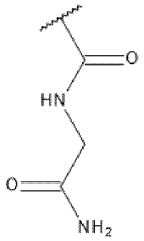
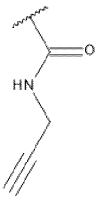
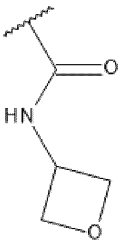
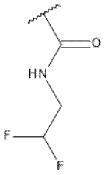
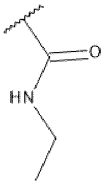
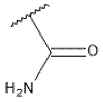
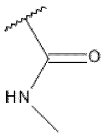
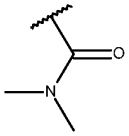
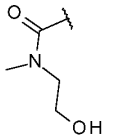
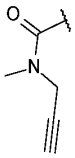
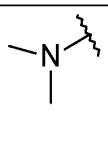
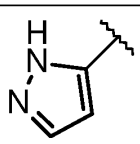
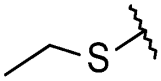
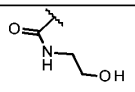
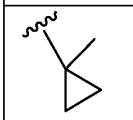
In some embodiments R^{A2} is selected from CN, methyl, Cl, -C(=O)CH$_3$, -C(C=O)OCH$_2$CH$_3$, cyclopropyl, -C(=O)NHCH$_2$C(=O)NH$_2$, -C(=O)NHCH$_2$CHCH, -C(=O)NH-oxetane, -C(=O)NHCH$_2$CHF$_2$, -C(=O)NHCH$_2$CH$_2$OH, -C(=O)NHCH$_2$CH$_3$, -C(=O)NH$_2$, -C(=O)NHCH$_3$, -C(=O)N(CH$_3$)$_2$, -OCHF$_2$, H, -OMe, and -OCF$_3$. These groups are as shown in the table below:

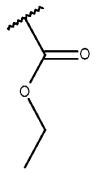
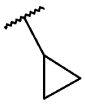
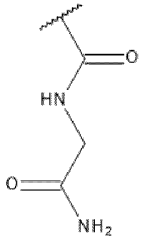
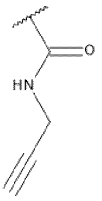
In some embodiments R^{A2} is selected from the following groups:

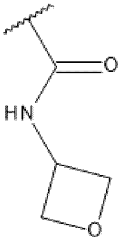
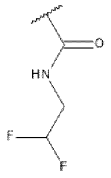
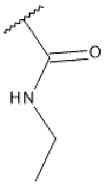
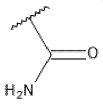
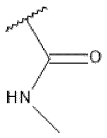
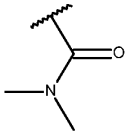
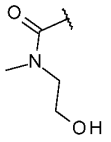
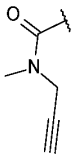
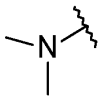
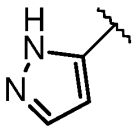
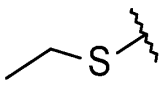
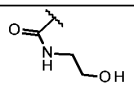
				

In some embodiments R^{A2} is selected from the following groups:

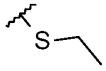
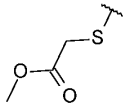
				
				
				
				
				

In some embodiments R^{A2} is selected from the following groups:

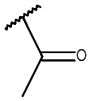
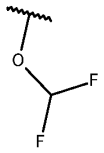
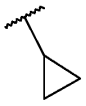
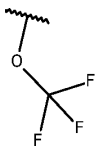
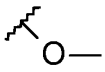
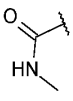
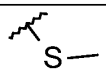
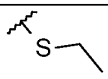
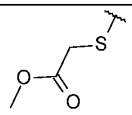
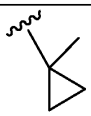
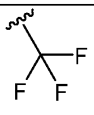
				

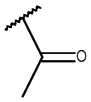
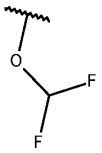
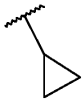
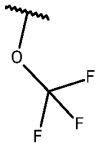
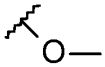
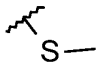
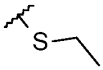
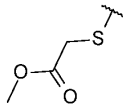
In some embodiments R^{A2} is selected from the following groups:

In some embodiments R^{A2} is selected from the following groups:

In some embodiments R^{A2} is selected from the following groups:

In some embodiments R^{A2} is selected from halo, C_{1-6} hydrocarbon and C_{1-6} alkoxy optionally substituted by one or more halo.

In some embodiments R^{A2} is selected from chloro, bromo, C_{1-6} alkyl, C_{3-6} cycloalkyl and C_{1-6} alkoxy optionally substituted by one, two or three halo.

In some embodiments R^{A2} is selected from chloro, methyl, $-CF_3$, cyclopropyl and $-OCF_2H$.

R^{A3}

In some embodiments R^{A3} is selected from the group consisting of:

(i) H;

(ii) halo;

(iii) CN;

(iv) C_{1-6} hydrocarbon optionally substituted by OH, CN, C_{1-6} thioalkyl, C_{1-6} alkoxy, C_{1-6} alkyl acyl, C_{1-6} acyloxy, carboxy, C_{1-6} alkyl ester, C_{1-6} alkylamino, $-C(=O)NH_2$, C_{1-6} alkyl amido, C_{1-6} alkyl acylamido, C_{1-6} alkyl sulfinyl, C_{1-6} alkyl sulfonyl or one or more halo groups;

(v) OH;

(vi) C_{1-6} alkoxy, optionally substituted by OH, NH_2, C_4 heterocyclyl or one or more halo groups;

(vii) C_{1-6} acyloxy;

(viii) C_4 heterocycyl;

(ix) $-NH_2$;

(x) C_{1-6} alkylamino, optionally substituted by CN, OH or C_4 heterocyclyl;

(xi) C_{1-6} dialkylamino, optionally substituted by $-NH_2$;

(xii) C_{1-6} acylamido (where acyl substituent is H or Me);

(xiii) carbaimidoyl or methyl-carbaimidoyl;
(xiv) carboxyamino;
(xv) C_{1-6} thioalkyl, optionally substituted by OH or NH_2;
(xvi) C_{1-6} alkyl sulfinyl;
(xvi) C_{1-6} alkyl sulfonyl, optionally substituted by one or more halo groups;
(xvii) C_{1-6} sulfonimodyl;
(xviii) C_{1-6} alkyl phosphinyl;
(xix) carboxy;
(xx) $C(=O)NH_2$;
(xxi) C_{1-6} alkyl ester;
(xxii) C_{1-6} alkyl acyl, optionally substituted by one or more halo groups; and
(xxiii) C_{1-6} alkyl amido.

In some embodiments R^{A3} is selected from the group consisting of:
(i) H;
(ii) halo;
(iii) CN;
(iv) C_{1-6} hydrocarbon, optionally substituted by OH, CN, C_{1-6} thioalkyl, C_{1-6} alkoxy, C_{1-6} alkyl acyl C_{1-6} acyloxy, carboxy, C_{1-6} alkyl ester, C_{1-6} alkylamino; $-C(=O)NH_2$, C_{1-6} alkyl amido, C_{1-6} alkylacylamido, C_{1-6} alkyl sulfinyl, C_{1-6} alkyl sulfonyl or one or more halo groups;
(v) OH; and
(vi) C_{1-6} alkoxy, optionally substituted by OH, NH_2, C_4 heterocyclyl or one or more halo groups.

In some embodiments R^{A3} is selected from the group consisting of:
(i) H;
(ii) halo;
(iii) CN;
(iv) C_{1-6} hydrocarbon, optionally substituted by OH, CN, C_{1-6} thioalkyl, C_{1-6} alkoxy, C_{1-6} alkylacyl, C_{1-6} acyloxy, carboxy, C_{1-6} alkyl ester, C_{1-6} alkylamino; $-C(=O)NH_2$, C_{1-6} alkyl amido, C_{1-6} alkylacylamido, C_{1-6} alkyl sulfinyl, C_{1-6} alkyl sulfonyl or one or more halo groups;
(v) OH;
(vi) C_{1-6} alkoxy, optionally substituted by OH, NH_2, C_4 heterocyclyl or one or more halo groups.

Where R^{A3} is halo, in some embodiments it is Br or Cl. In some embodiments it is Cl. In further embodiments R^{A3} is Br.

Where R^{A3} is an optionally substituted C_{1-6} hydrocarbon it is an optionally substituted C_{1-6} alkyl. In some embodiments it is optionally substituted methyl or optionally substituted ethyl. In further embodiments, it is optionally substituted methyl. In further embodiments, it is unsubstituted methyl.

When R^{A3} is optionally substituted C_{1-6} alkyl, in some embodiments the optionally substituents are selected from OH, CN, or one or more halo groups. In further embodiments the optional substituents are selected from OH, F and Br.

In some embodiments R^{A3} is OH.

When R^{A3} is optionally substituted C_{1-6} alkoxy, in some embodiments it is optionally substituted OMe or ethoxy. In further embodiments it is OMe.

When R^{A3} is optionally substituted C_{1-6} alkoxy, in some embodiments the optional substituents are selected from alkyl amido or one or more halo groups. In another embodiment the optional substituents are selected from one or more F.

In some embodiments R^{A3} is selected from H, CF_3, CN, C_{1-2} alkyl, NH_2 and halo. In other embodiments R^{A3} is selected from H, methyl, CN and Cl.

In some embodiments R^{A3} is selected from H, OMe, CF_3, CN, C_{1-2} alkyl, NH_2 and halo.

In some embodiments R^{A3} is CN.
In some embodiments R^{A3} is H.
In some embodiments R^{A3} is methyl.
In some embodiments R^{A3} is OMe.
In some embodiments R^{A3} is selected from methyl, H and CN.
In some embodiments R^{A3} is selected from H, methyl or OH.

R^{A2} and R^{A3}

When R^{A3} and R^{A2} together with the carbon atoms to which they are bound form an optionally substituted C_6 carboaromatic ring or C_{5-7} heteroaromatic ring they form an optionally substituted benzene ring or an optionally substituted pyridine ring.

When R^{A3} and R^{A2} together with the carbon atoms to which they are bound form an optionally substituted C_6 carboaromatic ring or C_{5-7} heteroaromatic ring the optional substituents are

selected from NH_2, C_{1-6} alkyl, C_{1-6} alkoxy and halo. In other embodiments the optional substituents are selected from methyl, ethyl, OMe, NH_2, F, Cl and Br. In other embodiments the optional substituents are selected from methyl, NH_2, Cl, F and OMe. In other embodiments the optional substituent is methyl.

In one embodiment when R^{A2} and R^{A3} together with the carbon atoms to which they are bound form an optionally substituted C_{5-7} heteroaromatic ring, they form an optionally substituted pyridine. In some embodiments the optional substituent is NH_2. In another embodiment R^{A2} and R^{A3} together with the carbon atoms to which they are bound form an unsubstituted pyridine. In another embodiment R^{A2} and R^{A3} together form an optionally substituted pyrazole, an optionally substituted pyrrole or an optionally substituted thiazole. In some embodiments the optional substituent is methyl.

When R^{A3} and R^{A2} together with the carbon atoms to which they are bound form an optionally substituted C_{5-7} heteroaromatic ring, the optional substituents are selected from C_{1-6} alkyl, C_{1-6} alkoxy, NH_2 and halo. In other embodiments the optional substituents are selected from methyl, ethyl, OMe, ethoxy, NH_2 and halo. In other embodiments the optional substituents are selected from NH_2 and methyl.

When R^{A3} and R^{A2} together with the carbon atoms to which they are bound form an optionally substituted C_{5-7} heterocycle ring, they form a 5 membered ring which comprises one or two atoms selected from N, O and S. In some embodiments the 5 membered ring contains one N and one S. In other embodiments the 5 membered ring contains one N. In other embodiments the 5 membered ring contains one N and one O. In other embodiments the 5 membered ring contains two Ns. In some embodiments R^{A3} and R^{A2} together with the carbon atoms to which they are bound form an optionally substituted pyrrole or pyrazole.

When R^{A3} and R^{A2} together with the carbon atoms to which they are bound form an optionally substituted C_{5-7} heterocycle ring, the optional substituents are selected from NH_2, C_{1-6} alkyl, C_{1-6} alkoxy and halo. In other embodiments the optional substituents are selected from methyl, ethyl, OMe, ethoxy, NH_2, F, Cl and Br. In other embodiments the optional substituent is methyl.

In other embodiments R^{A2} and R^{A3} together with the carbon atoms to which they are bound form:

(i) optionally substituted C_6 heteroaromatic ring; wherein the optional substituent is NH_2;

(ii) optionally substituted C_6 carboaromatic ring; wherein the optional substituent is F, OMe, Cl;

(iii) optionally substituted C_5 heteroaromatic or C_5 heterocycle ring wherein the optional substituent is methyl.

In some embodiments R^{A3} and R^{A2} together with the carbon atoms to which they are bound form an optionally substituted C_6 carboaromatic ring or C_{5-7} heteroaromatic ring wherein the optional substituents are selected from C_{1-6} alkyl, and halo.

In some embodiments R^{A2} and R^{A3} together form an unsubstituted 2-pyrazole, a 2-pyrrole substituted by methyl, a pyridine optionally substituted by NH_2, or a phenyl optionally substituted by Cl, F or OMe.

R^{A4}

R^{A4} is selected from the group consisting of:

(i) H;

(ii) halo;

(iii) CN;

(iv) C_{1-6} hydrocarbon, optionally substituted by one or more OH, CN, C_{1-6} alkyl acyl, C_{1-6} alkoxy or one or more halo groups;

(v) C_{1-6} alkoxy, optionally substituted by OH, one or more halo groups, C_{1-6} alkyl amido;

(vi) C_{1-6} alkyl ester;

(vii) C_{1-6} alkyl acyl;

(viii) OH; and

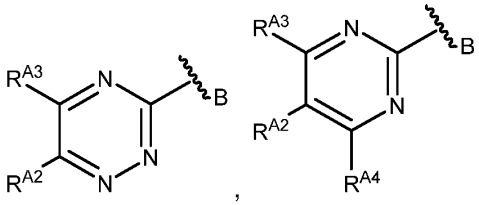
(ix) oxo;

X^3 is N-(C_{1-6} hydrocarbon)

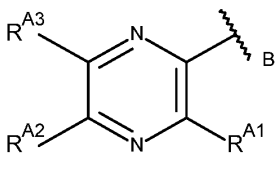
In some embodiments, when X^3 is N-(C_{1-6} hydrocarbon), X^1 is C-R^{A1} and X^2 is C=O. In some of these embodiments, R^{A1} and R^{A3} are H.

In some embodiments, when X^3 is N-(C_{1-6} hydrocarbon), the C_{1-6} hydrocarbon group is methyl or ethyl. In some of these embodiments, it is methyl, i.e. X^3 is N-Me.

In some embodiments, A is selected from one of the following formulae:

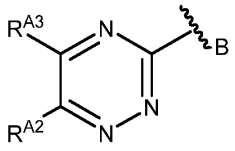


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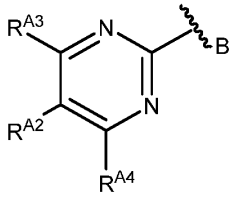
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In some embodiments, A is of the following formula:



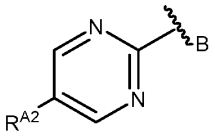
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In some embodiments, A is of the following formula:

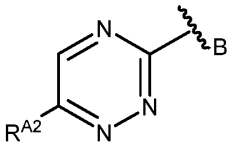


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In some embodiments, A is selected from one of the following formulae:

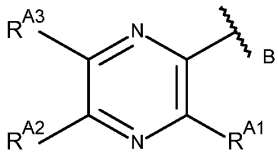


, and



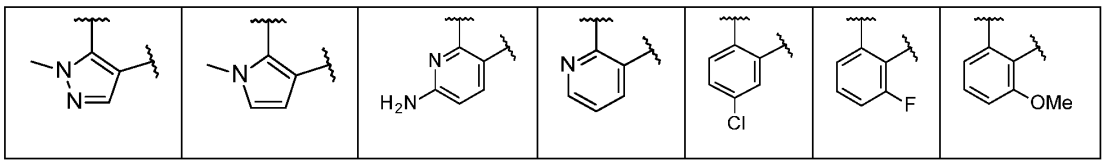
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In some embodiments, A is of the following formula:

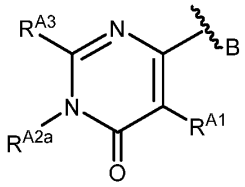


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In some embodiments R^{A2} and R^{A3} together form a ring selected from:



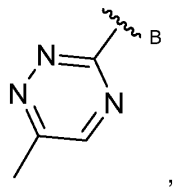
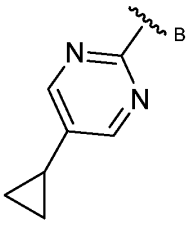
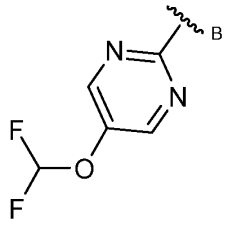
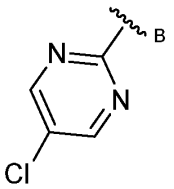
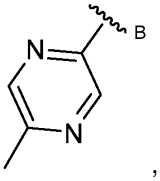
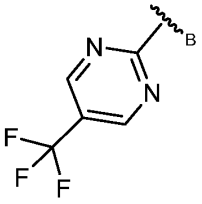
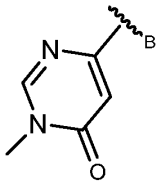
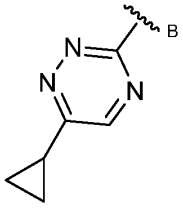
In some embodiments, A is of the following formula:



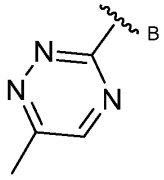
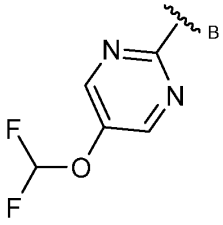
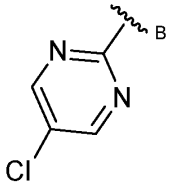
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where R^{A2a} is C_{1-6} hydrocarbon, and R^{A1} and R^{A3} are as defined in any other embodiment herein. In some embodiments R^{A2a} is methyl.

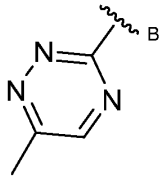
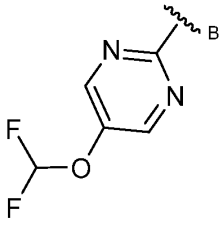
In some embodiments A is selected from one of the following formulae:


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In some embodiments, A is selected from one of the following formulae:


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In some embodiments, A is selected from one of the following formulae:

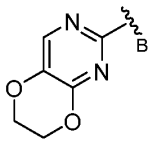
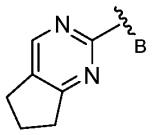

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In some embodiments, where the pyridine group of C is substituted by a monocyclic moiety, then the A group is also monocyclic.

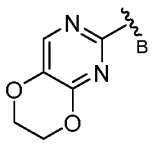
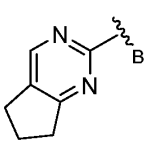
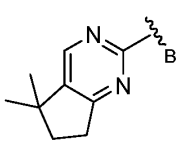
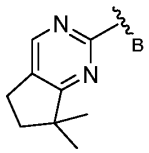
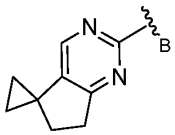
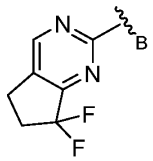
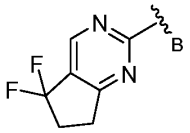
In some embodiments A does not comprise a bicyclic moiety, optionally only when the pyridine group of C is substituted by a monocyclic moiety.

In some embodiments A does not comprise a bicyclic pyrimidine moiety, optionally only when the pyridine group of C is substituted by a monocyclic moiety.

In some embodiments A is not selected from one of the following optionally substituted formulae, optionally only when the pyridine group of C is substituted by a monocyclic moiety.

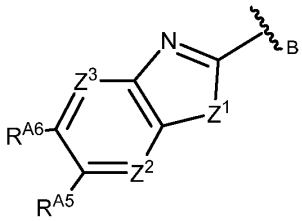
 and .

In some embodiments A is not selected from one of the following formulae, optionally only when the pyridine group of C is substituted by a monocyclic moiety.

. , , , , , and .

(A2a)

In some embodiments, A is (A2a).

 (A2a).

Z^1

In some embodiments Z^1 is O.

In some embodiments Z^1 is S.

In some embodiments Z^1 is NH and when Z^1 is NH and Z^2 is C-H then Z^3 is C-R^{A7}.

Z^2

In some embodiments Z^2 is N.

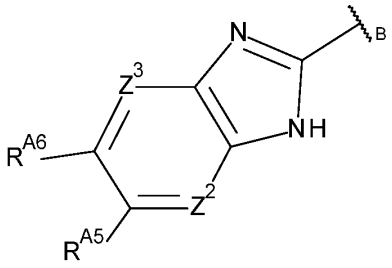
In some embodiments Z^2 is CH.

*Z*3

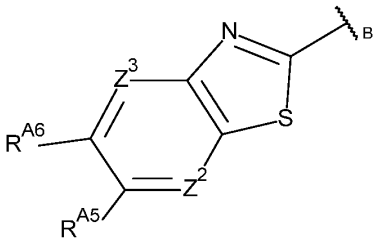
In some embodiments Z^3 is N.

In some embodiments Z^3 is C-R^{A7}.

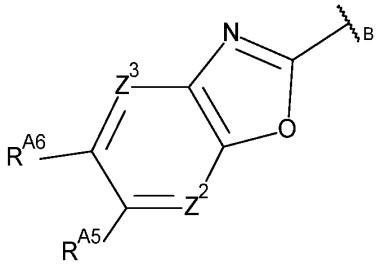
In some embodiments A is selected from one of the following formulae:

A2a1 

,

A2a2 

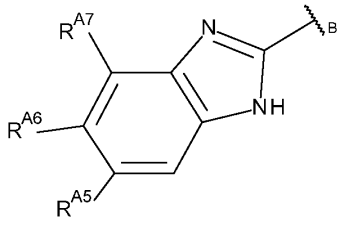
, and

A2a3 

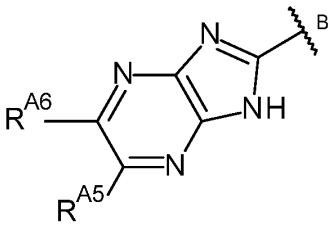
.

wherein the wavy line indicates the point of attachment to B.

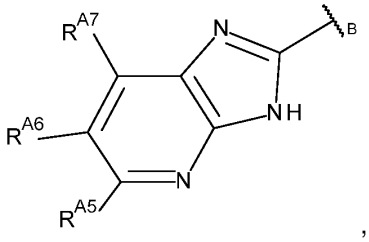
In further embodiments A is selected from one of the following formulae:

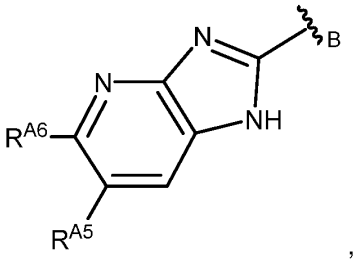
A2a4 

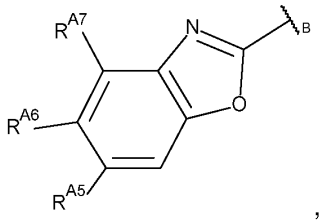
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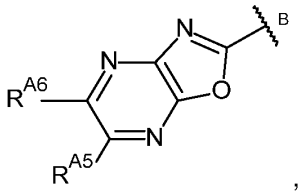
A2a5 

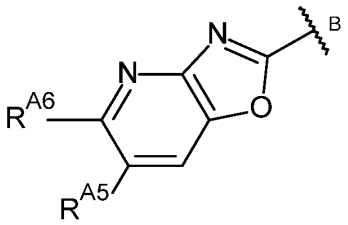
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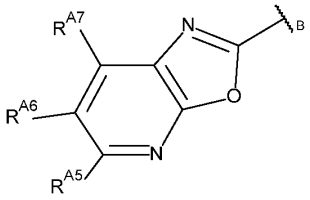
A2a6  ,

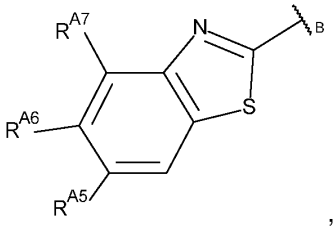
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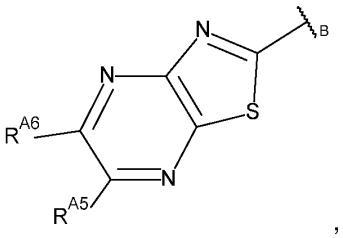
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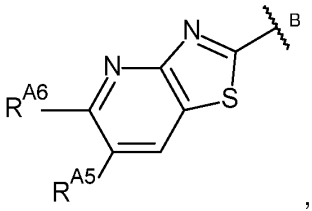
A2a9  ,

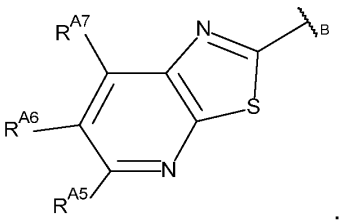
A2a10  ,

A2a11  ,

A2a12  ,

A2a13  ,

A2a14  , and

A2a15  .

when Z^1 is NH, R^{A5} is Z^4 and R^{A6} is Z^5.

when Z^2 is N and Z^1 is O or S, R^{A5} is Z^4 and R^{A6} is Z^5.

when Z^2 is CH and Z^1 is S, R^{A1} is Z^4 and R^{A2} is Z^5.

when Z^2 is CH and Z^1 is O, R^{A1} is Z^5 and R^{A2} is Z^4.

5

Z^4

Z^4 is selected from the group consisting of:

(i) H;

(ii) halo

(iii) CN;
(iv) C_1 alkyl optionally substituted by one or more OH, CN, or one or more halo groups; or
(v) C_1 alkoxy, optionally substituted by one or more halo groups.

In some embodiments when Z^4 is halo it is Cl, Br or F. In some embodiments when Z^4 is halo it is Br. In some embodiments when Z^4 is an optionally substituted C_1 alkyl it is methyl, CH_2OH, CH_2F, CHF_2, CH_2Br, $CHBr_2$, CH_2Cl or $CHCl_2$. In some embodiments when Z^4 is optionally substituted C_1 alkoxy it is OMe, $OCHF_2$ or OCF_3.

In some embodiments Z^4 is selected from H, halo, CN, or methyl optionally substituted by one or more OH groups or one or more halo groups.

In some embodiments Z^4 is selected from H, CN, CH_2OH, Br or methyl.

In some embodiments Z^4 is H.

Z^5

In some embodiments Z^5 is selected from the group consisting of:
(i) H;
(ii) halo;
(iii) CN;
(iv) C_{1-6} hydrocarbon, optionally substituted by OH, CN, C_{1-6} alkyl acyl, C_{1-6} alkoxy or one or more halo groups;
(v) C_{1-6} alkoxy, optionally substituted by C_{1-6} alkyl amido, C_{1-6} alkyl phosphonyl, or one or more halo groups;
(vi) C_{1-6} alkylamino;
(vii) C_{1-6} thioalkyl;
(viii) C_{1-6} alkyl phosphinyl; and
(ix) C_{1-6} alkyl phosphonyl.

In some embodiments Z^5 is selected from the group consisting of:
(i) H;
(ii) halo;
(iii) CN;
(iv) C_{1-6} hydrocarbon, optionally substituted by OH, CN, C_{1-6} alkyl acyl, C_{1-6} alkoxy or one or more halo groups;
(v) C_{1-6} alkoxy, optionally substituted by C_{1-6} alkyl amido, or one or more halo groups;

(vi) C_{1-6} alkylamino;
(vii) C_{1-6} thioalkyl; and
(viii) C_{1-6} alkyl phosphinyl.

In some embodiments Z^5 is selected from:
(i) H;
(ii) halo;
(iii) C_{1-6} alkyl, optionally substituted by one or more OH or one or more halo groups;
(iv) C_{1-6} alkoxy, optionally substituted by one or more halo groups;
(v) C_{3-5} cycloalkyl;
(vi) C_{1-6} thioalkyl; and
(vii) C_{1-6} alkyl phosphinyl.

In some embodiments Z^5 is H.

In some embodiments when Z^5 is halo it is F, Cl or Br.

In some embodiments when Z^5 is an optionally substituted C_{1-6} alkyl it is a methyl, ethyl, propyl, CH_2OH, CH_2F, CHF_2, CF_3. In further embodiments it is methyl, ethyl, CH_2OH or CF_3.

In some embodiments when Z^5 is an optionally substituted C_{1-6} alkoxy it is OMe, O-ethyl, O-propyl, OCF_2H, OCF_3, $OCFH_2$. In further embodiments it is OMe, OCF_3, OCF_2H.

In some embodiments when Z^5 is a cycloalkyl it is cyclopropyl or cyclobutyl. In some embodiments it is cyclopropyl.

In some embodiments when Z^5 is a C_{1-6} thioalkyl it is S-CH_3, S-CH_2CH_3 or S-$CH_2CH_2CH_3$. In some embodiments it is S-CH_3.

In some embodiments when Z^5 is a C_{1-6} alkyl phosphinyl it is P(=O)Me_2, P(=O)$(CH_2CH_3)_2$ or P(=O)$(CH_3)(CH_2CH_3)$. In some embodiments it is P(=O)Me_2.

In further embodiments Z^5 is selected from H, CH_2OH, OCF_2H, OCF_3, CF_3, F, Cl, Br, ethyl, cyclopropyl, methyl, P(=O)Me_2, S-CH_3 and OMe.

R^{A7}

In some embodiments R^{A7} is selected from:

(i) H;
(ii) halo
(iii) CN;
(iv) C_{1-6} alkyl optionally substituted by OH, or one or more halo groups;
(v) C_{2-6} alkenyl optionally substituted by OH, or one or more halo groups;
(vi) C_{2-6} alkynyl optionally substituted by OH, or one or more halo groups; and
(vii) C_{1-6} alkoxy, optionally substituted by one or more halo groups.

In some embodiments R^{A7} is H.

In some embodiments R^{A7} is CN.

In some embodiments when R^{A7} is halo it is selected from Cl, Br and F.

In some embodiments when R^{A7} is an optionally substituted C_{1-6} alkyl it is methyl, ethyl, propyl, CF_3, CF_2H, CH_2-CF_2H or CH_2-cyclopropyl. In further embodiments it is CF_3, CH_2-CF_2H, CF_2H or CH_2-cyclopropyl.

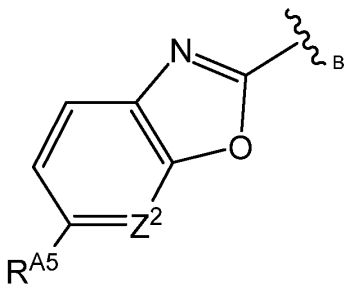
In some embodiments when R^{A7} is C_{2-6} alkenyl it is $CH{=}CH_2$, $CH{=}CHCH_3$ or $CH_2CH{=}CH_2$. In some embodiments it is $CH{=}CH_2$.

In some embodiments when R^{A7} is C_{2-6} alkynyl it is propargyl, acetylene or 1-butyne. In some embodiments it is propargyl.

In some embodiments when R^{A7} is optionally substituted C_{1-6} alkoxy it is OCF_3, OCF_2H or OMe.

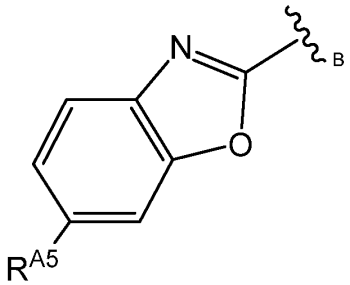
In some embodiments R^{A7} is selected from H, Cl, Br, OMe, $CH{=}CH_2$, OCF_3, OCF_2H, F, CH_2-CF_2H, CF_3, CF_2H, CN, propargyl and CH_2-cyclopropyl. In further embodiments R^{A3} is selected from H, Cl, Br and OMe.

In some embodiments A is of the following formula:



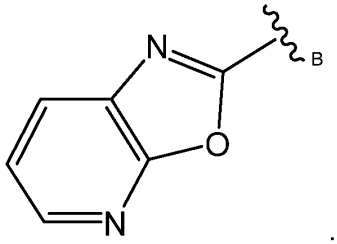
wherein Z^2 is selected from N and C-H and R^{A5} is selected from H, CN, CH_2OH, $OCHF_2$, methyl and Br.

In further embodiments A is of the following formula:



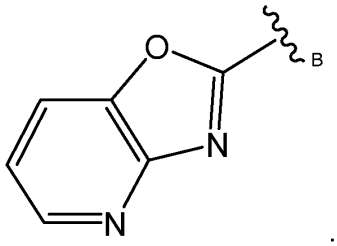
wherein R^{A5} is selected from H, CN, CH_2OH, methyl, $OCHF_2$, and Br.

In some embodiments A is of the following formula:



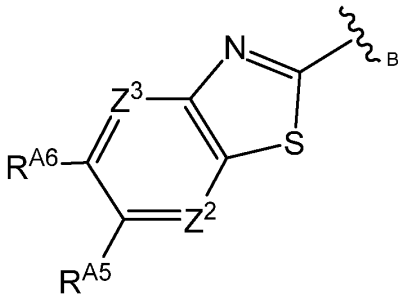
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In some embodiments A is of the following formula:



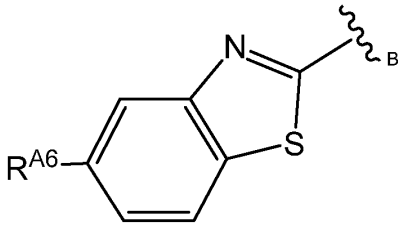
.

In some embodiments A is of the following formula:



wherein Z^2 is selected from N or C-H, and when Z^2 is N, Z^3 is either N or C-R^{A7}, and when Z^2 is C-H, Z^3 is C-R^{A7} or N, R^{A5} is selected from H, methyl and Br, R^{A6} is H, CN or CH_2OH and R^{A7} is H.

In some embodiments A is of the following formula:



wherein R^{A6} is selected from:

(i) H;

(ii) halo;

(iii) C_{1-6} alkyl, optionally substituted by one or more OH or one or more halo groups,

(iv) C_{1-6} alkoxy, optionally substituted by one or more halo groups;

(v) C_{3-5} cycloalkyl;

(vi) C_{1-6} thioalkyl;

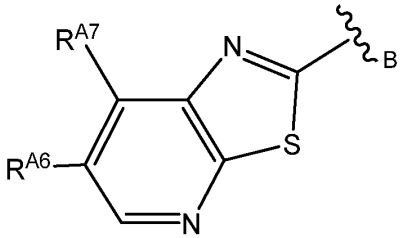
(vii) C_{1-6} alkyl phosphinyl; and

(viii) CN.

In further embodiments when A is of the formula above R^{A6} is selected from H, Br, CH_2OH, C_{1-6} alkyl and CN.

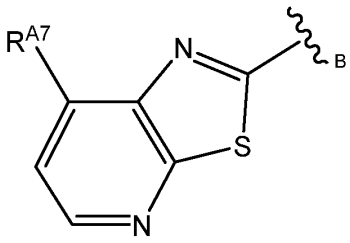
In further embodiments when A is of the formula above R^{A6} is selected from H, CH_2OH, C_{1-6} alkyl and CN.

In some embodiments A is of the following formula:



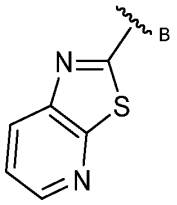
wherein R^{A7} is selected from H, halo and OMe and R^{A6} is selected from H, Br and CH_2OH.

In some embodiments A is of the following formula:



wherein R^{A7} is selected from H, halo and OMe.

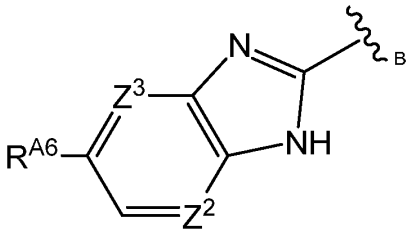
In some embodiments A is of the following formula:



.

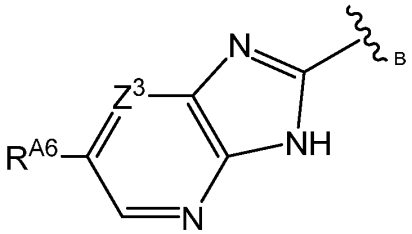
In further embodiments when A is of the formula above, R^{A7} is H.

In some embodiments A is of the following formula:



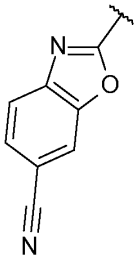
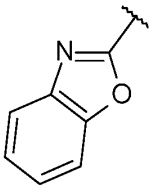
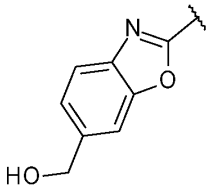
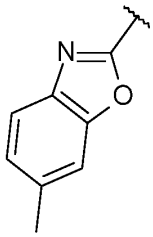
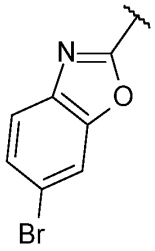
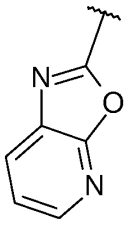
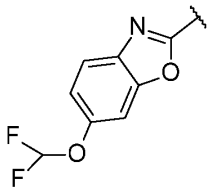
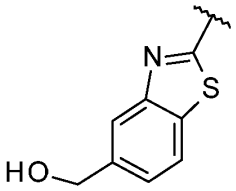
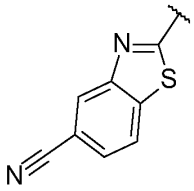
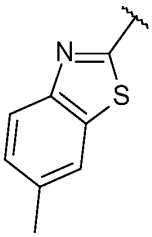
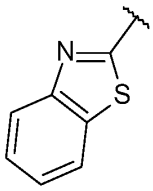
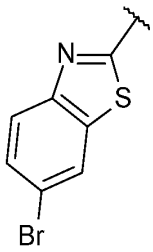
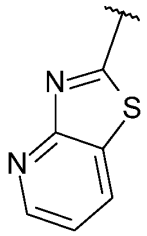
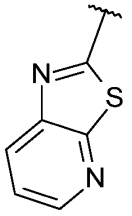
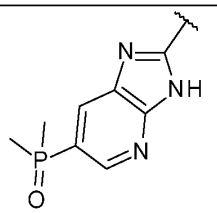
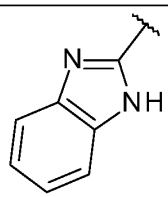
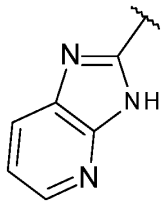
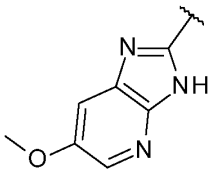
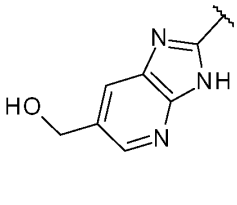
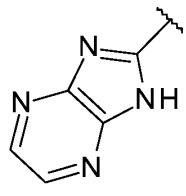
wherein Z^2 is N or C-H, when Z^2 is N, Z^3 is either N or C-R^{A7}, when Z^2 is C-H, Z^3 is C-R^{A7}, wherein R^{A7} is selected from H, Cl, Br and OMe, and R^{A6} is selected from H, CH_2OH, OCH_3, $OCHF_2$, OCF_3, CF_3, F, Cl, Br, ethyl, cyclopropyl, methyl, -P(=O)Me_2 and -S-CH_3.

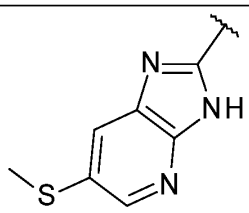
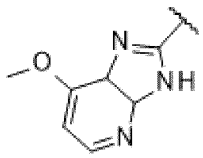
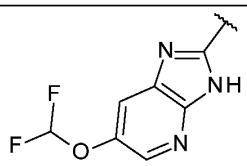
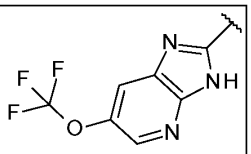
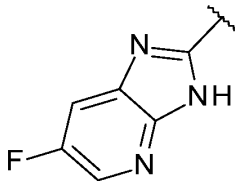
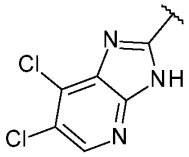
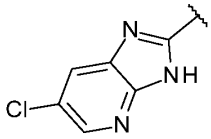
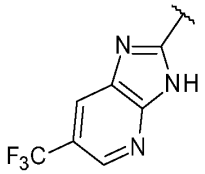
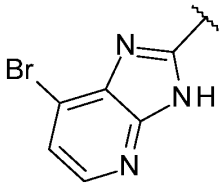
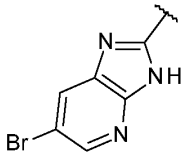
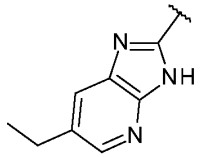
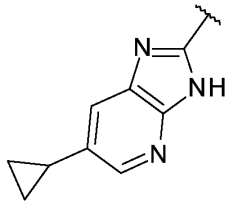
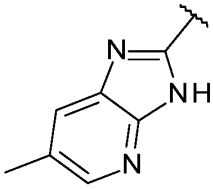
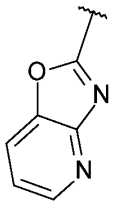
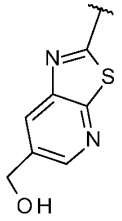
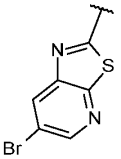
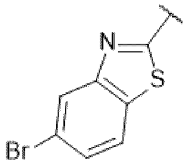
In some embodiments A is of the following formula:



wherein Z^3 is N or C-R^{A7}, wherein R^{A7} is selected from H, Cl, Br and OMe, R^{A6} is selected from H, CH_2OH, OCH_3, $OCHF_2$, OCF_3, CF_3, F, Cl, Br, ethyl, cyclopropyl, methyl, -P(=O)Me_2 and -S-CH_3.

In some embodiments A is selected from any one of the following groups listed in the table:

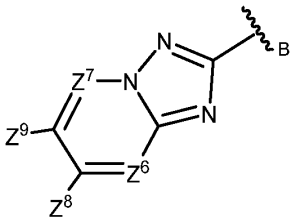
			
			
			
			
			

wherein the wavy line indicates the point of attachment to B.

(A2b)

In some embodiments, A is (A2b).



(A2b).

Z^6

In some embodiments Z^6 is N.

In some embodiments Z^6 is CH.

Z^7

In some embodiments Z^7 is N.

In some embodiments Z^7 is C-R^{A8}.

Z^6 and Z^7

In some embodiments, Z^6 is C-H, and Z^7 is C-R^{A8}. In some of these embodiments, R^{A8} is H.

Z^8 and Z^9

In some embodiments Z^8 and Z^9 are independently selected from the group consisting of:

(i) H;

(ii) halo;

(iii) CN;

(iv) C_{1-6} hydrocarbon, optionally substituted by OH, CN, C_{1-6} alkyl acyl, C_{1-6} alkoxy or one or more halo groups;

(v) C_{1-6} alkoxy, optionally substituted by C_{1-6} alkyl amido, C_{1-6} alkyl phosphonyl, or one or more halo groups;

(vi) C_{1-6} alkylamino;

(vii) C_{1-6} thioalkyl;

(viii) C_{1-6} alkyl phosphinyl; and

(ix) C_{1-6} alkyl phosphonyl.

In some embodiments Z^8 and Z^9 are independently selected from the group consisting of:

(i) H;

(ii) halo;

(iii) CN;

(iv) C_{1-6} hydrocarbon, optionally substituted by OH, CN, C_{1-6} alkyl acyl, C_{1-6} alkoxy or one or more halo groups;

(v) C_{1-6} alkoxy, optionally substituted by C_{1-6} alkyl amido, or one or more halo groups;

(vi) C_{1-6} alkylamino;

(vii) C_{1-6} thioalkyl; and

(viii) C_{1-6} alkyl phosphinyl.

In some embodiments Z^8 and Z^9 are independently selected from:

(i) H;

(ii) halo;
(iii) C_{1-6} alkyl, optionally substituted by one or more OH or one or more halo groups;
(iv) C_{1-6} alkoxy, optionally substituted by one or more halo groups;
(v) C_{3-5} cycloalkyl;
(vi) C_{1-6} thioalkyl; and
(vii) C_{1-6} alkyl phosphinyl.

In some embodiments Z^8 and Z^9 are H. In some embodiments, Z^6 and Z^7 are C-H, and Z^8 and Z^9 are H.

In some embodiments when one or both of Z^8 and Z^9 are halo it is F, Cl or Br.

In some embodiments when one or both of Z^8 and Z^9 are optionally substituted C_{1-6} alkyl it is a methyl, ethyl, propyl, CH_2OH, CH_2F, CHF_2, CF_3. In further embodiments it is methyl, ethyl, CH_2OH or CF_3.

In some embodiments when one or both of Z^8 and Z^9 are an optionally substituted C_{1-6} alkoxy it is OMe, O-ethyl, O-propyl, OCF_2H, OCF_3, $OCFH_2$. In further embodiments it is OMe, OCF_3, OCF_2H.

In some embodiments when one or both of Z^8 and Z^9 are a cycloalkyl it is cyclopropyl or cyclobutyl. In some embodiments it is cyclopropyl.

In some embodiments when one or both of Z^8 and Z^9 are a C_{1-6} thioalkyl it is S-CH_3, S-CH_2CH_3 or S-$CH_2CH_2CH_3$. In some embodiments it is S-CH_3.

In some embodiments when one or both of Z^8 and Z^9 are a C_{1-6} alkyl phosphinyl it is P(=O)Me_2, P(=O)$(CH_2CH_3)_2$ or P(=O)$(CH_3)(CH_2CH_3)$. In some embodiments it is P(=O)Me_2.

In further embodiments one or both of Z^8 and Z^9 are selected from H, CH_2OH, OCF_2H, OCF_3, CF_3, F, Cl, Br, ethyl, cyclopropyl, methyl, P(=O)Me_2, S-CH_3 and OMe.

R^{A8}

In some embodiments R^{A8} is selected from:
(i) H;
(ii) halo

(iii) CN;
(iv) C_{1-6} alkyl optionally substituted by OH, or one or more halo groups;
(v) C_{2-6} alkenyl optionally substituted by OH, or one or more halo groups;
(vi) C_{2-6} alkynyl optionally substituted by OH, or one or more halo groups; and
(vii) C_{1-6} alkoxy, optionally substituted by one or more halo groups.

In some embodiments R^{A8} is H.

In some embodiments R^{A8} is CN.

In some embodiments when R^{A8} is halo it is selected from Cl, Br and F.

In some embodiments when R^{A8} is an optionally substituted C_{1-6} alkyl it is methyl, ethyl, propyl, CF_3, CF_2H, CH_2-CF_2H or CH_2-cyclopropyl. In further embodiments it is CF_3, CH_2-CF_2H, CF_2H or CH_2-cyclopropyl.

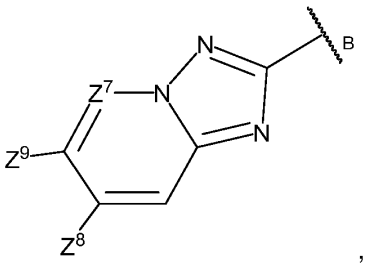
In some embodiments when R^{A8} is C_{2-6} alkenyl it is $CH{=}CH_2$, $CH{=}CHCH_3$ or $CH_2CH{=}CH_2$. In some embodiments it is $CH{=}CH_2$.

In some embodiments when R^{A8} is C_{2-6} alkynyl it is propargyl, acetylene or 1-butyne. In some embodiments it is propargyl.

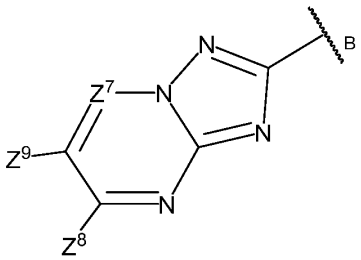
In some embodiments when R^{A8} is optionally substituted C_{1-6} alkoxy it is OCF_3, OCF_2H or OMe.

In some embodiments R^{A8} is selected from H, Cl, Br, OMe, $CH{=}CH_2$, OCF_3, OCF_2H, F, CH_2-CF_2H, CF_3, CF_2H, CN, propargyl and CH_2-cyclopropyl. In further embodiments R^{A8} is selected from H, Cl, Br and OMe.

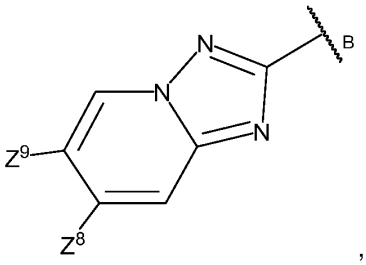
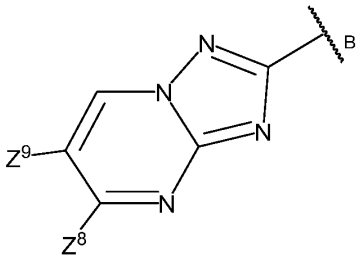
In some embodiments, A is selected from one of the following formulae:

A2b1 

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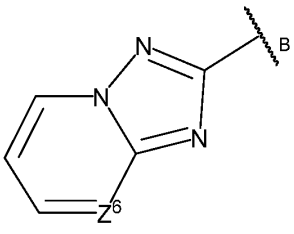
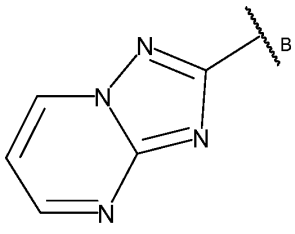
A2b2 

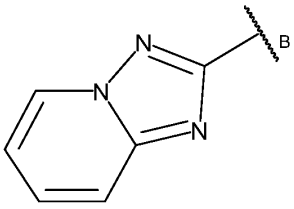
,

A2b3  , A2b4  ,

wherein the wavy line indicates the point of attachment to B and wherein Z^7, Z^8, and Z^9 are as defined in any other embodiment herein.

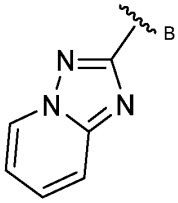
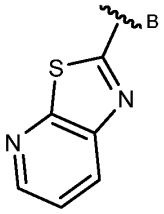
In some embodiments, A is selected from one of the following formulae:

A2b5  , A2b6  ,

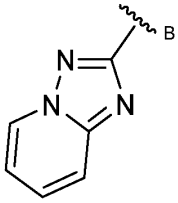
A2b7  ,

wherein the wavy line indicates the point of attachment to B, and Z^6 is as defined in any other embodiment herein. In some embodiments, A is formula A2b7.

In some embodiments A is selected from one of the following formulae:

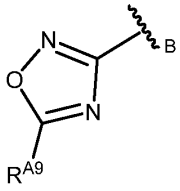
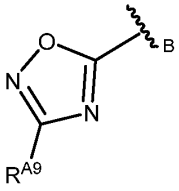
 and  .

In some embodiments A is the following formula:

 .

(A3a) and (A3b)

In some embodiments, A is A3a or A3b.


(A3a) or 
(A3b).

In some embodiments, A is A3a. In some embodiments, A is A3b.

R^{A9}

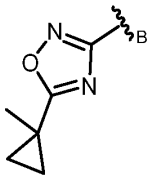
In some embodiments, R^{A9} is selected from methyl, ethyl, n-propyl, *i*-propyl, cyclopropyl, 1-methylcyclopropyl and 2-methylcyclopropyl.

In some embodiments, R^{A9} is selected from methyl, cyclopropyl, 1-methylcyclopropyl and 2-methylcyclopropyl.

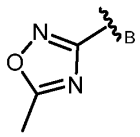
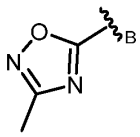
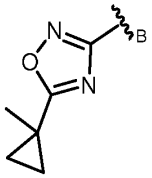
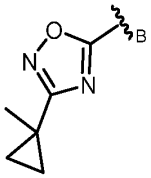
In some embodiments, R^{A9} is selected from methyl and 1-methylcyclopropyl.

In some embodiments, R^{A9} is methyl.

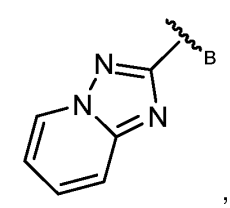
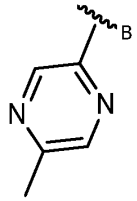
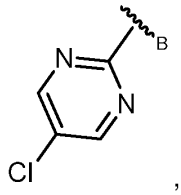
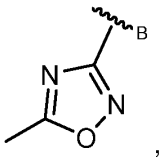
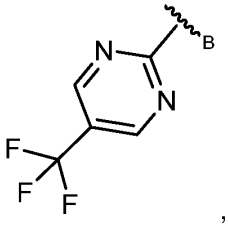
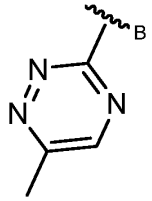
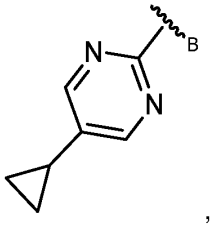
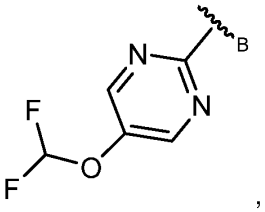
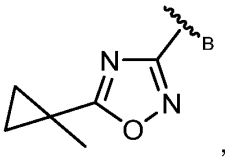
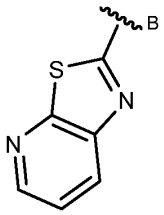
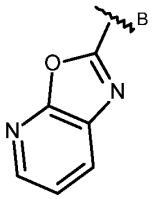
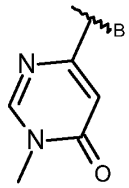
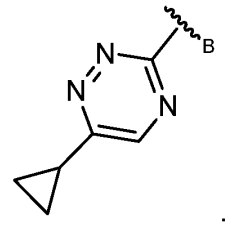
In some embodiments, A is:


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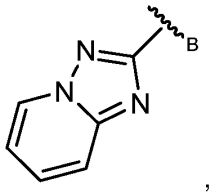
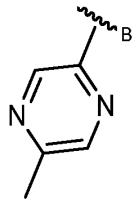
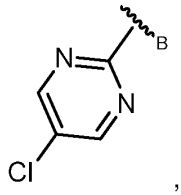
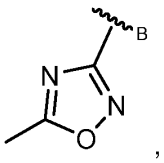
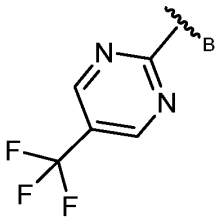
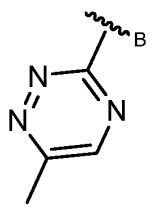
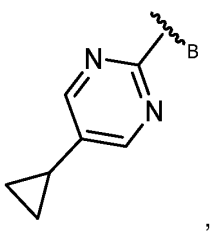
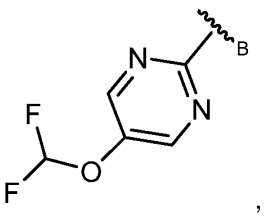
In some embodiments, A is selected from one of the following formulae:

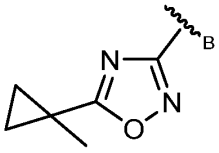
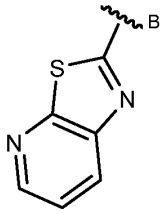

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In some embodiments, A is selected from one of the following formulae:

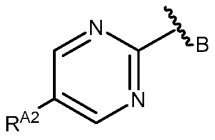
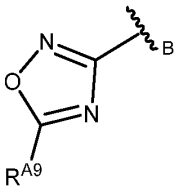
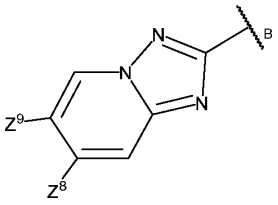
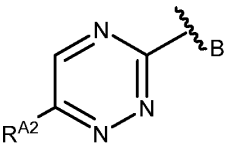
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and .

In some embodiments, A is selected from one of the following formulae:

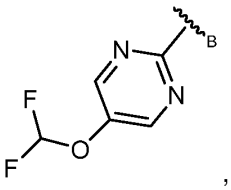
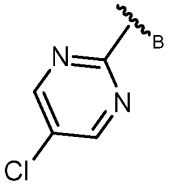
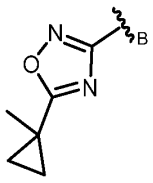
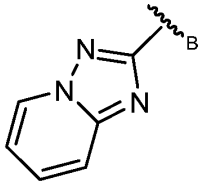
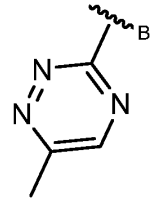
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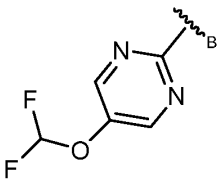
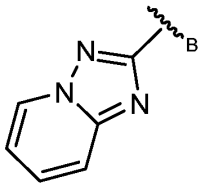
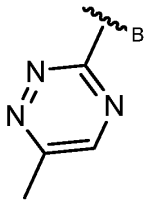
In some embodiments, A is selected from one of the following formulae:

In some embodiments, A is selected from one of the following formulae:

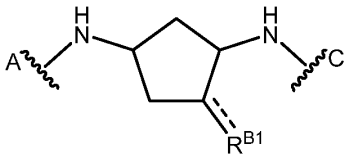






In some embodiments, A is selected from one of the following formulae:

(B-1)

In some embodiments B is of formula (B-1):



(B-1),

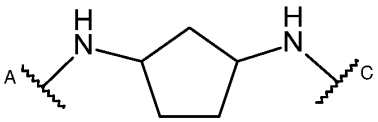
wherein the wavy line indicates the point of attachment to A and C; wherein R^{B1} is -H, -OH, -OMe, -O-ethyl, -CH_2OH, -CH_2CH_2OH or =$CHCH_2$-OH.

In other embodiments R^{B1} is H, -CH_2OH, -CH_2CH_2OH or =$CHCH_2$-OH.

In other embodiments R^{B1} is -CH_2OH, -CH_2CH_2OH or =$CHCH_2$-OH.

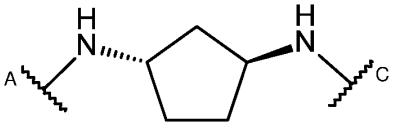
In other embodiments R^{B1} is H.

In another embodiment B is of the formula (B-1a):



(B-1a).

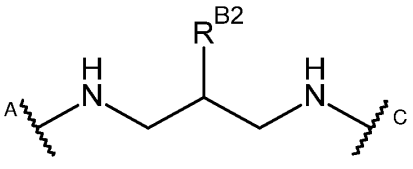
In further embodiments B is of the formula (B-1b):



(B-1b).

Therefore, in some embodiments the compounds of Formula (I) is the S,S-enantiomer.

Alternatively, it is disclosed that B may be of formula (B-2):



(B-2)

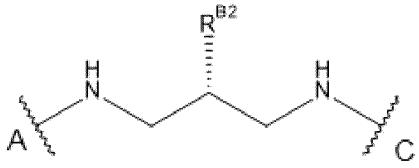
wherein the wavy lines indicate the point of attachment to A and C;
R^{B2} is C_{1-2} alkyl-OH, $CH_2CONHMe$ or C_{1-3} alkyl,
wherein when R^{A1} is H or halo, R^{B2} is C_{1-2} alkyl-OH or $CH_2C(=O)NHMe$,

In some of these alternatives, R^{B2} is C_{1-2} alkyl-OH, or C_{1-3} alkyl.

In some of these alternatives R^{B2} is C_{1-2} alkyl-OH or $CH_2C(=O)NHMe$.

In some of these alternatives when X^1 is O or S and R^{A1} is H or halo, R^{B2} is C_{1-2} alkyl-OH or $CH_2C(=O)NHMe$.

In some of these alternatives when B is of the formula (B-2) it is of the following formula (B-2a):

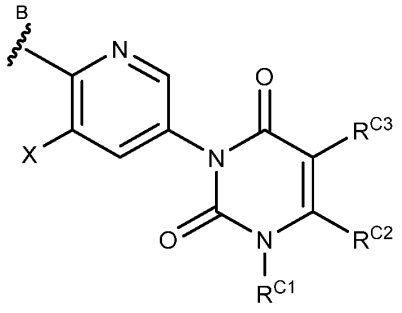


(B-2a)

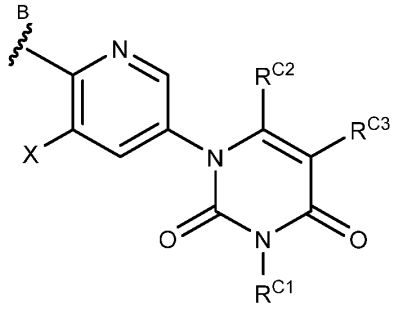
wherein the wavy lines indicate the point of attachment to A and C; and R^{B2} is C_{1-2}alkyl-OH, $CH_2CONHMe$ or C_{1-2}alkyl, wherein when R^{A1} is H or halo, R^{B2} is C_{1-2} alkyl-OH or $CH_2C(=O)NHMe$.

(C-1a) and (C-1b)

In some embodiments, C is (C-1a). In some embodiments, C is (C-1b).



(C-1a)

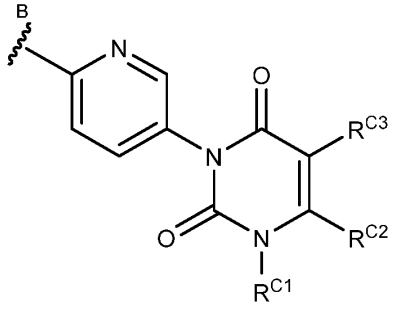


(C-1b)

In some embodiments, X is H.

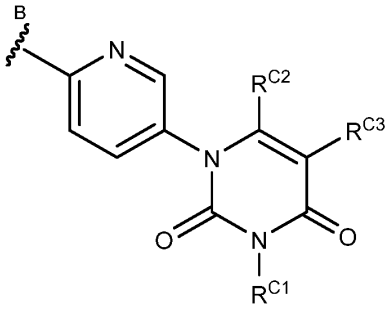
In some embodiments, X is F.

In some embodiments, C is of the formula (C-1);



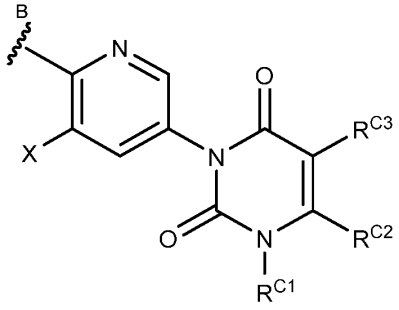
(C-1).

In some embodiments, C is of the formula (C-1c);

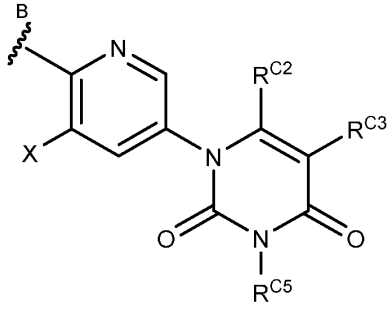


(C-1c).

In some embodiments, C is of the formulae (C-1a) or (C-1bz)



(C-1a)



(C-1bz)

wherein R^{C1} is selected from:

(i) H;

(ii) C_{1-6} alkyl optionally substituted by one or more halo groups;

(iv) C_{5-6} heterocyclyl or C_{5-6} heteroaryl with an optional methyl substituent;

(x) phenyl optionally substituted by one or more halo atoms;

and R^{C5} is selected from:

(i) H;

(ii) C_{1-6} alkyl optionally substituted by one or more halo groups;

(iv) C_{5-6} heterocyclyl or C_{5-6} heteroaryl with an optional methyl substituent;

(x) phenyl optionally substituted by one or more halo atoms.

In some embodiments, one of R^{C2} and R^{C3} is hydrogen and the other is C_{1-3} alkoxy. In some of these embodiments R^{C2} is hydrogen and R^{C3} is C_{1-3} alkoxy. In other of these embodiments, R^{C2} is C_{1-3} alkoxy and R^{C3} is hydrogen. In some embodiments of (C-1a), R^{C2} is hydrogen and R^{C3} is C_{1-3} alkoxy.

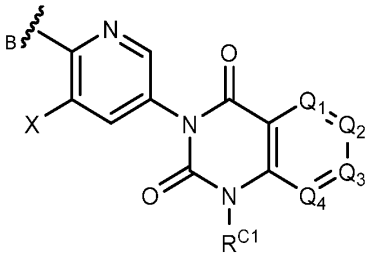
In some embodiments, R^{C2} and R^{C3} together represent a fused benzene ring, pyridine ring, thiophene ring, or 1,2,5-thiadiazole ring, which rings are optionally substituted by one or more R^{C4} groups;

In some embodiments, R^{C2} and R^{C3} together represent a fused benzene or pyridine ring, which rings are optionally substituted by one or more R^{C4} groups;

In some embodiments, R^{C1} is selected from H, methyl, cyclopropyl, 1-methyl-1*H*-pyrazolyl, (1-methyl-1H-pyrazol-4-yl)pyrido and phenyl. In some embodiments, R^{C1} is selected from H, methyl, cyclopropyl, 1-methyl-1*H*-pyrazolyl, and phenyl. In some embodiments, R^{C1} is methyl.

R^{C4} is selected from methyl, methoxy, C_{5-6} heterocyclyl, C_{5-6} heteroaryl, halo and CN.

In some embodiments, C is selected from the following formula:

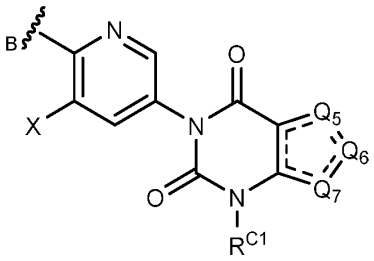


(C-2a);

wherein X and R^{C1} are as defined in any other embodiment herein, and none, one or two of Q_1, Q_2, Q_3 and Q_4 is N and the remainder are C-H.

In some embodiments, one of Q_1, Q_2, Q_3 and Q_4 is N and the remainder are C-H.

In some embodiments, C is selected from the following formula:



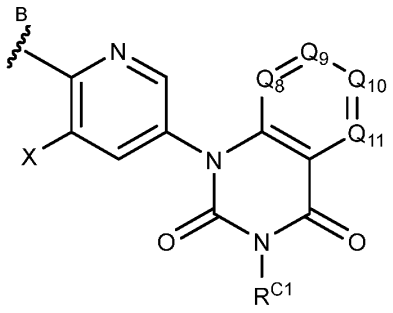
(C-3a)

wherein X and R^{C1} are as defined in any other embodiment herein, and none, one or two of Q_5, Q_6 and Q_7 is N, none or one of Q_5, Q_6 and Q_7 is S and the remainder are C-H.

In some embodiments, one of Q_5, Q_6 and Q_7 is S and the remainder are C-H.

In some embodiments, two of Q_5, Q_6 and Q_7 are N and the remainder is S.

In some embodiments, C is selected from the following formula:



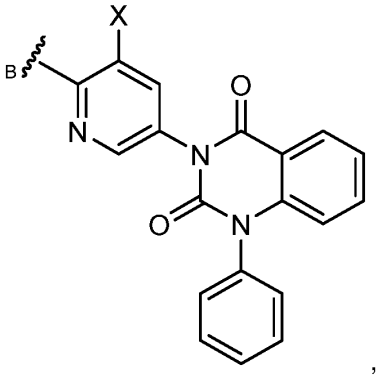
(C4a);

wherein none, one or two of Q_8, Q_9, Q_{10} and Q_{11} is N and the remainder are C-H.

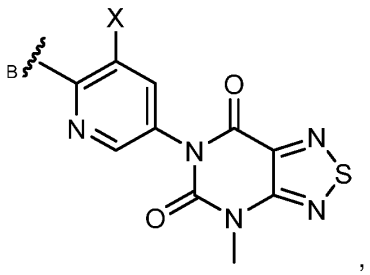
In some embodiments, all of Q_8, Q_9, Q_{10} and Q_{11} are C-H.

In some embodiments, one of Q_8, Q_9, Q_{10} and Q_{11} is N and the remainder are C-H.

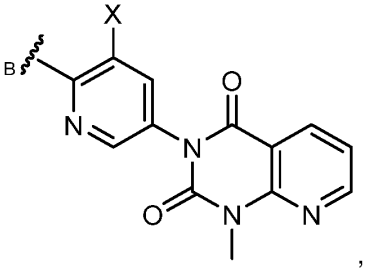
In another embodiment, C is selected from one of the formulae listed in the following table:



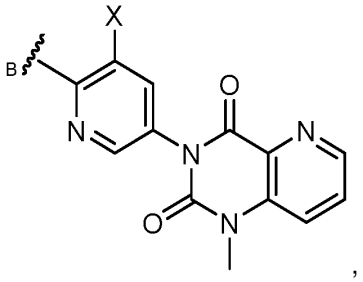
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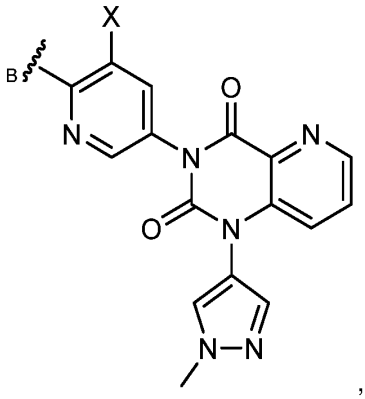
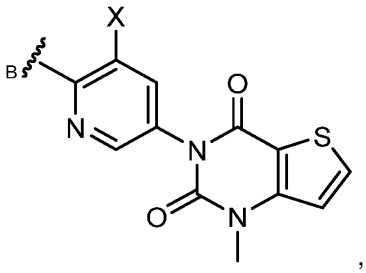
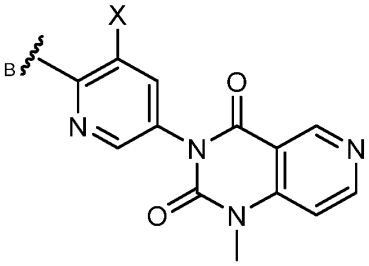
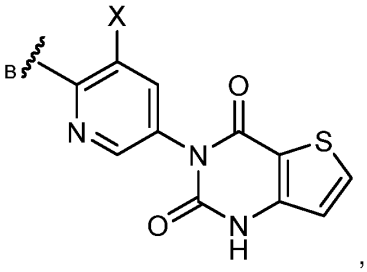
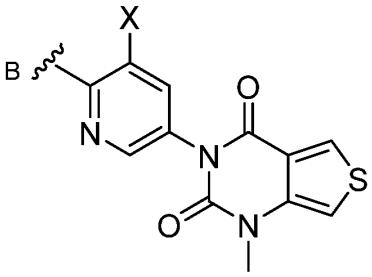
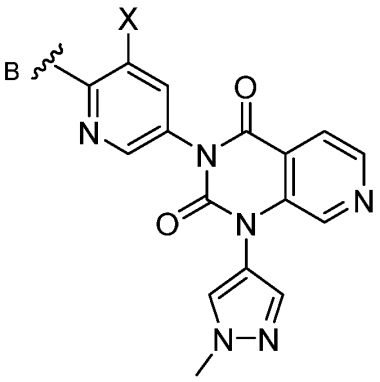
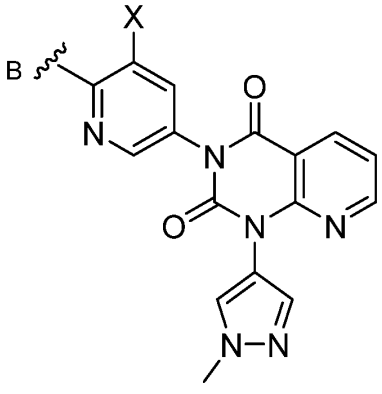
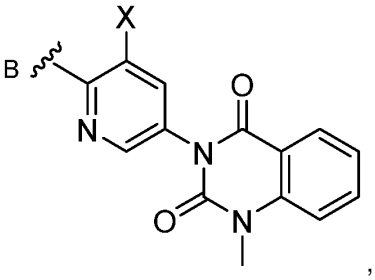
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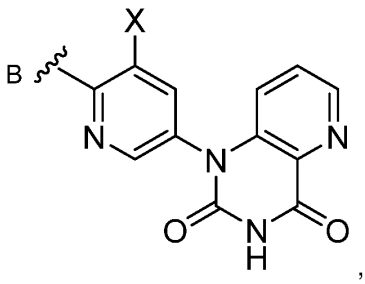
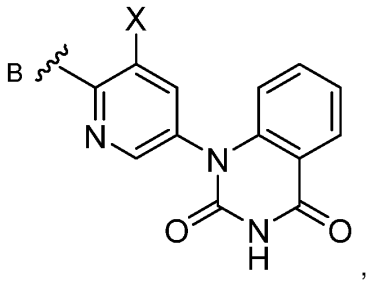
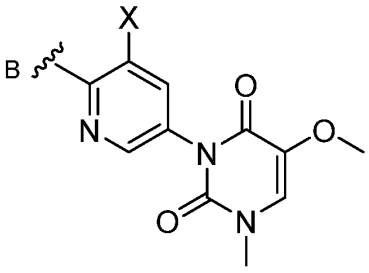
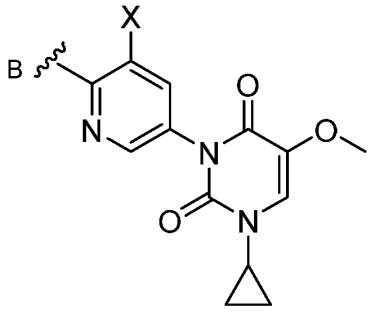


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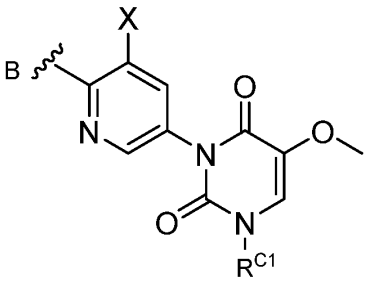
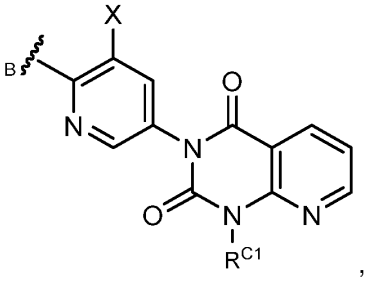
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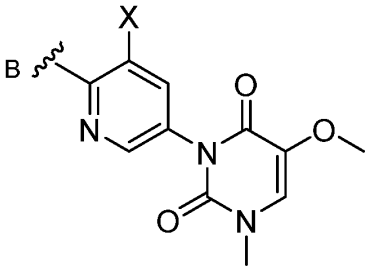
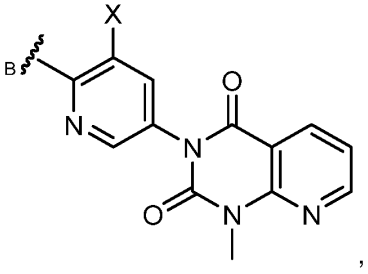
where X is hydrogen or fluorine. In some embodiments, X is hydrogen.

In some embodiments, C is selected from one of the following formulae:


, and

,

where X is hydrogen or fluorine. In some embodiments, X is hydrogen.

In some embodiments, C is selected from one of the following formulae:


, and

,

where X is hydrogen or fluorine. In some embodiments, X is hydrogen.

In some embodiments, where C is formula (C-1b), X^2 is C-R^{A4}.

In some embodiments, where one of R^{C2} and R^{C3} is hydrogen and the other is C_{1-3} alkoxy, X^2 is C-R^{A4}.

In some embodiments, where C is formula (C-1a) and X is fluorine, X^2 is C-R^{A4}.

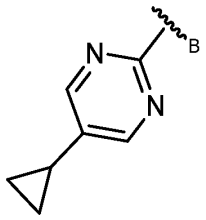
In some embodiments, where C is formula (C-1b), A is selected from (A1a), (A2b), (A3a), and (A3b).

In some embodiments, where one of R^{C2} and R^{C3} is hydrogen and the other is C_{1-3} alkoxy, A is selected from (A1a), (A2b), (A3a), and (A3b).

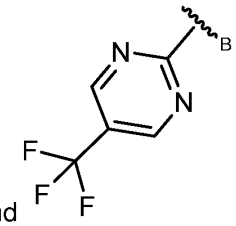
In some embodiments, where C is formula (C-1a) and X is fluorine, A is selected from (A1a), (A2b), (A3a), and (A3b).

A and C

In some embodiments A is selected from;

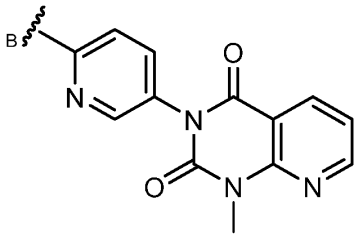


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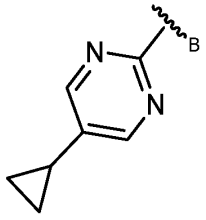
;

and C is;

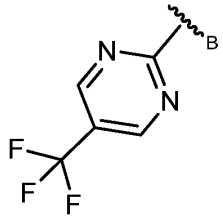


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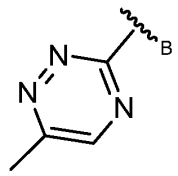
In some embodiments A is selected from:



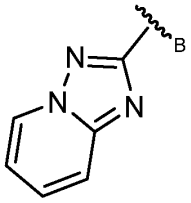
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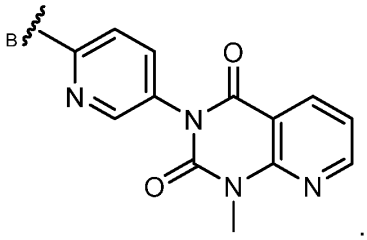
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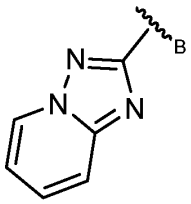
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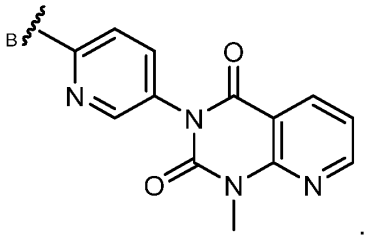
and C is:



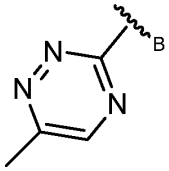
In some embodiments A is:



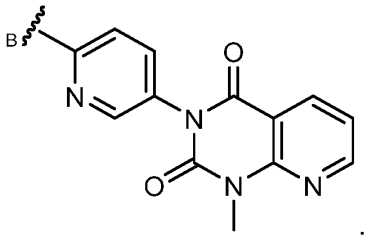
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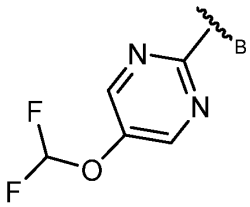
In some embodiments A is selected from:



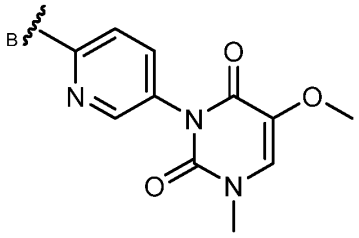
and C is



In some embodiments A is:

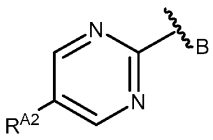
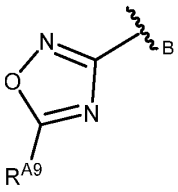
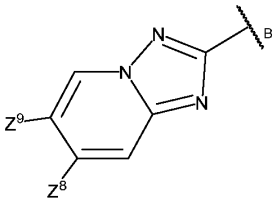
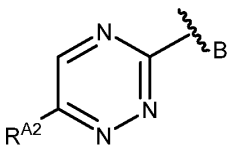


and C is:

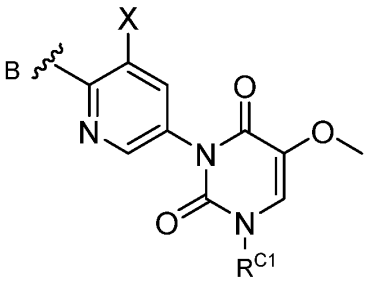
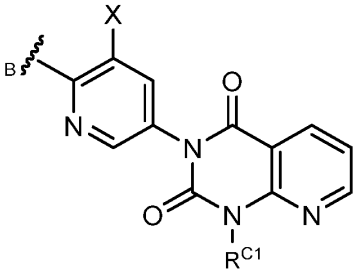


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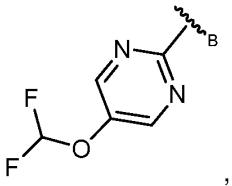
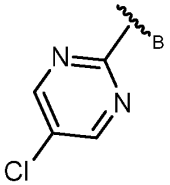
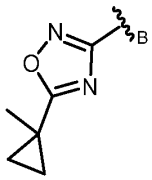
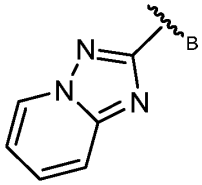
In some embodiments A is selected from:

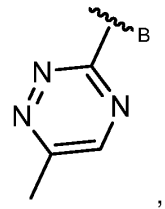
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and C is selected from:

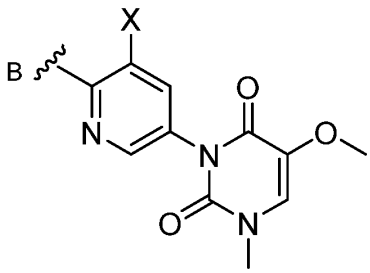
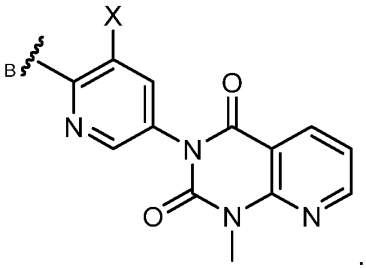
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In some embodiments A is selected from:

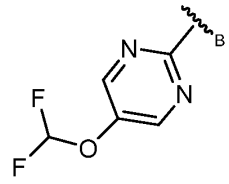
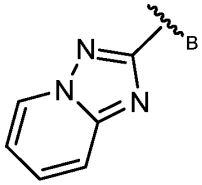
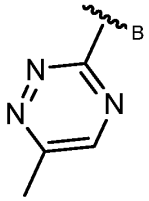
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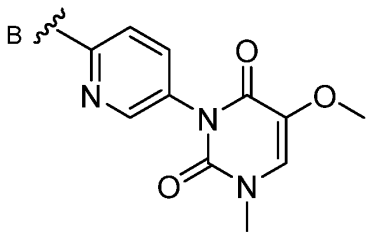
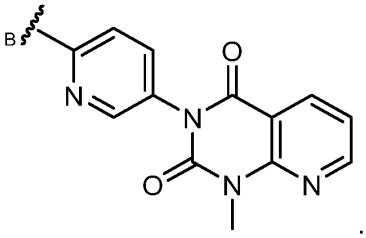
and C is selected from:


, and 
.

In some embodiments A is selected from:


, 
and, 
,

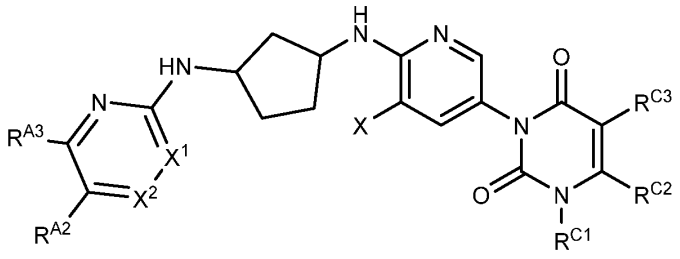
and C is selected from:


, and 
.

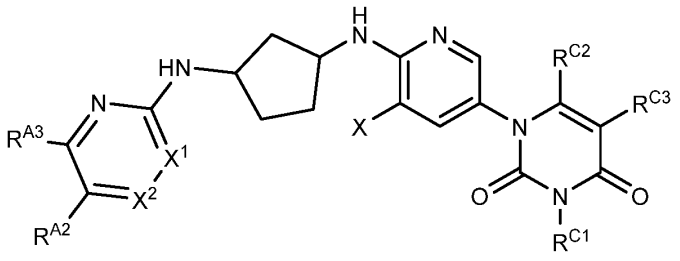
5

A-B-C (A1a)

In other embodiments the compound of formula A-B-C is of the formulae (I-Ax) or (I-Ay):



(I-Ax),



(I-Ay),

wherein X^1, X^2, R^{A2}, R^{A3}, X, R^{C1}, R^{C2} and R^{C3} are as defined in any other embodiment herein.

In some embodiments R^{A1} is H, OH, CN, Br, Cl, optionally substituted -OMe, -O-ethyl, methyl or ethyl, where the optional substituents on the -OMe, O-ethyl, methyl or ethyl groups are selected from OH, CN, and one or more halo groups. In some embodiments R^{A1} is H, CN, OH, Br, Cl, optionally substituted -OMe, -O-ethyl, methyl or ethyl, where the optional substituents on the -OMe, O-ethyl, methyl or ethyl groups are selected from OH, CN, and one or more halo groups. In further embodiments R^{A1} is optionally substituted O-methyl wherein the optional substituents are one or more F groups. In further embodiments R^{A1} is H. In further embodiments R^{A1} is OH.

In some embodiments R^{A2} is selected from the group consisting of: Br, Cl, CN, H, $-C(=O)CH_3$, C_{1-6} alkyl amido which alkyl amido is optionally substituted by C_{1-3} alkyl amido, a thioalkyl optionally substituted by C_{1-3} alkyl ester, CN, C_{2-3} alkynyl, C_{4-6} heterocyclyl, C_{1-3} alkyl which alkyl is optionally substituted with one or more halo or OH groups, optionally substituted methoxy, methyl, ethyl or cyclopropyl wherein the optional substituents are selected from OH, CN, and one or more halo groups, an optionally substituted methoxy or ethoxy wherein the optional substituents are selected from alkyl amido and one or more halo groups. In some embodiments R^{A2} is selected from the group consisting of: Br, Cl, CN, H, $-C(=O)CH_3$, C_{1-6} alkyl amido which alkyl amido is optionally substituted by C_{1-3} alkyl amido, CN, C_{2-3} alkynyl, C_{4-6} heterocyclyl, C_{1-3} alkyl which alkyl is optionally substituted with one or more halo or OH groups, optionally substituted methoxy, methyl, ethyl or cyclopropyl wherein the optional substituents are selected from OH, CN, and one or more halo groups, an optionally substituted methoxy or ethoxy wherein the optional substituents are selected from alkyl amido or one or more halo groups. In further embodiments R^{A2} is selected from CN, methyl, Cl, $-C(=O)CH_3$, $-C(=O)OCH_2CH_3$,

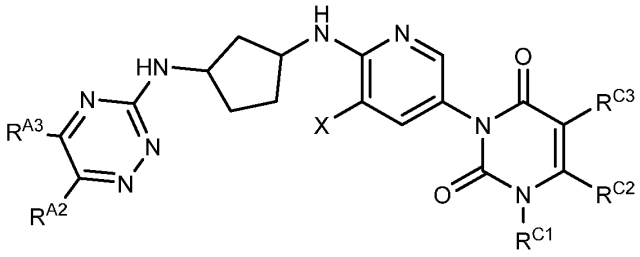
cyclopropyl, C(=O)NHCH$_2$C(=O)NH$_2$, -C(=O)NHCH$_2$CHCH, -C(=O)NH-oxetane, -C(=O)NHCH$_2$CHF$_2$, -C(=O)NHCH$_2$CH$_2$OH, -C(=O)NHCH$_2$CH$_3$, -C(=O)NH$_2$, -C(=O)NHCH$_3$, -C(=O)N(CH$_3$)$_2$, -OCF$_2$H, H, -OMe, -OCF$_3$. In some embodiments R^{A2} is selected from the group consisting of CN, methyl, Cl, -C(=O)CH$_3$, OCHF$_2$, cyclopropyl, CF$_3$, OCF$_3$, OCH$_3$, H, -C(=O)NH(CH$_3$), S-CH$_3$, SCH$_2$CH$_3$ and -S-CH$_2$-C(=O)-O-CH$_3$. In some embodiments R^{A2} is selected from the group consisting of methyl, Cl, OCHF$_2$, cyclopropyl, and CF$_3$.

In some embodiments R^{A3} is selected from the group consisting of CN, Br, Cl, OH, H, CF$_3$, C$_{1-2}$ alkyl, C$_{1-2}$ alkoxy, and NH$_2$. In further embodiments R^{A3} is selected from H, methyl and CN.

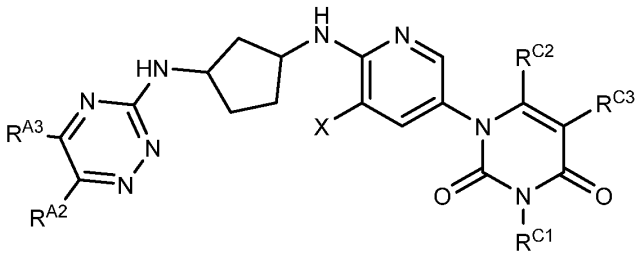
In other embodiments R^{A3} and R^{A2} together with the carbon atoms to which they are bound form an optionally substituted C$_6$ carboaromatic ring or C$_{5-7}$ heteroaromatic ring, the optional substituents are selected from NH$_2$, C$_{1-6}$ alkyl, C$_{1-6}$ alkoxy and halo. In other embodiments the optional substituents are selected from NH$_2$, methyl, ethyl, OMe, F, Cl and Br.

In some embodiments R^{A3} and R^{A2} together with the carbon atoms to which they are bound form an optionally substituted pyridine, an optionally substituted benzene, a pyrrole or a pyrazole. In some embodiments R^{A2} and R^{A3} together form an unsubstituted 2-pyrazole, a 2-pyrrole substituted by methyl, pyridine optionally substituted by NH$_2$ or benzene optionally substituted by Cl, F or OMe.

In other embodiments the compound of formula A-B-C is of the formulae (I-Bx) or (I-By):



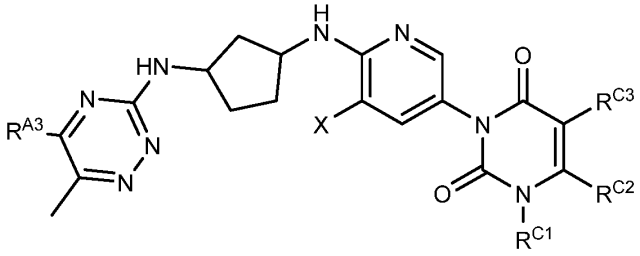
(I-Bx),



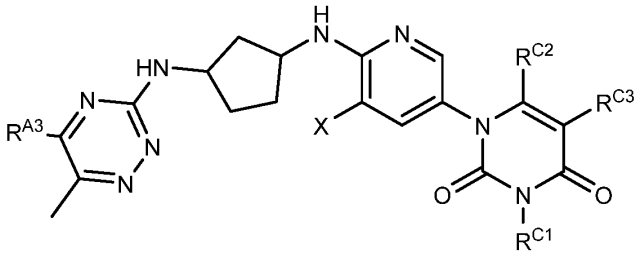
(I-By),

wherein R^{A2}, R^{A3}, X, R^{C1}, R^{C2} and R^{C3} are as defined in any other embodiment herein.

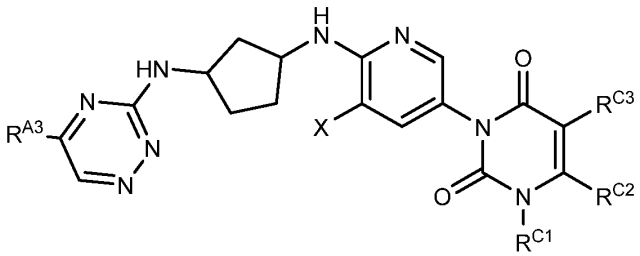
In some embodiments formulae (I-Bx) and (I-By) can be formulae (I-Bax), (I-Bay), (I-Bbx), (I-Bby), (I-Bcx) and (I-Bcy) as shown below:



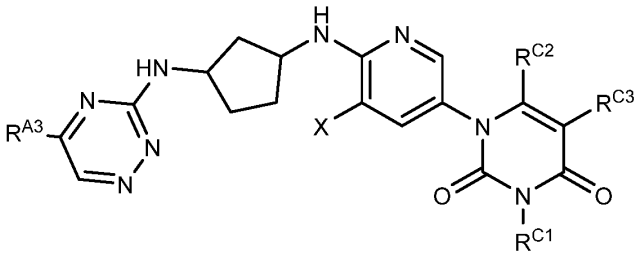
(I-Bax),



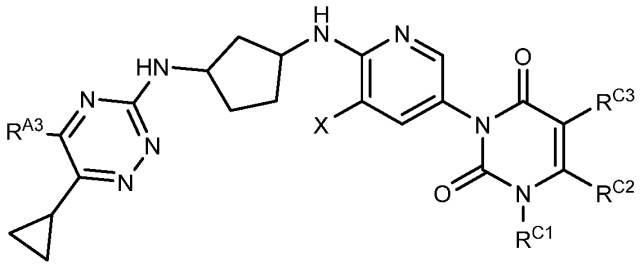
(I-Bay),



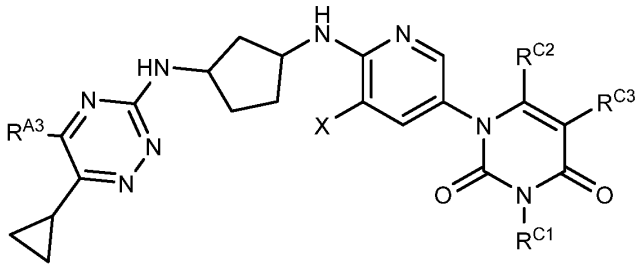
(I-Bbx),



(I-Bby),



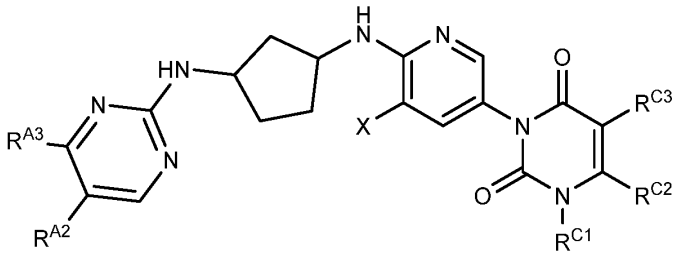
(I-Bcx),



(I-Bcy),

wherein R^{A3}, X, R^{C1}, R^{C2} and R^{C3} are as defined in any other embodiment herein.

In other embodiments the compound of formula A-B-C is of the formula (I-Cx):

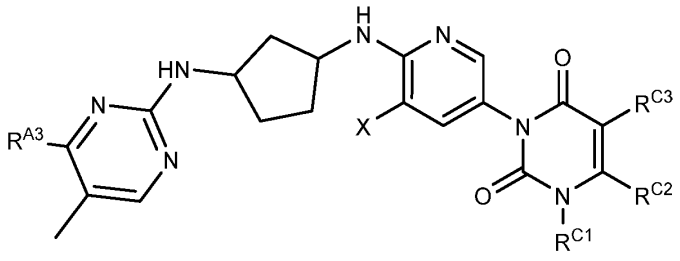


(I-Cx),

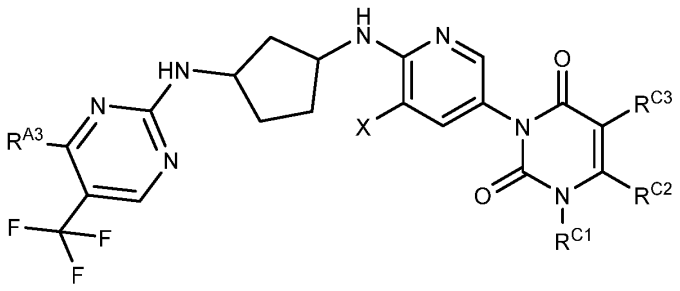
wherein R^{A2}, R^{A3}, X, R^{C1}, R^{C2} and R^{C3} are as defined in any other embodiment herein.

In some embodiments, R^{A2} in formula (I-Cx) is selected from fluoro, chloro, bromo or iodo. In some embodiments, R^{A2} in formula (I-Cx) is selected from cyclopropyl, methyl, CF_3 and $OCHF_2$. In some of these embodiments, R^{A3} is H.

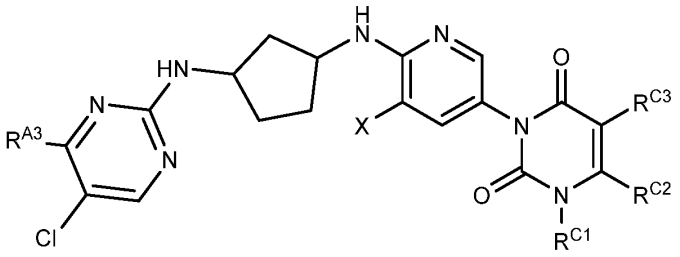
In some embodiments formula (I-Cx) can be any one of formulae (I-Cax) to (I-Cex) as shown below:



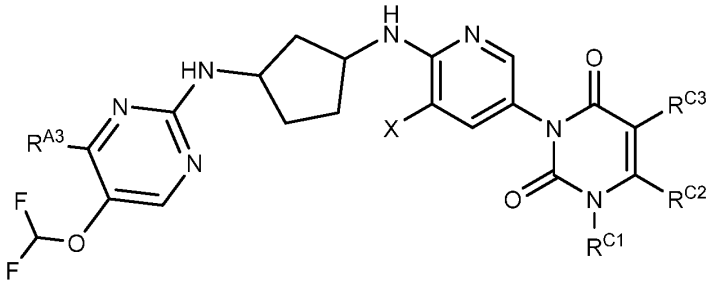
(I-Cax),



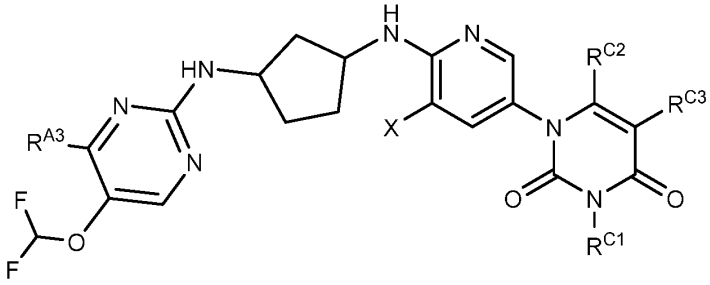
(I-Cbx),



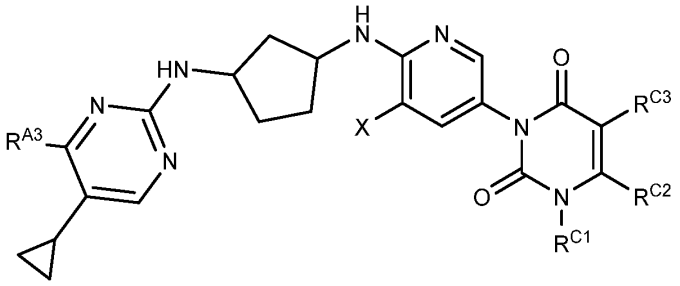
(I-Ccx),



(I-Cdx),



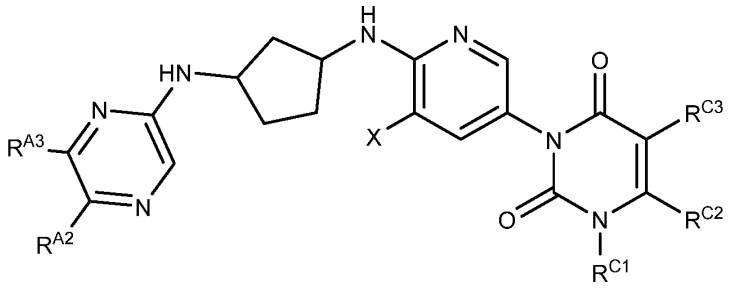
(I-Cdy),



(I-Cex),

wherein R^{A3}, X, R^{C1}, R^{C2} and R^{C3} are as defined in any other embodiment herein.

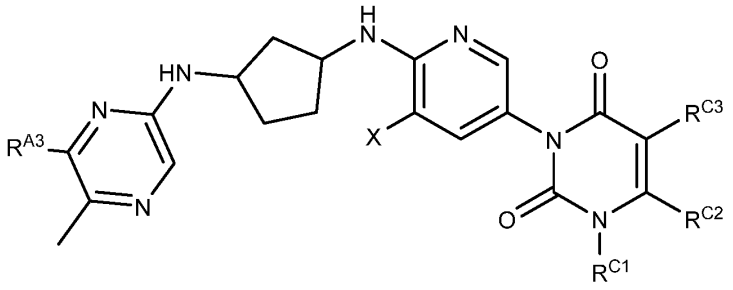
In other embodiments the compound of formula A-B-C is of the formula (I-Dx):



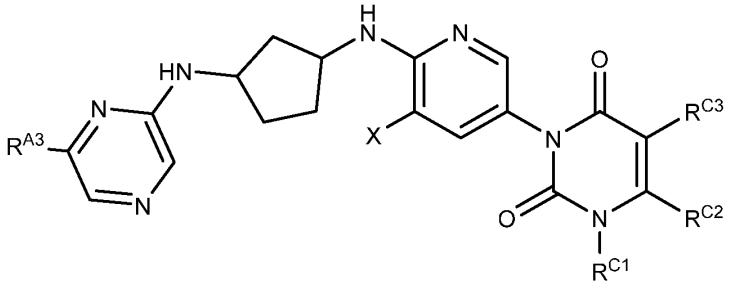
(I-Dx),

wherein R^{A2}, R^{A3}, X, R^{C1}, R^{C2} and R^{C3} are as defined in any other embodiment herein.

In some embodiments formula (I-Dx) can be formulae (I-Dax) or (I-Dbx) as shown below:



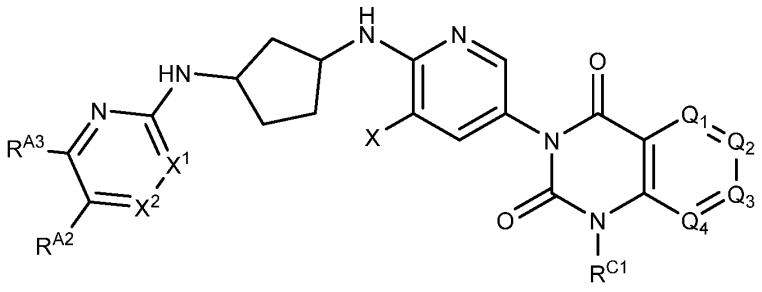
(I-Dax),



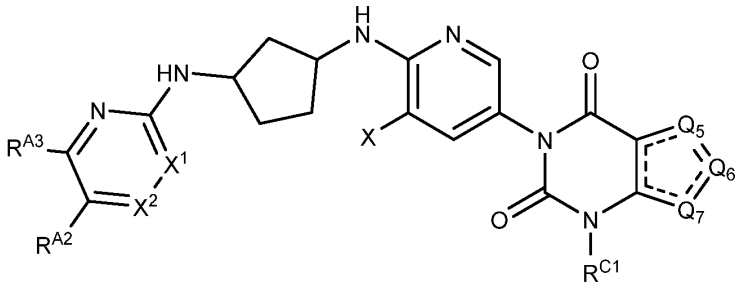
(I-Dbx),

wherein R^{A3}, X, R^{C1}, R^{C2} and R^{C3} are as defined in any other embodiment herein.

In other embodiments the compound of formula A-B-C is of the formulae (I-Eax), or (I-Ebx) as shown below:



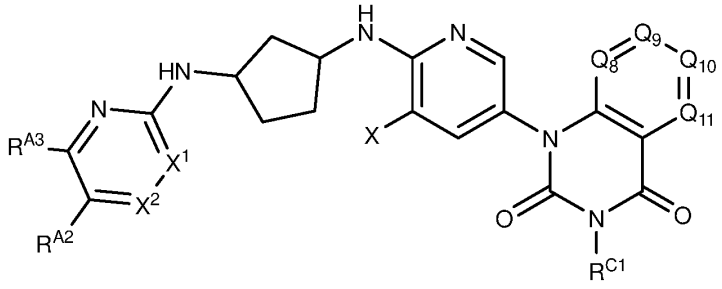
(I-Eax),



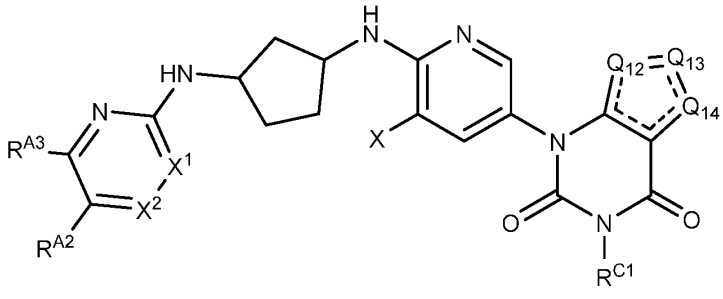
(I-Ebx),

wherein X^1, X^2, R^{A2}, R^{A3}, X and R^{C1} are as defined in any other embodiment herein; and wherein none, one or two of Q_1, Q_2, Q_3 and Q_4 is N and the remainder are C-H; none, one or two of Q_5, Q_6 and Q_7 is N, none or one of Q_5, Q_6 and Q_7 is S and the remainder are C-H.

In other embodiments the compound of formula A-B-C is of the formulae (I-Eay) or (I-Eby) as shown below:



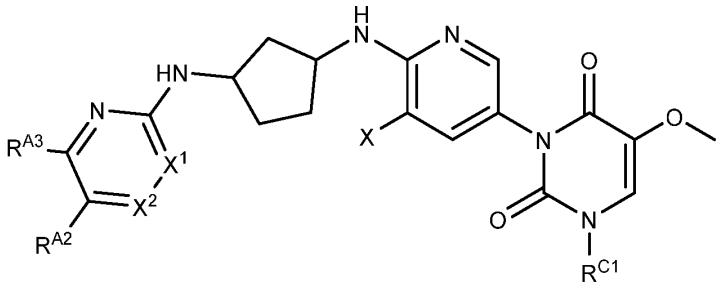
(I-Eay),



(I-Eby),

wherein X^1, X^2, R^{A2}, R^{A3}, X and R^{C1} are as defined in any other embodiment herein; and wherein none, one or two of Q_8, Q_9, Q_{10} and Q_{11} is N and the remainder are C-H; none, one or two of Q_{12}, Q_{13} and Q_{14} is N, none or one of Q_{12}, Q_{13} and Q_{14} is S and the remainder are C-H.

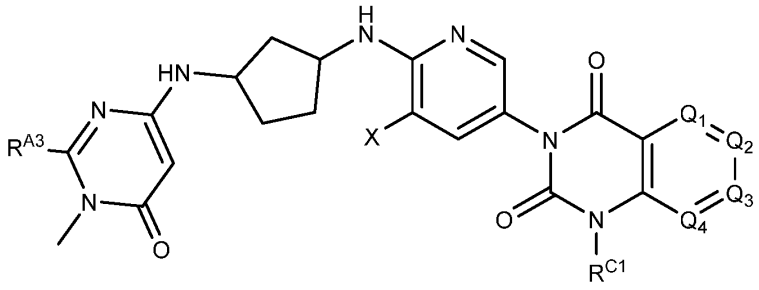
In other embodiments the compound of formula A-B-C is of the formula (I-Ec)) as shown below:



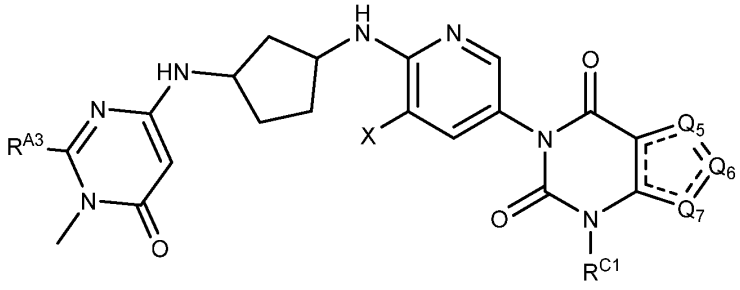
(I-Ec),

wherein X^1, X^2, R^{A2}, R^{A3}, X and R^{C1} are as defined in any other embodiment herein.

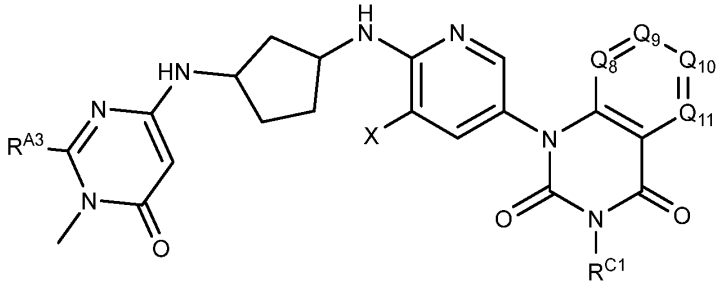
In other embodiments the compound of formula A-B-C is of the formulae (I-Fax), (I-Fbx), (I-Fay) or (I-Fby) as shown below:



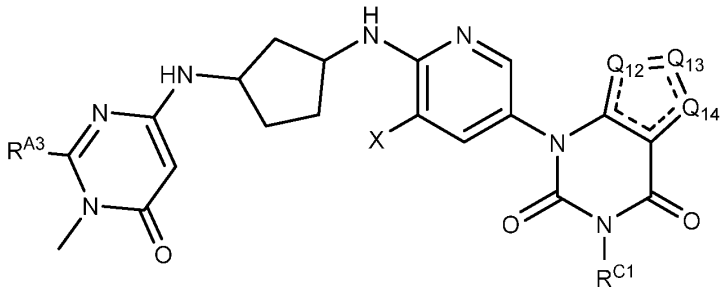
(I-Fax),



(I-Fbx),



(I-Fay),



(I-Fby),

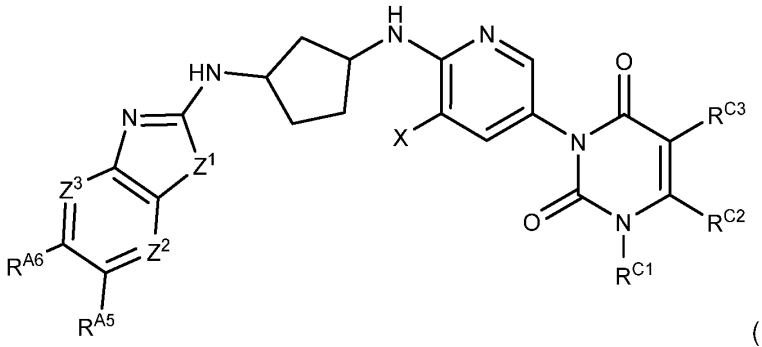
wherein R^{A3}, X and R^{C1} are as defined in any other embodiment herein; and

wherein none, one or two of Q_8, Q_9, Q_{10} and Q_{11} is N and the remainder are C-H;

none, one or two of Q_{12}, Q_{13} and Q_{14} is N, none or one of Q_{12}, Q_{13} and Q_{14} is S and the remainder are C-H.

A-B-C (A2a)

In other embodiments the compound of formula A-B-C is of the formula (II-Ax):

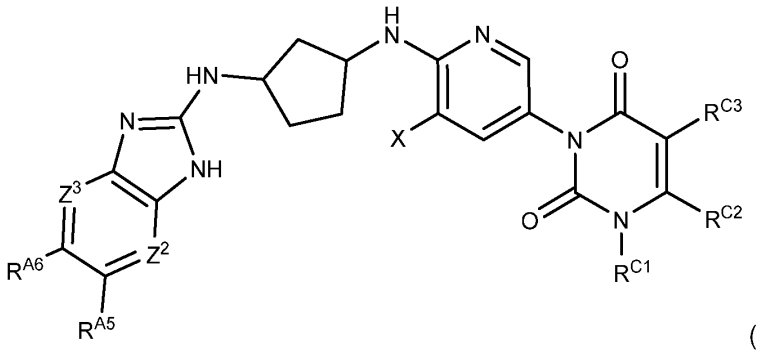


(II-Ax),

wherein Z^1, Z^2, Z^3, R^{A5}, R^{A6}, X, R^{C1}, R^{C2} and R^{C3} are as defined in any other embodiment herein.

In further embodiments when the compound of formula A-B-C is of the formula (II-Ax) it is of the formulae (II-A1x), (II-A2x) or (II-A3x).

In some embodiments formula (II-Ax) is formula (II-A1x):

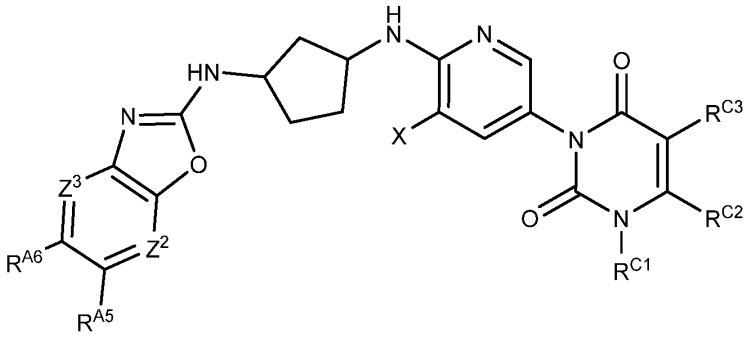


(II-A1x),

wherein R^{A5}, R^{A6}, X, R^{C1}, R^{C2} and R^{C3} are as defined in any other embodiment herein; and

wherein Z^2 is either N or C-H, Z^3 is either N or C-R^{A7} and when Z^2 is C-H then Z^3 is C-R^{A7}. R^{A5} is X^4 and R^{A2} is X^5.

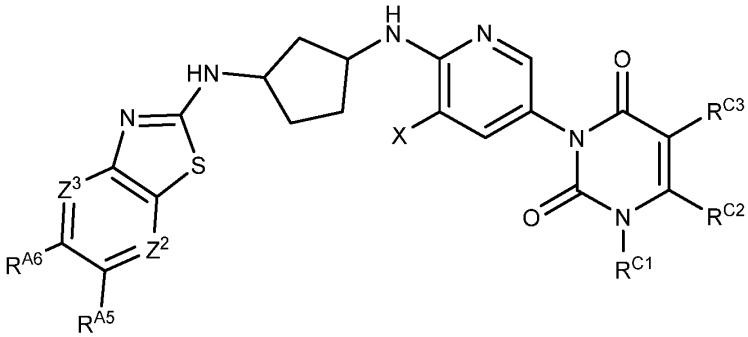
In some embodiments formula (II-Ax) is formula (II-A2x):



(II-A2x),

wherein R^{A5}, R^{A6}, X, R^{C1}, R^{C2} and R^{C3} are as defined in any other embodiment herein; and wherein Z^2 is either N or C-H, and when Z^2 is CH, R^{A5} is X^5 and R^{A6} is Z^4 and when Z^2 is N, R^{A5} is Z^4 and R^{A6} is Z^5. Z^3 is either N or C-R^{A7}.

In some embodiments formula (II-Ax) is formula (II-A3x):



(II-A3x),

wherein Z^2 is either N or C-H, and when Z^2 is N, R^{A5} is Z^4 and R^{A6} is Z^5, when Z^2 is C-H, R^{A5} is Z^4 and R^{A6} is Z^5. Z^3 is either N or C-R^{A3}.

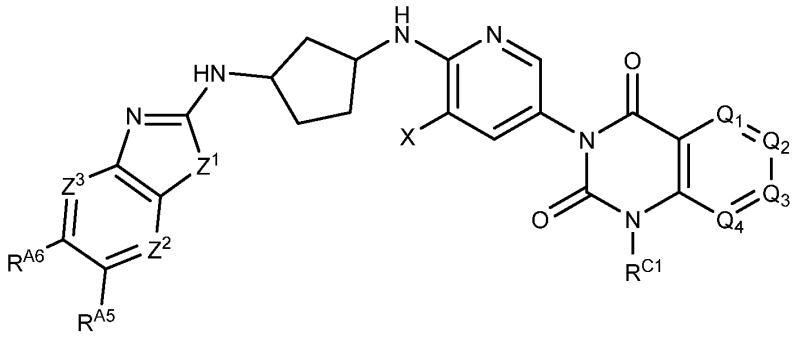
In some embodiments when A-B-C is of formulae (II-Ax), (II-A1x), (II-A2x) or (II-A3x) Z^4 is selected from the group consisting of H, halo, CN, C_1 alkyl optionally substituted by one or more OH, CN, or one or more halo groups or C_1 alkoxy, optionally substituted by one or more halo groups. In further embodiments Z^4 is selected from H, CN, CH_2OH, Br or methyl.

In some embodiments when A-B-C is of formulae (II-Ax), (II-A1x), (II-A2x) or (II-A3x) Z^5 is selected from the group consisting of H, one or more halo groups, CN, $C_{1\text{-}6}$ hydrocarbon,

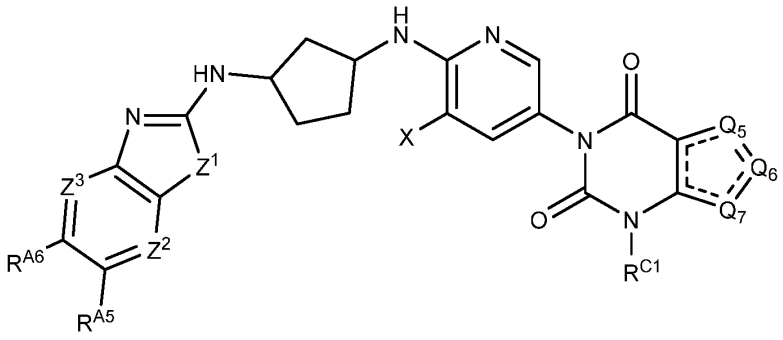
optionally substituted by OH, CN, C_{1-6} alkyl acyl, C_{1-6} alkoxy or one or more halo groups, C_{1-6} alkoxy, optionally substituted by C_{1-6} alkyl amido, or one or more halo groups, C_{1-6} alkylamino, C_{1-6} thioalkyl, or C_{1-6} alkyl phosphinyl. In further embodiments Z^5 is selected from H, CH_2OH, OCF_2H, OCF_3, CF_3, F, Cl, Br, ethyl, cyclopropyl, methyl, $P(=O)Me_2$, $S\text{-}CH_3$, CN, or OMe.

In some embodiments when A-B-C is of formulae (II-Ax), (II-A1x), (II-A2x) or (II-A3x), R^{A7} is selected from H, halo, CN, C_{1-6} alkyl optionally substituted by OH or one or more halo groups, C_{2-6} alkenyl optionally substituted by OH or one or more halo groups, C_{2-6} alkynyl optionally substituted by OH or one or more halo groups, and C_{1-6} alkoxy, optionally substituted by one or more halo groups. In further embodiments R^{A7} is selected from H, Cl, Br, OMe, $CH{=}CH_2$, OCF_3, OCF_2H, F, $CH_2\text{-}CF_2H$, CF_3, CF_2H, CN, propargyl and CH_2-cyclopropyl. In further embodiments R^{A7} is selected from H, Cl, Br and OMe.

In other embodiments the compound of formula A-B-C is of the formulae (II-Bax) or (II-Bbx) as shown below:



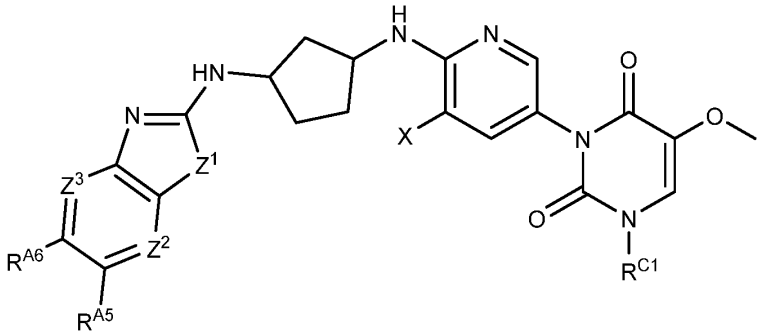
(II-Bax),



(II-Bbx),

wherein none, one or two of Q_1, Q_2, Q_3 and Q_4 is N and the remainder are C-H; and none, one or two of Q_5, Q_6 and Q_7 is N, none or one of Q_5, Q_6 and Q_7 is S and the remainder are C-H.

In other embodiments the compound of formula A-B-C is of the formula (II-Bc) as shown below:

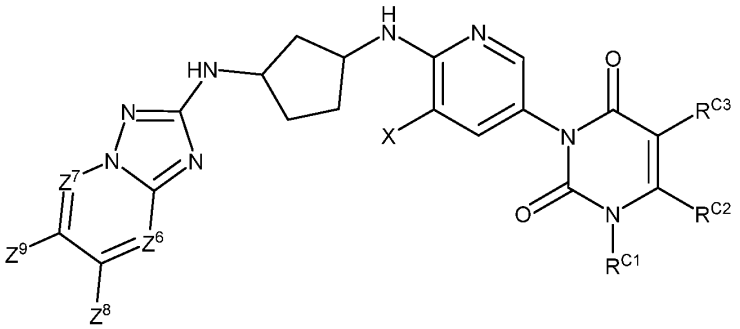


(II-Bc),

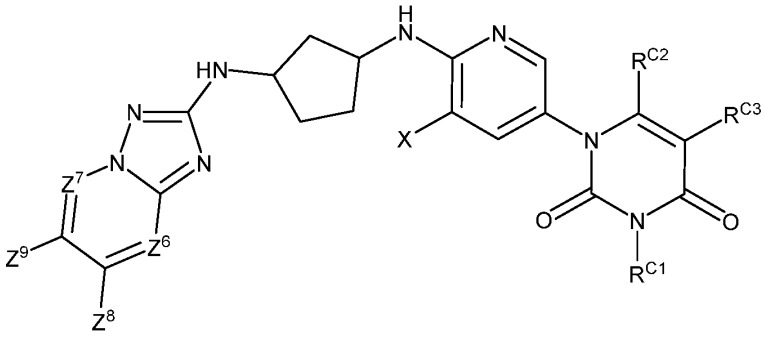
wherein Z^1, Z^2, Z^3, R^{A5}, R^{A6}, X and R^{C1} are as defined in any other embodiment herein.

A-B-C (A2b)

In other embodiments the compound of formula A-B-C is of the formulae (III-Ax) or (III-Ay):



(III-Ax),



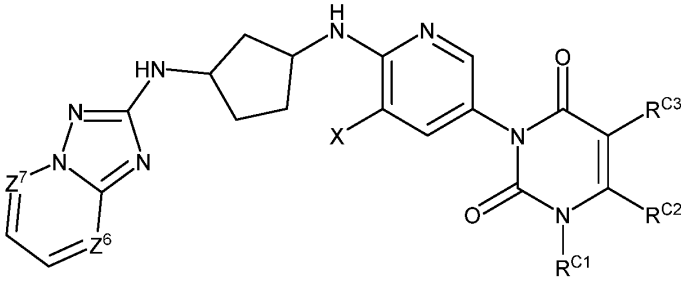
(III-Ay),

wherein Z^6, Z^7, Z^8, Z^9, X, R^{C1}, R^{C2} and R^{C3} are as defined in any other embodiment herein.

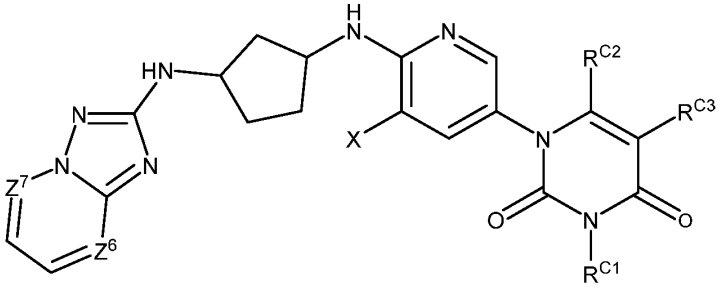
In some embodiments when A-B-C is of formulae (III-Ax) or (III-Ay), Z^8 and Z^9 are independently selected from the group consisting of H, one or more halo groups, CN, $C_{1\text{-}6}$ hydrocarbon, optionally substituted by OH, CN, $C_{1\text{-}6}$ alkyl acyl, $C_{1\text{-}6}$ alkoxy or one or more halo groups, $C_{1\text{-}6}$ alkoxy, optionally substituted by $C_{1\text{-}6}$ alkyl amido, or one or more halo groups, $C_{1\text{-}6}$ alkylamino, $C_{1\text{-}6}$ thioalkyl, and $C_{1\text{-}6}$ alkyl phosphinyl. In further embodiments Z^5 is selected from H, CH_2OH, OCF_2H, OCF_3, CF_3, F, Cl, Br, ethyl, cyclopropyl, methyl, $P(=O)Me_2$, $S\text{-}CH_3$ CN, and OMe.

In some embodiments when A-B-C is of formulae (III-Ax) or (III-Ay), R^{A8} is selected from H, halo, CN, C_{1-6} alkyl optionally substituted by OH or one or more halo groups, C_{2-6} alkenyl optionally substituted by OH or one or more halo groups, C_{2-6} alkynyl optionally substituted by OH or one or more halo groups, and C_{1-6} alkoxy, optionally substituted by one or more halo groups. In further embodiments R^{A8} is selected from H, Cl, Br, OMe, $CH{=}CH_2$, OCF_3, OCF_2H, F, CH_2-CF_2H, CF_3, CF_2H, CN, propargyl and CH_2-cyclopropyl. In further embodiments R^{A8} is selected from H, Cl, Br and OMe.

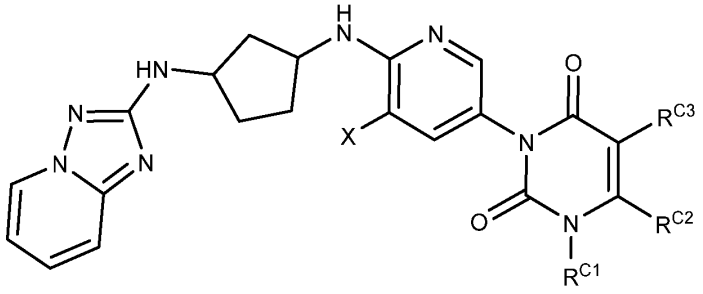
In some embodiments the compound of formula A-B-C is of the formulae (III-Bax), (III-Bay), (III-Bbx) or (III-Bby) as shown below:



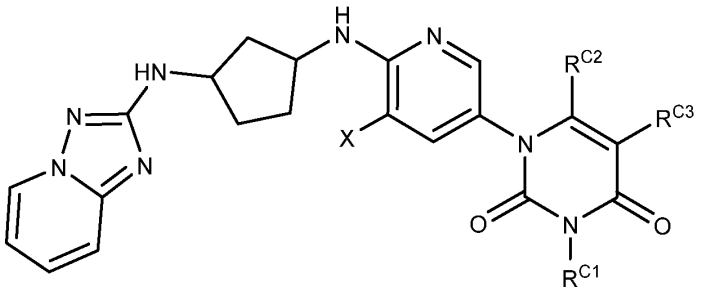
(III-Bax),



(III-Bay),



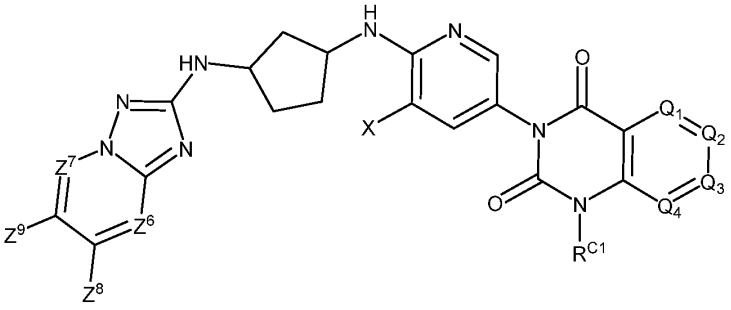
(III-Bbx),



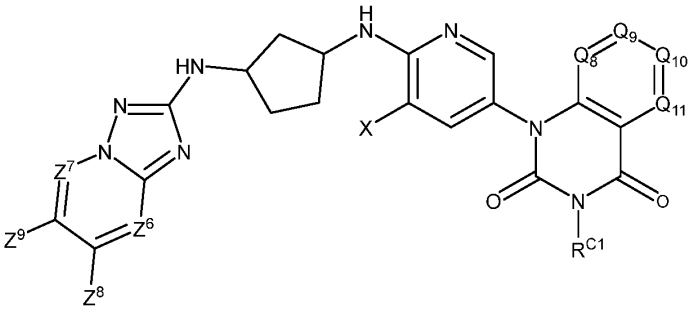
(III-Bby),

wherein Z^6, Z^7, X, R^{C1}, R^{C2} and R^{C3} are as defined in any other embodiment herein.

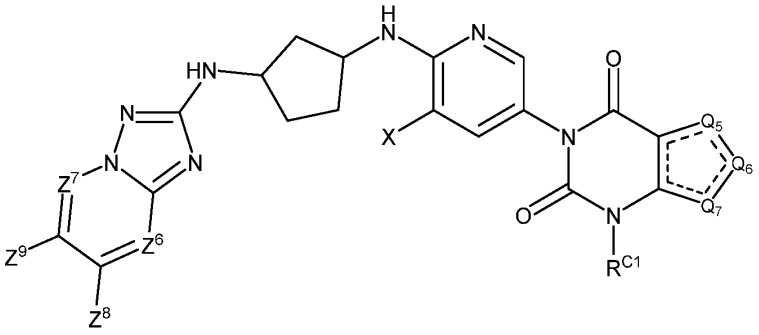
In other embodiments the compound of formula A-B-C is of the formulae (III-Cax), (III-Cay), (III-Cbx) or (III-Cby) as shown below:



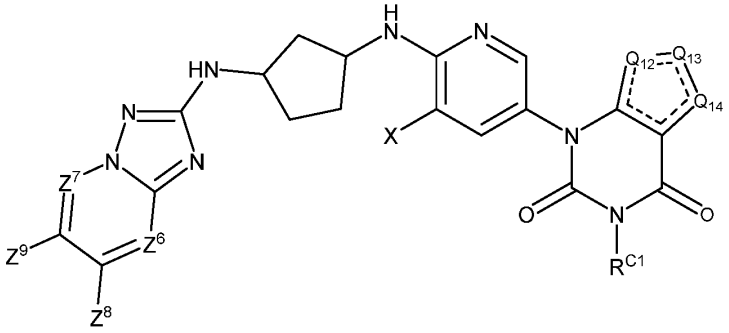
(III-Cax),



(III-Cay),



(III-Cbx),



(III-Cby),

wherein Z^6, Z^7, Z^8, Z^9, X and R^{C1} are as defined in any other embodiment herein,

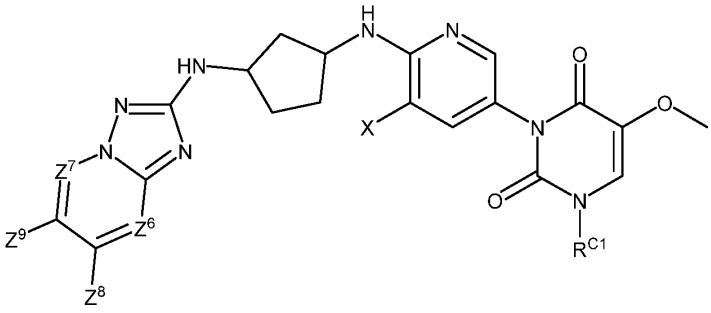
none, one or two of Q_1, Q_2, Q_3 and Q_4 is N and the remainder are C-H; and

none, one or two of Q_5, Q_6 and Q_7 is N, none or one of Q_5, Q_6 and Q_7 is S and the remainder are C-H;

none, one or two of Q_8, Q_9, Q_{10} and Q_{11} is N and the remainder are C-H; and

none, one or two of Q_{12}, Q_{13} and Q_{14} is N, none or one of Q_{12}, Q_{13} and Q_{14} is S and the remainder are C-H.

In other embodiments the compound of formula A-B-C is of the formula (III-Cc) as shown below:

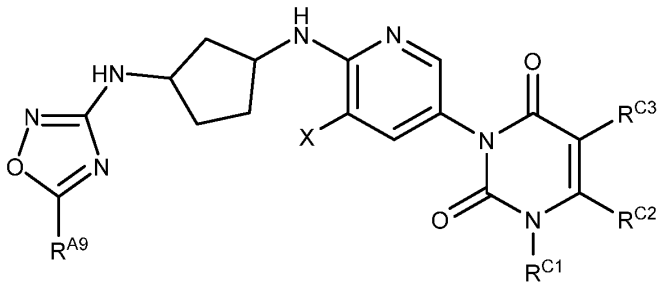


(III-Cc),

wherein Z^6, Z^7, Z^8, Z^9, X and R^{C1} are as defined in any other embodiment herein.

A-B-C (A3a) and (A3b)

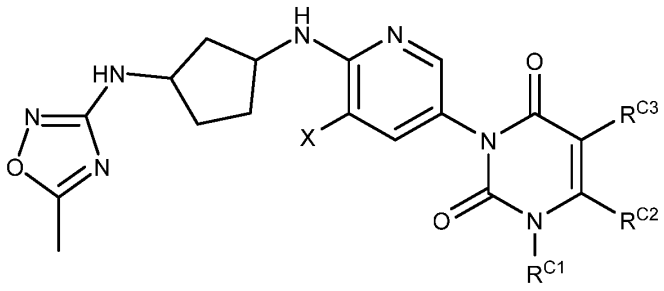
In other embodiments the compound of formula A-B-C is of the formula (IV-Ax):



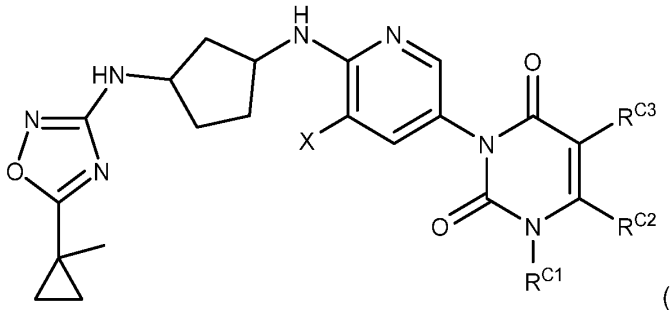
(IV-Ax),

wherein R^{A9}, X, R^{C1}, R^{C2} and R^{C3} are as defined in any other embodiment herein.

In other embodiments the compound of formula A-B-C is of the formulae (IV-Aax) or (IV-Abx) as shown below:



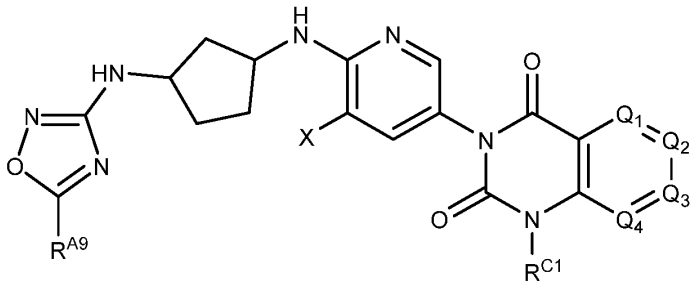
(IV-Aax),



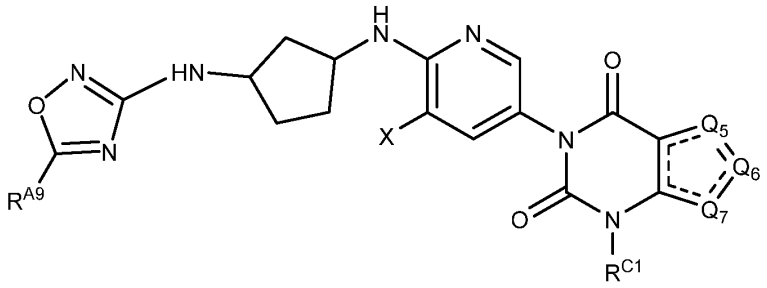
(IV-Abx),.

wherein X, R^{C1}, R^{C2} and R^{C3} are as defined in any other embodiment herein.

In other embodiments the compound of formula A-B-C is of the formulae (IV-Bax) or (IV-Bbx) as shown below:



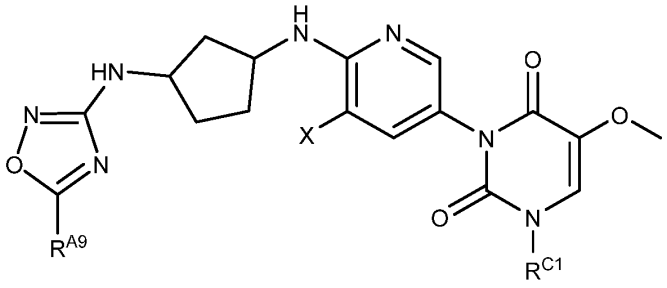
(IV-Bax),



(IV-Bbx),

wherein R^{A9}, X and R^{C1} are as defined in any other embodiment herein; and wherein none, one or two of Q_1, Q_2, Q_3 and Q_4 is N and the remainder are C-H; and none, one or two of Q_5, Q_6 and Q_7 is N, none or one of Q_5, Q_6 and Q_7 is S and the remainder are C-H.

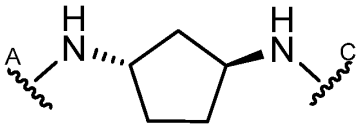
In other embodiments the compound of formula A-B-C is of the formula (IV-Bc) as shown below:



(IV-Bc),

wherein R^{A9}, X and R^{C1} are as defined in any other embodiment herein.

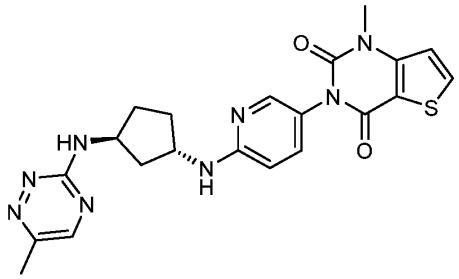
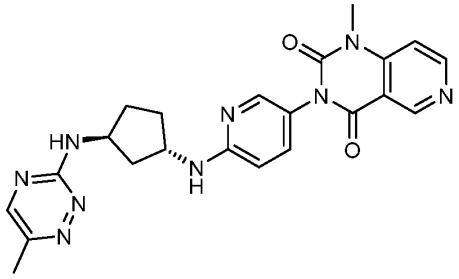
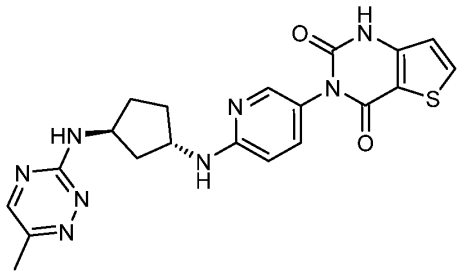
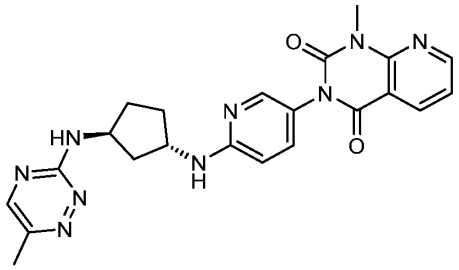
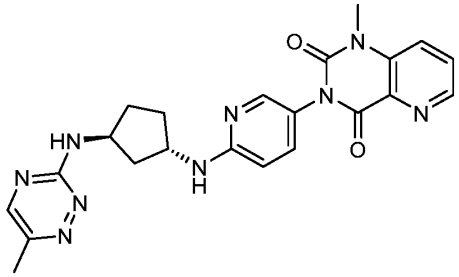
In some embodiments, the stereochemistry of the B group in any of the above A-B-C formulae (I-Ax), (I-Ay), (I-Bx), (I-By), (I-Bax), (I-Bay), (I-Bbx), (I-Bby), (I-Bcx). (I-Bcy), (I-Cx), (I-Cax), (I-Cbx), (I-Ccx), (I-Cdx), (I-Cex), (I-Dx), (I-Dax), (I-Dbx), (I-Eax), (I-Ebx), (I-Eay), (I-Eby), (I-Ec), (I-Fax), (I-Fbx), (I-Fay), (I-Fby), (II-Ax), (II-A1x), (II-A2x), (II-A3x), (II-Bax), (II-Bbx), (II-Bc), (III-Ax), (III-Ay), (III-Bax), (III-Bay), (III-Bbx), (III-Bby), (III-Cax), (III-Cay), (III-Cbx), (III-Cby), (III-Cc), (IV-Ax), (IV-Aax), (IV-Abx), (IV-Bax), (IV-Bbx) and (IV-Bc) is as follows:

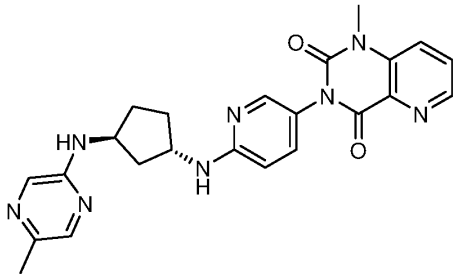
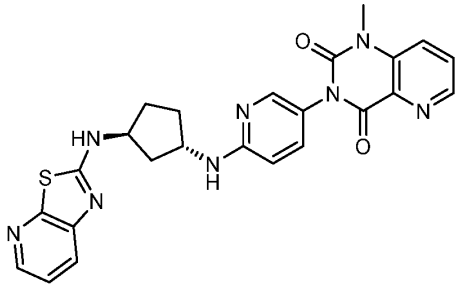
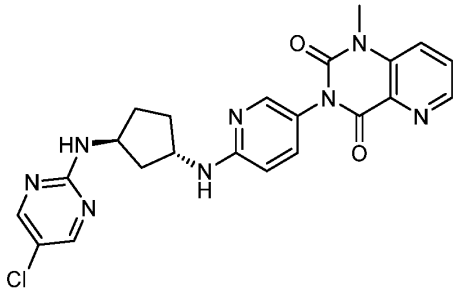
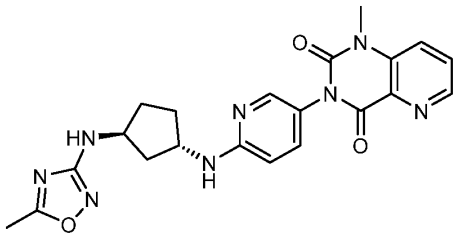


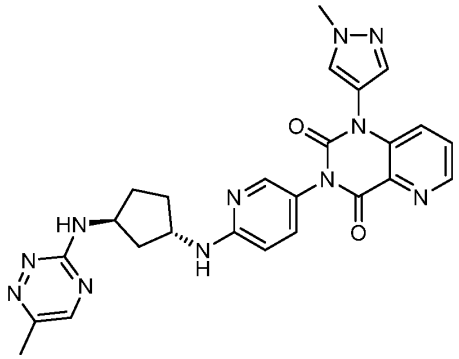
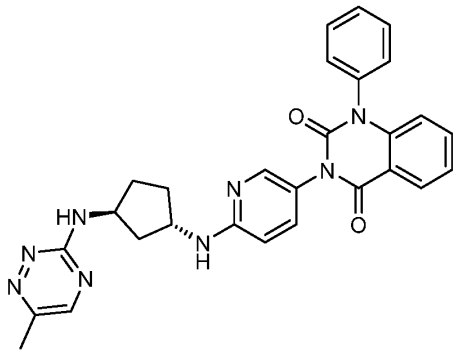
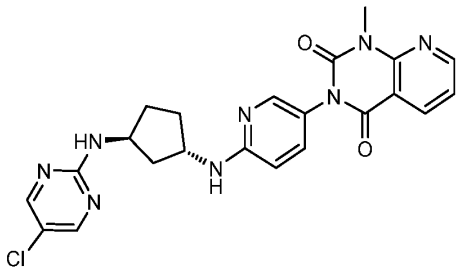
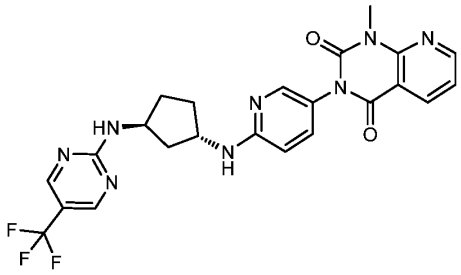
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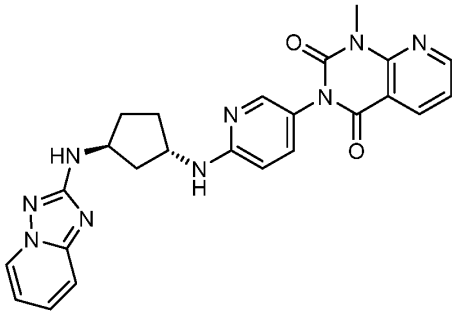
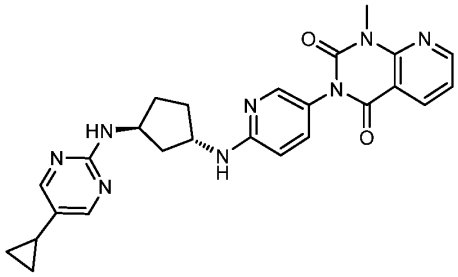
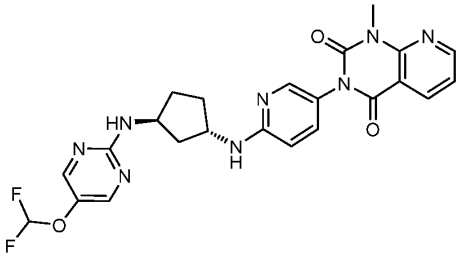
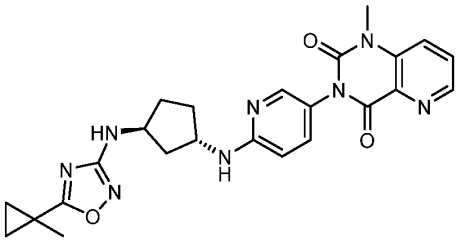
In some embodiments the compound of formula (I) is selected from the following in Table 1. In some embodiments, the compound is a pharmaceutically acceptable salt of a compound selected from the following in Table 1.

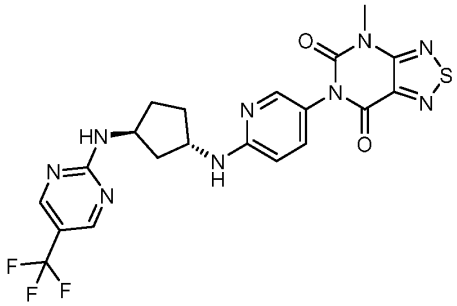
Table 1 - Examples 1 to 18

Example No	Structure	Example Name
1		1-Methyl-3-(6-(((1*S*,3*S*)-3-((6-methyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)thieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione
2		1-Methyl-3-(6-(((1*S*,3*S*)-3-((6-methyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyrido[4,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione
3		3-(6-(((1*S*,3*S*)-3-((6-Methyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)thieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione
4		1-Methyl-3-(6-(((1*S*,3*S*)-3-((6-methyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione
5		1-Methyl-3-(6-(((1*S*,3*S*)-3-((6-methyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione

Example No	Structure	Example Name
6		1-Methyl-3-(6-(((1*S*,3*S*)-3-((5-methylpyrazin-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione
7		1-Methyl-3-(6-(((1*S*,3*S*)-3-(thiazolo[5,4-*b*]pyridin-2-ylamino)cyclopentyl)amino)pyridin-3-yl)pyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione
8		3-(6-(((1*S*,3*S*)-3-((5-Chloropyrimidin-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)-1-methylpyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione
9		1-Methyl-3-(6-(((1*S*,3*S*)-3-((5-methyl-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione

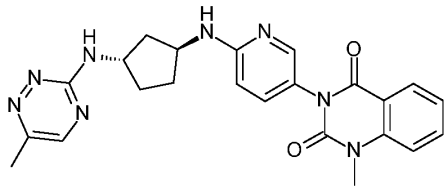
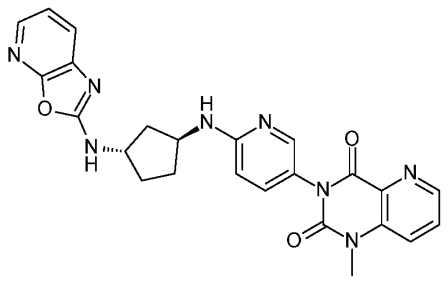
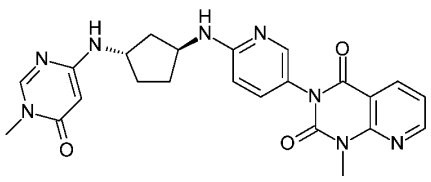
Example No	Structure	Example Name
10		3-(6-(((1*S*,3*S*)-3-((6-Methyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)-1-(1-methyl-1*H*-pyrazol-4-yl)pyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione
11		3-(6-(((1*S*,3*S*)-3-((6-Methyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)-1-phenylquinazoline-2,4(1*H*,3*H*)-dione
12		3-(6-(((1*S*,3*S*)-3-((5-Chloropyrimidin-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)-1-methylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione
13		1-Methyl-3-(6-(((1*S*,3*S*)-3-((5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione

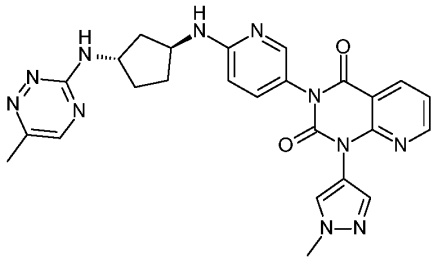
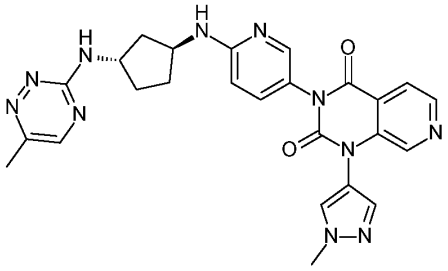
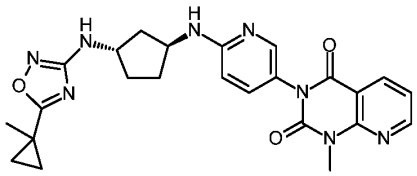
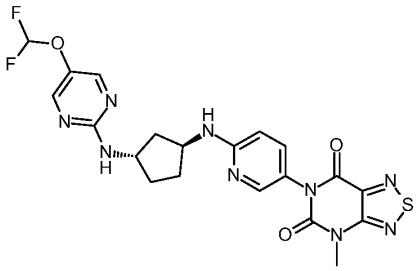
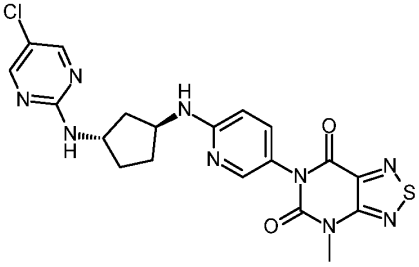
Example No	Structure	Example Name
14		3-(6-(((1*S*,3*S*)-3-([1,2,4]Triazolo[1,5-*a*]pyridin-2-ylamino)cyclopentyl)amino)pyridin-3-yl)-1-methylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione
15		3-(6-(((1*S*,3*S*)-3-((5-Cyclopropylpyrimidin-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)-1-methylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione
16		3-(6-(((1*S*,3*S*)-3-((5-(Difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)-1-methylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione
17		1-Methyl-3-(6-(((1*S*,3*S*)-3-((5-(1-methylcyclopropyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione

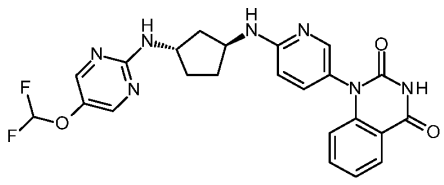
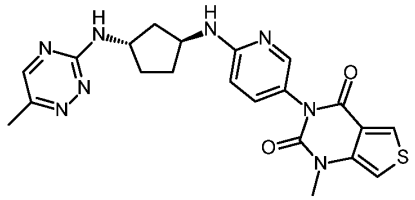
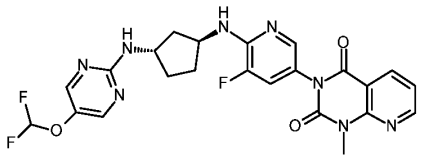
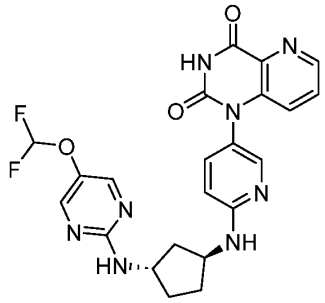
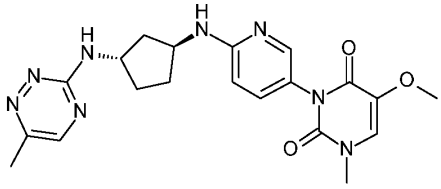
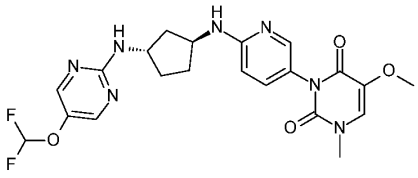
Example No	Structure	Example Name
18		4-Methyl-6-(6-(((1*S*,3*S*)-3-((5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)-[1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione

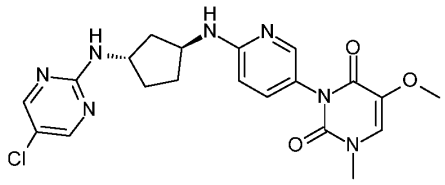
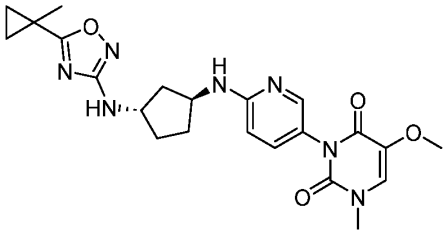
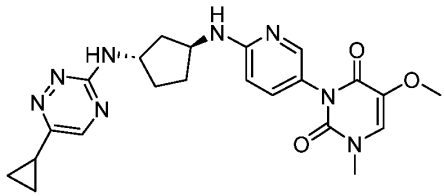
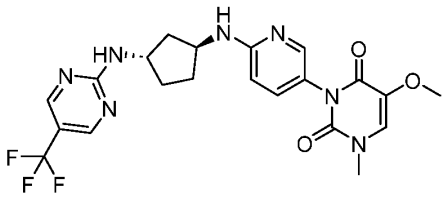
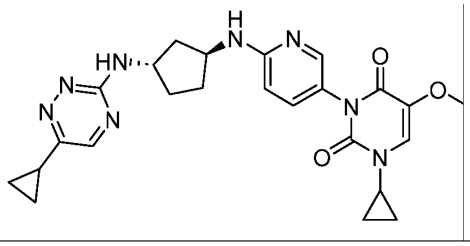
In some embodiments the compound of formula (I) is selected from the following in Table 2. In some embodiments, the compound is a pharmaceutically acceptable salt of a compound selected from the following in Table 2.

Table 2 - Examples 19 to 37

Example No	Structure	Example Name
19		1-Methyl-3-(6-(((1*S*,3*S*)-3-((6-methyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)quinazoline-2,4(1*H*,3*H*)-dione
20		1-Methyl-3-(6-(((1*S*,3*S*)-3-(oxazolo[5,4-*b*]pyridin-2-ylamino)cyclopentyl)amino)pyridin-3-yl)pyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione
21		1-Methyl-3-(6-(((1*S*,3*S*)-3-((1-methyl-6-oxo-1,6-dihydropyrimidin-4-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione

22		3-(6-(((1*S*,3*S*)-3-((6-Methyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)-1-(1-methyl-1*H*-pyrazol-4-yl)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione
23		3-(6-(((1*S*,3*S*)-3-((6-Methyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)-1-(1-methyl-1*H*-pyrazol-4-yl)pyrido[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione
24		1-Methyl-3-(6-(((1*S*,3*S*)-3-((5-(1-methylcyclopropyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione
25		6-(6-(((1*S*,3*S*)-3-((5-(Difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)-4-methyl-[1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione
26		6-(6-(((1*S*,3*S*)-3-((5-Chloropyrimidin-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)-4-methyl-[1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione

27		1-(6-(((1*S*,3*S*)-3-((5-(Difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)quinazoline-2,4(1*H*,3*H*)-dione
28		1-Methyl-3-(6-(((1*S*,3*S*)-3-((6-methyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)thieno[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione
29		3-(6-(((1*S*,3*S*)-3-((5-(Difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-5-fluoropyridin-3-yl)-1-methylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione
30		1-(6-(((1*S*,3*S*)-3-((5-(Difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione
31		5-Methoxy-1-methyl-3-(6-(((1*S*,3*S*)-3-((6-methyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyrimidine-2,4(1*H*,3*H*)-dione
32		3-(6-(((1*S*,3*S*)-3-((5-(Difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)-5-methoxy-1-methylpyrimidine-2,4(1*H*,3*H*)-dione

33		3-(6-(((1*S*,3*S*)-3-((5-Chloropyrimidin-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)-5-methoxy-1-methylpyrimidine-2,4(1*H*,3*H*)-dione
34		5-Methoxy-1-methyl-3-(6-(((1*S*,3*S*)-3-((5-(1-methylcyclopropyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyrimidine-2,4(1*H*,3*H*)-dione
35		3-(6-(((1*S*,3*S*)-3-((6-Cyclopropyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)-5-methoxy-1-methylpyrimidine-2,4(1*H*,3*H*)-dione
36		5-Methoxy-1-methyl-3-(6-(((1*S*,3*S*)-3-((5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyrimidine-2,4(1*H*,3*H*)-dione
37		1-Cyclopropyl-3-(6-(((1*S*,3*S*)-3-((6-cyclopropyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)-5-methoxypyrimidine-2,4(1*H*,3*H*)-dione

In some embodiments the compound is selected from Examples 1, 4, 7, 8, 13, 15. In some embodiments, the compound is a pharmaceutically acceptable salt of a compound selected from Examples 1, 4, 7, 8, 13, 15.

In some embodiments the compound is selected from Examples 8, 13 and 15. In some embodiments, the compound is a pharmaceutically acceptable salt of a compound selected from Examples 8, 13 and 15.

In some embodiments the compound is selected from Examples 1-20, 22-26, and 28. In some embodiments, the compound is a pharmaceutically acceptable salt of a compound selected from Examples 1-20, 22-26, and 28.

In some embodiments the compound is selected from Examples 4, 14, 19, 30, 31, 32, 33 and 34. In some embodiments, the compound is a pharmaceutically acceptable salt of a compound selected from Examples 4, 14, 19, 30, 31, 32, 33 and 34.

In some embodiments, the compound is selected from Examples 4, 14, and 32. In some embodiments, the compound is a pharmaceutically acceptable salt of a compound selected from Examples 4, 14, and 32.

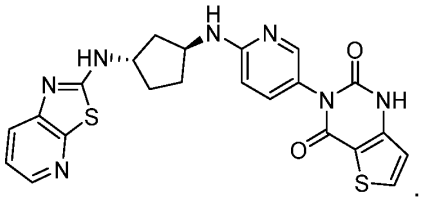
In some embodiments the compound is selected from Examples 4 and 14. In some embodiments, the compound is a pharmaceutically acceptable salt of a compound selected from Examples 4 and 14.

In some embodiments the compound is Example 4. In some embodiments, the compound is a pharmaceutically acceptable salt of Example 4.

In some embodiments the compound is Example 14. In some embodiments, the compound is a pharmaceutically acceptable salt of Example 14.

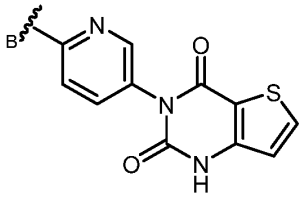
In some embodiments the compound is Example 32. In some embodiments, the compound is a pharmaceutically acceptable salt of Example 32.

In some embodiments, the compound is not;



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In some embodiments, C is not of the formula;



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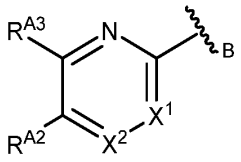
Any definitions herein relating to formula (A1a) and its substituents may be understood as being equally applicable to formula (A1), and vice versa.

In some embodiments, there is provided a compound of Formula (I)

A-B-C (I)

or a pharmaceutically acceptable salt thereof,

wherein A is of one of the following formulae:



(A1)

wherein the wavy line indicates the point of attachment to B;

X^1 is N or C-R^{A1};

X^2 is N or C-R^{A4};

R^{A1} is selected from the group consisting of:

(i) H;

(ii) halo;

(iii) CN;

(iv) C_{1-6} hydrocarbon, optionally substituted by OH, CN, C_{1-6} alkyl acyl, C_{1-6} alkoxy or one or more halo groups;

(v) C_{1-6} alkoxy, optionally substituted by OH, one or more halo groups, or C_{1-6} alkyl amido;

(vi) C_{1-6} alkyl ester;

(vii) C_{1-6} alkyl acyl; and

(viii) OH;

R^{A2} is selected from the group consisting of:

(i) H;

(ii) halo;

(iii) CN;

(iv) C_{1-6} hydrocarbon, optionally substituted by OH, CN, C_{1-6} alkyl acyl, C_{1-6} alkoxy or one or more halo groups;

(v) C_{1-6} alkoxy, optionally substituted by OH, C_{1-6} alkyl amido, or one or more halo groups;

(vi) C_{1-6} acylamido (wherein the acyl is optionally substituted by H or methyl);

(vii) C_{1-6} thioalkyl;

(viii) C_{1-6} alkyl ester;

(ix) C_{1-6} alkyl acyl;

(x) C_{4-5} heterocyclyl;

(xi) C_5 heteroaryl;

(xii) C_{1-6} alkyl amido, optionally substituted by C_{1-3} alkyl amido, CN, OH, C_{2-3} alkynyl, C_{4-6} heterocyclyl or C_{1-3} alkyl wherein the C_{1-3} alkyl is optionally substituted with one or more halo or OH groups;

(xiii) OH; and

(xiv) C_{1-6} alkylamino;

R^{A3} is selected from the group consisting of:

(i) H;

(ii) halo;

(iii) CN;

(iv) C_{1-6} hydrocarbon which is optionally substituted by OH, CN, C_{1-6} thioalkyl, C_{1-6} alkoxy, C_{1-6} alkyl acyl, C_{1-6} acyloxy, carboxy, C_{1-6} alkyl ester, C_{1-6} alkylamino, -C(=O)NH_2, C_{1-6} alkyl amido, C_{1-6} alkyl acylamido, C_{1-6} alkyl sulfinyl, C_{1-6} alkyl sulfonyl or one or more halo groups;

(v) OH;

(vi) C_{1-6} alkoxy, optionally substituted by OH, NH_2, C_4 heterocyclyl or one or more halo groups;

(vii) C_{1-6} acyloxy;

(viii) C_4 heterocycyl;

(ix) NH_2;

(x) C_{1-6} alkylamino, optionally substituted by CN, OH, or C_4 heterocyclyl;

(xi) C_{1-6} dialkylamino, optionally substituted by -NH_2;

(xii) C_{1-6} acylamido (where acyl substituent is H or Me);

(xiii) carbaimidoyl or methyl-carbaimidoyl;

(xiv) carboxyamino;

(xv) C_{1-6} thioalkyl, optionally substituted by OH or NH_2;

(xvi) C_{1-6} alkyl sulfinyl;

(xvii) C_{1-6} alkyl sulfonyl, optionally substituted by one or more halo groups;

(xviii) C_{1-6} sulfonimodyl;

(xix) C_{1-6} alkyl phosphinyl;

(xx) carboxy;

(xxi) C(=O)NH_2;

(xxii) C_{1-6} alkyl ester;

(xxiii) C_{1-6} alkyl acyl, optionally substituted by one or more halo groups; and

(xxiv) C_{1-6} alkyl amido;

or wherein R^{A3} and R^{A2} together with the carbon atoms to which they are bound form:

(i) an optionally substituted C_{5-7} heterocycle ring;

(ii) an optionally substituted C_{5-7} heteroaromatic ring;

(iii) an optionally substituted C_6 carboaromatic ring; or

(iv) an optionally substituted C_{5-7} carbocyclic ring

wherein, when present, the one, two, three or four optional substituents independently selected from C_{1-6}alkyl, halo, C_{1-6} alkoxy, NH_2, C_{1-6}alkylamino, OH, and CN;

R^{A4} is selected from the group consisting of:

(i) H;

(ii) halo;

(iii) CN;

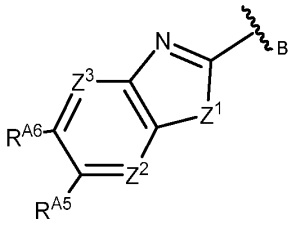
(iv) C_{1-6} hydrocarbon, optionally substituted by one or more OH, CN, C_{1-6} alkyl acyl, C_{1-6} alkoxy or one or more halo groups;

(v) C_{1-6} alkoxy, optionally substituted by OH, one or more halo groups, C_{1-6} alkyl amido;

(vi) C_{1-6} alkyl ester;

(vii) C_{1-6} alkyl acyl; and

(viii) OH;



(A2a)

wherein the wavy line indicates the point of attachment to B;

Z^1 is selected from O, S or NH;

Z^2 is either N or C-H

Z^3 is either N or C-R^{A7};

wherein if Z^1 is NH and Z^2 is C-H then Z^3 is C-R^{A7};

when Z^1 is NH, R^{A5} is Z^4 and R^{A6} is Z^5;

when Z^2 is N and Z^1 is O or S, R^{A5} is Z^4 and R^{A6} is Z^5;

when Z^2 is CH and Z^1 is S, R^{A5} is Z^4 and R^{A6} is Z^5;

when Z^2 is CH and Z^1 is O, R^{A5} is Z^5 and R^{A6} is Z^4;

Z^4 is selected from the group consisting of:

(i) H;

(ii) halo;

(iii) CN;

(iv) C_1 alkyl optionally substituted by one or more OH, CN, or one or more halo groups; and

(v) C_1 alkoxy, optionally substituted by one or more halo groups;

Z^5 is selected from the group consisting of:

(i) H;

(ii) halo;

(iii) CN;

(iv) C_{1-6} hydrocarbon, optionally substituted by OH, CN, C_{1-6} alkyl acyl, C_{1-6} alkoxy or one or more halo groups;

(v) C_{1-6} alkoxy, optionally substituted by C_{1-6} alkyl amido, C_{1-6} alkyl phosphonyl, or one or more halo groups;

(vi) C_{1-6} alkylamino;

(vii) C_{1-6} thioalkyl;

(viii) C_{1-6} alkyl phosphinyl; and

(ix) C_{1-6} alkyl phosphonyl;

R^{A7} is selected from the group consisting of:

(i) H;

(ii) halo;

(iii) CN;

(iv) C_{1-6} hydrocarbon, optionally substituted by OH, CN, C_{1-6} thioalkyl, C_{1-6} alkoxy, C_{1-6} alkyl acyl, C_{1-6} acyloxy, C(=O)OH, C_{1-6} alkyl ester, C_{1-6} alkylamino; $-C(=O)NH_2$, C_{1-6} alkyl amido, C_{1-6} acylamido, C_{1-6} alkyl sulfinyl, C_{1-6} alkyl sulfonyl or one or more halo groups;

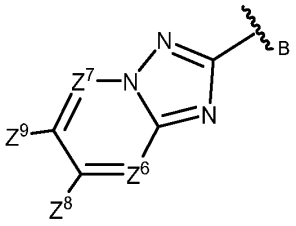
(v) C_{1-6} alkoxy, optionally substituted by NH_2, C_4 heterocyclyl and one or more halo groups;

(vi) C_4 heterocycyl;

(vii) C_{1-6} alkylamino, optionally substituted by CN, OH, C_4 heterocyclyl;

(viii) C_{1-6} dialkylamino, optionally substituted by $-NH_2$; and

(ix) C_{1-6} thioalkyl, optionally substituted by OH or $-NH_2$;



(A2b)

wherein the wavy line indicates the point of attachment to B;

Z^6 is either N or C-H

Z^7 is either N or C-R^{A8}

Z^8 and Z^9 are independently selected from the group consisting of:

(i) H;

(ii) halo;

(iii) CN;

(iv) C_{1-6} hydrocarbon, optionally substituted by OH, CN, C_{1-6} alkyl acyl, C_{1-6} alkoxy or one or more halo groups;

(v) C_{1-6} alkoxy, optionally substituted by C_{1-6} alkyl amido, C_{1-6} alkyl phosphonyl, or one or more halo groups;

(vi) C_{1-6} alkylamino

(vii) C_{1-6} thioalkyl,

(viii) C_{1-6} alkyl phosphinyl; and

(ix) C_{1-6} alkyl phosphonyl;

R^{A8} is selected from the group consisting of:

(i) H;

(ii) halo;

(iii) CN;

(iv) C_{1-6} hydrocarbon, optionally substituted by OH, CN, C_{1-6} thioalkyl, C_{1-6} alkoxy, C_{1-6} alkyl acyl, C_{1-6} acyloxy, C(=O)OH, C_{1-6} alkyl ester, C_{1-6} alkylamino; -C(=O)NH_2, C_{1-6} alkyl amido, C_{1-6} acylamido, C_{1-6} alkyl sulfinyl, C_{1-6} alkyl sulfonyl or one or more halo groups;

(v) C_{1-6} alkoxy, optionally substituted by NH_2, C_4 heterocyclyl or one or more halo groups;

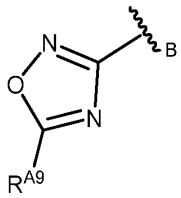
(vi) C_4 heterocycyl;

(vii) C_{1-6} alkylamino, optionally substituted by CN, OH, C_4 heterocyclyl;

(viii) C_{1-6} dialkylamino, optionally substituted by -NH_2; and

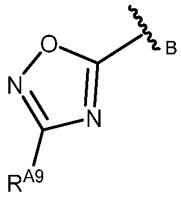
(ix) C_{1-6} thioalkyl, optionally substituted by OH or -NH_2;

(A3a)



; or

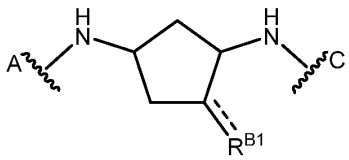
(A3b)



wherein the wavy line indicates the point of attachment to B;

where R^{A9} is selected from H; methyl, ethyl, n-propyl, *i*-propyl, cyclopropyl, 1-methylcyclopropyl and 2-methylcyclopropyl;

wherein B is of formula:

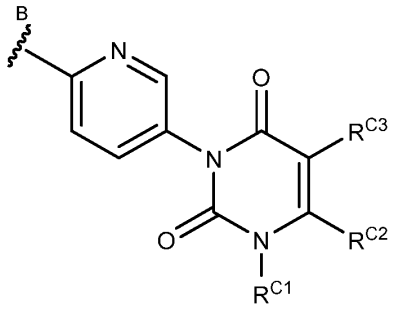


(B-1)

wherein the wavy lines indicate the points of attachment to A and C;

R^{B1} is H, OH, =$CHCH_2$-OH, C_{1-4} alkyoxy, or C_{1-4} alkyl which C_{1-4} alkyl is optionally substituted by OH or OMe;

wherein C is of formula:



(C-1)

R^{C2} and R^{C3} together represent a fused benzene ring or C_{5-6} heteroaromatic ring, which rings are optionally substituted by one or more R^{C4} groups;

R^{C1} is selected from:

(i) H;

(ii) C_{1-6} alkyl optionally substituted by one or more halo groups;

(iii) C_{5-6} heterocyclyl or C_{5-6}heteroaryl with an optional methyl substituent;

(iv) phenyl optionally substituted by one or more halo atoms;

R^{C4} is selected from:

(i) C_{1-6} alkyl optionally substituted by one or more halo groups;

(ii) C_{1-6} alkoxy optionally substituted by one or more halo groups;

(iii) C_{5-6} heterocyclyl or C_{5-6}heteroaryl with an optional methyl substituent;

(iv) di-C_{1-6} alkyl amido;

(v) C_{1-6} acylamido;

(vi) halo; and

(vii) CN.

In some embodiments, the compound of Formula (I) is not according to one or more of the specific compounds described in WO 2024078620 A1.

In some embodiments, the compound of Formula (I) is not according to one or more of the specific compounds described in WO 2025021188 A1.

In some embodiments, the compound of Formula (I) is not according to one or more of the specific compounds described in WO 2025007915 A1.

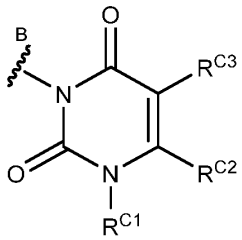
General synthesis

The compounds according to general formula (**I-G**), (**G9**) and (**G17**) can be prepared according to the following schemes 1, 2, 3, 4, 5 and 6. The schemes and procedures described below illustrate synthetic routes to the compounds of general formula (**I-G**), (**G9**) and (**G17**) and are

not intended to be limiting. It is clear that the order of transformations as exemplified in schemes 1, 2, 3, 4, 5 and 6 can be modified in various ways. The order of transformations exemplified in these schemes is therefore not intended to be limiting.

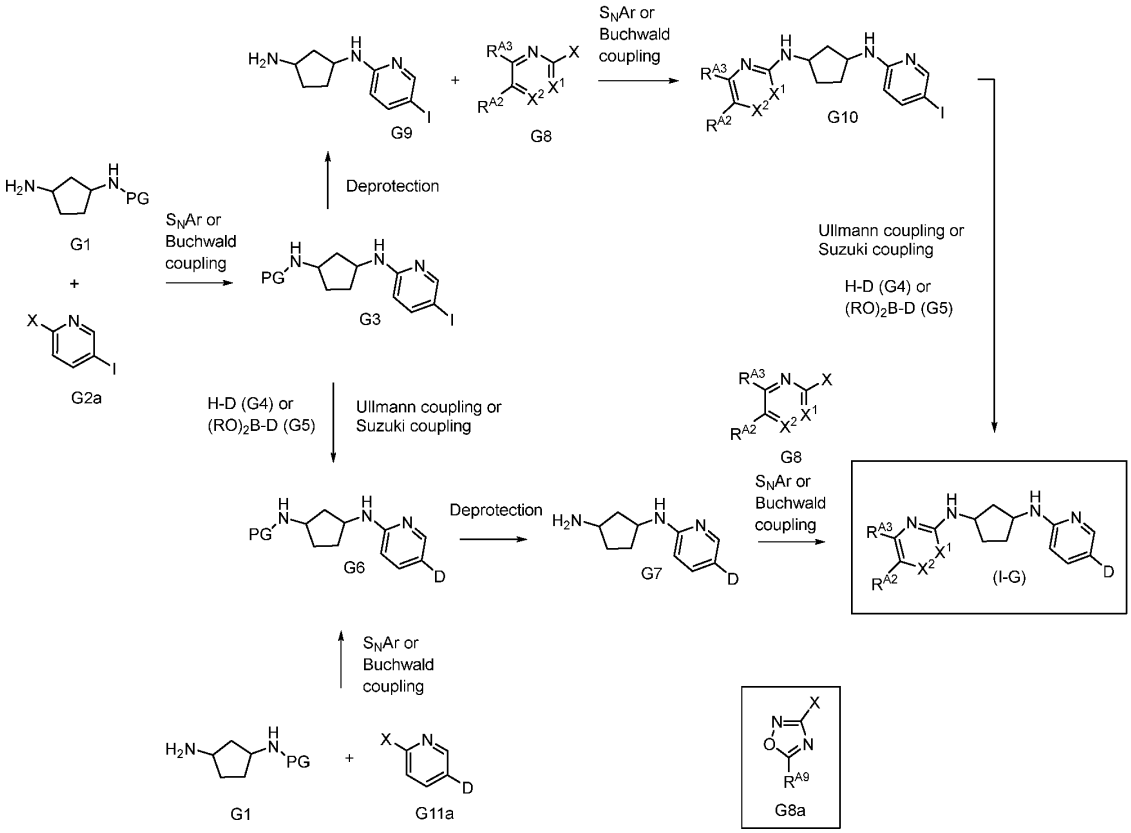
Routes for the preparation of compounds of general formula (**I-G**), (**G9**) and (**G17**) and corresponding intermediates are described in schemes 1, 2, 3, 4, 5 and 6.

In each of schemes 1 to 6, D has the formula:



wherein R^{C1}, R^{C2} and R^{C3} are as defined for (C-1).

Scheme 1



Scheme 1: Routes for the preparation of compounds of general formula (**I-G**) in which X is a leaving group, PG is a protective group and X^1, X^2, R^{A2} and R^{A3} have the meaning as given for formula (**A1a**), *supra*. D is defined above.

Monoarylated diamines of general formula (**G3**) can be obtained via nucleophilic aromatic substitution (S_NAr) or palladium catalyzed Buchwald-Hartwig amination between monoprotected diamines (**G1**) or their corresponding salts and heteroaryls (**G2a**) with X being a leaving group like halogen or -S(O)Me as depicted in Scheme 1. For S_NAr approaches with X being groups like for example fluorine or -S(O)Me, diamines (**G1**) may be reacted with (**G2a**) in the presence of inorganic bases like K_2CO_3 or Na_2CO_3 or in the presence of organic bases like triethylamine or DIPEA or without any additional base in polar solvents such as for example DMSO, NMP or *n*BuOH at temperatures between 100-130 °C. The reaction times may vary between 1 hour and 24 hours. In certain instances, it can be beneficial to apply microwave heating.

For palladium catalyzed Buchwald-Hartwig aminations all methods that are known in the art may be applied. For example, diamines (**G1**) may be reacted with (**G2a**) in the presence of a palladium catalyst like Pd PEPPSI-IpentCl [CAS Reg. No. 1612891-29-8], $Pd_2(dba)_3$ or

*t*BuXPhos Pd G3 [1447963-75-8] and a base like Cs_2CO_3 or NaO*t*Bu in aprotic solvents like 1,4-dioxane, DMF, toluene or DMA at temperatures between room temperature and 130 °C, preferably at 65-100 °C, for 15-24 h.

Diamines of general formula (**G1**) and heteroaryls of general formula (**G2a**) are either commercially available or can be prepared according to procedures available from the public domain. For the synthesis of diamines (**G1**) see for example WO2004004726 and references therein.

Arylated diamines of general formula (**G6**) can be obtained from (**G3**) via copper catalyzed Ullmann couplings with heterocycles (**G4**) or via palladium catalyzed Suzuki couplings with boronic acid derivatives (**G5**). For Ullmann couplings all methods that are known in the art may be applied. For example, (**G3**) may be reacted with (**G4**) in the presence of a copper catalyst like Cu(I)I, $Cu(Otf)_2$ or $Cu(Oac)_2$ and a base like Cs_2CO_3 or K_2CO_3 in polar, aprotic solvents like 1,4-dioxane, DMF or pyridine at temperatures between room temperature and 120 °C, preferably at 100 °C for 15-20 h. In some instances a ligand like N^1,N^2-dimethylcyclohexane-1,2-diamine, TMEDA, N^1,N^2-dimethylethane-1,2-diamine or *N*,*N*-dimethylglycine might be added to the reaction mixture.

For Suzuki couplings towards (**G6**) all methods that are known in the art may be applied. For example, (**G3**) may be reacted with boronic acid derivatives (**G5**) in the presence of a palladium catalyst like 1,1'-bis(di-*tert*-butylphosphino)ferrocene palladium dichloride [CAS Reg. No. 95408-45-0] or 1,1′-bis(diphenylphosphino)ferrocene palladium dichloride [CAS Reg. No. 72287-26-4] and a base like Cs_2CO_3, K_2CO_3 or K_3PO_4 in polar solvents such as 1,4-dioxane, THF and water or mixtures thereof at temperatures between room temperature and 120 °C for 2-15 hours.

Heterocycles of general formula (**G4**) and boronic acid derivatives of general formula (**G5**) are either commercially available or can be prepared according to procedures available from the public domain.

Primary amines of general formula (**G7**) can be obtained from monoprotected diamines of general formula (**G6**) via deprotection methods. Depending on the protective group applied these can be for example acidic, basic, oxidative or hydrogenation methods. Appropriate protective moieties for amino groups and their introduction and cleavage are well-known in the art. For an overview of protective group chemistry see for example Wuts 2014.

Final compounds of general formula (**I-G**) can be synthesized from primary amines of general formula (**G7**) via nucleophilic aromatic substitution (S_NAr) or palladium catalyzed Buchwald-Hartwig amination. Primary amines of general formula (**G7**) can be reacted with heteroaryls of

general formula (**G8**) with X being a leaving group like halogen such as chlorine or -S(O)Me applying procedures in analogy to those described for the synthesis of (**G3**) from (**G1**) and (**G2a**) in Scheme 1. Heteroaryls of general formula (**G8**) are either commercially available or can be prepared according to procedures available from the public domain. An analogous general scheme involves oxadiazoles of general formula (**G8a**) and its isomers.

An alternative route to compounds of general formula (**I-G**) starts with deprotection of diamines of general formula (**G3**) to give primary amines of general formula (**G9**) as depicted in Scheme 1. For deprotection the same procedures apply as described for the synthesis of (**G7**) from (**G6**).

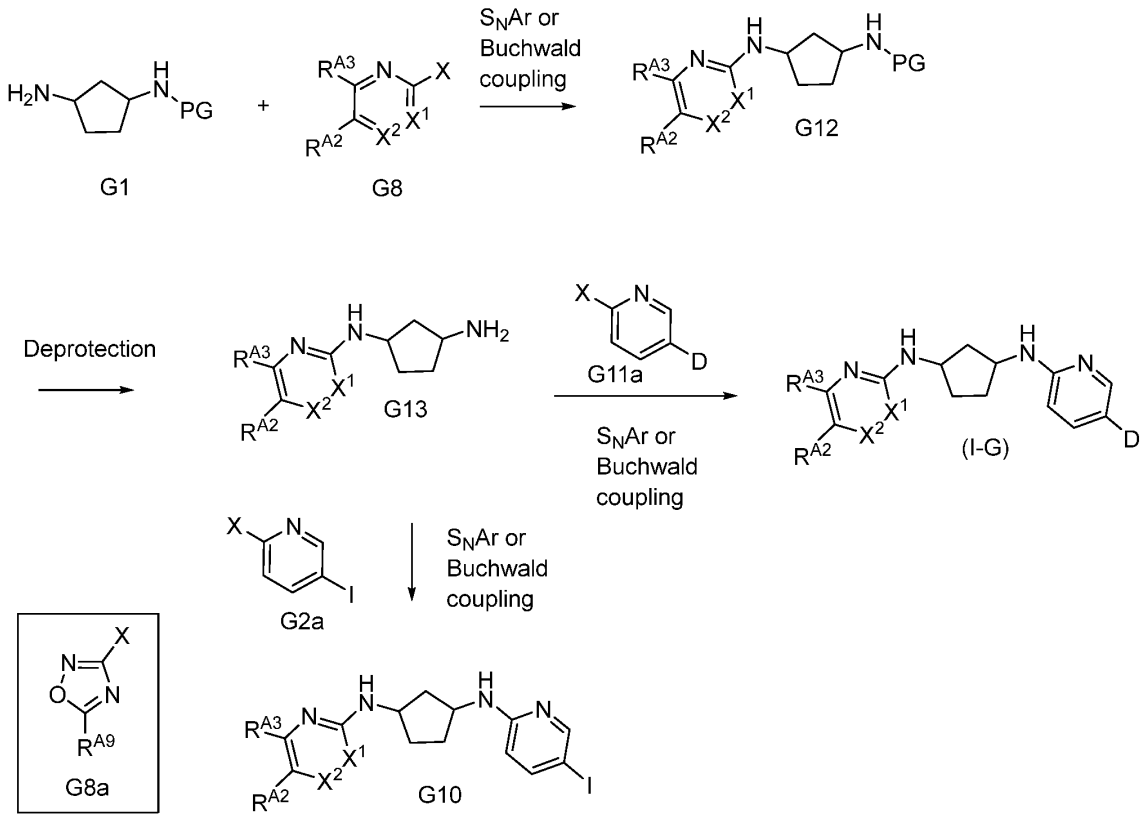
Primary amines of general formula (**G9**) in turn can be reacted with heteroaryls of general formula (**G8**) via nucleophilic aromatic substitution (S_NAr) or palladium catalyzed Buchwald-Hartwig amination to give aryl iodides of general formula (**G10**) applying procedures in analogy to those described for the synthesis of (**G3**) from (**G1**) and (**G2a**) in Scheme 1.

Final compounds of general formula (**I-G**) can be synthesized from aryl iodides of general formula (**G10**) via copper catalyzed Ullmann couplings with heterocycles H-D (**G4**) or via palladium catalyzed Suzuki couplings with boronic acid derivatives (**G5**) applying procedures in analogy to those described for the synthesis of compounds (**G6**) from (**G3**) in Scheme 1.

Yet another approach to compounds of general formula (**I-G**) starts from monoprotected diamines (**G1**) or their corresponding salts and preassembled heteroaryls (**G11a**) with X being a leaving group like halogen or -S(O)Me via nucleophilic aromatic substitution (S_NAr) or palladium catalyzed Buchwald-Hartwig amination to give arylated diamines of general formula (**G6**). The procedures that can be applied are in analogy to those described for the synthesis of (**G3**) from (**G1**) and (**G2a**) in Scheme 1. Heteroaryls of general formula (**G11a**) are either commercially available or can be prepared according to procedures available from the public domain (for example via Chan-Lam coupling). Specific examples of (**G11a**) are described in the subsequent paragraphs.

An alternative route for the preparation of compounds of general formula (**I-G**) and intermediates of general formula (**G10**) is depicted in Scheme 2.

Scheme 2



Scheme 2: Routes for the preparation of compounds of general formula (**I-G**) and intermediates (**G10**) in which X is a leaving group, PG is a protective group and X^1, X^2, R^{A2} and R^{A3} have the meaning as given for general formula (**A1a**), *supra*. D is defined above.

Monoarylated diamines of general formula (**G12**) can be obtained via nucleophilic aromatic substitution (S_NAr) or palladium catalyzed Buchwald-Hartwig amination between monoprotected diamines (**G1**) or their corresponding salts and heteroaryls (**G8**) with X being a leaving group such as halogen or -S(O)Me. The procedures that can be applied are in analogy to those described for the synthesis of (**G3**) from (**G1**) and (**G2a**) in Scheme 1. An analogous general scheme involves oxadiazoles of general formula (**G8a**) and its isomers.

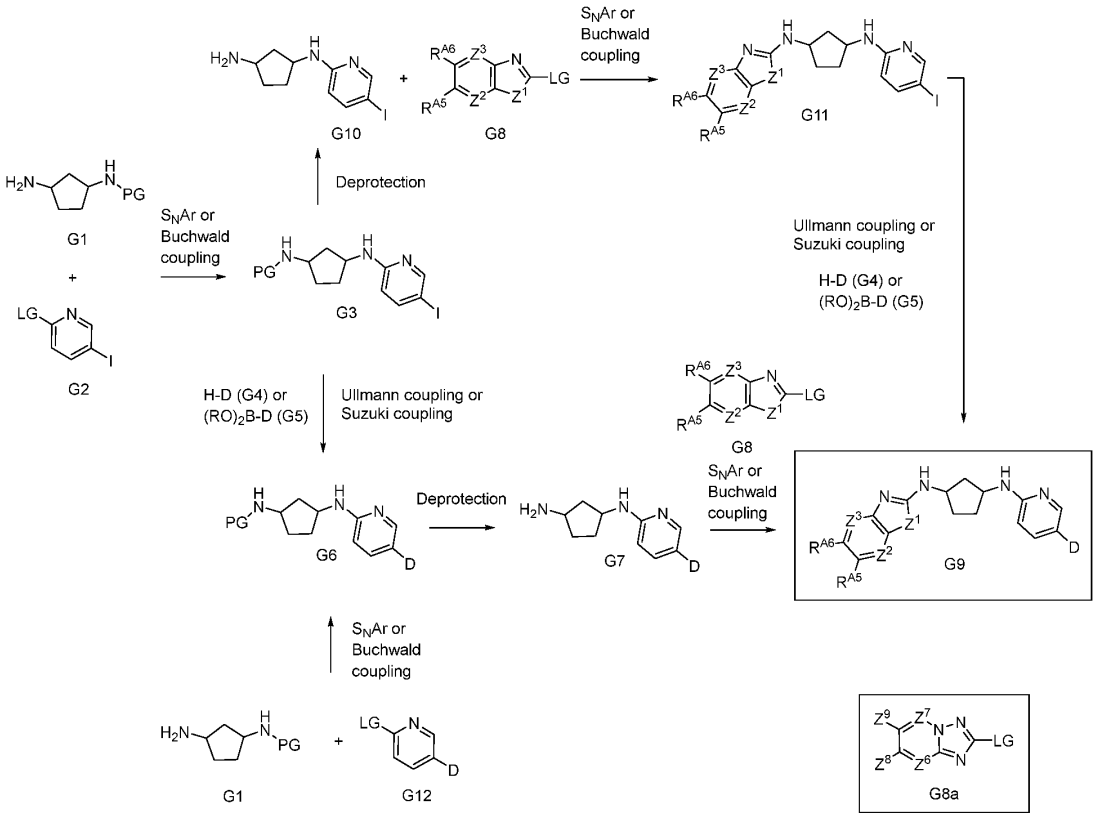
Deprotection of diamines of general formula (**G12**) can give primary amines of general formula (**G13**). For deprotection the same procedures apply as described for the synthesis of (**G7**) from (**G6**) in Scheme 1.

Final compounds of general formula (**I-G**) in turn can be synthesized from primary amines (**G13**) or their corresponding salts and preassembled heteroaryls (**G11a**) with X being a leaving group

like halogen or -S(O)Me via nucleophilic aromatic substitution (S_NAr) or palladium catalyzed Buchwald-Hartwig amination. The procedures that can be applied are in analogy to those described for the synthesis of (**G6**) from (**G1**) and (**G11a**) in Scheme 1.

For the synthesis of intermediates of general formula (**G10**) primary amines (**G13**) or their corresponding salts may be reacted with heteroaryls (**G2a**) with X being a leaving group like halogen or -S(O)Me in a nucleophilic aromatic substitution (S_NAr) or palladium catalyzed Buchwald-Hartwig amination. The procedures that can be applied are in analogy to those described for the synthesis of (**G3**) from (**G1**) and (**G2a**) in Scheme 1.

Scheme 3



Scheme 3: Routes for the preparation of compounds of general formula (**G9**) are described in the scheme in which LG is a leaving group, PG is a protective group, Z^1, Z^2, Z^3, R^{A5} and R^{A6} have the meaning as given for general formula (**A2a**), *supra*. D is defined above.

Monoarylated diamines of general formula (**G3**) can be obtained via nucleophilic aromatic substitution (S_NAr) or palladium catalyzed Buchwald-Hartwig amination between monoprotected diamines (**G1**), or their corresponding salts, and heteroaryls (**G2**) with LG being a leaving group

like halogen, e.g. fluorine, chlorine or bromine, or -$S(O)_{1-2}Me$ as depicted in Scheme 3. For S_NAr approaches with LG being groups like for example fluorine, chlorine or -S(O)Me, diamines (**G1**) may be reacted with (**G2**) in the presence of inorganic bases like K_2CO_3, Na_2CO_3 or Cs_2CO_3 or in the presence of organic bases like TEA or DIPEA, or without any additional base in polar solvents such as for example DMSO, NMP, *n*BuOH or 1,4-dioxane at temperatures between 100-130 °C. The reaction times may vary between 1 h and 24 h. In certain instances, it can be beneficial to apply microwave heating.

For palladium catalyzed Buchwald-Hartwig aminations all methods that are known in the art may be applied. For example, diamines (**G1**) may be reacted with (**G2**) in the presence of a palladium catalyst like Pd PEPPSI-IpentCl [CAS Reg. No. 1612891-29-8], $Pd_2(dba)_3$, *t*BuXPhos Pd G3 [1447963-75-8] or *t*BuBrettPhos G3 and a base like Cs_2CO_3, NaO*t*Bu or MTBD in aprotic solvents like 1,4-dioxane, DMF, toluene, NMP or DMA at temperatures between room temperature and 130 °C, preferably at 65-100 °C, for 15-24 h.

Diamines of general formula (**G1**) and heteroaryls of general formula (**G2**) are either commercially available or can be prepared according to procedures available from the public domain. For the synthesis of diamines (**G1**) see for example WO2004004726 and references therein.

Arylated diamines of general formula (**G6**) can be obtained from (**G3**) via copper catalyzed Ullmann couplings with heterocycles (**G4**) or via palladium catalyzed Suzuki couplings with boronic acid derivatives (**G5**). For Ullmann couplings all methods that are known in the art may be applied. For example, (**G3**) may be reacted with (**G4**) in the presence of a copper catalyst like Cu(I)I, $Cu(OTf)_2$ or $Cu(Oac)_2$ and a base like Cs_2CO_3 or K_2CO_3 in polar, aprotic solvents like 1,4-dioxane, DMF or pyridine at temperatures between room temperature and 120 °C, preferably at 100 °C for 15-20 h. In some instances a ligand like DMCDA, TMEDA, N^1,N^2-dimethylethane-1,2-diamine or *N*,*N*-dimethylglycine might be added to the reaction mixture.

For Suzuki couplings towards (**G6**) all methods that are known in the art may be applied. For example, (**G3**) may be reacted with boronic acid derivatives (**G5**) in the presence of a palladium catalyst like $Pd(dtbpf)Cl_2$ [CAS Reg. No. 95408-45-0] or $Pd(dppf)Cl_2$ [CAS Reg. No. 72287-26-4] and a base like Cs_2CO_3, K_2CO_3 or K_3PO_4 in polar solvents such as 1,4-dioxane, THF and water or mixtures thereof at temperatures between room temperature and 120 °C for 2-15 h.

Heterocycles of general formula (**G4**) and boronic acid derivatives of general formula (**G5**) are either commercially available or can be prepared according to procedures available from the public domain.

Primary amines of general formula (**G7**) can be obtained from monoprotected diamines of general formula (**G6**) via deprotection methods. Depending on the protective group applied these can be for example acidic, basic, oxidative or hydrogenation methods. Appropriate protective moieties for amino groups and their introduction and cleavage are well-known in the art. For an overview of protective group chemistry see for example P.G.M. Wuts, T.W. Greene, Greene's Protective Groups in Organic Synthesis 4th ed., J. Wiley & Sons, 2006.

Final compounds of general formula (**G9**) can be synthesized from primary amines of general formula (**G7**) via S_NAr or palladium catalyzed Buchwald-Hartwig amination. Primary amines of general formula (**G7**) can be reacted with heteroaryls of general formula (**G8**) with LG being a leaving group like halogen, such as chlorine or bromine, or $-S(O)_2Me$ applying procedures in analogy to those described for the synthesis of (**G3**) from (**G1**) and (**G2**) in Scheme 3. Heteroaryls of general formula (**G8**) are either commercially available or can be prepared according to procedures available from the public domain. An analogous general scheme involves heteroaryls of general formula (**G8a**).

An alternative route to compounds of general formula (**G9**) starts with deprotection of diamines of general formula (**G3**) to give primary amines of general formula (**G10**) as depicted in Scheme 3. For deprotection the same procedures apply as described for the synthesis of (**G7**) from (**G6**).

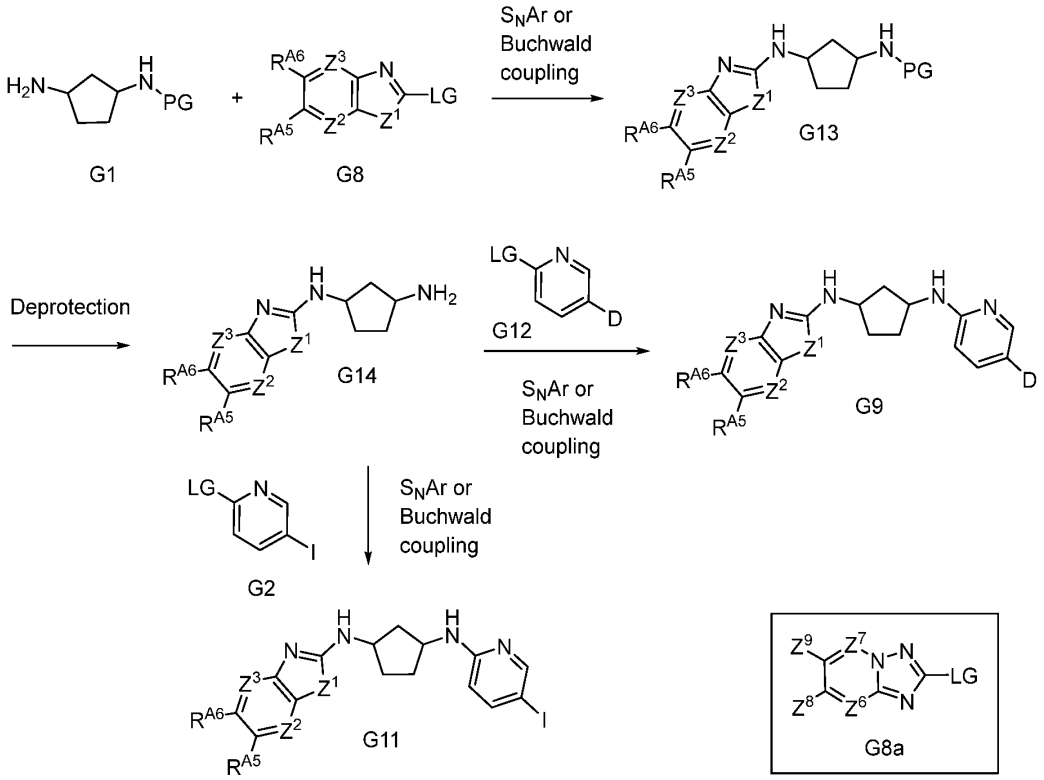
Primary amines of general formula (**G10**) in turn can be reacted with heteroaryls of general formula (**G8**) via S_NAr or palladium catalyzed Buchwald-Hartwig amination to give aryl iodides of general formula (**G11**) applying procedures in analogy to those described for the synthesis of (**G3**) from (**G1**) and (**G2**) in Scheme 3.

Final compounds of general formula (**G9**) can be synthesized from aryl iodides of general formula (**G11**) via copper catalyzed Ullmann couplings with heterocycles H-D (**G4**) or via palladium catalyzed Suzuki couplings with boronic acid derivatives (**G5**) applying procedures in analogy to those described for the synthesis of compounds (**G6**) from (**G3**) in Scheme 3.

Yet another approach to compounds of general formula (**G9**) starts from monoprotected diamines (**G1**) or their corresponding salts and preassembled heteroaryls (**G12**) with LG being a leaving group like halogen, e.g. fluorine, chlorine or bromine, or $-S(O)_{1\text{-}2}Me$ via S_NAr or palladium catalyzed Buchwald-Hartwig amination to give arylated diamines of general formula (**G6**). The procedures that can be applied are in analogy to those described for the synthesis of (**G3**) from (**G1**) and (**G2**) in Scheme 3. Heteroaryls of general formula (**G12**) are either commercially available or can be prepared according to procedures available from the public domain (for example via Chan-Lam coupling, see for example Chen 2020).

An alternative route for the preparation of compounds of general formula (**G9**) and intermediates of general formula (**G11**) is depicted in Scheme 4.

Scheme 4



Scheme 4: Routes for the preparation of compounds of general formula (**G9**) and intermediates (**G11**) are described in the scheme in which LG is a leaving group, PG is a protective group, and Z^1, Z^2, Z^3, R^{A5} and R^{A6} have the meaning as given for general formula (**A2a**), *supra*. D is defined above.

Monoarylated diamines of general formula (**G13**) can be obtained via S_NAr or palladium catalyzed Buchwald-Hartwig amination between monoprotected diamines (**G1**) or their corresponding salts and heteroaryls (**G8**) with LG being a leaving group like halogen, such as chlorine or bromine, or -$S(O)_2$Me. The procedures that can be applied are in analogy to those described for the synthesis of (**G3**) from (**G1**) and (**G2**) in Scheme 3. An analogous general scheme involves heteroaryls of general formula (**G8a**).

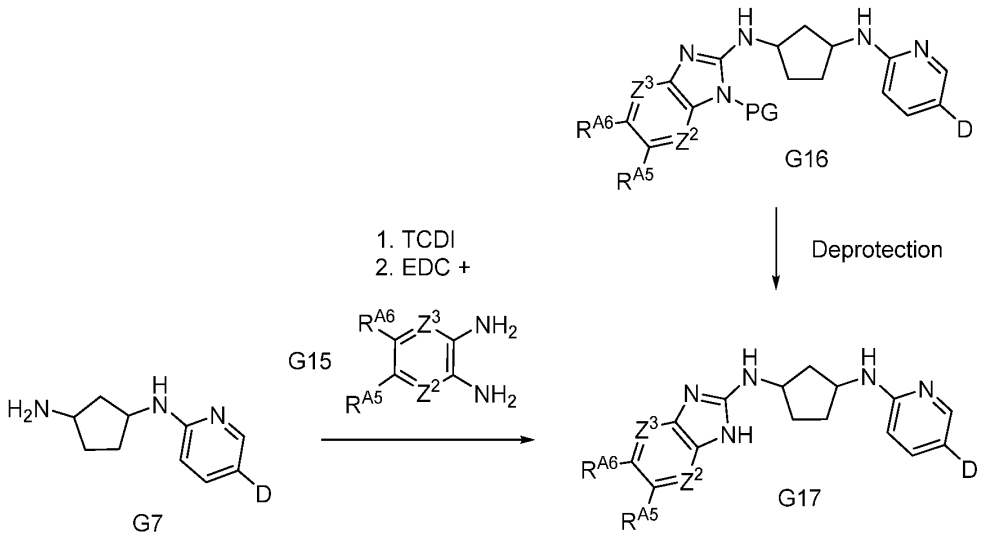
Deprotection of diamines of general formula (**G13**) can give primary amines of general formula (**G14**). For deprotection the same procedures apply as described for the synthesis of (**G7**) from (**G6**) in Scheme 3.

Final compounds of general formula (**G9**) in turn can be synthesized from primary amines (**G14**) or their corresponding salts and preassembled heteroaryls (**G12**) with LG being a leaving group like halogen, e.g. fluorine, chlorine or bromine, or -$S(O)_{1-2}Me$ via S_NAr or palladium catalyzed Buchwald-Hartwig amination. The procedures that can be applied are in analogy to those described for the synthesis of (**G6**) from (**G1**) and (**G12**) in Scheme 3.

For the synthesis of intermediates of general formula (**G11**) primary amines (**G14**) or their corresponding salts may be reacted with heteroaryls (**G2**) with LG being a leaving group like halogen, e.g. fluorine, chlorine or bromine, or -$S(O)_{1-2}Me$ in an S_NAr or palladium catalyzed Buchwald-Hartwig amination. The procedures that can be applied are in analogy to those described for the synthesis of (**G3**) from (**G1**) and (**G2**) in Scheme 3.

Final compounds of general formula (**G17**) may be synthesized according to the routes depicted in Scheme 5. Primary amines of general formula (**G7**) or their corresponding salts (prepared according to Scheme 3) can be reacted with one carbon equivalents like CDI or TCDI in the presence of inorganic bases like sodium hydroxide or in the presence of organic bases like TEA or DIPEA, or without any additional base in polar, aprotic solvents like DMF at temperatures between rt and the boiling point of the solvent, preferably at 100 °C for 1-2 h to give an acylimidazole intermediate. This intermediate may be reacted *in situ* with 1,2-dianilines (**G15**) in the presence of a carbodiimide reagent like EDC at temperatures between rt and the boiling point of the solvent, preferably at 100 °C for 15-24 h to give (**G17**).

Scheme 5



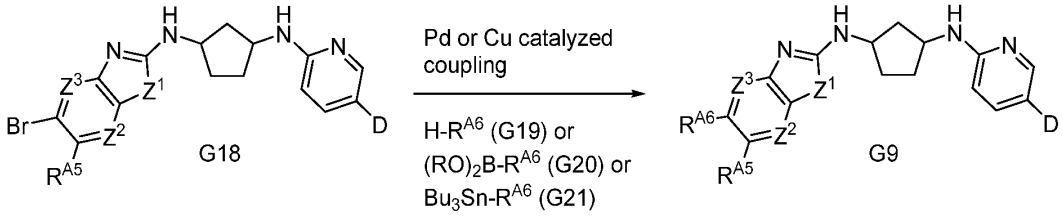
Scheme 5: Routes for the preparation of compounds of general formula (**G17**) in which Z^2, Z^3, R^{A5} and R^{A6} have the meaning as given for general formula (**A2a**), *supra*. D is defined above.

Alternatively, protected intermediates of general formula (**G16**), prepared according to the routes depicted in schemes 3 or 4, may be deprotected to give compounds of general formula (**G17**). Depending on the protective group applied these can be for example acidic, basic, oxidative or hydrogenation methods. Suitable protective groups may be groups such as para-methoxybenzyl (PMB), 4-methylbenzenesulfonyl (Ts) or benzyl (Bn). Deprotection of a PMB group for example could be achieved by reaction with acids such as TFA in solvents like DCM, or without any additional solvent, at temperatures between rt and the boiling point of the solvent, preferably at 60-100 °C for 15 min to 18 h. Deprotection of a Ts group may be performed by reaction with a base such as K_2CO_3 or Na_2CO_3 in polar, protic solvent such as MeOH or EtOH at temperatures between rt and the boiling point of the solvent, preferably at 60 °C for 1-4 h.

Yet another approach to compounds of general formula (**G9**) is depicted in Scheme 6. Aryl bromides of general formula (**G18**), prepared according to the procedures depicted in schemes 3-5, can be functionalized under metal or metallaphotoredox catalysis (see for example Chan 2022), e.g. via late-stage functionalisation, with nucleophiles of general formula (**G19**) (see for example Ley and Thomas) or boronic acid derivatives (**G20**) (see for example Miyaura and Suzuki 1995) or stannanes (**G21**) (see for example Cordovilla 2015) to give final compounds of general formula (**G9**). For metal or metallaphotoredox catalysis all methods that are known in the art may be applied.

Nucleophiles of general formula (**G19**) and boronic acid derivatives of general formula (**G20**) and stannanes (**G21**) are either commercially available or can be prepared according to procedures available from the public domain.

Scheme 6



Scheme 6: Route for the preparation of compounds of general formula (**G9**) in which Z^1, Z^2, Z^3, R^{A5} and R^{A6} have the meaning as given for general formula (**A2a**), *supra* (provided that R^{A6} is not halogen). D is defined above.

Further compounds with different formulae as described above can be prepared by similar methods.

Persons skilled in the art will appreciate that in order to obtain compounds of the disclosure in an alternative, and on some occasions, more convenient, manner, the individual process steps mentioned hereinbefore may be performed in different order, and/or the individual reactions may be performed at a different stage in the overall route (i.e. substituents may be added to and/or chemical transformations performed upon different intermediates to those mentioned hereinbefore in conjunction with a particular reaction). This may negate, or render necessary, the need for protecting groups.

Persons skilled in the art will appreciate that chiral isomers of compounds herein can be resolved at any stage in the synthetic process using chiral resolving agents described in the literature and known to person skilled in the art, or using chiral chromatography methods described in the literature and known to person skilled in the art. Stereo centers may also be introduced by asymmetric synthesis. All stereoisomers are included within the scope of the disclosure.

Persons skilled in the art will appreciate that starting materials for any of the above processes can in some cases be commercially available.

Persons skilled in the art will appreciate that processes for some starting materials above could be found in the general common knowledge.

It will also be understood that some of the compounds described in the processes above may exhibit the phenomenon of tautomerism and the processes described above include any tautomeric form.

All novel intermediates form a further aspect of the disclosure.

EXPERIMENTAL SECTION

NMR peak forms are stated as they appear in the spectra, possible higher order effects have not been considered.

The following table lists the abbreviations used in this paragraph and in the examples section as far as they are not explained within the text body. Other abbreviations have their meanings customary *per se* to the skilled person.

Abbreviations

A	Adenosine
AH	AminoHexyl
ACN	Acetonitrile

AcOH	Acetic acid
ASO	Antisense oligonucleotide
aq	Aqueous
Avi	AviTag™
Boc	*tert*-Butoxycarbonyl
Brine	Saturated aqueous sodium chloride solution
Bu	Butyl
*t*Bu	*tert*-Butyl
*t*BuBrettPhos	Di-*tert*-butyl(2',4',6'-triisopropyl-3,6-dimethoxy-[1,1'-biphenyl]-2-yl)phosphine
n-BuOH	1-Butanol
*t*BuXPhos Pd G3	[(2-Di-*tert*-butylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)-2-(2′-amino-1,1′-biphenyl)] palladium(II) methanesulfonate (CAS Reg. No. 1447963-75-8)
C	Cytosine
5meC	5-Methylcytosine
calcd	Calculated
CataCXium A	Di(adamantan-1-yl)(butyl)phosphane (CAS Reg. No. 321921-71-5)
CataCXium A Pd G3	Methanesulfonato(diadamantyl-*n*-butylphosphino)-2'-amino-1,1'-biphenyl-2-yl)palladium(II) precatalyst generation 3 (CAS Reg. No. 1651823-59-4)
CDI	1,1-Carbonyldiimidazole
CHAPS	3-[(3-Cholamidopropyl)dimethylammonio]-1-propanesulfonate
CO_2	Carbon dioxide
m-CPBA	3-Chlorobenzoperoxoic acid
cPs	Centipoises
DCM	Dichloromethane
DCE	Dichloroethane
DCM	Dichloromethane
DIPEA	*N*-Ethyl-*N*-isopropyl-propan-2-amine
DMA	*N,N*-Dimethylacetamide
DMAP	*N,N*-Dimethylpyridin-4-amine
DMCDA	*rel*-(1*R*,2*R*)-N^1,N^2-Dimethylcyclohexane-1,2-diamine
DME	1,2-Dimethoxyethane
DMF	*N,N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
Dppf	1,1'-Bis(diphenylphosphino)ferrocene

dR	Deoxyribose
EDC	3-(((Ethylimino)methylene)amino)-*N*,*N*-dimethylpropan-1-amine hydrochloride
eq	Equivalent(s)
ESI	Electrospray ionization
Et	Ethyl
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethanol
FA	Formic acid
G	Guanosine
(g)	Gas
GalNAc	N-acetylgalactosamine
GalNAc THA	GalNAc TrisHexylAmine
G2	Generation 2
G3	Generation 3
HA	Hexylamine
HATU	(1-(Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium-3-oxo hexafluorophosphate
HEPES	(4-(2-Hydroxyethyl)-1-piperazineethanesulfonic acid)
HPLC	High performance liquid chromatography
HPMC	Hydroxypropyl methylcellulose
HRMS	High resolution mass spectrometry
IC_{50}	Half maximal inhibitory concentration
iPrOH	Isopropanol
K_2CO_3	Potassium carbonate
k_a	Association rate constant (also written k_{on})
K_D	Dissociation constant
k_d	Dissociation rate constant (also written k_{off})
LC	Liquid chromatography
LG	Leaving group
$LiAlH_4$	Lithium aluminium hydride
LNA	Locked Nucleic Acid
Me	CH_3
MeCN	Acetonitrile
MeOH	Methanol
MMTr-ON	MMTr-protected oligonucleotide
MS	Mass spectrometry

MTBD	7-Methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene
MTBE	Methyl *tert*-butyl ether
m/z	Mass to charge ratio
NaCl	Sodium chloride
NaH	Sodium hydride
NaOAc	Sodium acetate
NaOH	Sodium hydroxide
NaO*t*Bu	Sodium *tert*-butoxide
Na_2SO_4	Sodium sulfate
NMP	1-Methylpyrrolidin-2-one
NMR	Nuclear magnetic resonance
OAc	$O(CO)CH_3$
OEt	OCH_2CH_3
OTf	Trifluoromethanesulfonate
OtBu	$OC(CH_3)_3$
P	Phosphate
PBS	Phosphate buffered saline
Pd/C	Palladium on charcoal
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium(0)
$Pd(dppf)Cl_2$•DCM	[1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) CH_2Cl_2 (1:1)
$Pd(dtbpf)Cl_2$	[1,1′-Bis(di-*tert*-butylphosphino)ferrocene]dichloropalladium(II)
PDL	Poly-D-Lysine
$Pd(OAc)_2$	Palladium (II) acetate
Pd-PEPPSI-IpentCl 2-methylpyridine	(*SP*-4-1)-[1,3-Bis[2,6-bis(1-ethylpropyl)phenyl]-4,5-dichloro-1,3-dihydro-2*H*-imidazol-2-ylidene]dichloro(2-methylpyridine)palla-dium (CAS Reg. No. 1612891-29-8)
$Pd(PPh_3)_4$	$Pd[(C_6H_5)_3P]_4$
PE	Petroleum ether
PG	Protective group
Ph	Phenyl
PMB	Paramethoxybenzyl
PPh_3	Triphenylphosphane
PS80	Polysorbate 80
pTSA	4-Methylbenzenesulfonic acid
qToF	Quadrupole time-of-flight

R_{max}	Maximum observed binding signal
rt	Room temperature
RU	Response unit(s)
(s)	Solid
sat	Saturated
SFC	Supercritical fluid chromatography
S_NAr	Nucleophilic aromatic substitution
sP	Thiophosphate
SPR	Surface Plasmon Resonance
T	Thymine
*t*BuBrettPhos G3	2-(Di-*tert*-butylphosphino)-2′,4′,6′- triisopropyl-3,6-dimethoxy-1,1′-biphenyl)-2-(2′-amino-1,1′-biphenyl)]palladium(II) methanesulfonate (CAS Reg. No. 1536473-72-9)
TCDI	Di(1*H*-imidazol-1-yl)methanethione
TCFH	Chloro-*N*,*N*,*N*′,*N*′-tetramethylformamidinium hexafluorophosphate
TEA	Triethylamine
TFA	Trifluoroacetic acid
TFAA	2,2,2-Trifluoroacetic anhydride
THF	Tetrahydrofuran
TMEDA	N^1,N^1,N^2,N^2-Tetramethylethane-1,2-diamine
TLC	Thin layer chromatography
Ts	Tosyl or 4-methylbenzenesulfonyl
TsCl	4-Methylbenzenesulfonyl chloride
TsOH	para-Toluenesulfonic acid
UPLC	Ultra performance liquid chromatography
UV	Ultraviolet
XPhos	Dicyclohexyl(2',4',6'-triisopropyl-[1,1'-biphenyl]-2-yl)phosphane
XPhos Pd G2	Chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II) (CAS Reg. No. 1310584-14-5)
XantPhos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene, or (9,9-dimethyl-9*H*-xanthene-4,5-diyl)bis(diphenylphosphine)

Units

Å	Ångström
atm	atmosphere
C	Celcius
g	gram

h	hour(s)
L	litre
M	mole per liter
mg	milligram
MHz	megahertz
min	minute(s)
mL	milliliter
mm	millimeter
mol	mole
mmol	millimole(s)
µCi	microcurie
µm	micrometer
µmol	micromole(s)
µL	microlitre
nm	nanometer
ppm	parts per million
s	second(s)
v/v	volume by volume
W	watt
w/v	weight by volume

The various embodiments described in this application are illustrated by the following examples which are not meant to limit the compound of Formula (I) in any way.

The example testing experiments described herein serve to illustrate the present embodiments and is not limited to the examples given.

EXPERIMENTAL SECTION – GENERAL PART

General conditions

(i) operations were carried out at room temperature (rt), *i.e.* in the range 17 to 28°C and where needed under an atmosphere of an inert gas such as N_2 or Ar; optionally reactions were carried out using a MBRAUN UNILab Plus ECO or a MBRAUN UNILab SP Eco glovebox workstation, in which case it is indicated;

(ii) where reactions refer to being degassed or purged, this can be performed for example by purging the reaction solvent with a constant flow of nitrogen for a suitable period of time (for example 5 to 10 min) or by repeatedly evacuating the vessel and backfill with appropriate inert atmosphere (for example N_2(g) or Ar(g));

(iii) where reactions refer to the use of a microwave reactor, one of the following microwave reactors were used: Biotage Initiator, Personal Chemistry Emrys Optimizer, Personal Chemistry Smith Creator or CEM Explorer;

(iv) in general, the course of reactions was followed by thin layer chromatography (TLC) and/or analytical high performance liquid chromatography (HPLC or UPLC) which was usually coupled to a mass spectrometer (LCMS).

(v) when necessary, organic solutions were dried over anhydrous $MgSO_4$ or Na_2SO_4, or by using ISOLUTE® Phase Separator, and work-up procedures were carried out using traditional phase separating techniques. When a drying agent such as e.g. $MgSO_4$ or Na_2SO_4 is used for drying an organic layer, it is understood that said organic layer is filtered before concentration of said layer.

(vi) it is understood that washing solutions used in the work-up procedures or reagent used for acidifying such as e.g. brine (sat aq NaCl solution), $NaHCO_3$, NH_4Cl, HCl, NaH_2PO_4 are presumed to be aqueous solutions unless otherwise stated;

(vii) evaporations were carried out either by rotary evaporation *in vacuo* or in a Genevac HT-4 / EZ-2 or Biotage V10;

(viii) unless otherwise stated, flash column chromatography was performed on normal phase silica, using either Merck Silica Gel (Art. 9385) or prep-packed cartridges such as Biotage® SNAP cartridges (40-63 µm silica, 4–330 g), Biotage® Sfär Silica HC D cartridges (20 µm, 10–100 g), Interchim puriFlash™ cartridges (25 µm, 4–120 g), Interchim puriFlash™ cartridges (50 µm, 25–330 g), Grace™ GraceResolv™ Silica Flash Cartridges (4–120 g) or Agela Flash Colum Silica-CS cartridges (80–330 g), or on reversed phase silica using Agela Technologies C-18, spherical cartridges (20–35 µm, 100 A, 80–330 g), manually or automated using a Grace Reveleris® X2 Flash system or similar system;

(ix) purification using ion exchange columns were performed on standard ion exchange columns e.g. ISOLUTE SCX-2 columns from Biotage;

(x) preparative reversed phase HPLC and preparative reversed phase SFC were performed using standard HPLC and SFC instruments, respectively, equipped with either a MS and/or UV triggered fraction collecting instrument, using either isocratic or a gradient of the mobile phase as described in the experimental section and using one of the following methods:

PrepMethod A: The compound was purified by preparative HPLC on a XBridge™ C18 OBD column (5 µm, 150×30 mm ID) using a gradient of MeCN in a H_2O/NH_4HCO_3 (10 mM)/NH_3 (0.1%, aq) buffer system as mobile phase;

PrepMethod B: The compound was purified by preparative HPLC on a Xbridge™ C18 OBD column (5 µm, 150×30 mm ID) using a gradient of MeCN in a H_2O/NH_4HCO_3 (10 mM)/NH_3 (0.05%, aq) buffer system as mobile phase;

PrepMethod C: The compound was purified by preparative HPLC on a Waters Xselect CSH C18 OBD column (5 µm, 150×30 mm ID) using a gradient of MeCN in a H_2O/NH_4HCO_3 (10 mM)/NH_3 (0.05%, aq) buffer system as mobile phase;

PrepMethod D: The compound was purified by preparative HPLC on a Waters Xselect CSH C18 OBD column (5 µm, 150×30 mm ID) using a gradient of MeCN in a H_2O/NH_4HCO_3 (10 mM)/NH_3 (0.1%, aq) buffer system as mobile phase;

PrepMethod E: The compound was purified by preparative HPLC on a XBridge™ C18 OBD column (5 µm, 250×19 mm ID) using a gradient of MeOH in a H_2O/NH_4HCO_3 (10 mM)/NH_3 (0.05%, aq) buffer system as mobile phase;

PrepMethod F: The compound was purified by preparative HPLC on a YMC-Actus Triart C18 ExRs column (5 µm, 150×30 mm ID) using a gradient of MeCN in H_2O/NH_4HCO_3 (10 mM) buffer system as mobile phase;

PrepMethod G: The compound was purified by preparative HPLC on a YMC-Actus Triart C18 ExRs column (5 µm, 150×30 mm ID) using a gradient of MeCN in H_2O/NH_4HCO_3 (10 mM)/NH_3 (0.05%, aq) buffer system as mobile phase;

PrepMethod H: The compound was purified by preparative HPLC on a Waters Xselect CSH C18 OBD column (5 µm, 150×30 mm ID) using a gradient of MeCN in H_2O/FA (0.1%) buffer system as mobile phase;

PrepMethod I: The compound was purified by preparative HPLC on a XBridge™ C18 OBD column (3.5 µm, 75×30 mm ID) using a gradient of MeCN in a H_2O/NH_4HCO_3 (10 mM)/NH_3 (0.05%, aq) buffer system as mobile phase;

PrepMethod J: The compound was purified by preparative HPLC on a XBridge™ C18 OBD column (5 µm, 150×30 mm ID) using a gradient of MeCN in a H_2O/NH_4HCO_3 (10 mM)/NH_3 (0.1%, aq) buffer system as mobile phase;

Relevant fractions were collected, combined, and freeze-dried or evaporated to give the purified compound or relevant fractions were collected, combined, and concentrated at reduced pressure, the aqueous layer was extracted with DCM or EtOAc, and the organic layer was dried, either over Na_2SO_4 or by using a phase-separator, and then concentrated at reduced pressure and when needed dried in vacuo, to give the purified compound.

(xi) yields, where present, are not necessarily the maximum attainable, and when necessary, reactions were repeated if a larger amount of the reaction product was required;

(xii) where certain compounds were obtained as an acid-addition salt, for example a mono-hydrochloride salt or a di-hydrochloride salt, the stoichiometry of the salt was based on the number and nature of the basic groups in the compound, the exact stoichiometry of the salt was generally not determined, for example by means of elemental analysis data; where stated

the salts were treated according to literature-known processes to generate the corresponding free base prior to being used;

(xiii) in general, the structures of the end-products of the Formula (I) were confirmed by NMR and/or mass spectral techniques; proton NMR chemical shift values were measured on the delta scale using Bruker Avance III 300, 400, 500 and 600 spectrometers, operating at ^{1}H frequencies of 300, 400, 500 and 600 MHz, respectively. The experiments were typically recorded at 25 °C. Chemical shifts are given in ppm with the solvent as internal reference. Protons on heteroatoms such as NH and OH protons are only reported when detected in NMR and can therefore be missing. 19F spectra are recorded with proton decoupling. In certain instances, protons can be masked or partially masked by solvent peaks and will therefore either be missing and not reported or reported as multiplets overlapping with solvent. The following abbreviations have been used (and derivatives thereof), e.g. s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; qn, quintet; p, pentet; h heptet; dd, doublet of doublets, etc. It is understood, where the NMR spectra contains residual impurities and/or residual solvent(s), this is not reported unless it partially coincides with peaks of intermediates and/or structures of Formula (I), in which case said peaks of intermediates and/or structures of Formula (I) are reported as multiplets partially overlapping with said solvent or impurity, and the integral is omitted. In some cases, compounds of Formula (I) appear as tautomers in the NMR-spectrum, in which instances only peaks of the major tautomer are reported.
In some cases, compounds of Formula (I) appear as tautomers in a more equal relationship, in such instances the peaks of such tautomers are either reported as multiplets, if the signals of said tautomer are partially overlapping with other peaks, or as individual peaks, if the signals of said tautomers are well separated. The integral of such peaks are reported as fractions of protons, indicating the ratio of the tautomer in the mixture.

(xiv) Electrospray mass spectral data were obtained using a Waters Acquity UPLC coupled to a Waters single quadrupole mass spectrometer or similar equipment, acquiring both positive and negative ion data, and generally, only ions relating to the parent structure are reported; high resolution electrospray mass spectral data were obtained using a Waters XEVO qToF mass spectrometer or similar equipment, coupled to a Waters Acquity UPLC, acquiring either positive and negative ion data, and generally, only ions relating to the parent structure are reported;

(xv) intermediates were not necessarily fully purified but their structures and purity were assessed by TLC, analytical HPLC/UPLC, and/or NMR analysis and/or mass spectrometry;

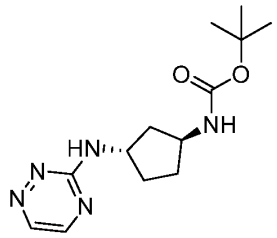
(xvi) in general Examples and intermediate compounds are named using ChemDraw Professional version 20.1.1.125 or version 21.0.0 from PerkinElmer. ChemDraw Professional version 20.1.1.125 or version 21.0.0 generates the names of chemical structures using the Cahn-Ingold-Prelog (CIP) rules for stereochemistry and follows IUPAC rules as closely as

possible when generating chemical names. Stereoisomers are differentiated from each other by stereodescriptors cited in names and assigned in accordance with the CIP rules.

Intermediates

Intermediate 1

tert-Butyl ((1*S*,3*S*)-3-((1,2,4-triazin-3-yl)amino)cyclopentyl)carbamate

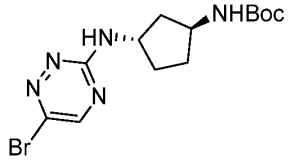


(i-1)

m-CPBA (5.60 g, 25.95 mmol) was added in small portions to a solution of 3-(methylthio)-1,2,4-triazine (CAS Reg. No. 28735-21-9) (3.0 g, 23.6 mmol) in DCM (80 mL) at 0 °C and the resulting suspension was stirred at 20 °C for 2 h. The solvent was removed under reduced pressure without heating, the residue dissolved in *n*-butanol (40 mL) and *tert*-butyl ((1*S*,3*S*)-3-aminocyclopentyl)carbamate (CAS Reg. No. 645400-44-8) (5.20 g, 26.0 mmol) was added and the resulting solution was stirred at 120 °C for 18 h. The reaction mixture was poured into 1 M NaOH (250 mL) and extracted with EtOAc (3 x 200 mL). The combined organic layers were dried (Na_2SO_4), filtered and evaporated to afford the crude product as a brown solid which was purified by flash chromatography on silica (gradient: 5-60% EtOAc in PE) to give (3.7 g, 56%) of the title compound as a yellow solid. MS (ESI): *m/z* $[M+H]^+$ 280.

Intermediate 2

tert-Butyl ((1*S*,3*S*)-3-((6-bromo-1,2,4-triazin-3-yl)amino)cyclopentyl)carbamate

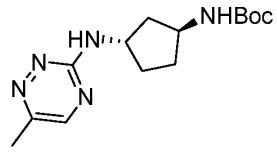


(i-2)

A solution of Br_2 in DCM (1 M, 15.9 mL, 15.9 mmol) was added dropwise to a solution of *tert*-butyl ((1*S*,3*S*)-3-((1,2,4-triazin-3-yl)amino)cyclopentyl)carbamate **intermediate 1** (3.7 g, 13.2 mmol) in a mixture of MeOH (60 mL) and water (30 mL) and the mixture was stirred at rt for 15 h. The solvent was removed under reduced pressure and the residue was poured into sat. Na_2SO_3(aq) (150 mL) and extracted with EtOAc (3 x 100 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford the crude product as brown solid which was purified by flash chromatography on silica (gradient: 5-30% EtOAc in PE) to give (3.5 g, 74%) of the title compound as a yellow solid. MS (ESI): *m/z* $[M+H]^+$ 358.

Intermediate 3

***tert*-Butyl ((1*S*,3*S*)-3-((6-methyl-1,2,4-triazin-3-yl)amino)cyclopentyl)carbamate**

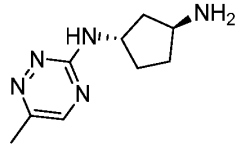


(i-3)

tert-Butyl ((1*S*,3*S*)-3-((6-bromo-1,2,4-triazin-3-yl)amino)cyclopentyl)carbamate **intermediate 2** (300 mg, 0.84 mmol) was added to 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane in THF (2.10 g, 8.37 mmol), K_3PO_4 (356 mg, 1.67 mmol) and 1,1'-bis(di-*tert*-butylphosphino)ferrocene palladium dichloride (CAS Reg. No. 95408-45-0) (55 mg, 0.08 mmol) in a mixture of dioxane (4 mL) and water (1 mL) at 20 °C. The resulting mixture was stirred at 100 °C for 15 h under a nitrogen atmosphere. The reaction mixture was poured into brine (150 mL) and extracted with EtOAc (4 x 100 mL). The combined organic layers were dried (Na_2SO_4), filtered and evaporated to afford the crude product. The residue was first purified by preparative TLC (MeOH : DCM = 1:20) followed by C18-flash chromatography (gradient: 0-49% MeOH in water) the title compound (103 mg, 42%) as a brown solid. MS (ESI): *m/z* $[M+H]^+$ 294.

Intermediate 4

(1*S*,3*S*)-*N*^{1}-(6-Methyl-1,2,4-triazin-3-yl)cyclopentane-1,3-diamine.2TFA

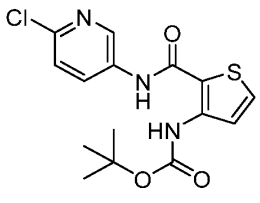


(i-4)

tert-Butyl ((1*S*,3*S*)-3-((6-methyl-1,2,4-triazin-3-yl)amino)cyclopentyl)carbamate **intermediate 3** (100 mg, 0.34 mmol) was added to a mixture of TFA (5 mL) in DCM (5 mL) at 20 °C and it was stirred at this temperature for 15 h. The reaction mixture was concentrated under reduced pressure to afford (100 mg, 95%) of the title compound as a white solid. MS (ESI): *m/z* $[M+H]^+$ 194.

Intermediate 5

***tert*-Butyl (2-((6-chloropyridin-3-yl)carbamoyl)thiophen-3-yl)carbamate**



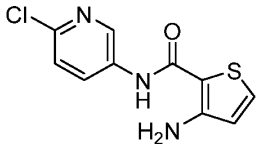
(i-5)

A mixture of 3-((*tert*-butoxycarbonyl)amino)thiophene-2-carboxylic acid (CAS Reg. No. 101537-64-8) (2.00 g, 8.22 mmol), 6-chloropyridin-3-amine (CAS Reg. No. 5350-93-6) (1.27 g,

9.87 mmol), HOBt (2.22 g, 16.4 mmol) and EDC (3.15 g, 16.4 mmol) in DMF (50 mL) was treated with TEA (3.4 mL, 25 mmol) and the resulting mixture was stirred at 60 °C for 3 h. The reaction mixture was poured into brine (200 mL) and it was extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (3 x 200 mL), dried over Na_2SO_4, filtered and evaporated. The crude material was purified by flash chromatography on silica (gradient: 0-100% EtOAc in PE) to give the title compound (800 mg, 28%) as a white solid. MS (ESI): *m/z* $[M+H]^+$ 353.9/356 (Cl isotope pattern).

Intermediate 6

3-Amino-*N*-(6-chloropyridin-3-yl)thiophene-2-carboxamide

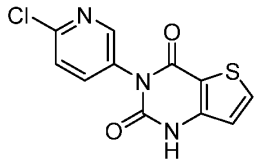


(i-6)

A mixture of *tert*-butyl (2-((6-chloropyridin-3-yl)carbamoyl)thiophen-3-yl)carbamate **intermediate 5** (780 mg, 2.20 mmol) in 1,4-dioxane (20 mL) was treated with HCl in dioxane (4 M, 5.5 mL, 22 mmol) at 15 °C and it was stirred at 60 °C for 15 h. The reaction mixture was concentrated under reduced pressure to afford an unspecified HCl salt of the title compound (550 mg, 98%) as a white solid. MS (ESI): *m/z* $[M+H]^+$ 253.9/256 (Cl isotope pattern).

Intermediate 7

3-(6-Chloropyridin-3-yl)thieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione

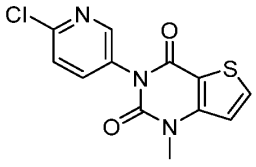


(i-7)

Triphosgene (CAS Reg. No. 32315-10-9) (1.72 g, 5.79 mmol) was added to a solution of 3-amino-*N*-(6-chloropyridin-3-yl)thiophene-2-carboxamide **intermediate 6** (780 mg, 2.20 mmol) in DCM (20 mL) at rt and the mixture was stirred at 40 °C for 2 days. The reaction mixture was concentrated under reduced pressure to give the title compound (529 mg, 98%) as a tan solid. MS (ESI): *m/z* $[M+H]^+$ 279.8/282 (Cl isotope pattern).

Intermediate 8

3-(6-Chloropyridin-3-yl)-1-methylthieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione

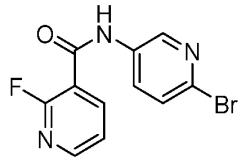


i-8

Iodomethane (1.65 g, 11.6 mmol) was added to a mixture of 3-(6-chloropyridin-3-yl)thieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione **intermediate 7** (650 mg, 2.32 mmol) and K_2CO_3 (642 mg, 4.65 mmol) in DMF (20 mL) and the resulting suspension was stirred at 60 °C for 3 h. The reaction mixture was cooled to rt and filtered through a pad of Celite. The filter cake was washed with DCM (3 x 10 mL) and the combined filtrates concentrated under reduced pressure. The obtained material was triturated with EtOAc:PE = 1:5 (25 mL), the solid collected by filtration and dried in vacuum to give the title compound (646 mg, 95%) as a tan solid. MS (ESI): *m/z* $[M+H]^+$ 293.8/296 (Cl isotope pattern). ^1H NMR (300 MHz, DMSO-d_6) δ ppm 3.54 (3H, s), 7.43 (1H, d), 7.70 (1H, d), 7.91 (1H, dd), 8.27 (1H, d), 8.42 (1H, d).

Intermediate 9

***N*-(6-Bromopyridin-3-yl)-2-fluoronicotinamide**

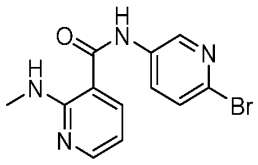


(i-9)

1-Methyl-1*H*-imidazole (1.90 g, 23.1 mmol) was added to 2-fluoronicotinic acid (CAS Reg. No. 393-55-5) (3.26 g, 23.1 mmol), 6-bromopyridin-3-amine (CAS Reg. No. 13534-97-9) (2.0 g, 11.6 mmol) and TCFH (CAS Reg. No. 207915-99-9) (6.49 g, 23.1 mmol) in MeCN (50 mL) at 25 °C. The resulting solution was stirred at 25 °C for 4 h. The solvent was removed under reduced pressure. The crude solid was triturated with DCM (20 mL), collected by filtration and dried under vacuum to give the title compound (2.80 g, 82%) as a yellow solid. MS (ESI) m/z $[M+H]^+$ 295.7 and 297.7 (Br isotope pattern).

Intermediate 10

***N*-(6-Bromopyridin-3-yl)-2-(methylamino)nicotinamide**



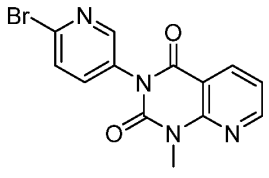
(i-10)

N-(6-Bromopyridin-3-yl)-2-fluoronicotinamide **intermediate 9** (2.0 g, 6.75 mmol) and methanamine (30 %w/w in EtOH, 5 mL, 123 mmol) were dissolved in iPrOH (15 mL) and sealed into a microwave tube. The reaction was heated to 100 °C for 1 h in a microwave reactor. The

reaction was cooled to rt and the solvent was removed under reduced pressure. The crude solid was triturated with PE, collected by filtration and dried under vacuum to give the title compound (1.7 g, 82%) as a white solid. MS (ESI) m/z $[M+H]^+$ 306.7 and 308.7 (Br isotope pattern).

Intermediate 11

3-(6-Bromopyridin-3-yl)-1-methylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione

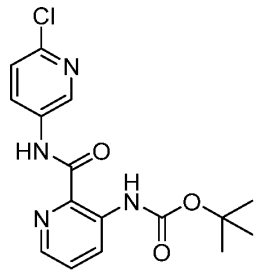


(i-11)

Triphosgene (CAS Reg. No. 32315-10-9)(1.807 g, 6.09 mmol) was added to *N*-(6-bromopyridin-3-yl)-2-(methylamino)nicotinamide **intermediate 10** (1.7 g, 5.53 mmol), DMAP (0.338 g, 2.77 mmol) and TEA (6.17 mL, 44.28 mmol) in DCE (100 mL) at 0 °C. The solution was stirred at 80 °C for 5 h. The reaction mixture was poured into sat. $NaHCO_3$ (200 mL) and extracted with DCM (3 x 150 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated. The crude was purified by column chromatography on silica (gradient: 2-30% EtOAc in PE) to give the title compound (1.5 g, 81%) as a pale-yellow solid. MS (ESI) m/z $[M+H]^+$ 333.1 and 335.1 (Br isotope pattern).

Intermediate 12

***tert*-Butyl (2-((6-chloropyridin-3-yl)carbamoyl)pyridin-3-yl)carbamate**

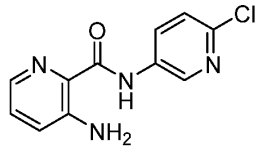


(i-12)

3-((*tert*-Butoxycarbonyl)amino)picolinic acid (CAS Reg. No. 569687-82-7) (5.0 g, 21 mmol) was added to 6-chloropyridin-3-amine (CAS Reg. No. 5350-93-6) (4.05 g, 31.5 mmol), TCFH (8.83 g, 31.5 mmol) and 1-methyl-1*H*-imidazole (5.17 g, 63.0 mmol) in acetonitrile (100 mL) at rt and the resulting mixture was stirred for 3 hours. The reaction mixture was quenched with water (300 mL) and extracted with EtOAc (3 x 200 mL). The combined organic layers were dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude product was purified by flash chromatography on silica (gradient: 0-100% EtOAc in PE) to give (5.67 g, 77%) of the title compound as a white solid. MS (ESI): *m/z* $[M+H]^+$ 349.0/351 (Cl isotope pattern).

Intermediate 13

3-Amino-*N*-(6-chloropyridin-3-yl)picolinamide

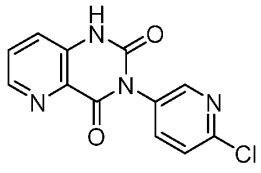


(i-13)

tert-Butyl (2-((6-chloropyridin-3-yl)carbamoyl)pyridin-3-yl)carbamate **intermediate 12** (5.60 g, 16.1 mmol) was added to a mixture of TFA (15 mL) and DCM (45 mL) at 25 °C and the resulting mixture was stirred at this temperature for 3 h. The reaction mixture was quenched with sat. $NaHCO_3$ (aq) (250 mL) and extracted with DCM (3 x 150 mL). The combined organic layers were dried (Na_2SO_4), filtered and evaporated to afford (3.66 g, 92%) of the crude title compound (white solid) which was used in the next step without further purification. MS (ESI): *m/z* $[M+H]^+$ 249.0/251 (Cl isotope pattern).

Intermediate 14

3-(6-Chloropyridin-3-yl)pyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione

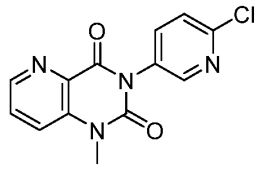


(i-14)

The 3HCl salt of 3-amino-*N*-(6-chloropyridin-3-yl)picolinamide **intermediate 13** (700 mg, 1.96 mmol) was added to triphosgene (290 mg, 0.98 mmol) and TEA (0.818 mL, 5.87 mmol) in DCM (20 mL) at rt and the resulting mixture was stirred at rt for 3 h. The reaction mixture was filtered through celite, the filter cake washed with MeOH (3 x 20 mL) and the combined filtrates concentrated under reduced pressure. The obtained crude product was purified by preparative TLC (MeOH: DCM = 1: 10) to afford (240 mg, 45%) of the title compound as a white solid. MS (ESI): *m/z* $[M+H]^+$ 274.9/277 (Cl isotope pattern).

Intermediate 15

3-(6-Chloropyridin-3-yl)-1-methylpyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione



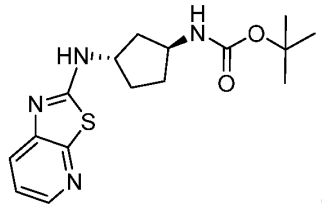
(i-15)

3-(6-Chloropyridin-3-yl)pyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione **intermediate 14** (370 mg, 1.35 mmol) was added to MeI (0.168 mL, 2.69 mmol) and K_2CO_3 (559 mg, 4.04 mmol) in DMF (15 mL) at rt and the resulting mixture was stirred at 60 °C for 3 h. The reaction mixture was quenched with brine (150 mL) and extracted with EtOAc (3 x 100 mL). The combined organic

layers were dried (Na_2SO_4), filtered and evaporated to afford crude product. The residue was purified by preparative TLC (MeOH: DCM = 1: 10) to afford (230 mg, 59%) of the title compound as a yellow solid. MS (ESI): *m/z* $[M+H]^+$ 289.0/291 (Cl isotope pattern).

Intermediate 16

tert-Butyl ((1*S*,3*S*)-3-(thiazolo[5,4-*b*]pyridin-2-ylamino)cyclopentyl)carbamate

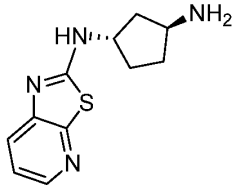


(i-16)

2-Bromothiazolo[5,4-*b*]pyridine (CAS Reg. No. 412923-40-1) (200 mg, 0.93 mmol) was added to *tert*-butyl ((1*S*,3*S*)-3-aminocyclopentyl)carbamate (186 mg, 0.93 mmol), Pd-PEPPSI-IpentCl 2-methylpyridine (39 mg, 0.05 mmol) and Cs_2CO_3 (909 mg, 2.79 mmol) in 1,4-dioxane (10 mL). The resulting mixture was stirred at 100 °C for 15 h under a nitrogen atmosphere. The reaction mixture was filtered through Celite. The filter cake was washed with EtOAc (3×20 mL) and the combined filtrates were concentrated under reduced pressure. The residue was purified by preparative TLC (EtOAc:PE = 2:1) to give the title compound (220 mg, 70%) as a yellow oil. MS (ESI) *m/z* $[M+H]^+$ 335.0.

Intermediate 17

(1*S*,3*S*)-*N*^{1}-(Thiazolo[5,4-*b*]pyridin-2-yl)cyclopentane-1,3-diamine

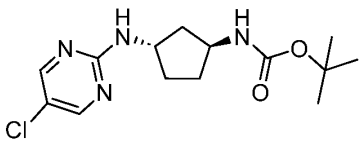


(i-17)

tert-Butyl ((1*S*,3*S*)-3-(thiazolo[5,4-*b*]pyridin-2-ylamino)cyclopentyl)carbamate **intermediate 16** (200 mg, 0.60 mmol) was added to TFA (2 mL) and DCM (6 mL). The resulting mixture was stirred at 25 °C for 3 h. The reaction mixture was concentrated under reduced pressure to give an unspecified TFA salt of the crude title compound (370 mg) as a brown oil. MS (ESI) *m/z* $[M+H]^+$ 235.0.

Intermediate 18

tert-Butyl ((1*S*,3*S*)-3-((5-chloropyrimidin-2-yl)amino)cyclopentyl)carbamate

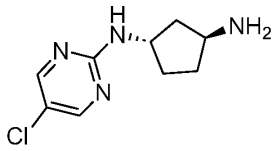


(i-18)

2,5-Dichloropyrimidine (1 g, 6.71 mmol) was added to Na_2CO_3 (1.067 g, 10.07 mmol) and *tert*-butyl ((1*S*,3*S*)-3-aminocyclopentyl)carbamate (1.412 g, 7.05 mmol) in DMSO (12 mL) at 25 °C. The suspension was stirred at 100 °C for 90 min. The reaction mixture was diluted with brine (350 mL) and washed sequentially with EtOAc (3 x 250 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated. The crude solid was triturated with EtOAc:PE, 20:1 (100 mL), collected by filtration and dried under vacuum to give the title compound (1.69 g, 81%) as a pale-orange solid. MS (ESI) m/z $[M+H]^+$ 313.1/315 (Cl isotope pattern).

Intermediate 19

(1*S*,3*S*)-*N*^{1}-(5-Chloropyrimidin-2-yl)cyclopentane-1,3-diamine.3HCl

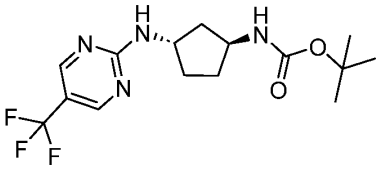


(i-19)

HCl in MeOH (4 M, 6.72 mL, 26.87 mmol) was added dropwise to *tert*-butyl ((1*S*,3*S*)-3-((5-chloropyrimidin-2-yl)amino)cyclopentyl)carbamate **intermediate 18** (1.68 g, 5.37 mmol) in MeOH (20 mL) at 30 °C. The reaction mixture was stirred at 60 °C for 3 h. The solvent was removed under reduced pressure to give the crude title compound (1.6 g, 92%). MS (ESI) m/z $[M+H]^+$ 213.1/215 (Cl isotope pattern).

Intermediate 20

***tert*-Butyl ((1*S*,3*S*)-3-((5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclopentyl)carbamate**

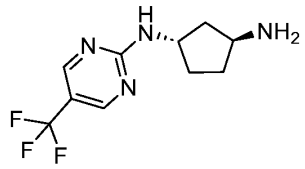


(i-20)

2-Chloro-5-(trifluoromethyl)pyrimidine (1 g, 5.48 mmol) was added to Na_2CO_3 (0.871 g, 8.22 mmol) and *tert*-butyl ((1*S*,3*S*)-3-aminocyclopentyl)carbamate (1.152 g, 5.75 mmol) in DMSO (12 mL) at 25 °C and the suspension was stirred at 100 °C for 3 h. The reaction mixture was diluted with brine (350 mL) and washed sequentially with EtOAc (3 x 250 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated. The crude solid was triturated with EtOAc:PE, 20:1 (42 mL), collected by filtration and dried under vacuum to give the title compound (1.8 g, 95%) as a white solid. MS (ESI) m/z $[M+H]^+$ 347.1.

Intermediate 21

(1*S*,3*S*)-*N*^{1}-(5-(Trifluoromethyl)pyrimidin-2-yl)cyclopentane-1,3-diamine x HCl

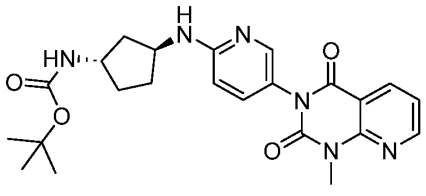


(i-21)

HCl in MeOH (4 M, 6.5 mL, 26 mmol) was added dropwise to *tert*-butyl ((1*S*,3*S*)-3-((5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclopentyl)carbamate **intermediate 20** (1.8 g, 5.2 mmol) in MeOH (20 mL) at 30 °C. The reaction mixture was stirred at 60 °C for 3 h. The solvent was removed under reduced pressure to give crude title compound (0.927 g, 63%) as a white solid. MS (ESI) m/z $[M+H]^+$ 247.1.

Intermediate 22

tert-Butyl ((1*S*,3*S*)-3-((5-(1-methyl-2,4-dioxo-1,4-dihydropyrido[2,3-*d*]pyrimidin-3(2*H*)-yl)pyridin-2-yl)amino)cyclopentyl)carbamate

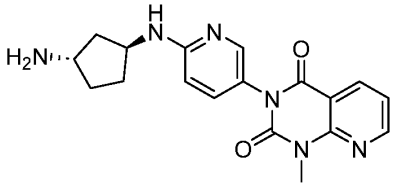


(i-22)

Pd-PEPPSI-IpentCl 2-methylpyridine (0.126 g, 0.15 mmol) was added to 3-(6-bromopyridin-3-yl)-1-methylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione **intermediate 11** (1.0 g, 3.00 mmol), *tert*-butyl ((1*S*,3*S*)-3-aminocyclopentyl)carbamate (0.661 g, 3.30 mmol) and K_3PO_4 (1.27 g, 6.00 mmol) in 1,4-dioxane (10 mL) at 20 °C under a N_2 (g) atmosphere. The mixture was stirred at 100 °C for 15 h. The reaction mixture was filtered through Celite and the filtrate evaporated under reduced pressure. The residue was purified by preparative TLC (DCM MeOH, 10:1) to afford the title compound (1.27 g, 93%) as a yellow solid. MS (ESI) m/z $[M+H]^+$ 453.0.

Intermediate 23

3-(6-(((1*S*,3*S*)-3-Aminocyclopentyl)amino)pyridin-3-yl)-1-methylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione.4HCl



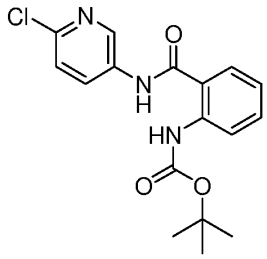
(i-23)

HCl in MeOH (4 M, 5 mL, 20.00 mmol) was added to *tert*-butyl ((1*S*,3*S*)-3-((5-(1-methyl-2,4-dioxo-1,4-dihydropyrido[2,3-*d*]pyrimidin-3(2*H*)-yl)pyridin-2-yl)amino)cyclopentyl)carbamate **intermediate 22** (500 mg, 1.10 mmol) in MeOH (8 mL) at 20 °C. The reaction mixture was

stirred at 60 °C for 1 h and concentrated under reduced pressure to give crude title compound (528 mg, 96%) as a yellow solid. MS (ESI) m/z $[M+H]^+$ 353.0.

Intermediate 24

tert-Butyl (2-((6-chloropyridin-3-yl)carbamoyl)phenyl)carbamate

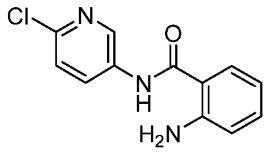


(i-24)

Triethylamine (853 mg, 8.43 mmol) was added to a mixture of 5-amino-2-chloropyridine (CAS Reg. No. 5350-93-6) (1.08 g, 8.43 mmol), 2-((*tert*-butoxycarbonyl)amino)benzoic acid (CAS Reg. No. 68790-38-5) (1.00 g, 4.21 mmol) and propylphosphonic anhydride (2.68 g, 8.43 mmol) in DMF (20 mL) at 25 °C. The reaction mixture was stirred at 60 °C for 3 h and concentrated under reduced pressure. The residue was diluted with EtOAc (300 mL) and washed with sat. brine (5 x 75 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated and the crude product purified by C18-flash chromatography (gradient: 0-40% MeCN in water) to give the title compound (1.3 g, 89%) as a yellow solid. MS (ESI) m/z $[M-H]^-$ 346.0.

Intermediate 25

2-Amino-_N_-(6-chloropyridin-3-yl)benzamide

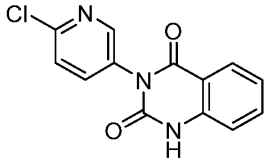


(i-25)

HCl in MeOH (4 M, 5.0 mL, 20 mmol) was added to *tert*-butyl (2-((6-chloropyridin-3-yl)carbamoyl)phenyl)carbamate **intermediate 24** (1.5 g, 4.3 mmol) in MeOH (2 mL) at 25 °C. The reaction mixture was stirred at 60 °C for 3 h and concentrated under reduced pressure to give crude title compound (1.3 g, 94%) as a yellow solid. MS (ESI) m/z $[M+H]^+$ 247.7.

Intermediate 26

3-(6-Chloropyridin-3-yl)quinazoline-2,4(1_H_,3_H_)-dione

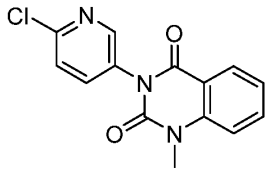


(i-26)

Triethylamine (2.86 g, 28.3 mmol) was added to 2-amino-*N*-(6-chloropyridin-3-yl)benzamide **intermediate 25** (700 mg, 2.83 mmol) and triphosgene (CAS Reg. No. 32315-10-9) (1.68 g, 5.65 mmol) in dichloromethane (30 mL) at 25 °C and the reaction mixture was stirred at this temperature for 3 h. The mixture was concentrated under reduced pressure, the residue diluted with EtOAc (300 mL) and washed with sat. brine (5 x 75 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to give a precipitate. The precipitate was filtered off, the filter cake washed with MeOH and dried to give the crude title compound (659 mg, 85%) as a yellow solid. MS (ESI) m/z $[M+H]^+$ 273.7.

Intermediate 27

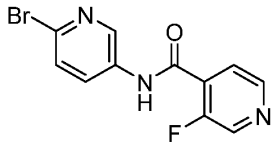
3-(6-Chloropyridin-3-yl)-1-methylquinazoline-2,4(1*H*,3*H*)-dione


(i-27)

Iodomethane (207 mg, 1.46 mmol) was added to 3-(6-chloropyridin-3-yl)quinazoline-2,4(1*H*,3*H*)-dione **intermediate 26** (200 mg, 0.73 mmol) and K_2CO_3 (303 mg, 2.19 mmol) in DMF (10 mL) at 25 °C. The reaction mixture was stirred at 60 °C for 15 h and concentrated under reduced pressure. The residue was diluted with EtOAc (300 mL) and washed with sat. brine (5 x 75 mL). The organic layer was dried over Na2SO4, filtered and evaporated. The obtained crude product was triturated with MeCN, the solid material filtered off and dried to give the title compound (196 mg, 93%) as a brown solid. MS (ESI) m/z $[M+H]^+$ 288.1/290 (Cl isotope pattern).

Intermediate 28

***N*-(6-Bromopyridin-3-yl)-3-fluoroisonicotinamide**

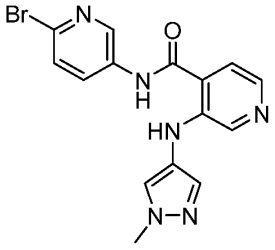

(i-28)

6-Bromopyridin-3-amine (CAS Reg. No. 13534-97-9) (1.35 g, 7.80 mmol) was added to a mixture of 3-fluoroisonicotinic acid (CAS Reg. No. 393-53-3) (1.00 g, 7.09 mmol), HATU (4.04 g, 10.6 mmol) and DIPEA (2.48 mL, 14.2 mmol) in DMF (20 mL) at 25 °C under nitrogen and it was stirred at this temperature for 2 h. The reaction mixture was concentrated under reduced pressure, the residue diluted with EtOAc (50 mL) and washed with sat. brine (3 x 50 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated and the crude product purified by flash chromatography on silica (gradient: 0-60% EtOAc in PE) to give the title compound (1.5 g,

72%) as a pale-yellow solid. MS (ESI) m/z $[M+H]^+$ 296/298 (Br isotope pattern). ^{19}F NMR (471 MHz, DMSO-d_6) δ ppm -129.57 (1F, s).

Intermediate 29

_N_-(6-Bromopyridin-3-yl)-3-((1-methyl-1_H_-pyrazol-4-yl)amino)isonicotinamide

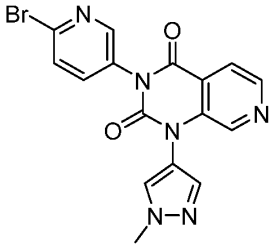


(i-29)

A mixture of _N_-(6-bromopyridin-3-yl)-3-fluoroisonicotinamide **intermediate 28** (500 mg, 1.69 mmol), 1-methyl-1_H_-pyrazol-4-amine (CAS Reg. No. 69843-13-6) (410 mg, 4.22 mmol) and bis(trimethylaluminum)-1,4-diazabicyclo[2.2.2]octane adduct (CAS Reg. No. 137203-34-0) (952 mg, 3.71 mmol) in THF (20 mL) was sealed in a microwave tube and heated in a microwave reactor to 80 °C for 1 h. The reaction mixture was cooled to rt and quenched with water (150 mL). The aqueous phase was extracted with EtOAc (3 x 100 mL) and the combined organic layer was dried over Na_2SO_4, filtered and evaporated. The obtained material was purified by preparative TLC (EtOAc:PE = 5:1) to give the title compound (540 mg, 86%) as yellow solid. MS (ESI) m/z $[M+H]^+$ 372.9/374.9 (Br isotope pattern).

Intermediate 30

3-(6-Bromopyridin-3-yl)-1-(1-methyl-1_H_-pyrazol-4-yl)pyrido[3,4-_d_]pyrimidine-2,4(1_H_,3_H_)-dione



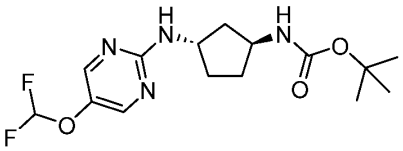
(i-30)

_N_-(6-Bromopyridin-3-yl)-3-((1-methyl-1_H_-pyrazol-4-yl)amino)isonicotinamide **intermediate 29** (500 mg, 1.34 mmol) was added to a mixture of triphosgene (CAS Reg. No. 32315-10-9) (398 mg, 1.34 mmol), DMAP (82 mg, 0.67 mmol) and triethylamine (1.87 mL, 13.4 mmol) in dichloromethane (10 mL) at 25 °C and the reaction mixture was stirred at 20 °C for 15 h. The reaction mixture was diluted with sat. aq. $NaHCO_3$ (150 mL) and the phases separated. The aqueous phase was extracted with DCM (3 x 100 mL) and the combined organic layers were dried over Na_2SO_4, filtered and evaporated. The obtained material was purified by preparative

TLC (EtOAc:PE = 5:1) to give the title compound (457 mg, 85%) as yellow solid. MS (ESI) m/z $[M+H]^+$ 399/400.8 (Br isotope pattern).

Intermediate 31

***tert*-Butyl ((1*S*,3*S*)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)carbamate**

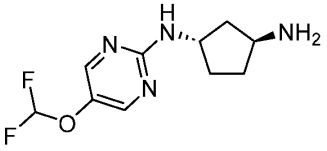


(i-31)

2-Chloro-5-(difluoromethoxy)pyrimidine (CAS Reg. No. 1192813-64-1) (5.00 g, 27.7 mmol) was added to *tert*-butyl ((1*S*,3*S*)-3-aminocyclopentyl)carbamate (CAS Reg. No. 645400-44-8) (6.10 g, 30.5 mmol) and Na_2CO_3 (4.40 g, 41.5 mmol) in DMSO (80 mL) at 20 °C. The resulting mixture was stirred at 100 °C for 15 h. The reaction mixture was poured into water (250 mL) and extracted with EtOAc (4 x 150 mL). The organic layers were combined and washed with sat. brine (4 x 100 mL), dried over Na_2SO_4, filtered and evaporated to afford crude product. The crude product was purified by flash chromatography on silica (gradient: 46-50% EtOAc in PE) to give the title compound (8.5 g, 89%) as a white solid. MS (ESI) m/z $[M+H]^+$ 345.2.

Intermediate 32

(1*S*,3*S*)-*N*^{1}-(5-(Difluoromethoxy)pyrimidin-2-yl)cyclopentane-1,3-diamine

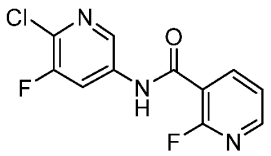


(i-32)

4 M HCl in MeOH (20 mL, 80 mmol) was added to *tert*-butyl ((1*S*,3*S*)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)carbamate **intermediate 31** (8.7 g, 25 mmol) in MeOH (60 mL) at 20 °C. The resulting mixture was stirred at 60 °C for 2 h. The solvent was removed under reduced pressure to give an unspecified HCl salt of the crude title compound (9.9 g) as a white solid that was used directly without further purification. MS (ESI) m/z $[M+H]^+$ 245.0.

Intermediate 33

***N*-(6-Chloro-5-fluoropyridin-3-yl)-2-fluoronicotinamide**

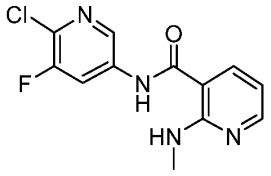


(i-33)

1-Methylimidazole (CAS Reg. No. 616-47-7) (560 mg, 6.82 mmol) was added to a mixture of 2-fluoronicotinic acid (CAS Reg. No. 393-55-5) (722 mg, 5.12 mmol), 6-chloro-5-fluoropyridin-3-amine (CAS Reg. No. 1256806-83-3) (500 mg, 3.41 mmol) and TCFH (CAS Reg. No. 94790-35-9) (1.92 g, 6.82 mmol) in MeCN (40 mL) at 20 °C. The reaction mixture was stirred at 60 °C for 15 h and concentrated under reduced pressure. The obtained material was triturated with dichloromethane, the solid collected by filtration and dried in vacuum to give the title compound (500 mg, 54%) as a white solid. MS (ESI) m/z $[M+H]^+$ 270/272 (Cl isotope pattern).

Intermediate 34

_N_-(6-Chloro-5-fluoropyridin-3-yl)-2-(methylamino)nicotinamide

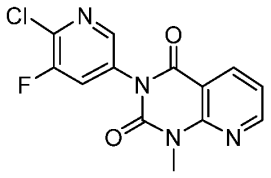


(i-34)

A mixture of *N*-(6-chloro-5-fluoropyridin-3-yl)-2-fluoronicotinamide **intermediate 33** (490 mg, 1.82 mmol) and methanamine in water (30wt%, 4 mL) in EtOH (16 mL) was sealed in a microwave tube and heated in a microwave reactor to 80 °C for 2 h. The reaction mixture was cooled to rt and concentrated under reduced pressure. The obtained material was triturated with dichloromethane, the solid collected by filtration and dried in vacuum to give the title compound (220 mg, 43%) as a white solid. MS (ESI) m/z $[M+H]^+$ 281.2/283 (Cl isotope pattern).

Intermediate 35

3-(6-Chloro-5-fluoropyridin-3-yl)-1-methylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione

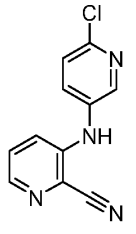


(i-35)

Triethylamine (0.298 mL, 2.14 mmol) was added to *N*-(6-chloro-5-fluoropyridin-3-yl)-2-(methylamino)nicotinamide **intermediate 34** (200 mg, 0.71 mmol) and triphosgene (CAS Reg. No. 32315-10-9) (317 mg, 1.07 mmol) in DCE (15 mL) at 15 °C and the reaction mixture was subsequently stirred at 80 °C for 15 h. The mixture was poured into sat. aq. $NaHCO_3$ (125 mL) and the aqueous phase was extracted with dichloromethane (3 x 75 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated. The obtained gum was triturated with EtOAc, the solid collected by filtration and dried in vacuum to give the title compound (160 mg, 73%) as a white solid. MS (ESI) m/z $[M+H]^+$ 307/309 (Cl isotope pattern).

Intermediate 36

3-((6-Chloropyridin-3-yl)amino)picolinonitrile

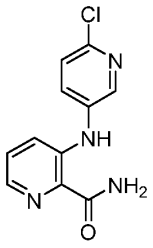

(i-36)

The reaction was run in two parallel batches of identical size. Both crude reaction mixtures were combined before work-up.

$Pd(dppf)Cl_2$•DCM (446 mg, 0.546 mmol) was added to a mixture of 3-bromopicolinonitrile (CAS Reg. No. 55758-02-6) (500 mg, 2.73 mmol), 5-amino-2-chloropyridine (CAS Reg. No. 5350-93-6) (281 mg, 2.19 mmol), XantPhos (316 mg, 0.546 mmol) and K_2CO_3 (1.13 g, 8.20 mmol) in 1,4-dioxane (8 mL) at 20 °C under nitrogen. The reaction mixture was subsequently stirred at 80 °C for 15 h and combined with the crude reaction mixture of another batch with identical size. The combined batches were filtered through Celite, the filter cake washed with DCM (2 x 3 mL) and the combined filtrates concentrated under reduced pressure. The obtained material was purified by preparative TLC (EtOAc:PE = 1:1) to give the title compound (750 mg) as yellow solid. MS (ESI) m/z $[M+H]^+$ 231/233 (Cl isotope pattern).

Intermediate 37

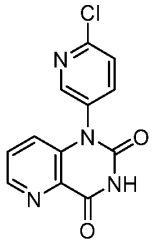
3-((6-chloropyridin-3-yl)amino)picolinamide


(i-37)

Hydrogen peroxide (30% in water, 0.30 mL, 3.2 mmol) was added dropwise to a mixture of 3-((6-chloropyridin-3-yl)amino)picolinonitrile **intermediate 36** (730 mg, 3.16 mmol) and K_2CO_3 (66 mg, 0.47 mmol) in DMSO (15 mL) at 20 °C and it was stirred at this temperature for 4 h. The mixture was diluted with water (20 mL) and the aqueous phase extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated. The obtained crude material was purified by C18-flash chromatography (gradient: 20-30% MeCN in water) to give the title compound (276 mg, 35%) as a yellow solid. MS (ESI) m/z $[M+H]^+$ 249.1/251 (Cl isotope pattern).

Intermediate 38

1-(6-Chloropyridin-3-yl)pyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione

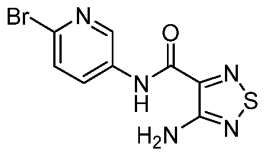


(i-38)

NaH (46.3 mg, 1.93 mmol) was added to a mixture of 3-((6-chloropyridin-3-yl)amino)picolinamide **intermediate 37** (160 mg, 0.64 mmol) in DMF (8 mL) at 20 °C and it was stirred at this temperature for 10 min. CDI (209 mg, 1.29 mmol) was subsequently added and stirring at 20 °C continued for another 15 h. The reaction mixture was filtered through Celite, the filter cake washed with DCM (2 x 5 mL) and the combined filtrates concentrated under reduced pressure to give the crude title compound (170 mg, 96%) as a yellow solid which was not further purified. MS (ESI) m/z $[M+H]^+$ 275/277 (Cl isotope pattern).

Intermediate 39

4-Amino-*N*-(6-bromopyridin-3-yl)-1,2,5-thiadiazole-3-carboxamide

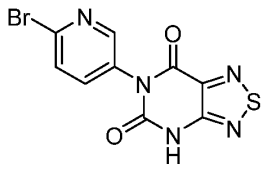


(i-39)

4-Fluoro-1,2,5-thiadiazole-3-carboxylic acid (6.42 g, 43.4 mmol) was added to a mixture of 6-bromopyridin-3-amine (CAS Reg. No. 13534-97-9) (5.00 g, 28.9 mmol), TCFH (12.2 g, 43.4 mmol) and 1-methyl-1*H*-imidazole (7.12 g, 86.7 mmol) in acetonitrile (130 mL) at 25 °C and the resulting mixture was stirred at 20 °C for 3 hours. The reaction mixture was concentrated under reduced pressure and the residue taken up with MeOH (50 mL). The mixture was filtered through Celite, the filter cake washed sequentially with MeOH (3 x 50 mL) and DCM (3 x 50 mL) and the combined filtrates concentrated under reduced pressure to give the crude title compound (8.0 g, 92%) as a white solid which was not further purified. MS (ESI): *m/z* $[M+H]^+$ 300/302 (Br isotope pattern).

Intermediate 40

6-(6-Bromopyridin-3-yl)-[1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione

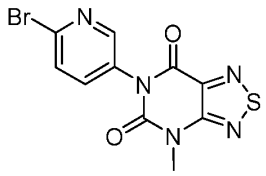


(i-40)

Bis(trichloromethyl) carbonate (4.94 g, 16.7 mmol) was added to a mixture of 4-amino-*N*-(6-bromopyridin-3-yl)-1,2,5-thiadiazole-3-carboxamide **intermediate 39** (5.00 g, 16.7 mmol), DMAP (1.02 g, 8.33 mmol) and pyridine (13.5 mL, 167 mmol) in DCE (100 mL) at 0 °C. The reaction mixture was stirred at 80 °C for 3 h and quenched with sat. $NaHCO_3$ (300 mL). The aqueous phase was extracted with DCM (3 x 200 mL), the combined organic layers dried over Na_2SO_4, filtered, and evaporated to give the crude title compound (3.6 g, 67%) as a white solid. MS (ESI) m/z $[M+H]^+$ 327.8.

Intermediate 41

6-(6-Bromopyridin-3-yl)-4-methyl-[1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione

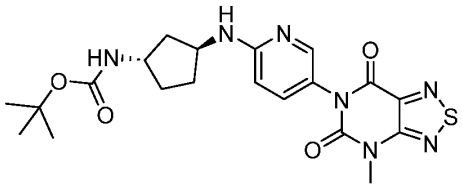


(i-41)

Iodomethane (1.38 mL, 22.1 mmol) was added to 6-(6-bromopyridin-3-yl)-[1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione **intermediate 40** (3.60 g, 11.0 mmol) and K_2CO_3 (4.58 g, 33.1 mmol) in DMF (60 mL) at 20 °C. The reaction mixture was stirred at 60 °C for 3 h and quenched with sat. brine (500 mL). The aqueous phase was extracted with EtOAc (3 x 300 mL), the combined organic layers dried over Na_2SO_4, filtered, and evaporated. The crude material was purified by flash chromatography on silica (gradient: 0-100% EtOAc in PE) to give the title compound (2.4 g, 65%) as a white solid. MS (ESI) m/z $[M+H]^+$ 339.8/341.8 (Br isotope pattern).

Intermediate 42

***tert*-Butyl ((1*S*,3*S*)-3-((5-(4-methyl-5,7-dioxo-4,5-dihydro-[1,2,5]thiadiazolo[3,4-*d*]pyrimidin-6(7*H*)-yl)pyridin-2-yl)amino)cyclopentyl)carbamate**



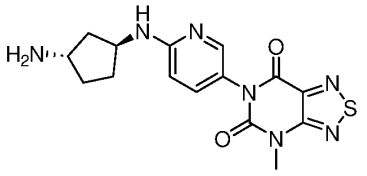
(i-42)

Pd-PEPPSI-IpentCl 2-methylpyridine (346 mg, 0.41 mmol) was added to a mixture of 6-(6-bromopyridin-3-yl)-4-methyl-[1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione **intermediate 41** (1.40 g, 4.12 mmol), *tert*-butyl ((1*S*,3*S*)-3-aminocyclopentyl)carbamate (1.24 g, 6.17 mmol)

and CsF (1.25 g, 8.23 mmol) in 1,4-dioxane (30 mL) at 15 °C under a nitrogen atmosphere. The mixture was stirred at 100 °C for 15 h and quenched with sat. brine (200 mL). The aqueous phase was extracted with EtOAc (3 x 125 mL), the combined organic layers dried over Na_2SO_4, filtered, and evaporated. The crude material was purified by flash chromatography on silica (gradient: 0-30% MeOH in DCM) to give the title compound (1.09 g, 58%) as a white solid. MS (ESI) m/z $[M+H]^+$ 460.0.

Intermediate 43

6-(6-(((1*S*,3*S*)-3-Aminocyclopentyl)amino)pyridin-3-yl)-4-methyl-[1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione

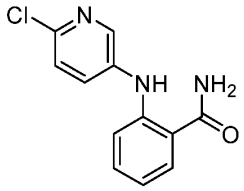


(i-43)

tert-Butyl ((1*S*,3*S*)-3-((5-(4-methyl-5,7-dioxo-4,5-dihydro-[1,2,5]thiadiazolo[3,4-*d*]pyrimidin-6(7*H*)-yl)pyridin-2-yl)amino)cyclopentyl)carbamate **intermediate 42** (1.00 g, 2.18 mmol) was added to a mixture of TFA (6 mL) in DCM (18 mL) at 15 °C and it was stirred at 20 °C for 3 h. The reaction mixture was concentrated under reduced pressure to afford an unspecified TFA salt of the title compound (960 mg) as a brown oil. MS (ESI): *m/z* $[M+H]^+$ 360.0.

Intermediate 44

2-((6-Chloropyridin-3-yl)amino)benzamide

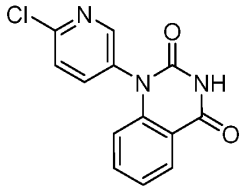


(i-44)

$Pd(OAc)_2$ (82 mg, 0.37 mmol) was added to a mixture of 2-aminobenzamide (CAS Reg. No. 88-68-6) (500 mg, 3.67 mmol), 2-chloro-5-iodopyridine (CAS Reg. No. 69045-79-0) (1.32 g, 5.51 mmol), XPhos (350 mg, 0.73 mmol) and K_2CO_3 (1.52 g, 11.0 mmol) in *tert*-BuOH (50 mL) at 25 °C under nitrogen and it was stirred at 110 °C for 15 h. The reaction mixture was diluted with EtOAc (100 mL) and washed with sat. brine (5 x 50 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated and the crude product purified by flash chromatography on silica (gradient: 50-60% EtOAc in PE) to give the title compound (187 mg, 21%) as a yellow solid. MS (ESI) m/z $[M+H]^+$ 248/250 (Cl isotope pattern).

Intermediate 45

1-(6-Chloropyridin-3-yl)quinazoline-2,4(1*H*,3*H*)-dione

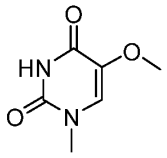


(i-45)

A solution of triphosgene (89 mg, 0.30 mmol) in THF (3 mL) was added to a mixture of 2-((6-chloropyridin-3-yl)amino)benzamide **intermediate 44** (148 mg, 0.60 mmol), triethylamine (250 µL, 1.79 mmol) and DMAP (7 mg, 0.06 mmol) in THF (20 mL) at 0 °C and the mixture was subsequently stirred at 60 °C for 15 h. The formed precipitate was filtered off and washed with PE (50 mL). The combined filtrates were concentrated under reduced pressure and the obtained material purified by preparative TLC (EtOAc:PE = 1:1) to give the title compound (108 mg, 66%) as white solid.

Intermediate 46

5-Methoxy-1-methylpyrimidine-2,4(1*H*,3*H*)-dione

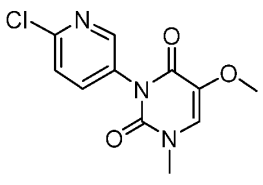


(i-46)

Ammonium sulfate (619 mg, 4.69 mmol) was added to a mixture of 5-methoxyuracil (CAS Reg. No. 6623-81-0) (3.7 g, 26 mmol) in hexamethyldisilazane (45 mL) at 25 °C and it was stirred at 130 °C for 15 h. The reaction mixture was cooled to 25 °C and treated with a solution of KI (2.2 g, 13 mmol) and iodomethane (7.4 g, 52 mmol) in MeCN (90 mL). The resulting suspension was stirred at 90 °C for 5 h, cooled to rt and concentrated under reduced pressure. The obtained residue was triturated with MeOH (20 mL), the solid material filtered off and dried under reduced pressure to give the title compound (3.8 g, 93%) as a beige solid. MS (ESI) m/z $[M+H]^+$ 157.3.

Intermediate 47

3-(6-Chloropyridin-3-yl)-5-methoxy-1-methylpyrimidine-2,4(1*H*,3*H*)-dione



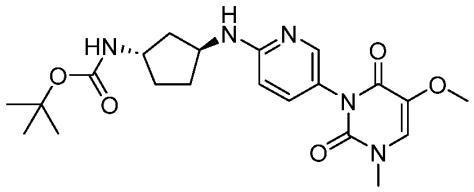
(i-47)

Pyridine (800 µL, 9.9 mmol) was added to a mixture of 5-methoxy-1-methylpyrimidine-2,4(1*H*,3*H*)-dione **intermediate 46** (770 mg, 4.93 mmol), (6-chloropyridin-3-yl)boronic acid

(CAS Reg. No. 444120-91-6) (1.55 g, 9.86 mmol) and $Cu(OAc)_2$ (1.79 g, 9.86 mmol) in DCM (10 mL) at 20 °C and the resulting mixture was stirred at this temperature for 4 days. The reaction mixture was filtered through Celite, the filtrate diluted with DCM (500 mL) and washed sequentially with 1M citric acid (3 x 100 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated. The obtained crude product was purified by preparative TLC (DCM: MeOH = 10:1) to give the title compound (600 mg, 46%) as a white solid. MS (ESI): *m/z* $[M+H]^+$ 268/270 (Cl isotope pattern).

Intermediate 48

***tert*-Butyl ((1*S*,3*S*)-3-((5-(5-methoxy-3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl)pyridin-2-yl)amino)cyclopentyl)carbamate**

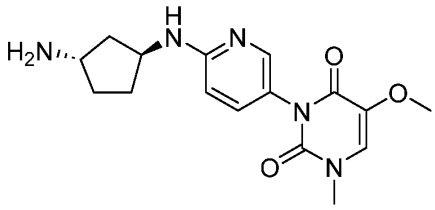


(i-48)

Pd-PEPPSI-IpentCl 2-methylpyridine (47 mg, 0.06 mmol) was added to a mixture of 3-(6-chloropyridin-3-yl)-5-methoxy-1-methylpyrimidine-2,4(1*H*,3*H*)-dione **intermediate 47** (300 mg, 1.12 mmol), *tert*-butyl ((1*S*,3*S*)-3-aminocyclopentyl)carbamate (269 mg, 1.34 mmol) and K_3PO_4 (714 mg, 3.36 mmol) in 1,4-dioxane (8 mL) at 20 °C under a nitrogen atmosphere. The mixture was stirred at 100 °C for 15 h , cooled to rt and filtered through Celite. The filtrate was concentrated under reduced pressure and the obtained material purified by preparative TLC (7 M NH_3 in MeOH : DCM = 1:10) to give the title compound (298 mg, 62%) as a white solid. MS (ESI) m/z $[M+H]^+$ 432.1.

Intermediate 49

3-(6-(((1*S*,3*S*)-3-Aminocyclopentyl)amino)pyridin-3-yl)-5-methoxy-1-methylpyrimidine-2,4(1*H*,3*H*)-dione



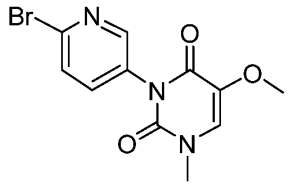
(i-49)

HCl in MeOH (4 M, 3.0 mL, 0.65 mmol) was added to *tert*-butyl ((1*S*,3*S*)-3-((5-(5-methoxy-3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl)pyridin-2-yl)amino)cyclopentyl)carbamate **intermediate 48** (280 mg, 0.65 mmol) in MeOH (6 mL) at 20 °C. The reaction mixture was

stirred at 60 °C for 2 h and concentrated under reduced pressure to give an unspecified HCl salt of the title compound (276 mg) as a yellow solid. MS (ESI) m/z $[M+H]^+$ 332.0.

Intermediate 50

3-(6-Bromopyridin-3-yl)-5-methoxy-1-methylpyrimidine-2,4(1*H*,3*H*)-dione

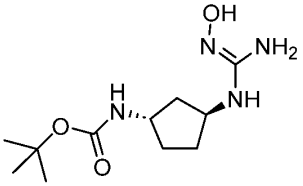


(i-50)

Pyridine (207 µL, 2.56 mmol) was added to a mixture of 5-methoxy-1-methylpyrimidine-2,4(1*H*,3*H*)-dione **intermediate 46** (200 mg, 1.28 mmol), (6-bromopyridin-3-yl)boronic acid (CAS Reg. No. 223463-14-7) (517 mg, 2.56 mmol) and $Cu(OAc)_2$ (465 mg, 2.56 mmol) in DCM (8 mL) at 20 °C and the resulting mixture was stirred at this temperature for 15 h. The reaction mixture was filtered through Celite, the filtrate diluted with DCM (200 mL) and washed sequentially with 1M citric acid (3 x 50 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated. The obtained crude product was purified by preparative TLC (DCM: MeOH = 10:1) to give the title compound (326 mg, 82%) as a white solid. MS (ESI): *m/z* $[M+H]^+$ 312/314 (Br isotope pattern).

Intermediate 51

***tert*-Butyl ((1*S*,3*S*)-3-(2-hydroxyguanidino)cyclopentyl)carbamate**

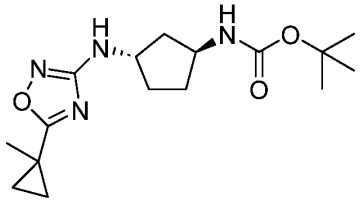


(i-51)

Cyanogen bromide (CAS Reg. No. 506-68-3) (1.98 g, 18.7 mmol) was added to *tert*-butyl ((1*S*,3*S*)-3-aminocyclopentyl)carbamate (CAS Reg. No. 645400-44-8) (2.5 g, 12.5 mmol) and sodium acetate (3.07 g, 37.4 mmol) in THF (20 mL) at 20 °C. The resulting solution was stirred at 20 °C for 15 h. The reaction mixture was filtered over Celite and the filtrate concentrated under reduced pressure. The residue was diluted with EtOH (20 mL). Hydroxylamine (50%, aq) (6.60 g, 99.9 mmol) was added slowly at 20 °C. The resulting solution was stirred at 20 °C for 2 h. The solvent was removed under reduced pressure to give crude title compound (3.2 g, 99%) as a yellow gum that was used directly without further purification. MS (ESI) m/z $[M+H]^+$ 259.0.

Intermediate 52

***tert*-Butyl ((1*S*,3*S*)-3-((5-(1-methylcyclopropyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)carbamate**

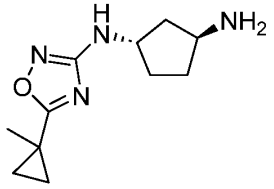


(i-52)

1-Methylcyclopropane-1-carbonyl chloride (CAS Reg. No. 16480-05-0) (441 mg, 3.72 mmol) was added to a mixture of *tert*-butyl ((1*S*,3*S*)-3-(2-hydroxyguanidino)cyclopentyl)carbamate **intermediate 51** (800 mg, 3.10 mmol) and triethylamine (1.3 mL, 9.3 mmol) in DCE (25 mL) at 20 °C and it was stirred at this temperature for 20 min. The mixture was subsequently heated to 80 °C and stirring at this temperature continued for 10 h. The reaction mixture was concentrated under reduced pressure and the obtained material purified by flash chromatography on silica (gradient: 2-25% EtOAc in PE) to give the title compound (700 mg, 70%) as a pale-yellow gum. MS (ESI): *m/z* $[M+H]^+$ 323.1.

Intermediate 53

(1*S*,3*S*)-*N*^{1}-(5-(1-Methylcyclopropyl)-1,2,4-oxadiazol-3-yl)cyclopentane-1,3-diamine

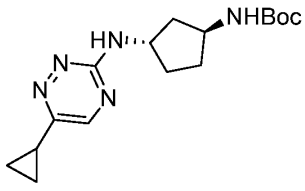


(i-53)

TsOH (748 mg, 4.34 mmol) was added to a mixture of *tert*-butyl ((1*S*,3*S*)-3-((5-(1-methylcyclopropyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)carbamate **intermediate 52** (700 mg, 2.17 mmol) in MeCN (2 mL) at 20 °C. The reaction mixture was stirred at 60 °C for 18 h and concentrated under reduced pressure to give an unspecified TsOH salt of the title compound (1.85 g) as a brown solid. MS (ESI): *m/z* $[M+H]^+$ 223.

Intermediate 54

***tert*-Butyl ((1*S*,3*S*)-3-((6-cyclopropyl-1,2,4-triazin-3-yl)amino)cyclopentyl)carbamate**

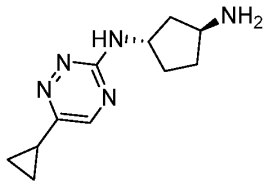


i-54

tert-Butyl ((1*S*,3*S*)-3-((6-bromo-1,2,4-triazin-3-yl)amino)cyclopentyl)carbamate **intermediate 2** (1.5 g, 4.2 mmol), potassium cyclopropyltrifluoroborate (2.48 g, 16.8 mmol), Cs_2CO_3 (5.46 g, 16.8 mmol) and CataCXium A Pd G3 (CAS Reg. No. 1651823-59-4) (0.61 g, 0.84 mmol) were reacted in dioxane (70 mL) at 100 °C for 15 h. Upon combination with a second batch (prepared in the same manner, 1.12 mmol scale) the material was purified by preparative TLC (EtOAc : PE = 1:3) to afford (1.12 g, 66%) of the title compound as a pale-yellow solid. MS (ESI): *m/z* $[M+H]^+$ 320.

Intermediate 55

(1*S*,3*S*)-*N*^{1}-(6-Cyclopropyl-1,2,4-triazin-3-yl)cyclopentane-1,3-diamine x 4 TFA

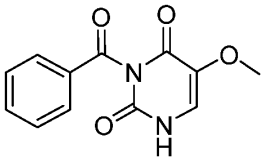


i-55

tert-Butyl ((1*S*,3*S*)-3-((6-cyclopropyl-1,2,4-triazin-3-yl)amino)cyclopentyl)carbamate **intermediate 54** (500 mg, 1.57 mmol) was reacted with TFA (5.0 mL, 65 mmol) in DCM (20 mL) at rt for 15 h to give (940 mg, 89 %) of the title compound as a yellow gum (contains 4 mol eq of residual TFA). MS (ESI): *m/z* $[M+H]^+$ 220.

Intermediate 56

3-Benzoyl-5-methoxypyrimidine-2,4(1*H*,3*H*)-dione

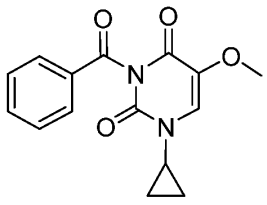


(i-56)

Benzoyl chloride (2.47 g, 17.6 mmol) was added to a mixture of 5-methoxyuracil (CAS Reg. No. 6623-81-0) (1.0 g, 7.0 mmol) in pyridine (10 mL) at 20 °C and it was stirred at 60 °C for 15 h. The reaction mixture was diluted with DCM (800 mL) and washed sequentially with 1M citric acid (3 x 200 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated. The obtained crude product was triturated with PE:EtOAc = 1:1 (10 mL) and the inorganic solid material filtered off. The filter cake was washed with DCM (3 x 10 mL) and the combined filtrates concentrated under reduced pressure to give the title compound (1.3 g, 75%) as a brown solid. MS (ESI) m/z $[M+H]^+$ 247.1.

Intermediate 57

3-Benzoyl-1-cyclopropyl-5-methoxypyrimidine-2,4(1*H*,3*H*)-dione

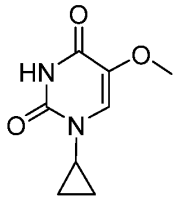


(i-57)

$Cu(OAc)_2$ (959 mg, 5.28 mmol) was added to a mixture of 3-benzoyl-5-methoxypyrimidine-2,4(1*H*,3*H*)-dione **intermediate 56** (1.3 g, 5.3 mmol), cyclopropylboronic acid (907 mg, 10.6 mmol), 2,2'-bipyridine (660 mg, 4.22 mmol) and K_2CO_3 (1.46 g, 10.6 mmol) in DCE (20 mL) at 20 °C and the resulting mixture was stirred at 70 °C for 15 h. The reaction mixture was filtered through Celite, the filtrate diluted with EtOAc (750 mL) and washed sequentially with water (3 x 150 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated. The obtained crude product was purified by preparative TLC (EtOAc) to give the title compound (651 mg, 43%) as a yellow solid. MS (ESI) m/z $[M+H]^+$ 286.9.

Intermediate 58

1-Cyclopropyl-5-methoxypyrimidine-2,4(1*H*,3*H*)-dione

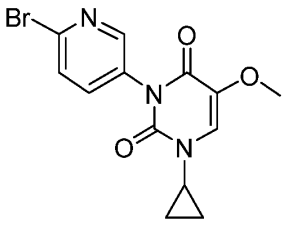


(i-58)

A solution of NH_3 in MeOH (7 M, 5.0 mL, 35 mmol) was added to a mixture of 3-benzoyl-1-cyclopropyl-5-methoxypyrimidine-2,4(1*H*,3*H*)-dione **intermediate 57** (1.3 g, 5.3 mmol) in MeOH (8 mL) at 20 °C and the resulting mixture was stirred at 60 °C for 2 h. The reaction mixture was concentrated under reduced pressure to give the title compound (410 mg) as a yellow gum which was not further purified. MS (ESI) m/z $[M+H]^+$ 182.9.

Intermediate 59

3-(6-Bromopyridin-3-yl)-1-cyclopropyl-5-methoxypyrimidine-2,4(1*H*,3*H*)-dione



(i-59)

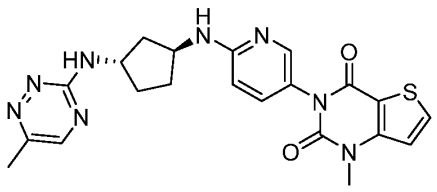
Pyridine (364 µL, 4.50 mmol) was added to a mixture of 1-cyclopropyl-5-methoxypyrimidine-2,4(1*H*,3*H*)-dione **intermediate 58** (410 mg, 2.25 mmol), (6-bromopyridin-3-yl)boronic acid

(CAS Reg. No. 223463-14-7) (908 mg, 4.50 mmol) and $Cu(OAc)_2$ (818 mg, 4.50 mmol) in DCM (10 mL) at 20 °C and the resulting mixture was stirred at this temperature for 3 days. The reaction mixture was filtered through Celite, the filtrate diluted with DCM (300 mL) and washed sequentially with 0.5M citric acid (3 x 100 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated. The obtained crude product was purified by preparative TLC (DCM: MeOH = 10:1) to give the title compound (530 mg, 70%) as a yellow solid. MS (ESI): *m/z* $[M+H]^+$ 338/340 (Br isotope pattern).

Examples

Example 1

1-Methyl-3-(6-(((1*S*,3*S*)-3-((6-methyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)thieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione – compound 1

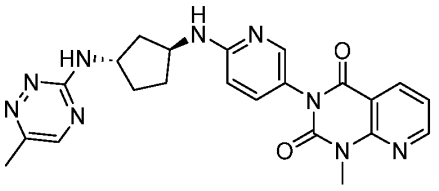


(1)

3-(6-Chloropyridin-3-yl)-1-methylthieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione **intermediate 8** (80 mg, 0.27 mmol) was added to (1*S*,3*S*)-*N*^{1}-(6-methyl-1,2,4-triazin-3-yl)cyclopentane-1,3-diamine 4.5HCl **intermediate 4** (195 mg, 0.54 mmol), Cs_2CO_3 (266 mg, 0.82 mmol) and Pd-PEPPSI-IpentCl 2-methylpyridine (22.9 mg, 0.03 mmol) in 1,4-dioxane (5 mL). The resulting mixture was stirred at 100 °C for 15 h under a nitrogen atmosphere. The reaction mixture was quenched with water (100 mL) and extracted with EtOAc (3 x 75 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated and the crude product purified by preparative HPLC (PrepMethod A, gradient: 10-25%) to give the title compound (24 mg, 19%) as a white solid. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{23}N_8O_2S$: 451.1658, found: 451.1694. ^{1}H NMR (400 MHz, MeOH-d_4) δ ppm 1.60 - 1.74 (2H, m), 2.00 - 2.14 (2H, m), 2.26 - 2.37 (2H, m), 2.47 (3H, s), 3.65 (3H, s), 4.34 - 4.41 (1H, m), 4.43 - 4.51 (1H, m), 6.65 (1H, d), 7.29 - 7.36 (2H, m), 7.86 (1H, d), 8.09 (1H, d), 8.21 (1H, s).

Example 4

1-Methyl-3-(6-(((1*S*,3*S*)-3-((6-methyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione – compound 4

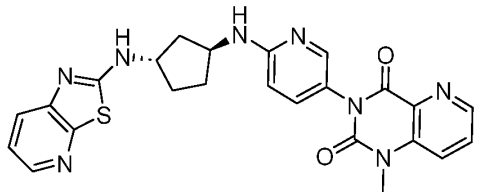


(4)

3-(6-Bromopyridin-3-yl)-1-methylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione **intermediate 11** (220 mg, 0.66 mmol) was added to (1*S*,3*S*)-*N*^{1}-(6-methyl-1,2,4-triazin-3-yl)cyclopentane-1,3-diamine **intermediate 4** (191 mg, 0.99 mmol), Pd-PEPPSI-IpentCl 2-methylpyridine (55.5 mg, 0.07 mmol) and K_2CO_3 (274 mg, 1.98 mmol) in DMF (15 mL) at 25 °C. The mixture was stirred at 100 °C for 15 h under a N_2 (g) atmosphere. The reaction mixture was quenched with brine (150 mL) and extracted with EtOAc (3 x 100 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to give crude product. The crude product was purified by preparative TLC (MeOH:DCM, 1:10) and then by preparative HPLC (PrepMethod B, gradient: 18-39%) to give the title compound (31 mg, 10%) as a white solid. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{24}N_9O_2$: 446.2048, found: 446.2022. ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.47–1.65 (2H, m), 1.85–2 (2H, m), 2.11–2.23 (2H, m), 2.39 (3H, s), 3.60 (3H, s), 4.29–4.47 (2H, m), 6.54 (1H, d), 6.87 (1H, d), 7.30 (1H, dd), 7.38 (1H, dd), 7.57 (1H, s), 7.86 (1H, d), 8.18 (1H, s), 8.40 (1H, dd), 8.78 (1H, dd).

Example 7

1-Methyl-3-(6-(((1*S*,3*S*)-3-(thiazolo[5,4-*b*]pyridin-2-ylamino)cyclopentyl)amino)pyridin-3-yl)pyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione – compound 7



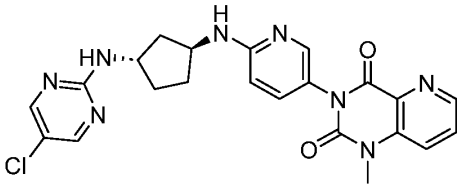
(7)

3-(6-Chloropyridin-3-yl)-1-methylpyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione **intermediate 15** (150 mg, 0.52 mmol) was added to Pd-PEPPSI-IpentCl 2-methylpyridine (44 mg, 0.05 mmol), K_2CO_3 (215 mg, 1.56 mmol) and (1*S*,3*S*)-*N*^{1}-(thiazolo[5,4-*b*]pyridin-2-yl)cyclopentane-1,3-diamine **intermediate 17** (183 mg, 0.78 mmol) in DMF (10 mL) at rt and the resulting mixture was stirred at 100 °C for 15 h under nitrogen. The reaction mixture was quenched with saturated brine (150 mL), extracted with EtOAc (3 x 100 mL), the organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude product was first purified by preparative TLC (MeOH: DCM = 1: 10) followed by preparative HPLC (PrepMethod C, gradient: 21-46%) to afford (20 mg, 8%) of the title compound as a white solid. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{23}N_8O_2S$: 487.1658, found: 487.1678. ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.69 – 1.48 (2H, m), 1.9 – 2.1 (2H, m), 2.28 – 2.13 (2H, m), 3.52 (3H, s), 4.3 – 4.5 (2H, m), 6.56

(1H, d), 6.91 (1H, d), 7.25 (1H, dd), 7.30 (1H, dd), 7.68 (1H, dd), 7.81 (1H, dd), 7.86 (d, 1H), 7.99 - 8.01 (1H, m), 8.09 (1H, dd), 8.47 (1H, d), 8.58 (1H, dd).

Example 8

3-(6-(((1*S*,3*S*)-3-((5-Chloropyrimidin-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)-1-methylpyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione – compound 8

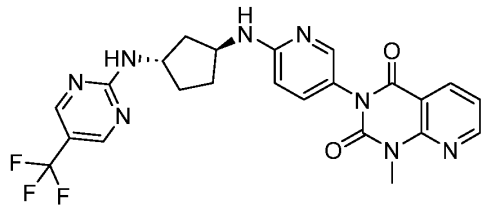


(8)

3-(6-Chloropyridin-3-yl)-1-methylpyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione **intermediate 15** (100 mg, 0.35 mmol) was added to Pd-PEPPSI-IpentCl 2-methylpyridine (29.1 mg, 0.03 mmol), K_2CO_3 (144 mg, 1.04 mmol) and (1*S*,3*S*)-*N*^{1}-(5-chloropyrimidin-2-yl)cyclopentane-1,3-diamine **intermediate 19** (111 mg, 0.52 mmol) in DMF (15 mL) at 20 °C. The resulting mixture was stirred at 100 °C for 15 h under a N_2 (g) atmosphere. The reaction mixture was quenched with brine (150 mL) and extracted with EtOAc (3 x 100 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated. The crude product was purified by preparative TLC (MeOH:DCM, 1:10) and then by preparative HPLC (PrepMethod C, gradient: 21-46%) to give the title compound (10 mg, 6 %) as a white solid. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{22}ClN_8O_2$: 465.1548, found: 465.1532. ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.46–1.62 (2H, m), 1.85–1.97 (2H, m), 2.09–2.21 (2H, m), 3.52 (3H, s), 4.24–4.4 (2H, m), 6.54 (1H, d), 6.85 (1H, d), 7.29 (1H, dd), 7.59 (1H, d), 7.81 (1H, dd), 7.84 (1H, d), 8.00 (1H, dd), 8.33 (2H, s), 8.58 (1H, dd).

Example 13

1-Methyl-3-(6-(((1*S*,3*S*)-3-((5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione – compound 13



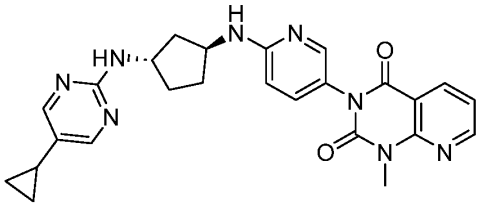
(13)

Pd-PEPPSI-IpentCl 2-methylpyridine (18.91 mg, 0.02 mmol) was added to 3-(6-bromopyridin-3-yl)-1-methylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione **intermediate 11** (150 mg, 0.45 mmol), (1*S*,3*S*)-*N*^{1}-(5-(trifluoromethyl)pyrimidin-2-yl)cyclopentane-1,3-diamine **intermediate 21** (222 mg, 0.90 mmol) and K_2CO_3 (187 mg, 1.35 mmol) in DMF (8 mL) at 20 °C under a N_2 (g)

atmosphere. The mixture was stirred at 100 °C for 15 h. The reaction mixture was filtered through Celite. The filtrate was diluted with EtOAc (200 mL) and washed sequentially with sat. brine (3 x 75 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated. The crude was purified by preparative TLC (DCM:MeOH, 10:1) and then by preparative HPLC (PrepMethod A, gradient: 40-65%) to give the title compound (82 mg, 36.4%) as a white solid; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{22}F_3N_8O_2$: 499.1812, found: 499.1812; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.41–1.71 (2H, m), 1.86–2.03 (2H, m), 2.1–2.28 (2H, m), 3.59 (3H, s), 4.18–4.56 (2H, m), 6.55 (1H, d), 6.88 (1H, d), 7.22–7.5 (2H, m), 7.86 (1H, d), 8.21 (1H, d), 8.40 (1H, dd), 8.62 (2H, d), 8.78 (1H, dd).

Example 15

3-(6-(((1*S*,3*S*)-3-((5-Cyclopropylpyrimidin-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)-1-methylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione – compound 15

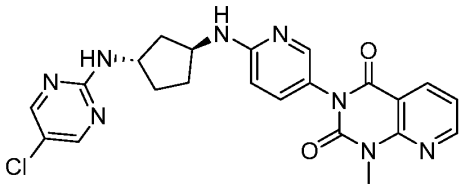


(15)

Pd-PEPPSI-IpentCl 2-methylpyridine (27.2 mg, 0.03 mmol) was added to 2-chloro-5-cyclopropylpyrimidine (CAS Reg. No. 166740-44-9) (100 mg, 0.65 mmol), 3-(6-(((1*S*,3*S*)-3-aminocyclopentyl)amino)pyridin-3-yl)-1-methylpyrido[2,3-d]pyrimidine-2,4(1*H*,3*H*)-dione **intermediate 23** (274 mg, 0.78 mmol) and K_2CO_3 (268 mg, 1.94 mmol) in DMF (8 mL) at 20 °C under a N_2 (g) atmosphere. The mixture was stirred at 100 °C for 15 h. The reaction mixture was filtered through Celite, the filtrate was diluted with EtOAc (200 mL) and washed sequentially withbrine (3 x 75 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated. The residue was purified by preparative TLC (DCM:MeOH, 10:1) followed by preparative HPLC (PrepMethod A, gradient: 24-43%) to give the title compound (84 mg, 27%) as a yellow solid. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{27}N_8O_2$: 471.2252, found: 471.2268. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.52–0.69 (2H, m), 0.76–0.91 (2H, m), 1.43–1.6 (2H, m), 1.64–1.79 (1H, m), 1.83–1.96 (2H, m), 2.08–2.25 (2H, m), 3.59 (3H, s), 4.22–4.43 (2H, m), 6.54 (1H, d), 6.84 (1H, d), 7.02 (1H, d), 7.29 (1H, dd), 7.37 (1H, dd), 7.85 (1H, d), 8.08 (2H, s), 8.40 (1H, dd), 8.78 (1H, dd).

Example 12

3-(6-(((1*S*,3*S*)-3-((5-Chloropyrimidin-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)-1-methylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione – compound 12

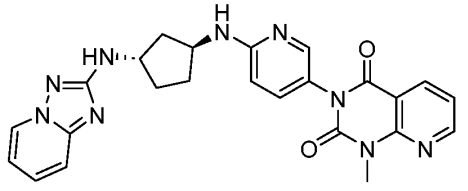


(12)

Pd-PEPPSI-IpentCl 2-methylpyridine (19 mg, 0.02 mmol) was added to a mixture of 3-(6-bromopyridin-3-yl)-1-methylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione **intermediate 11** (150 mg, 0.45 mmol), (1*S*,3*S*)-*N*^{1}-(5-chloropyrimidin-2-yl)cyclopentane-1,3-diamine **intermediate 19** (192 mg, 0.90 mmol) and Cs_2CO_3 (440 mg, 1.35 mmol) in 1,4-dioxane (10 mL) at 20 °C under a nitrogen atmosphere. The mixture was stirred at 100 °C for 15 h. The reaction mixture was filtered through Celite and the filtrate concentrated under reduced pressure. The obtained residue was purified by preparative TLC (DCM:MeOH, 10:1) followed by preparative HPLC (PrepMethod D, gradient: 25-45%) to give the title compound (65 mg, 31%) as a white solid. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{22}ClN_8O_2$: 465.1548, found: 465.1512. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.43–1.61 (2H, m), 1.82–1.96 (2H, m), 2.04–2.22 (2H, m), 3.59 (3H, s), 4.25–4.37 (2H, m), 6.53 (1H, d), 6.85 (1H, d), 7.29 (1H, dd), 7.37 (1H, dd), 7.58 (1H, d), 7.85 (1H, d), 8.32 (2H, s), 8.39 (1H, dd), 8.78 (1H, dd).

Example 14

3-(6-(((1*S*,3*S*)-3-([1,2,4]Triazolo[1,5-*a*]pyridin-2-ylamino)cyclopentyl)amino)pyridin-3-yl)-1-methylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione – compound 14



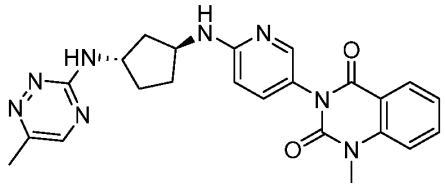
(14)

Pd-PEPPSI-IpentCl 2-methylpyridine (21 mg, 0.03 mmol) was added to a mixture of 2-bromo-[1,2,4]triazolo[1,5-*a*]pyridine (CAS Reg. No. 1021019-03-3) (100 mg, 0.50 mmol), 3-(6-(((1*S*,3*S*)-3-aminocyclopentyl)amino)pyridin-3-yl)-1-methylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione x 4HCl **intermediate 23** (302 mg, 0.61 mmol) and K_2CO_3 (209 mg, 1.51 mmol) in DMF (8 mL) at 20 °C under a N_2 atmosphere. The mixture was stirred at 100 °C for 15 h. The reaction mixture was filtered through Celite, the filtrate was diluted with EtOAc (200 mL) and washed sequentially with sat. brine (3 x 75 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated. The residue was purified by preparative TLC (DCM:MeOH, 10:1) followed by preparative HPLC (PrepMethod E, gradient: 25-33%) to give the title compound (39 mg, 16%) as a white solid. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{24}N_9O_2$: 470.2048, found: 470.2034. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.47–1.61 (2H, m), 1.85–2.03 (2H, m), 2.11–2.21

(2H, m), 3.58 (3H, s), 4.19 (1H, q), 4.32 (1H, q), 6.54 (1H, d), 6.64 (1H, d), 6.84–6.86 (2H, m), 7.29 (1H, dd), 7.34-7.44 (3H, m), 7.85 (1H, d), 8.39 (1H, dd), 8.59 (1H, d), 8.78 (1H, dd).

Example 19

1-Methyl-3-(6-(((1*S*,3*S*)-3-((6-methyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)quinazoline-2,4(1*H*,3*H*)-dione – compound 19

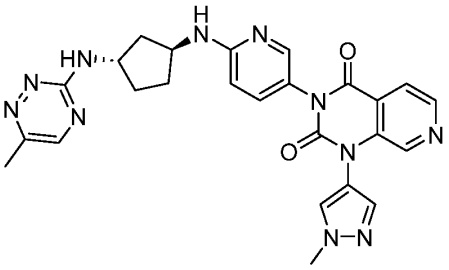


(19)

Pd-PEPPSI-IpentCl 2-methylpyridine (64 mg, 0.08 mmol) was added to a mixture of (1*S*,3*S*)-*N*^{1}-(6-methyl-1,2,4-triazin-3-yl)cyclopentane-1,3-diamine **intermediate 4** (443 mg, 2.29 mmol), 3-(6-chloropyridin-3-yl)-1-methylquinazoline-2,4(1*H*,3*H*)-dione **intermediate 27** (440 mg, 1.53 mmol) and Cs_2CO_3 (1.50 g, 4.59 mmol) in 1,4-dioxane (20 mL) at 20 °C under a N_2 atmosphere. The mixture was stirred at 100 °C for 3 h. The reaction mixture was concentrated under reduced pressure and the residue taken up with EtOAc (250 mL). The organic layer was washed sequentially with sat. brine (3 x 75 mL), dried over Na_2SO_4, filtered and evaporated. The crude material was purified by preparative TLC (DCM:MeOH, 20:1) followed by preparative HPLC (PrepMethod F, gradient: 18-45%) to give the title compound (117 mg, 17%) as a white solid. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{25}N_8O_2$: 445.2094, found: 445.2136. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.48–1.61 (2H, m), 1.85–2.01 (2H, m), 2.12–2.20 (2H, m), 2.38 (3H, s), 3.53 (3H, s), 4.29–4.41 (2H, m), 6.53 (1H, d), 6.85 (1H, d), 7.26–7.35 (2H, m), 7.50 (1H, d), 7.58 (1H, brs), 7.79–7.84 (2H, m), 8.05 (1H, dd), 8.17 (1H, s).

Example 23

3-(6-(((1*S*,3*S*)-3-((6-Methyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)-1-(1-methyl-1*H*-pyrazol-4-yl)pyrido[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione – compound 23



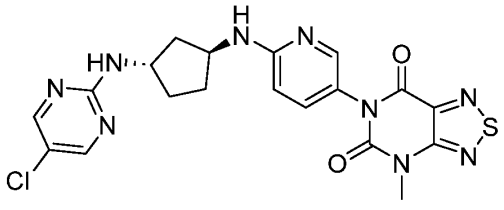
(23)

Pd-PEPPSI-IpentCl 2-methylpyridine (27 mg, 0.03 mmol) was added to a mixture of (1*S*,3*S*)-*N*^{1}-(6-methyl-1,2,4-triazin-3-yl)cyclopentane-1,3-diamine **intermediate 4** as 2TsOH salt (175 mg, 0.33 mmol), 3-(6-bromopyridin-3-yl)-1-(1-methyl-1*H*-pyrazol-4-yl)pyrido[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione **intermediate 30** (130 mg, 0.33 mmol) and K_2CO_3 (135 mg, 0.98 mmol) in

DMF (15 mL) at 20 °C under a N_2 atmosphere. The mixture was stirred at 100 °C for 15 h. The reaction mixture was diluted with sat. brine (150 mL) and the aqueous layer extracted with EtOAc (3 x 125 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated. The crude material was purified by preparative TLC (DCM:MeOH, 10:1) followed by preparative HPLC (PrepMethod A, gradient: 15-35%) to give the title compound (28 mg, 17%) as a white solid. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{26}N_{11}O_2$: 512.2266, found: 512.2266. ^1H NMR (500 MHz, DMSO-d_6) δ 1.49–1.61 (2H, m), 1.87–1.98 (2H, m), 2.12–2.19 (2H, m), 2.38 (3H, s), 3.95 (3H, s), 4.29–4.41 (2H, m), 6.54 (1H, d), 6.89 (1H, d), 7.31 (1H, dd), 7.56 (1H, brs), 7.61 (1H, s), 7.88 (1H, d), 7.93 (1H, d), 8.03 (1H, s), 8.17 (1H, s), 8.26 (1H, s), 8.53 (1H, d).

Example 26

6-(6-(((1*S*,3*S*)-3-((5-Chloropyrimidin-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)-4-methyl-[1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione – compound 26

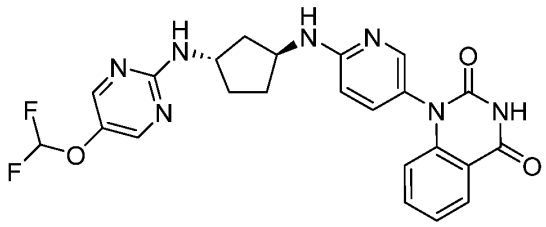


(26)

Pd-PEPPSI-IpentCl 2-methylpyridine (36 mg, 0.04 mmol) was added to a mixture of 6-(6-(((1*S*,3*S*)-3-aminocyclopentyl)amino)pyridin-3-yl)-4-methyl-[1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione **intermediate 43** as unspecified TFA salt (200 mg, 0.42 mmol), 2-bromo-5-chloropyrimidine (CAS Reg. No. 124405-67-0) (123 mg, 0.63 mmol) and CsF (193 mg, 1.27 mmol) in 1,4-dioxane (10 mL) at 15 °C under a nitrogen atmosphere. The mixture was stirred at 100 °C for 15 h. The reaction mixture was diluted with water (150 mL) and the aqueous layer extracted with EtOAc (3 x 125 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated. The crude material was purified by preparative TLC (DCM:MeOH, 10:1) followed by preparative HPLC (PrepMethod H, gradient: 16-36%) to give the title compound (28 mg, 14%) as a white solid. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{19}ClN_9O_2S$: 472.1066, found: 472.1066. ^1H NMR (300 MHz, DMSO-d_6) δ 1.43–1.61 (2H, m), 1.83–1.97 (2H, m), 2.04–2.21 (2H, m), 3.54 (3H, s), 4.24–4.37 (2H, m), 6.55 (1H, d), 6.90 (1H, d), 7.25 (1H, dd), 7.58 (1H, d), 7.82 (1H, dd), 8.32 (2H, s).

Example 27

1-(6-(((1*S*,3*S*)-3-((5-(Difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)quinazoline-2,4(1*H*,3*H*)-dione – compound 27

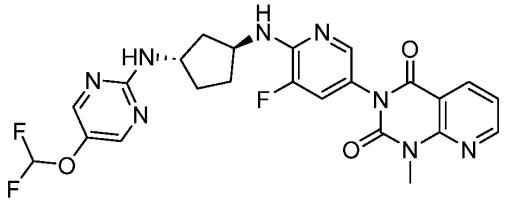


(27)

Pd-PEPPSI-IpentCl 2-methylpyridine (28 mg, 0.03 mmol) was added to a mixture of 1-(6-chloropyridin-3-yl)quinazoline-2,4(1*H*,3*H*)-dione **intermediate 45** (90 mg, 0.33 mmol), (1*S*,3*S*)-*N*^{1}-(5-(difluoromethoxy)pyrimidin-2-yl)cyclopentane-1,3-diamine **intermediate 32** (96 mg, 0.39 mmol) and Cs_2CO_3 (321 mg, 0.99 mmol) in 1,4-dioxane (30 mL) at 25 °C under a N_2 atmosphere. The mixture was stirred at 100 °C for 15 h. The reaction mixture was diluted with sat. brine (100 mL) and the aqueous layer extracted with EtOAc (3 x 75 mL). The combined organic layers were washed with brine (3 x 50 mL), dried over Na_2SO_4, filtered and evaporated. The crude material was purified by preparative HPLC (PrepMethod I, gradient: 41-61%) to give the title compound (14 mg, 9%) as a white solid. (ESI): *m/z* $[M-NCO]^+$ 438.1.^{1}H NMR (300 MHz, DMSO-d_6) δ 1.40–1.59 (2H, m), 1.79–1.95 (2H, m), 2.06–2.16 (2H, m), 4.23–4.33 (2H, m), 6.49 (1H, d), 6.56 (1H, d), 6.68 (1H, d), 6.74 (1H, dt), 7.03 (1H, t), 7.25 (1H, dd), 7.34 (1H, ddd), 7.47 (1H, d), 7.52 (1H, dd), 7.85 (1H, d), 7.89 (1H, s), 8.23 (2H, s). ^{19}F NMR (282 MHz, DMSO-d_6) δ ppm -81.79 (2F, s).

Example 29

3-(6-(((1*S*,3*S*)-3-((5-(Difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-5-fluoropyridin-3-yl)-1-methylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione – compound 29



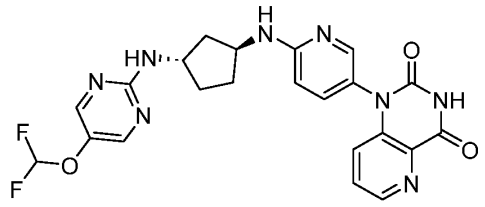
(29)

Pd-PEPPSI-IpentCl 2-methylpyridine (16 mg, 0.02 mmol) was added to a mixture (1*S*,3*S*)-*N*^{1}-(5-(difluoromethoxy)pyrimidin-2-yl)cyclopentane-1,3-diamine **intermediate 32** as 3HCl salt (166 mg, 0.47 mmol), 3-(6-chloro-5-fluoropyridin-3-yl)-1-methylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione **intermediate 35** (120 mg, 0.39 mmol) and Cs_2CO_3 (637 mg, 1.96 mmol) in 1,4-dioxane (15 mL) at 20 °C under a N_2 atmosphere. The mixture was stirred at 100 °C for 15 h. The reaction mixture was cooled to rt and filtered through a pad of Celite. The filter cake was washed with DCM (2 x 15 mL) and the combined filtrates concentrated under reduced pressure. The obtained crude material was purified by preparative TLC (7 M NH_3 in MeOH : DCM = 1:15) followed by preparative HPLC (PrepMethod G, gradient: 37-57%) to give the title compound (38 mg, 19%) as a white solid. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{22}F_3N_8O_3$:

515.1756, found: 515.1780. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.48–1.67 (2H, m), 1.88–2.02 (2H, m), 2.07–2.22 (2H, m), 3.59 (3H, s), 4.33 (1H, quint), 4.51 (1H, quint), 6.87 (1H, dd), 7.03 (1H, t), 7.36–7.42 (2H, m), 7.48 (1H, d), 7.79 (1H, d), 8.24 (2H, s), 8.41 (1H, dd), 8.79 (1H, dd). ^{19}F NMR (282 MHz, DMSO-d_6) δ ppm -81.74 (2F, s), -138.73 (1F, s).

Example 30

1-(6-(((1*S*,3*S*)-3-((5-(Difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione – compound 30

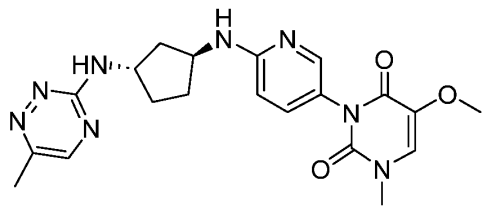


(30)

Pd-PEPPSI-IpentCl 2-methylpyridine (43 mg, 0.05 mmol) was added to a mixture (1*S*,3*S*)-*N*^{1}-(5-(difluoromethoxy)pyrimidin-2-yl)cyclopentane-1,3-diamine **intermediate 32** as 3HCl salt (360 mg, 1.02 mmol), 1-(6-chloropyridin-3-yl)pyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione **intermediate 38** (140 mg, 0.51 mmol) and Cs_2CO_3 (498 mg, 1.53 mmol) in DMF (8 mL) at 20 °C under a N_2 atmosphere. The mixture was stirred at 100 °C for 15 h, diluted with EtOAc (200 mL) and washed sequentially with sat. brine (3 x 100 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated. The residue was purified by preparative TLC (DCM : MeOH = 10:1) followed by preparative HPLC (PrepMethod G, gradient: 21-41%) to give the title compound (16 mg, 7%) as a white solid. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{21}F_2N_8O_3$: 505.1514, found: 505.1544. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.45–1.61 (2H, m), 1.88–1.94 (2H, m), 2.09–2.20 (2H, m), 4.30–4.37 (2H, m), 6.62 (1H, d), 7.03 (1H, t), 7.03–7.11 (2H, m), 7.39 (1H, dd), 7.50 (1H, dd), 7.57 (1H, ddd), 7.96 (1H, d), 8.24 (2H, s), 8.50 (1H, dd), 11.84 (1H, s). ^{19}F NMR (282 MHz, DMSO-d_6) δ ppm -81.79 (2F, s).

Example 31

5-Methoxy-1-methyl-3-(6-(((1*S*,3*S*)-3-((6-methyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyrimidine-2,4(1*H*,3*H*)-dione – compound 31



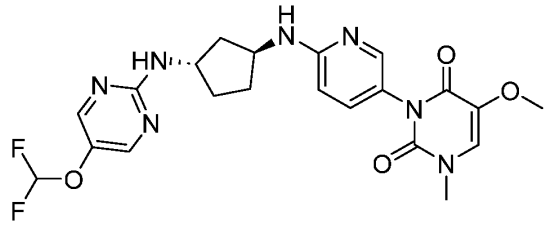
(31)

Pd-PEPPSI-IpentCl 2-methylpyridine (44 mg, 0.05 mmol) was added to a mixture of 3-(6-chloropyridin-3-yl)-5-methoxy-1-methylpyrimidine-2,4(1*H*,3*H*)-dione **intermediate 47** (140 mg,

0.52 mmol), (1*S*,3*S*)-*N*^{1}-(6-methyl-1,2,4-triazin-3-yl)cyclopentane-1,3-diamine **intermediate 4** as undefined HCl salt (202 mg, 1.05 mmol) and Cs_2CO_3 (511 mg, 1.57 mmol) in DMF (6 mL) at 20 °C under a N_2 atmosphere. The mixture was stirred at 100 °C for 15 h. The reaction mixture was cooled to rt and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and the obtained residue taken up with DCM (300 mL). The organic phase was washed sequentially with water (3 x 100 mL), dried over Na_2SO_4, filtered and evaporated. The obtained crude material was purified by preparative TLC (7 M NH_3 in MeOH : DCM = 1:10) followed by preparative HPLC (PrepMethod J, gradient: 5-30%) to give the title compound (91 mg, 41%) as a white solid. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{25}N_8O_3$: 425.2044, found: 425.2076. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.44–1.62 (2H, m), 1.84–1.99 (2H, m), 2.07–2.22 (2H, m), 2.38 (3H, s), 3.29 (3H, s), 3.65 (3H, s), 4.27–4.42 (2H, m), 6.50 (1H, d), 6.83 (1H, d), 7.18 (1H, dd), 7.48 (1H, s), 7.55 (1H, brs), 7.73 (1H, d), 8.16 (1H, s).

Example 32

3-(6-(((1S,3S)-3-((5-(Difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)-5-methoxy-1-methylpyrimidine-2,4(1*H*,3*H*)-dione – compound 32

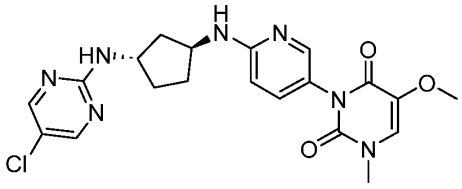


(32)

Pd-PEPPSI-IpentCl 2-methylpyridine (26 mg, 0.03 mmol) was added to a mixture of 2-chloro-5-(difluoromethoxy)pyrimidine (CAS Reg. No. 1192813-64-1) (55 mg, 0.30 mmol), 3-(6-(((1*S*,3*S*)-3-aminocyclopentyl)amino)pyridin-3-yl)-5-methoxy-1-methylpyrimidine-2,4(1*H*,3*H*)-dione **intermediate 49** as unspecified HCl salt (121 mg, 0.37 mmol), and K_2CO_3 (126 mg, 0.91 mmol) in DMF (6 mL) at 20 °C under a N_2 atmosphere. The mixture was stirred at 100 °C for 15 h. The reaction mixture was diluted with DCM (200 mL) and washed sequentially with water (3 x 75 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated. The obtained crude material was purified by preparative TLC (MeOH : DCM = 1:10) followed by preparative HPLC (PrepMethod C, gradient: 19-34%) to give the title compound (48 mg, 33%) as a white solid. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{24}F_2N_7O_4$: 476.1852, found: 476.1886. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.42–1.60 (2H, m), 1.81–1.96 (2H, m), 2.07–2.17 (2H, m), 3.29 (3H, s), 3.65 (3H, s), 4.23–4.37 (2H, m), 6.50 (1H, d), 6.81 (1H, d), 7.03 (1H, t), 7.17 (1H, dd), 7.47 (1H, d), 7.49 (1H, s), 7.73 (1H, d), 8.23 (2H, s). ^{19}F NMR (282 MHz, DMSO-d_6) δ ppm -81.74 (2F, s).

Example 33

3-(6-(((1*S*,3*S*)-3-((5-Chloropyrimidin-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)-5-methoxy-1-methylpyrimidine-2,4(1*H*,3*H*)-dione – compound 33

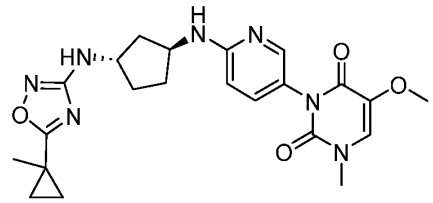


(33)

Pd-PEPPSI-IpentCl 2-methylpyridine (26 mg, 0.03 mmol) was added to a mixture of 2-bromo-5-chloropyrimidine (CAS Reg. No. 124405-67-0) (60 mg, 0.31 mmol), 3-(6-(((1*S*,3*S*)-3-aminocyclopentyl)amino)pyridin-3-yl)-5-methoxy-1-methylpyrimidine-2,4(1*H*,3*H*)-dione **intermediate 49** as unspecified HCl salt (123 mg, 0.37 mmol), and K_2CO_3 (129 mg, 0.93 mmol) in DMF (6 mL) at 20 °C under a N_2 atmosphere. The mixture was stirred at 100 °C for 15 h. The reaction mixture was diluted with DCM (200 mL) and washed sequentially with water (3 x 75 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated. The obtained crude material was purified by preparative TLC (MeOH : DCM = 1:10) followed by preparative HPLC (PrepMethod C, gradient: 19-34%) to give the title compound (50 mg, 36%) as a white solid. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{23}ClN_7O_3$: 444.1546, found: 444.1560. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.41–1.60 (2H, m), 1.80–1.95 (2H, m), 2.07–2.17 (2H, m), 3.29 (3H, s), 3.65 (3H, s), 4.23–4.36 (2H, m), 6.50 (1H, d), 6.81 (1H, d), 7.17 (1H, dd), 7.49 (1H, s), 7.57 (1H, d), 7.73 (1H, d), 8.31 (2H, s).

Example 34

5-Methoxy-1-methyl-3-(6-(((1*S*,3*S*)-3-((5-(1-methylcyclopropyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyrimidine-2,4(1*H*,3*H*)-dione – compound 34



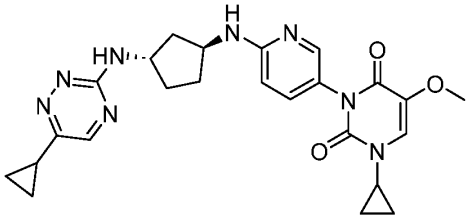
(34)

Pd-PEPPSI-IpentCl 2-methylpyridine (243 mg, 0.29 mmol) was added to a mixture of 3-(6-bromopyridin-3-yl)-5-methoxy-1-methylpyrimidine-2,4(1*H*,3*H*)-dione **intermediate 50** (90 mg, 0.29 mmol), (1*S*,3*S*)-*N*^{1}-(5-(1-methylcyclopropyl)-1,2,4-oxadiazol-3-yl)cyclopentane-1,3-diamine **intermediate 53** as 4TsOH salt (394 mg, 0.43 mmol) and K_2CO_3 (40 mg, 0.29 mmol) in DMF (15 mL) at 20 °C under a N_2 atmosphere. The mixture was stirred at 100 °C for 15 h. The reaction mixture was quenched with sat. brine (150 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated. The crude product was purified by preparative TLC (MeOH : DCM = 1:10) followed by preparative HPLC (PrepMethod A, gradient: 18-39%) to give the title compound (32 mg, 25%) as a white solid.

HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{28}N_7O_4$: 454.2198, found: 454.2230. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.97–1.00 (2H, m), 1.18–1.21 (2H, m), 1.41–1.57 (5H, m), 1.75–1.82 (1H, m), 1.89–1.95 (1H, m), 2.01–2.15 (2H, m), 3.29 (3H, s), 3.65 (3H, s), 3.80–3.88 (1H, m), 4.21–4.29 (1H, m), 6.48 (1H, d), 6.80 (1H, d), 6.85 (1H, dd), 7.17 (1H, dd), 7.49 (1H, s), 7.72 (1H, d).

Example 37

1-Cyclopropyl-3-(6-(((1*S*,3*S*)-3-((6-cyclopropyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)-5-methoxypyrimidine-2,4(1H,3H)-dione – compound 37



(37)

Pd-PEPPSI-IpentCl 2-methylpyridine (6.7 mg, 8.0 µmol) was added to a mixture of (1*S*,3*S*)-*N*^{1}-(6-cyclopropyl-1,2,4-triazin-3-yl)cyclopentane-1,3-diamine **intermediate 55** as 3TFA salt (90 mg, 0.16 mmol), 3-(6-bromopyridin-3-yl)-1-cyclopropyl-5-methoxypyrimidine-2,4(1*H*,3*H*)-dione **intermediate 59** (65 mg, 0.19 mmol) and Cs_2CO_3 (157 mg, 0.48 mmol) in 1,4-dioxane (5 mL) at 20 °C under a N_2 atmosphere. The mixture was stirred at 100 °C for 15 h. The reaction mixture was quenched with water (25 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated. The crude product was purified by preparative TLC (MeOH : DCM : PE = 2:50:1) followed by preparative HPLC (PrepMethod C, gradient: 19-34%) to give the title compound (20 mg, 26%) as a white solid. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{29}N_8O_3$: 477.2356, found: 477.2330. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.87–0.99 (8H, m), 1.44–1.63 (2H, m), 1.83–2.21 (5H, m), 3.09 (1H, quint), 3.67 (3H, s), 4.24–4.40 (2H, m), 6.50 (1H, d), 6.82 (1H, d), 7.18 (1H, dd), 7.24 (1H, s), 7.54 (1H, brd), 7.73 (1H, d), 8.18 (1H, s).

Assays and methods used

Assay 1 - Biochemical human PCSK9 assay

This assay measures binding of compounds to PCSK9 by homogenous time-resolved fluorescence resonance energy transfer (TR-FRET).

To determine the IC_{50} of inhibitors of the interaction between the human PCSK9 and Alexa647 labelled small molecule, fluorescent probe displacement was monitored by homogenous TR-FRET technology. Upon binding of a terbium (Tb) cryptate conjugated anti-His mouse antibody (mAb Anti-6His Tb cryptate Gold, Cisbio) to PCSK9-TEV-His6, the displacement of the probe

from PCSK9 was assessed by reduction of the proximity and FRET signal between the Tb cryptate that serves as a FRET-donor and the Alexa647 probe that serves as acceptor.

Recombinantly expressed and purified PCSK9-TEV-His6 (1 nM) was mixed with a fluorescent probe (5 nM) and anti His-Tb-cryptate antibody (0.2 nM) in assay buffer (10 mM HEPES/NaOH, pH 7.4, 150 mM NaCl, 0.005 (v/v) % Tween 20). 6 µL were subsequently added to an assay-ready plate containing 0.06 µL of controls and test compound 10 dose-response serial dilutions starting at a concentration of 10 mM (with 100 µM top and 3.2 nM lowest final concentration) by using Certus flex dispenser. The plate was sealed, and the reaction was incubated overnight (18-24h) at RT in the dark.

FRET signal quantification was achieved by PHERAstar FSX (BMG) plate reader. The created data file contained the emission of FRET acceptor channel (665 nm, probe), FRET donor channel (620 nm, Tb-cryptate, excitation at 337 nm) and the FRET ratio (665 nm/620 nm signal x 10.000) which was used for calculation of a test compound´s IC_{50}. N≥3 for all examples unless indicated otherwise.

Assays 2 and 2a - Biophysical human PCSK9 assays

These assays measure binding of compounds to PCSK9 by SPR (“surface plasmon resonance”, a biophysical method) at plasma and a representative endosomal pH (7.4 and 5.6 respectively).

The pH 7.4 (Assay 2) SPR binding experiments were performed on a Biacore S200 optical biosensor unit at 30 °C. A Series S Sensor Chip SA that is designed to bind biotinylated molecules for interaction analysis in Biacore systems was equilibrated at room temperature prior to use. The running buffer for protein tethering and subsequent ligand binding experiments was 10mM HEPES pH 7.4, 150mM NaCl, 0.05% (v/v) Tween 20 pH 7.4.

For the surface tethering of PCSK9, biotinylated human PCSK9 (31-692)-Avi-His6 (Charles River Laboratories) at a concentration of 0.5mg/mL was used. Prior to the surface tethering, the surface was exposed to a solution of 50mM NaOH, 500mM NaCl via 3 consecutive injections of this solution with a contact time of 60 s and a flowrate of 10 µL min^{-1} to remove non-conjugated streptavidin. The PCSK9 protein was diluted to a concentration of 20 µg/mL using running buffer and injected with a contact time of 180-300 s and a flowrate of 10 µL min^{-1} over a single flow channel (typically flow channel 2 or flow channel 4) with the aim to achieve protein capture levels of > 5000 response units (RU). Remaining biotin binding sites were blocked via 2 consecutive injections of a 10 µM D-biotin solution in running buffer with a contact time of 60 s

and a flowrate of 10 µL min^{-1} over all flow-channels. Flow-channels 1 and 3 typically served as a reference surface throughout the subsequent binding experiments.

The binding experiments were all performed at a flow rate of 30 µL min^{-1} and by employing the method of single-cycle kinetics. This approach involves the sequential injection of a compound concentration series without regeneration steps. A contact time between 90-150 s was selected, which was followed by a 40 min dissociation phase to allow for a proper estimation of the dissociation rate constant. Test compounds were delivered in DMSO at a concentration of 10 mM and a digital dispenser HP D300 was used to set up the compound concentration series using 6 concentrations. The tested concentrations have been 30, 100, 300, 1000, 3000 and 10000 nM. Prior to injecting any compound, the surfaces were equilibrated by injecting running buffer over them in three separate pulses. The data collection rate was set to 10 Hz.

The raw sensorgrams of the compound injections were first subjected to reference subtraction (subtracting the signal from flow channel 1 and/or 3 from the signal from channels 2 and/or 4 respectively) and then blank subtraction (subtracting the signal from injecting DMSO controls from the reference subtracted data). The resulting double-referenced sensorgrams were then fitted using a 1:1 binding interaction model using the manufactures software package to extract kinetic- and affinity data. Active compounds have been defined by creating a detectable binding signal at the highest compound concentration (10mM) of ≥ 3 RUs. Kinetic- and affinity data on active compounds are only provided for those compounds where the binding signal at the highest compound concentration (10mM) is ≥ 50% of the theoretical maximum binding signal for a 1:1 binding interaction (R_{max}, typically between 15-20 RUs) in order to enable a proper fitting of the data.

The pH 5.6 (Assay 2a) SPR experiments were performed on a Biacore 8K optical biosensor unit (Cytiva) at 37 °C. A Series S Sensor Chip SA (Cytiva – Lot#10315802) that is designed to bind biotinylated molecules for interaction analysis in Biacore systems was equilibrated at room temperature prior to use. Buffer A for protein tethering was 10 mM Hepes, 150 mM NaCl, 0.05% (v/v) Tween 20 pH 7.4. (Cytiva, Product#BR100671). Buffer B used for the subsequent ligand binding experiments was 20 mM Cacodylate, 150 mM NaCl, 0.05% (v/v) Tween 20, pH 5.60.

Prior to the surface tethering of biotinylated PCSK9, the surface was exposed to a solution of 50 mM NaOH (Merck, Product#1.06469.1000), 500 mM NaCl (Sigma-Aldrich, 71380-M) via 3 consecutive injections of this solution with a contact time of 60 s and a flowrate of 10 µL.min^{-1} to remove non-conjugated streptavidin. The biotinylated human PCSK9 (31-692)-Avi-His6 (Charles River Laboratories) at a concentration of 0.5 mg/mL was diluted to a concentration of 20 µg/mL using Buffer A and injected over flow cell 2 with a contact time of 600 s and a flowrate of 5 µL.min^{-1} with the aim to achieve protein capture levels of 6000-7000 RU. Remaining biotin binding sites

were blocked with a single injections of a 10 µM D-biotin solution (Avidity, Product#BIO200) in running buffer with a contact time of 60 s and a flowrate of 10 µL.min^{-1} over all flow cells. Flow cells 1 served as a reference surface during the subsequent ligand binding experiments. The protein surface was stabilised over night using standby flow, and Buffer A was exchanged with Buffer B by priming the system the next day prior to the ligand binding experiments

The binding experiments were all performed at a flow rate of 30 µL.min^{-1} and by employing the method of single-cycle kinetics. This approach involves the sequential injection of a compound concentration series without regeneration steps. A contact time of 120 s was used, which was followed by a 40 min dissociation phase to allow for a proper estimation of the dissociation rate constant. Compounds have been tested in a concentration series using 6 concentrations. The tested concentrations have been 30, 100, 300, 1000, 3000 and 10000 nM.

The raw sensorgrams of the compound injections were first subjected to reference subtraction (subtracting the signal from flow-channel 1 from signal from channel 2) and then blank subtraction (subtracting the signal from injecting 2 DMSO controls from the reference subtracted data). The resulting double-referenced sensorgrams were then fitted using a 1:1 binding interaction model using the manufactures software package (BIAcore Insight Evaluation software V 5.0.18.22102) to extract kinetic- and affinity data.

The comparator compound used in Assays 2 and 2a is example 493 in WO 2020/150473 A2.

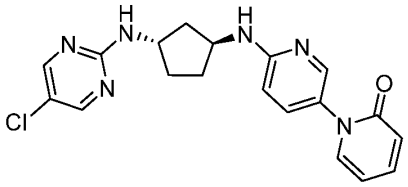


Table 3: SPR Data

Example No.	Assay 2 (PCSK9 BIAcore DBA CR) Mean k_a ($M^{-1}.s^{-1}$)	Assay 2 (PCSK9 BIAcore DBA CR) Mean k_d (1/s)	Assay 2 (PCSK9 BIAcore DBA CR) GMean K_D (M)	Assay 2a pH 5.6 SPR K_D mean (M)	Assay 2a pH 5.6 SPR k_a mean ($M^{-1}.s^{-1}$)	Assay 2a pH 5.6 SPR k_d mean (1/s)
Comparative 493	47868	1.74E-4	3.87E-9	2.86E-07	2.63E5	7.56E-02
4	20658	1.70E-5	8.21E-10	4.00E-08	1.20E5	4.81E-03
14	48517	1.46E-5	3.00E-10	1.04E-08	1.49E5	1.54E-03
19	48900	1.12E-5	2.29E-10	3.08E-08	1.19E5	3.67E-03
31	8690	1.76E-5	2.02E-9	9.49E-08	7.42E4	7.02E-03
32	22700	8.18E-6	3.61E-10	2.78E-08	9.11E4	2.53E-03
34				5.26E-08	9.88E4	5.20E-03

Assays 3 and 3a - PCSK9 LDL-C uptake assays

Profiling compounds for PCSK9 antagonist activity is based on their capacity to restore LDL-uptake in HepG2 cells. The assay is based on exogenous PCSK9 protein (WT, assay 3 or D374Y mutant, assay 3a) and LDL complexed with a pH-sensitive dye (pHrodo™ Red-LDL). Outside the cells, at neutral pH, the pHrodo™ Red-LDL is dimly fluorescent but upon LDLR mediated endocytosis it fluoresces brightly. PCSK9 trafficks the LDL receptor (LDLR) to intrecellular degradation and reduces uptake of LDL. Inhibition of PCSK9 reduces LDLR degradation and the increased LDL uptake is quantified by fluorescence microscopy.

Preparation of assay reagents

Assay medium: OptiMem (Gibco #51985) + Penicilin/Streptomycin (Gibco #15140122, 1:100 dilution)

Labelled LDL: Low Density Lipoprotein From Human Plasma, pHrodo™ Red (pHrodo™ Red-LDL) (Invitrogen #L34356)

Cells: HepG2 (ATCC #HB-8065)

WT PCSK9 protein: In-house. Sequence: MGTVSSRRSW WPLPLLLLLL LLLGPAGARA QEDEDGDYEE LVLALRSEED GLAEAPEHGT TATFHRCAKD PWRLPGTYVV VLKEETHLSQ SERTARRLQA QAARRGYLTK ILHVFHGLLP GFLVKMSGDL LELALKLPHV DYIEEDSSVF AQSIPWNLER ITPPRYRADE YQPPDGGSLV EVYLLDTSIQ SDHREIEGRV MVTDFENVPE EDGTRFHRQA SKCDSHGTHL AGVVSGRDAG VAKGASMRSL RVLNCQGKGT VSGTLIGLEF IRKSQLVQPV GPLVVLLPLA GGYSRVLNAA CQRLARAGVV LVTAAGNFRD DACLYSPASA PEVITVGATN AQDQPVTLGT LGTNFGRCVD LFAPGEDIIG ASSDCSTCFV SQSGTSQAAA HVAGIAAMML SAEPELTLAE LRQRLIHFSA KDVINEAWFP EDQRVLTPNL VAALPPSTHG AGWQLFCRTV WSAHSGPTRM ATAIARCAPD EELLSCSSFS RSGKRRGERM EAQGGKLVCR AHNAFGGEGV YAIARCCLLP QANCSVHTAP PAEASMGTRV HCHQQGHVLT GCSSHWEVED LGTHKPPVLR PRGQPNQCVG HREASIHASC CHAPGLECKV KEHGIPAPQE QVTVACEEGW TLTGCSALPG TSHVLGAYAV DNTCVVRSRD VSTTGSTSEE AVTAVAICCR SRHLAQASQE LQENLYFQGH HHHHH (SEQ ID NO.: 1)

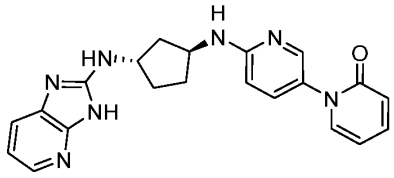
PCSK9 protein (D374Y mutant): Human PCSK9 (D374Y) Protein, His Tag, MALS verified (Acro Biosystems PCY-H5225)

Assay 3 Neutral Control: DMSO (100%)

Assay 3 Inhibitor Control: 6'-(((1*S*,3*S*)-3-((3*H*-Imidazo[4,5-b]pyridin-2-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one (10 µM)

Synthesis of Assay 3 Inhibitor Control

6'-(((1*S*,3*S*)-3-((3*H*-Imidazo[4,5-*b*]pyridin-2-yl)amino)cyclopentyl)amino)-2*H*-[1,3'-bipyridin]-2-one

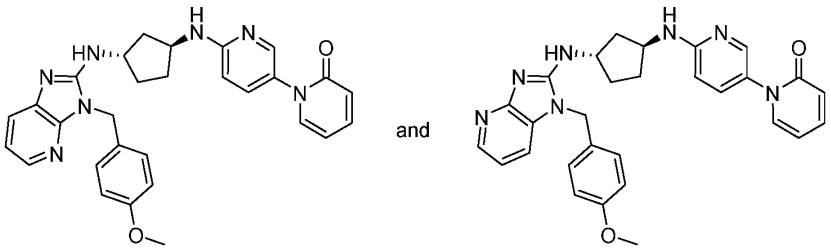


A mixture of 6'-(((1*S*,3*S*)-3-((3-(4-methoxybenzyl)-3*H*-imidazo[4,5-*b*]pyridin-2-yl)amino)cyclopentyl)amino)-2*H*-[1,3'-bipyridin]-2-one and 6'-(((1*S*,3*S*)-3-((1-(4-methoxybenzyl)-1*H*-imidazo[4,5-*b*]pyridin-2-yl)amino)cyclopentyl)amino)-2*H*-[1,3'-bipyridin]-2-one **Intermediate X3** (100 mg, 0.20 mmol) was treated with TFA (3 mL) at 20°C and the resulting solution was stirred at 80°C for 18 h under a nitrogen atmosphere. The reaction mixture was cooled to rt, filtered through Celite and the filter cake was washed with DCM (2×5 mL). The combined filtrates were concentrated under reduced pressure and the obtained residue was purified by reversed phase flash chromatography on a C18 column (gradient 0–29% MeCN in water (1% TFA)) followed by preparative HPLC, MC-Actus Triart C18, 30*150 mm, 5µm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3 + 0.1% aqueous NH_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 10% B to 40% B, to give the title compound (10 mg, 13%) as a white solid. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{22}N_7O$: 388.1880, found: 388.1896. ^1H NMR (300 MHz, Methanol-d_4) 1.55 – 1.74 (2 H, m), 2.04 – 2.13 (2 H, m), 2.22 – 2.42 (2 H, m), 4.38 (2 H, h), 6.46 (1 H, td), 6.57 – 6.67 (2 H, m), 6.96 (1 H, dd), 7.39 – 7.54 (2 H, m), 7.54 – 7.68 (2 H, m), 7.82 – 8.00 (2 H, m).

Intermediate X3

6'-(((1*S*,3*S*)-3-((3-(4-Methoxybenzyl)-3*H*-imidazo[4,5-*b*]pyridin-2-yl)amino)cyclopentyl)amino)-2*H*-[1,3'-bipyridin]-2-one *and*

6'-(((1*S*,3*S*)-3-((1-(4-Methoxybenzyl)-1*H*-imidazo[4,5-b]pyridin-2-yl)amino)cyclopentyl)amino)-2*H*-[1,3'-bipyridin]-2-one

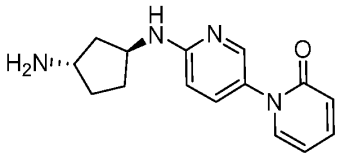


1-(Chloromethyl)-4-methoxybenzene (117 mg, 0.75 mmol) was added to 2-chloro-1*H*-imidazo[4,5-*b*]pyridine (125 mg, 0.81 mmol) and MTBD (300 mg, 1.96 mmol) in DMA (4 mL) at

20°C and the resulting solution was stirred at 20°C for 18 h under a nitrogen atmosphere. Pd-PEPPSI-IpentCl 2-methylpyridine (27.4 mg, 0.03 mmol) and 6'-(((1*S*,3*S*)-3-aminocyclopentyl)amino)-2*H*-[1,3'-bipyridin]-2-one × HCl **Intermediate X2** (100 mg, 0.33 mmol) were added and the resulting suspension was stirred at 100°C for 16 h. The crude reaction mixture was directly purified by reversed phase flash chromatography on a C18 column (gradient: 5–30% of MeCN in water) to give a mixture of the regioisomeric title compounds (120 mg, 73%) as a yellow gum; MS (ESI) *m/z* $[M+H]^+$ 508.35.

Intermediate X2

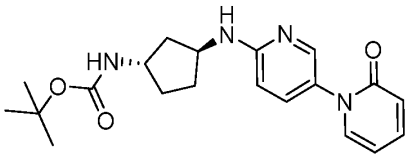
6'-(((1*S*,3*S*)-3-Aminocyclopentyl)amino)-2*H*-[1,3'-bipyridin]-2-one



2 M HCl in Et_2O (27 mL, 54 mmol) was added slowly to *tert*-butyl ((1*S*,3*S*)-3-((2-oxo-2*H*-[1,3'-bipyridin]-6'-yl)amino)cyclopentyl)carbamate **Intermediate X1** (1 g, 2.70 mmol) in DCM (10 mL) at 25 °C. The resulting mixture was stirred at 25°C for 3 h. This synthesis procedure was repeated for a second batch of *tert*-butyl ((1*S*,3*S*)-3-((2-oxo-2*H*-[1,3'-bipyridin]-6'-yl)amino)cyclopentyl)carbamate **Intermediate X1** (1.7 g, 4.6 mmol). The two batches were combined and concentrated. The crude product was recrystallised from EtOAc:PE (5:1) to give a solid which was collected by filtration and dried *in vacuo* to give an unspecified HCl salt of the title compound (2.5 g, 100%) as a yellow solid; MS (ESI) *m/z* $[M+H]^+$ 270.9.

Intermediate X1

tert-Butyl ((1*S*,3*S*)-3-((2-oxo-2*H*-[1,3'-bipyridin]-6'-yl)amino)cyclopentyl)carbamate



rel-(1*R*,2*R*)-N^1,N^2-Dimethylcyclohexane-1,2-diamine (0.212 g, 1.49 mmol) and Cu(I)I (0.283 g, 1.49 mmol) were added to *tert*-butyl ((1*S*,3*S*)-3-((5-iodopyridin-2-yl)amino)cyclopentyl)carbamate **intermediate 1** (3.0 g, 7.44 mmol), K_2CO_3 (3.08 g, 22.3 mmol) and 174yridine-2(1*H*)-one (1.42 g, 14.9 mmol) in 1,4-dioxane (20 mL). The resulting solution was stirred at 110°C for 18 h under a nitrogen atmosphere. The reaction mixture was diluted with EtOAc (25 mL) and washed sequentially with water (3×25 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated. The crude material was triturated with EtOAc:PE (5:1) to give a solid. The solid was collected by filtration and dried *in vacuo* to give the title compound (2.70 g, 98%) as a yellow solid; MS (ESI) *m/z* $[M+H]^+$ 371.2.

Step by step protocol for running the assays:

Day 1

1. Cryopreserved HepG2 cells were thawed in cell medium and centrifuged for 5 min at 250 g. Supernatant was discarded and the cell pellet resuspended in cell medium and counted with a Nucleocounter (ChemoMetec). Cells were again centrifuged for 5 min at 250 g and the pellet was resuspended to 500000 cells/mL in assay medium.
2. 20 µL of above cell mix was dispensed into black µclear PDL coated Greiner #781091 (Assay 3) or Greiner #781946 (Assays 3 and 3a) 384 well plates with Multidrop Combi (ThermoFisher) and left at room temperature for 20 minutes.
3. Plates were incubated at 37 °C, 5% CO_2 for 24 h.

Day 2

1. (Assay 3 only) Test compounds were prepared in concentration response in DMSO with a half-log dilution factor in DMSO in Echo 384 LDV plates (Labcyte LP-#0200) starting at 10 mM.
2. 30 nL of above test compounds were dispensed with Echo 655 (Labcyte) to cells for a top concentration of 10 µM (Assay 3) or single concentration of 0.1 µM (Assay 3a).
3. Assay 3: WT PCSK9 protein was diluted to 375 nM with assay medium and dispensed to cells with Multidrop Combi (ThermoFisher), 10 µL per well, for a final concentration of 125 nM.
   Assay 3a: PCSK9 protein (D374Y mutant) was diluted to 6 nM with assay medium and dispensed to cells with Multidrop Combi (ThermoFisher), 10 µL per well, for a final concentration of 2 nM.
4. Plates were incubated at 37 °C, 5% CO_2 for 24 h.

Day 3

1. 6 µg/mL pHrodo™ Red-LDL in assay medium was dispensed to cells with Multidrop Combi (ThermoFisher), 10 µL per well.
2. Plates were incubated at 37 °C, 5% CO_2 and imaged with the Incucyte S3 (Sartorius) after 4 h (Assay 3) or 24 h (Assay 3a).

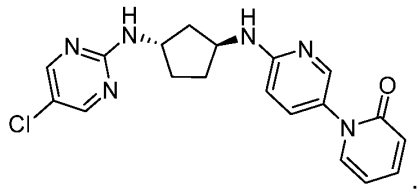
Image data was processed using Incucyte 2022B Rev2 software (Sartorius) to identify cells and red fluorescence intensity.

Assay 3: Genedata Screener (Genedata AG) was used to further process data by fitting data with the normalization setting “Neutral Controls Minus Inhibitors” using a four parameter logistic

fit. For compounds exceeding the efficacy of the inhibitor control a manual curve fit adjusting the sinf curve parameter had to be applied. For the reported %efficacy values, the mean of all values at the indicated concentration was used, regardless of curve fitting.

Assay 3a: Genedata Screener (Genedata AG) was used to further process data by fitting data with the normalization setting "Neutral Controls Minus Inhibitors". Wells with no addition of compounds and no addition of PCSK9 protein were used as Inhibitor Control, giving a high signal in the assay due to uninhibited uptake of LDL into the cells. Wells without addition of compounds but with addition of PCSK9 were used as Neutral Control, giving a low signal in the assay due to PCSK9-inhibited uptake of LDL into the cells. For the reported %efficacy values, the mean of all values at the indicated concentration was used. The number of replicates is n=7 for all compounds unless indicated otherwise.

The comparator compound used in Assays 3 and 3a is example 493 in WO 2020/150473 A2.



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Assay 4 – hERG assay (human Ether-á-go-go-Related Gene)

This assay (human Ether-á-go-go-Related Gene) measures activity of the compounds at the potassium ion channel hERG (human Ether-á-go-go-Related Gene).

Experiments were performed on the SyncroPatch 384PE high throughput patch clamp platform at room temperature and medium resistance chips with 4 patch holes per site. Chinese hamster ovary K1 (CHO) cell lines over-expressing the ion channel of choice (hERG) were used in assay-ready format and kept in liquid nitrogen or were used from live culture. Cells were either thawed and diluted in HBSS or were detached from flasks and resuspended in HBSS. HBSS comprised 140 mM NaCl, 4 mM KCl, 10 mM HEPES and 5 mM Glucose (pH 7.4). The internal patch clamp solution was KF 120 mM, KCl 20 mM, HEPES 10 mM, EGTA 10 mM, and 25 µM Escin (pH 7.2). After the sealing process was complete, the external solution was exchanged for external patch clamp solution comprising NaCl 80 mM, KCl 4 mM, HEPES 10 mM, $CaCl_2$ 2 mM, $MgCl_2$ 1 mM, glucose 5 mM, and NMDG 60 mM (pH 7.4). All solutions were stored at room temperature, except Escin, which was stored at 4 °C. All test compounds were dispensed in greiner-bio 384 well plates and tested in a 6 point cumulative assay (final DMSO concentration

0.33%). Only wells that passed previously agreed acceptance criteria for this platform were used in this analysis (30 MegaOhm seal resistance, Z prime >0.4 and current size >0.2 nA).

High concentration hERG

Experiments were performed on the QPatchII high throughput patch clamp platform at room temperature using single holes QChips. Chinese hamster ovary K1 (CHO) cell lines over-expressing the ion channel of choice (hERG) were used from live culture. All solutions were stored at 4 °C or -20 °C. All compounds were dispensed as 10 or 50mM DMSO stocks, in 96 well plates and diluted to a format that allowed testing in a 6 point cumulative assay (final DMSO concentration 2% or 0.4% DMSO). Only wells that passed previously agreed acceptance criteria for this platform were used in this analysis (500 MegaOhm seal resistance and current size >0.2 nA, with positive controls including Verapamil and DMSO being consistent).

Assay 5 – GSK3β Assay (ThermoFisher assay)

This assay measures the activity of the compounds at GSK3b (Glycogen synthase kinase-3 beta).

The test compounds were screened in 1% DMSO (final) in the well. For 10-point titrations, 3-fold serial dilutions are conducted from the starting concentration of 10 µM.

Assay Protocol

Bar-coded Corning, low volume NBS, black 384-well plate

1. 2.5 µL – 4X Test Compound or 100 nL 100X plus 2.4 µL kinase buffer
2. 5 µL – 2X Peptide/Kinase Mixture
3. 2.5 µL – 4X ATP Solution
4. 30-second plate shake
5. 60-minute Kinase Reaction incubation at room temperature
6. 5 µL – Development Reagent Solution
7. 30-second plate shake
8. 60-minute Development Reaction incubation at room temperature
9. Read on fluorescence plate reader and analyse the data

In step 2, the 2X GSK3β (GSK3 beta) / Ser/Thr (Glycogen synthase kinase-3 beta/ Serine/ Threonine) 09 mixture is prepared in 50 mM HEPES (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid) pH 7.5, 0.01% BRIJ-35, 10 mM $MgCl_2$, 1 mM EGTA (egtazic acid). The final 10 µL Kinase Reaction consists of 0.22 - 0.92 ng GSK3β (GSK3 beta) and 2 µM Ser/Thr 09 in 50 mM HEPES pH 7.5, 0.01% BRIJ-35, 10 mM $MgCl_2$, 1 mM EGTA.

In step 3 the ATP Solution is diluted to a 4X working concentration in Kinase Buffer (50 mM HEPES pH 7.5, 0.01% BRIJ-35, 10 mM $MgCl_2$, 1 mM EGTA).

In Step 6 the Development Reagent is diluted 1:512 in Development Buffer (10X Novel PKC Lipid Mix: 2 mg/mL Phosphatidyl Serine, 0.2 mg/mL DAG in 20 mM HEPES, pH 7.4, 0.3% CHAPS).

Graphing Software

SelectScreen® Kinase Profiling Service uses XLfit from IDBS. The dose response curve is curve fit to model number 205 (sigmoidal dose-response model). If the bottom of the curve does not fit between -20% & 20% inhibition, it is set to 0% inhibition. If the top of the curve does not fit between 70% and 130% inhibition, it is set to 100% inhibition.

Assay 6 – in vivo

Mouse GalNAc ASO for in vivo

Nucleobase Sequence: 5'-AACTACAAAACCCTGC-3' where C = 5MeC (SEQ ID NO.: 2)

HELM: [GalNAc THA]-[AH]-{P.[LR](A)[sP].[LR](A)[sP].[LR]([5meC])[sP].[dR](T)[sP].[dR](A)[sP].[dR]([5meC])[sP].[dR](A)[sP].[dR](A)[sP].[dR](A)[sP].[dR](A)[sP].[dR]([5meC])[sP].[dR]([5meC])[sP].[dR]([5meC])[sP].[LR](T)[sP].[LR](G)[sP].[LR]([5meC]) where LR = LNA (Locked Nucleic Acid), dR = deoxyribose, sP = thiophosphate, P = phosphate, A = adenosine, G = guanosine, C = 5-methylcytosine, T = thymine, GalNAc THA = GalNAc TrisHexylAmine, AH = AminoHexyl

Molecular Formula: $C_{232}H_{326}N_{70}O_{109}P_{16}S_{15}$

Molecular Weight: 6816.0172 Da

Structure is provided in Figure 1.

Synthesis

MMTr-protected oligonucleotide (MMTr-ON) with the above sequence was synthesised on an ÄKTA OligoPilot Plus 100 synthesizer (GE Healthcare), on a 940 µmol scale, using a standard synthesis cycle of detritylation (3% dichloroacetic acid in toluene), coupling (coupling agent: 0.25 M 5-[3,5-bis(trifluoromethyl)phenyl]-1H-tetrazole solution in acetonitrile), capping (Cap A: 20% N-methylimidazole and 80% acetonitrile; Cap B: 20% pyridine, 20% acetic anhydride and 60% acetonitrile), oxidation (0.05 M iodine in pyridine and water) or thiolation (0.2 M xanthane

hydride in pyridine), and solid supports (UNY Primer Support 5G ~353 µmol/g, GE Healthcare). All fully protected β-cyanoethyl phosphoramidite monomers were dissolved in dry acetonitrile or 15% DMF in dry acetonitrile (0.2 M) under argon immediately prior to use. The phosphoramidite re-circulation time/coupling time for DNA monomers was 5 min and was extended to 10 min for LNA monomers. Stepwise coupling efficiencies and overall yields were determined by automated trityl cation absorption monitoring exceeding 98% for all oligonucleotides synthesized.

At the end of assembly, the solid-support bound MMTr-ON was treated with ammonia (aq. 26%) solution (40 mL) at 55 °C for 18 h. The solution was filtered, and the MMTr-ON product was purified using HPLC (XBridge C18, 10 µm 50x250 mm column; 5-45% acetonitrile in aqueous NH_4HCO_3 (50 mM).

Fractions containing the MMTr-ON product were combined, and volatiles were removed on a Speedvac. The residue was dissolved in water (4 mL) and the MMTr group was removed by treating the obtained solution with acetic acid 10% (1 mL) at 40 °C for 60 min. NaOAc (3 M aq, 0.6 mL) and EtOH (95%, 20 mL) were sequentially added. The mixture was stored at -20 °C for 120 min and centrifuged for 15 min at 4 °C. The resulting supernatant was decanted off and the formed pellet was re-suspended in EtOH (85%, 12 mL) and the procedure repeated. Finally, the pellet was dissolved in water (20 mL) and lyophilized to yield the desired HA-oligonucleotide.

GalNac conjugation

In a falcon tube HA-oligonucleotide (1074 mg) was dissolved in water (11.176 mL), TEA (0.38 mL) was added and the pH was immediately checked, then 765 mg of GalNAc ligand **1**-OPfp ester (Kim 2024, dissolved in 2.79 mL of ACN) was added to the tube. The mixture was shaken for 4 h, at room temperature. LCMS showed the desired product mass. The reaction mixture was mixed with 5 mL of aq NH_3 solution shaken overnight at room temperature and freeze-dried overnight. Crude after ammonia treatment and freeze dried white foamy material was purified by preparative-HPLC. Stationary phase: Waters Premier BEH C18, 1.7µm, 2.1x100mm, Mobile phase: Gradient 5-30% in 10 min, 0.6 mL/min, 45 °C, 260 nm, A: 50 mM NH4HCO3 in water (pH 8), B: ACN. Purity of purified fraction 96.8 Area %. The fractions were concentrated (ammonia buffer), and the oligo was precipitated with NaOAc in EtOH (10% NaOAc in 20 mL 80% EtOH) overnight. Then, the fractions were centrifuged and immediately submitted to desalt. The ASO was desalted using an ÄKTA system using WorkBeads Dsalt (50 mL) column at a flowrate of 10mL/min of water over 20 mins. Injected in 15 mL of 1 M aq NaCl and fractions were collected based on absorbance at 260 nm. The pure fraction was collected and freeze-dried overnight. A sample was taken to check absorbance with nanodrop.

In vivo study protocol and results

Heterozygous male human PCSK9 knock-in (hPCSK9-KI) mice (Carreras 2019) were fed a regular chow diet throughout and dosed via subcutaneous injections with murine Pcsk9 GalNAc-ASO (*Mouse GalNAc ASO for in vivo* above) at 5 mg/kg/week formulated in PBS for 4 weeks with one additional loading dose in week 1 to ablate endogenous hepatic murine Pcsk9 expression levels prior to compound dosing.

Compounds were formulated in 0.5% HPMC 10000 cPs, 0.1% PS80 in Milli-Q® (Merck Millipore) purified water with or without 5% mannitol, and dosed by oral gavage at the doses indicated twice daily for 7 days. Blood samples of 50 µL were drawn one day before the first dose (baseline) and at termination after 7 days of dosing (4 hours post dose) for measurements of plasma LDL-C. Plasma concentrations of LDL-C were assessed using an enzymatic method (Crystal Chem, product# 79980 and 79983). LDL-C reduction (%) was calculated as follows = ((LDL-C concentration post dosing)–(baseline LDL-C)) / (baseline LDL-C) * 100% followed by subtraction of corresponding effect in the vehicle group.

The comparator compound used in Assay 6 is example 493 in WO 2020/150473 A2.

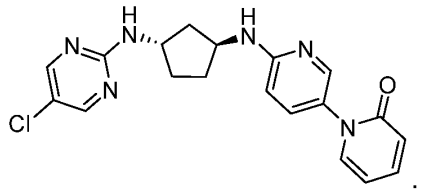


Table 4 – in vivo data

Example No.	Dose (mg/kg/day)	LDL-C reduction (%)
Comparative Example 493 in WO 2020/150473 A2	30	-27.5%
4	10	-26

Table 5 – Activity results in Assays 1, 2, 4, 5, 3 and 3a for compounds 1-37

Example No.	Assay 1 (PCSK9 Hu Bind TRF) Gmean IC_{50} (nM)	Assay 2 (PCSK9 BIAcore DBA CR) Gmean K_D (nM)	Assay 4 (hERG Hu CHO IF Eph CR-Syncro) Gmean IC_{50} (μM)	Assay 5 (GSK3β FRET-Z-Lyte CR) Gmean IC_{50} (μM) ATP Conc: 10.000 (μM)	Assay 3 LDL-C uptake assay Gmean IC_{50} (μM)	Assay 3 LDL-C uptake assay Mean effect (@ 3.16 μM) (%)	Assay 3a LDL-C uptake assay Mean effect @ 0.1 μM compound (%)
1	0.9	0.2	>40.1	>10.0	0.110	-194	-35.6
2	1.3	0.7	>200.0	>10.0	0.132	-203	-26.3
3	3.2	2.9	>40.0	>10.0	0.455	-221	-38.3
4	1.1	0.8	>40.0	>10.0	0.102	-208	-37.2
5	1.3	0.7	>40.0	>10.0	0.111	-220	-34.3
6	1.8	1.7	>40.0	>10.0	0.118	-141	-33.5
7	0.7	0.2	>40.0		0.118	-161	-41.0
8	0.7	0.3	>40.0	>10.0	0.112	-195	-40.7
9	1.3				0.132	-152	-34.9
10	4.2		>40.1	>10.0	0.152	-181	-38.9
11	1.2		>40.1		0.103	-181	-40.1
12	0.6		5.7	8.8	0.250	-153	-38.5
13	0.6		9.9	4.1	0.488	-195	-38.6
14	0.6	0.3	>40.1	>10.0	0.129	-160	-34.4
15	0.4		10.9		0.397	-285	-39.7
16	0.5		3.0	>10.0	0.277	-156	-40.0
17	0.9		>40.1	>10.0	0.158	-225	-36.7
18	0.6		8.1		0.613	-150	-29.8
19	0.6	0.2	38.4	>10.0	0.085	-177	-38.3
20	1.0		>40.1	>10.0	0.133	-157	-30.0
21	1.8				0.208	-121	-37.3
22	2.4		>40.1	>10.0	0.086	-178	-39.4
23	2.4		>40.1	6.8	0.141	-165	-31.7
24	0.5				0.097	-167	-37.3
25	0.5		4.3	>10.0	0.101	-167	-33.3
26	0.4				0.213	-136	-34.8
27	56.2				0.478	-121	-11.4
28	0.4 (n=1)						-36.5
29	0.4 (n=1)		9.1				-34.1
30	0.8		>40.1	>10.0			-32.3
31	3.5	2.0	>40.1	>10.0	0.182	-202	-26.1 (n=5)
32	1.1	0.4	>40.1	>10.0	0.095	-216	-26.0 (n=5)
33	1.0	0.7	>40.1	9.1	0.099	-169	-29.0 (n=5)
34	1.3		>40.1	>10.0	0.127	-196	-29.8 (n=5)
35	2.1	3.4	>40	>10.0	0.139	-187	-24.1 (n=5)
36	2.7	1.2	>40.1	6.7	0.143	-191	-22.5 (n=5)
37	1.9		>40.1		0.119	-162	-19.4 (n=5)

***

The features disclosed in the foregoing description, or in the following claims, or in the accompanying drawings, expressed in their specific forms or in terms of a means for performing

the disclosed function, or a method or process for obtaining the disclosed results, as appropriate, may, separately, or in any combination of such features, be utilised for realising the disclosure in diverse forms thereof.

While the disclosure has been described in conjunction with the exemplary embodiments described above, many equivalent modifications and variations will be apparent to those skilled in the art when given this disclosure. Accordingly, the exemplary embodiments of the disclosure set forth above are considered to be illustrative and not limiting. Various changes to the described embodiments may be made without departing from the spirit and scope of the disclosure.

For the avoidance of any doubt, any theoretical explanations provided herein are provided for the purposes of improving the understanding of a reader. The inventors do not wish to be bound by any of these theoretical explanations.

Any section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

Throughout this specification, including the claims which follow, unless the context requires otherwise, the word “comprise” and “include”, and variations such as “comprises”, “comprising”, and “including” will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

It must be noted that, as used in the specification and the appended claims, the singular forms “a,” “an,” and “the” include plural referents unless the context clearly dictates otherwise. Ranges may be expressed herein as from “about” one particular value, and/or to “about” another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by the use of the antecedent “about,” it will be understood that the particular value forms another embodiment. The term “about” in relation to a numerical value is optional and means for example +/- 10%.

References

A number of publications are cited above in order to more fully describe and disclose the compound of Formula (I) and the state of the art to which it pertains. Full citations for these references are provided below. The entirety of each of these references is incorporated herein.

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Miyaura and Suzuki 1995	Miyaura and Suzuki, *Chem. Rev.* **1995**, 95, 2457-2483	10.1021/cr00039a007

Cordovilla 2015	Cordovilla et al.,, *ACS Catal.* **2015**, 5, 3040−3053	10.1021/acscatal.5b00448
Chen 2020	Chen et al,, *Adv. Synth. Catal.* **2020**, *362,* 3311-3331	10.1002/adsc.202000495
Chan 2022	Chan et al., *Chem. Rev.* **2022**, 122, 1485−1542	10.1021/acs.chemrev.1c00383
Kim 2024	Kim et al., *Org. Process Res. Dev.* **2024**, 28, 1, 188–209	10.1021/acs.oprd.3c00281
Grundy 2018	Grundy et al., *J. Am. Coll. Cardiol.*, **2019**, 73(24), 3237-3241	10.1016/j.jacc.2018.11.003
Phan 2012	Phan et al., *Vasc Health Risk Manag.* **2012**, 8, 415-27	10.2147/VHRM.S33664
Awad 2018	Awad et al., *Drugs*, **2018**, 78(4), 453-462	10.1007/s40265-018-0870-1
Agarwala and Goldberg 2020	Agarwala and Goldberg, *Future Cardiol.*, **2020**, 16(5), 361-371	10.2217/fca-2020-0016

For standard molecular biology techniques, see Sambrook, J., Russel, D.W. *Molecular Cloning, A Laboratory Manual.* 3 ed. 2001, Cold Spring Harbor, New York: Cold Spring Harbor Laboratory Press.

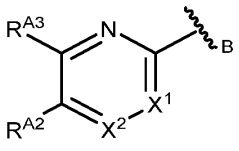
Numbered Statements A

A1. A compound of Formula (I)

A-B-C (I)

or a pharmaceutically acceptable salt thereof,

wherein A is of one of the following formulae:



(A1)

wherein the wavy line indicates the point of attachment to B;

X^1 is N or C-R^{A1};
X^2 is N or C-R^{A4};

R^{A1} is selected from the group consisting of:
(i) H;
(ii) halo;
(iii) CN;
(iv) C_{1-6} hydrocarbon, optionally substituted by OH, CN, C_{1-6} alkyl acyl, C_{1-6} alkoxy or one or more halo groups;
(v) C_{1-6} alkoxy, optionally substituted by OH, one or more halo groups, or C_{1-6} alkyl amido;
(vi) C_{1-6} alkyl ester;
(vii) C_{1-6} alkyl acyl; and
(viii) OH;

R^{A2} is selected from the group consisting of:
(i) H;
(ii) halo;
(iii) CN;
(iv) C_{1-6} hydrocarbon, optionally substituted by OH, CN, C_{1-6} alkyl acyl, C_{1-6} alkoxy or one or more halo groups;
(v) C_{1-6} alkoxy, optionally substituted by OH, C_{1-6} alkyl amido, or one or more halo groups;

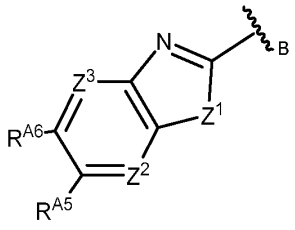
(vi) C_{1-6} acylamido (wherein the acyl is optionally substituted by H or methyl);
(vii) C_{1-6} thioalkyl;
(viii) C_{1-6} alkyl ester;
(ix) C_{1-6} alkyl acyl;
(x) C_{4-5} heterocyclyl;
(xi) C_5 heteroaryl;
(xii) C_{1-6} alkyl amido, optionally substituted by C_{1-3} alkyl amido, CN, OH, C_{2-3} alkynyl, C_{4-6} heterocyclyl or C_{1-3} alkyl wherein the C_{1-3} alkyl is optionally substituted with one or more halo or OH groups;
(xiii) OH; and
(xiv) C_{1-6} alkylamino;

R^{A3} is selected from the group consisting of:
(i) H;
(ii) halo;
(iii) CN;
(iv) C_{1-6} hydrocarbon which is optionally substituted by OH, CN, C_{1-6} thioalkyl, C_{1-6} alkoxy, C_{1-6} alkyl acyl, C_{1-6} acyloxy, carboxy, C_{1-6} alkyl ester, C_{1-6} alkylamino, -C(=O)NH_2, C_{1-6} alkyl amido, C_{1-6} alkyl acylamido, C_{1-6} alkyl sulfinyl, C_{1-6} alkyl sulfonyl or one or more halo groups;
(v) OH;
(vi) C_{1-6} alkoxy, optionally substituted by OH, NH_2, C_4 heterocyclyl or one or more halo groups;
(vii) C_{1-6} acyloxy;
(viii) C_4 heterocycyl;
(ix) NH_2;
(x) C_{1-6} alkylamino, optionally substituted by CN, OH, or C_4 heterocyclyl;
(xi) C_{1-6} dialkylamino, optionally substituted by -NH_2;
(xii) C_{1-6} acylamido (where acyl substituent is H or Me);
(xiii) carbaimidoyl or methyl-carbaimidoyl;
(xiv) carboxyamino;
(xv) C_{1-6} thioalkyl, optionally substituted by OH or NH_2;
(xvi) C_{1-6} alkyl sulfinyl;
(xvii) C_{1-6} alkyl sulfonyl, optionally substituted by one or more halo groups;
(xviii) C_{1-6} sulfonimodyl;
(xix) C_{1-6} alkyl phosphinyl;
(xx) carboxy;
(xxi) C(=O)NH_2;
(xxii) C_{1-6} alkyl ester;

(xxiii) C_{1-6} alkyl acyl, optionally substituted by one or more halo groups; and
(xxiv) C_{1-6} alkyl amido;

or wherein R^{A3} and R^{A2} together with the carbon atoms to which they are bound form:
(i) an optionally substituted C_{5-7} heterocycle ring;
(ii) an optionally substituted C_{5-7} heteroaromatic ring;
(iii) an optionally substituted C_6 carboaromatic ring; or
(iv) an optionally substituted C_{5-7} carbocyclic ring
wherein, when present, the one, two, three or four optional substituents independently selected from C_{1-6}alkyl, halo, C_{1-6} alkoxy, NH_2, C_{1-6}alkylamino, OH, and CN;

R^{A4} is selected from the group consisting of:
(i) H;
(ii) halo;
(iii) CN;
(iv) C_{1-6} hydrocarbon, optionally substituted by one or more OH, CN, C_{1-6} alkyl acyl, C_{1-6} alkoxy or one or more halo groups;
(v) C_{1-6} alkoxy, optionally substituted by OH, one or more halo groups, C_{1-6} alkyl amido;
(vi) C_{1-6} alkyl ester;
(vii) C_{1-6} alkyl acyl; and
(viii) OH;



(A2a)

wherein the wavy line indicates the point of attachment to B;
Z^1 is selected from O, S or NH;
Z^2 is either N or C-H
Z^3 is either N or C-R^{A7};
wherein if Z^1 is NH and Z^2 is C-H then Z^3 is C-R^{A7};

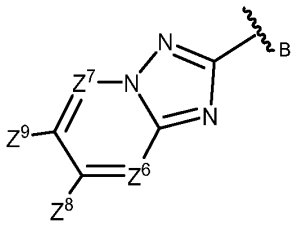
when Z^1 is NH, R^{A5} is Z^4 and R^{A6} is Z^5;
when Z^2 is N and Z^1 is O or S, R^{A5} is Z^4 and R^{A6} is Z^5;
when Z^2 is CH and Z^1 is S, R^{A5} is Z^4 and R^{A6} is Z^5;

when Z^2 is CH and Z^1 is O, R^{A5} is Z^5 and R^{A6} is Z^4;

Z^4 is selected from the group consisting of:
(i) H;
(ii) halo;
(iii) CN;
(iv) C_1 alkyl optionally substituted by one or more OH, CN, or one or more halo groups; and
(v) C_1 alkoxy, optionally substituted by one or more halo groups;

Z^5 is selected from the group consisting of:
(i) H;
(ii) halo;
(iii) CN;
(iv) C_{1-6} hydrocarbon, optionally substituted by OH, CN, C_{1-6} alkyl acyl, C_{1-6} alkoxy or one or more halo groups;
(v) C_{1-6} alkoxy, optionally substituted by C_{1-6} alkyl amido, C_{1-6} alkyl phosphonyl, or one or more halo groups;
(vi) C_{1-6} alkylamino;
(vii) C_{1-6} thioalkyl;
(viii) C_{1-6} alkyl phosphinyl; and
(ix) C_{1-6} alkyl phosphonyl;

R^{A7} is selected from the group consisting of:
(i) H;
(ii) halo;
(iii) CN;
(iv) C_{1-6} hydrocarbon, optionally substituted by OH, CN, C_{1-6} thioalkyl, C_{1-6} alkoxy, C_{1-6} alkyl acyl, C_{1-6} acyloxy, C(=O)OH, C_{1-6} alkyl ester, C_{1-6} alkylamino; -C(=O)NH_2, C_{1-6} alkyl amido, C_{1-6} acylamido, C_{1-6} alkyl sulfinyl, C_{1-6} alkyl sulfonyl or one or more halo groups;
(v) C_{1-6} alkoxy, optionally substituted by NH_2, C_4 heterocyclyl and one or more halo groups;
(vi) C_4 heterocycyl;
(vii) C_{1-6} alkylamino, optionally substituted by CN, OH, C_4 heterocyclyl;
(viii) C_{1-6} dialkylamino, optionally substituted by -NH_2; and
(ix) C_{1-6} thioalkyl, optionally substituted by OH or -NH_2;



(A2b)

wherein the wavy line indicates the point of attachment to B;

Z^6 is either N or C-H

Z^7 is either N or C-R^{A8}

Z^8 and Z^9 are independently selected from the group consisting of:

(i) H;

(ii) halo;

(iii) CN;

(iv) C_{1-6} hydrocarbon, optionally substituted by OH, CN, C_{1-6} alkyl acyl, C_{1-6} alkoxy or one or more halo groups;

(v) C_{1-6} alkoxy, optionally substituted by C_{1-6} alkyl amido, C_{1-6} alkyl phosphonyl, or one or more halo groups;

(vi) C_{1-6} alkylamino

(vii) C_{1-6} thioalkyl,

(viii) C_{1-6} alkyl phosphinyl; and

(ix) C_{1-6} alkyl phosphonyl;

R^{A8} is selected from the group consisting of:

(i) H;

(ii) halo;

(iii) CN;

(iv) C_{1-6} hydrocarbon, optionally substituted by OH, CN, C_{1-6} thioalkyl, C_{1-6} alkoxy, C_{1-6} alkyl acyl, C_{1-6} acyloxy, C(=O)OH, C_{1-6} alkyl ester, C_{1-6} alkylamino; -C(=O)NH_2, C_{1-6} alkyl amido, C_{1-6} acylamido, C_{1-6} alkyl sulfinyl, C_{1-6} alkyl sulfonyl or one or more halo groups;

(v) C_{1-6} alkoxy, optionally substituted by NH_2, C_4 heterocyclyl or one or more halo groups;

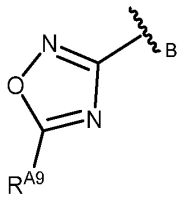
(vi) C_4 heterocycyl;

(vii) C_{1-6} alkylamino, optionally substituted by CN, OH, C_4 heterocyclyl;

(viii) C_{1-6} dialkylamino, optionally substituted by -NH_2; and

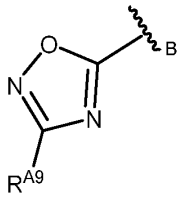
(ix) C_{1-6} thioalkyl, optionally substituted by OH or -NH_2;

(A3a)



; or

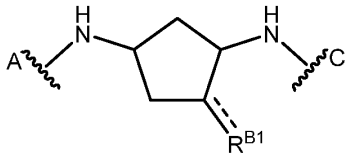
(A3b)



wherein the wavy line indicates the point of attachment to B;

where R^{A9} is selected from H; methyl, ethyl, n-propyl, *i*-propyl, cyclopropyl, 1-methylcyclopropyl and 2-methylcyclopropyl;

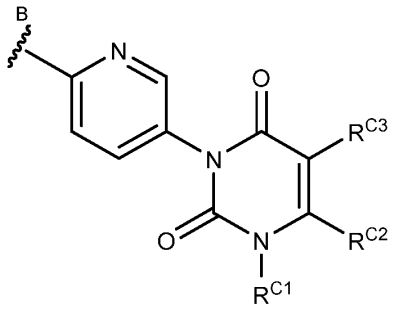
wherein B is of formula:



(B-1)

wherein the wavy lines indicate the points of attachment to A and C;
R^{B1} is H, OH, =$CHCH_2$-OH, C_{1-4} alkyoxy, or C_{1-4} alkyl which C_{1-4} alkyl is optionally substituted by OH or OMe;

wherein C is of formula:



(C-1)

R^{C2} and R^{C3} together represent a fused benzene ring or C_{5-6} heteroaromatic ring, which rings are optionally substituted by one or more R^{C4} groups;

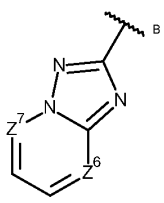
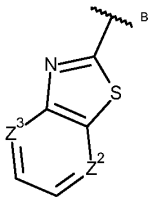
R^{C1} is selected from:
(i) H;
(ii) C_{1-6} alkyl optionally substituted by one or more halo groups;
(iii) C_{5-6} heterocyclyl or C_{5-6}heteroaryl with an optional methyl substituent;
(iv) phenyl optionally substituted by one or more halo atoms;

R^{C4} is selected from:
(i) C_{1-6} alkyl optionally substituted by one or more halo groups;
(ii) C_{1-6} alkoxy optionally substituted by one or more halo groups;
(iii) C_{5-6} heterocyclyl or C_{5-6}heteroaryl with an optional methyl substituent;
(iv) di-C_{1-6} alkyl amido;
(v) C_{1-6} acylamido;
(vi) halo; and
(vii) CN.

A2. The compound of statement A1 or a pharmaceutically acceptable salt thereof, wherein R^{A2} is selected from H, chloro, methyl, trifluoromethyl, cyclopropyl and OCF_2H.

A3. The compound of statement A1 or statement A2 or a pharmaceutically acceptable salt thereof, wherein R^{A3} is selected from the group consisting of H, methyl and OH.

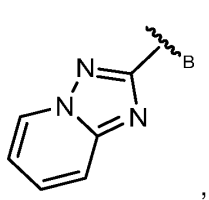
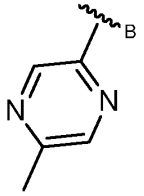
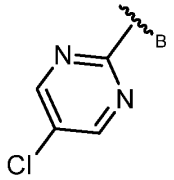
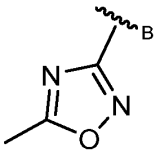
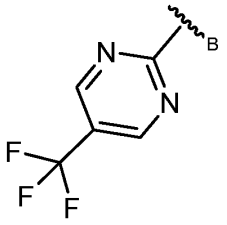
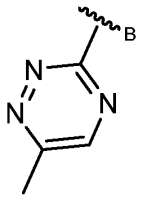
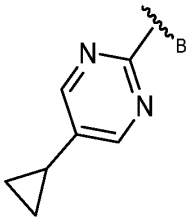
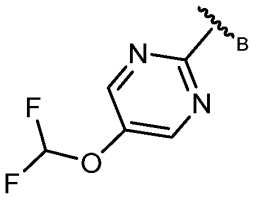
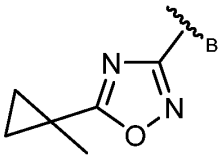
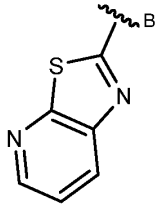
A4. The compound of any one of statements A1 to A3 or a pharmaceutically acceptable salt thereof, wherein A is according to the formula:

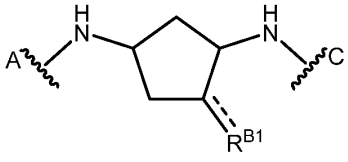
and

wherein the wavy line indicates the point of attachment to B and Z^2, Z^3, Z^6 and Z^7 are as defined in statement A1.

A5. The compound according to statement A1, or a pharmaceutically acceptable salt thereof, wherein A is selected from one of the following formulae;

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, and
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A6. The compound of any one of statements A1 to A5 or a pharmaceutically acceptable salt thereof, wherein B is of formula (B-1)

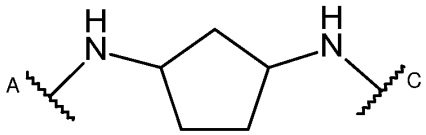


(B-1)

wherein the wavy lines indicate the point of attachment to A and C;

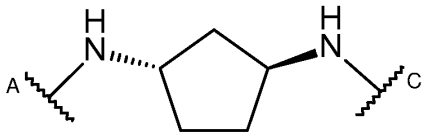
wherein R^{B1} is selected from the group consisting of H, OH, OMe, -O-ethyl, $-CH_2OH$, $-CH_2CH_2OH$ and $=CHCH_2-OH$.

A7. The compound of any one of statements A1 to A6 or a pharmaceutically acceptable salt thereof, wherein B is of the following formula (B-1a):



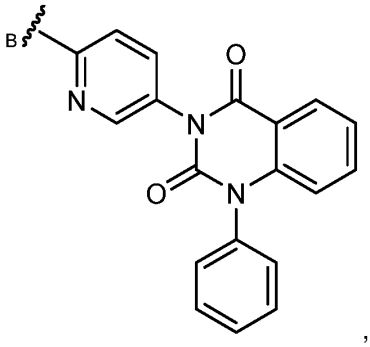
(B-1a).

A8. The compound of any one of statements A1 to A7 or a pharmaceutically acceptable salt thereof, wherein B is of the following formula (B-1b):

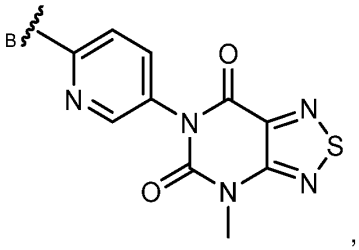


(B-1b).

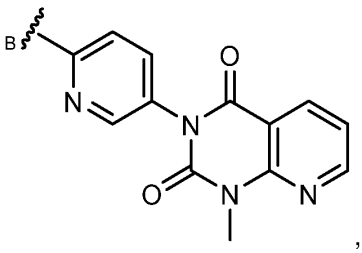
A9. The compound according to any one of statements A1 to A8, or a pharmaceutically acceptable salt thereof, wherein C is selected from one of the following formulae:



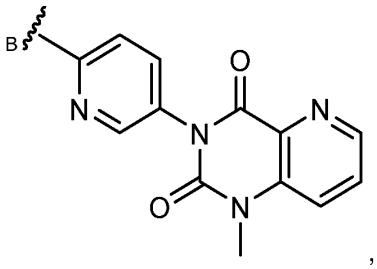
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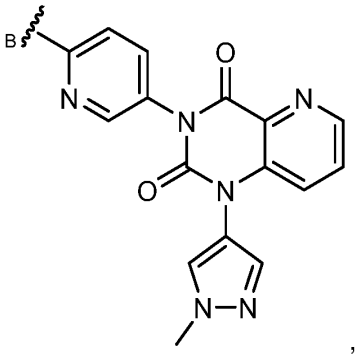
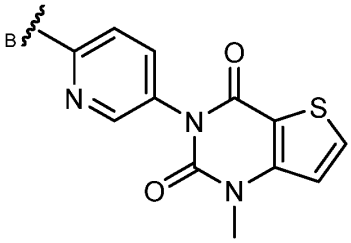
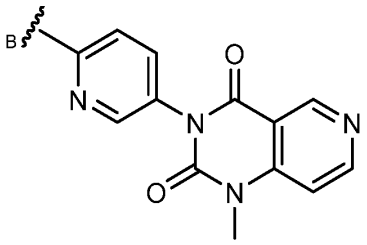
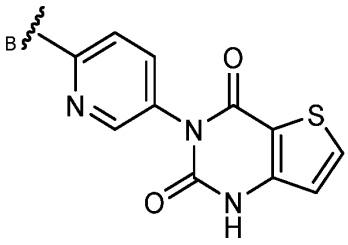
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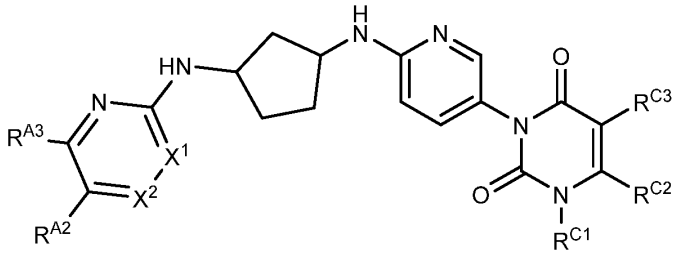

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and

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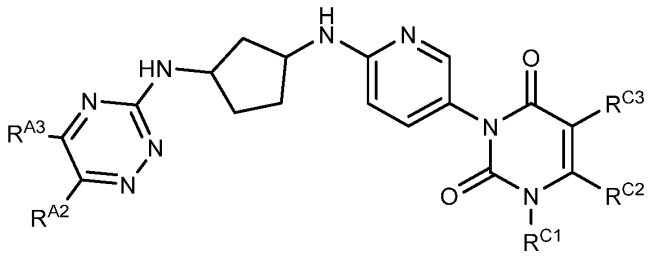
A10. The compound of statement A1 or a pharmaceutically acceptable salt thereof, wherein A-B-C is of the formula (I-A), (I-B), (I-Ba), (I-Bb), (I-C), (I-Ca), (I-Cb), (I-Cc), (I-Cd), (I-Ce), (I-D), (I-Da), (I-Db), (I-Ea) or (I-Eb);

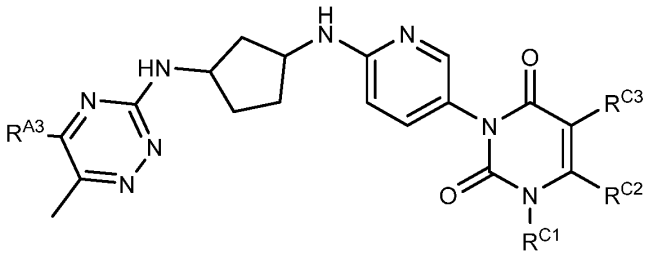
wherein none, one or two of Q_1, Q_2, Q_3 and Q_4 is N and the remainder are C-H;

wherein none, one or two of Q_5, Q_6 and Q_7 is N, none or one of Q_5, Q_6 and Q_7 is S and the remainder are C-H; and

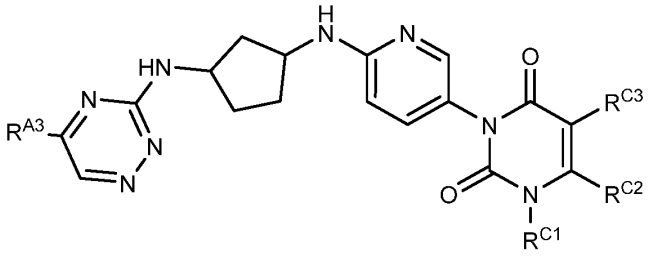
wherein all other definitions are according to statement A1:


(I-A),

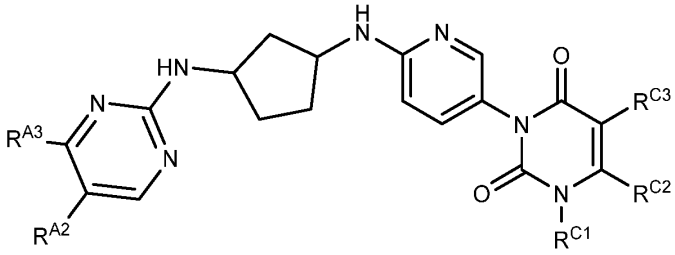

(I-B),



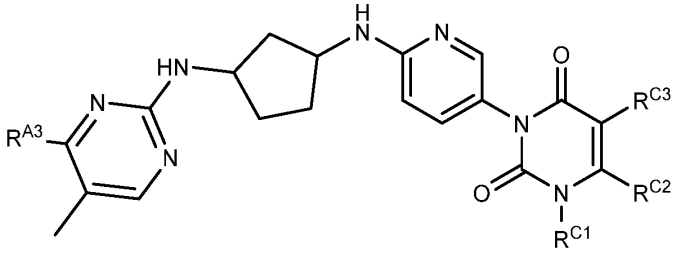
(I-Ba),



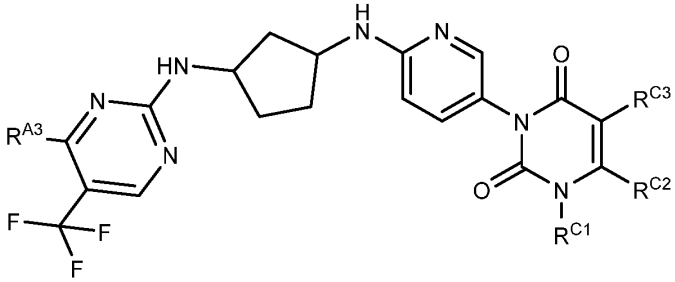
(I-Bb),



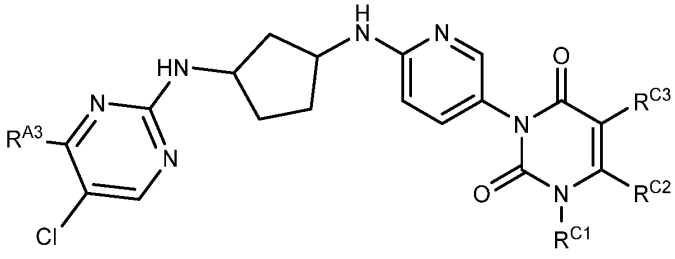
(I-C),



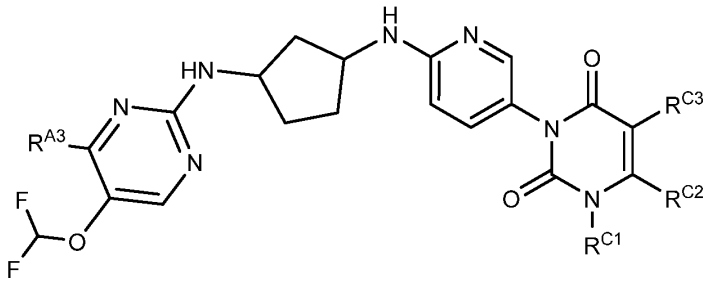
(I-Ca),



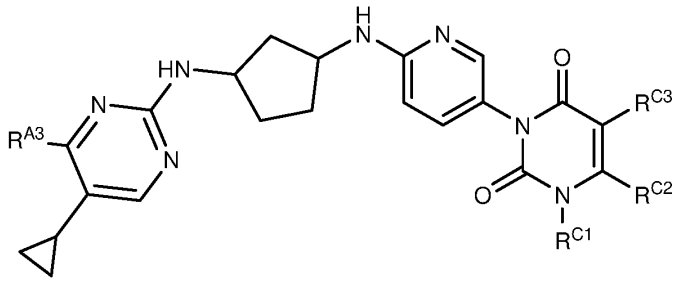
(I-Cb),



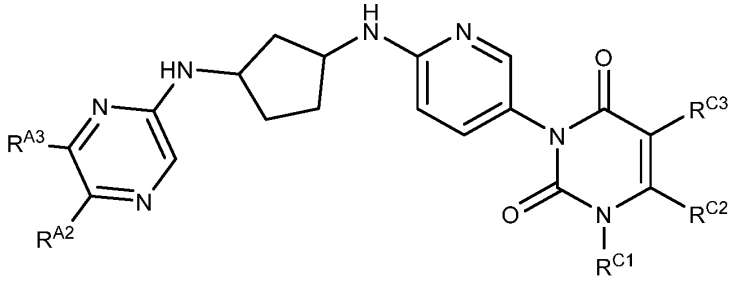
(I-Cc),



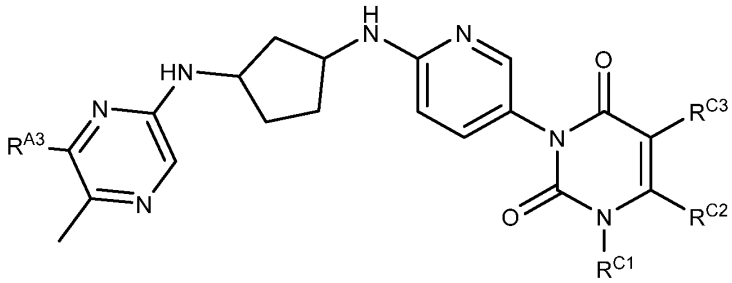
(I-Cd),



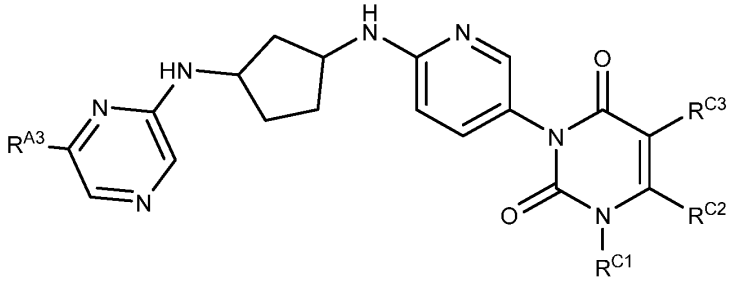
(I-Ce).



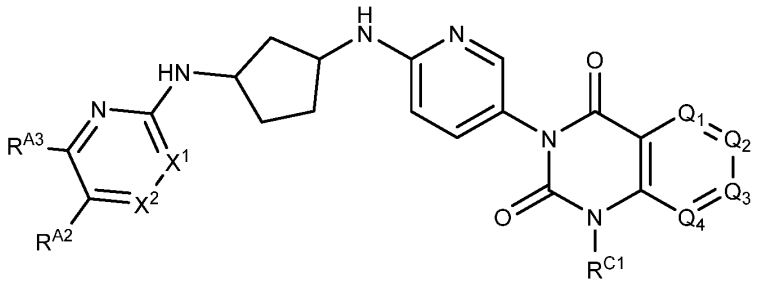
(I-D),



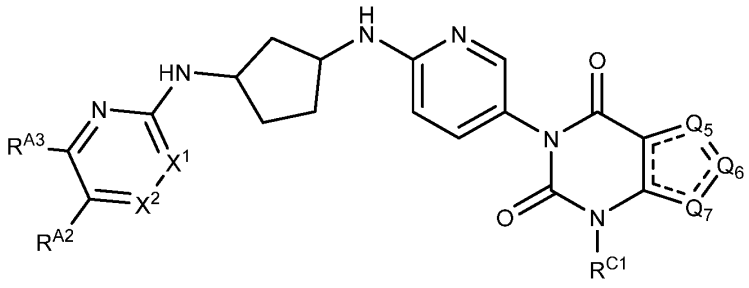
(I-Da),



(I-Db).



(I-Ea), and



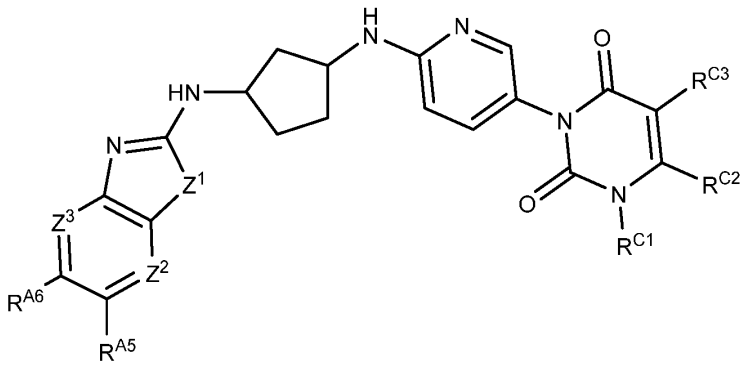
(I-Eb).

A11. The compound of any of the preceding statements or a pharmaceutically acceptable salt thereof, wherein A-B-C is of the formula (II-A), (II-Aa), (II-Ab), (II-Ac), (II-Ba) or (II-Bb);

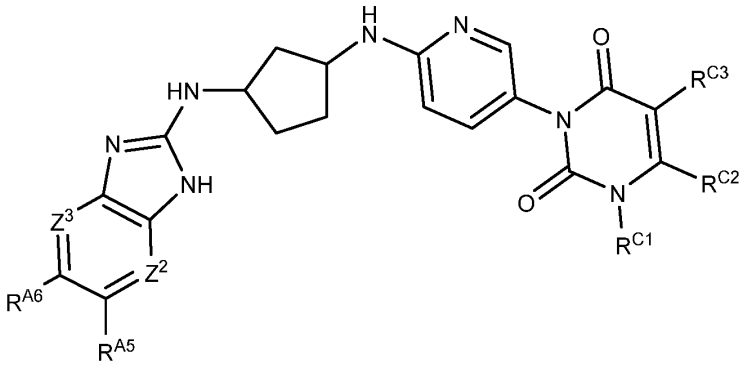
wherein none, one or two of Q_1, Q_2, Q_3 and Q_4 is N and the remainder are C-H;

wherein none, one or two of Q_5, Q_6 and Q_7 is N, none or one of Q_5, Q_6 and Q_7 is S and the remainder are C-H; and

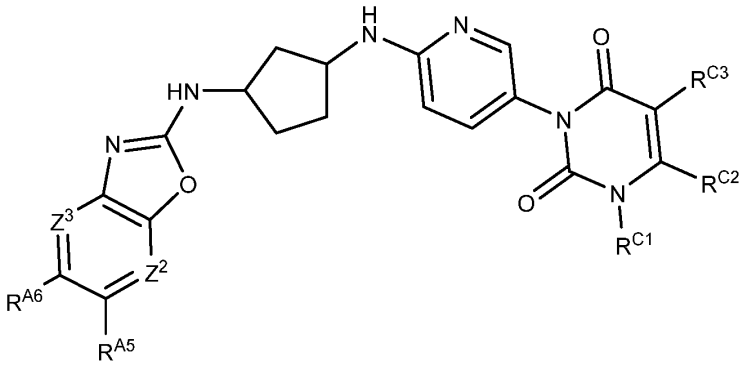
wherein all other definitions are according to statement A1;



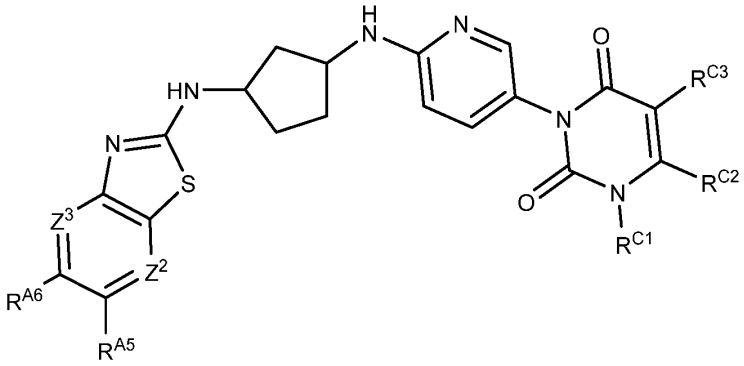
(II-A)



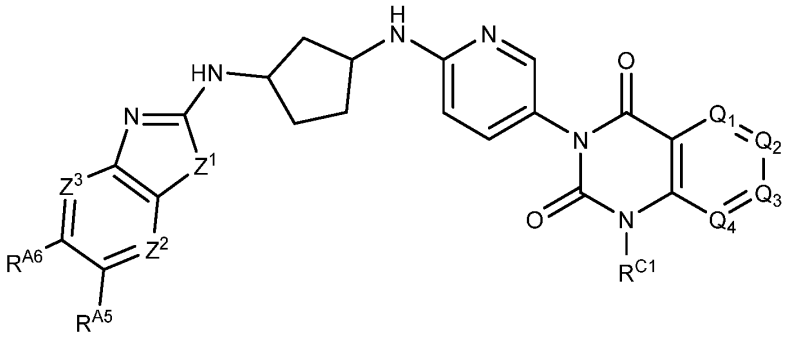
(II-Aa),



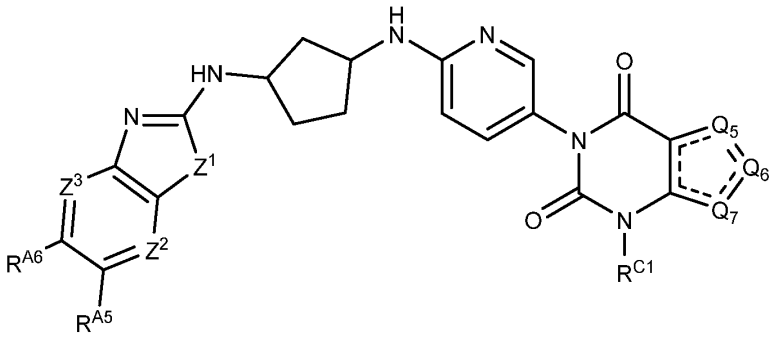
(II-Ab)



(II-Ac).



(II-Ba), and



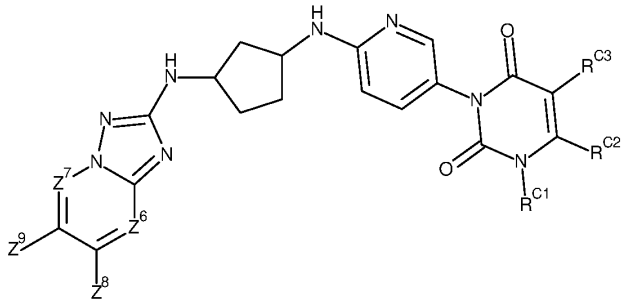
(II-Bb).

A12. The compound of statement A1 or a pharmaceutically acceptable salt thereof, wherein A-B-C is of the formula (III-A), (III-Ba) or (III-Bb), (III-Ca) or (III-Cb);

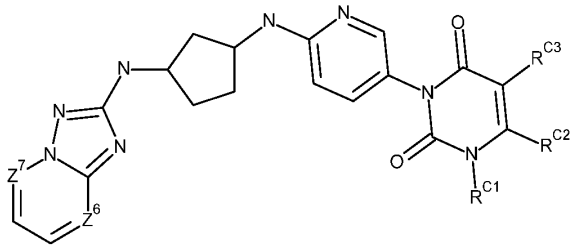
wherein none, one or two of Q_1, Q_2, Q_3 and Q_4 is N and the remainder are C-H;

wherein none, one or two of Q_5, Q_6 and Q_7 is N, none or one of Q_5, Q_6 and Q_7 is S and the remainder are C-H; and

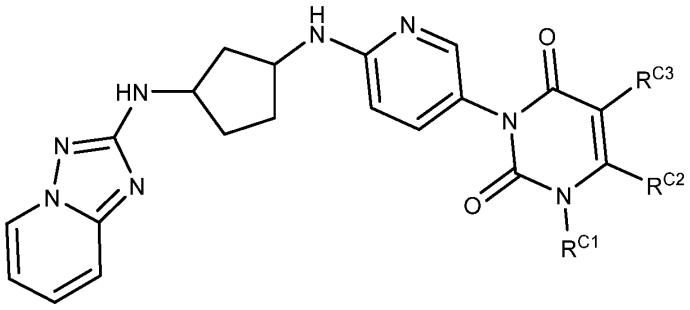
wherein all other definitions are according to statement A1;



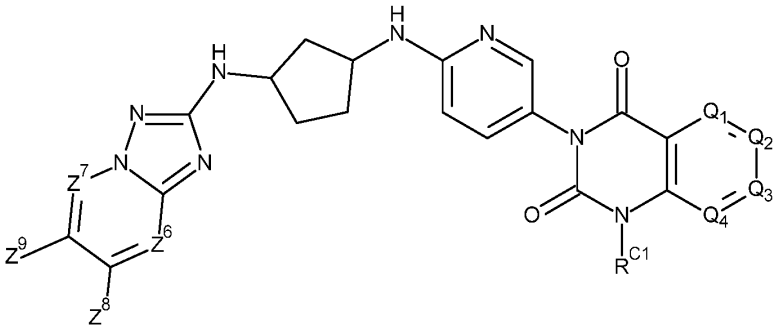
(III-A)



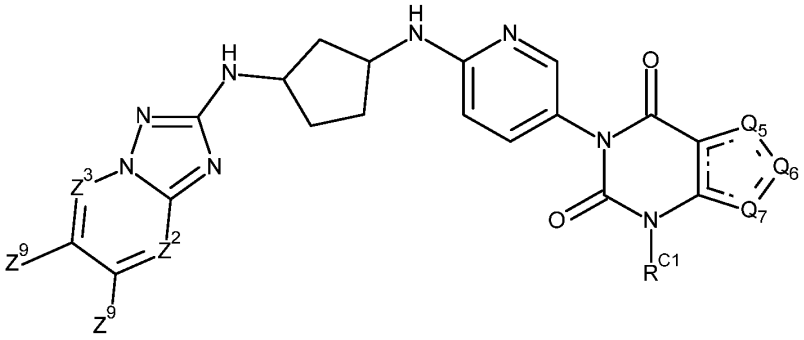
(III-Ba),



(III-Bb),



(III-Ca), and



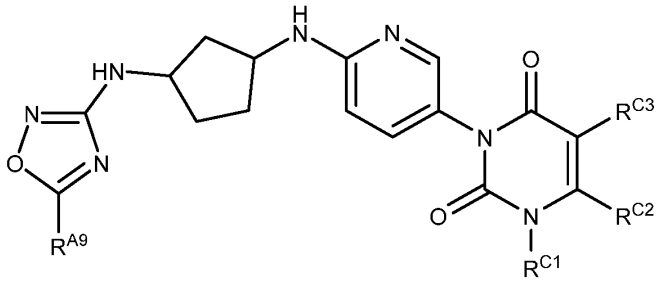
(III-Cb).

A13. The compound of statement A1 or a pharmaceutically acceptable salt thereof, wherein A-B-C is of the formula (IV-A), (IV-Aa), (IV-Ab), (IV-Ba) or (IV-Bb);

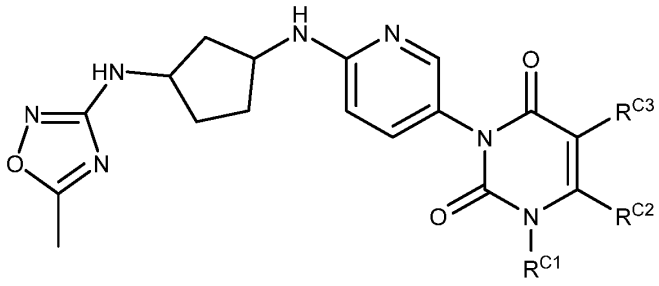
wherein none, one or two of Q_1, Q_2, Q_3 and Q_4 is N and the remainder are C-H;

wherein none, one or two of Q_5, Q_6 and Q_7 is N, none or one of Q_5, Q_6 and Q_7 is S and the remainder are C-H; and

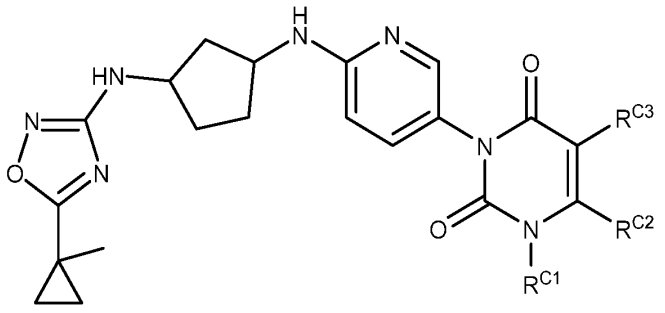
wherein all other definitions are according to statement A1;



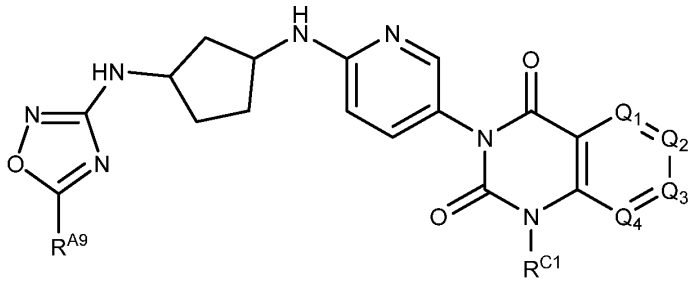
(IV-A)



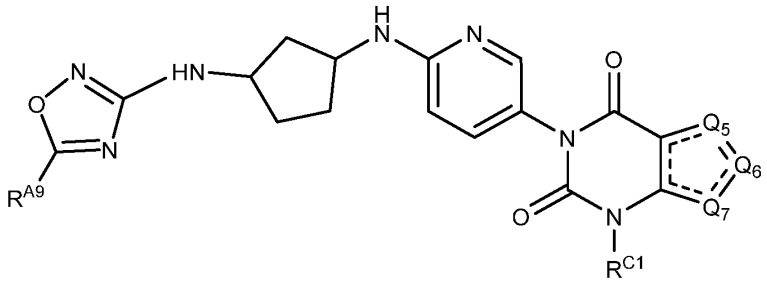
(IV-Aa),



(IV-Ab),



(IV-Ba), and



(IV-Bb).

A14. A compound listed in Table 1 or a pharmaceutically acceptable salt thereof.

A15. The compound of any one of statements A1 to A14 or a pharmaceutically acceptable salt thereof, for use in therapy.

A16. A pharmaceutical composition comprising the compound of any one of statements A1 to A14 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent, carrier or excipient.

A17. The compound of any one of statements A1 to A14 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to statement A16 for use in the treatment of a cardiovascular disease.

A18. The compound for use according to statement A17 wherein the compound is administered simultaneously, separately or sequentially in combination with an additional active ingredient selected from the group consisting of:

i) a statin;
ii) a cholesterol absorption inhibitor;
iii) a SGLT2 inhibitor;
iv) a P2Y12 inhibitor;
v) an ATP-citrate lyase inhibitor; and
vi) anti-hypertensive drugs.

A19. The compound for use according to statement A17 or A18 wherein the cardiovascular disease is selected from dyslipidemia, hypercholesterolemia, hypertriglyceridemia, hyperlipidemia, hypoalphalipoproteinemia, metabolic syndrome, diabetic complications, atherosclerosis, stroke, vascular dementia, chronic kidney disease, coronary heart disease, coronary artery disease, retinopathy, inflammation, thrombosis, peripheral vascular disease heart failure and congestive heart failure.

A20. Use of a compound of any one of statements A1 to A14 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to statement A16 in a method of medical treatment.

A21. A method of medical treatment comprising administering to the patient the pharmaceutical composition of statement A16.

A22. Use of a compound of any one of statements A1 to A14 in the manufacture of a medicament for use in therapy.

A23. A method of treating PCSK9-mediated disease or disorder in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the compound or pharmaceutically acceptable salt thereof according to any one of statements A1 to A14 or the pharmaceutical composition according to statement A16.

A24. The method according to statement A23, wherein the disease or disorder is a cardiovascular disease or disorder.

A25. The method according to statement A24, wherein the cardiovascular disease or disorder is selected from dyslipidemia, hypercholesterolemia, hypertriglyceridemia, hyperlipidemia,

hypoalphalipoproteinemia, metabolic syndrome, diabetic complications, atherosclerosis, stroke, vascular dementia, chronic kidney disease, coronary heart disease, coronary artery disease, retinopathy, inflammation, thrombosis, peripheral vascular disease heart failure or congestive heart failure.

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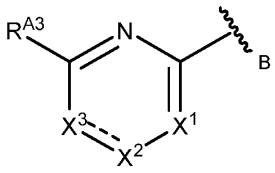
Numbered Statements B

B1. A compound of Formula (I)

A-B-C (I)

or a pharmaceutically acceptable salt thereof,

wherein A is of one of the following formulae:



(A1a)

wherein the wavy line indicates the point of attachment to B;

X^1 is N or C-R^{A1};
X^2 is N or C-R^{A4};
X^3 is N-(C_{1-6} hydrocarbon) or C-R^{A2};

R^{A1} is selected from the group consisting of:
(i) H;
(ii) halo;
(iii) CN;
(iv) C_{1-6} hydrocarbon, optionally substituted by OH, CN, C_{1-6} alkyl acyl, C_{1-6} alkoxy or one or more halo groups;
(v) C_{1-6} alkoxy, optionally substituted by OH, one or more halo groups, or C_{1-6} alkyl amido;
(vi) C_{1-6} alkyl ester;
(vii) C_{1-6} alkyl acyl; and
(viii) OH;

R^{A2} is selected from the group consisting of:
(i) H;
(ii) halo;
(iii) CN;
(iv) C_{1-6} hydrocarbon, optionally substituted by OH, CN, C_{1-6} alkyl acyl, C_{1-6} alkoxy or one or more halo groups;

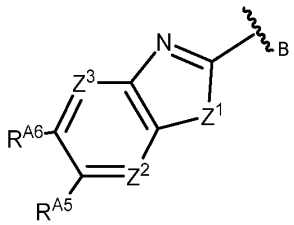
(v) C_{1-6} alkoxy, optionally substituted by OH, C_{1-6} alkyl amido, or one or more halo groups;
(vi) C_{1-6} acylamido (wherein the acyl is optionally substituted by H or methyl);
(vii) C_{1-6} thioalkyl;
(viii) C_{1-6} alkyl ester;
(ix) C_{1-6} alkyl acyl;
(x) C_{4-5} heterocyclyl;
(xi) C_5 heteroaryl;
(xii) C_{1-6} alkyl amido, optionally substituted by C_{1-3} alkyl amido, CN, OH, C_{2-3} alkynyl, C_{4-6} heterocyclyl or C_{1-3} alkyl wherein the C_{1-3} alkyl is optionally substituted with one or more halo or OH groups;
(xiii) OH; and
(xiv) C_{1-6} alkylamino;

R^{A3} is selected from the group consisting of:
(i) H;
(ii) halo;
(iii) CN;
(iv) C_{1-6} hydrocarbon which is optionally substituted by OH, CN, C_{1-6} thioalkyl, C_{1-6} alkoxy, C_{1-6} alkyl acyl, C_{1-6} acyloxy, carboxy, C_{1-6} alkyl ester, C_{1-6} alkylamino, -C(=O)NH_2, C_{1-6} alkyl amido, C_{1-6} alkyl acylamido, C_{1-6} alkyl sulfinyl, C_{1-6} alkyl sulfonyl or one or more halo groups;
(v) OH;
(vi) C_{1-6} alkoxy, optionally substituted by OH, NH_2, C_4 heterocyclyl or one or more halo groups;
(vii) C_{1-6} acyloxy;
(viii) C_4 heterocycyl;
(ix) NH_2;
(x) C_{1-6} alkylamino, optionally substituted by CN, OH, or C_4 heterocyclyl;
(xi) C_{1-6} dialkylamino, optionally substituted by -NH_2;
(xii) C_{1-6} acylamido (where acyl substituent is H or Me);
(xiii) carbaimidoyl or methyl-carbaimidoyl;
(xiv) carboxyamino;
(xv) C_{1-6} thioalkyl, optionally substituted by OH or NH_2;
(xvi) C_{1-6} alkyl sulfinyl;
(xvii) C_{1-6} alkyl sulfonyl, optionally substituted by one or more halo groups;
(xviii) C_{1-6} sulfonimodyl;
(xix) C_{1-6} alkyl phosphinyl;
(xx) carboxy;
(xxi) C(=O)NH_2;

(xxii) C_{1-6} alkyl ester;
(xxiii) C_{1-6} alkyl acyl, optionally substituted by one or more halo groups; and
(xxiv) C_{1-6} alkyl amido;

or wherein R^{A3} and R^{A2} together with the carbon atoms to which they are bound form:
(i) an optionally substituted C_{5-7} heterocycle ring;
(ii) an optionally substituted C_{5-7} heteroaromatic ring;
(iii) an optionally substituted C_6 carboaromatic ring; or
(iv) an optionally substituted C_{5-7} carbocyclic ring
wherein, when present, the one, two, three or four optional substituents independently selected from C_{1-6}alkyl, halo, C_{1-6} alkoxy, NH_2, C_{1-6}alkylamino, OH, and CN;

R^{A4} is selected from the group consisting of:
(i) H;
(ii) halo;
(iii) CN;
(iv) C_{1-6} hydrocarbon, optionally substituted by one or more OH, CN, C_{1-6} alkyl acyl, C_{1-6} alkoxy or one or more halo groups;
(v) C_{1-6} alkoxy, optionally substituted by OH, one or more halo groups, C_{1-6} alkyl amido;
(vi) C_{1-6} alkyl ester;
(vii) C_{1-6} alkyl acyl;
(viii) OH; and
(ix) oxo;



(A2a)

wherein the wavy line indicates the point of attachment to B;
Z^1 is selected from O, S or NH;
Z^2 is either N or C-H
Z^3 is either N or C-R^{A7};
wherein if Z^1 is NH and Z^2 is C-H then Z^3 is C-R^{A7};

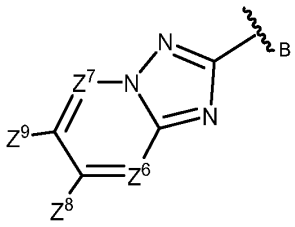
when Z^1 is NH, R^{A5} is Z^4 and R^{A6} is Z^5;

when Z^2 is N and Z^1 is O or S, R^{A5} is Z^4 and R^{A6} is Z^5;
when Z^2 is CH and Z^1 is S, R^{A5} is Z^4 and R^{A6} is Z^5;
when Z^2 is CH and Z^1 is O, R^{A5} is Z^5 and R^{A6} is Z^4;

Z^4 is selected from the group consisting of:
(i) H;
(ii) halo;
(iii) CN;
(iv) C_1 alkyl optionally substituted by one or more OH, CN, or one or more halo groups; and
(v) C_1 alkoxy, optionally substituted by one or more halo groups;

Z^5 is selected from the group consisting of:
(i) H;
(ii) halo;
(iii) CN;
(iv) C_{1-6} hydrocarbon, optionally substituted by OH, CN, C_{1-6} alkyl acyl, C_{1-6} alkoxy or one or more halo groups;
(v) C_{1-6} alkoxy, optionally substituted by C_{1-6} alkyl amido, C_{1-6} alkyl phosphonyl, or one or more halo groups;
(vi) C_{1-6} alkylamino;
(vii) C_{1-6} thioalkyl;
(viii) C_{1-6} alkyl phosphinyl; and
(ix) C_{1-6} alkyl phosphonyl;

R^{A7} is selected from the group consisting of:
(i) H;
(ii) halo;
(iii) CN;
(iv) C_{1-6} hydrocarbon, optionally substituted by OH, CN, C_{1-6} thioalkyl, C_{1-6} alkoxy, C_{1-6} alkyl acyl, C_{1-6} acyloxy, C(=O)OH, C_{1-6} alkyl ester, C_{1-6} alkylamino; -C(=O)NH_2, C_{1-6} alkyl amido, C_{1-6} acylamido, C_{1-6} alkyl sulfinyl, C_{1-6} alkyl sulfonyl or one or more halo groups;
(v) C_{1-6} alkoxy, optionally substituted by NH_2, C_4 heterocyclyl and one or more halo groups;
(vi) C_4 heterocycyl;
(vii) C_{1-6} alkylamino, optionally substituted by CN, OH, C_4 heterocyclyl;
(viii) C_{1-6} dialkylamino, optionally substituted by -NH_2; and
(ix) C_{1-6} thioalkyl, optionally substituted by OH or -NH_2;



(A2b)

wherein the wavy line indicates the point of attachment to B;

Z^6 is either N or C-H

Z^7 is either N or C-R^{A8}

Z^8 and Z^9 are independently selected from the group consisting of:

(i) H;

(ii) halo;

(iii) CN;

(iv) C_{1-6} hydrocarbon, optionally substituted by OH, CN, C_{1-6} alkyl acyl, C_{1-6} alkoxy or one or more halo groups;

(v) C_{1-6} alkoxy, optionally substituted by C_{1-6} alkyl amido, C_{1-6} alkyl phosphonyl, or one or more halo groups;

(vi) C_{1-6} alkylamino

(vii) C_{1-6} thioalkyl,

(viii) C_{1-6} alkyl phosphinyl; and

(ix) C_{1-6} alkyl phosphonyl;

R^{A8} is selected from the group consisting of:

(i) H;

(ii) halo;

(iii) CN;

(iv) C_{1-6} hydrocarbon, optionally substituted by OH, CN, C_{1-6} thioalkyl, C_{1-6} alkoxy, C_{1-6} alkyl acyl, C_{1-6} acyloxy, C(=O)OH, C_{1-6} alkyl ester, C_{1-6} alkylamino; -C(=O)NH_2, C_{1-6} alkyl amido, C_{1-6} acylamido, C_{1-6} alkyl sulfinyl, C_{1-6} alkyl sulfonyl or one or more halo groups;

(v) C_{1-6} alkoxy, optionally substituted by NH_2, C_4 heterocyclyl or one or more halo groups;

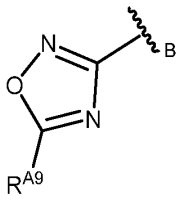
(vi) C_4 heterocycyl;

(vii) C_{1-6} alkylamino, optionally substituted by CN, OH, C_4 heterocyclyl;

(viii) C_{1-6} dialkylamino, optionally substituted by -NH_2; and

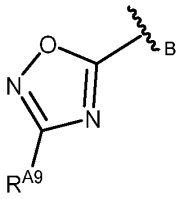
(ix) C_{1-6} thioalkyl, optionally substituted by OH or -NH_2;

(A3a)



; or

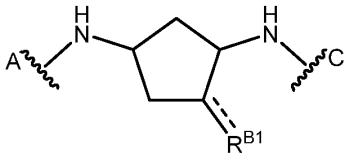
(A3b)



wherein the wavy line indicates the point of attachment to B;

where R^{A9} is selected from H; methyl, ethyl, n-propyl, *i*-propyl, cyclopropyl, 1-methylcyclopropyl and 2-methylcyclopropyl;

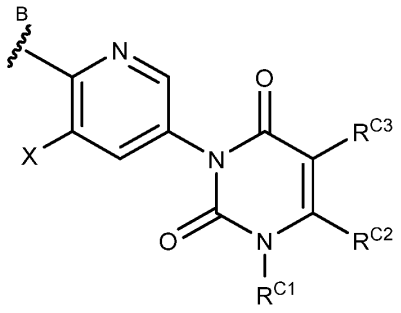
wherein B is of formula:



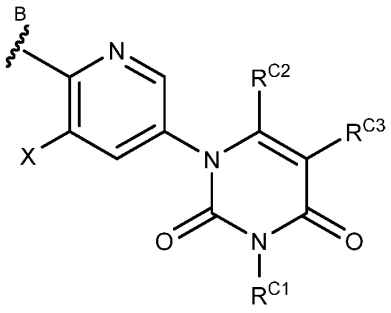
(B-1)

wherein the wavy lines indicate the points of attachment to A and C;
R^{B1} is H, OH, =$CHCH_2$-OH, C_{1-4} alkyoxy, or C_{1-4} alkyl which C_{1-4} alkyl is optionally substituted by OH or OMe;

wherein C is of formula:



(C-1a) or



(C-1b)

X is hydrogen or fluorine;

one of R^{C2} and R^{C3} is hydrogen and the other is C_{1-3} alkoxy;

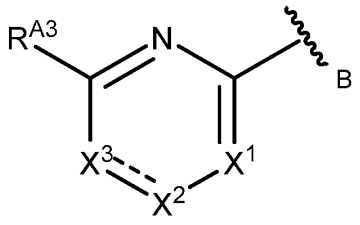
or R^{C2} and R^{C3} together represent a fused benzene ring or C_{5-6} heteroaromatic ring, which rings are optionally substituted by one or more R^{C4} groups;

R^{C1} is selected from:
(i) H;
(ii) C_{1-6} alkyl optionally substituted by one or more halo groups;
(iii) C_{5-6} heterocyclyl or C_{5-6}heteroaryl with an optional methyl substituent;
(iv) phenyl optionally substituted by one or more halo atoms;

R^{C4} is selected from:
(i) C_{1-6} alkyl optionally substituted by one or more halo groups;
(ii) C_{1-6} alkoxy optionally substituted by one or more halo groups;
(iii) C_{5-6} heterocyclyl or C_{5-6}heteroaryl with an optional methyl substituent;
(iv) di-C_{1-6} alkyl amido;
(v) C_{1-6} acylamido;
(vi) halo; and
(vii) CN.

B2. The compound of statement B1, or a pharmaceutically acceptable salt thereof, wherein if the pyridine group of C is substituted by a monocyclic moiety, then the A group is also monocyclic.

B3. The compound of statement B1, or a pharmaceutically acceptable salt thereof, wherein (A1a) is:



(A1a)

wherein the wavy line indicates the point of attachment to B;

X^1 is N or C-R^{A1};
X^2 is N or C-R^{A4};
X^3 is N-(C_{1-6} hydrocarbon) or C-R^{A2};

R^{A1} is selected from the group consisting of:
(i) H;
(ii) halo;
(iii) CN;
(iv) C_{1-6} hydrocarbon, optionally substituted by OH, CN, C_{1-6} alkyl acyl, C_{1-6} alkoxy or one or more halo groups;
(v) C_{1-6} alkoxy, optionally substituted by OH, one or more halo groups, or C_{1-6} alkyl amido;
(vi) C_{1-6} alkyl ester;
(vii) C_{1-6} alkyl acyl; and
(viii) OH;

R^{A2} is selected from the group consisting of:
(i) H;
(ii) halo;
(iii) CN;
(iv) C_{1-6} hydrocarbon, optionally substituted by OH, CN, C_{1-6} alkyl acyl, C_{1-6} alkoxy or one or more halo groups;
(v) C_{1-6} alkoxy, optionally substituted by OH, C_{1-6} alkyl amido, or one or more halo groups;
(vi) C_{1-6} acylamido (wherein the acyl is optionally substituted by H or methyl);
(vii) C_{1-6} thioalkyl;
(viii) C_{1-6} alkyl ester;
(ix) C_{1-6} alkyl acyl;
(x) C_{4-5} heterocyclyl;
(xi) C_5 heteroaryl;

(xii) C_{1-6} alkyl amido, optionally substituted by C_{1-3} alkyl amido, CN, OH, C_{2-3} alkynyl, C_{4-6} heterocyclyl or C_{1-3} alkyl wherein the C_{1-3} alkyl is optionally substituted with one or more halo or OH groups;
(xiii) OH; and
(xiv) C_{1-6} alkylamino;

R^{A3} is selected from the group consisting of:
(i) H;
(ii) halo;
(iii) CN;
(iv) C_{1-6} hydrocarbon which is optionally substituted by OH, CN, C_{1-6} thioalkyl, C_{1-6} alkoxy, C_{1-6} alkyl acyl, C_{1-6} acyloxy, carboxy, C_{1-6} alkyl ester, C_{1-6} alkylamino, -C(=O)NH_2, C_{1-6} alkyl amido, C_{1-6} alkyl acylamido, C_{1-6} alkyl sulfinyl, C_{1-6} alkyl sulfonyl or one or more halo groups;
(v) OH;
(vi) C_{1-6} alkoxy, optionally substituted by OH, NH_2, C_4 heterocyclyl or one or more halo groups;
(vii) C_{1-6} acyloxy;
(viii) C_4 heterocycyl;
(ix) NH_2;
(x) C_{1-6} alkylamino, optionally substituted by CN, OH, or C_4 heterocyclyl;
(xi) C_{1-6} dialkylamino, optionally substituted by -NH_2;
(xii) C_{1-6} acylamido (where acyl substituent is H or Me);
(xiii) carbaimidoyl or methyl-carbaimidoyl;
(xiv) carboxyamino;
(xv) C_{1-6} thioalkyl, optionally substituted by OH or NH_2;
(xvi) C_{1-6} alkyl sulfinyl;
(xvii) C_{1-6} alkyl sulfonyl, optionally substituted by one or more halo groups;
(xviii) C_{1-6} sulfonimodyl;
(xix) C_{1-6} alkyl phosphinyl;
(xx) carboxy;
(xxi) C(=O)NH_2;
(xxii) C_{1-6} alkyl ester;
(xxiii) C_{1-6} alkyl acyl, optionally substituted by one or more halo groups; and
(xxiv) C_{1-6} alkyl amido;

R^{A4} is selected from the group consisting of:
(i) H;
(ii) halo;

(iii) CN;

(iv) C_{1-6} hydrocarbon, optionally substituted by one or more OH, CN, C_{1-6} alkyl acyl, C_{1-6} alkoxy or one or more halo groups;

(v) C_{1-6} alkoxy, optionally substituted by OH, one or more halo groups, C_{1-6} alkyl amido;

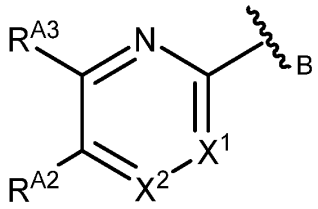
(vi) C_{1-6} alkyl ester;

(vii) C_{1-6} alkyl acyl;

(viii) OH; and

(ix) oxo.

B4. The compound of statement B1, or a pharmaceutically acceptable salt thereof, wherein (A1a) is of formula (A1):



(A1)

wherein the wavy line indicates the point of attachment to B;

X^1 is N or C-R^{A1};

X^2 is N or C-R^{A4};

R^{A1} is selected from the group consisting of:

(i) H;

(ii) halo;

(iii) CN;

(iv) C_{1-6} hydrocarbon, optionally substituted by OH, CN, C_{1-6} alkyl acyl, C_{1-6} alkoxy or one or more halo groups;

(v) C_{1-6} alkoxy, optionally substituted by OH, one or more halo groups, or C_{1-6} alkyl amido;

(vi) C_{1-6} alkyl ester;

(vii) C_{1-6} alkyl acyl; and

(viii) OH;

R^{A2} is selected from the group consisting of:

(i) H;

(ii) halo;

(iii) CN;

(iv) C_{1-6} hydrocarbon, optionally substituted by OH, CN, C_{1-6} alkyl acyl, C_{1-6} alkoxy or one or more halo groups;
(v) C_{1-6} alkoxy, optionally substituted by OH, C_{1-6} alkyl amido, or one or more halo groups;
(vi) C_{1-6} acylamido (wherein the acyl is optionally substituted by H or methyl);
(vii) C_{1-6} thioalkyl;
(viii) C_{1-6} alkyl ester;
(ix) C_{1-6} alkyl acyl;
(x) C_{4-5} heterocyclyl;
(xi) C_5 heteroaryl;
(xii) C_{1-6} alkyl amido, optionally substituted by C_{1-3} alkyl amido, CN, OH, C_{2-3} alkynyl, C_{4-6} heterocyclyl or C_{1-3} alkyl wherein the C_{1-3} alkyl is optionally substituted with one or more halo or OH groups;
(xiii) OH; and
(xiv) C_{1-6} alkylamino;

R^{A3} is selected from the group consisting of:
(i) H;
(ii) halo;
(iii) CN;
(iv) C_{1-6} hydrocarbon which is optionally substituted by OH, CN, C_{1-6} thioalkyl, C_{1-6} alkoxy, C_{1-6} alkyl acyl, C_{1-6} acyloxy, carboxy, C_{1-6} alkyl ester, C_{1-6} alkylamino, -C(=O)NH_2, C_{1-6} alkyl amido, C_{1-6} alkyl acylamido, C_{1-6} alkyl sulfinyl, C_{1-6} alkyl sulfonyl or one or more halo groups;
(v) OH;
(vi) C_{1-6} alkoxy, optionally substituted by OH, NH_2, C_4 heterocyclyl or one or more halo groups;
(vii) C_{1-6} acyloxy;
(viii) C_4 heterocycyl;
(ix) NH_2;
(x) C_{1-6} alkylamino, optionally substituted by CN, OH, or C_4 heterocyclyl;
(xi) C_{1-6} dialkylamino, optionally substituted by -NH_2;
(xii) C_{1-6} acylamido (where acyl substituent is H or Me);
(xiii) carbaimidoyl or methyl-carbaimidoyl;
(xiv) carboxyamino;
(xv) C_{1-6} thioalkyl, optionally substituted by OH or NH_2;
(xvi) C_{1-6} alkyl sulfinyl;
(xvii) C_{1-6} alkyl sulfonyl, optionally substituted by one or more halo groups;
(xviii) C_{1-6} sulfonimodyl;
(xix) C_{1-6} alkyl phosphinyl;

(xx) carboxy;
(xxi) $C(=O)NH_2$;
(xxii) C_{1-6} alkyl ester;
(xxiii) C_{1-6} alkyl acyl, optionally substituted by one or more halo groups; and
(xxiv) C_{1-6} alkyl amido;

R^{A4} is selected from the group consisting of:
(i) H;
(ii) halo;
(iii) CN;
(iv) C_{1-6} hydrocarbon, optionally substituted by one or more OH, CN, C_{1-6} alkyl acyl, C_{1-6} alkoxy or one or more halo groups;
(v) C_{1-6} alkoxy, optionally substituted by OH, one or more halo groups, C_{1-6} alkyl amido;
(vi) C_{1-6} alkyl ester;
(vii) C_{1-6} alkyl acyl; and
(viii) OH;

B5. The compound of any one of statements B1-B4, or a pharmaceutically acceptable salt thereof, wherein X^1 is N and X^2 is N.

B6. The compound of any one of statements B1-B4, or a pharmaceutically acceptable salt thereof, wherein X^1 is N, X^2 is C-R^{A4}, and X^3 is C-R^{A2}.

B7. The compound of any one of the preceding statements, or a pharmaceutically acceptable salt thereof, wherein R^{A4} is H, R^{A2} is C_{1-6} alkoxy, optionally substituted by OH, C_{1-6} alkyl amido, or one or more halo groups and R^{A3} is H.

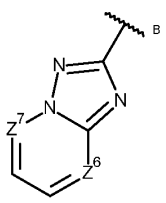
B8. The compound of any one of statements B1 to B6 or a pharmaceutically acceptable salt thereof, wherein R^{A2} is selected from H, chloro, methyl, trifluoromethyl, cyclopropyl and OCF_2H.

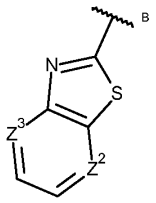
B9. The compound of statement B8, or a pharmaceutically acceptable salt thereof, wherein R^{A2} is methyl or OCF_2H.

B10. The compound of any one of statements B1 to B6, B8, or B9 or a pharmaceutically acceptable salt thereof, wherein R^{A3} is selected from the group consisting of H, methyl and OH.

B11. The compound of statement B10, or a pharmaceutically acceptable salt thereof, wherein R^{A3} is H.

B12. The compound of any one of statements B1 to B3 or a pharmaceutically acceptable salt thereof, wherein A is according to the formula:

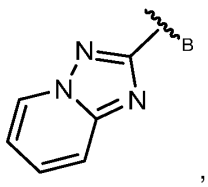


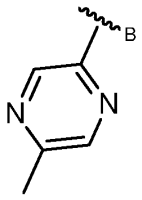
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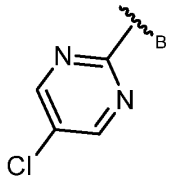
wherein the wavy line indicates the point of attachment to B and Z^2, Z^3, Z^6 and Z^7 are as defined in statement 1.

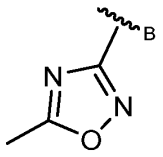
B13. The compound of statement B1, or a pharmaceutically acceptable salt thereof, wherein A is of formula (A2b).

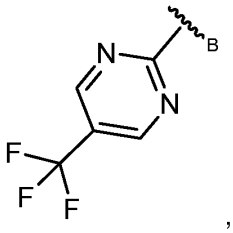
B14. The compound according to statement B1, or a pharmaceutically acceptable salt thereof, wherein A is selected from one of the following formulae:

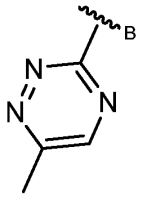


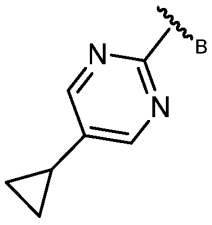
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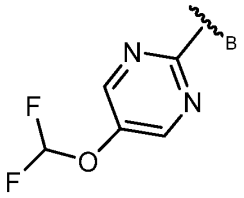
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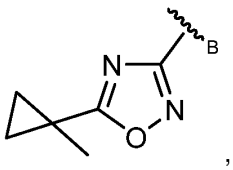
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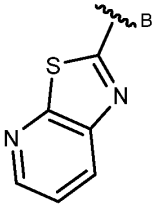
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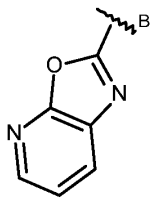
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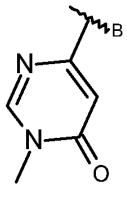
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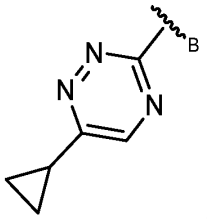
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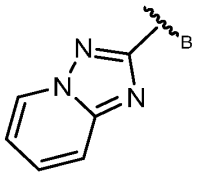
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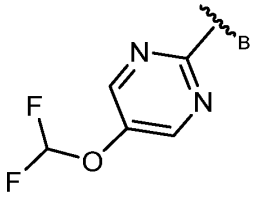


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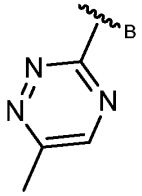
B15. The compound according to statement B1, or a pharmaceutically acceptable salt thereof, wherein A is selected from one of the following formulae:



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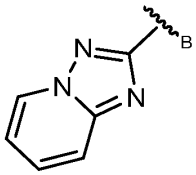


, and



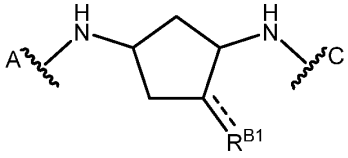
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B16. The compound according to statement B1, or a pharmaceutically acceptable salt thereof, wherein A is:



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B17. The compound of any one of the preceding statements or a pharmaceutically acceptable salt thereof, wherein B is of formula (B-1)

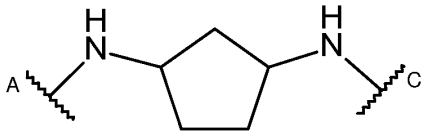


(B-1)

wherein the wavy lines indicate the point of attachment to A and C;

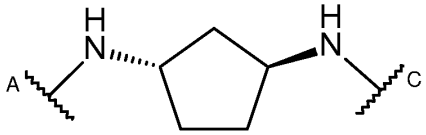
wherein R^{B1} is selected from the group consisting of H, OH, OMe, -O-ethyl, $-CH_2OH$, $-CH_2CH_2OH$ and $=CHCH_2-OH$.

B18. The compound of any one of the preceding statements or a pharmaceutically acceptable salt thereof, wherein B is of the following formula (B-1a):



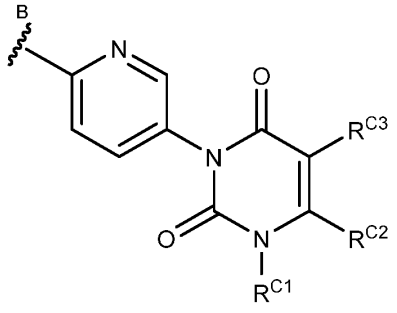
(B-1a).

B19 The compound of any one of the preceding statements or a pharmaceutically acceptable salt thereof, wherein B is of the following formula (B-1b):



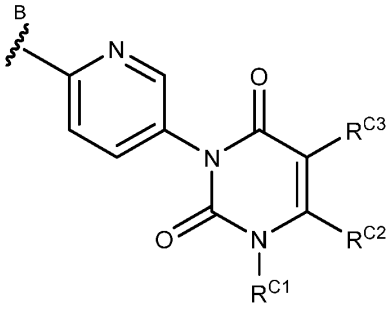
(B-1b).

B20.The compound according to any one of the preceding statements, or a pharmaceutically acceptable salt thereof, wherein C is of formula (C-1):



(C-1).

B21. The compound according to any one of statements B1-B19, or a pharmaceutically acceptable salt thereof, wherein C is of formula:



(C-1)

R^{C2} and R^{C3} together represent a fused benzene ring or C_{5-6} heteroaromatic ring, which rings are optionally substituted by one or more R^{C4} groups;

R^{C1} is selected from:
(i) H;
(ii) C_{1-6} alkyl optionally substituted by one or more halo groups;
(iii) C_{5-6} heterocyclyl or C_{5-6}heteroaryl with an optional methyl substituent;
(iv) phenyl optionally substituted by one or more halo atoms;

R^{C4} is selected from:
(i) C_{1-6} alkyl optionally substituted by one or more halo groups;
(ii) C_{1-6} alkoxy optionally substituted by one or more halo groups;
(iii) C_{5-6} heterocyclyl or C_{5-6}heteroaryl with an optional methyl substituent;
(iv) di-C_{1-6} alkyl amido;
(v) C_{1-6} acylamido;
(vi) halo; and
(vii) CN.

B22. The compound according to any one of statements B1-B19, or a pharmaceutically acceptable salt thereof, wherein C is of formula (C-1a).

B23. The compound according to any one of statements B1-B19, or a pharmaceutically acceptable salt thereof, wherein C is of formula (C-1b).

B24. The compound according to any one of statements B1-B23, or a pharmaceutically acceptable salt thereof, wherein R^{C1} is C_{1-6} alkyl optionally substituted by one or more halo groups.

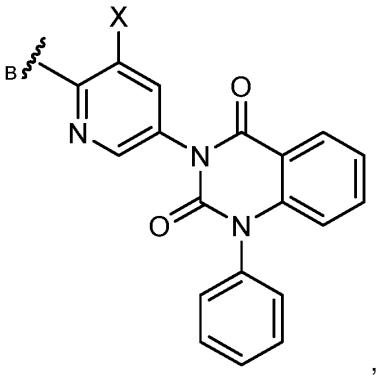
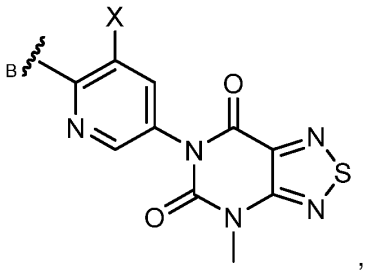
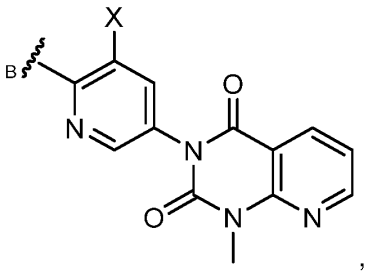
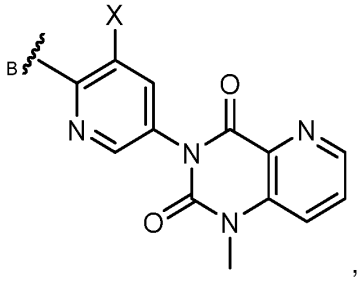
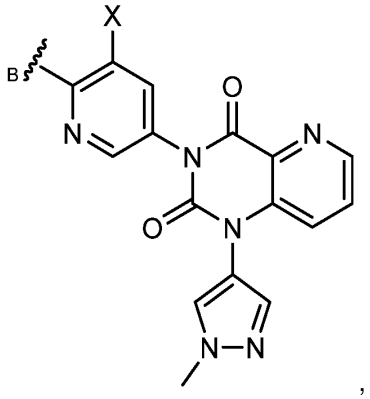
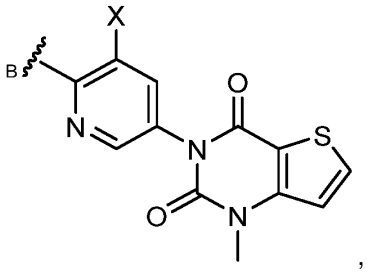
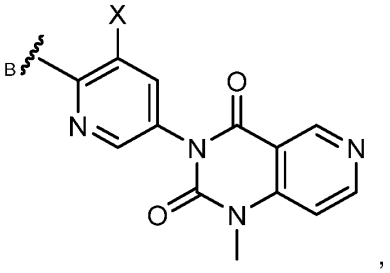
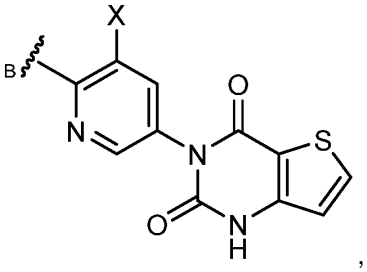
B25. The compound according to any one of statements B1-B24, or a pharmaceutically acceptable salt thereof, wherein R^{C1} is methyl.

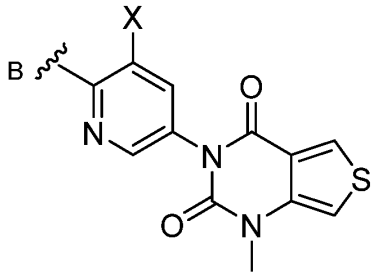
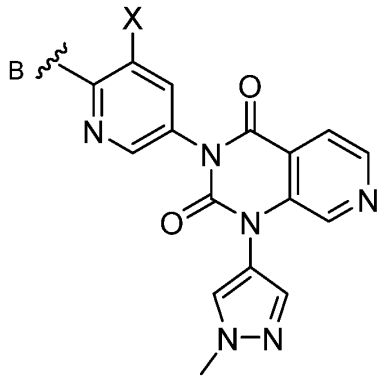
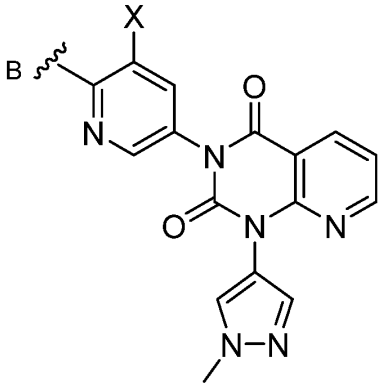
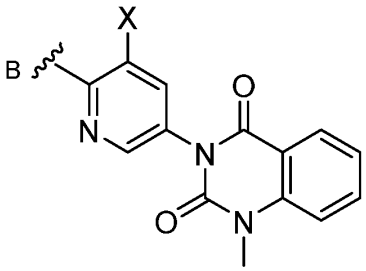
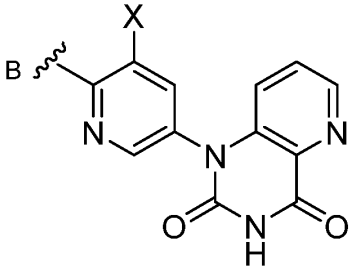
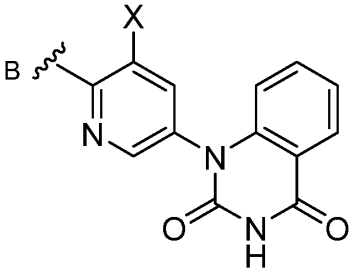
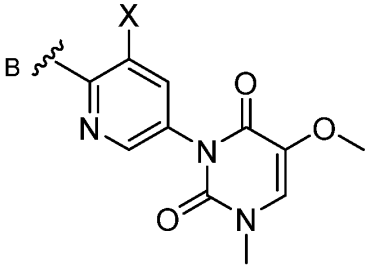
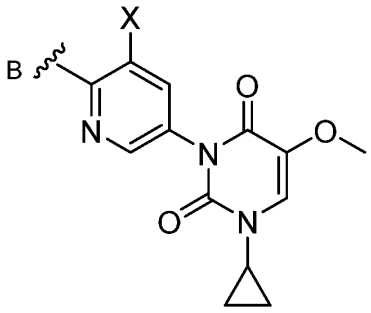
B26 The compound according to any one of statements B1-B25, or a pharmaceutically acceptable salt thereof, wherein R^{C3} is methoxy and R^{C2} is hydrogen.

B27. The compound according to any one of statements B1-B25, or a pharmaceutically acceptable salt thereof, wherein R^{C2} and R^{C3} together represent a fused C_6 heteroaromatic ring optionally substituted by one or more R^{C4} groups.

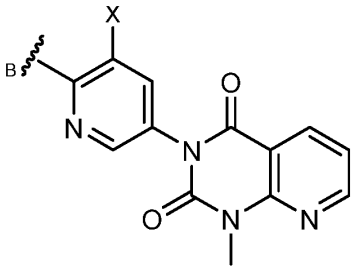
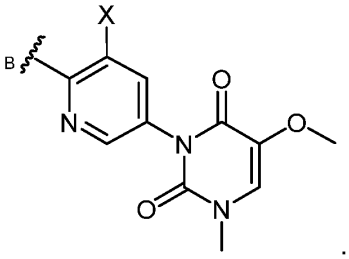
B28. The compound according to statement B27, or a pharmaceutically acceptable salt thereof, wherein R^{C2} and R^{C3} together represent a fused unsubstituted C_6 heteroaromatic ring.

B29. The compound according to any one of statements B1-B19, or a pharmaceutically acceptable salt thereof, wherein C is selected from one of the following formulae;

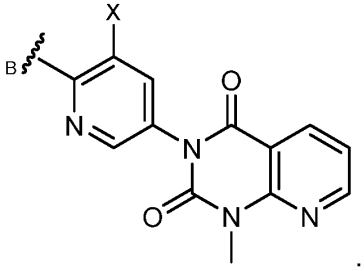

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and

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B30. The compound according to any one of statements B1 to B19, or a pharmaceutically acceptable salt thereof, wherein C is selected from one of the following formulae:


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B31. The compound according to any one of statements B1 to B19, or a pharmaceutically acceptable salt thereof, wherein C is:

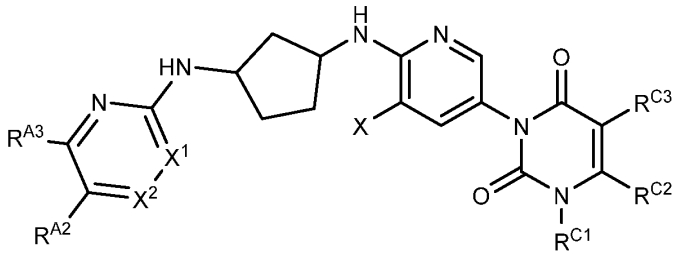

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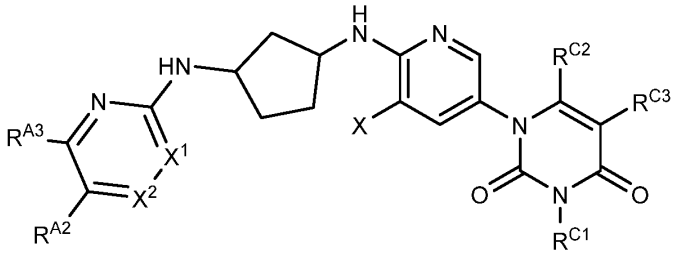
B32. The compound of statement B1 or a pharmaceutically acceptable salt thereof, wherein A-B-C is of the formula (I-Ax), (I-Ay), (I-Bx), (I-By), (I-Bax), (I-Bay), (I-Bbx), (I-Bby), (I-Cx), (I-Cax), (I-Cbx), (I-Ccx), (I-Cdx), (I-Cdy), (I-Cex), (I-Dx), (I-Dax), (I-Dbx), (I-Eax), (I-Ebx), (I-Ebx), (I-Eby), (I-Ec), (I-Fax), (I-Fbx), (I-Fay) or (I-Fby);

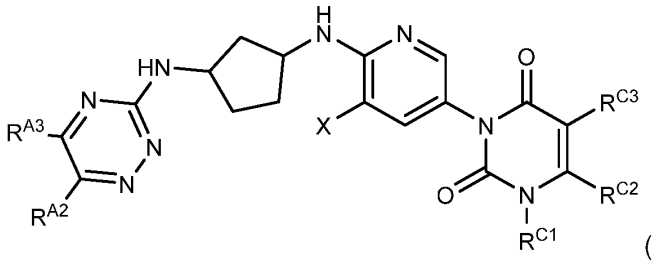
wherein none, one or two of Q_1, Q_2, Q_3 and Q_4 is N and the remainder are C-H;

wherein none, one or two of Q_5, Q_6 and Q_7 is N, none or one of Q_5, Q_6 and Q_7 is S and the remainder are C-H; and

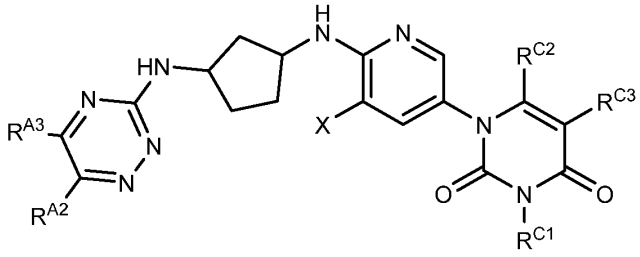
wherein all other definitions are according to statement 1;


(I-Ax),

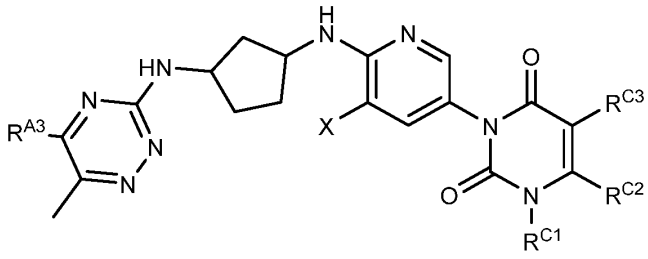

(I-Ay),



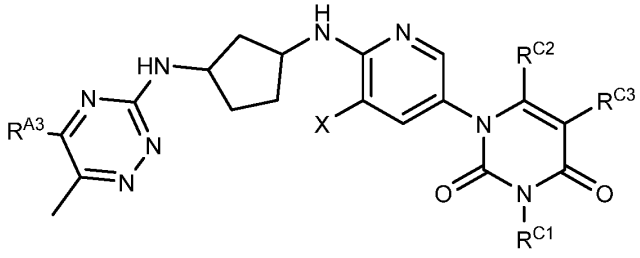
(I-Bx),



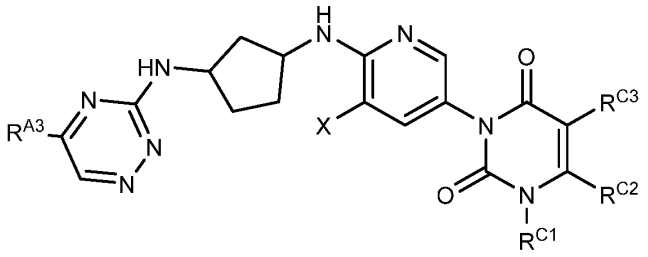
(I-By),



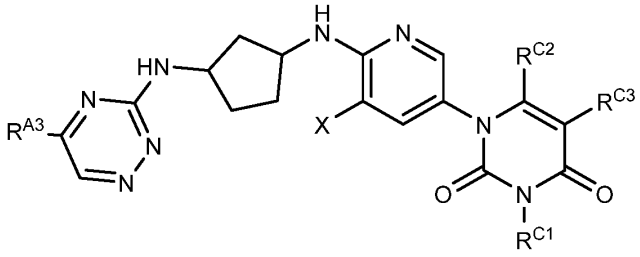
(I-Bax),



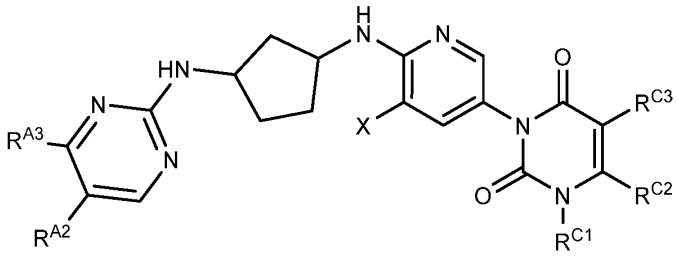
(I-Bay),



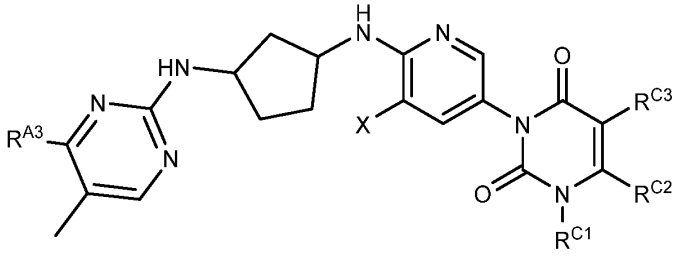
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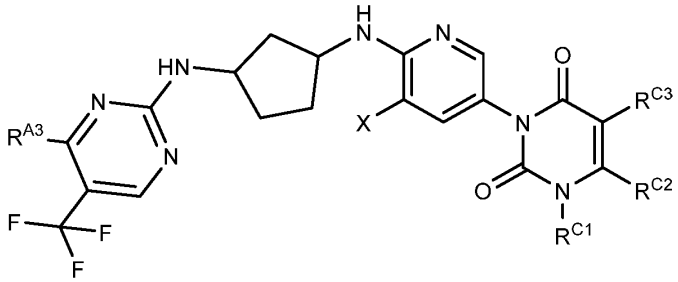
(I-Bby),



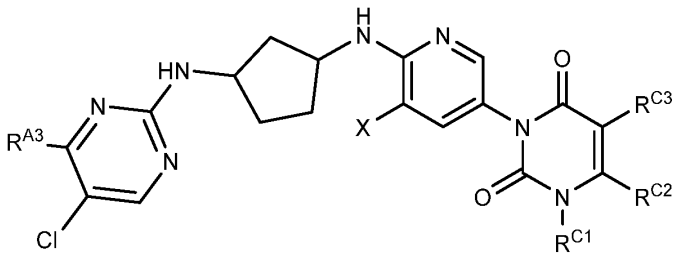
(I-Cx),



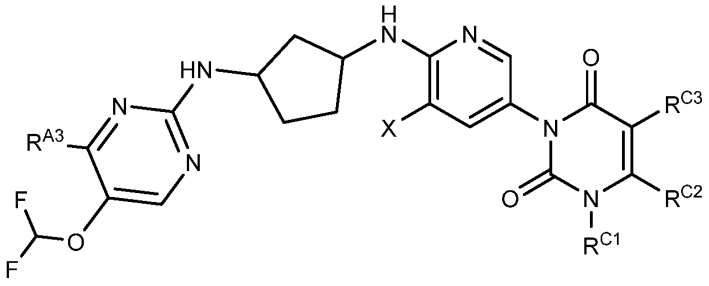
(I-Cax),



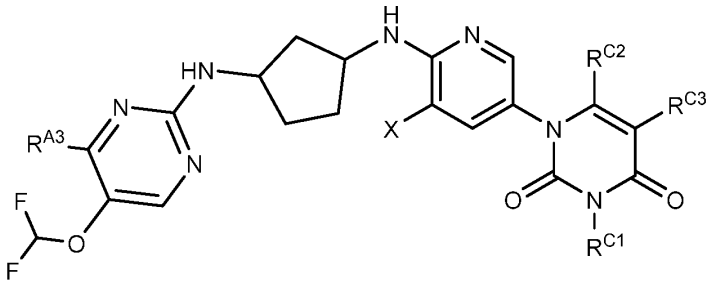
(I-Cbx),



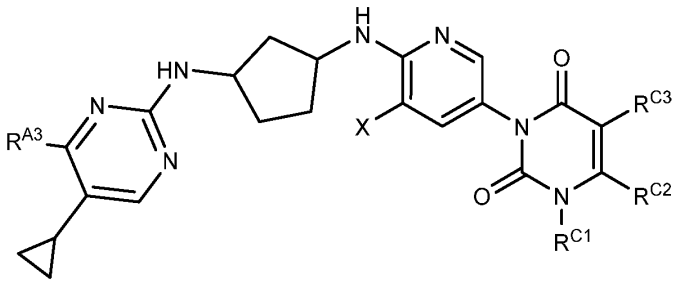
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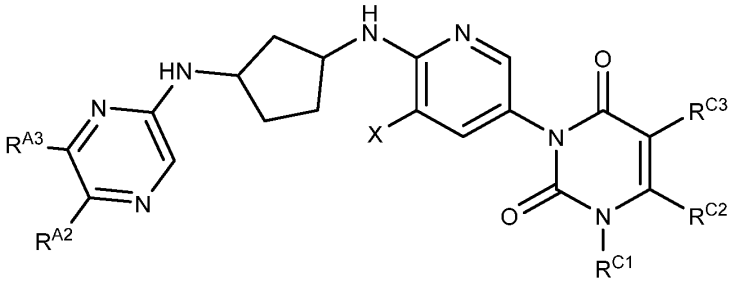
(I-Cdx),



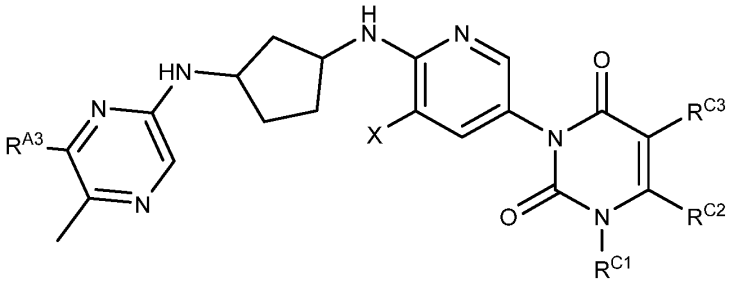
(I-Cdy),



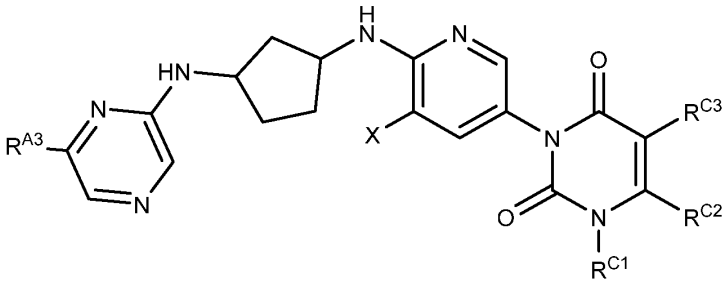
(I-Cex).



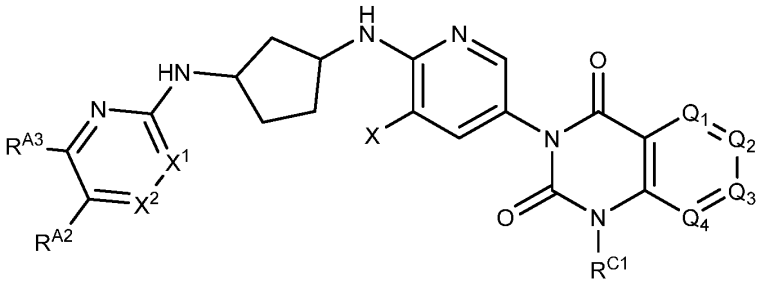
(I-Dx),



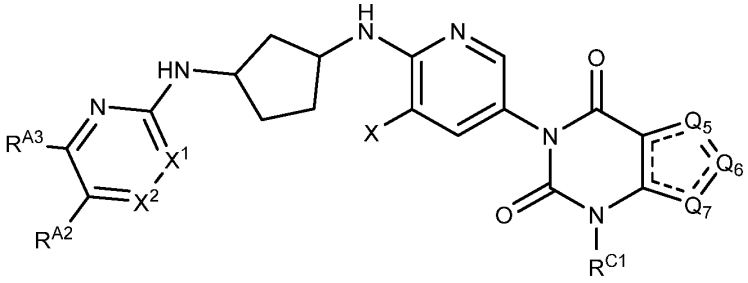
(I-Dax),



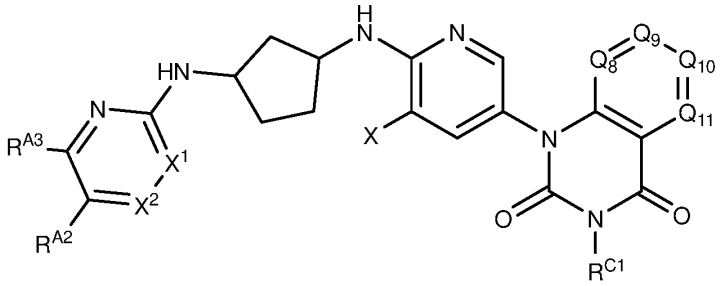
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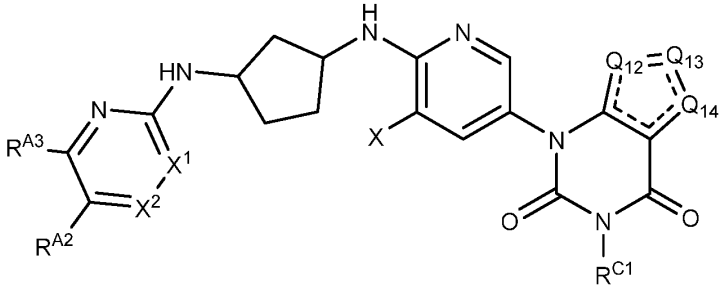
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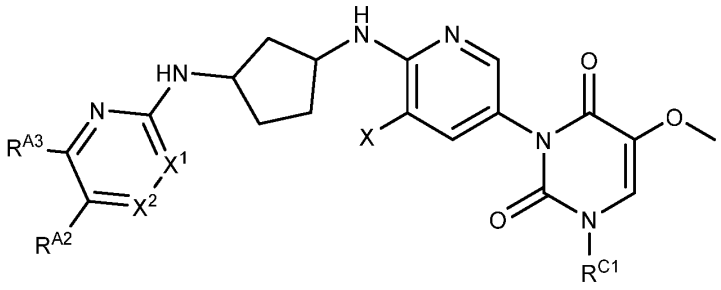
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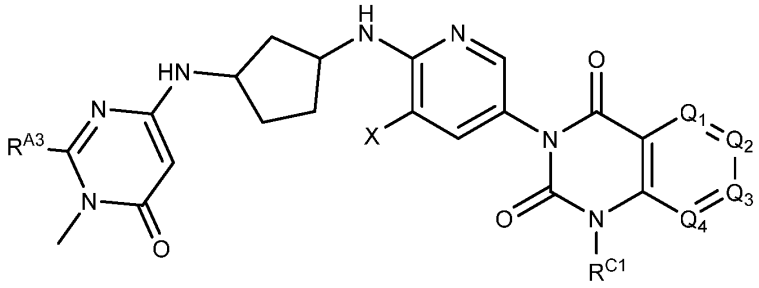
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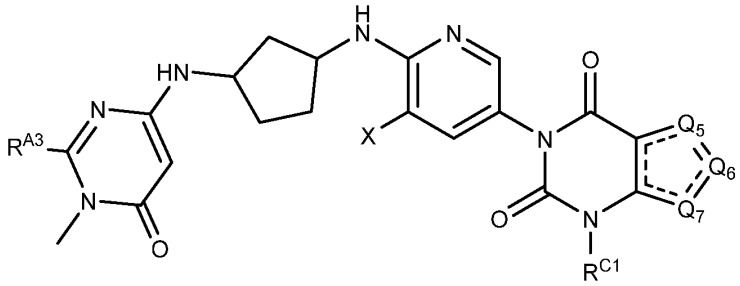
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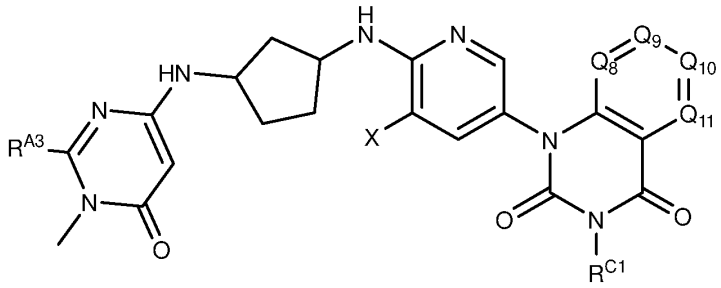
(I-Ec),



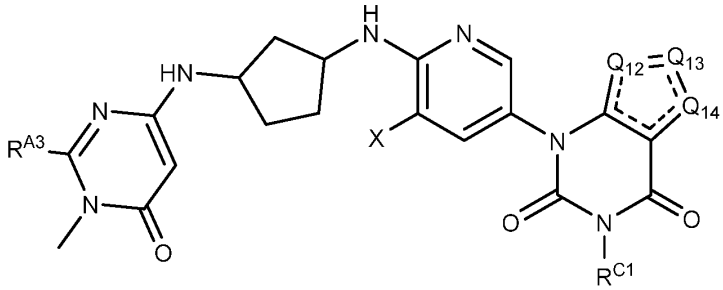
(I-Fax),



(I-Fbx),



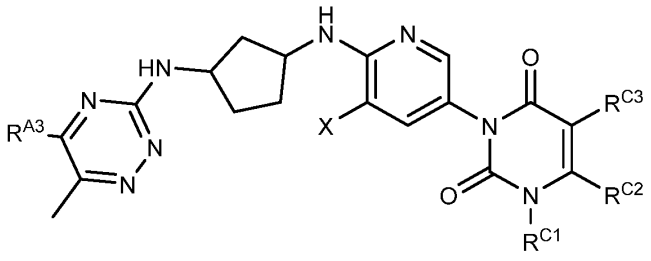
(I-Fay),



(I-Fby).

B33. The compound of statement B1 or B32, or a pharmaceutically acceptable salt thereof, wherein A-B-C is of the formula (I-Ax) or (I-Ay).

B34. The compound of statement B32, or a pharmaceutically acceptable salt thereof, wherein A-B-C is of the formula (I-Bax):



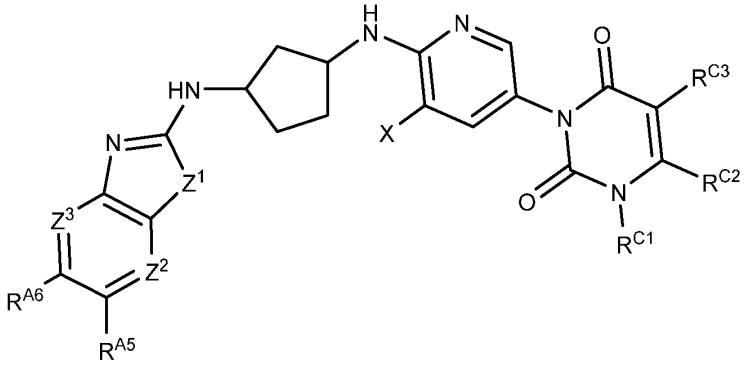
(I-Bax).

B35. The compound of statement B1 or a pharmaceutically acceptable salt thereof, wherein A-B-C is of the formula (II-Ax), (II-A1x), (II-A2x), (II-A3x), (II-Bax) (II-Bbx), (II-Bc);

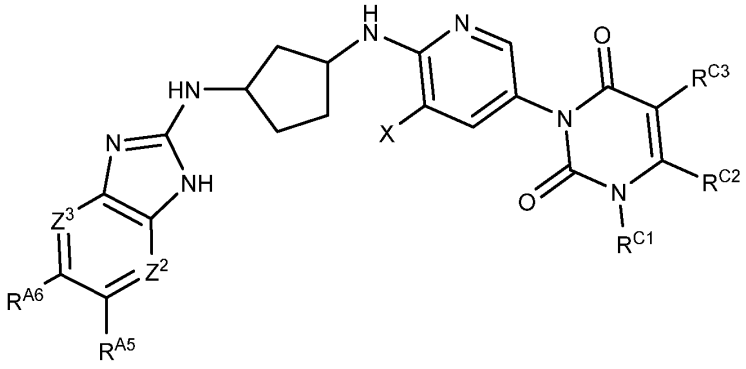
wherein none, one or two of Q_1, Q_2, Q_3 and Q_4 is N and the remainder are C-H;

wherein none, one or two of Q_5, Q_6 and Q_7 is N, none or one of Q_5, Q_6 and Q_7 is S and the remainder are C-H; and

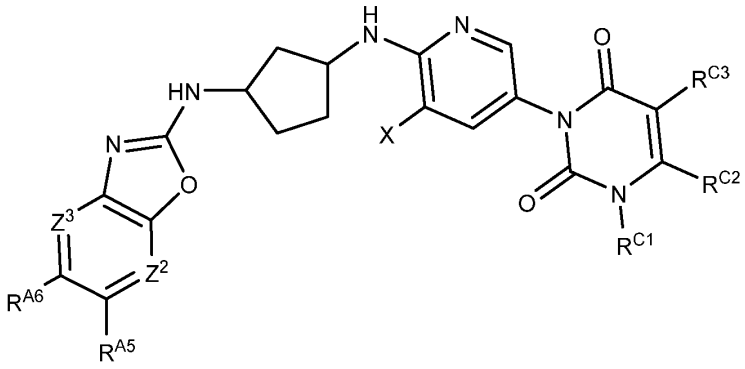
wherein all other definitions are according to statement B1;



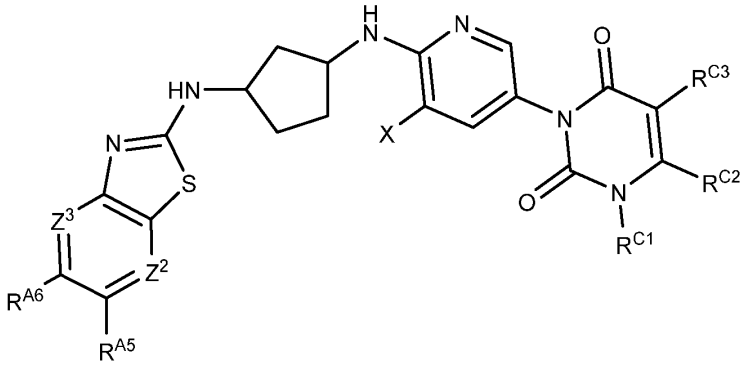
(II-Ax),



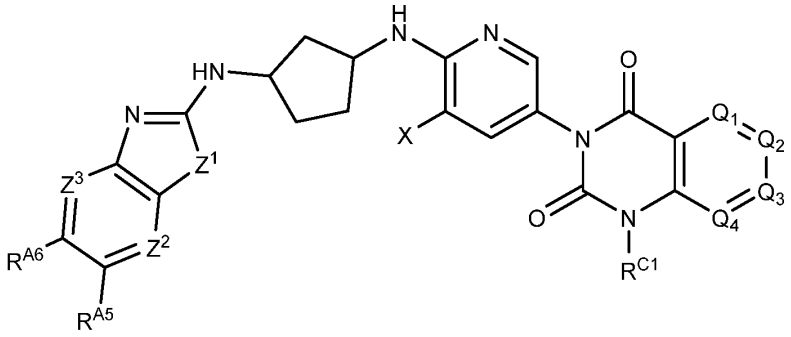
(II-A1x),



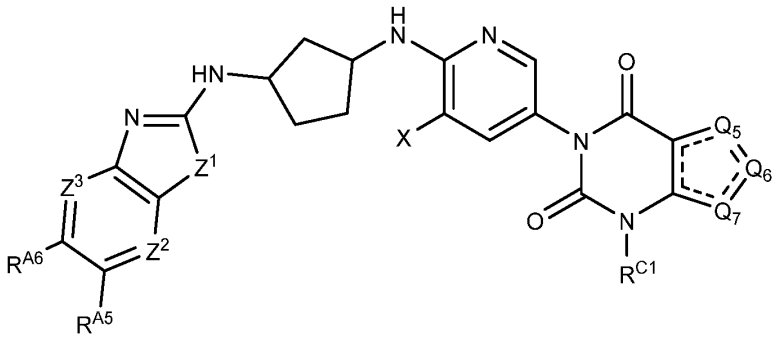
(II-A2x),



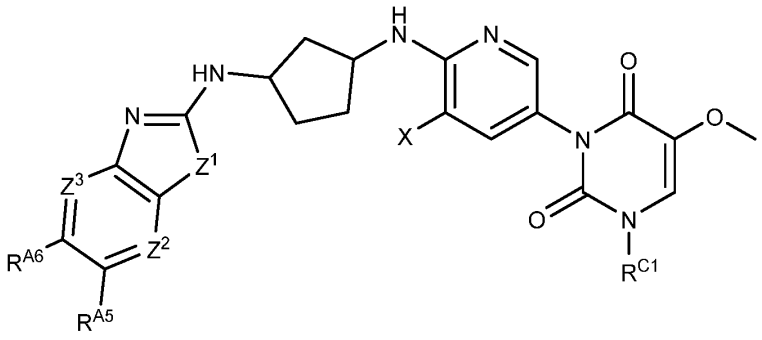
(II-A3x),



(II-Bax),,



(II-Bbx),



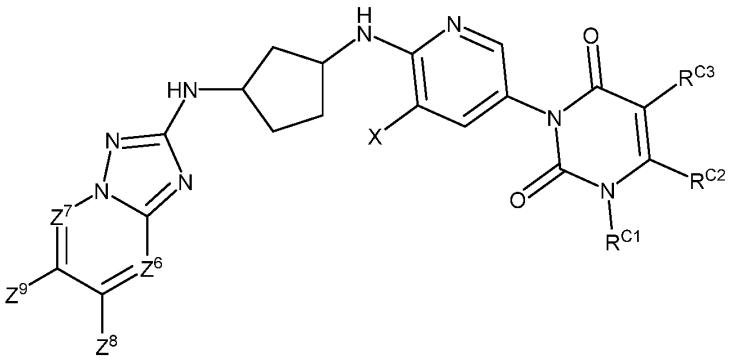
(II-Bc).

B36. The compound of statement B1 or a pharmaceutically acceptable salt thereof, wherein A-B-C is of the formula (III-Ax), (III-Bax), (III-Bbx), (III-Cax), (III-Cbx), or (III-Cc);

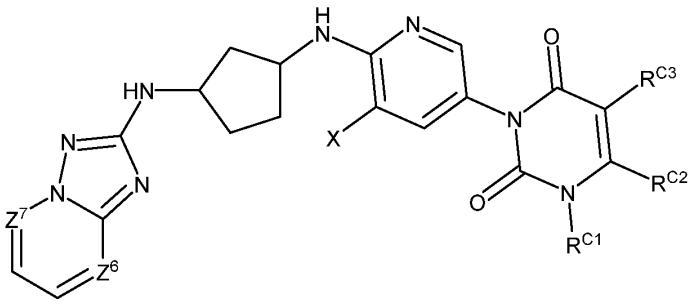
wherein none, one or two of Q_1, Q_2, Q_3 and Q_4 is N and the remainder are C-H;

wherein none, one or two of Q_5, Q_6 and Q_7 is N, none or one of Q_5, Q_6 and Q_7 is S and the remainder are C-H; and

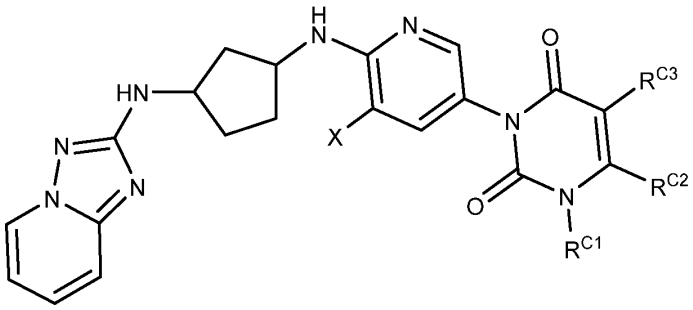
wherein all other definitions are according to statement B1;



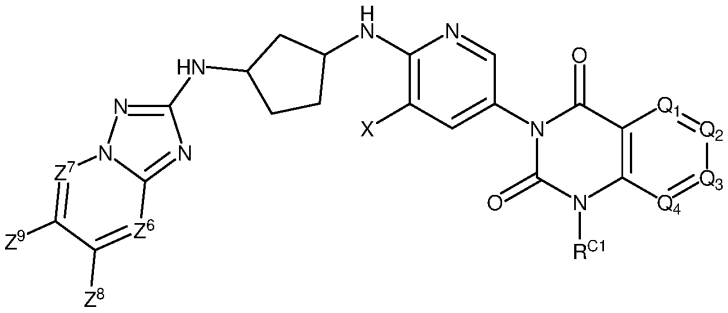
(III-Ax),



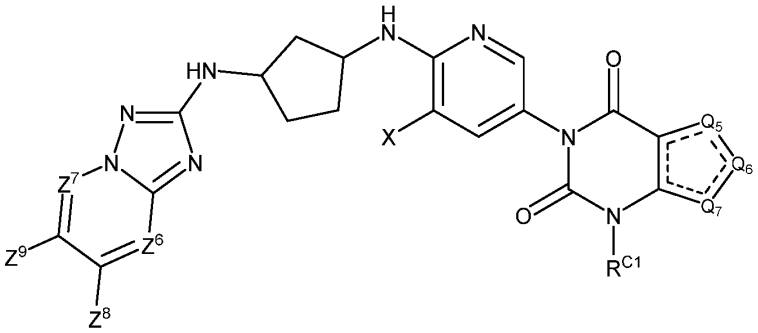
(III-Bax),



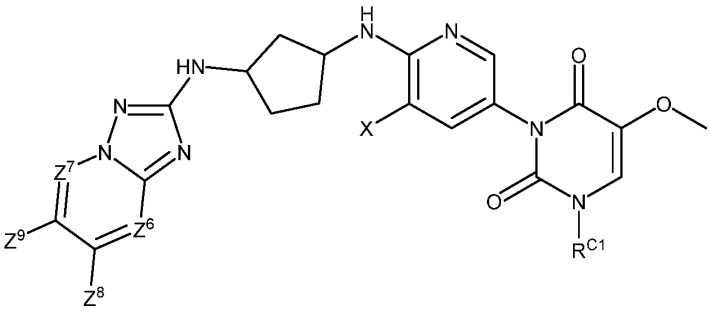
(III-Bbx),



(III-Cax),

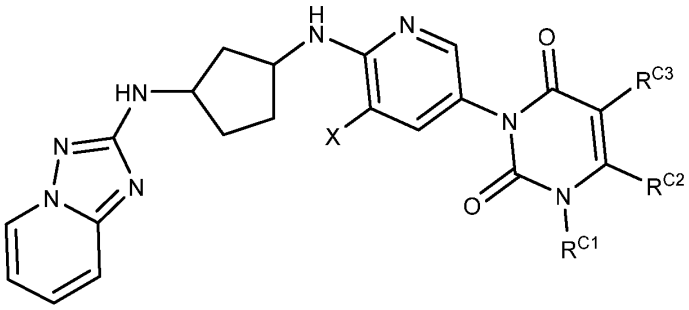


(III-Cbx), and



(III-Cc).

B37. The compound of statement B36, or a pharmaceutically acceptable salt thereof, wherein A-B-C is of the formula (III-Bbx):



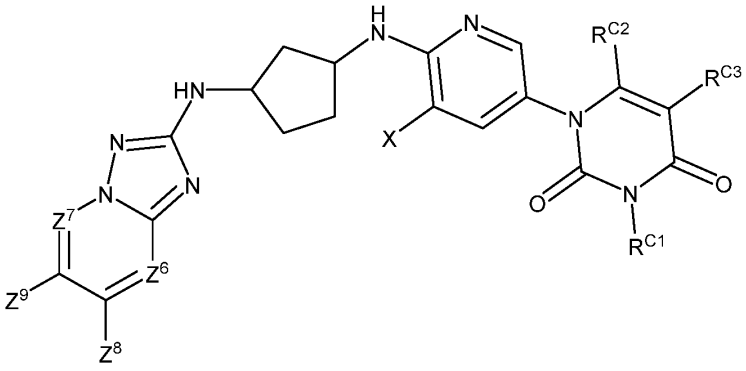
(III-Bbx).

B38. The compound of statement B1, or a pharmaceutically acceptable salt thereof, wherein A-B-C is of the formula (III-Ay), (III-Bay) or (III-Bby), (III-Cay) or (III-Cby);

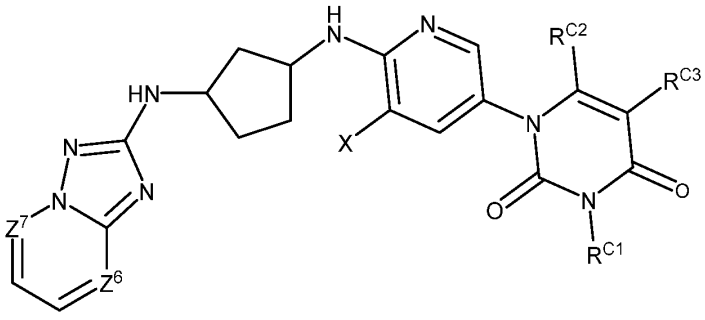
wherein none, one or two of Q_8, Q_9, Q_{10} and Q_{11} is N and the remainder are C-H;

wherein none, one or two of Q_{12}, Q_{13} and Q_{14} is N, none or one of Q_{12}, Q_{13} and Q_{14} is S and the remainder are C-H; and

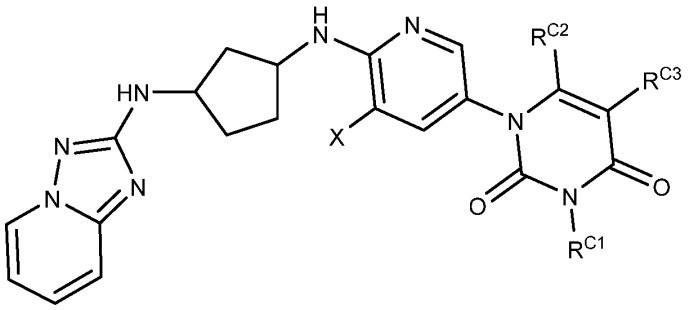
wherein all other definitions are according to statement B1;



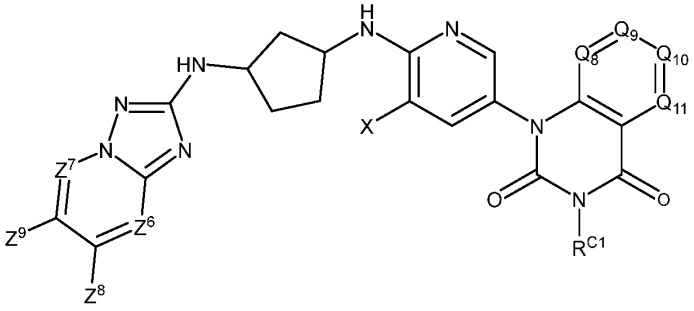
(III-Ay),



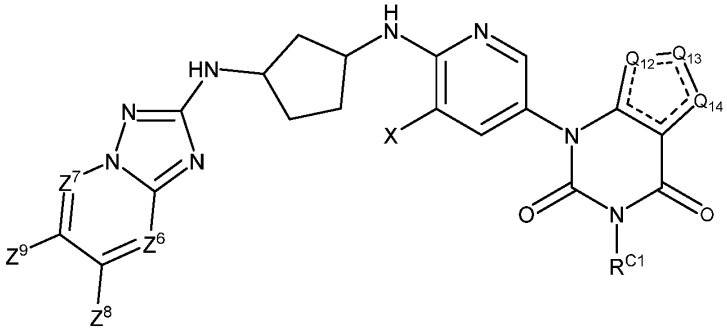
(III-Bay),



(III-Bby),



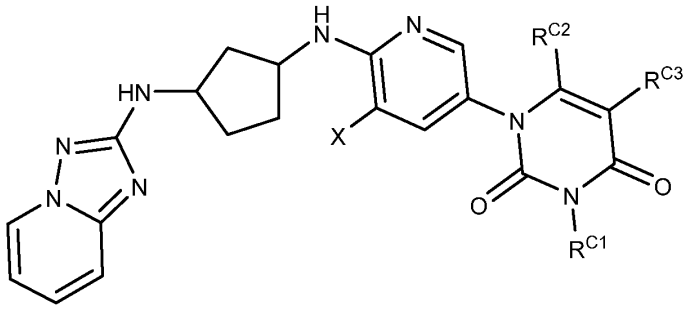
(III-Cay), and



(III-Cby).

B39. The compound of statement B1, or a pharmaceutically acceptable salt thereof, wherein A-B-C is of the formula (III-Ax) or (III-Ay).

B40. The compound of statement B38, or a pharmaceutically acceptable salt thereof, wherein A-B-C is of the formula (III-Bby):



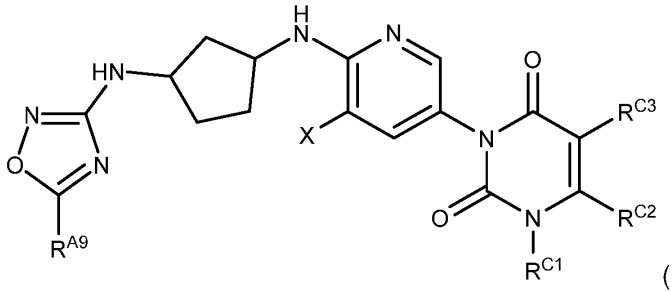
(III-Bby).

B41. The compound of statement B1 or a pharmaceutically acceptable salt thereof, wherein A-B-C is of the formula (IV-Ax), (IV-Aax), (IV-Abx), (IV-Bax), (IV-Bbx) or (IV-Bc);

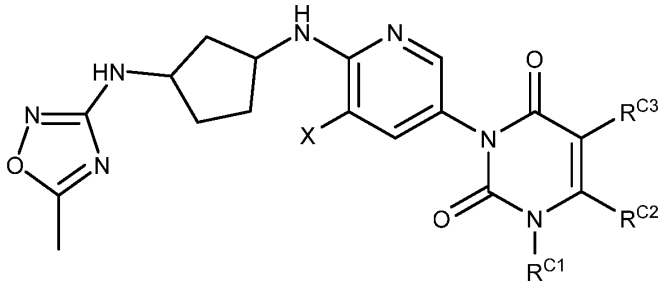
wherein none, one or two of Q_1, Q_2, Q_3 and Q_4 is N and the remainder are C-H;

wherein none, one or two of Q_5, Q_6 and Q_7 is N, none or one of Q_5, Q_6 and Q_7 is S and the remainder are C-H; and

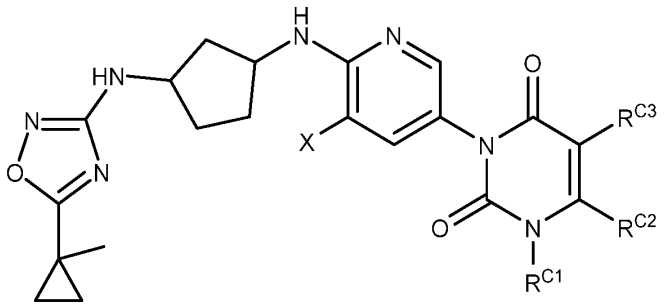
wherein all other definitions are according to statement B1;



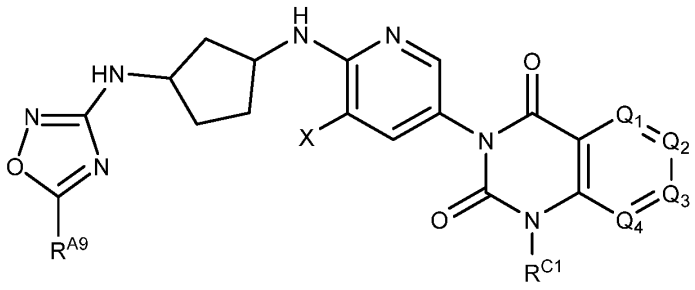
(IV-Ax),



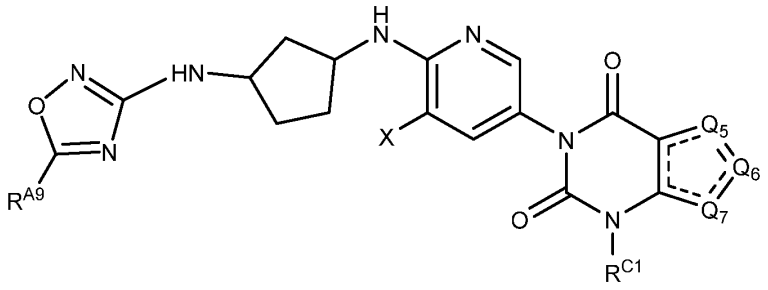
(IV-Aax),



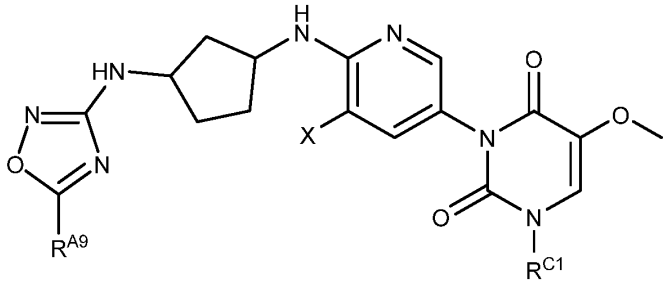
(IV-Abx),



(IV-Bax),

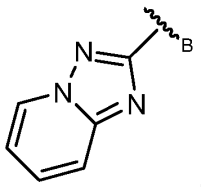
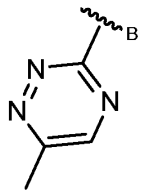
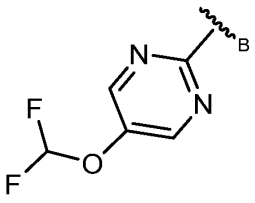


(IV-Bbx),

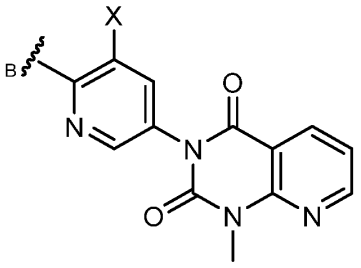
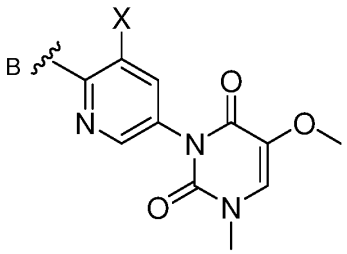


(IV-Bc).

B42. The compound or a pharmaceutically acceptable salt thereof according to statement B1, wherein A is selected from one of:


,

,
and

.

and C is selected from one of:

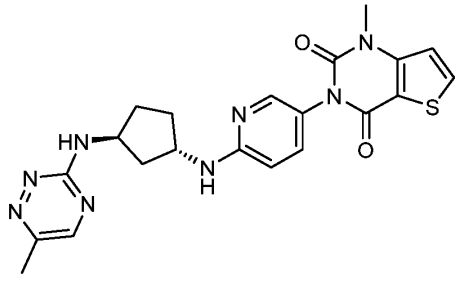

and

.

B43. The compound of any one of statements B1-B42, or a pharmaceutically acceptable salt thereof, wherein X is H.

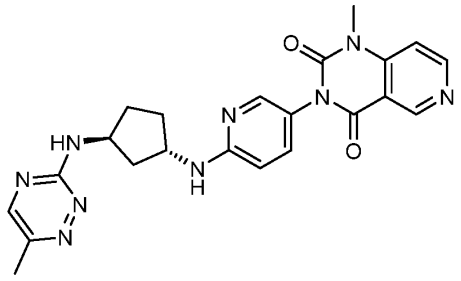
B44. The compound of any one of statements B1-B42, or a pharmaceutically acceptable salt thereof, wherein X is F.

B45. The compound of statement B1, wherein the compound is selected from the compounds listed in Table 1 or Table 2, or a pharmaceutically acceptable salt thereof.

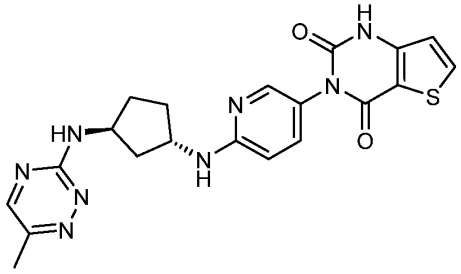
B46. The compound of statement B1, wherein the compound is selected from one of the following compounds, or a pharmaceutically acceptable salt thereof:

1 

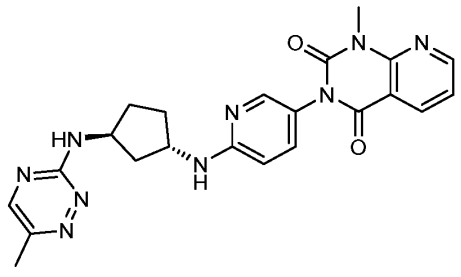
1-Methyl-3-(6-(((1*S*,3*S*)-3-((6-methyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)thieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione,

2 

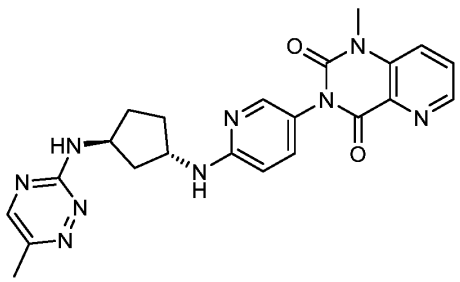
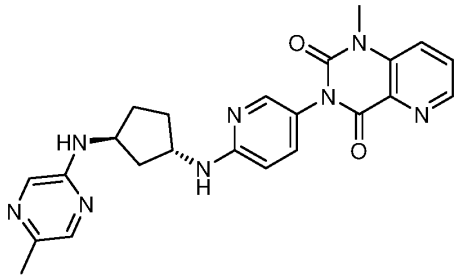
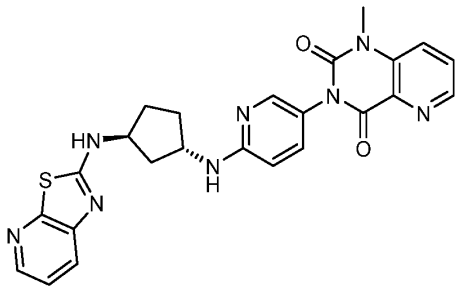
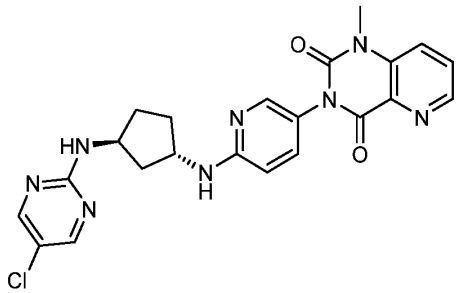
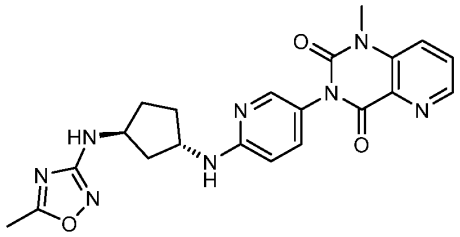
1-Methyl-3-(6-(((1*S*,3*S*)-3-((6-methyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyrido[4,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione,

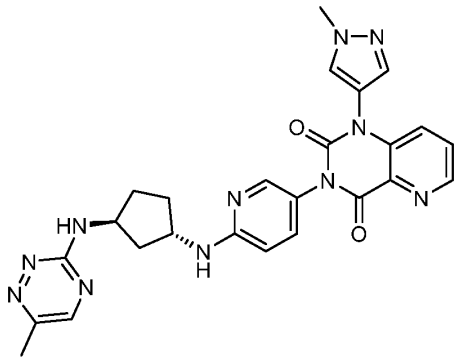
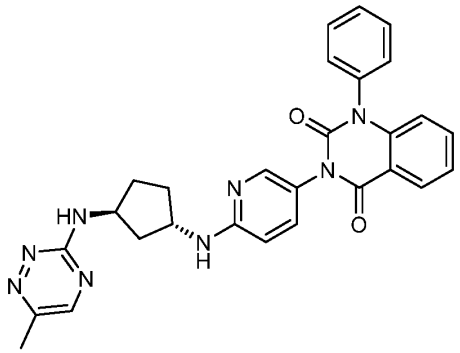
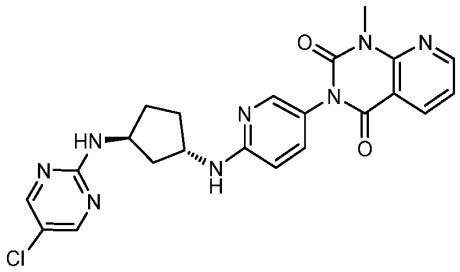
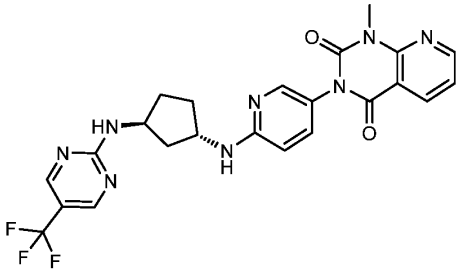
3 

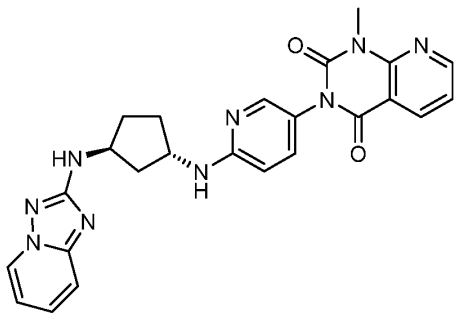
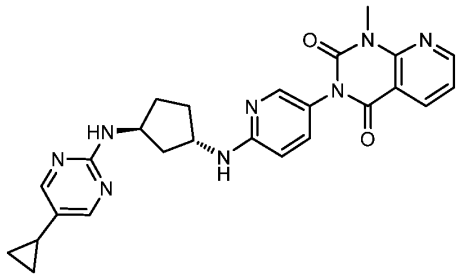
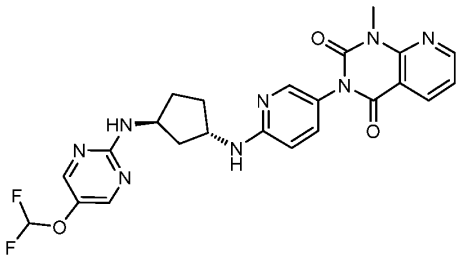
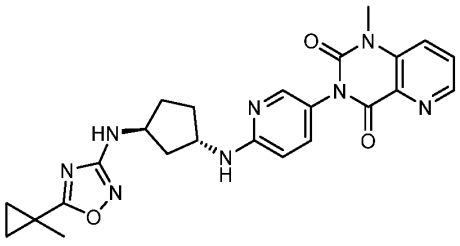
3-(6-(((1*S*,3*S*)-3-((6-Methyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)thieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione,

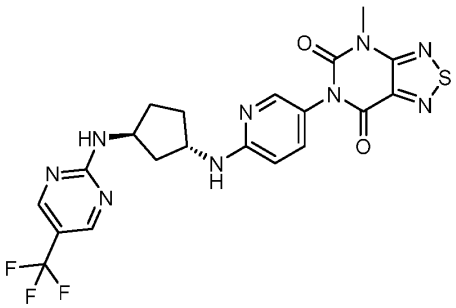
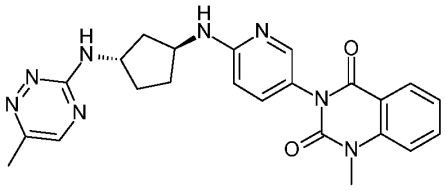
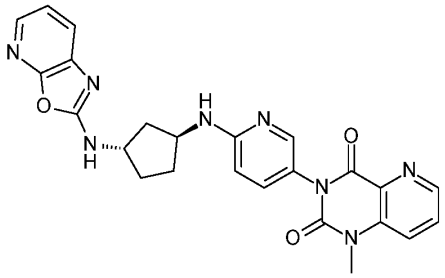
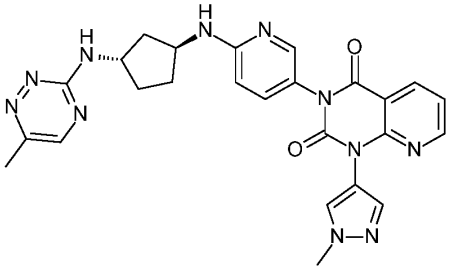
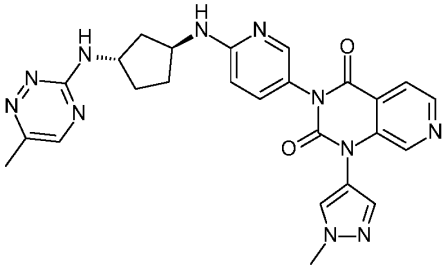
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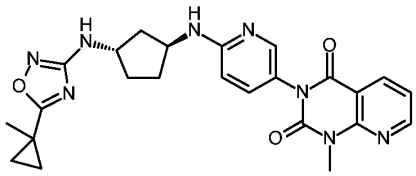
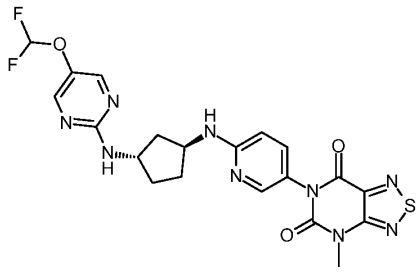
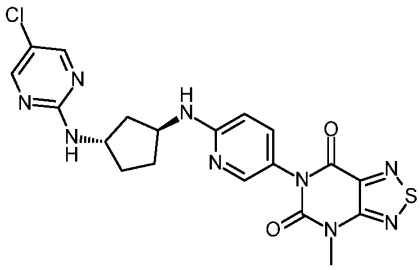
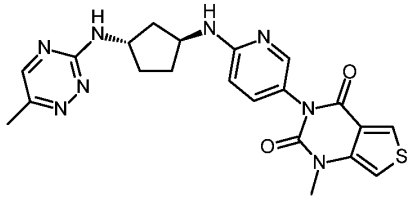
1-Methyl-3-(6-(((1*S*,3*S*)-3-((6-methyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione,

5		1-Methyl-3-(6-(((1*S*,3*S*)-3-((6-methyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione,
6		1-Methyl-3-(6-(((1*S*,3*S*)-3-((5-methylpyrazin-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione,
7		1-Methyl-3-(6-(((1*S*,3*S*)-3-(thiazolo[5,4-*b*]pyridin-2-ylamino)cyclopentyl)amino)pyridin-3-yl)pyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione,
8		3-(6-(((1*S*,3*S*)-3-((5-Chloropyrimidin-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)-1-methylpyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione,
9		1-Methyl-3-(6-(((1*S*,3*S*)-3-((5-methyl-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione,

10		3-(6-(((1*S*,3*S*)-3-((6-Methyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)-1-(1-methyl-1*H*-pyrazol-4-yl)pyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione,
11		3-(6-(((1*S*,3*S*)-3-((6-Methyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)-1-phenylquinazoline-2,4(1*H*,3*H*)-dione,
12		3-(6-(((1*S*,3*S*)-3-((5-Chloropyrimidin-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)-1-methylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione,
13		1-Methyl-3-(6-(((1*S*,3*S*)-3-((5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione,

14		3-(6-(((1*S*,3*S*)-3-([1,2,4]Triazolo[1,5-*a*]pyridin-2-ylamino)cyclopentyl)amino)pyridin-3-yl)-1-methylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione,
15		3-(6-(((1*S*,3*S*)-3-((5-Cyclopropylpyrimidin-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)-1-methylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione,
16		3-(6-(((1*S*,3*S*)-3-((5-(Difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)-1-methylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione,
17		1-Methyl-3-(6-(((1*S*,3*S*)-3-((5-(1-methylcyclopropyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione,

18		4-Methyl-6-(6-(((1*S*,3*S*)-3-((5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)-[1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione,
19		1-Methyl-3-(6-(((1*S*,3*S*)-3-((6-methyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)quinazoline-2,4(1*H*,3*H*)-dione,
20		1-Methyl-3-(6-(((1*S*,3*S*)-3-(oxazolo[5,4-*b*]pyridin-2-ylamino)cyclopentyl)amino)pyridin-3-yl)pyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione,
22		3-(6-(((1*S*,3*S*)-3-((6-Methyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)-1-(1-methyl-1*H*-pyrazol-4-yl)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione,
23		3-(6-(((1*S*,3*S*)-3-((6-Methyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)-1-(1-methyl-1*H*-pyrazol-4-yl)pyrido[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione,

24		1-Methyl-3-(6-(((1*S*,3*S*)-3-((5-(1-methylcyclopropyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione,
25		6-(6-(((1*S*,3*S*)-3-((5-(Difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)-4-methyl-[1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione,
26		6-(6-(((1*S*,3*S*)-3-((5-Chloropyrimidin-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)-4-methyl-[1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione,
28		1-Methyl-3-(6-(((1*S*,3*S*)-3-((6-methyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)thieno[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione.

or a pharmaceutically acceptable salt thereof.

B47. The compound or pharmaceutically acceptable salt thereof of statement B1, wherein the compound is selected from the compounds listed Table 1, or a pharmaceutically acceptable salt thereof.

B48. The compound of any one of the preceding statements or a pharmaceutically acceptable salt thereof, for use in therapy.

B49. A pharmaceutical composition comprising the compound of any one of statements B1-B47 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent, carrier or excipient.

B50. The compound of any one of statements B1-B47or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to the preceding pharmaceutical composition statement, for use in the treatment of a cardiovascular disease.

B51. The compound or pharmaceutically acceptable salt thereof, for use according to statement B50 wherein the treatment comprises the separate, sequential or simultaneous administration of i) the compound of Formula (I) or a pharmaceutically acceptable salt thereof, and ii) at least one additional active ingredient to a subject in need thereof.

B52. The compound or pharmaceutically acceptable salt thereof for use according to statement B50 or B51, wherein the treatment comprises administering to a subject in need thereof, a first amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof and a second amount of at least one additional active ingredient, wherein the first amount and the second amount together comprise a therapeutically effective amount.

B53. The compound or pharmaceutically acceptable salt thereof for use according to statement B51, wherein the at least one additional active ingredient may be selected from (a) a statin or pharmaceutically acceptable salt thereof, (b) ezetimibe or a pharmaceutically acceptable salt thereof, and/or (c) bempedoic acid, or a pharmaceutically acceptable salt thereof.

B54. The compound or pharmaceutically acceptable salt thereof for use according to statement B51 or 53, wherein the at least one additional active ingredient is a statin or a pharmaceutically acceptable salt thereof.

B55. The compound or pharmaceutically acceptable salt thereof for use according to statement B52 or B53, wherein the at least one additional active ingredient is a statin or a pharmaceutically acceptable salt thereof and ezetimibe or a pharmaceutically acceptable salt thereof.

B56. The compound or pharmaceutically acceptable salt thereof for use according to any one of statements B53 to B55, wherein the statin is selected from atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, velostatin, compactin,

dihydrocompactin, dalvastatin, fluindostatin, rosuvastatin, and simvastatin; and pharmaceutically acceptable salts thereof.

B57. The compound or pharmaceutically acceptable salt thereof for use according to statement B56, wherein the statin is selected from atorvastatin, rosuvastatin, lovastatin, pravastatin, simvastatin and fluvastatin; and pharmaceutically acceptable salts thereof.

B58. The compound or pharmaceutically acceptable salt thereof for use according to statement B57, wherein the statin is rosuvastatin or a pharmaceutically acceptable salt thereof.

B59. The compound or pharmaceutically acceptable salt thereof for use according to any one of statements B54 to B58, wherein the statin is administered in a moderate-intensity dosing.

B60. The compound or pharmaceutically acceptable salt thereof for use according to any one of statements B54 to B58, wherein the statin is administered in a high-intensity dosing.

B61. The compound or pharmaceutically acceptable salt thereof for use according to statement B53, wherein the at least one additional active ingredient is ezetimibe.

B62. The compound or pharmaceutically acceptable salt thereof for use according to statement B61, wherein ezetimibe is administered in a dose of from 5 to 15 mg per day.

B63. The compound or pharmaceutically acceptable salt thereof for use according to statement B61, wherein the ezetimibe is administered in a dose of 10 mg per day.

B64. The compound or pharmaceutically acceptable salt thereof for use according to statement B53, wherein the at least one additional active ingredient is bempedoic acid.

B65. The compound or pharmaceutically acceptable salt thereof for use according to statement B64, wherein bempedoic acid is administered in a dose of 150 to 200 mg per day.

B66. The compound or pharmaceutically acceptable salt thereof for use according to statement B64, wherein bempedoic acid is administered in a does of 180 mg per day.

B67.The compound or pharmaceutically acceptable salt thereof for use according to statement B50wherein the compound or pharmaceutically acceptable salt thereof is administered

simultaneously, separately or sequentially in combination with an additional active ingredient selected from the group consisting of:
a statin or pharmaceutically acceptable salt thereof;
a cholesterol absorption inhibitor or pharmaceutically acceptable salt thereof;
a SGLT2 inhibitor or pharmaceutically acceptable salt thereof;
a P2Y12 inhibitor or pharmaceutically acceptable salt thereof;
an ATP citrate lyase inhibitor or pharmaceutically acceptable salt thereof; and
anti-hypertensive drugs or pharmaceutically acceptable salt thereof.

B68. The compound or pharmaceutically acceptable salt thereof for use according to any one of statements B50-B67 wherein the cardiovascular disease is selected from dyslipidemia, hypercholesterolemia, hypertriglyceridemia, hyperlipidemia, hypoalphalipoproteinemia, metabolic syndrome, diabetic complications, atherosclerosis, stroke, vascular dementia, chronic kidney disease, coronary heart disease, coronary artery disease, retinopathy, inflammation, thrombosis, peripheral vascular disease heart failure and congestive heart failure.

B69. Use of a compound of any one of statements B1-B47 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to statement B44 in a method of medical treatment.

B70. A method of medical treatment comprising administering to the patient the pharmaceutical composition of statement B49.

B71. Use of a compound of any one of statements B1-B47, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in therapy.

B72. Use of a compound or pharmaceutically acceptable salt thereof according to statement B71, wherein the medicament is for use in the treatment of a cardiovascular disease.

B73. Use of a compound or pharmaceutically acceptable salt thereof according to statement B72, wherein said treatment comprises the separate, sequential or simultaneous administration of i) said medicament comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof and ii) at least one additional active ingredient to a subject in need thereof.

B74. Use of a compound or pharmaceutically acceptable salt thereof according to statement B73, wherein the at least one additional active ingredient may be selected from (a) a statin or a

pharmaceutically acceptable salt thereof, (b) ezetimibe or a pharmaceutically acceptable salt thereof, and/or (c) bempedoic acid or a pharmaceutically acceptable salt thereof.

B75. A method of treating PCSK9-mediated disease or disorder in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the compound or pharmaceutically acceptable salt thereof according to any one of statements B1-B47 or the pharmaceutical composition according to statement B49.

B76. The method according to statement B75, further comprising the separate, sequential or simultaneous administration of at least one additional active ingredient to a subject in need thereof.

B77. The method according to statement B76, further comprising administering to a subject in need thereof, a first amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof and a second amount of the at least one additional active ingredient, wherein the first amount and the second amount together comprise a therapeutically effective amount.

B78. The method according to statement B77, wherein the at least one additional active ingredient may be selected from (a) a statin or a pharmaceutically acceptable salt thereof, (b) ezetimibe or a pharmaceutically acceptable salt thereof, and/or (c) bempedoic acid, or a pharmaceutically acceptable salt thereof.

B79. The method according to statement B78, wherein the at least one additional active ingredient is a statin or a pharmaceutically acceptable salt thereof.

B80. The method according to statement B78, wherein the at least one additional active ingredient is a statin or a pharmaceutically acceptable salt thereof and ezetimibe or a pharmaceutically acceptable salt thereof.

B81. The method according to any one of statements B78 to B80, wherein the statin is selected from atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, velostatin, compactin, dihydrocompactin, dalvastatin, fluindostatin, rosuvastatin, and simvastatin; and pharmaceutically acceptable salts thereof.

B82. The method according to statement B81, wherein the statin is selected from atorvastatin, rosuvastatin, lovastatin, pravastatin, simvastatin and fluvastatin, and pharmaceutically acceptable salts thereof.

B83. The method according to statement B82, wherein the statin is rosuvastatin or a pharmaceutically acceptable salt thereof.

B84. The method according to any one of statements B81-B83, wherein the statin is administered in a moderate-intensity dosing.

B85. The method according to statement B81-B83, wherein the statin is administered in a high-intensity dosing.

B86. The method according to statement B78, wherein the at least one additional active ingredient is ezetimibe, or a pharmaceutically acceptable salt thereof.

B87. The method according to statement B86, wherein ezetimibe is administered in a dose of from 5 to 15 mg per day.

B88. The method according to statement B86, wherein the ezetimibe is administered in a dose of 10 mg per day.

B89. The method according to statement B78, wherein the at least one additional active ingredient is bempedoic acid, or a pharmaceutically acceptable salt thereof.

B90. The method according to statement B89, wherein bempedoic acid is administered in a dose of 150 to 200 mg per day.

B91. The method according to statement B89, wherein bempedoic acid is administered in a dose of 180 mg per day.

B92. The method according to any one of statements B75-B91, wherein the disease or disorder is a cardiovascular disease or disorder.

B93. The method according to statement B92, wherein the cardiovascular disease or disorder is selected from dyslipidemia, hypercholesterolemia, hypertriglyceridemia, hyperlipidemia, hypoalphalipoproteinemia, metabolic syndrome, diabetic complications, atherosclerosis, stroke, vascular dementia, chronic kidney disease, coronary heart disease, coronary artery disease, retinopathy, inflammation, thrombosis, peripheral vascular disease heart failure or congestive heart failure.

B94. The compound for use according to B68, or the method according to statement B93, wherein the cardiovascular disease or disorder is dyslipidemia.

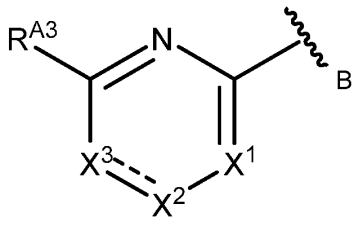
Claims

1. A compound of Formula (I)

A-B-C (I)

or a pharmaceutically acceptable salt thereof,

wherein A is of one of the following formulae:



(A1a)

wherein the wavy line indicates the point of attachment to B;

X^1 is N or C-R^{A1};
X^2 is N or C-R^{A4};
X^3 is N-(C_{1-6} hydrocarbon) or C-R^{A2};

R^{A1} is selected from the group consisting of:
(i) H;
(ii) halo;
(iii) CN;
(iv) C_{1-6} hydrocarbon, optionally substituted by OH, CN, C_{1-6} alkyl acyl, C_{1-6} alkoxy or one or more halo groups;
(v) C_{1-6} alkoxy, optionally substituted by OH, one or more halo groups, or C_{1-6} alkyl amido;
(vi) C_{1-6} alkyl ester;
(vii) C_{1-6} alkyl acyl; and
(viii) OH;

R^{A2} is selected from the group consisting of:
(i) H;
(ii) halo;

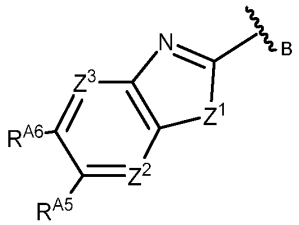
(iii) CN;
(iv) C_{1-6} hydrocarbon, optionally substituted by OH, CN, C_{1-6} alkyl acyl, C_{1-6} alkoxy or one or more halo groups;
(v) C_{1-6} alkoxy, optionally substituted by OH, C_{1-6} alkyl amido, or one or more halo groups;
(vi) C_{1-6} acylamido (wherein the acyl is optionally substituted by H or methyl);
(vii) C_{1-6} thioalkyl;
(viii) C_{1-6} alkyl ester;
(ix) C_{1-6} alkyl acyl;
(x) C_{4-5} heterocyclyl;
(xi) C_5 heteroaryl;
(xii) C_{1-6} alkyl amido, optionally substituted by C_{1-3} alkyl amido, CN, OH, C_{2-3} alkynyl, C_{4-6} heterocyclyl or C_{1-3} alkyl wherein the C_{1-3} alkyl is optionally substituted with one or more halo or OH groups;
(xiii) OH; and
(xiv) C_{1-6} alkylamino;

R^{A3} is selected from the group consisting of:
(i) H;
(ii) halo;
(iii) CN;
(iv) C_{1-6} hydrocarbon which is optionally substituted by OH, CN, C_{1-6} thioalkyl, C_{1-6} alkoxy, C_{1-6} alkyl acyl, C_{1-6} acyloxy, carboxy, C_{1-6} alkyl ester, C_{1-6} alkylamino, -C(=O)NH_2, C_{1-6} alkyl amido, C_{1-6} alkyl acylamido, C_{1-6} alkyl sulfinyl, C_{1-6} alkyl sulfonyl or one or more halo groups;
(v) OH;
(vi) C_{1-6} alkoxy, optionally substituted by OH, NH_2, C_4 heterocyclyl or one or more halo groups;
(vii) C_{1-6} acyloxy;
(viii) C_4 heterocycyl;
(ix) NH_2;
(x) C_{1-6} alkylamino, optionally substituted by CN, OH, or C_4 heterocyclyl;
(xi) C_{1-6} dialkylamino, optionally substituted by -NH_2;
(xii) C_{1-6} acylamido (where acyl substituent is H or Me);
(xiii) carbaimidoyl or methyl-carbaimidoyl;
(xiv) carboxyamino;
(xv) C_{1-6} thioalkyl, optionally substituted by OH or NH_2;
(xvi) C_{1-6} alkyl sulfinyl;
(xvii) C_{1-6} alkyl sulfonyl, optionally substituted by one or more halo groups;
(xviii) C_{1-6} sulfonimodyl;

(xix) C_{1-6} alkyl phosphinyl;
(xx) carboxy;
(xxi) $C(=O)NH_2$;
(xxii) C_{1-6} alkyl ester;
(xxiii) C_{1-6} alkyl acyl, optionally substituted by one or more halo groups; and
(xxiv) C_{1-6} alkyl amido;

or wherein R^{A3} and R^{A2} together with the carbon atoms to which they are bound form:
(i) an optionally substituted C_{5-7} heterocycle ring;
(ii) an optionally substituted C_{5-7} heteroaromatic ring;
(iii) an optionally substituted C_6 carboaromatic ring; or
(iv) an optionally substituted C_{5-7} carbocyclic ring
wherein, when present, the one, two, three or four optional substituents independently selected from C_{1-6} alkyl, halo, C_{1-6} alkoxy, NH_2, C_{1-6}alkylamino, OH, and CN;

R^{A4} is selected from the group consisting of:
(i) H;
(ii) halo;
(iii) CN;
(iv) C_{1-6} hydrocarbon, optionally substituted by one or more OH, CN, C_{1-6} alkyl acyl, C_{1-6} alkoxy or one or more halo groups;
(v) C_{1-6} alkoxy, optionally substituted by OH, one or more halo groups, C_{1-6} alkyl amido;
(vi) C_{1-6} alkyl ester;
(vii) C_{1-6} alkyl acyl;
(viii) OH; and
(ix) oxo;



(A2a)

wherein the wavy line indicates the point of attachment to B;
Z^1 is selected from O, S or NH;
Z^2 is either N or C-H
Z^3 is either N or C-R^{A7};

wherein if Z^1 is NH and Z^2 is C-H then Z^3 is C-R^{A7};

when Z^1 is NH, R^{A5} is Z^4 and R^{A6} is Z^5;
when Z^2 is N and Z^1 is O or S, R^{A5} is Z^4 and R^{A6} is Z^5;
when Z^2 is CH and Z^1 is S, R^{A5} is Z^4 and R^{A6} is Z^5;
when Z^2 is CH and Z^1 is O, R^{A5} is Z^5 and R^{A6} is Z^4;

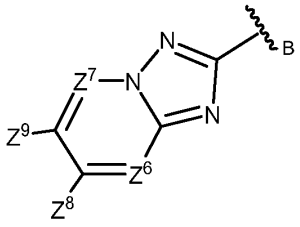
Z^4 is selected from the group consisting of:
(i) H;
(ii) halo;
(iii) CN;
(iv) C_1 alkyl optionally substituted by one or more OH, CN, or one or more halo groups; and
(v) C_1 alkoxy, optionally substituted by one or more halo groups;

Z^5 is selected from the group consisting of:
(i) H;
(ii) halo;
(iii) CN;
(iv) C_{1-6} hydrocarbon, optionally substituted by OH, CN, C_{1-6} alkyl acyl, C_{1-6} alkoxy or one or more halo groups;
(v) C_{1-6} alkoxy, optionally substituted by C_{1-6} alkyl amido, C_{1-6} alkyl phosphonyl, or one or more halo groups;
(vi) C_{1-6} alkylamino;
(vii) C_{1-6} thioalkyl;
(viii) C_{1-6} alkyl phosphinyl; and
(ix) C_{1-6} alkyl phosphonyl;

R^{A7} is selected from the group consisting of:
(i) H;
(ii) halo;
(iii) CN;
(iv) C_{1-6} hydrocarbon, optionally substituted by OH, CN, C_{1-6} thioalkyl, C_{1-6} alkoxy, C_{1-6} alkyl acyl, C_{1-6} acyloxy, C(=O)OH, C_{1-6} alkyl ester, C_{1-6} alkylamino; -C(=O)NH_2, C_{1-6} alkyl amido, C_{1-6} acylamido, C_{1-6} alkyl sulfinyl, C_{1-6} alkyl sulfonyl or one or more halo groups;
(v) C_{1-6} alkoxy, optionally substituted by NH_2, C_4 heterocyclyl and one or more halo groups;
(vi) C_4 heterocycyl;
(vii) C_{1-6} alkylamino, optionally substituted by CN, OH, C_4 heterocyclyl;

(viii) C_{1-6} dialkylamino, optionally substituted by $-NH_2$; and

(ix) C_{1-6} thioalkyl, optionally substituted by OH or $-NH_2$;



(A2b)

wherein the wavy line indicates the point of attachment to B;

Z^6 is either N or C-H

Z^7 is either N or C-R^{A8}

Z^8 and Z^9 are independently selected from the group consisting of:

(i) H;

(ii) halo;

(iii) CN;

(iv) C_{1-6} hydrocarbon, optionally substituted by OH, CN, C_{1-6} alkyl acyl, C_{1-6} alkoxy or one or more halo groups;

(v) C_{1-6} alkoxy, optionally substituted by C_{1-6} alkyl amido, C_{1-6} alkyl phosphonyl, or one or more halo groups;

(vi) C_{1-6} alkylamino

(vii) C_{1-6} thioalkyl,

(viii) C_{1-6} alkyl phosphinyl; and

(ix) C_{1-6} alkyl phosphonyl;

R^{A8} is selected from the group consisting of:

(i) H;

(ii) halo;

(iii) CN;

(iv) C_{1-6} hydrocarbon, optionally substituted by OH, CN, C_{1-6} thioalkyl, C_{1-6} alkoxy, C_{1-6} alkyl acyl, C_{1-6} acyloxy, C(=O)OH, C_{1-6} alkyl ester, C_{1-6} alkylamino; $-C(=O)NH_2$, C_{1-6} alkyl amido, C_{1-6} acylamido, C_{1-6} alkyl sulfinyl, C_{1-6} alkyl sulfonyl or one or more halo groups;

(v) C_{1-6} alkoxy, optionally substituted by NH_2, C_4 heterocyclyl or one or more halo groups;

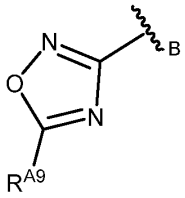
(vi) C_4 heterocycyl;

(vii) C_{1-6} alkylamino, optionally substituted by CN, OH, C_4 heterocyclyl;

(viii) C_{1-6} dialkylamino, optionally substituted by $-NH_2$; and

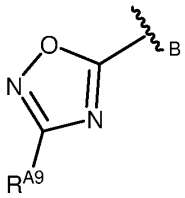
(ix) C_{1-6} thioalkyl, optionally substituted by OH or $-NH_2$;

(A3a)



; or

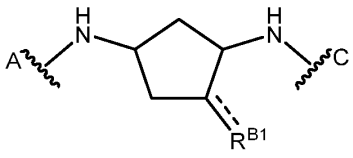
(A3b)



wherein the wavy line indicates the point of attachment to B;

where R^{A9} is selected from H, methyl, ethyl, n-propyl, *i*-propyl, cyclopropyl, 1-methylcyclopropyl and 2-methylcyclopropyl;

wherein B is of formula:

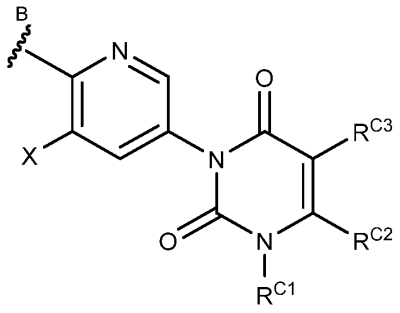


(B-1)

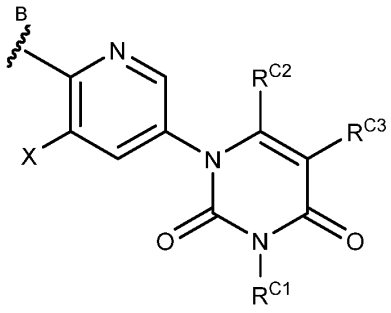
wherein the wavy lines indicate the points of attachment to A and C;

R^{B1} is H, OH, $=CHCH_2$-OH, C_{1-4} alkyoxy, or C_{1-4} alkyl which C_{1-4} alkyl is optionally substituted by OH or OMe;

wherein C is of formula:



(C-1a) or



(C-1b)

X is hydrogen or fluorine;

one of R^{C2} and R^{C3} is hydrogen and the other is C_{1-3} alkoxy;

or R^{C2} and R^{C3} together represent a fused benzene ring or C_{5-6} heteroaromatic ring, which rings are optionally substituted by one or more R^{C4} groups;

R^{C1} is selected from:
(i) H;
(ii) C_{1-6} alkyl optionally substituted by one or more halo groups;
(iii) C_{5-6} heterocyclyl or C_{5-6}heteroaryl with an optional methyl substituent;
(iv) phenyl optionally substituted by one or more halo atoms;

R^{C4} is selected from:
(i) C_{1-6} alkyl optionally substituted by one or more halo groups;
(ii) C_{1-6} alkoxy optionally substituted by one or more halo groups;
(iii) C_{5-6} heterocyclyl or C_{5-6}heteroaryl with an optional methyl substituent;
(iv) di-C_{1-6} alkyl amido;
(v) C_{1-6} acylamido;
(vi) halo; and
(vii) CN.

2. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein X^1 is N and X^2 is N.

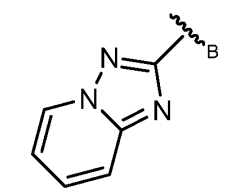
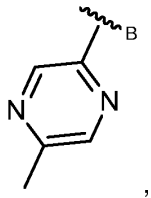
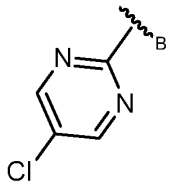
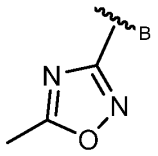
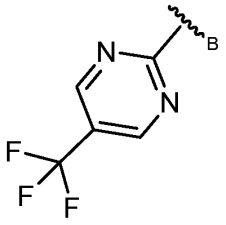
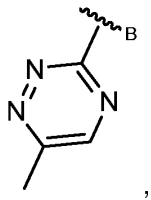
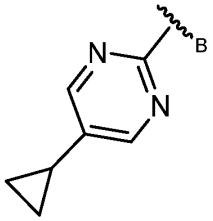
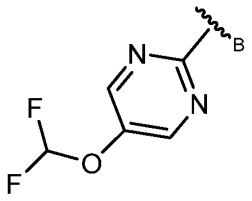
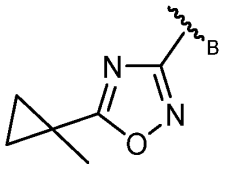
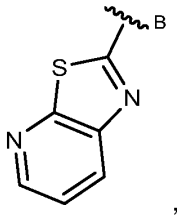
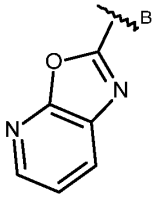
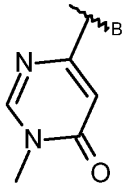
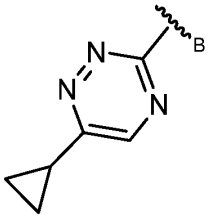
3. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein X^1 is N, X^2 is C-R^{A4}, and X^3 is C-R^{A2}.

4. The compound according to any one of claims 1 to 3 or a pharmaceutically acceptable salt thereof, wherein R^{A2} is selected from H, chloro, methyl, trifluoromethyl, cyclopropyl and OCF_2H.

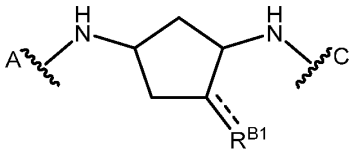
5. The compound according to any one of claims 1 to 4 or a pharmaceutically acceptable salt thereof, wherein R^{A3} is selected from the group consisting of H, methyl and OH.

6. The compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein A is of formula (A2b).

7. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein A is selected from one of the following formulae;


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and

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8. The compound according to any one of claims 1 to 7 or a pharmaceutically acceptable salt thereof, wherein B is of formula (B-1)

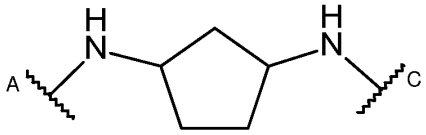


(B-1)

wherein the wavy lines indicate the point of attachment to A and C;

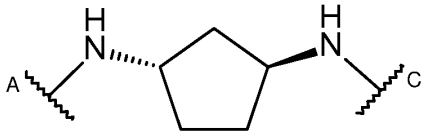
wherein R^{B1} is selected from the group consisting of H, OH, OMe, -O-ethyl, $-CH_2OH$, $-CH_2CH_2OH$ and $=CHCH_2-OH$.

9. The compound according to any one of claims 1 to 8 or a pharmaceutically acceptable salt thereof, wherein B is of the following formula (B-1a):



(B-1a).

10. The compound according to any one of claims 1 to 9 or a pharmaceutically acceptable salt thereof, wherein B is of the following formula (B-1b):

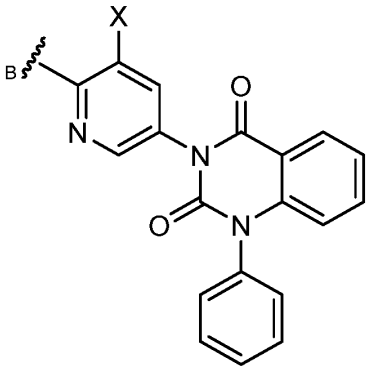
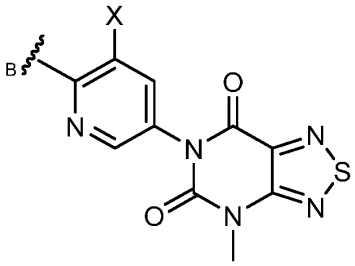
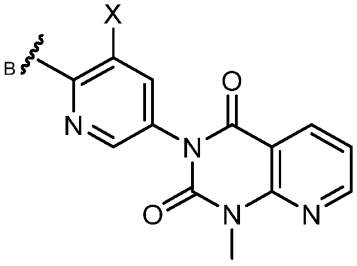
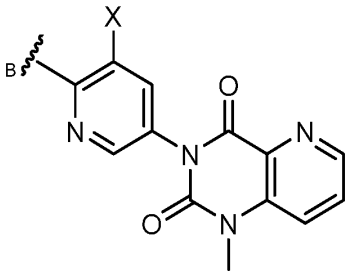
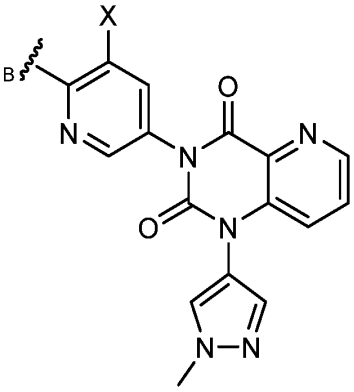
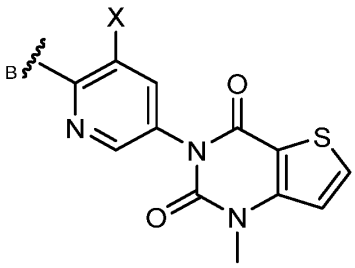
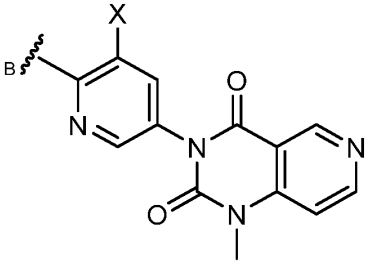
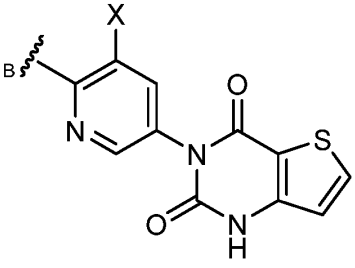


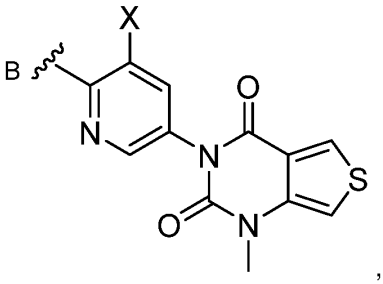
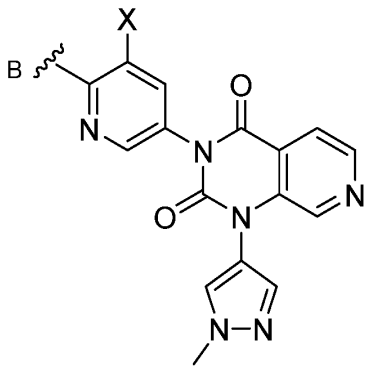
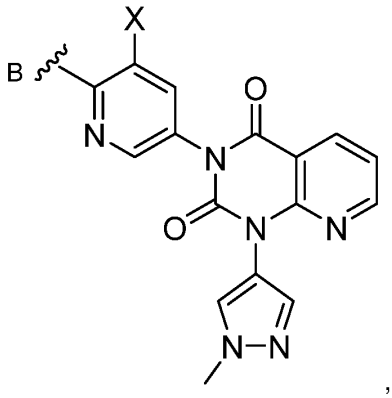
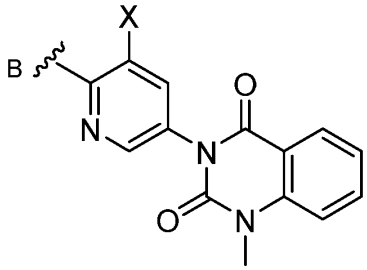
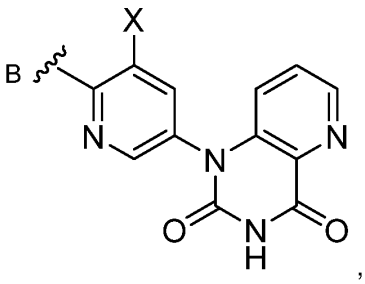
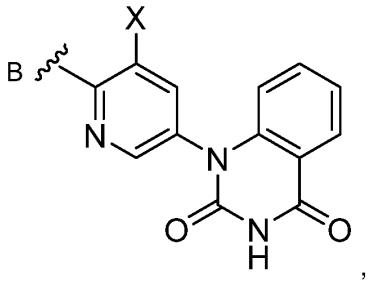
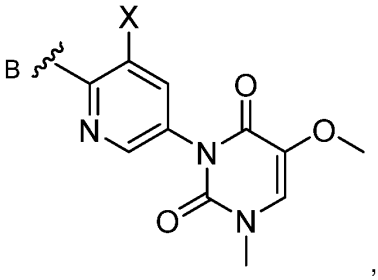
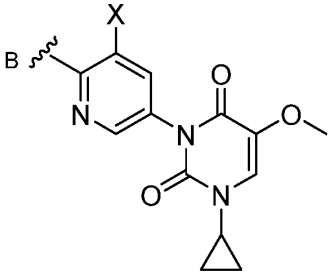
(B-1b).

11. The compound according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein C is of formula (C-1a).

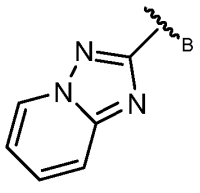
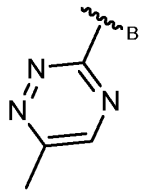
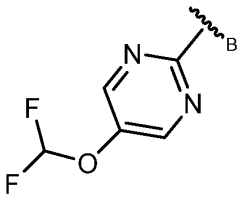
12. The compound according to any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, wherein R^{C1} is C_{1-6} alkyl optionally substituted by one or more halo groups.

13. The compound according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein C is selected from one of the following formulae;

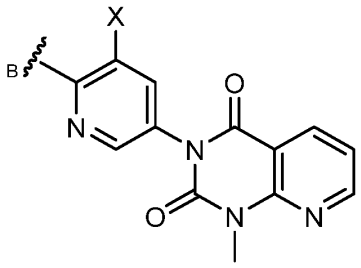
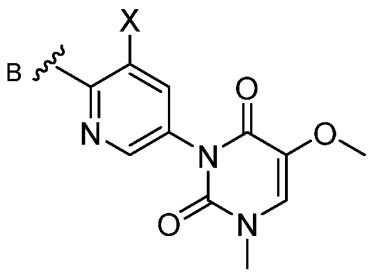

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14. The compound or pharmaceutically acceptable salt thereof according to claim 1, wherein A is selected from one of:


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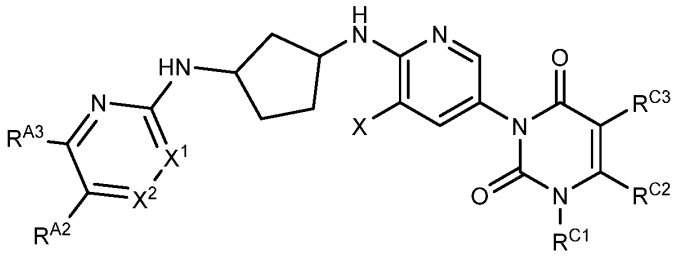
and C is selected from one of:

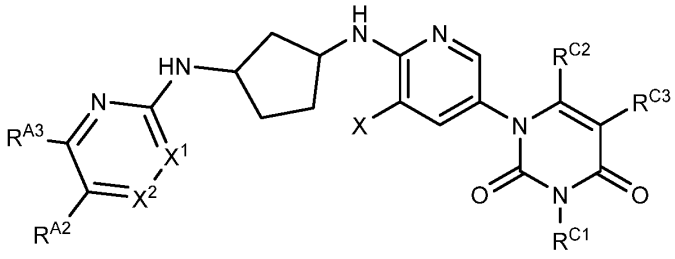

,and

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15. The compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein A-B-C is of the formula (I-Ax), or (I-Ay);

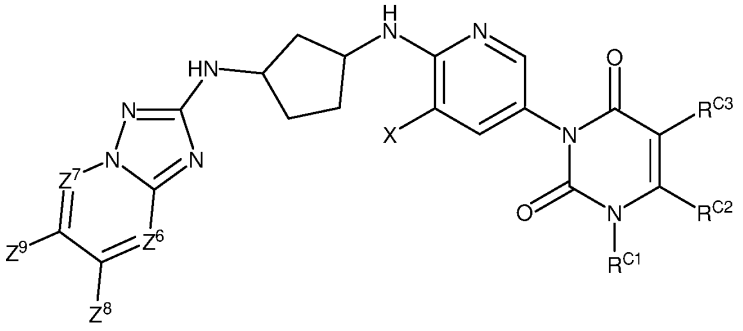
wherein all other definitions are according to claim 1;


(I-Ax),

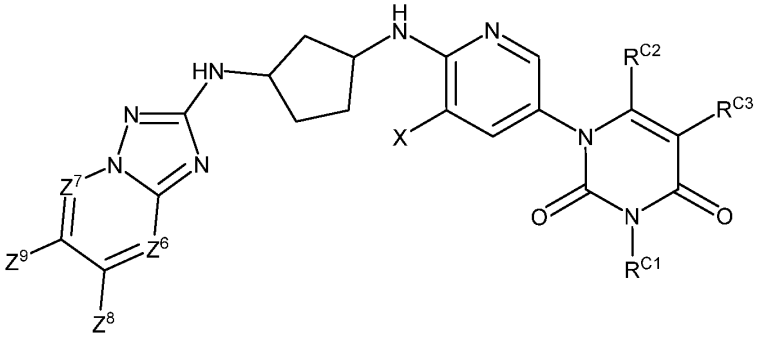

(I-Ay).

16. The compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein A-B-C is of the formula (III-Ax), or (III-Ay),

wherein all other definitions are according to claim 1;



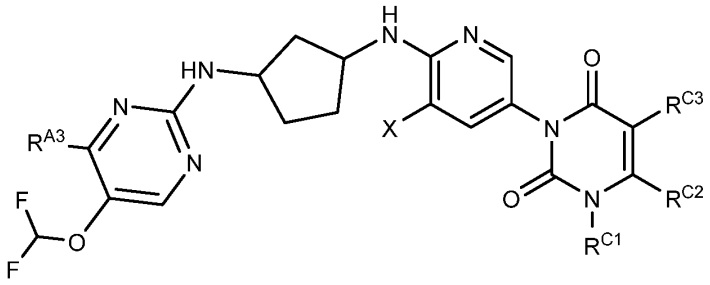
(III-Ax),



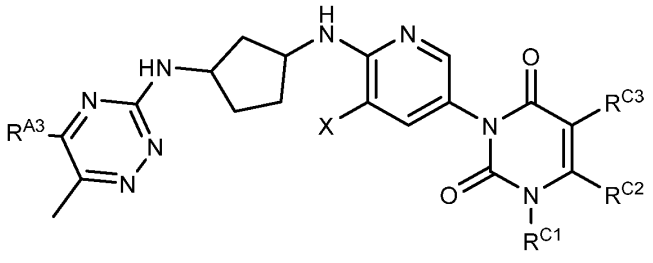
(III-Ay).

17. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein A-B-C is of the formulae (I-Cdx), (I-Bax) or (III-Bbx),

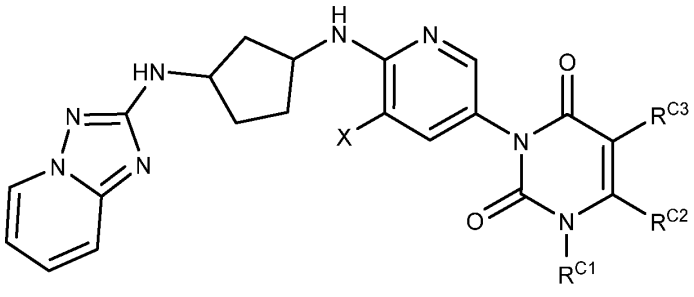
wherein all other definitions are according to claim 1;



(I-Cdx),



(I-Bax),



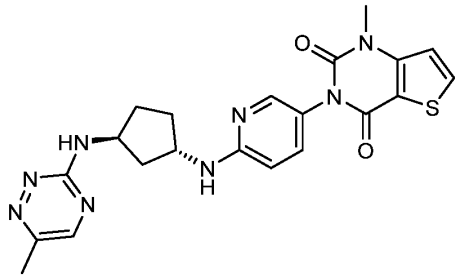
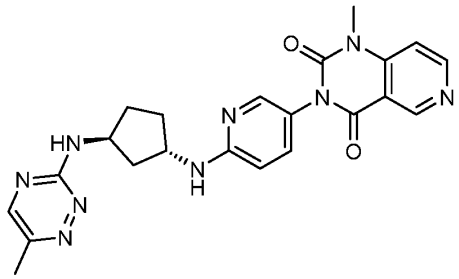
(III-Bbx).

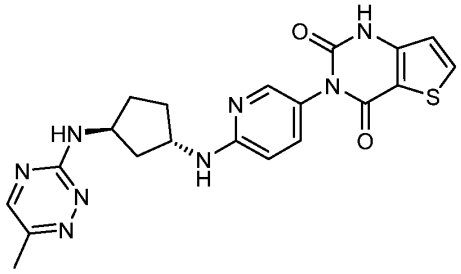
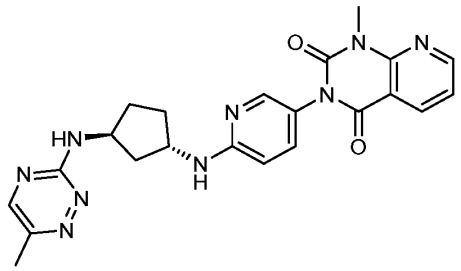
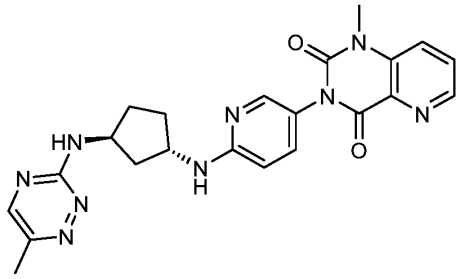
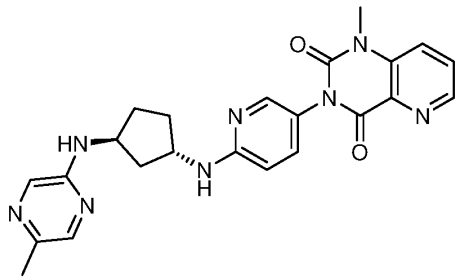
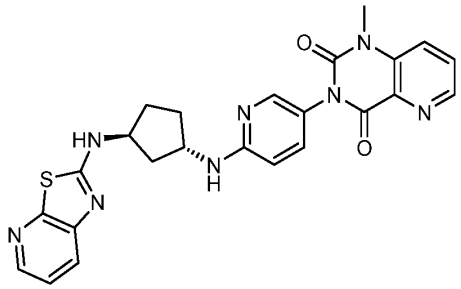
18.The compound according to any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof, wherein X is F.

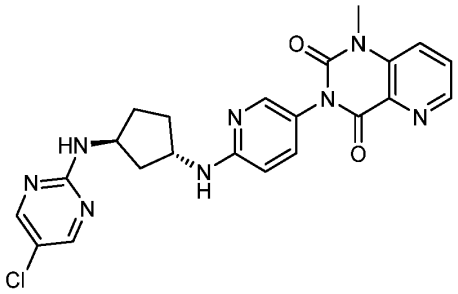
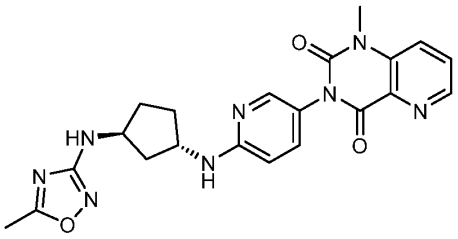
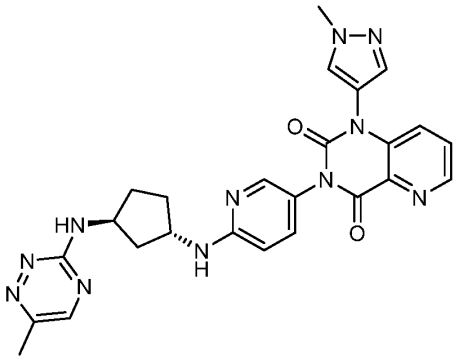
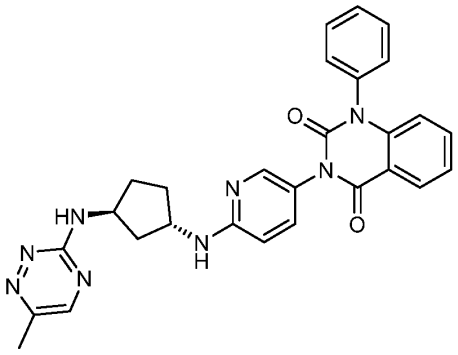
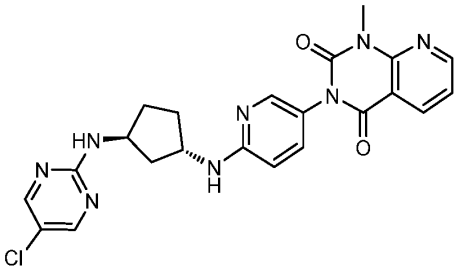
19. The compound according to any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof, wherein X is H.

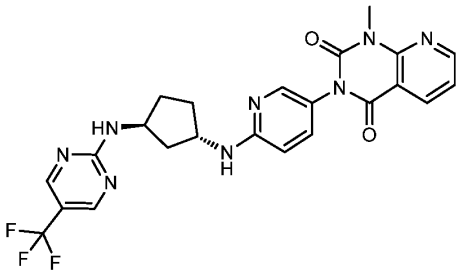
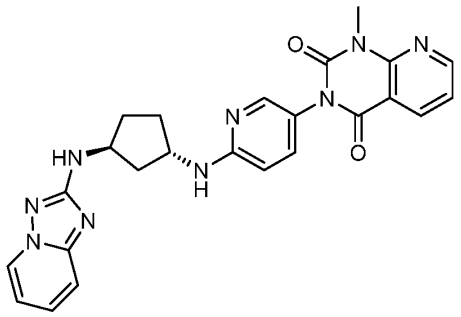
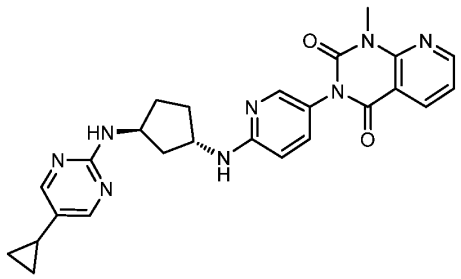
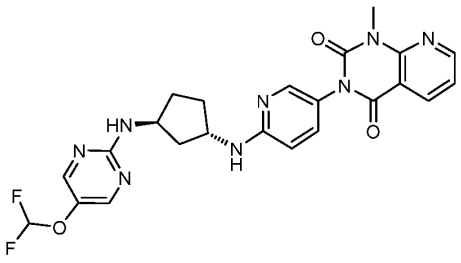
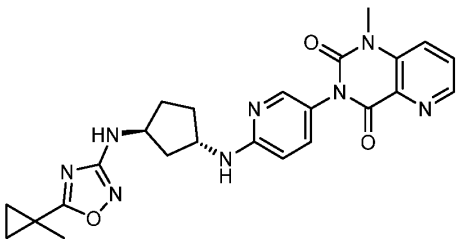
20. The compound or pharmaceutically acceptable salt thereof according to claim 1, wherein the compound is selected from a compound listed in Table 1 or Table 2 or a pharmaceutically acceptable salt thereof.

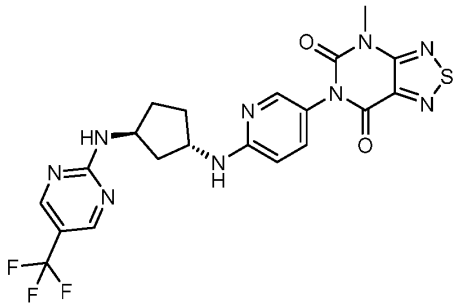
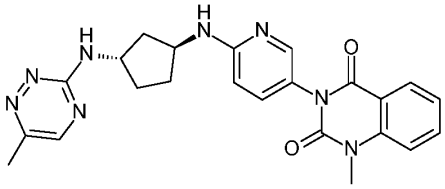
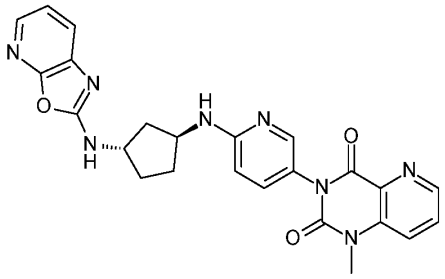
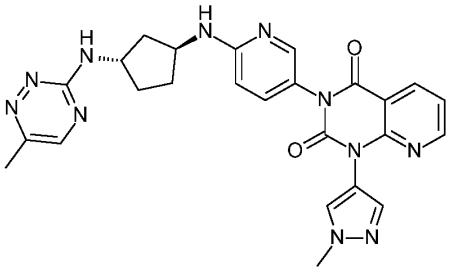
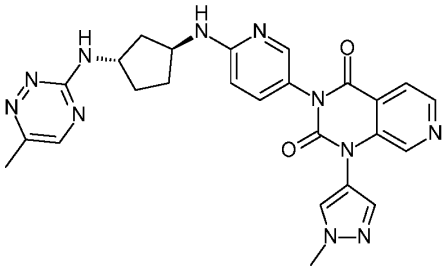
21. The compound according to claim 1, wherein the compound is selected from one of the following compounds:

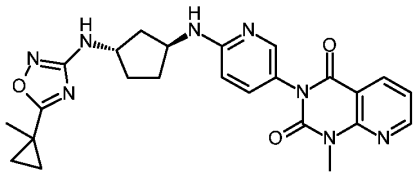
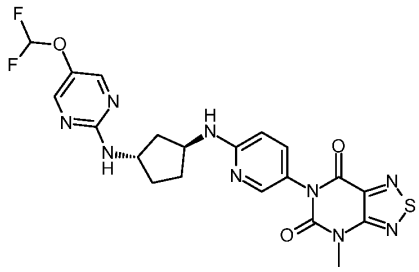
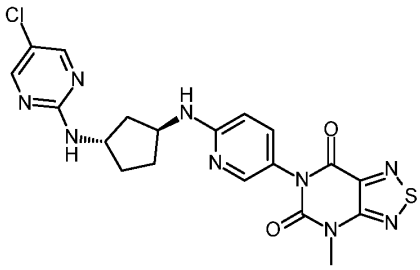
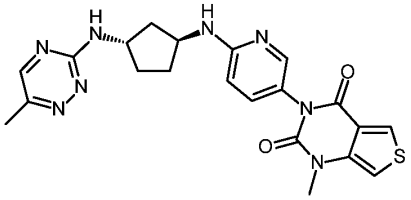
1		1-Methyl-3-(6-(((1*S*,3*S*)-3-((6-methyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)thieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione,
2		1-Methyl-3-(6-(((1*S*,3*S*)-3-((6-methyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyrido[4,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione,

3		3-(6-(((1*S*,3*S*)-3-((6-Methyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)thieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione,
4		1-Methyl-3-(6-(((1*S*,3*S*)-3-((6-methyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione,
5		1-Methyl-3-(6-(((1*S*,3*S*)-3-((6-methyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione,
6		1-Methyl-3-(6-(((1*S*,3*S*)-3-((5-methylpyrazin-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione,
7		1-Methyl-3-(6-(((1*S*,3*S*)-3-(thiazolo[5,4-*b*]pyridin-2-ylamino)cyclopentyl)amino)pyridin-3-yl)pyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione,

8		3-(6-(((1*S*,3*S*)-3-((5-Chloropyrimidin-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)-1-methylpyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione,
9		1-Methyl-3-(6-(((1*S*,3*S*)-3-((5-methyl-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione,
10		3-(6-(((1*S*,3*S*)-3-((6-Methyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)-1-(1-methyl-1*H*-pyrazol-4-yl)pyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione,
11		3-(6-(((1*S*,3*S*)-3-((6-Methyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)-1-phenylquinazoline-2,4(1*H*,3*H*)-dione,
12		3-(6-(((1*S*,3*S*)-3-((5-Chloropyrimidin-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)-1-methylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione,

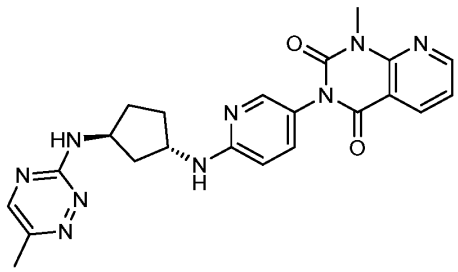
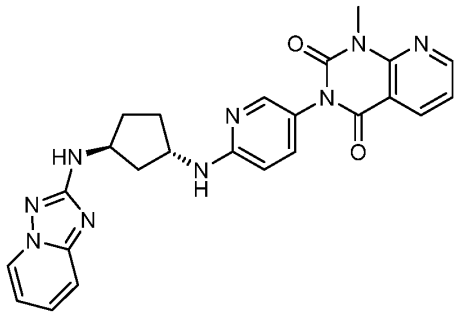
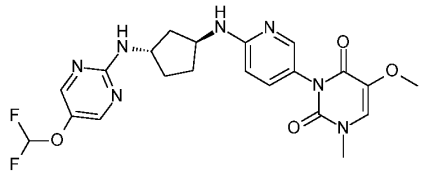
13		1-Methyl-3-(6-(((1*S*,3*S*)-3-((5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione,
14		3-(6-(((1*S*,3*S*)-3-([1,2,4]Triazolo[1,5-*a*]pyridin-2-ylamino)cyclopentyl)amino)pyridin-3-yl)-1-methylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione,
15		3-(6-(((1*S*,3*S*)-3-((5-Cyclopropylpyrimidin-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)-1-methylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione,
16		3-(6-(((1*S*,3*S*)-3-((5-(Difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)-1-methylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione,
17		1-Methyl-3-(6-(((1*S*,3*S*)-3-((5-(1-methylcyclopropyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione,

18		4-Methyl-6-(6-(((1*S*,3*S*)-3-((5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)-[1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione,
19		1-Methyl-3-(6-(((1*S*,3*S*)-3-((6-methyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)quinazoline-2,4(1*H*,3*H*)-dione,
20		1-Methyl-3-(6-(((1*S*,3*S*)-3-(oxazolo[5,4-*b*]pyridin-2-ylamino)cyclopentyl)amino)pyridin-3-yl)pyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione,
22		3-(6-(((1*S*,3*S*)-3-((6-Methyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)-1-(1-methyl-1*H*-pyrazol-4-yl)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione,
23		3-(6-(((1*S*,3*S*)-3-((6-Methyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)-1-(1-methyl-1*H*-pyrazol-4-yl)pyrido[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione,

24		1-Methyl-3-(6-(((1*S*,3*S*)-3-((5-(1-methylcyclopropyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione,
25		6-(6-(((1*S*,3*S*)-3-((5-(Difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)-4-methyl-[1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione,
26		6-(6-(((1*S*,3*S*)-3-((5-Chloropyrimidin-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)-4-methyl-[1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione,
28		1-Methyl-3-(6-(((1*S*,3*S*)-3-((6-methyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)thieno[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione,

or a pharmaceutically acceptable salt thereof.

22.The compound according to claim 1, wherein the compound is selected from one of the following compounds:

4		1-Methyl-3-(6-(((1*S*,3*S*)-3-((6-methyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione,
14		3-(6-(((1*S*,3*S*)-3-([1,2,4]Triazolo[1,5-*a*]pyridin-2-ylamino)cyclopentyl)amino)pyridin-3-yl)-1-methylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione,
32		3-(6-(((1*S*,3*S*)-3-((5-(Difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)-5-methoxy-1-methylpyrimidine-2,4(1*H*,3*H*)-dione.

or a pharmaceutically acceptable salt thereof.

23. The compound according to any one of claims 1 to 22 or a pharmaceutically acceptable salt thereof, for use in therapy.

24. A pharmaceutical composition comprising the compound according to any one of claims 1 to 22 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent, carrier or excipient.

25. The compound according to any one of claims 1 to 22 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 24 for use in the treatment of a cardiovascular disease.