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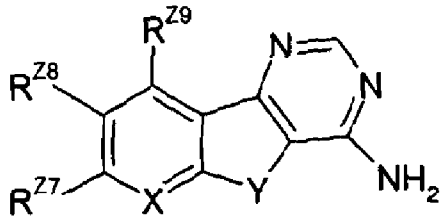
(54) **Title**: PYRIDO [3',2' :4,5] THIENO [3, 2-D] PYRIMIDIN- 4 - YLAMINE DERIVATIVES AND THEIR THERAPEUTICAL USE



(57) **Abstract**: The present invention pertains generally to the field of therapeutic compounds, and more specifically to certain fused triaryl amine compounds of the following formula (for convenience, collectively referred to herein as "FTA compounds"), which, *inter alia*, inhibit LIM kinase (LIMK) activity. The present invention also pertains to pharmaceutical compositions comprising such compounds, and the use of such compounds and compositions, both in vitro and in vivo, to inhibit LIMK activity, and in the treatment of diseases and conditions that are mediated by LIMK, that are ameliorated by the inhibition of LIMK activity, etc., including proliferative conditions such as cancer (e.g., breast cancer, prostate cancer, melanoma, glioma, etc.), as well as vasodilation (including, e.g., hypertension, angina, cerebral vasospasm, and ischemia following subarachnoid hemorrhage), neurodegenerative disorders, atherosclerosis, fibrosis, and inflammatory diseases (including, e.g., Crohn's disease and chronic obstructive pulmonary disease (COPD)), and glaucoma (also known as ocular hypertension).

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PYRIDO [3' ,2' :4,5] THIENO [3, 2-D] PYRIMIDIN- 4 - YLAMINE DERIVATIVES AND THEIR THERAPEUTICAL USE

RELATED APPLICATION

This application is related to United States (US) provisional patent application number 61/468,136 filed 28 March 2011, the contents of which are incorporated herein by reference in their entirety.

TECHNICAL FIELD

The present invention pertains generally to the field of therapeutic compounds, and more specifically to certain fused triaryl amine compounds (for convenience, collectively referred to herein as "FTA compounds"), which, *inter alia*, inhibit LIM kinase (LIMK) activity. The present invention also pertains to pharmaceutical compositions comprising such compounds, and the use of such compounds and compositions, both *in vitro* and *in vivo*, to inhibit LIMK activity, and in the treatment of diseases and conditions that are mediated by LIMK, that are ameliorated by the inhibition of LIMK activity, etc., including proliferative conditions such as cancer (e.g., breast cancer, prostate cancer, melanoma, glioma, etc.), as well as vasodilation (including, e.g., hypertension, angina, cerebral vasospasm, and ischemia following subarachnoid hemorrhage), neurodegenerative disorders, atherosclerosis, fibrosis, and inflammatory diseases (including, e.g., Crohn's disease and chronic obstructive pulmonary disease (COPD)), and glaucoma (also known as ocular hypertension).

BACKGROUND

A number of patents and publications are cited herein in order to more fully describe and disclose the invention and the state of the art to which the invention pertains. Each of these references is incorporated herein by reference in its entirety into the present disclosure, to the same extent as if each individual reference was specifically and individually indicated to be incorporated by reference.

Throughout this specification, including the claims which follow, unless the context requires otherwise, the word "comprise," and variations such as "comprises" and "comprising," 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. Thus, for example, reference to "a pharmaceutical carrier" includes mixtures of two or more such carriers, and the like.

Ranges are often 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.

This disclosure includes information that may be useful in understanding the present invention. It is not an admission that any of the information provided herein is prior art or relevant to the presently claimed invention, or that any publication specifically or implicitly referenced is prior art.

LIMK

The LIM kinase (LIMK) family of serine/threonine protein kinases sit at the centre of multiple signalling pathways downstream of the Rho family of GTPases. There are two members of the family, LIMK1 and LIMK2, both of which are directly involved in regulating multiple cellular processes via their ability to reorganise the actin-cytoskeleton network (see, e.g., Scott et al., 2007). Overall, the LIMKs share 50% homology (see, e.g., Mizuno et al., 1994; Nunoue et al., 1995). They are composed of two N-terminal LIM domains, each of which contains a double zinc-finger motif. The LIM domains play an important role in regulating kinase activity (see, e.g., Nagata et al., 1999; Tomiyoshi et al., 2004) and may also contribute to LIMK function by mediating protein-to-protein and protein-to-DNA interactions (see, e.g., Hiraoka et al., 1996; Nishiya et al., 1998). Next lies a PDZ domain which also influences protein-protein interactions but additionally contains two nuclear export signals (see, e.g., Yang et al., 1998; Yang et al., 1999) which together with nuclear localisation signals (see, e.g., Goyal et al., 2006) most likely regulate nuclear/cytoplasmic shuttling. A proline/serine rich region then follows with the kinase domain of the protein being located at the extreme C-terminus. The kinase domains of LIMK1 and LIMK2 are 70% identical and phosphorylation within the activation loop enhances their activity.

LIMK is activated via a number of signalling networks downstream of growth factors, integrins and cytokines (for a comprehensive review see, e.g., Scott et al., 2007). Specifically, the Rho effector, Rho kinase (ROCK) has been shown to phosphorylate LIMK on conserved threonine residues (Thr-508 on LIMK1 or Thr-505 LIMK2), modifications that are essential for kinase activation (see, e.g., Amano et al., 2001; Ohashi et al., 2000; Sumi et al., 2001a), Pak1 (see, e.g., Edwards et al., 1999), Pak4 (see, e.g., Dan et al., 2001), and the myotonic dystrophy kinase-related Cdc42-binding kinase (MRCKα) have also been shown to phosphorylate LIMK1 with MRCKα also phosphorylating LIMK2 (see, e.g., Sumi et al., 2001b). Transphosphorylation of LIMK1, following association with HSP90, has been shown to increase the half life of the protein and increases its specific activity (see, e.g., Li et al., 2006). Autophosphorylation of LIMK also occurs, although the site of phosphorylation and functional consequence remains

uncertain (see, e.g., Kobayashi et al., 2006; Proschel et al., 1995). Conversely, LIMK is subject to deactivation by the direct action of phosphatases. Slingshot1 (SSH1) binds directly to the kinase domain and dephosphorylates LIMK1 on Thr-508 and additional autophosphorylated serine residues resulting in decreased activity (see, e.g., Soosairajah et al., 2005).

Downstream of LIMK there are relatively few substrates known. The best characterised are the cofilin family of proteins, cofilin1 (non-muscle cofilin), cofilin2 (muscle cofilin) and destrin (also known as actin depolymerizing factor, ADF). Unphosphorylated active cofilin binds to actin filaments *in vivo*, depolymerises filamentous actin (F-actin), and produces free barbed ends that serve to nucleate new actin filaments (see, e.g., Ghosh et al., 2004; Lorenz et al., 2004). Ultimately it is a balance between phosphorylated and dephosphorylated cofilin that determines a cell's ability to reorganise the cytoskeleton, controlling cell shape and influencing its ability to move, invade or metastasise. LIMK reorganises actin-cytoskeleton dynamics through direct phosphorylation of cofilin on serine-3 resulting in its inactivation and subsequent inhibition of its actin-severing activity (see, e.g., Maekawa et al., 1999; Sumi et al., 1999). Through this modulation of the actin-cytoskeleton, LIMK is implicated to play pivotal a role in several human diseases with inhibition via small molecule kinase inhibitors having potential utility.

LIMK and Cancer

Enhanced LIMK activity has been associated with tumour types. LIMK1 has been found unregulated via chromosomal translocation in malignant melanoma cells (see, e.g., Okamoto et al., 2005), breast cancer tumours (see, e.g., Bagheri-Yarmand et al., 2006) and breast cancer cell lines (see, e.g., Yoshioka et al., 2003), in prostate tumours (see, e.g., Davila et al., 2003) and prostate cancer cell lines (see, e.g., Bagheri-Yarmand et al., 2006; Yoshioka et al., 2003). In line with increased LIMK activity, co-ordinately increased phosphorylated cofilin has also been found in several studies (see, e.g., Davila et al., 2003; Wang et al., 2004; Wang et al., 2005).

LIMK expression levels have been linked to tumour cell growth. For example, reduction in LIMK1 caused a decrease in prostate cancer cell proliferation, arresting cells in G2/M (see, e.g., Davila et al., 2003). Similarly, lowering expression of LIMK2 in human fibrosarcoma cells limited their ability to form colonies in a long term growth assay (see, e.g., Suyama et al., 2004). LIMK has been reported to modify the p53 pathway (see, e.g., Freidman et al., 2002). p53 is a potent tumour suppressor protein which is stabilised in response to cellular stress signals to induce cell-cycle arrest or apoptosis depending on signal strength and duration (see, e.g., Vousden et al., 2009). The exact mechanism by which LIMK regulates p53 signalling however remains unclear.

Consistent with LIMKs ability to reorganise the actin-cytoskeleton network, the most convincing role for LIMK in cancer is to modulate tumour cell invasion and metastasis.

Metastasis occurs through a series of complex biological events which together allow tumour cells to detach and extravasate from their site of origin and repopulate at a distal site within the body (see, e.g., Klein, 2009).

Currently there are no therapeutic strategies to control metastasis although it is estimated to account for over 90% of all human deaths from cancer (see, e.g., Sporn, 1996). Overexpression of LIMK has been shown to increase the motility and invasive capacity of tumour cells in several different systems. Overexpression of LIMK1 increased motility, invasiveness and metastatic ability of human breast cancer cells (see, e.g., Bagheri-Yarmand et al., 2006; Yoshioka et al., 2003) as well as increasing the invasive phenotype of benign prostate cells (see, e.g., Davila et al., 2003).

Importantly, it has been demonstrated in several studies that interfering with LIMK function reduces tumour cell invasion. Silencing of LIMK expression with anti-sense oligonuceotides in metastatic prostate cells resulted in decreased cell invasion (see, e.g., Davila et al., 2003), and ribozyme-mediated knockdown of LIMK2 inhibited the motility of metastatic fibrosarcoma cells (see, e.g., Suyama et al., 2004). Furthermore, expression of dominant-negative LIMK1 resulted in decreased invasion of metastatic breast cancer cells *in vitro* and in an *in vivo* model of breast cancer metastasis caused a decrease in the number osteolytic lesions formed after tumour cells were injected into nude mice (see, e.g., Yoshioka et al., 2003). Collectively these studies suggest that targeting LIMK may be a viable therapeutic strategy for preventing or controlling metastatic disease.

LIMK and Glaucoma

Glaucoma is one of the leading causes of irreversible blindness in the world. It is characterized by degeneration of the optic nerve and progressive visual field loss and is often associated with elevated intraocular pressure (IOP) (see, e.g., Ferrer, 2006). The actin cytoskeleton network is thought to be an important modulator of IOP and subsequently LIMK has been proposed to play a role in regulating IOP. Downregulation of LIMK1 with short-interfering RNA in cultured corneal fibroblasts was shown to reduce actin polymerization, focal adhesion formation and delay cell migration. In an *in vivo* mouse model, deletion or downregulation of LIMK1 significantly reduced ocular inflammation (see, e.g., Gorovoy et al., 2008). Accordingly, LIMK inhibitors have been proposed for the treatment of glaucoma (see, e.g., Hizaki et al., 2004; Harrison et al., 2009; Burgoon et al., 2009).

SUMMARY OF THE INVENTION

One aspect of the invention pertains to certain fused triaryl amine compounds (for convenience, collectively referred to herein as "FTA compounds"), as described herein.

Another aspect of the invention pertains to a composition (e.g., a pharmaceutical composition) comprising a FTA compound, as described herein, and a pharmaceutically acceptable carrier or diluent.

Another aspect of the invention pertains to method of preparing a composition (e.g., a pharmaceutical composition) comprising the step of admixing a FTA compound, as described herein, and a pharmaceutically acceptable carrier or diluent.

Another aspect of the present invention pertains to a method of inhibiting LIM kinase (LIMK) activity (e.g., LIMK1 activity and/or LIMK2 activity) in a cell, *in vitro* or *in vivo*, comprising contacting the cell with an effective amount of a FTA compound, as described herein.

Another aspect of the present invention pertains to a method of regulating (e.g., inhibiting) cell proliferation (e.g., proliferation of a cell), inhibiting cell cycle progression, promoting apoptosis, or a combination of one or more these, *in vitro* or *in vivo*, comprising contacting a cell with an effective amount of a FTA compound, as described herein.

Another aspect of the present invention pertains to a method of treatment comprising administering to a subject in need of treatment a therapeutically-effective amount of a FTA compound, as described herein, preferably in the form of a pharmaceutical composition.

Another aspect of the present invention pertains to a FTA compound as described herein for use in a method of treatment of the human or animal body by therapy.

Another aspect of the present invention pertains to use of a FTA compound, as described herein, in the manufacture of a medicament for use in treatment.

In one embodiment, the treatment is treatment of a disease or condition that is mediated by LIM kinase (LIMK) (e.g., LIMK1 and/or LIMK2).

In one embodiment, the treatment is treatment of a disease or condition that is ameliorated by the inhibition of LIM kinase (LIMK) activity (e.g., LIMK1 activity and/or LIMK2 activity).

In one embodiment, the treatment is treatment of a proliferative condition.

In one embodiment, the treatment is treatment of cancer.

In one embodiment, the treatment is treatment of cancer characterised by, or further characterised by, cancer cells which overexpress LIM kinase (LIMK) (e.g., LIMK1 and/or LIMK2).

In one embodiment, the treatment is treatment of solid tumour cancer.

In one embodiment, the treatment is treatment of breast cancer, prostate cancer, melanoma, or glioma.

In one embodiment, the treatment is treatment of vasodilation.

In one embodiment, the treatment is treatment of hypertension, angina, cerebral vasospasm, or ischemia following subarachnoid hemorrhage.

In one embodiment, the treatment is treatment of a neurodegenerative disorder.

In one embodiment, the treatment is treatment of atherosclerosis.

In one embodiment, the treatment is treatment of fibrosis.

In one embodiment, the treatment is treatment of an inflammatory disease.

In one embodiment, the treatment is treatment of Crohn's disease or chronic obstructive pulmonary disease (COPD).

In one embodiment, the treatment is treatment of glaucoma (also known as ocular hypertension).

Another aspect of the present invention pertains to a kit comprising (a) a FTA compound, as described herein, preferably provided as a pharmaceutical composition and in a suitable container and/or with suitable packaging; and (b) instructions for use, for example, written instructions on how to administer the compound.

Another aspect of the present invention pertains to a FTA compound *obtainable* by a method of synthesis as described herein, or a method comprising a method of synthesis as described herein.

Another aspect of the present invention pertains to a FTA compound *obtained* by a method of synthesis as described herein, or a method comprising a method of synthesis as described herein.

Another aspect of the present invention pertains to novel intermediates, as described herein, which are suitable for use in the methods of synthesis described herein.

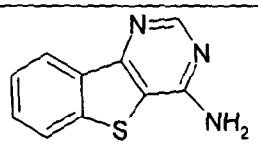
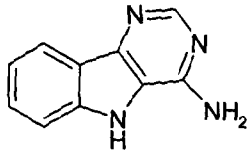
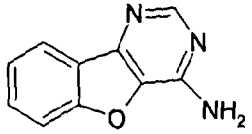
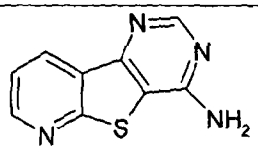
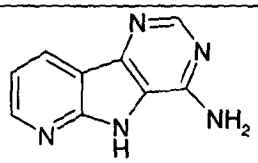
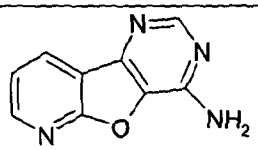
Another aspect of the present invention pertains to the use of such novel intermediates, as described herein, in the methods of synthesis described herein.

As will be appreciated by one of skill in the art, features and preferred embodiments of one aspect of the invention will also pertain to other aspect of the invention.

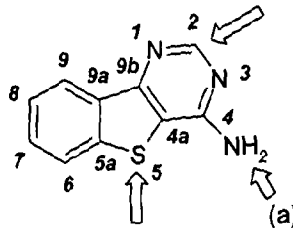
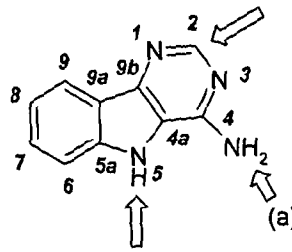
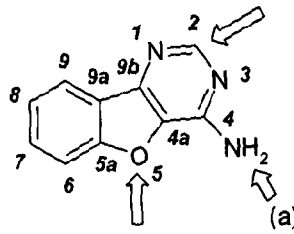
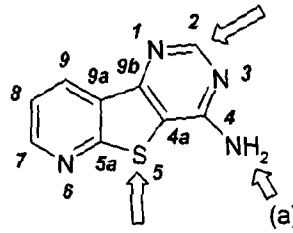
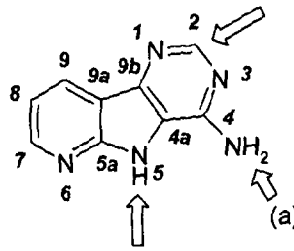
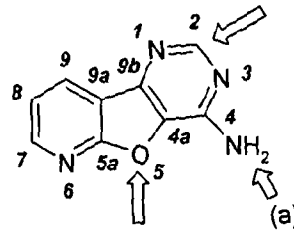
DETAILED DESCRIPTION OF THE INVENTION

Compounds

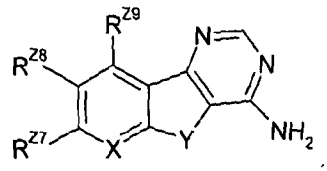
The present invention relates to certain compounds which are structurally related to the following compounds:

1		Benzo[4,5]thieno[3,2-d]pyrimidin-4-ylamine
2		5H-Pyrimido[5,4-b]indol-4-ylamine
3		Benzo[4,5]furo[3,2-d]pyrimidin-4-ylamine
4		Pyrido[3',2':4,5]thieno[3,2-d]pyrimidin-4-ylamine
5		9H-1,5,7,9-Tetraaza-fluoren-8-ylamine
6		Pyrido[3',2':4,5]furo[3,2-d]pyrimidin-4-ylamine

The compounds are also characterized by (a) an amino group at the 4-position of the pyrimidine ring, (b) the lack of a substituent at the 2-position of the pyrimidine ring, and (c) the presence of a heteroatom (i.e., S, N, or O) at the 5-position in the central ring, for example, as shown below:

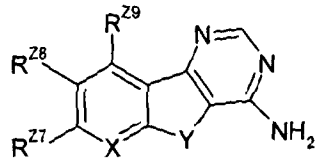
(1)  (c) no substituent; (a) amino group; (c) heteroatom	(2)  (c) no substituent; (a) amino group; (c) heteroatom
(3)  (c) no substituent; (a) amino group; (c) heteroatom	(4)  (c) no substituent; (a) amino group; (c) heteroatom
(5)  (c) no substituent; (a) amino group; (c) heteroatom	(6)  (c) no substituent; (a) amino group; (c) heteroatom

Thus, one aspect of the present invention pertains to compounds selected from compounds of the following formulae, and salts, hydrates, and solvates thereof (e.g., pharmaceutically acceptable salts, hydrates, and solvates thereof), wherein -Y-, -X=, -R^{Z7}, -R^{Z8}, and -R^{Z9} are as defined herein (for convenience, collectively referred to herein as "fused triaryl amine compounds" or "FTA compounds"):



Some embodiments of the invention include the following:

(1) A compound selected from compounds of the following formula, and pharmaceutically acceptable salts, hydrates, and solvates thereof:



wherein:

-X= is independently -CR^{Z6}= or -N=;
-Y- is independently -S-, -NR^{Y}-, or -O-;
-R^{Y} is independently -H or saturated aliphatic C_{1-6}alkyl;

and wherein, if -X= *is* -CR^{Z6}=, *then*:

-R^{Z6} is independently -H, -R^{QS}, or -R^{QL};
-R^{Z7} is independently -H, -R^{QS}, or -R^{QL};
-R^{Z8} is independently -H, -R^{QS}, or -R^{QL}; and
-R^{Z9} is independently -H, -R^{QS}, or -R^{QL};
with the proviso that *at least one* of -R^{Z6}, -R^{Z7}, -R^{Z8}, and -R^{Z9} is -R^{QL};

and wherein, if -X= is -N=, then:

-R^{Z7} is independently -H, -R^{QS}, or -R^{QL};
-R^{Z8} is independently -H, -R^{QS}, or -R^{QL}; and
-R^{Z9} is independently -H, -R^{QS}, or -R^{QL};
with the proviso that *at least one* of -R^{Z7}, -R^{Z8}, and -R^{Z9} is -R^{QL};

wherein:

each -R^{QL} is independently -R^{CA}, -R^{HA}, -R^{CC}, or -R^{HC};
wherein:
-R^{CA} is independently phenyl or naphthyl, and is optionally substituted;
-R^{HA} is independently C_{5-12}heteroaryl, and is optionally substituted;
-R^{CC} is independently non-aromatic C_{3-7}cycloalkyl or non-aromatic C_{3-7}cycloalkenyl, and is optionally substituted;
-R^{HC} is independently non-aromatic C_{3-7}heterocyclyl, and is optionally substituted;

and wherein:

each -R^{QS} is independently -F, -Cl, -Br, -I, -R^S, -CF_3, -OH, -OR^S, -OCF_3, -NH_2, -NHR^S, -NR^S_2, -NHC(=O)R^S, -NHC(=O)OR^S, -C(=O)OH, -C(=O)OR^S, -C(=O)NH_2, -C(=O)NHR^S, -C(=O)NR^S_2, -SH, -SR^S, -CN, or -NO_2;

wherein each -R^S is independently saturated aliphatic C_{1-6}alkyl, phenyl, -CH_2-phenyl, -CH_2CH_2-phenyl, or -CH=CH-phenyl, wherein each phenyl is optionally substituted with one or more groups selected from: -F, -Cl, -Br, -I, -R^{SS}, -CF_3, -OH, -OR^{SS}, and -OCF_3, wherein each -R^{SS} is independently saturated aliphatic C_{1-4}alkyl.

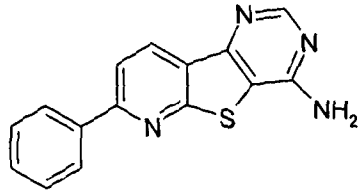
Optional Provisos

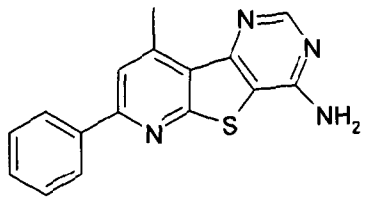
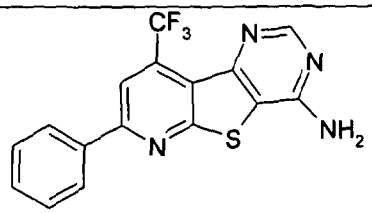
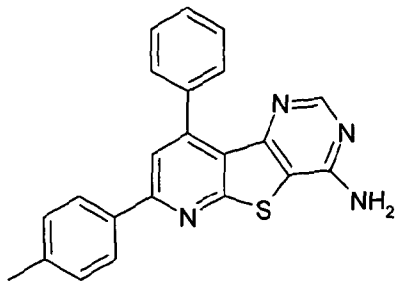
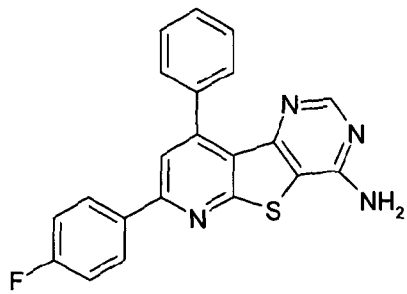
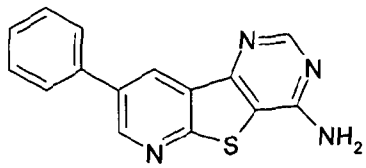
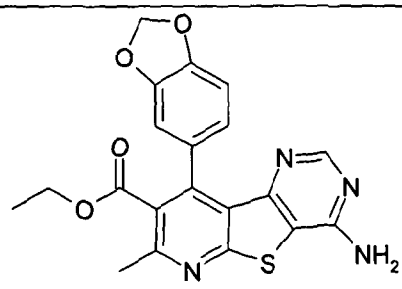
In one or more aspects of the present invention (e.g., compounds, compositions, methods of treatment, compounds for use in therapy, use of compounds in the manufacture of a medicament, etc.), the compounds are optionally as defined herein, but with a proviso as defined in this section.

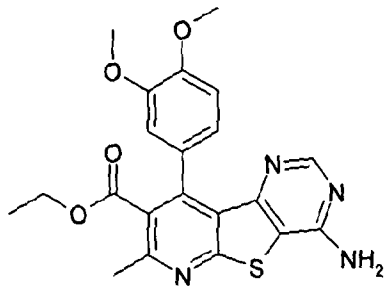
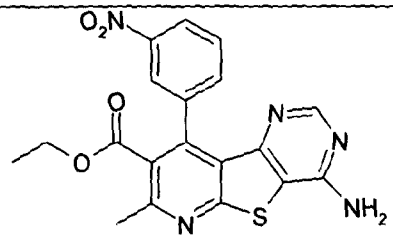
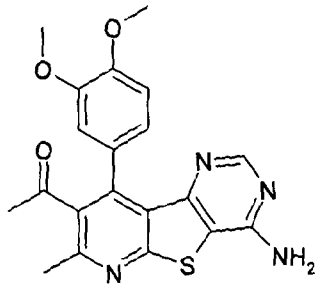
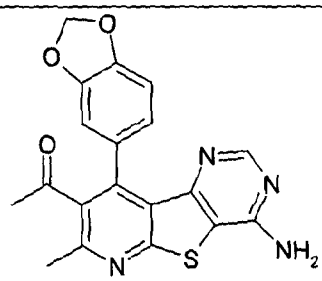
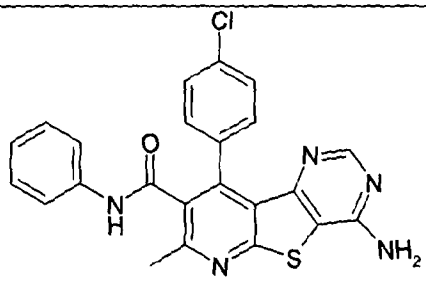
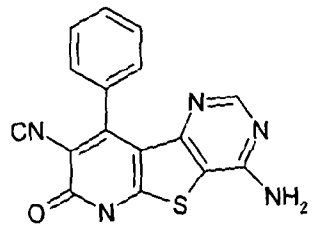
In one or more aspects of the present invention (e.g., compounds for use in therapy, use of compounds in the manufacture of a medicament, methods, methods of treatment, etc.), the compounds are optionally as defined herein, but without the proviso as defined in this section.

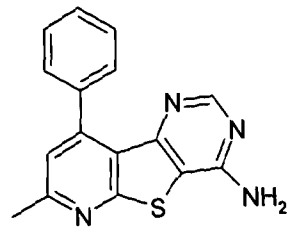
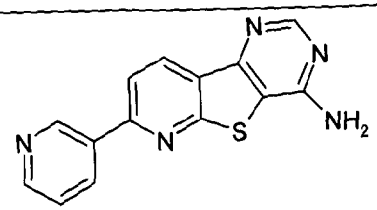
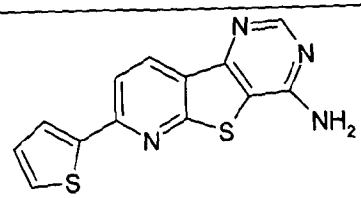
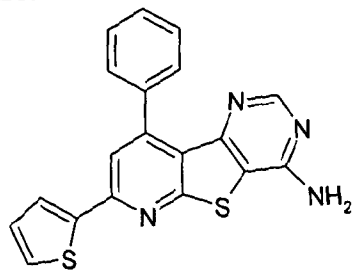
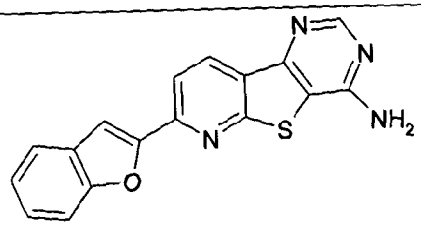
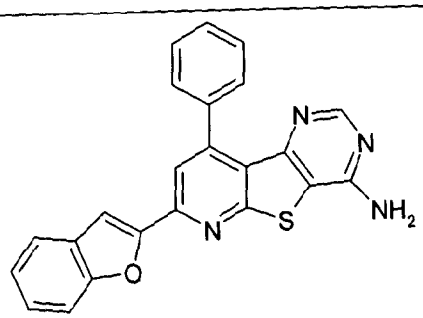
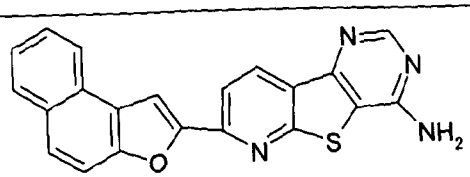
For example, a reference to a particular group of compounds "*without the recited proviso*" (e.g., for use in therapy) is intended to be a reference to the compounds as defined, but wherein the definition no longer includes the indicated proviso. In such cases, it is as if the indicated proviso has been deleted from the definition of compounds, and the definition has been expanded to encompass those compounds which otherwise would have been excluded by the indicated proviso.

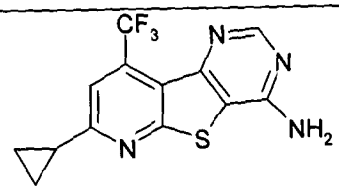
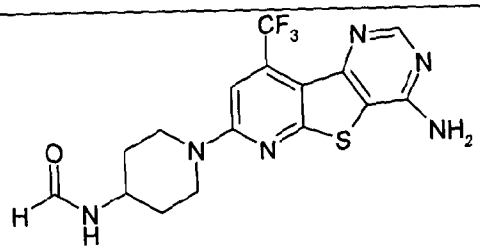
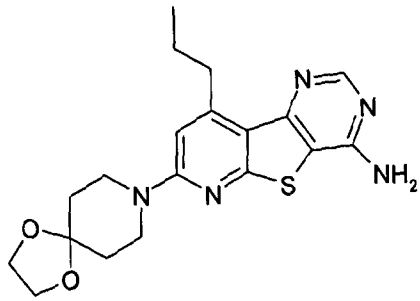
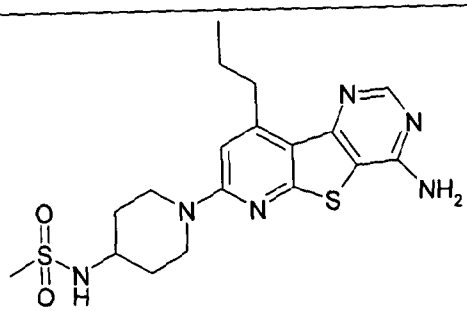
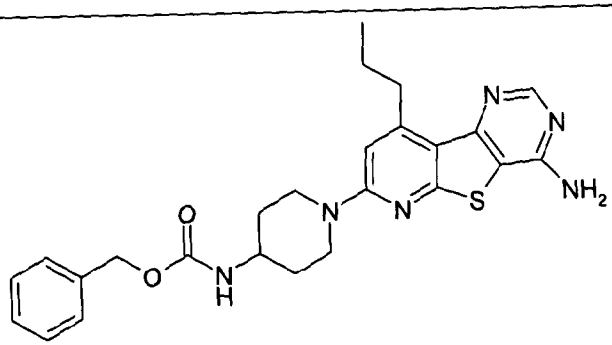
(2) A compound according to (1), with the proviso that the compound is not a compound selected from: compounds PP-001 to PP-034, and pharmaceutically acceptable salts, hydrates, and solvates thereof.

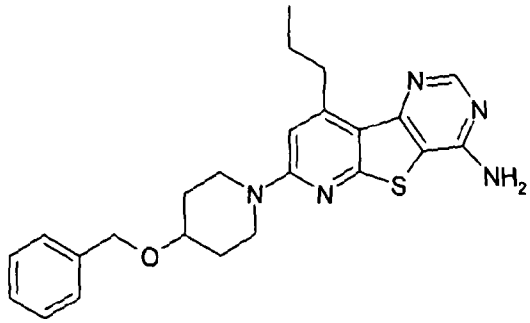
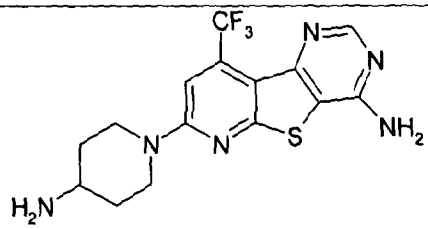
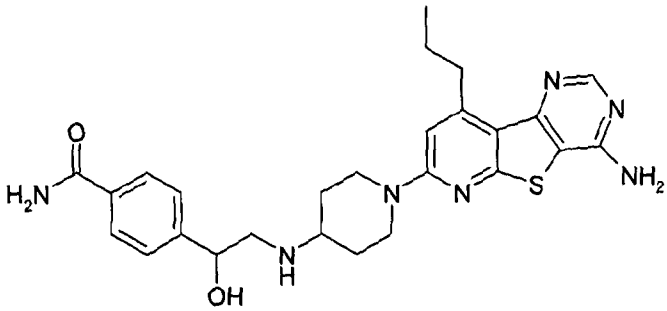
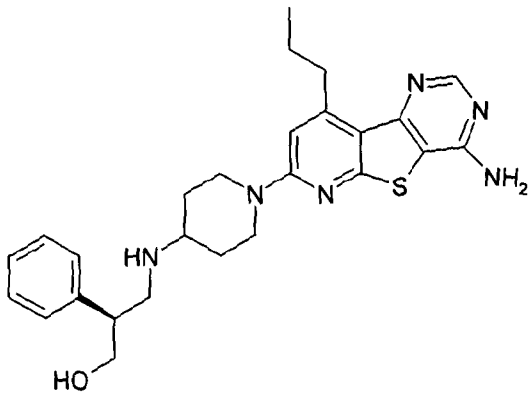
Code	Reg No	Structure
PP-001	340816-57-1	

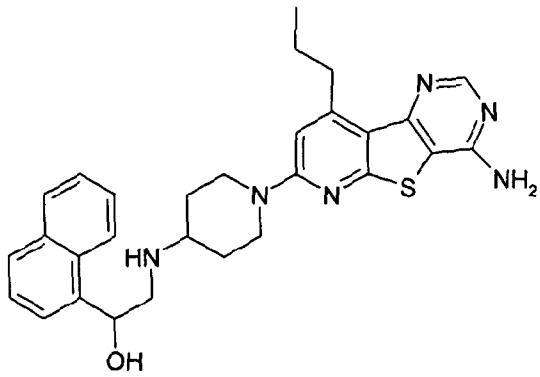
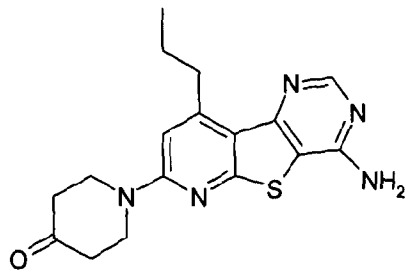
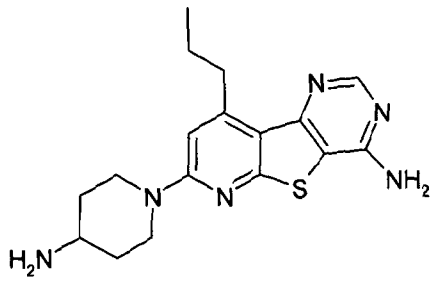
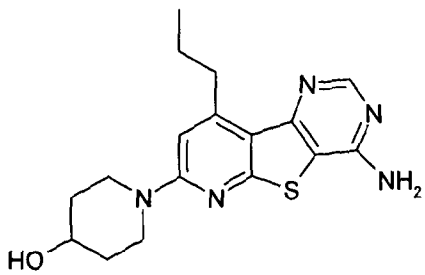
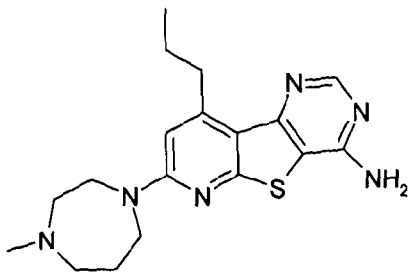
Code	Reg No	Structure
PP-002	371949-36-9	
PP-003	104960-60-3	
PP-004	78564-40-6	
PP-005	78564-39-3	
PP-006	1122023-25-9	
PP-007	1186047-84-6	

Code	Reg No	Structure
PP-008	1186047-85-7	
PP-009	1021183-91-4	
PP-010	1006595-85-2	
PP-011	1006595-84-1	
PP-012	745813-89-2	
PP-013	141481-05-2	

Code	Reg No	Structure
PP-014	94638-84-3	
PP-015	118947-70-9	
PP-016	879083-78-0	
PP-017	400738-23-0	
PP-018	1187925-97-8	
PP-019	1173187-58-0	
PP-020	860269-36-9	

Code	Reg No	Structure
PP-021	1122023-24-8	
PP-022	850180-47-1	
PP-023	850180-43-7	
PP-024	850180-34-6	
PP-025	850180-33-5	

Code	Reg No	Structure
PP-026	850180-32-4	
PP-027	850180-30-2	
PP-028	850180-27-7	
PP-029	850180-26-6	

Code	Reg No	Structure
PP-030	850180-25-5	
PP-031	850180-24-4	
PP-032	850180-23-3	
PP-033	850180-22-2	
PP-034	850180-21-1	

The Group -Y-

(3) A compound according to (1) or (2), wherein -Y- is independently -S- or -O-.

(4) A compound according to (1) or (2), wherein -Y- is independently -S- or -NR^Y-.

(5) A compound according to (1) or (2), wherein -Y- is independently -S-.

(6) A compound according to (1) or (2), wherein -Y- is independently -O-.

(7) A compound according to (1) or (2), wherein -Y- is independently -NR^Y-.

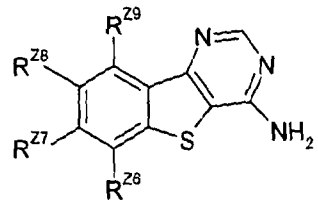
The Group -X=

(8) A compound according to any one of (1) to (7), wherein -X= is independently -CR^{Z8}=.

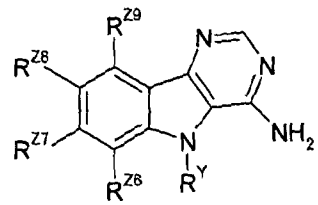
(9) A compound according to any one of (1) to (7), wherein -X= is independently -N=.

Combinations of the Group -Y- and the Group -X=

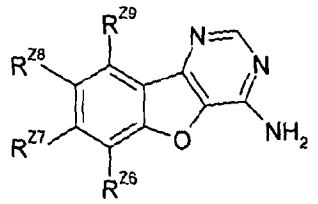
(10) A compound according to (1), wherein the compound is selected from compounds of the following formula, and pharmaceutically acceptable salts, hydrates, and solvates thereof:



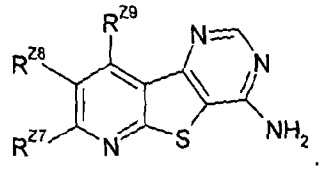
(11) A compound according to (1), wherein the compound is selected from compounds of the following formula, and pharmaceutically acceptable salts, hydrates, and solvates thereof:



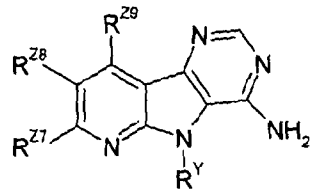
(12) A compound according to (1), wherein the compound is selected from compounds of the following formula, and pharmaceutically acceptable salts, hydrates, and solvates thereof:



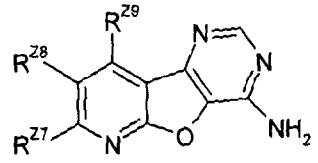
(13) A compound according to (1) or (2), wherein the compound is selected from compounds of the following formula, and pharmaceutically acceptable salts, hydrates, and solvates thereof:



(14) A compound according to (1), wherein the compound is selected from compounds of the following formula, and pharmaceutically acceptable salts, hydrates, and solvates thereof:



(15) A compound according to (1), wherein the compound is selected from compounds of the following formula, and pharmaceutically acceptable salts, hydrates, and solvates thereof:



The Group -R^Y

(16) A compound according to any one of (1) to (15), wherein -R^Y, if present, is independently -H, -Me, -Et, -nPr, -iPr, -nBu, -iBu, -sBu, or -tBu.

(17) A compound according to any one of (1) to (15), wherein -R^Y, if present, is independently -H, -Me, or -Et.

(18) A compound according to any one of (1) to (15), wherein $-R^Y$, if present, is independently -H or -Me.

(19) A compound according to any one of (1) to (15), wherein $-R^Y$, if present, is independently -Me.

(20) A compound according to any one of (1) to (15), wherein $-R^Y$, if present, is independently -H.

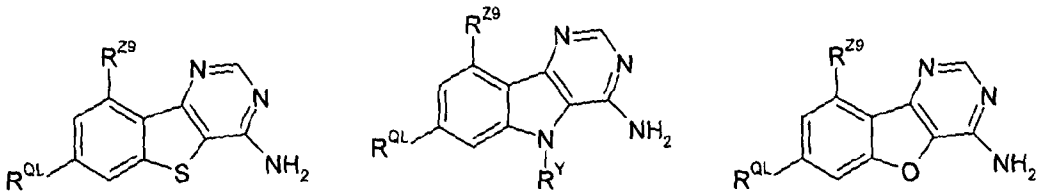
The Groups $-R^{Z6}$, $-R^{Z7}$, $-R^{Z8}$, and $-R^{Z9}$

(21) A compound according to any one of (1) to (20), wherein, if -X= is $-CR^{Z6}=$, then:
$-R^{Z6}$ is independently -H, $-R^{QS}$, or $-R^{QL}$;
$-R^{Z7}$ is independently -H, $-R^{QS}$, or $-R^{QL}$;
$-R^{Z8}$ is independently -H, $-R^{QS}$, or $-R^{QL}$; and
$-R^{Z9}$ is independently -H, $-R^{QS}$, or $-R^{QL}$;
with the proviso that *exactly one* of $-R^{Z6}$, $-R^{Z7}$, $-R^{Z8}$, and $-R^{Z9}$ is $-R^{QL}$.

(22) A compound according to any one of (1) to (20), wherein, if -X= is $-CR^{Z6}=$, then:
$-R^{Z6}$ is independently -H or $-R^{QS}$;
$-R^{Z7}$ is independently $-R^{QL}$;
$-R^{Z8}$ is independently -H or $-R^{QS}$; and
$-R^{Z9}$ is independently -H or $-R^{QS}$.

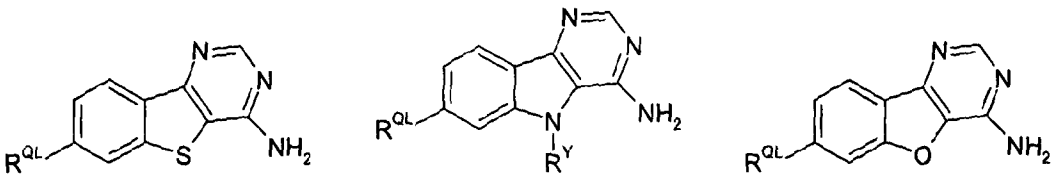
(23) A compound according to any one of (1) to (20), wherein, if -X= is $-CR^{Z6}=$, then:
$-R^{Z6}$ is independently -H;
$-R^{Z7}$ is independently $-R^{QL}$;
$-R^{Z8}$ is independently -H; and
$-R^{Z9}$ is independently -H or $-R^{QS}$.

Examples of the previous embodiment include the following:



(24) A compound according to any one of (1) to (20), wherein, if -X= is $-CR^{Z6}=$, then:
$-R^{Z6}$ is independently -H;
$-R^{Z7}$ is independently $-R^{QL}$;
$-R^{Z8}$ is independently -H; and
$-R^{Z9}$ is independently -H.

Examples of the previous embodiment include the following:

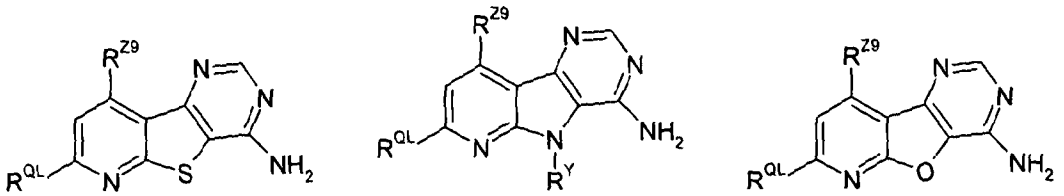


(25) A compound according to any one of (1) to (20), wherein, if -X= is -N=, then:
-R^{Z7} is independently -H, -R^{QS}, or -R^{QL};
-R^{Z8} is independently -H, -R^{QS}, or -R^{QL}; and
-R^{Z9} is independently -H, -R^{QS}, or -R^{QL};
with the proviso that *exactly one* of -R^{Z7}, -R^{Z8}, and -R^{Z9} is -R^{QL};

(26) A compound according to any one of (1) to (20), wherein, if -X= is -N=, then:
-R^{Z7} is independently -R^{QL};
-R^{Z8} is independently -H or -R^{QS}; and
-R^{Z9} is independently -H or -R^{QS}.

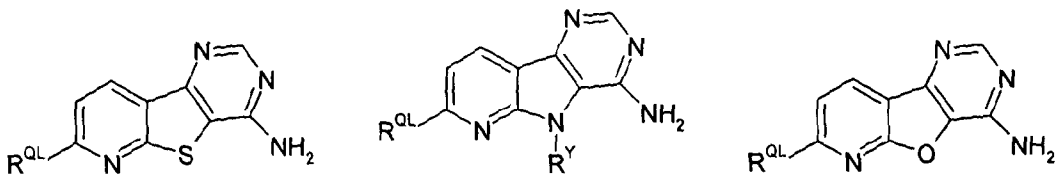
(27) A compound according to any one of (1) to (20), wherein, if -X= is -N=, then:
-R^{Z7} is independently -R^{QL};
-R^{Z8} is independently -H; and
-R^{Z9} is independently -H or -R^{QS}.

Examples of the previous embodiment include the following:



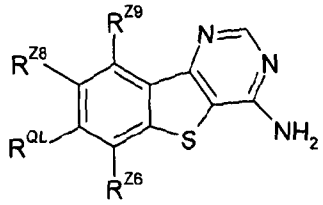
(28) A compound according to any one of (1) to (20), wherein, if -X= is -N=, then:
-R^{Z7} is independently -R^{QL};
-R^{Z8} is independently -H; and
-R^{Z9} is independently -H.

Examples of the previous embodiment include the following:



Some Preferred Combinations

(29) A compound according to (1), selected from compounds of the following formula, and pharmaceutically acceptable salts, hydrates, and solvates thereof:



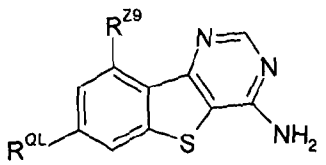
wherein:

$-R^{Z6}$ is independently -H or $-R^{QS}$;

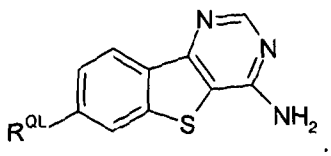
$-R^{Z8}$ is independently -H or $-R^{QS}$; and

$-R^{Z9}$ is independently -H or $-R^{QS}$.

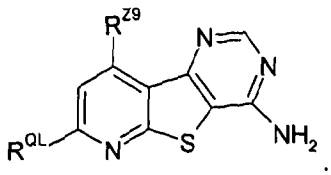
(30) A compound according to (1), selected from compounds of the following formula, and pharmaceutically acceptable salts, hydrates, and solvates thereof, wherein $-R^{Z9}$ is independently -H or $-R^{QS}$:



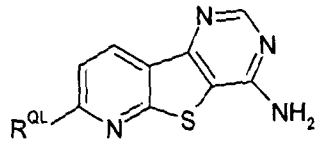
(31) A compound according to (1), selected from compounds of the following formula, and pharmaceutically acceptable salts, hydrates, and solvates thereof:



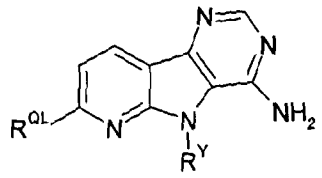
(32) A compound according to (1), selected from compounds of the following formula, and pharmaceutically acceptable salts, hydrates, and solvates thereof, wherein $-R^{Z9}$ is independently -H or $-R^{QS}$:



(32) A compound according to (1) or (2), selected from compounds of the following formula, and pharmaceutically acceptable salts, hydrates, and solvates thereof:



(33) A compound according to (1), selected from compounds of the following formula, and pharmaceutically acceptable salts, hydrates, and solvates thereof:



The Group -R^{QS}

(34) A compound according to any one of (1) to (33), wherein each -R^{QS}, if present, is independently -F, -Cl, -Br, -I, -R^S, -CF_3, -OH, -OR^S, -OCF_3, -NH_2, -NHR^S, -NR^S_2, -NHC(=O)R^S, -NHC(=O)OR^S, -C(=O)OH, -C(=O)OR^S, -C(=O)NH_2, -C(=O)NHR^S, or -C(=O)NR^S_2.

(35) A compound according to any one of (1) to (33), wherein each -R^{QS}, if present, is independently -F, -Cl, -Br, -I, -R^S, -CF_3, -OH, -OR^S, or -OCF_3.

(36) A compound according to any one of (1) to (33), wherein each -R^{QS}, if present, is independently -R^S.

(37) A compound according to any one of (1) to (33), wherein each -R^S, if present, is independently saturated aliphatic C_{1-4}alkyl or phenyl, wherein said phenyl is optionally substituted with one or more groups selected from: -F, -Cl, -Br, -I, -R^{SSS}, -CF_3, -OH, -OR^{SSS}, or -OCF_3, wherein each -R^{SSS} is independently saturated aliphatic C_{1-4}alkyl.

(38) A compound according to any one of (1) to (33), wherein each -R^S, if present, is independently saturated aliphatic C_{1-4}alkyl or phenyl.

(39) A compound according to any one of (1) to (33), wherein each -R^S, if present, is independently saturated aliphatic C_{1-4}alkyl.

(40) A compound according to any one of (1) to (33), wherein each -R^S, if present, is independently -Me, -Et, -nPr, -iPr, -nBu, -iBu, or -tBu.

(41) A compound according to any one of (1) to (33), wherein each $-R^S$, if present, is independently -Me.

The Group $-R^{QL}$

(42) A compound according to any one of (1) to (41), wherein $-R^{QL}$, or each $-R^{QL}$, is independently $-R^{CA}$ or $-R^{HA}$.

(42) A compound according to any one of (1) to (41), wherein $-R^{QL}$, or each $-R^{QL}$, is independently $-R^{CA}$.

(44) A compound according to any one of (1) to (41), wherein $-R^{QL}$, or each $-R^{QL}$, is independently $-R^{HA}$.

(45) A compound according to any one of (1) to (41), wherein $-R^{QL}$, or each $-R^{QL}$, is independently $-R^{CC}$.

(46) A compound according to any one of (1) to (41), wherein $-R^{QL}$, or each $-R^{QL}$, is independently $-R^{HC}$.

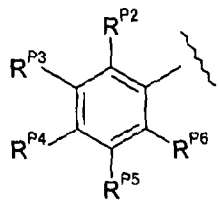
The Group $-R^{CA}$

(47) A compound according to any one of (1) to (46), wherein $-R^{CA}$, if present, or each $-R^{CA}$, if present, is independently phenyl; and is optionally substituted, for example, with one or more groups $-R^X$.

(48) A compound according to any one of (1) to (46), wherein $-R^{CA}$, if present, or each $-R^{CA}$, if present, is independently naphthyl; and is optionally substituted, for example, with one or more groups $-R^X$.

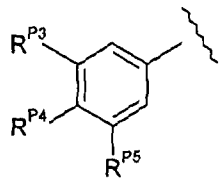
The Group $-R^{CA}$: Phenyl

(49) A compound according to any one of (1) to (46), wherein $-R^{CA}$, if present, or each $-R^{CA}$, if present, is independently:



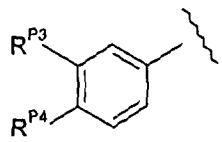
wherein each of $-R^{P2}$, $-R^{P3}$, $-R^{P4}$, $-R^{P5}$, and $-R^{P6}$ is independently -H or a ring substituent; for example, wherein each ring substituent is independently $-R^X$.

(50) A compound according to any one of (1) to (46), wherein $-R^{CA}$, if present, or each $-R^{CA}$, if present, is independently:



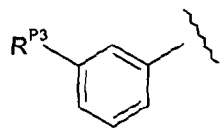
wherein each of $-R^{P3}$, $-R^{P4}$, and $-R^{P5}$ is independently -H or a ring substituent; for example, wherein each ring substituent is independently $-R^{X}$.

(51) A compound according to any one of (1) to (46), wherein $-R^{CA}$, if present, or each $-R^{CA}$, if present, is independently:



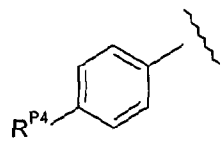
wherein each of $-R^{P3}$ and $-R^{P4}$ is independently -H or a ring substituent; for example, wherein each ring substituent is independently $-R^{X}$.

(52) A compound according to any one of (1) to (46), wherein $-R^{CA}$, if present, or each $-R^{CA}$, if present, is independently:



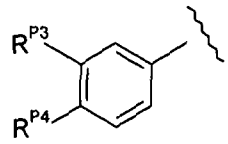
wherein $-R^{P3}$ is independently a ring substituent; for example, wherein the ring substituent is independently $-R^{X}$.

(53) A compound according to any one of (1) to (46), wherein $-R^{CA}$, if present, or each $-R^{CA}$, if present, is independently:



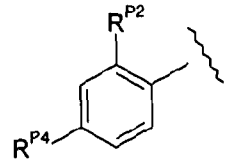
wherein $-R^{P4}$ is independently a ring substituent; for example, wherein the ring substituent is independently $-R^{X}$.

(54) A compound according to any one of (1) to (46), wherein $-R^{CA}$, if present, or each $-R^{CA}$, if present, is independently:



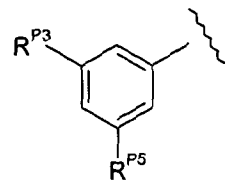
wherein each of $-R^{P3}$ and $-R^{P4}$ is independently a ring substituent; for example, wherein each ring substituent is independently $-R^{X}$.

(55) A compound according to any one of (1) to (46), wherein $-R^{CA}$, if present, or each $-R^{CA}$, if present, is independently:



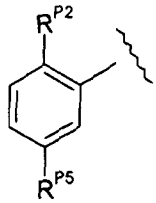
wherein each of $-R^{P2}$ and $-R^{P4}$ is independently -H or a ring substituent; for example, wherein each ring substituent is independently $-R^{X}$.

(56) A compound according to any one of (1) to (46), wherein $-R^{CA}$, if present, or each $-R^{CA}$, if present, is independently:



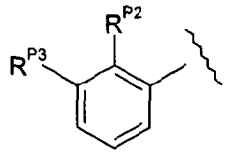
wherein each of $-R^{P3}$ and $-R^{P5}$ is independently a ring substituent; for example, wherein each ring substituent is independently $-R^{X}$.

(57) A compound according to any one of (1) to (46), wherein $-R^{CA}$, if present, or each $-R^{CA}$, if present, is independently:



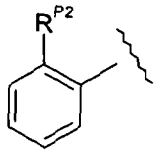
wherein each of $-R^{P2}$ and $-R^{P5}$ is independently a ring substituent; for example, wherein each ring substituent is independently $-R^{X}$.

(58) A compound according to any one of (1) to (46), wherein -R^{CA}, if present, or each -R^{CA}, *if present, is independently*:



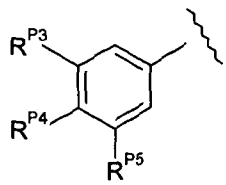
wherein each of -R^{P2} and -R^{P3} is independently a ring substituent; for example, wherein each ring substituent is independently -R^{X}.

(59) A compound according to any one of (1) to (46), wherein -R^{CA}, if present, or each -R^{CA}, if present, is independently:



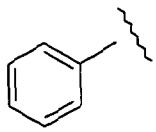
wherein -R^{P2} is independently a ring substituent; for example, wherein the ring substituent is independently -R^{X}.

(60) A compound according to any one of (1) to (46), wherein -R^{CA}, if present, or each -R^{CA}, if present, is independently:



wherein each of -R^{P3}, -R^{P4}, and -R^{P5} is independently a ring substituent; for example, wherein each ring substituent is independently -R^{X}.

(61) A compound according to any one of (1) to (46), wherein -R^{CA}, if present, or each -R^{CA}, if present, is independently:



The Group -R^{HA}

(62) A compound according to any one of (1) to (61), wherein -R^{HA}, if present, or each -R^{HA}, if present, is independently furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, pyridazinyl, indolyl, isoindolyl, indazolyl, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, benzoisoxazolyl, quinolinyl, isoquinolinyl,

dihydroisoquinolinyl, cinnolinyl, or quinazolinyl; and is optionally substituted, for example, with one or more groups -R^X.

(63) A compound according to any one of (1) to (61), wherein -R^{HA}, if present, or each -R^{HA}, if present, is independently furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, pyridazinyl, and indolyl; and is optionally substituted, for example, with one or more groups -R^X.

(64) A compound according to any one of (1) to (61), wherein -R^{HA}, if present, or each -R^{HA}, if present, is independently thienyl, pyrazolyl, pyridyl, pyrimidinyl, and indolyl; and is optionally substituted, for example, with one or more groups -R^X.

(65) A compound according to any one of (1) to (61), wherein -R^{HA}, if present, or each -R^{HA}, if present, is independently pyridyl; and is optionally substituted, for example, with one or more groups -R^X.

(66) A compound according to any one of (1) to (61), wherein -R^{HA}, if present, or each -R^{HA}, if present, is independently pyrid-2-yl; and is optionally substituted, for example, with one or more groups -R^X.

(67) A compound according to any one of (1) to (61), wherein -R^{HA}, if present, or each -R^{HA}, if present, is independently pyrid-3-yl; and is optionally substituted, for example, with one or more groups -R^X.

(68) A compound according to any one of (1) to (61), wherein -R^{HA}, if present, or each -R^{HA}, if present, is independently pyrid-4-yl; and is optionally substituted, for example, with one or more groups -R^X.

(69) A compound according to any one of (1) to (61), wherein -R^{HA}, if present, or each -R^{HA}, if present, is independently thienyl; and is optionally substituted, for example, with one or more groups -R^X.

(70) A compound according to any one of (1) to (61), wherein -R^{HA}, if present, or each -R^{HA}, if present, is independently thien-3-yl; and is optionally substituted, for example, with one or more groups -R^X.

(71) A compound according to any one of (1) to (61), wherein -R^{HA}, if present, or each -R^{HA}, if present, is independently pyrazolyl; and is optionally substituted, for example, with one or more groups -R^X.

(72) A compound according to any one of (1) to (61), wherein -R^{HA}, if present, or each -R^{HA}, if present, is independently 1H-pyrazolyl; and is optionally substituted, for example, with one or more groups -R^X.

(73) A compound according to any one of (1) to (61), wherein -R^{HA}, if present, or each -R^{HA}, if present, is independently 1H-pyrazol-4-yl; and is optionally substituted, for example, with one or more groups -R^{X}.

(74) A compound according to any one of (1) to (61), wherein -R^{HA}, if present, or each -R^{HA}, if present, is independently 1H-pyrazol-1-yl; and is optionally substituted, for example, with one or more groups -R^{X}.

(75) A compound according to any one of (1) to (61), wherein -R^{HA}, if present, or each -R^{HA}, if present, is independently pyrimidinyl; and is optionally substituted, for example, with one or more groups -R^{X}.

(76) A compound according to any one of (1) to (61), wherein -R^{HA}, if present, or each -R^{HA}, if present, is independently pyrimidin-5-yl; and is optionally substituted, for example, with one or more groups -R^{X}.

(77) A compound according to any one of (1) to (61), wherein -R^{HA}, if present, or each -R^{HA}, if present, is independently indolyl; and is optionally substituted, for example, with one or more groups -R^{X}.

(78) A compound according to any one of (1) to (61), wherein -R^{HA}, if present, or each -R^{HA}, if present, is independently indol-5-yl; and is optionally substituted, for example, with one or more groups -R^{X}.

(79) A compound according to any one of (1) to (61), wherein -R^{HA}, if present, or each -R^{HA}, if present, is independently benzo[d]isoxazol-3-one-5-yl; and is optionally substituted, for example, with one or more groups -R^{X}.

(80) A compound according to any one of (1) to (61), wherein -R^{HA}, if present, or each -R^{HA}, if present, is independently benzo[d]isoxazol-3-one-5-yl.

(81) A compound according to any one of (1) to (61), wherein -R^{HA}, if present, or each -R^{HA}, if present, is independently 3,4-dihydro-2H-isoquinolin-1-one-7-yl; and is optionally substituted, for example, with one or more groups -R^{X}.

(82) A compound according to any one of (1) to (61), wherein -R^{HA}, if present, or each -R^{HA}, if present, is independently 3,4-dihydro-2H-isoquinolin-1-one-7-yl.

The Group -R^{CC}

(83) A compound according to any one of (1) to (82), wherein -R^{CC}, if present, or each -R^{CC}, if present, is non-aromatic C_{3-7}cycloalkyl; and is optionally substituted, for example, with one or more groups -R^{X}.

(84) A compound according to any one of (1) to (82), wherein -R^{CC}, if present, or each -R^{CC}, if present, is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl; and is optionally substituted, for example, with one or more groups -R^{X}.

(85) A compound according to any one of (1) to (82), wherein -R^{CC}, if present, or each -R^{CC}, if present, is cyclopentyl or cyclohexyl; and is optionally substituted, for example, with one or more groups -R^{X}.

(86) A compound according to any one of (1) to (82) wherein -R^{CC}, if present, or each -R^{CC}, if present, is non-aromatic C_{3-7}cycloalkenyl; and is optionally substituted, for example, with one or more groups -R^{X}.

(87) A compound according to any one of (1) to (82), wherein -R^{CC}, if present, or each -R^{CC}, if present, is cyclopropenyl, cyclobutenyl, cyclopentenyl, or cyclohexenyl; and is optionally substituted, for example, with one or more groups -R^{X}.

(88) A compound according to any one of (1) to (82), wherein -R^{CC}, if present, or each -R^{CC}, if present, is cyclopentenyl or cyclohexenyl; and is optionally substituted, for example, with one or more groups -R^{X}.

(89) A compound according to any one of (1) to (82), wherein -R^{CC}, if present, or each -R^{CC}, if present, is cyclohexenyl; and is optionally substituted, for example, with one or more groups -R^{X}.

The Group -R^{HC}

(90) A compound according to any one of (1) to (89), wherein -R^{HC}, if present, or each -R^{HC}, if present, is non-aromatic C_{3-7}heterocyclyl; and is optionally substituted, for example, with one or more groups -R^{X}; wherein the non-aromatic C_{3-7}heterocyclyl has from 3 to 7 ring atoms, wherein exactly 1 or exactly 2 of said ring atoms is N, and the remaining ring atoms are C.

(91) A compound according to any one of (1) to (89), wherein -R^{HC}, if present, or each -R^{HC}, if present, is non-aromatic C_{5-6}heterocyclyl; and is optionally substituted, for example, with one or more groups -R^{X}; wherein the non-aromatic C_{3-7}heterocyclyl has from 5 to 6 ring atoms, wherein exactly 1 or exactly 2 of said ring atoms is N, and the remaining ring atoms are C.

(92) A compound according to any one of (1) to (89), wherein $-R^{HC}$, if present, or each $-R^{HC}$, if present, is tetrahydropyranyl, azetidinyl, pyrrolidinyl, imidazolidinyl, piperidinyl, piperizinyl, morpholinyl, azepinyl, or diazepinyl; and is optionally substituted, for example, with one or more groups $-R^{X}$.

(93) A compound according to any one of (1) to (89), wherein $-R^{HC}$, if present, or each $-R^{HC}$, if present, is azetidino, pyrrolidino, imidazolidino, piperidino, piperizino, morpholino, azepino, or diazepino; and is optionally substituted, for example, with one or more groups $-R^{X}$.

(94) A compound according to any one of (1) to (89), wherein $-R^{HC}$, if present, or each $-R^{HC}$, if present, is piperidino, piperizino, or morpholino; and is optionally substituted, for example, with one or more groups $-R^{X}$.

(95) A compound according to any one of (1) to (89), wherein $-R^{HC}$, if present, or each $-R^{HC}$, if present, is piperidino; and is optionally substituted, for example, with one or more groups $-R^{X}$.

(96) A compound according to any one of (1) to (89), wherein $-R^{HC}$, if present, or each $-R^{HC}$, if present, is piperizino; and is optionally substituted, for example, with one or more groups $-R^{X}$.

(97) A compound according to any one of (1) to (89), wherein $-R^{HC}$, if present, or each $-R^{HC}$, if present, is morpholino; and is optionally substituted, for example, with one or more groups $-R^{X}$.

Optional Substituents on $-R^{CA}$, $-R^{HA}$, $-R^{CC}$, and $-R^{HC}$

(98) A compound according to any one of (1) to (84), wherein each of $-R^{CA}$, $-R^{HA}$, $-R^{CC}$, and $-R^{HC}$, if present, is optionally substituted with one or more substituents, $-R^{X}$, wherein each $-R^{X}$ is independently selected from $-R^{X1}$ and $-R^{X2}$, wherein:

each $-R^{X1}$ is independently:

$-R^{Z}$,
$-F$, $-Cl$, $-Br$, $-I$,
$-CF_3$, $-OCF_3$,
$-OH$, $-R^{ZL}-OH$, $-O-R^{ZL}-OH$, $-NH-R^{ZL}-OH$, $-NR^{Z}-R^{ZL}-OH$,
$-OR^{Z}$, $-R^{ZL}-OR^{Z}$, $-O-R^{ZL}-OR^{Z}$, $-NH-R^{ZL}-OR^{Z}$, $-NR^{Z}-R^{ZL}-OR^{Z}$,
$-SH$, $-SR^{Z}$,
$-CN$,
$-NO_2$,

-C(=O)OH, -C(=O)OR^{Z},
-C(=O)R^{Z},
-NH$_2$, -NHR^{Z}, -NR$^{Z}_2$, -R^{NZ},
-R^{ZL}-NH$_2$, -R^{ZL}-NHR^{Z}, -R^{ZL}-NR$^{Z}_2$, -R^{ZL}-R^{NZ},
-O-R^{ZL}-NH$_2$, -O-R^{ZL}-NHR^{Z}, -O-R^{ZL}-NR$^{Z}_2$, -O-R^{ZL}-R^{NZ},
-NH-R^{ZL}-NH$_2$, -NH-R^{ZL}-NHR^{Z}, -NH-R^{ZL}-NR$^{Z}_2$, -NH-R^{ZL}-R^{NZ},
-NR^{Z}-R^{ZL}-NH$_2$, -NR^{Z}-R^{ZL}-NHR^{Z}, -NR^{Z}-R^{ZL}-NR$^{Z}_2$, -NR^{Z}-R^{ZL}-R^{NZ},
-C(=O)NH$_2$, -C(=O)NHR^{Z}, -C(=O)NR$^{Z}_2$, -C(=O)R^{NZ},
-R^{ZL}-C(=O)NH$_2$, -R^{ZL}-C(=O)NHR^{Z}, -R^{ZL}-C(=O)NR$^{Z}_2$, -R^{ZL}-C(=O)R^{NZ},
-O-R^{ZL}-C(=O)NH$_2$, -O-R^{ZL}-C(=O)NHR^{Z}, -O-R^{ZL}-C(=O)NR$^{Z}_2$, -O-R^{ZL}-C(=O)R^{NZ},
-NH-C(=O)R^{Z}, -NR^{Z}-C(=O)R^{Z},
-NH-C(=O)OH, -NR^{Z}-C(=O)OH, -NH-C(=O)OR^{Z}, -NR^{Z}-C(=O)OR^{Z},
-OC(=O)NH$_2$, -OC(=O)NHR^{Z}, -OC(=O)NR$^{Z}_2$, -OC(=O)R^{NZ},
-NHC(=O)NH$_2$, -NHC(=O)NHR^{Z}, -NHC(=O)NR$^{Z}_2$, -NHC(=O)R^{NZ},
-NR^{Z}C(=O)NH$_2$, -NR^{Z}C(=O)NHR^{Z}, -NR^{Z}C(=O)NR$^{Z}_2$, -NR^{Z}C(=O)R^{NZ},
-S(=O)$_2$R^{Z},
-S(=O)$_2$NH$_2$, -S(=O)$_2$NHR^{Z}, -S(=O)$_2$NR$^{Z}_2$, -S(=O)$_2$R^{NZ},
-NH-S(=O)$_2$R^{Z}, -NR^{Z}-S(=O)$_2$R^{Z}, or
=O;

and additionally, two or more adjacent substituents -R^{X1}, if present, may together form -OCH$_2$O-, -OCH$_2$CH$_2$O-, or -OCH$_2$CH$_2$CH$_2$O-;

wherein:

each -R^{ZL}- is independently saturated aliphatic C$_{1-4}$alkylene;

each -R^{NZ} is independently azetidino, pyrrolidino, piperidino, piperazino, morpholino, azepino, or diazepino, and is optionally substituted with one or more substitutents selected from saturated aliphatic C$_{1-4}$alkyl;

each -R^{Z} is independently saturated aliphatic C$_{1-6}$alkyl, phenyl, benzyl, or C$_{5-6}$heteroaryl, wherein phenyl, benzyl, and C$_{5-6}$heteroaryl are each optionally substituted with one or more substituents selected from -F, -Cl, -Br, -I, -R^{ZZ}, -CF$_3$, -OH, -OR^{ZZ}, -OCF$_3$, -NH$_2$, -NHR^{ZZ}, -NR$^{ZZ}_2$, -C(=O)OH, -C(=O)NH$_2$, -C(=O)NHR^{ZZ}, and -C(=O)NR$^{ZZ}_2$, wherein each -R^{ZZ} is independently saturated aliphatic C$_{1-4}$alkyl; and

each -R^{X2} is independently:

-NH-C(=J)-NH$_2$, -NR^{K1}-C(=J)-NH$_2$,
-NH-C(=J)-NHR^{K2}, -NR^{K1}-C(=J)-NHR^{K2},
-NH-C(=J)-NR$^{K2}_2$, -NR^{K1}-C(=J)-NR$^{K2}_2$,
-NH-C(=J)-NR^{K3}R^{K4}, -NR^{K1}-C(=J)-NR^{K3}R^{K4},

-NH-C(=O)H, -NR^{K1}-C(=O)H,
-NH-C(=O)R^{K5}, -NR^{K1}-C(=O)R^{K5},

$-C(=O)-NH_2$, $-C(=O)-NHR^{K2}$, $-C(=O)-NR^{K2}{}_2$, $-C(=O)-NR^{K3}R^{K4}$,

-OH, or $-OR^{K6}$;

wherein each =J is independently =O or =S;

and wherein each $-R^{K1}$ *is independently saturated aliphatic* C_{1-4}*alkyl*;

and wherein each $-R^{K2}$ is independently:

saturated aliphatic C_{1-4}alkyl, aliphatic C_{2-4}alkenyl, or saturated C_{3-6}cycloalkyl;

each optionally substituted with one or more groups independently selected from: -F, -Cl, -Br, -I, -OH, $-OR^{A1}$, $-OCF_3$, $-SR^{A1}$, $-S(=O)R^{A1}$, $-S(=O)_2R^{A1}$, $-NH_2$, $-NHR^{A1}$, $-NR^{A1}{}_2$, pyrrolidinyl, piperidinyl, morpholinyl, piperizinyl, -C(=O)OH, $-C(=O)OR^{A1}$, $-OC(=O)R^{A1}$, $-C(=O)NH_2$, $-C(=O)NHR^{A1}$, $-C(=O)NR^{A1}{}_2$, pyrrolidino-C(=O)-, piperidino-C(=O)-, morpholino-C(=O)-, piperizino-C(=O)-, and $-R^{A2}$;

wherein:

each pyrrolidinyl, piperidinyl, morpholinyl, piperizinyl, pyrrolidino, piperidino, morpholino, and piperizino is optionally substituted with one or more groups independently selected from -F, $-R^{A1}$, -OH, $-OR^{A1}$, $-NH_2$, $-NHR^{A1}$, $-NR^{A1}{}_2$, pyrrolidino, piperidino, morpholino, piperizino, -C(=O)OH, $-C(=O)OR^{A1}$, $-C(=O)R^{A1}$, $-C(=O)NH_2$, $-C(=O)NHR^{A1}$, $-C(=O)NR^{A1}{}_2$, pyrrolidino-C(=O)-, piperidino-C(=O)-, morpholino-C(=O)-, piperizino-C(=O)-, and $-OCH_2CH_2O-$;

each $-R^{A1}$ is independently saturated aliphatic C_{1-4}alkyl; and

each $-R^{A2}$ is independently phenyl, C_{5-6}heteroaryl, or non-aromatic C_{5-7}heterocyclyl;

and wherein each $-NR^{K3}R^{K4}$ is independently:

pyrrolidino, piperidino, morpholino, or piperizino;

each optionally substituted with one or more groups independently selected from -F, $-R^{A3}$, -OH, $-OR^{A3}$, $-NH_2$, $-NHR^{A3}$, $-NR^{A3}{}_2$, pyrrolidino, piperidino, morpholino, piperizino, -C(=O)OH, $-C(=O)OR^{A3}$, $-C(=O)R^{A3}$, $-C(=O)NH_2$, $-C(=O)NHR^{A3}$, $-C(=O)NR^{A3}{}_2$, pyrrolidino-C(=O)-, piperidino-C(=O)-, morpholino-C(=O)-, piperizino-C(=O)-, and $-OCH_2CH_2O-$;

wherein each $-R^{A3}$ is independently saturated aliphatic C_{1-4}alkyl, optionally substituted with one or more groups independently selected from -OH, $-OR^{A4}$, $-NH_2$, $-NHR^{A4}$, $-NR^{A4}{}_2$, *pyrrolidino, piperidino, morpholino, and piperizino*;

wherein each $-R^{A4}$ is independently saturated aliphatic C_{1-4}alkyl;

and wherein each $-R^{K5}$ is independently saturated aliphatic C_{1-4}alkyl, and is optionally substituted with one or more groups independently selected from: -F, -Cl, -Br, -I, $-CF_3$, -OH, $-OR^{A5}$, $-OCF_3$, $-NH_2$, $-NHR^{A5}$, and $-NR^{A5}{}_2$, wherein each $-R^{A5}$ is independently saturated aliphatic C_{1-4}alkyl;

and wherein each -R^{K6} is independently saturated aliphatic C_{1-4}alkyl, and is optionally substituted with one or more groups independently selected from: -F, -Cl, -Br, -I, -CF_3, -OH, -OR^{A6}, -OCF_3, -NH_2, -NHR^{A6}, and -NR^{A6}_2, wherein each -R^{A6} is independently saturated aliphatic C_{1-4}alkyl.

Optional Substituents -R^X

(99) A compound according to (98), wherein:
if exactly one group -R^X is present, then -R^X is -R^{X2}; and
if a plurality of groups -R^X are present, then at least one -R^X is -R^{X2}.

(100) A compound according to (98), wherein:
if exactly one group -R^X is present, then -R^X is -R^{X2}; and
if a plurality of groups -R^X are present, then exactly one -R^X is -R^{X2}.

(101) A compound according to (98), wherein:
exactly one group -R^X is present, and -R^X is -R^{X2}.

(102) A compound according to (98), wherein:
exactly two groups -R^X are present, one -R^X is -R^{X2}, and the other -R^X is -R^{X1}.

Optional Substituents -R^{X1}

(103) A compound according to any one of (98) to (102), wherein each -R^{X1}, if present, is independently:
-R^Z,
-F, -Cl, -Br, -I,
-CF_3, -OCF_3,
-OH, -R^{ZL}-OH, -O-R^{ZL}-OH, -NH-R^{ZL}-OH, -NR^Z-R^{ZL}-OH,
-OR^Z, -R^{ZL}-OR^Z, -O-R^{ZL}-OR^Z, -NH-R^{ZL}-OR^Z, -NR^Z-R^{ZL}-OR^Z,
-CN,
-NO_2,
-C(=O)OH, -C(=O)OR^Z,
-C(=O)R^Z,
-NH_2, -NHR^Z, -NR^Z_2, -R^{NZ},
-R^{ZL}-NH_2, -R^{ZL}-NHR^Z, -R^{ZL}-NR^Z_2, -R^{ZL}-R^{NZ},
-O-R^{ZL}-NH_2, -O-R^{ZL}-NHR^Z, -O-R^{ZL}-NR^Z_2, -O-R^{ZL}-R^{NZ},
-NH-R^{ZL}-NH_2, -NH-R^{ZL}-NHR^Z, -NH-R^{ZL}-NR^Z_2, -NH-R^{ZL}-R^{NZ},
-NR^Z-R^{ZL}-NH_2, -NR^Z-R^{ZL}-NHR^Z, -NR^Z-R^{ZL}-NR^Z_2, -NR^Z-R^{ZL}-R^{NZ},
-C(=O)NH_2, -C(=O)NHR^Z, -C(=O)NR^Z_2, -C(=O)R^{NZ},
-NH-C(=O)R^Z, -NR^Z-C(=O)R^Z,
-$S(=O)_2R^Z$,
-$S(=O)_2NH_2$, -$S(=O)_2NHR^Z$, -$S(=O)_2NR^Z_2$, -$S(=O)_2R^{NZ}$,

-NH-S(=O)$_2$R^Z, or -NR^Z-S(=O)$_2$R^Z.

(104) A compound according to any one of (98) to (102), wherein each -R^{X1}, if present, is independently:

-R^Z,
-F, -Cl, -Br, -I,
-CF$_3$, -OCF$_3$,
-OH, -R^{ZL}-OH, -O-R^{ZL}-OH,
-OR^Z, -R^{ZL}-OR^Z, -O-R^{ZL}-OR^Z,
-CN,
-NO$_2$,
-C(=O)OH, -C(=O)OR^Z,
-C(=O)R^Z,
-NH$_2$, -NHR^Z, -NR$^Z_2$, -R^{NZ},
-R^{ZL}-NH$_2$, -R^{ZL}-NHR^Z, -R^{ZL}-NR$^Z_2$, -R^{ZL}-R^{NZ},
-NH-R^{ZL}-NH$_2$, -NH-R^{ZL}-NHR^Z, -NH-R^{ZL}-NR$^Z_2$, -NH-R^{ZL}-R^{NZ},
-C(=O)NH$_2$, -C(=O)NHR^Z, -C(=O)NR$^Z_2$, -C(=O)R^{NZ},
-NH-C(=O)R^Z, or -NR^Z-C(=O)R^Z.

(105) A compound according to any one of (98) to (102), wherein each -R^{X1}, if present, is independently:

-R^Z,
-F, -Cl, -Br, -I,
-CF$_3$, -OCF$_3$,
-OH, -R^{ZL}-OH,
-OR^Z, -R^{ZL}-OR^Z,
-CN,
-NO$_2$,
-C(=O)OH, -C(=O)OR^Z,
-C(=O)R^Z,
-NH$_2$, -NHR^Z, -NR$^Z_2$, -R^{NZ},
-R^{ZL}-NH$_2$, -R^{ZL}-NHR^Z, -R^{ZL}-NR$^Z_2$, -R^{ZL}-R^{NZ},
-C(=O)NH$_2$, -C(=O)NHR^Z, -C(=O)NR$^Z_2$, or
-NH-C(=O)R^Z.

(106) A compound according to any one of (98) to (102), wherein each -R^{X1}, if present, is independently:

-R^Z,
-F, -Cl, -Br,
-OH,
-OR^Z,
-C(=O)OH, -C(=O)OR^Z,
-NH$_2$, -NHR^Z, -NR$^Z_2$, -R^{NZ},

$-C(=O)NH_2$, $-C(=O)NHR^Z$, $-C(=O)NR^Z{}_2$, or
$-NH-C(=O)R^Z$.

(107) A compound according to any one of (98) to (102), wherein each $-R^{X1}$, if present, is independently $-R^Z$, -F, -Cl, -Br, -OH, or $-OR^Z$.

(108) A compound according to any one of (98) to (107), wherein each $-R^{ZL}-$, if present, is independently saturated aliphatic C_{2-4}alkylene.

(109) A compound according to any one of (98) to (107), wherein each $-R^{ZL}-$, if present, is independently $-CH_2CH_2-$.

(110) (A compound according to any one of (98) to (109), wherein each $-R^{NZ}$, if present, is independently pyrrolidino, piperidino, piperazino, or morpholino, and is optionally substituted with one or more substitutents selected from saturated aliphatic C_{1-4}alkyl.

(111) A compound according to any one of (98) to (110), wherein each $-R^Z$, if present, is independently saturated aliphatic C_{1-6}alkyl, phenyl, or benzyl.

(112) A compound according to any one of (98) to (110), wherein each $-R^Z$, if present, is independently saturated aliphatic C_{1-6}alkyl.

(113) A compound according to any one of (98) to (110), wherein each $-R^Z$, if present, is independently saturated aliphatic C_{1-4}alkyl.

Optional Substituents $-R^{X2}$

(114) A compound according to any one of (98) to (113), wherein each $-R^{X2}$, if present, is independently:

$-NH-C(=J)-NH_2$, $-NR^{K1}-C(=J)-NH_2$,
$-NH-C(=J)-NHR^{K2}$, $-NR^{K1}-C(=J)-NHR^{K2}$,
$-NH-C(=J)-NR^{K2}{}_2$, $-NR^{K1}-C(=J)-NR^{K2}{}_2$,
$-NH-C(=J)-NR^{K3}R^{K4}$, or $-NR^{K1}-C(=J)-NR^{K3}R^{K4}$.

(115) A compound according to any one of (98) to (113), wherein each $-R^{X2}$, if present, is independently:

$-NH-C(=O)-NH_2$, $-NR^{K1}-C(=O)-NH_2$,
$-NH-C(=O)-NHR^{K2}$, $-NR^{K1}-C(=O)-NHR^{K2}$,
$-NH-C(=O)-NR^{K2}{}_2$, $-NR^{K1}-C(=O)-NR^{K2}{}_2$,
$-NH-C(=O)-NR^{K3}R^{K4}$, or $-NR^{K1}-C(=O)-NR^{K3}R^{K4}$.

(116) A compound according to any one of (98) to (113), wherein each $-R^{X2}$, if present, is independently:

$-NH-C(=O)H$, $-NR^{K1}-C(=O)H$,
$-NH-C(=O)R^{K5}$, $-NR^{K1}-C(=O)R^{K5}$,
$-C(=O)-NH_2$, $-C(=O)-NHR^{K2}$, $-C(=O)-NR^{K2}{}_2$, or $-C(=O)-NR^{K3}R^{K4}$.

(117) A compound according to any one of (98) to (113), wherein each $-R^{X2}$, if present, is independently:

$-NH-C(=O)H$, $-NR^{K1}-C(=O)H$,
$-NH-C(=O)R^{K5}$, or $-NR^{K1}-C(=O)R^{K5}$.

(118) A compound according to any one of (98) to (113), wherein each $-R^{X2}$, if present, is independently:

$-C(=O)-NH_2$, $-C(=O)-NHR^{K2}$, $-C(=O)-NR^{K2}{}_2$, or $-C(=O)-NR^{K3}R^{K4}$.

(119) A compound according to any one of (98) to (113), wherein each $-R^{X2}$, if present, is independently:

$-OH$ or $-OR^{K6}$.

The Group $-R^{K1}$

(120) A compound according to any one of (98) to (119), wherein each $-R^{K1}$, if present, is independently -Me, -Et, -nPr, -iPr, -nBu, -iBu, -sBu, or -tBu.

(121) A compound according to any one of (98) to (119), wherein each $-R^{K1}$, if present, is independently -Me or -Et.

(122) A compound according to any one of (98) to (119), wherein each $-R^{K1}$, if present, is independently -Me.

The Group $-R^{K2}$

(123) A compound according to any one of (98) to (122), wherein each $-R^{K2}$, if present, is independently: saturated aliphatic C_{1-4}alkyl, optionally substituted with one or more groups independently selected from: -F, -Cl, -Br, -I, -OH, $-OR^{A1}$, $-OCF_3$, $-SR^{A1}$, $-S(=O)R^{A1}$, $-S(=O)_2R^{A1}$, $-NH_2$, $-NHR^{A1}$, $-NR^{A1}{}_2$, pyrrolidinyl, piperidinyl, morpholinyl, piperizinyl, $-C(=O)OH$, $-C(=O)OR^{A1}$, $-OC(=O)R^{A1}$, $-C(=O)NH_2$, $-C(=O)NHR^{A1}$, $-C(=O)NR^{A1}{}_2$, pyrrolidino-C(=O)-, piperidino-C(=O)-, morpholino-C(=O)-, piperizino-C(=O)-, and $-R^{A2}$.

(124) A compound according to any one of (98) to (122), wherein each $-R^{K2}$, if present, is independently saturated aliphatic C_{1-4}alkyl.

(125) A compound according to any one of (98) to (122), wherein each $-R^{K2}$, if present, is independently aliphatic C_{2-4}alkenyl.

(126) A compound according to any one of (98) to (122), wherein each $-R^{K2}$, if present, is independently saturated C_{3-6}cycloalkyl.

The Group $-R^{A1}$

(127) A compound according to any one of (98) to (126), wherein each $-R^{A1}$, if present, is independently -Me, -Et, -nPr, -iPr, -nBu, -iBu, -sBu, or -tBu.

(128) A compound according to any one of (98) to (126), wherein each $-R^{A1}$, if present, is independently -Me or -Et.

(129) A compound according to any one of (98) to (126), wherein each $-R^{A1}$, if present, is independently -Me.

The Group $-R^{A2}$

(130) A compound according to any one of (98) to (129), wherein each $-R^{A2}$, if present, is independently phenyl or C_{5-6}heteroaryl.

(131) A compound according to any one of (98) to (129), wherein each $-R^{A2}$, if present, is independently phenyl.

The Group $-NR^{K3}R^{K4}$

(132) A compound according to any one of (98) to (131), wherein each $-NR^{K3}R^{K4}$, if present, is independently pyrrolidino, piperidino, morpholino, or piperizino.

The Group $-R^{A3}$

(133) A compound according to any one of (98) to (132), wherein each $-R^{A3}$, if present, is independently saturated aliphatic C_{1-4}alkyl.

(134) A compound according to any one of (98) to (132), wherein each $-R^{A3}$, if present, is independently -Me, -Et, -nPr, -iPr, -nBu, -iBu, -sBu, or -tBu.

(135) A compound according to any one of (98) to (132), wherein each $-R^{A3}$, if present, is independently -Me or -Et.

(136) A compound according to any one of (98) to (132), wherein each $-R^{A3}$, if present, is independently -Me.

The Group -R^{A4}

(137) A compound according to any one of (98) to (136), wherein each -R^{A4}, if present, is independently -Me, -Et, -nPr, -iPr, -nBu, -iBu, -sBu, or -tBu.

(138) A compound according to any one of (98) to (136), wherein each -R^{A4}, if present, is independently -Me or -Et.

(139) A compound according to any one of (98) to (136), wherein each -R^{A4}, if present, is independently -Me.

The Group -R^{K5}

(140) A compound according to any one of (98) to (139), wherein each -R^{K5}, if present, is independently saturated aliphatic C_{1-4}alkyl, and is optionally substituted with one or more groups independently selected from: -OH, -OR^{A5}, -NH_2, -NHR^{A5}, and -NR^{A5}_2.

(141) A compound according to any one of (98) to (139), wherein each -R^{K5}, if present, is independently saturated aliphatic C_{1-4}alkyl.

The Group -R^{A5}

(142) A compound according to any one of (98) to (141), wherein each -R^{A5}, if present, is independently -Me, -Et, -nPr, -iPr, -nBu, -iBu, -sBu, or -tBu.

(143) A compound according to any one of (98) to (141), wherein each -R^{A5}, if present, is independently -Me or -Et.

(144) A compound according to any one of (98) to (141), wherein each -R^{A5}, if present, is independently -Me.

The Group -R^{K6}

(145) A compound according to any one of (98) to (144), wherein each -R^{K6}, if present, is independently saturated aliphatic C_{1-4}alkyl, and is optionally substituted with one or more groups independently selected from: -OH, -OR^{A6}, -NH_2, -NHR^{A6}, and -NR^{A6}_2.

(146) A compound according to any one of (98) to (144), wherein each -R^{K6}, if present, is independently saturated aliphatic C_{1-4}alkyl.

The Group -R^{A6}

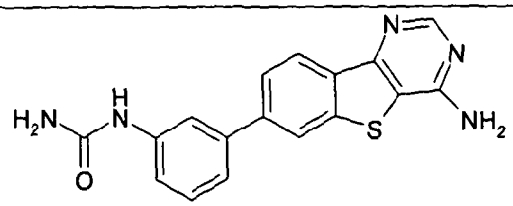
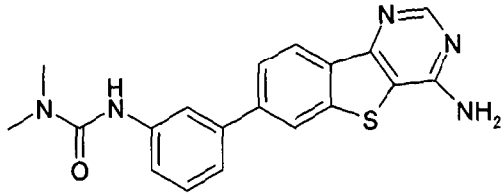
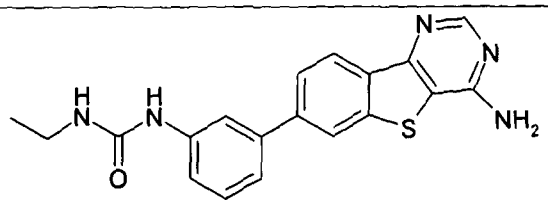
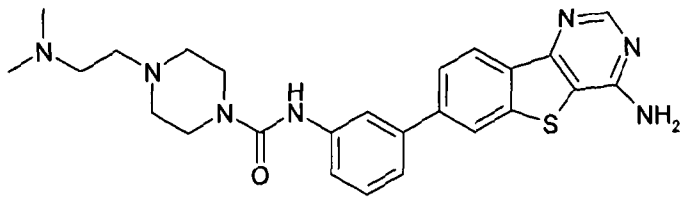
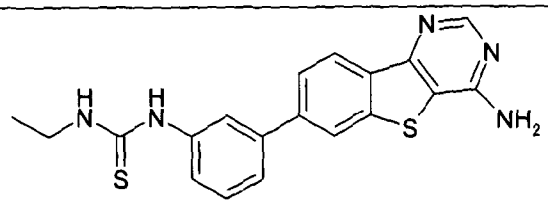
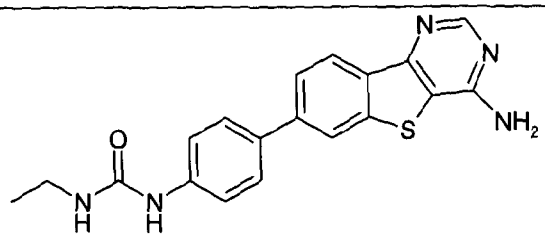
(147) A compound according to any one of (98) to (146), wherein each -R^{A6}, if present, is independently -Me, -Et, -nPr, -iPr, -nBu, -iBu, -sBu, or -tBu.

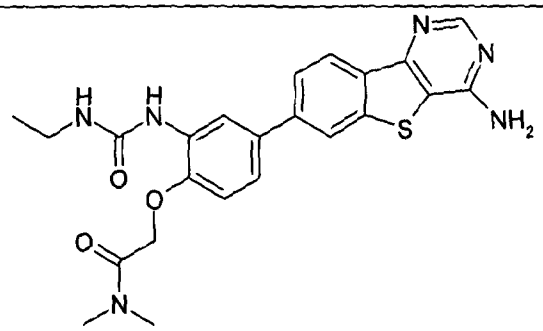
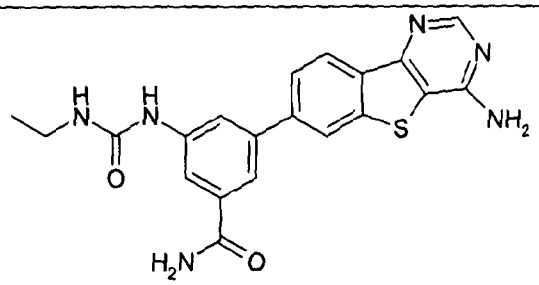
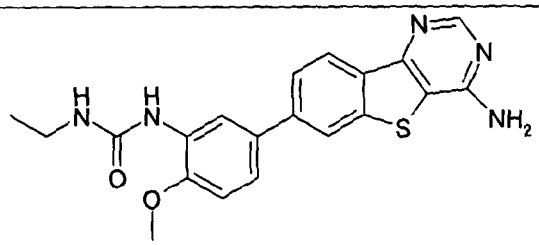
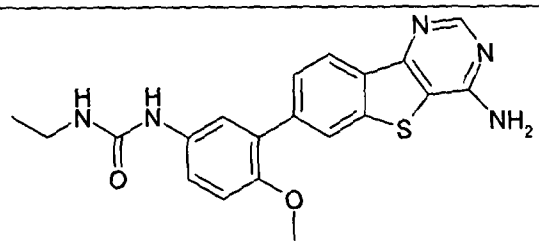
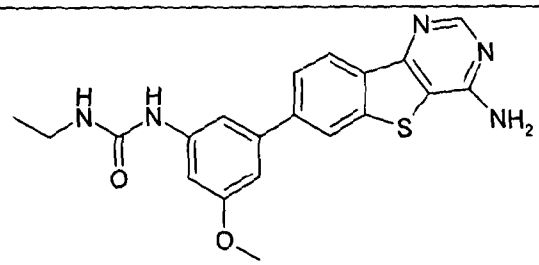
(148) A compound according to any one of (98) to (146), wherein each -R^{A6}, if present, is independently -Me or -Et.

(149) A compound according to any one of (98) to (146), wherein each -R^{A6}, if present, is independently -Me.

Examples of Some Specific Embodiments

(150) A compound according to (1), selected from compounds of the following formulae and pharmaceutically acceptable salts, hydrates, and solvates thereof:

Code	Chemical Structure
AA-001	
AA-002	
AA-003	
AA-004	
AA-005	
AA-006	

Code	Chemical Structure
AA-007	
AA-008	
AA-009	
AA-010	
AA-011	

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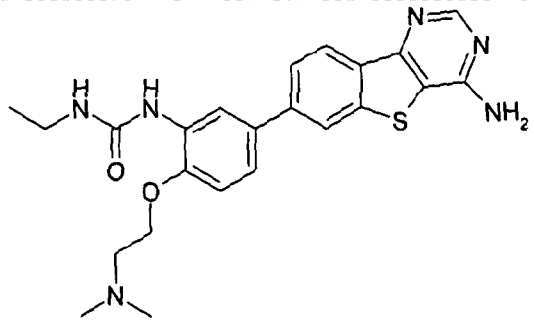
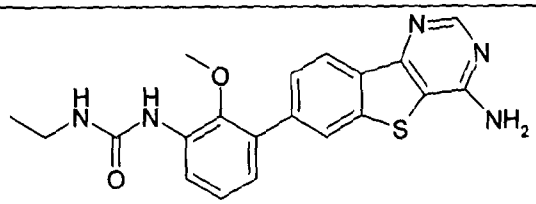
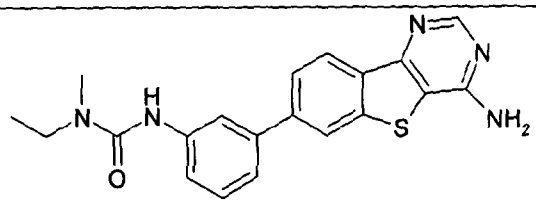
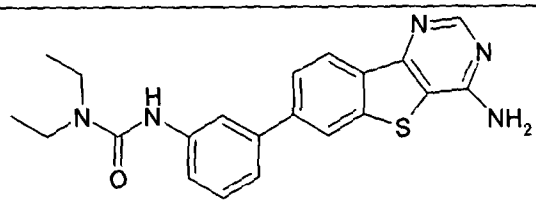
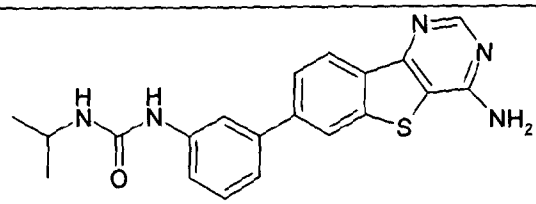
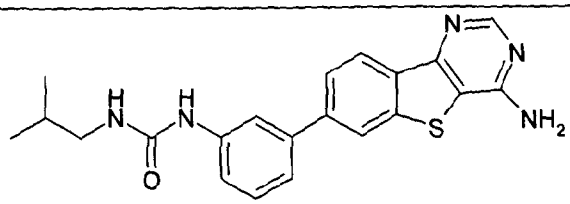
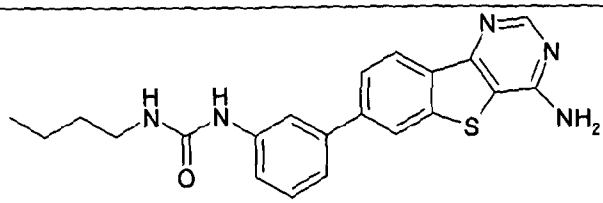
AA-012	
AA-013	
AA-014	
AA-015	
AA-016	
AA-017	
AA-018	

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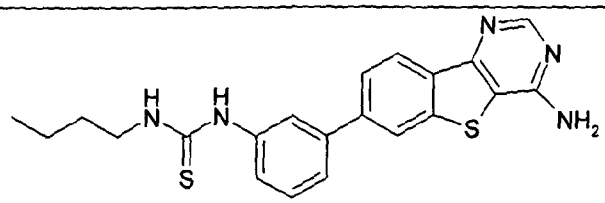
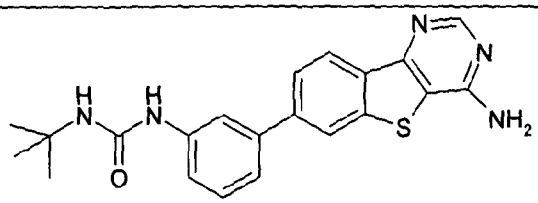
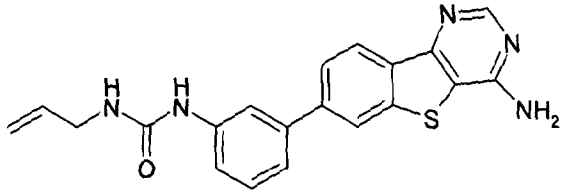
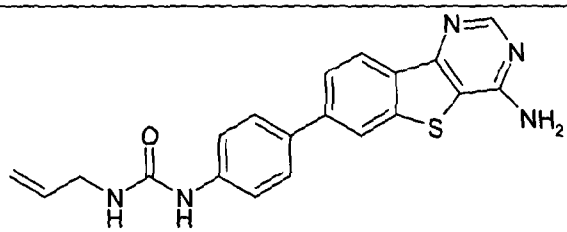
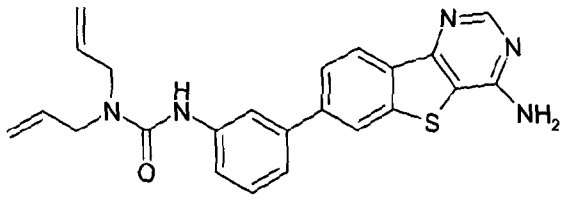
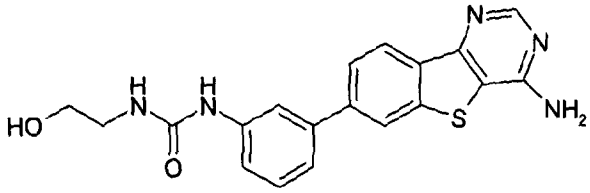
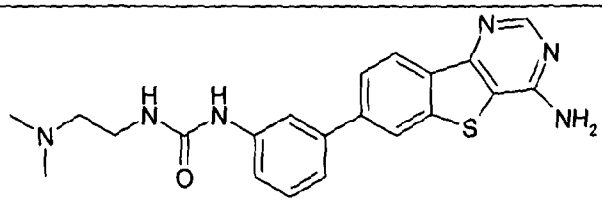
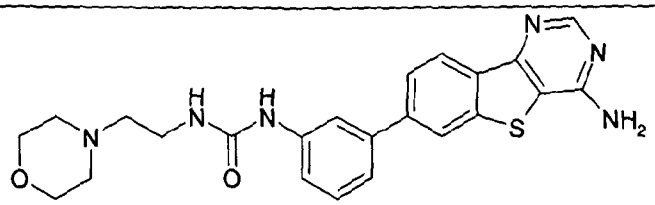
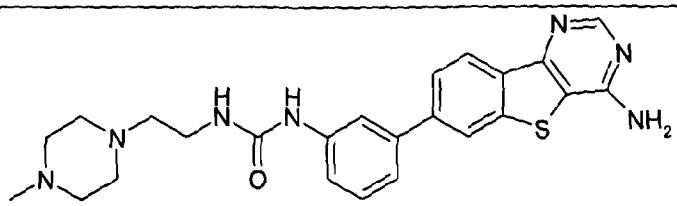
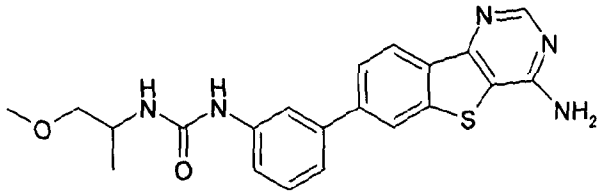
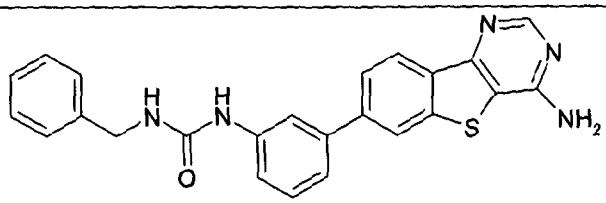
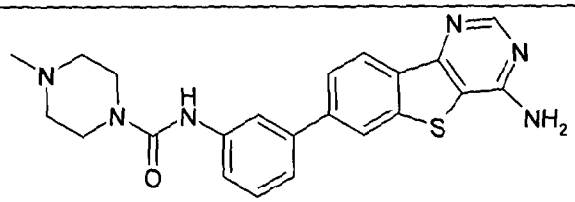
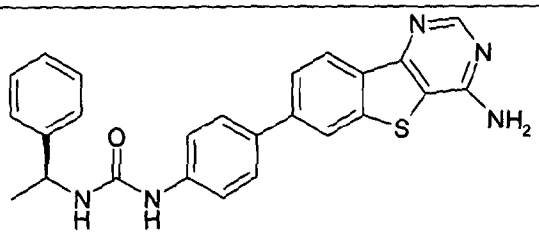
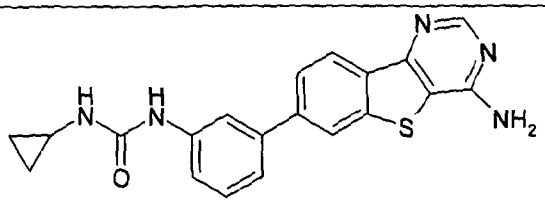
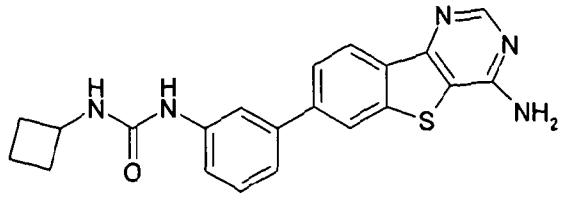
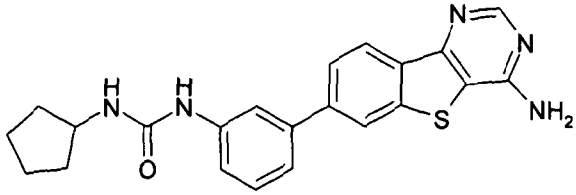
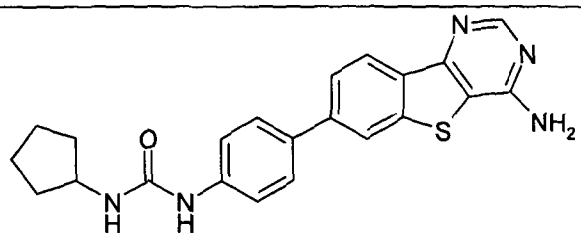
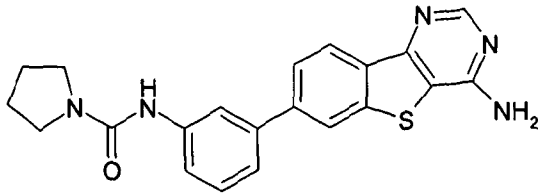
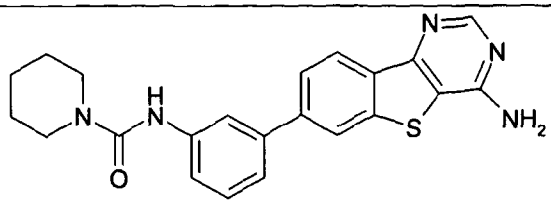
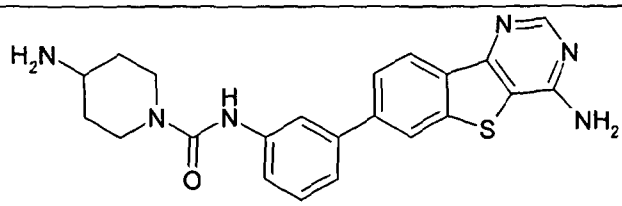
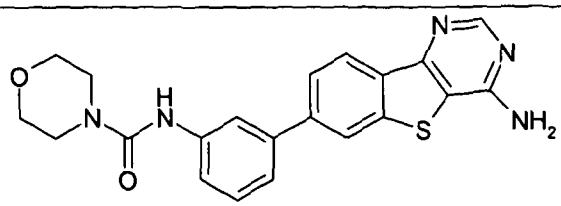
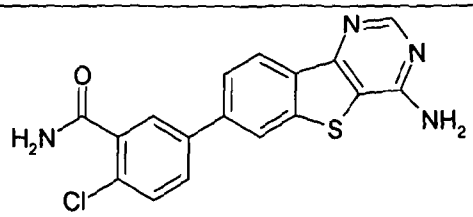
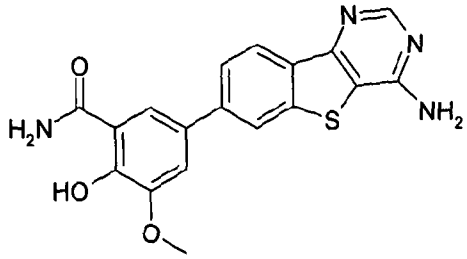
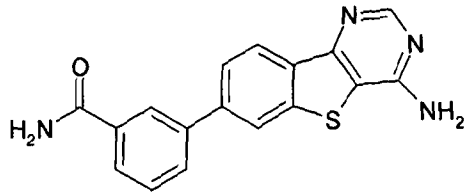
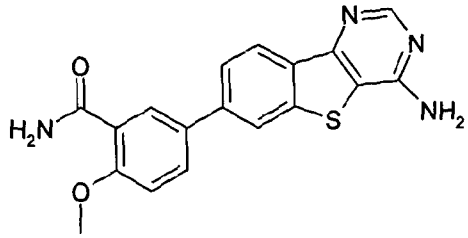
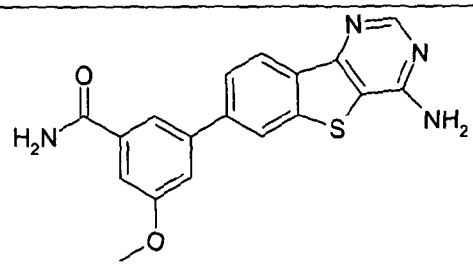
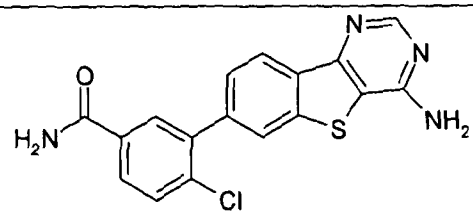
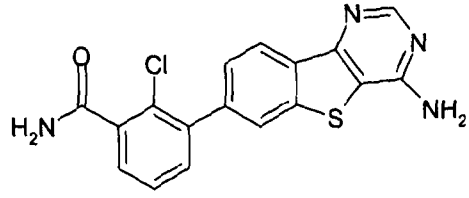
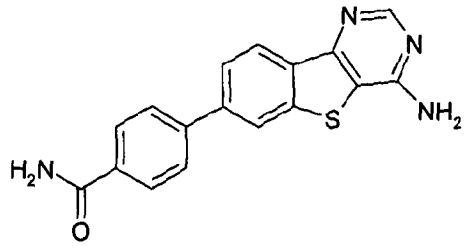
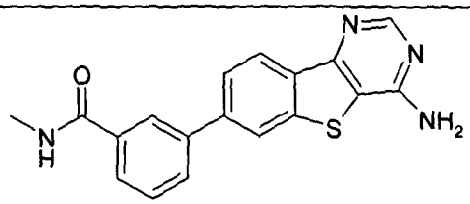
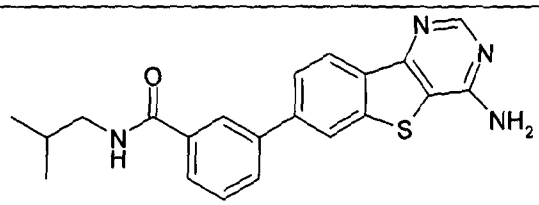
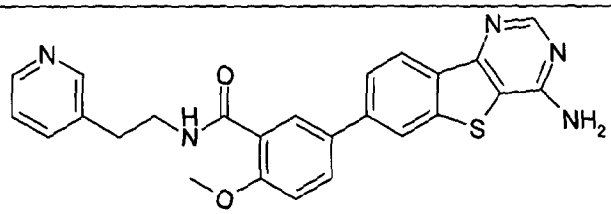
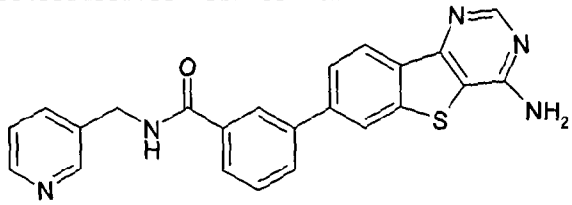
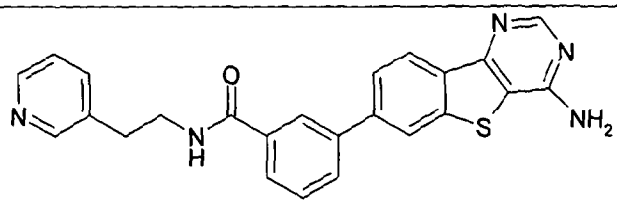
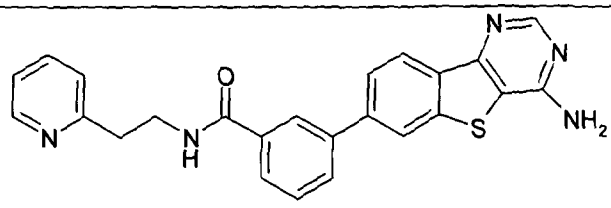
AA-019	
AA-020	
AA-021	
AA-022	
AA-023	
AA-024	
AA-025	

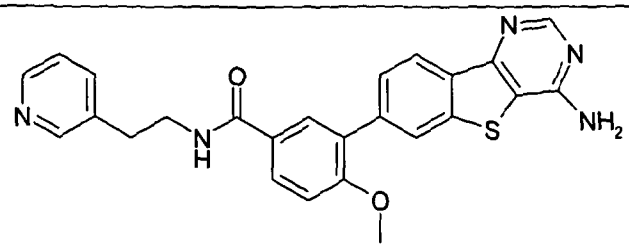
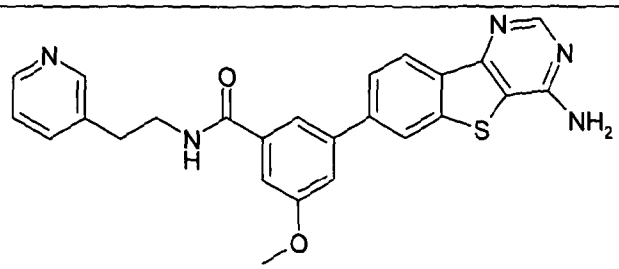
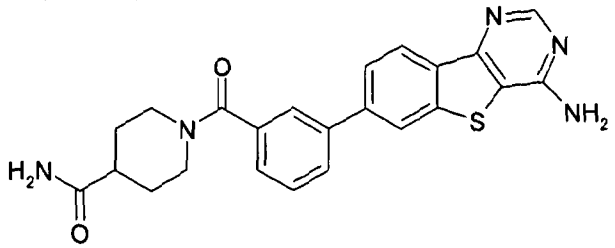
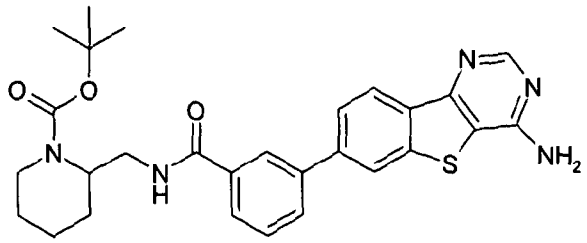
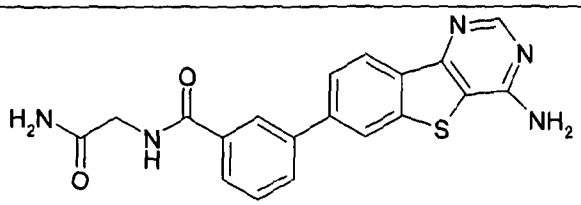
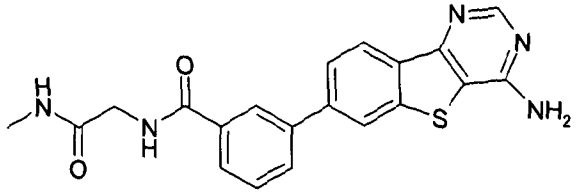
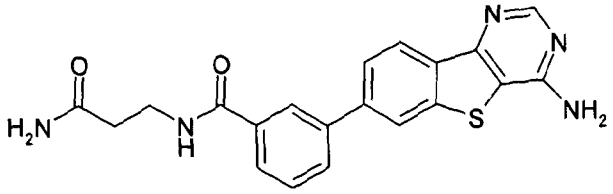
Code	Chemical Structure
AA-026	
AA-027	
AA-028	
AA-029	
AA-030	
AA-031	
AA-032	

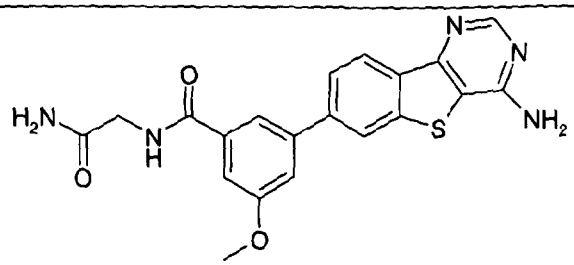
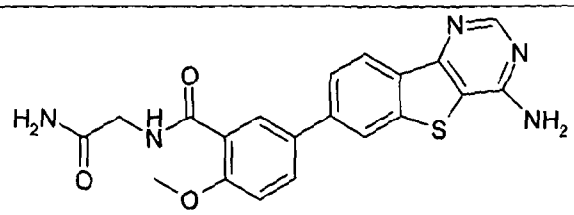
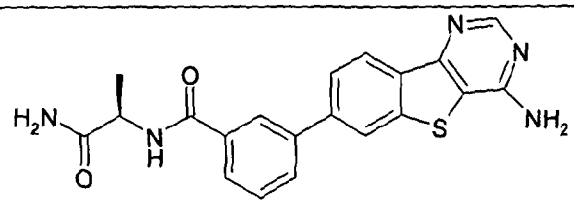
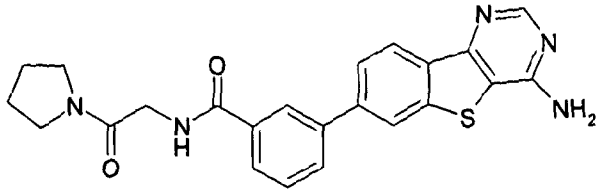
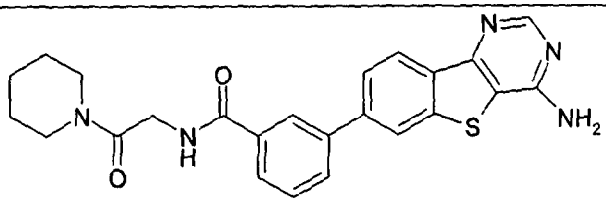
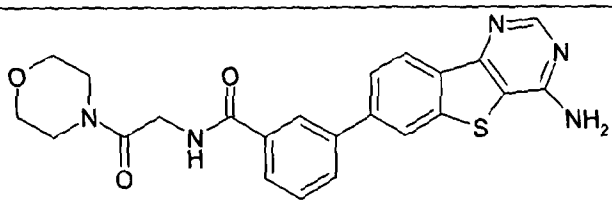
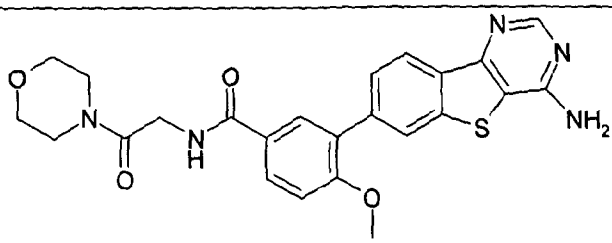
Code	Chemical Structure
AA-033	
AA-034	
AA-035	
AA-036	
AA-037	
AA-038	
AA-039	

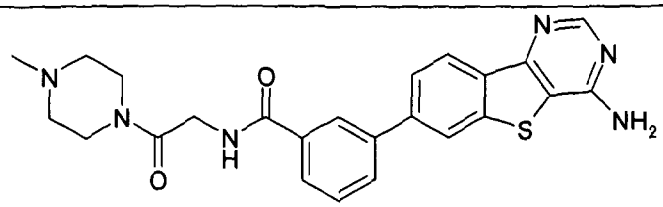
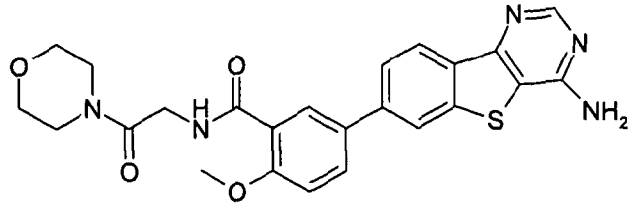
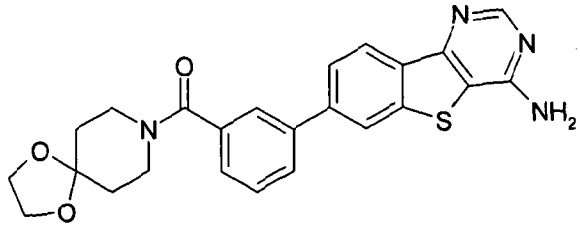
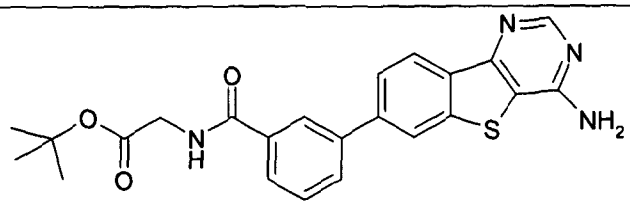
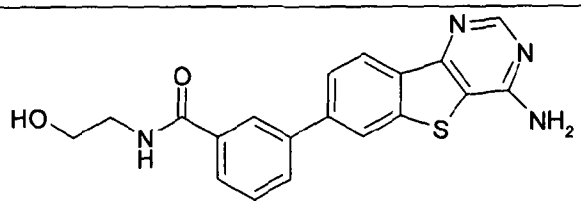
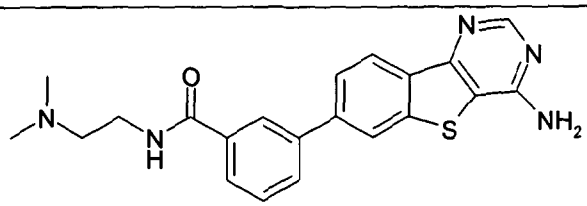
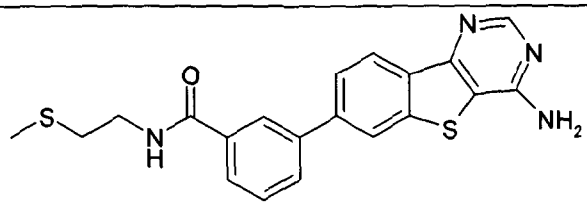
(151) A compound according to (1), selected from compounds of the following formulae and pharmaceutically acceptable salts, hydrates, and solvates thereof:

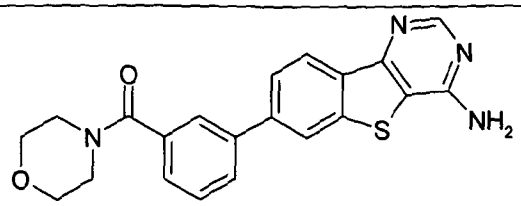
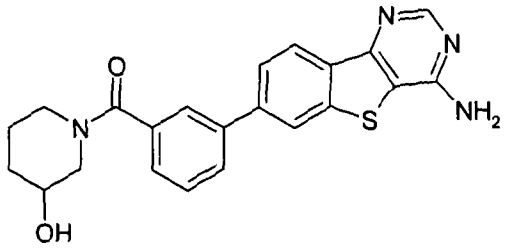
Code	Chemical Structure
AB-001	
AB-002	
AB-003	
AB-004	
AB-005	
AB-006	
AB-007	

Code	Chemical Structure
AB-008	
AB-009	
AB-010	
AB-011	
AB-012	
AB-013	
AB-014	

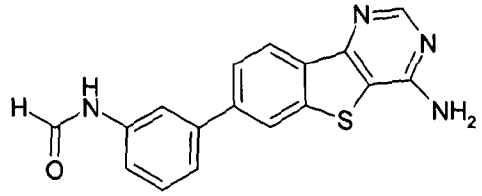
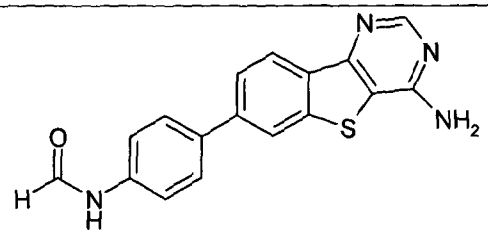
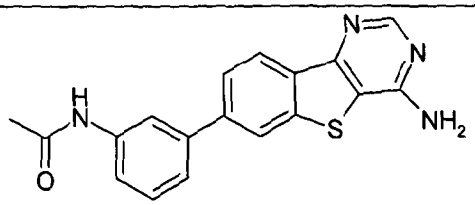
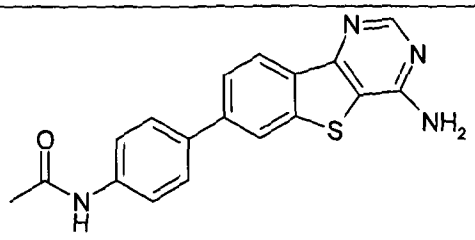
Code	Chemical Structure
AB-015	
AB-016	
AB-017	
AB-018	
AB-019	
AB-020	
AB-021	

Code	Chemical Structure
AB-022	
AB-023	
AB-024	
AB-025	
AB-026	
AB-027	
AB-028	

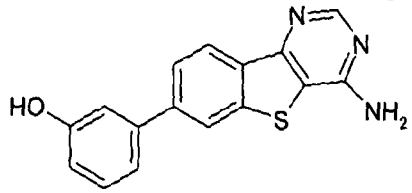
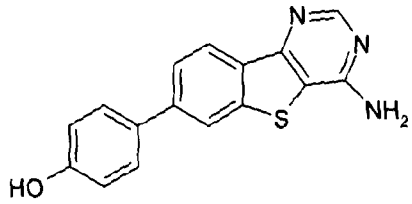
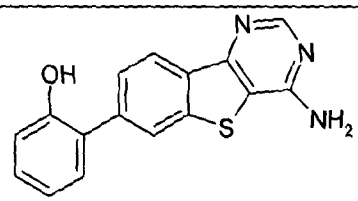
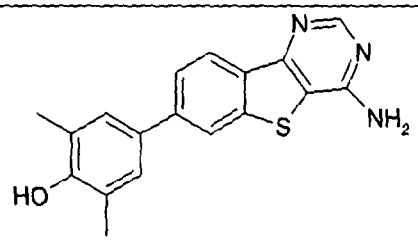
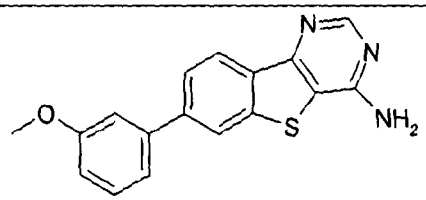
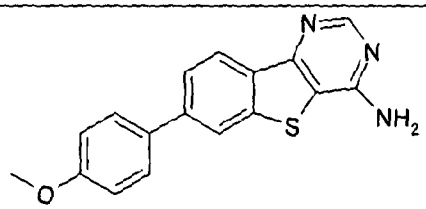
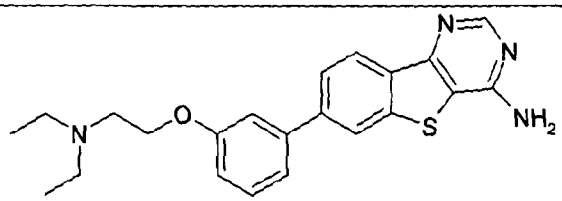
Code	Chemical Structure
AB-029	
AB-030	
AB-031	
AB-032	
AB-033	
AB-034	
AB-035	

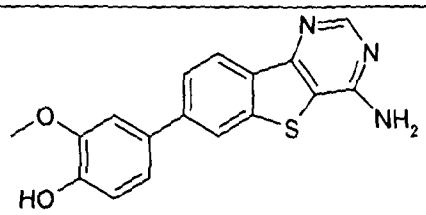
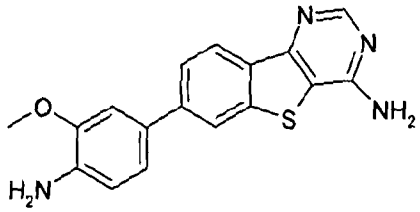
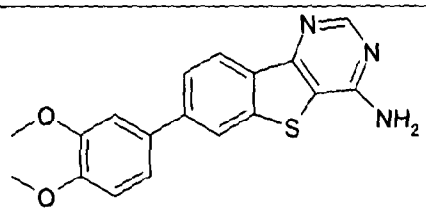
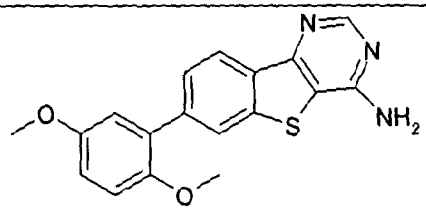
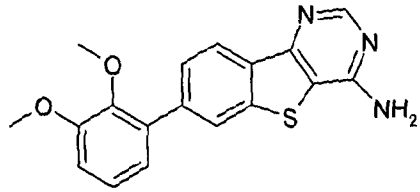
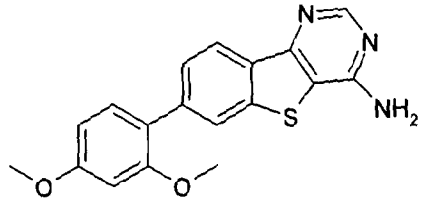
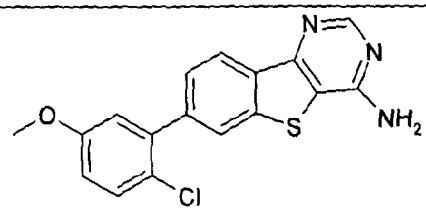
Code	Chemical Structure
AB-036	
AB-037	

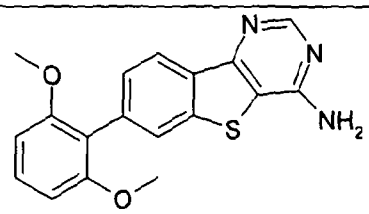
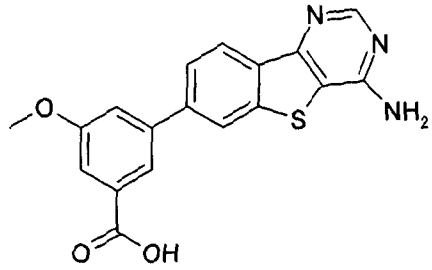
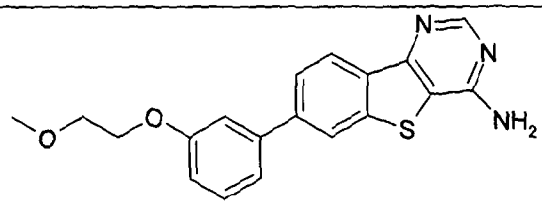
(152) A compound according to (1), selected from compounds of the following formulae and pharmaceutically acceptable salts, hydrates, and solvates thereof:

Code	Chemical Structure
AC-001	
AC-002	
AC-003	
AC-004	

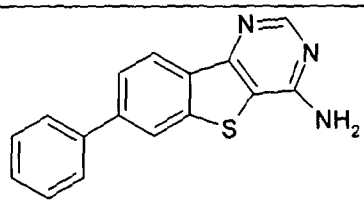
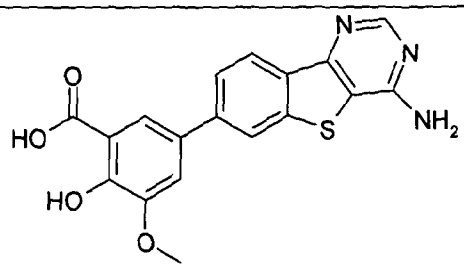
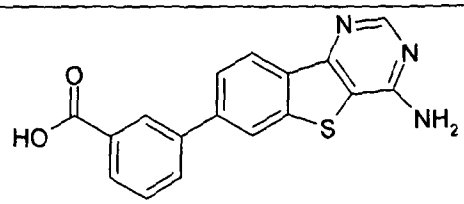
(153) A compound according to (1), selected from compounds of the following formulae and pharmaceutically acceptable salts, hydrates, and solvates thereof:

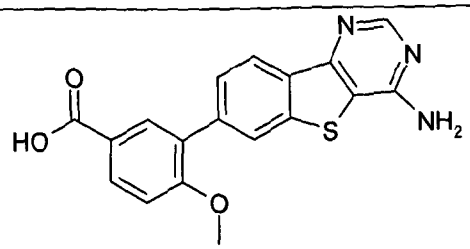
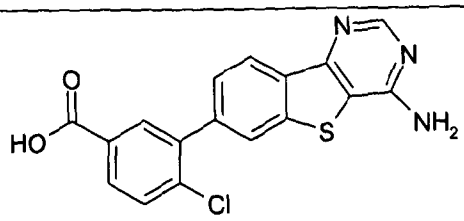
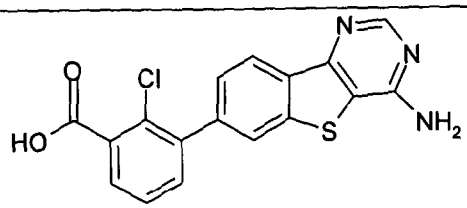
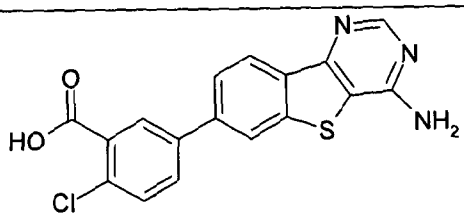
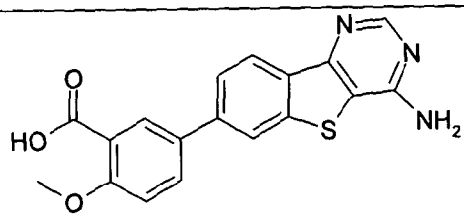
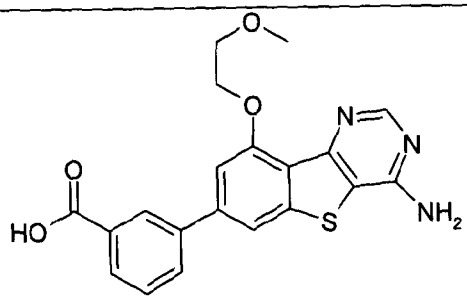
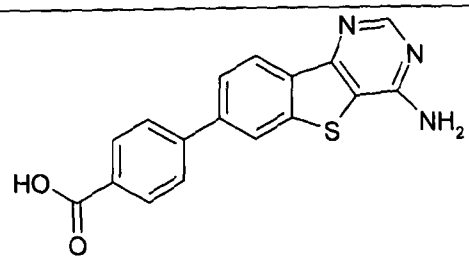
Code	Chemical Structure
AD-001	
AD-002	
AD-003	
AD-004	
AD-005	
AD-006	
AD-007	

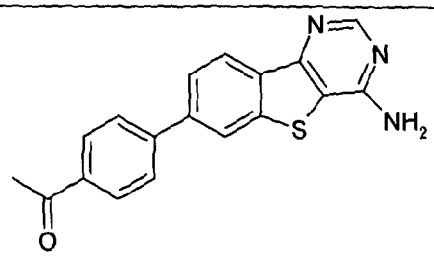
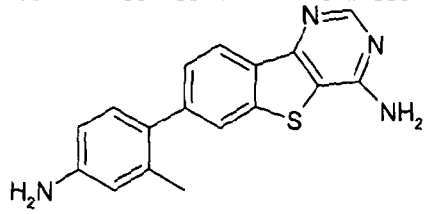
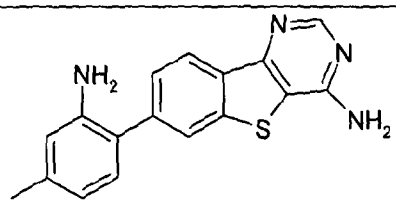
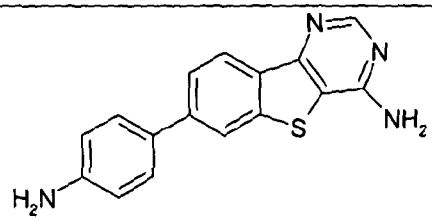
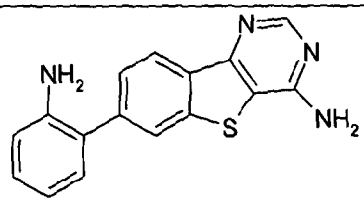
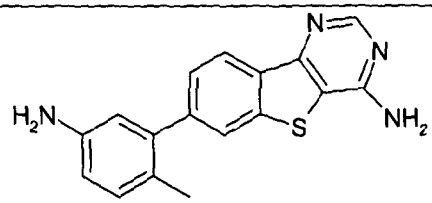
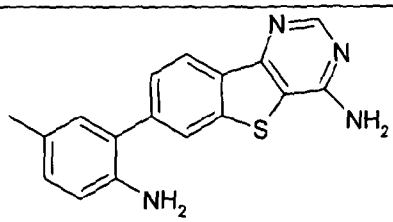
Code	Chemical Structure
AD-008	
AD-009	
AD-010	
AD-011	
AD-012	
AD-013	
AD-014	

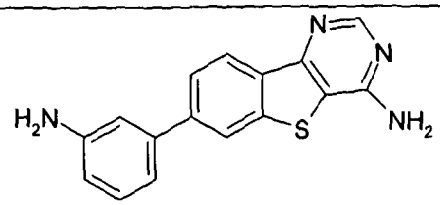
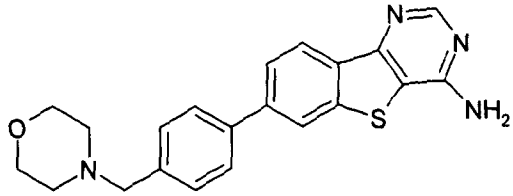
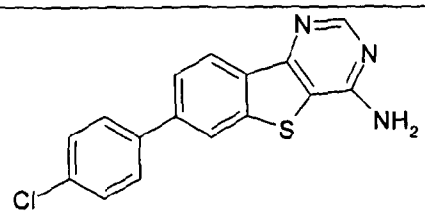
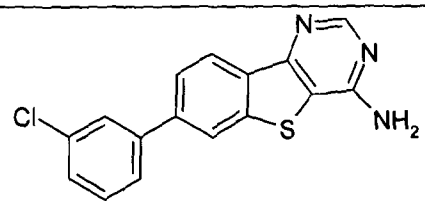
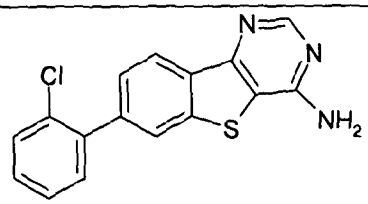
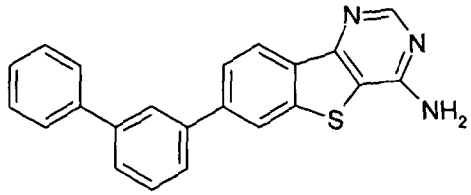
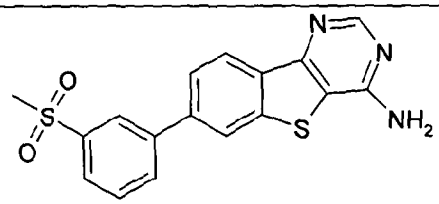
Code	Chemical Structure
AD-015	
AD-016	
AD-017	

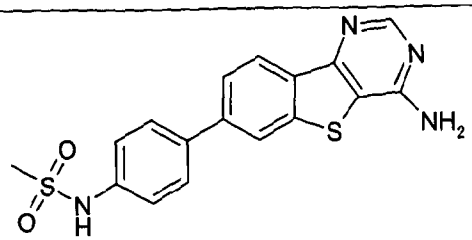
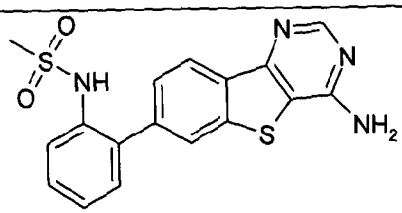
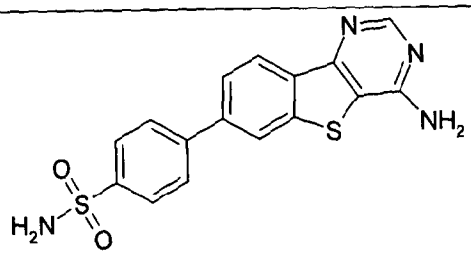
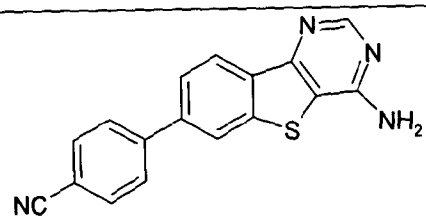
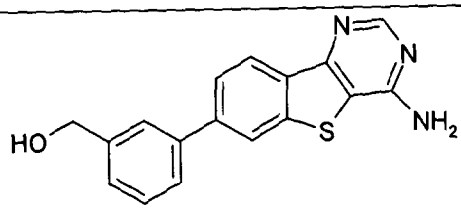
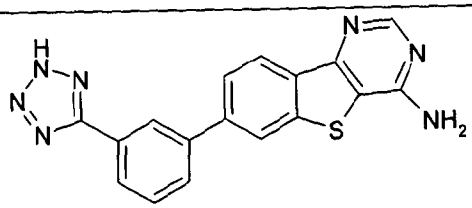
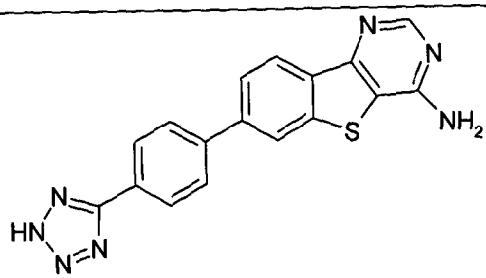
(154) A compound according to (1), selected from compounds of the following formulae and pharmaceutically acceptable salts, hydrates, and solvates thereof:

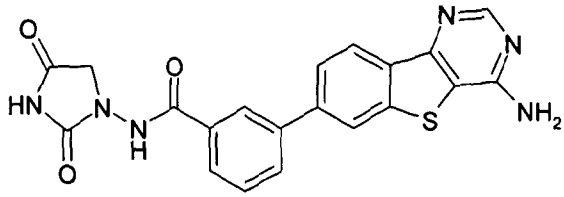
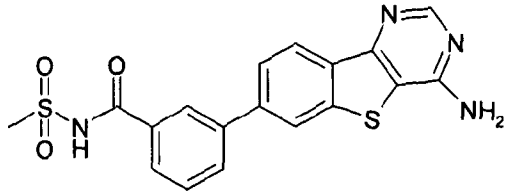
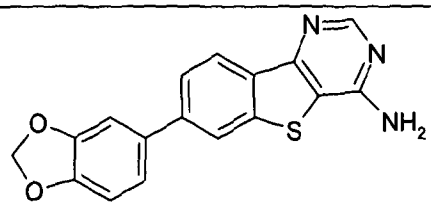
Code	Chemical Structure
AE-001	
AE-002	
AE-003	

Code	Chemical Structure
AE-004	
AE-005	
AE-006	
AE-007	
AE-008	
AE-009	
AE-010	

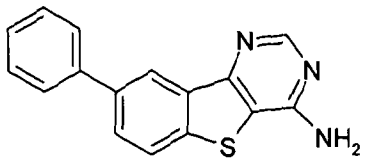
Code	Chemical Structure
AE-011	
AE-012	
AE-013	
AE-014	
AE-015	
AE-016	
AE-017	

Code	Chemical Structure
AE-018	
AE-019	
AE-020	
AE-021	
AE-022	
AE-023	
AE-024	

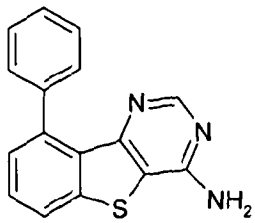
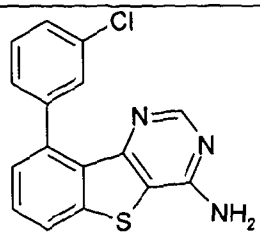
Code	Chemical Structure
AE-025	
AE-026	
AE-027	
AE-028	
AE-029	
AE-030	
AE-031	

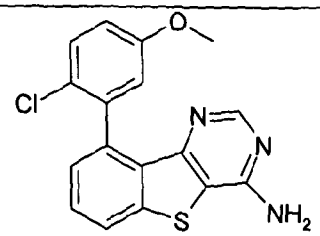
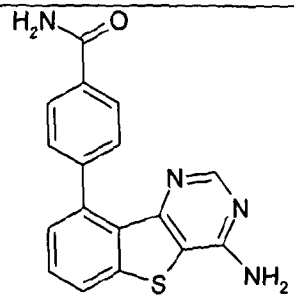
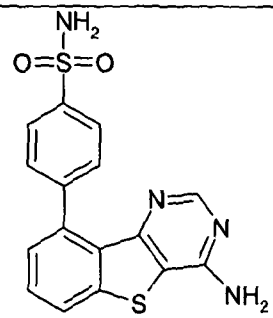
Code	Chemical Structure
AE-032	
AE-033	
AE-034	

(155) A compound according to (1), selected from compounds of the following formulae and pharmaceutically acceptable salts, hydrates, and solvates thereof:

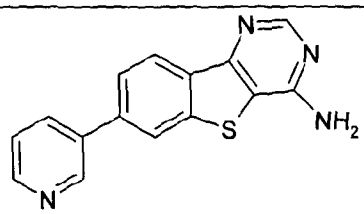
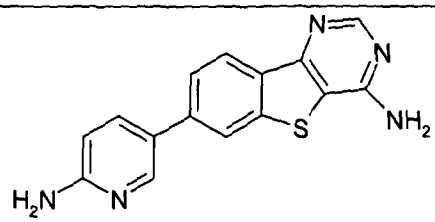
Code	Chemical Structure
AF-001	

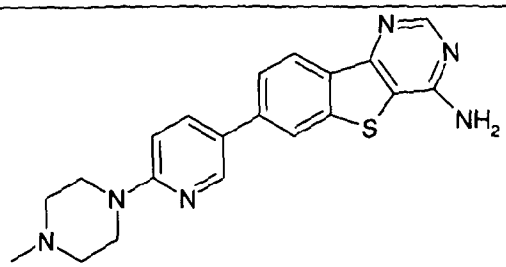
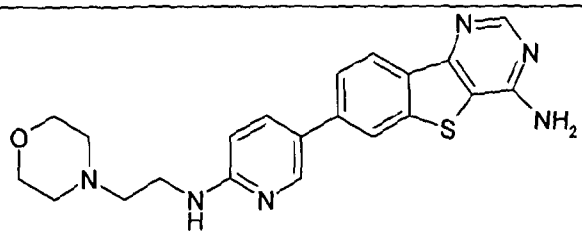
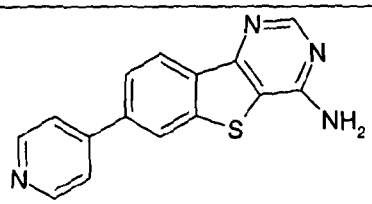
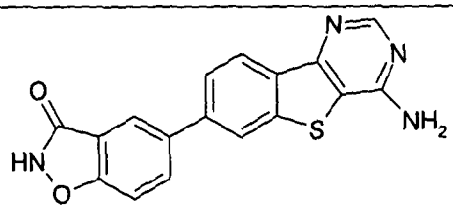
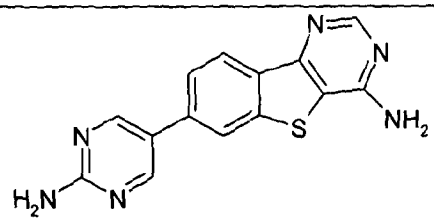
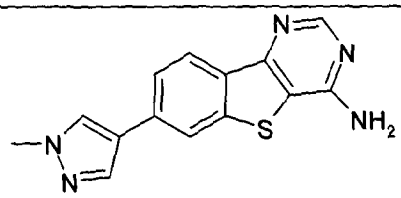
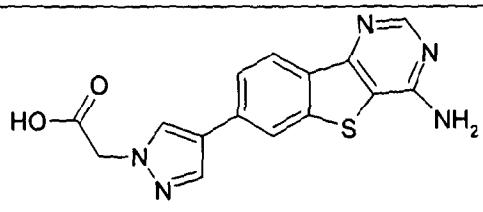
(156) A compound according to (1), selected from compounds of the following formulae and pharmaceutically acceptable salts, hydrates, and solvates thereof:

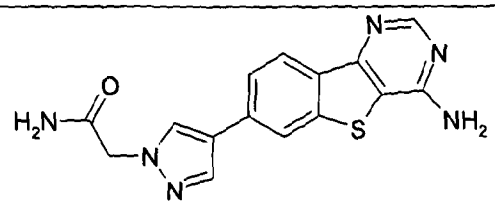
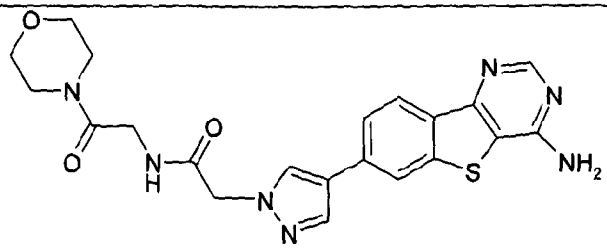
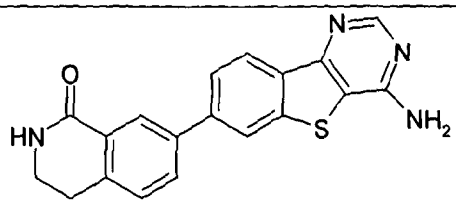
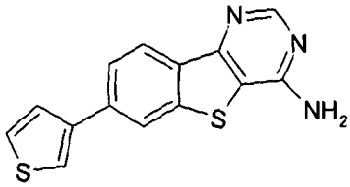
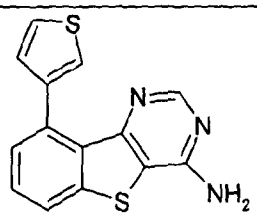
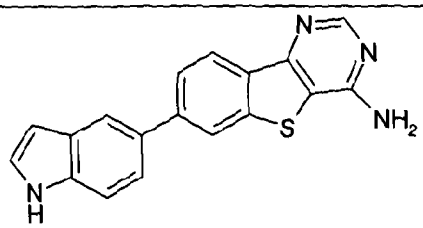
Code	Chemical Structure
AG-001	
AG-002	

Code	Chemical Structure
AG-003	
AG-004	
AG-005	

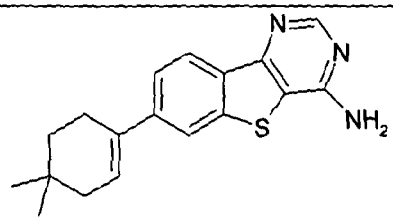
(157) A compound according to (1), selected from compounds of the following formulae and pharmaceutically acceptable salts, hydrates, and solvates thereof:

Code	Chemical Structure
AH-001	
AH-002	

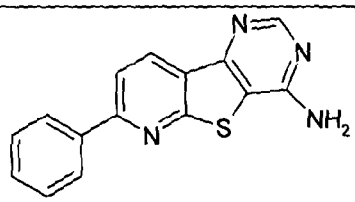
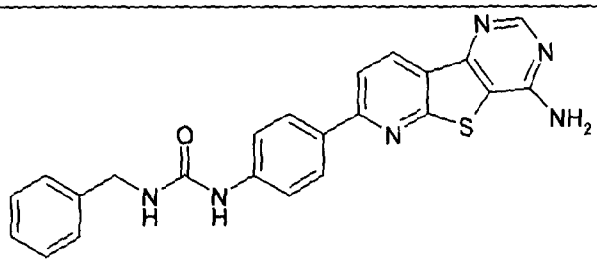
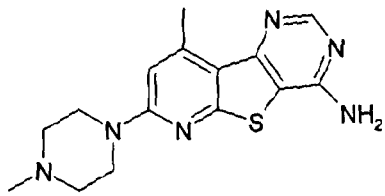
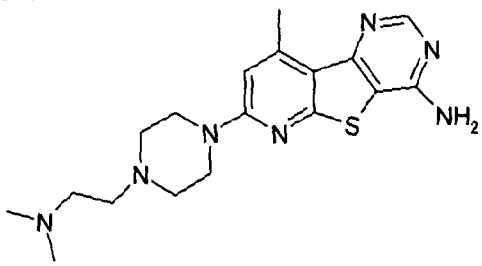
Code	Chemical Structure
AH-003	
AH-004	
AH-005	
AH-006	
AH-007	
AH-008	
AH-009	

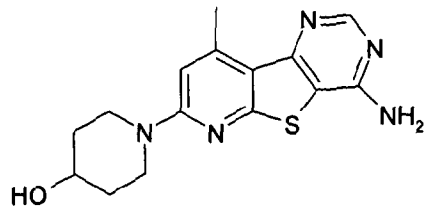
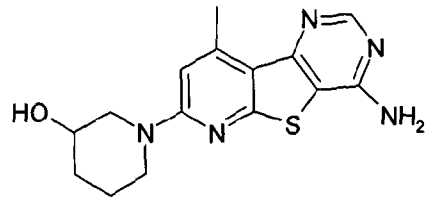
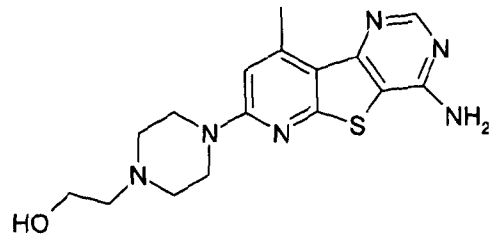
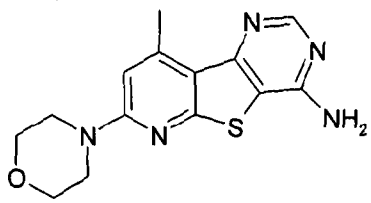
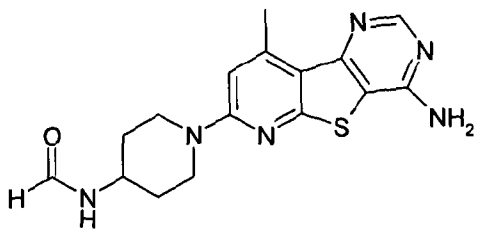
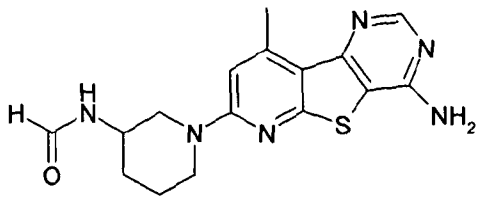
Code	Chemical Structure
AH-010	
AH-011	
AH-012	
AH-013	
AH-014	
AH-015	

(158) A compound according to (1), selected from compounds of the following formulae and pharmaceutically acceptable salts, hydrates, and solvates thereof:

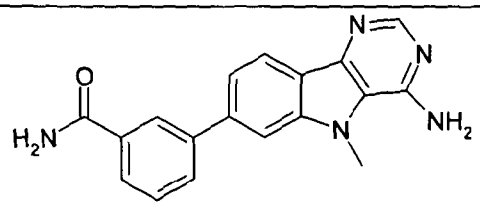
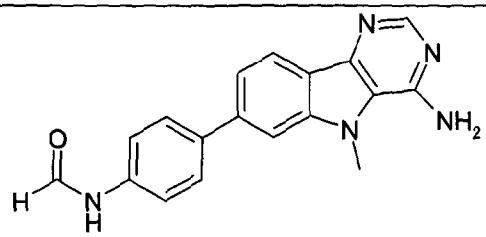
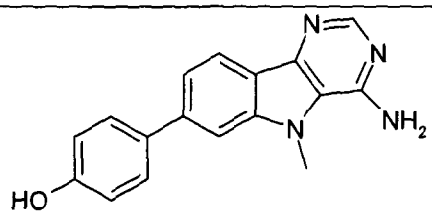
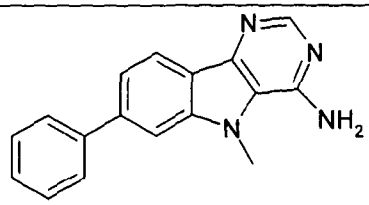
Code	Chemical Structure
AJ-001	

(159) A compound according to (1), selected from compounds of the following formulae and pharmaceutically acceptable salts, hydrates, and solvates thereof:

Code	Chemical Structure
BB-001	
BB-002	
BB-003	
BB-004	

Code	Chemical Structure
BB-005	
BB-006	
BB-007	
BB-008	
BB-009	
BB-010	

(160) A compound according to (1), selected from compounds of the following formulae and pharmaceutically acceptable salts, hydrates, and solvates thereof:

Code	Chemical Structure
CC-001	
CC-002	
CC-003	
CC-004	

5

Combinations

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable sub-combination. All combinations of the embodiments pertaining to the chemical groups represented by the variables (e.g., -X=, -Y-, $-R^{Y}$, $-R^{Z6}$, $-R^{Z7}$, $-R^{Z8}$, $-R^{Z9}$, $-R^{QS}$, $-R^{QL}$, $-R^{CA}$, $-R^{HA}$, $-R^{CC}$, $-R^{HC}$, $-R^{S}$, $-R^{SS}$, $-R^{SSS}$, $-R^{X}$, $-R^{P2}$, $-R^{P3}$, $-R^{P4}$, $-R^{P5}$, $-R^{P6}$, $-R^{X1}$, $-R^{X2}$, $-R^{Z}$, $-R^{ZL}$-, $-R^{NZ}$, $-R^{ZZ}$, $-R^{K1}$, $-R^{K2}$, $-NR^{K3}R^{K4}$, $-R^{K5}$, $-R^{K6}$, =J, $-R^{A1}$, $-R^{A2}$, $-R^{A3}$, $-R^{A4}$, $-R^{A5}$, $-R^{A6}$, etc.) are specifically embraced by the present invention and are disclosed herein just as if each and every combination was individually and explicitly disclosed, to the extent that such combinations embrace compounds that are stable compounds (i.e., compounds that can be isolated, characterised, and tested for biological activity). In addition, all sub-combinations of the chemical groups listed in the embodiments describing such variables are also specifically embraced by the present invention and are disclosed herein just as if each and every such sub-combination of chemical groups was individually and explicitly disclosed herein.

Substantially Purified Forms

One aspect of the present invention pertains to FTA compounds, as described herein, in substantially purified form and/or in a form substantially free from contaminants.

In one embodiment, the substantially purified form is at least 50% by weight, e.g., at least 60% by weight, e.g., at least 70% by weight, e.g., at least 80% by weight, e.g., at least 90% by weight, e.g., at least 95% by weight, e.g., at least 97% by weight, e.g., at least 98% by weight, e.g., at least 99% by weight.

Unless specified, the substantially purified form refers to the compound in any stereoisomeric or enantiomeric form. For example, in one embodiment, the substantially purified form refers to a mixture of stereoisomers, i.e., purified with respect to other compounds. In one embodiment, the substantially purified form refers to one stereoisomer, e.g., optically pure stereoisomer. In one embodiment, the substantially purified form refers to a mixture of enantiomers. In one embodiment, the substantially purified form refers to a equimolar mixture of enantiomers (i.e., a racemic mixture, a racemate). In one embodiment, the substantially purified form refers to one enantiomer, e.g., optically pure enantiomer.

In one embodiment, the contaminants represent no more than 50% by weight, e.g., no more than 40% by weight, e.g., no more than 30% by weight, e.g., no more than 20% by weight, e.g., no more than 10% by weight, e.g., no more than 5% by weight, e.g., no more than 3% by weight, e.g., no more than 2% by weight, e.g., no more than 1% by weight.

Unless specified, the contaminants refer to other compounds, that is, other than stereoisomers or enantiomers. In one embodiment, the contaminants refer to other compounds and other stereoisomers. In one embodiment, the contaminants refer to other compounds and the other enantiomer.

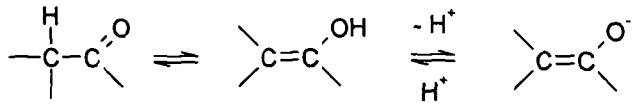
In one embodiment, the substantially purified form is at least 60% optically pure (i.e., 60% of the compound, on a molar basis, is the desired stereoisomer or enantiomer, and 40% is the undesired stereoisomer or enantiomer), e.g., at least 70% optically pure, e.g., at least 80% optically pure, e.g., at least 90% optically pure, e.g., at least 95% optically pure, e.g., at least 97% optically pure, e.g., at least 98% optically pure, e.g., at least 99% optically pure.

Isomers

Certain compounds may exist in one or more particular geometric, optical, enantiomeric, diastereoisomeric, epimeric, atropic, stereoisomeric, tautomeric, conformational, or anomeric forms, including but not limited to, cis- and trans-forms; E- and Z-forms; c-, t-, and r- forms; endo- and exo-forms; R-, S-, and meso-forms; D- and L-forms; d- and l-forms; (+) and (-) forms; keto-, enol-, and enolate-forms; syn- and anti-forms; synclinal- and anticlinal-forms; α- and β-forms; axial and equatorial forms; boat-, chair-, twist-, envelope-, and halfchair-forms; and combinations thereof, hereinafter collectively referred to as "isomers" (or "isomeric forms").

A reference to a class of structures may well include structurally isomeric forms falling within that class (e.g., C_{1-7}alkyl includes n-propyl and iso-propyl; butyl includes n-, iso-, sec-, and tert-butyl; methoxyphenyl includes ortho-, meta-, and para-methoxyphenyl). However, reference to a specifc group or substitution pattern is not intended to include other structural (or constitutional isomers) which differ with respect to the connections between atoms rather than by positions in space. For example, a reference to a methoxy group, $-OCH_3$, is not to be construed as a reference to its structural isomer, a hydroxymethyl group, $-CH_2OH$. Similarly, a reference to ortho-chlorophenyl is not to be construed as a reference to its structural isomer, meta-chlorophenyl.

The above exclusion does not pertain to tautomeric forms, for example, keto-, enol-, and enolate-forms, as in, for example, the following tautomeric pairs: keto/enol (illustrated below), imine/enamine, amide/imino alcohol, amidine/amidine, nitroso/oxime, thioketone/enethiol, N-nitroso/hydroxyazo, and nitro/aci-nitro.



keto enol enolate

Note that specifically included in the term "isomer" are compounds with one or more isotopic substitutions. For example, H may be in any isotopic form, including ^{1}H, ^{2}H (D), and ^{3}H (T); C may be in any isotopic form, including ^{12}C, ^{13}C, and ^{14}C; O may be in any isotopic form, including ^{16}O and ^{18}O; and the like.

Unless otherwise specified, a reference to a particular compound includes all such isomeric forms, including mixtures (e.g., racemic mixtures) thereof. Methods for the preparation (e.g., asymmetric synthesis) and separation (e.g., fractional crystallisation and chromatographic means) of such isomeric forms are either known in the art or are readily obtained by adapting the methods taught herein, or known methods, in a known manner.

Salts

It may be convenient or desirable to prepare, purify, and/or handle a corresponding salt of the compound, for example, a pharmaceutically-acceptable salt. Examples of pharmaceutically acceptable salts are discussed in Berge *et al.*, 1977, "Pharmaceutically Acceptable Salts," J. Pharm. Sci., Vol. 66, pp. 1-19.

For example, if the compound is anionic, or has a functional group which may be anionic (e.g., -COOH may be $-COO^{-}$), then a salt may be formed with a suitable cation. Examples of suitable inorganic cations include, but are not limited to, alkali metal ions such as Na^{+} and K^{+}, alkaline earth cations such as Ca^{2+} and Mg^{2+}, and other cations such as Al^{+3}. Examples of suitable organic cations include, but are not limited to, ammonium ion (i.e., NH_4^{+}) and substituted ammonium ions (e.g., NH_3R^{+}, $NH_2R_2^{+}$, NHR_3^{+}, NR_4^{+}). Examples of some suitable substituted ammonium ions are those derived from: ethylamine, diethylamine, dicyclohexylamine, triethylamine, butylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, benzylamine, phenylbenzylamine, choline, meglumine, and tromethamine, as well as amino acids, such as lysine and arginine. An example of a common quaternary ammonium ion is $N(CH_3)_4^{+}$.

If the compound is cationic, or has a functional group which upon protonation may become cationic (e.g., $-NH_2$ may become $-NH_3^{+}$), then a salt may be formed with a suitable anion. Examples of suitable inorganic anions include, but are not limited to, those derived from the following inorganic acids: hydrochloric, hydrobromic, hydroiodic, sulfuric, sulfurous, nitric, nitrous, phosphoric, and phosphorous.

Examples of suitable organic anions include, but are not limited to, those derived from the following organic acids: 2-acetyoxybenzoic, acetic, trifluoroacetic, ascorbic, aspartic, benzoic, camphorsulfonic, cinnamic, citric, edetic, ethanedisulfonic, ethanesulfonic, fumaric, glucheptonic, gluconic, glutamic, glycolic, hydroxymaleic, hydroxynaphthalene carboxylic, isethionic, lactic, lactobionic, lauric, maleic, malic, methanesulfonic, mucic, oleic, oxalic, palmitic, pamoic, pantothenic, phenylacetic, phenylsulfonic, propionic,

pyruvic, salicylic, stearic, succinic, sulfanilic, tartaric, toluenesulfonic, and valeric. Examples of suitable polymeric organic anions include, but are not limited to, those derived from the following polymeric acids: tannic acid, carboxymethyl cellulose.

Unless otherwise specified, a reference to a particular compound also includes salt forms thereof.

Solvates and Hydrates

It may be convenient or desirable to prepare, purify, and/or handle a corresponding solvate of the compound. The term "solvate" is used herein in the conventional sense to refer to a complex of solute (e.g., compound, salt of compound) and solvent. If the solvent is water, the solvate may be conveniently referred to as a hydrate, for example, a mono-hydrate, a di-hydrate, a tri-hydrate, etc.

Unless otherwise specified, a reference to a particular compound also includes solvate and hydrate forms thereof.

Chemically Protected Forms

It may be convenient or desirable to prepare, purify, and/or handle the compound in a chemically protected form. The term "chemically protected form" is used herein in the conventional chemical sense and pertains to a compound in which one or more reactive functional groups are protected from undesirable chemical reactions under specified conditions (e.g., pH, temperature, radiation, solvent, and the like). In practice, well known chemical methods are employed to reversibly render unreactive a functional group, which otherwise would be reactive, under specified conditions. In a chemically protected form, one or more reactive functional groups are in the form of a protected or protecting group (also known as a masked or masking group or a blocked or blocking group). By protecting a reactive functional group, reactions involving other unprotected reactive functional groups can be performed, without affecting the protected group; the protecting group may be removed, usually in a subsequent step, without substantially affecting the remainder of the molecule. See, for example, Protective Groups in Organic Synthesis (T. Green and P. Wuts; 4th Edition; John Wiley and Sons, 2006).

A wide variety of such "protecting," "blocking," or "masking" methods are widely used and well known in organic synthesis. For example, a compound which has two nonequivalent reactive functional groups, both of which would be reactive under specified conditions, may be derivatized to render one of the functional groups "protected," and therefore unreactive, under the specified conditions; so protected, the compound may be used as a reactant which has effectively only one reactive functional group. After the desired reaction (involving the other functional group) is complete, the protected group may be "deprotected" to return it to its original functionality.

For example, a hydroxy group may be protected as an ether (-OR) or an ester (-OC(=O)R), for example, as: a t-butyl ether; a benzyl, benzhydryl (diphenylmethyl), or trityl (triphenylmethyl) ether; a trimethylsilyl or t-butyldimethylsilyl ether; or an acetyl ester (-OC(=O)CH_3, -OAc).

For example, an aldehyde or ketone group may be protected as an acetal (R-CH$(OR)_2$) or ketal ($R_2C(OR)_2$), respectively, in which the carbonyl group (>C=O) is converted to a diether (>C$(OR)_2$), by reaction with, for example, a primary alcohol. The aldehyde or ketone group is readily regenerated, for example, by hydrolysis using water in the presence of acid.

For example, an amine group may be protected, for example, as an amide (-NRCO-R) or a urethane (-NRCO-OR), for example, as: a methyl amide (-NHCO-CH_3); a benzyloxy amide (-NHCO-$OCH_2C_6H_5$, -NH-Cbz); as a t-butoxy amide (-NHCO-$OC(CH_3)_3$, -NH-Boc); a 2-biphenyl-2-propoxy amide (-NHCO-$OC(CH_3)_2C_6H_4C_6H_5$, -NH-Bpoc), as a 9-fluorenylmethoxy amide (-NH-Fmoc), as a 6-nitroveratryloxy amide (-NH-Nvoc), as a 2-trimethylsilylethyloxy amide (-NH-Teoc), as a 2,2,2-trichloroethyloxy amide (-NH-Troc), as an allyloxy amide (-NH-Alloc), as a 2-(phenylsulfonyl)ethyloxy amide (-NH-Psec); or, in suitable cases (e.g., cyclic amines), as a nitroxide radical (>N-O•).

For example, a carboxylic acid group may be protected as an ester for example, as: an C_{1-7}alkyl ester (e.g., a methyl ester; a t-butyl ester); a C_{1-7}haloalkyl ester (e.g., a C_{1-7}trihaloalkyl ester); a triC_{1-7}alkylsilyl-C_{1-7}alkyl ester; or a C_{5-20}aryl-C_{1-7}alkyl ester (e.g., a benzyl ester; a nitrobenzyl ester); or as an amide, for example, as a methyl amide.

For example, a thiol group may be protected as a thioether (-SR), for example, as: a benzyl thioether; an acetamidomethyl ether (-S-$CH_2NHC(=O)CH_3$).

Prodrugs

It may be convenient or desirable to prepare, purify, and/or handle the compound in the form of a prodrug. The term "prodrug," as used herein, pertains to a compound which yields the desired active compound *in vivo*. Typically, the prodrug is inactive, or less active than the desired active compound, but may provide advantageous handling, administration, or metabolic properties.

For example, some prodrugs are esters of the active compound (e.g., a physiologically acceptable metabolically labile ester). During metabolism, the ester group (-C(=O)OR) is cleaved to yield the active drug. Such esters may be formed by esterification, for example, of any of the carboxylic acid groups (-C(=O)OH) in the parent compound, with, where appropriate, prior protection of any other reactive groups present in the parent compound, followed by deprotection if required.

Also, some prodrugs are activated enzymatically to yield the active compound, or a compound which, upon further chemical reaction, yields the active compound (for example, as in antibody directed enzyme prodrug therapy (ADEPT), gene directed enzyme prodrug therapy (GDEPT), lipid directed enzyme prodrug therapy (LIDEPT), etc.). For example, the prodrug may be a sugar derivative or other glycoside conjugate, or may be an amino acid ester derivative.

Chemical Synthesis

Several methods for the chemical synthesis of FTA compounds of the present invention are described herein. These and/or other well known methods may be modified and/or adapted in known ways in order to facilitate the synthesis of additional compounds within the scope of the present invention.

Compositions

One aspect of the present invention pertains to a composition (e.g., a pharmaceutical composition) comprising a FTA compound, as described herein, and a pharmaceutically acceptable carrier, diluent, or excipient.

Another aspect of the present invention pertains to a method of preparing a composition (e.g., a pharmaceutical composition) comprising admixing a FTA compound, as described herein, and a pharmaceutically acceptable carrier, diluent, or excipient.

Uses

The compounds described herein are useful, for example, in the treatment of diseases and conditions that are ameliorated by the inhibition of LIM kinase (LIMK) activity (e.g., LIMK1 activity and/or LIMK2 activity), such as, for example, proliferative conditions, cancer, etc.

Use in Methods of Inhibiting LIM Kinase (LIMK)

One aspect of the present invention pertains to a method of inhibiting LIM kinase (LIMK) activity (e.g., LIMK1 activity and/or LIMK2 activity), *in vitro* or *in vivo,* comprising contacting LIMK (e.g., LIMK1 and/or LIMK2) with an effective amount of a FTA compound, as described herein.

One aspect of the present invention pertains to a method of inhibiting LIM kinase (LIMK) activity (e.g., LIMK1 activity and/or LIMK2 activity) in a cell, *in vitro* or *in vivo,* comprising contacting the cell with an effective amount of a FTA compound, as described herein.

Suitable assays for determining LIMK activity inhibition are described herein and/or are known in the art.

Use in Methods of Inhibiting Cell Proliferation, Etc.

The FTA compounds described herein, e.g., (a) regulate (e.g., inhibit) cell proliferation; (b) inhibit cell cycle progression; (c) promote apoptosis; or (d) a combination of one or more of these.

One aspect of the present invention pertains to a method of regulating (e.g., inhibiting) cell proliferation (e.g., proliferation of a cell), inhibiting cell cycle progression, promoting apoptosis, or a combination of one or more these, *in vitro* or *in vivo,* comprising contacting a cell with an effective amount of a FTA compound, as described herein.

In one embodiment, the method is a method of regulating (e.g., inhibiting) cell proliferation (e.g., proliferation of a cell), *in vitro* or *in vivo,* comprising contacting a cell with an effective amount of a FTA compound, as described herein.

In one embodiment, the method is performed *in vitro*.

In one embodiment, the method is performed *in vivo*.

In one embodiment, the FTA compound is provided in the form of a pharmaceutically acceptable composition.

Any type of cell may be treated, including but not limited to, lung, gastrointestinal (including, e.g., bowel, colon), breast (mammary), ovarian, prostate, liver (hepatic), kidney (renal), bladder, pancreas, brain, and skin.

One of ordinary skill in the art is readily able to determine whether or not a candidate compound regulates (e.g., inhibits) cell proliferation, etc. For example, assays which may conveniently be used to assess the activity offered by a particular compound are described herein.

For example, a sample of cells (e.g., from a tumour) may be grown *in vitro* and a compound brought into contact with said cells, and the effect of the compound on those cells observed. As an example of "effect," the morphological status of the cells (e.g., alive or dead, etc.) may be determined. Where the compound is found to exert an influence on the cells, this may be used as a prognostic or diagnostic marker of the efficacy of the compound in methods of treating a patient carrying cells of the same cellular type.

Use in Methods of Therapy

Another aspect of the present invention pertains to a FTA compound, as described herein, for use in a method of treatment of the human or animal body by therapy.

Use in the Manufacture of Medicaments

Another aspect of the present invention pertains to use of a FTA compound, as described herein, in the manufacture of a medicament for use in treatment.

In one embodiment, the medicament comprises the FTA compound.

Methods of Treatment

Another aspect of the present invention pertains to a method of treatment comprising administering to a patient in need of treatment a therapeutically effective amount of a FTA compound, as described herein, preferably in the form of a pharmaceutical composition.

Conditions Treated - Conditions Mediated by LIM Kinase (LIMK)

In one embodiment (e.g., of use in methods of therapy, of use in the manufacture of medicaments, of methods of treatment), the treatment is treatment of a disease or condition that is mediated by LIM kinase (LIMK) (e.g., LIMK1 and/or LIMK2).

Conditions Treated - Conditions Ameliorated by the Inhibition of LIMK Activity

In one embodiment (e.g., of use in methods of therapy, of use in the manufacture of medicaments, of methods of treatment), the treatment is treatment of: a disease or condition that is ameliorated by the inhibition of LIM kinase (LIMK) activity (e.g., LIMK1 activity and/or LIMK2 activity).

Conditions Treated - Proliferative Conditions

In one embodiment (e.g., of use in methods of therapy, of use in the manufacture of medicaments, of methods of treatment), the treatment is treatment of: a proliferative condition.

The term "proliferative condition," as used herein, pertains to an unwanted or uncontrolled cellular proliferation of excessive or abnormal cells which is undesired, such as, neoplastic or hyperplastic growth.

In one embodiment, the treatment is treatment of: a proliferative condition characterised by benign, pre-malignant, or malignant cellular proliferation, including but not limited to, neoplasms, hyperplasias, and tumours (e.g., histocytoma, glioma, astrocyoma, osteoma), cancers (see below), psoriasis, bone diseases, fibroproliferative disorders (e.g., of connective tissues), pulmonary fibrosis, atherosclerosis, smooth muscle cell proliferation in the blood vessels, such as stenosis or restenosis following angioplasty.

Conditions Treated - Cancer

In one embodiment (e.g., of use in methods of therapy, of use in the manufacture of medicaments, of methods of treatment), the treatment is treatment of cancer.

In one embodiment, the treatment is treatment of cancer characterised by, or further characterised by, cancer cells which overexpress LIM kinase (LIMK) (e.g., LIMK1 and/or LIMK2).

In one embodiment, the treatment is treatment of lung cancer, small cell lung cancer, non-small cell lung cancer, gastrointestinal cancer, stomach cancer, bowel cancer, colon cancer, rectal cancer, colorectal cancer, thyroid cancer, breast cancer, ovarian cancer, endometrial cancer, prostate cancer, testicular cancer, liver cancer, kidney cancer, renal cell carcinoma, bladder cancer, pancreatic cancer, brain cancer, glioma, sarcoma, osteosarcoma, bone cancer, nasopharyngeal cancer (e.g., head cancer, neck cancer), skin cancer, squamous cancer, Kaposi's sarcoma, melanoma, malignant melanoma, lymphoma, or leukemia.

In one embodiment, the treatment is treatment of:

a carcinoma, for example a carcinoma of the bladder, breast, colon (e.g., colorectal carcinomas such as colon adenocarcinoma and colon adenoma), kidney, epidermal, liver, lung (e.g., adenocarcinoma, small cell lung cancer and non-small cell lung carcinomas), oesophagus, gall bladder, ovary, pancreas (e.g., exocrine pancreatic carcinoma), stomach, cervix, thyroid, prostate, skin (e.g., squamous cell carcinoma);

a hematopoietic tumour of lymphoid lineage, for example leukemia, acute lymphocytic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma, or Burkett's lymphoma;

a hematopoietic tumor of myeloid lineage, for example acute and chronic myelogenous leukemias, myelodysplastic syndrome, or promyelocytic leukemia;

a tumour of mesenchymal origin, for example fibrosarcoma or habdomyosarcoma;

a tumor of the central or peripheral nervous system, for example astrocytoma, neuroblastoma, glioma or schwannoma;

melanoma; seminoma; teratocarcinoma; osteosarcoma; xenoderoma pigmentoum; keratoctanthoma; thyroid follicular cancer; or Kaposi's sarcoma.

In one embodiment, the treatment is treatment of solid tumour cancer.

In one embodiment, the treatment is treatment of breast cancer, prostate cancer, melanoma, or glioma.

In one embodiment, the treatment is treatment of cancer metastasis.

In one embodiment, the cancer is characterised by, or further characterised by, cancer stem cells.

The anti-cancer effect may arise through one or more mechanisms, including but not limited to, the regulation of cell proliferation, the inhibition of cell cycle progression, the inhibition of angiogenesis (the formation of new blood vessels), the inhibition of metastasis (the spread of a tumour from its origin), the inhibition of cell migration (the spread of cance cells to other parts of the body), the inhibition of invasion (the spread of tumour cells into neighbouring normal structures), or the promotion of apoptosis (programmed cell death). The compounds of the present invention may be used in the treatment of the cancers described herein, independent of the mechanisms discussed herein.

Conditions Treated - Additional Conditions

In one embodiment, the treatment is treatment of vasodilation.

In one embodiment, the treatment is treatment of hypertension, angina, cerebral vasospasm, or ischemia following subarachnoid hemorrhage.

In one embodiment, the treatment is treatment of a neurodegenerative disorder.

In one embodiment, the treatment is treatment of atherosclerosis.

In one embodiment, the treatment is treatment of fibrosis.

In one embodiment, the treatment is treatment of an inflammatory disease.

In one embodiment, the treatment is treatment of Crohn's disease or chronic obstructive pulmonary disease (COPD).

In one embodiment, the treatment is treatment of glaucoma (also known as ocular hypertension).

Treatment

The term "treatment," as used herein in the context of treating a condition, pertains generally to treatment and therapy, whether of a human or an animal (e.g., in veterinary applications), in which some desired therapeutic effect is achieved, for example, the inhibition of the progress of the condition, and includes a reduction in the rate of progress, a halt in the rate of progress, alleviatiation of symptoms of the condition, amelioration of the condition, and cure of the condition. Treatment as a prophylactic measure (i.e., prophylaxis) is also included. For example, use with patients who have not yet developed the condition, but who are at risk of developing the condition, is encompassed by the term "treatment."

For example, treatment includes the prophylaxis of cancer, reducing the incidence of cancer, alleviating the symptoms of cancer, etc.

The term "therapeutically-effective amount," as used herein, pertains to that amount of a compound, or a material, composition or dosage form comprising a compound, which is effective for producing some desired therapeutic effect, commensurate with a reasonable benefit/risk ratio, when administered in accordance with a desired treatment regimen.

Combination Therapies

The term "treatment" includes combination treatments and therapies, in which two or more treatments or therapies are combined, for example, sequentially or simultaneously. For example, the compounds described herein may also be used in combination therapies, e.g., in conjunction with other agents, for example, cytotoxic agents, anticancer agents, etc. Examples of treatments and therapies include, but are not limited to, chemotherapy (the administration of active agents, including, e.g., drugs, antibodies (e.g., as in immunotherapy), prodrugs (e.g., as in photodynamic therapy, GDEPT, ADEPT, etc.); surgery; radiation therapy; photodynamic therapy; gene therapy; and controlled diets.

For example, it may be beneficial to combine treatment with a compound as described herein with one or more other (e.g., 1, 2, 3, 4) agents or therapies that regulates cell growth or survival or differentiation via a different mechanism, thus treating several characteristic features of cancer development.

One aspect of the present invention pertains to a compound as described herein, in combination with one or more additional therapeutic agents, as described below.

The particular combination would be at the discretion of the physician who would select dosages using his common general knowledge and dosing regimens known to a skilled practitioner.

The agents (i.e., the compound described herein, plus one or more other agents) may be administered simultaneously or sequentially, and may be administered in individually varying dose schedules and via different routes. For example, when administered sequentially, the agents can be administered at closely spaced intervals (e.g., over a period of 5-10 minutes) or at longer intervals (e.g., 1, 2, 3, 4 or more hours apart, or even longer periods apart where required), the precise dosage regimen being commensurate with the properties of the therapeutic agent(s).

The agents (i.e., the compound described here, plus one or more other agents) may be formulated together in a single dosage form, or alternatively, the individual agents may be formulated separately and presented together in the form of a kit, optionally with instructions for their use.

Other Uses

The FTA compounds described herein may also be used as cell culture additives to inhibit (LIMK) activity (e.g., LIMK1 activity and/or LIMK2 activity), e.g., to inhibit cell proliferation, etc.

The FTA compounds described herein may also be used as part of an *in vitro* assay, for example, in order to determine whether a candidate host is likely to benefit from treatment with the compound in question.

The FTA compounds described herein may also be used as a standard, for example, in an assay, in order to identify other compounds, other LIMK activity inhibitors, other anti-proliferative agents, other anti-cancer agents, etc.

Kits

One aspect of the invention pertains to a kit comprising (a) a FTA compound as described herein, or a composition comprising a FTA compound as described herein, e.g., preferably provided in a suitable container and/or with suitable packaging; and (b) instructions for use, e.g., written instructions on how to administer the compound or composition.

The written instructions may also include a list of indications for which the active ingredient is a suitable treatment.

Routes of Administration

The FTA compound or pharmaceutical composition comprising the FTA compound may be administered to a subject by any convenient route of administration, whether systemically/peripherally or topically (i.e., at the site of desired action).

Routes of administration include, but are not limited to, oral (e.g., by ingestion); buccal; sublingual; transdermal (including, e.g., by a patch, plaster, etc.); transmucosal (including, e.g., by a patch, plaster, etc.); intranasal (e.g., by nasal spray); ocular (e.g., by eyedrops); pulmonary (e.g., by inhalation or insufflation therapy using, e.g., via an aerosol, e.g., through the mouth or nose); rectal (e.g., by suppository or enema); vaginal (e.g., by pessary); parenteral, for example, by injection, including subcutaneous, intradermal, intramuscular, intravenous, intraarterial, intracardiac, intrathecal, intraspinal, intracapsular, subcapsular, intraorbital, intraperitoneal, intratracheal, subcuticular, intraarticular, subarachnoid, and intrasternal; by implant of a depot or reservoir, for example, subcutaneously or intramuscularly.

The Subject/Patient

The subject/patient may be a chordate, a vertebrate, a mammal, a placental mammal, a marsupial (e.g., kangaroo, wombat), a rodent (e.g., a guinea pig, a hamster, a rat, a mouse), murine (e.g., a mouse), a lagomorph (e.g., a rabbit), avian (e.g., a bird), canine (e.g., a dog), feline (e.g., a cat), equine (e.g., a horse), porcine (e.g., a pig), ovine (e.g., a sheep), bovine (e.g., a cow), a primate, simian (e.g., a monkey or ape), a monkey (e.g., marmoset, baboon), an ape (e.g., gorilla, chimpanzee, orangutang, gibbon), or a human.

Furthermore, the subject/patient may be any of its forms of development, for example, a foetus.

In one preferred embodiment, the subject/patient is a human.

Formulations

While it is possible for the FTA compound to be administered alone, it is preferable to present it as a pharmaceutical formulation (e.g., composition, preparation, medicament) comprising at least one FTA compound, as described herein, together with one or more other pharmaceutically acceptable ingredients well known to those skilled in the art, including, but not limited to, pharmaceutically acceptable carriers, diluents, excipients, adjuvants, fillers, buffers, preservatives, anti-oxidants, lubricants, stabilisers, solubilisers, surfactants (e.g., wetting agents), masking agents, colouring agents, flavouring agents, and sweetening agents. The formulation may further comprise other active agents, for example, other therapeutic or prophylactic agents.

Thus, the present invention further provides pharmaceutical compositions, as defined above, and methods of making a pharmaceutical composition comprising admixing at least one FTA compound, as described herein, together with one or more other pharmaceutically acceptable ingredients well known to those skilled in the art, e.g., carriers, diluents, excipients, etc. If formulated as discrete units (e.g., tablets, etc.), each unit contains a predetermined amount (dosage) of the compound.

The term "pharmaceutically acceptable," as used herein, pertains to compounds, ingredients, materials, compositions, dosage forms, etc., which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of the subject in question (e.g., human) without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. Each carrier, diluent, excipient, etc. must also be "acceptable" in the sense of being compatible with the other ingredients of the formulation.

Suitable carriers, diluents, excipients, etc. can be found in standard pharmaceutical texts, for example, Remington's Pharmaceutical Sciences, 18th edition, Mack Publishing Company, Easton, Pa., 1990; and Handbook of Pharmaceutical Excipients, 5th edition, 2005.

The formulations may be prepared by any methods well known in the art of pharmacy. Such methods include the step of bringing into association the compound with a carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the compound with carriers (e.g., liquid carriers, finely divided solid carrier, etc.), and then shaping the product, if necessary.

The formulation may be prepared to provide for rapid or slow release; immediate, delayed, timed, or sustained release; or a combination thereof.

Formulations may suitably be in the form of liquids, solutions (e.g., aqueous, non-aqueous), suspensions (e.g., aqueous, non-aqueous), emulsions (e.g., oil-in-water, water-in-oil), elixirs, syrups, electuaries, mouthwashes, drops, tablets (including, e.g., coated tablets), granules, powders, losenges, pastilles, capsules (including, e.g., hard and soft gelatin capsules), cachets, pills, ampoules, boluses, suppositories, pessaries, tinctures, gels, pastes, ointments, creams, lotions, oils, foams, sprays, mists, or aerosols.

Formulations may suitably be provided as a patch, adhesive plaster, bandage, dressing, or the like which is impregnated with one or more compounds and optionally one or more other pharmaceutically acceptable ingredients, including, for example, penetration, permeation, and absorption enhancers. Formulations may also suitably be provided in the form of a depot or reservoir.

The compound may be dissolved in, suspended in, or admixed with one or more other pharmaceutically acceptable ingredients. The compound may be presented in a liposome or other microparticulate which is designed to target the compound, for example, to blood components or one or more organs.

Formulations suitable for oral administration (e.g., by ingestion) include liquids, solutions (e.g., aqueous, non-aqueous), suspensions (e.g., aqueous, non-aqueous), emulsions (e.g., oil-in-water, water-in-oil), elixirs, syrups, electuaries, tablets, granules, powders, capsules, cachets, pills, ampoules, boluses.

Formulations suitable for buccal administration include mouthwashes, lozenges, pastilles, as well as patches, adhesive plasters, depots, and reservoirs. Lozenges typically comprise the compound in a flavored basis, usually sucrose and acacia or tragacanth. Pastilles typically comprise the compound in an inert matrix, such as gelatin and glycerin, or sucrose and acacia. Mouthwashes typically comprise the compound in a suitable liquid carrier.

Formulations suitable for sublingual administration include tablets, lozenges, pastilles, capsules, and pills.

Formulations suitable for oral transmucosal administration include liquids, solutions (e.g., aqueous, non-aqueous), suspensions (e.g., aqueous, non-aqueous), emulsions (e.g., oil-in-water, water-in-oil), mouthwashes, lozenges, pastilles, as well as patches, adhesive plasters, depots, and reservoirs.

Formulations suitable for non-oral transmucosal administration include liquids, solutions (e.g., aqueous, non-aqueous), suspensions (e.g., aqueous, non-aqueous), emulsions (e.g., oil-in-water, water-in-oil), suppositories, pessaries, gels, pastes, ointments, creams, lotions, oils, as well as patches, adhesive plasters, depots, and reservoirs.

Formulations suitable for transdermal administration include gels, pastes, ointments, creams, lotions, and oils, as well as patches, adhesive plasters, bandages, dressings, depots, and reservoirs.

Tablets may be made by conventional means, e.g., compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the compound in a free-flowing form such as a powder or granules, optionally mixed with one or more binders (e.g., povidone, gelatin, acacia, sorbitol, tragacanth, hydroxypropylmethyl cellulose); fillers or diluents (e.g., lactose, microcrystalline cellulose, calcium hydrogen phosphate); lubricants (e.g., magnesium stearate, talc, silica); disintegrants (e.g., sodium starch glycolate, cross-linked povidone, cross-linked sodium carboxymethyl cellulose); surface-active or dispersing or wetting

agents (e.g., sodium lauryl sulfate); preservatives (e.g., methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, sorbic acid); flavours, flavour enhancing agents, and sweeteners. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the compound therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided with a coating, for example, to affect release, for example an enteric coating, to provide release in parts of the gut other than the stomach.

Ointments are typically prepared from the compound and a paraffinic or a water-miscible ointment base.

Creams are typically prepared from the compound and an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example, at least about 30% w/w of a polyhydric alcohol, i.e., an alcohol having two or more hydroxyl groups such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the compound through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogues.

Emulsions are typically prepared from the compound and an oily phase, which may optionally comprise merely an emulsifier (otherwise known as an emulgent), or it may comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabiliser. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabiliser(s) make up the so-called emulsifying wax, and the wax together with the oil and/or fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

Suitable emulgents and emulsion stabilisers include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate and sodium lauryl sulfate. The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the compound in most oils likely to be used in pharmaceutical emulsion formulations may be very low. Thus the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in

combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for intranasal administration, where the carrier is a liquid, include, for example, nasal spray, nasal drops, or by aerosol administration by nebuliser, include aqueous or oily solutions of the compound.

Formulations suitable for intranasal administration, where the carrier is a solid, include, for example, those presented as a coarse powder having a particle size, for example, in the range of about 20 to about 500 microns which is administered in the manner in which snuff is taken, i.e., by rapid inhalation through the nasal passage from a container of the powder held close up to the nose.

Formulations suitable for pulmonary administration (e.g., by inhalation or insufflation therapy) include those presented as an aerosol spray from a pressurised pack, with the use of a suitable propellant, such as dichlorodifluoromethane, trichlorofluoromethane, dichoro-tetrafluoroethane, carbon dioxide, or other suitable gases.

Formulations suitable for ocular administration include eye drops wherein the compound is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the compound.

Formulations suitable for rectal administration may be presented as a suppository with a suitable base comprising, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols, for example, cocoa butter or a salicylate; or as a solution or suspension for treatment by enema.

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

Formulations suitable for parenteral administration (e.g., by injection), include aqueous or non-aqueous, isotonic, pyrogen-free, sterile liquids (e.g., solutions, suspensions), in which the compound is dissolved, suspended, or otherwise provided (e.g., in a liposome or other microparticulate). Such liquids may additional contain other pharmaceutically acceptable ingredients, such as anti-oxidants, buffers, preservatives, stabilisers, bacteriostats, suspending agents, thickening agents, and solutes which render the formulation isotonic with the blood (or other relevant bodily fluid) of the intended recipient. Examples of excipients include, for example, water, alcohols, polyols, glycerol, vegetable oils, and the like. Examples of suitable isotonic carriers for use in such formulations include Sodium Chloride Injection, Ringer's Solution, or Lactated Ringer's Injection. Typically, the concentration of the compound in the liquid is from about 1 ng/ml to about 10 µg/ml, for example from about 10 ng/ml to about 1 µg/ml. The formulations may be

presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules, and tablets.

Dosage

It will be appreciated by one of skill in the art that appropriate dosages of the FTA compounds, and compositions comprising the FTA compounds, can vary from patient to patient. Determining the optimal dosage will generally involve the balancing of the level of therapeutic benefit against any risk or deleterious side effects. The selected dosage level will depend on a variety of factors including, but not limited to, the activity of the particular FTA compound, the route of administration, the time of administration, the rate of excretion of the FTA compound, the duration of the treatment, other drugs, compounds, and/or materials used in combination, the severity of the condition, and the species, sex, age, weight, condition, general health, and prior medical history of the patient. The amount of FTA compound and route of administration will ultimately be at the discretion of the physician, veterinarian, or clinician, although generally the dosage will be selected to achieve local concentrations at the site of action which achieve the desired effect without causing substantial harmful or deleterious side-effects.

Administration can be effected in one dose, continuously or intermittently (e.g., in divided doses at appropriate intervals) throughout the course of treatment. Methods of determining the most effective means and dosage of administration are well known to those of skill in the art and will vary with the formulation used for therapy, the purpose of the therapy, the target cell(s) being treated, and the subject being treated. Single or multiple administrations can be carried out with the dose level and pattern being selected by the treating physician, veterinarian, or clinician.

In general, a suitable dose of the FTA compound is in the range of about 10 µg to about 250 mg (more typically about 100 µg to about 25 mg) per kilogram body weight of the subject per day. Where the compound is a salt, an ester, an amide, a prodrug, or the like, the amount administered is calculated on the basis of the parent compound and so the actual weight to be used is increased proportionately.

EXAMPLES

The following examples are provided solely to illustrate the present invention and are not intended to limit the scope of the invention, as described herein.

Chemical Synthesis

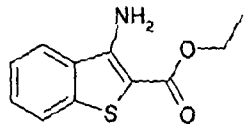
General

All non-aqueous reactions were performed in oven-dried glassware under an atmosphere of dry nitrogen, unless otherwise specified. Tetrahydrofuran was freshly distilled from sodium/benzophenone under N_2. Dichloromethane was freshly distilled from CaH_2 under N_2. All other solvents were reagent grade. Petroleum ether describes a mixture of hexanes in the bp range 40-60°C. Analytical thin-layer chromatography was performed on Merck silica gel $60F_{254}$ aluminium-backed plates which were visualised by fluorescence quenching under UV light. Flash chromatography was performed with silica gel 60 (particle size 0.040-0.063 mm). All NMR spectra were recorded on a Bruker Avance DRX 300 with the solvents indicated (^{1}H NMR at 300 MHz). Chemical shifts are reported in ppm on the δ scale, referenced to the appropriate solvent peak. Mass spectrometry was performed on a Finnigan LCQ Advantage MAX and a Waters ZQ3100.

Method 1: 4-Aminobenzothieno[3,2-d]pyrimdine

Synthesis 1A

Ethyl 3-aminobenzo[b]thiophene-2-carboxylate

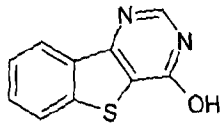


2-Fluorobenzonitrile (8.25 mmol), diisopropylethylamine (8.25 mmol) and ethyl 2-mercaptoacetate (8.25 mmol) in anhydrous N,N-dimethylformamide (5 mL) was allowed to stir for 30 min at room temperature. Potassium carbonate (8.25 mmol) was added and the solution was heated to 80°C for 20 h. Ice-water was added and the resulting precipitate was filtered off, washing with water to obtain the carboxylate as a white solid (92%).

LCMS rt 7.43, M+H 222; ^{1}H-NMR ($CDCl_3$) δ 7.43 (1H, d, J 8.1 Hz), 7.65 (1H, d, J 8.1 Hz), 7.49-7.44 (1H, m), 7.39-7.34 (1H, m), 4.36 (2H, q, J 7.1 Hz), 1.40 (3H, t, J 7.1 Hz).

Synthesis 1B

3H-[1]benzothieno[3,2-d]pyrimid-4-one

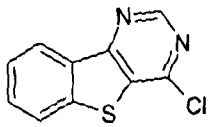


A stirred mixture of ethyl 3-aminobenzo[b]thiophene-2-carboxylate (3.62 mmol) in formamide (5 mL) was heated to 150°C. Formamidine acetate (3.62 mmol) was added and the mixture heated at 150°C for 45 min. The addition of formamidine acetate (3.62 mmol) was repeated every 45 min for 6 h. Ice-water was added and the precipitate that was formed was filtered off, washed with water, and dried in a vacuum oven to obtain the pyrimidine as a tanned solid (95%).

LCMS rt 5.20; M+H 203; ^{1}H-NMR (DMSO) δ □8.33 (1H, s), 8.26-8.21 (1H, m), 8.16-8.12 (1H, m), 7.69-7.56 (1H, m).

Synthesis 1C

4-Chlorobenzothieno[3,2-d]pyrimidine

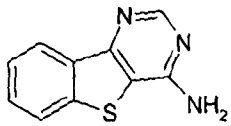


A mixture of 3H-benzothieno[3,2-d]pyrimid-4-one (2.48 mmol) and N,N-dimethylformamide (0.025 mmol) in phosphorous oxychloride (6 mL) was allowed to stir at 90°C for 20 h. The phosphorous oxychloride was removed in vacuo. Ice-water was added and the solution neutralized by portionwise addition of solid sodium hydrogen carbonate. The resulting precipitate was filtered off, washed with water and dried in a vacuum oven to give the chloro pyrimidine as a tanned solid (86%).

LCMS rt 7.73, M+H 221; ^{1}H-NMR (DMSO) δ 9.17 (1H, s), 8.48 (1H, d, J 7.8 Hz), 8.29 (1H, d, J 8.1 Hz), 7.84 (1H, dt, J 7.2 and 1.2 Hz), 7.71 (1H, dt, J 7.2 Hz and 0.9).

Synthesis 1D

4-Aminobenzothieno[3,2-d]pyrimidine



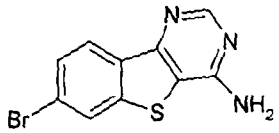
A suspension of 4-chlorobenzothieno[3,2-d]pyrimidine (0.45 mmol) in concentrated ammonium hydroxide (1 mL) and dioxane (3 mL) was heated to 100°C under microwave irradiation (250 W) for 2 h. Ice-water was added and the precipitate that resulted was filtered off, washed with water, and dried in a vacuum oven to obtain the amino pyrimidine as a pale-yellow solid (95%).

LCMS rt 4.08, M+H 402; ^{1}H-NMR (DMSO) δ 8.51 (1H,s), 8.30 (1H, s, J 7.2 Hz), 8.12 (1H, s, J 8.1 Hz), 7.68-7.51 (4H, m).

Method 2: 7-Phenyl-4-aminobenzothieno[3,2-d]pyrimidine (AE-001)

Synthesis 2A

7-Bromo-4-aminobenzothieno[3,2-d]pyrimidine

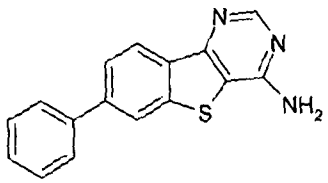


The 7-bromo-4-aminobenzothieno[3,2-d]pyrimidine was synthesised from 4-bromo-2-fluorobenzonitrile in the same manner as Method 1.

LCMS rt 5.50, M+H 280; ^{1}H-NMR (DMSO) δ 8.51 (1H, s), 8.47 (1H, d, J 1.7 Hz), 8.18 (1H, d, J 8.4 Hz), 7.70 (1H, dd, J 8.5 and 1.8 Hz), 7.60 (1H, bs).

Synthesis 2B

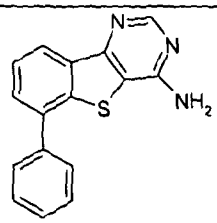
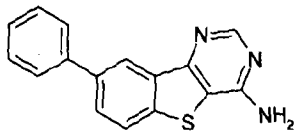
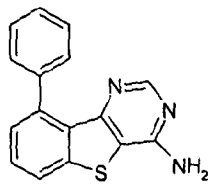
7-Phenyl-aminobenzothieno[3,2-d]pyrimidine (AE-001)



A mixture of 7-bromo-aminobenzothieno[3,2-d]pyrimidine (0.36 mmol), potassium carbonate (0.89 mmol), phenylboronic acid (0.4 mmol), tetrabutylammonium bromide (0.036 mmol) and $PdCl_2(PPh_3)_4$ (0.036 mmol) in a solution of dioxane (4 mL) and water (1 mL) were heated at 120°C under microwave irradiation for 2 h. 10% Citric acid solution (10 mL) was added and the precipitate that resulted was filtered off, washed with water, and dried in a vacuum oven. The solid was dissolved in a dilute methanol/tetrahydrofuran mixture with warming, and filtered. The filtrate was concentrated to dryness in vacuo. The resulting residue is triturated with diethylether, and filtered off to give a tanned solid (70%). Alternatively, the crude residue is applied to column chromatography gradient eluting with 100% dichloromethane to 15% methanol dichloromethane.

LCMS rt 7.53, M+H 278; ^{1}H-NMR (DMSO) δ 8.52 (1H, s), 8.46-8.45 (1H, m), 8.33 (1H, d, J 8.8 Hz), 7.88-7.81 (3H, m), 7.54-7.41 (5H, m).

The following 6-phenyl-, 8-phenyl-, and 9-phenyl- 4-aminobenzothieno[3,2-d]pyrimidines were synthesised in the same manner as Method 2, using the corresponding nitriles (listed) in place of 4-bromo-2-fluorobenzonitrile.

Table 1 Phenyl-4-aminobenzothieno[3,2-d]pyrimidines			
Code	Structure	Reagent used	LCMS
AE-023		3-bromo-2-fluorobenzonitrile	rt 7.53, M+H 278
AF-001		5-bromo-2-fluorobenzonitrile	rt 7.54, M+H 278
AG-001		6-bromo-2-fluorobenzonitrile	rt 7.19, M+H 278

The following substituted 9-phenyl-4-aminobenzothieno[3,2-d]pyrimidines were synthesised in the same manner as Method 2, using the corresponding boronic acids (listed) in place of phenylboronic acid.

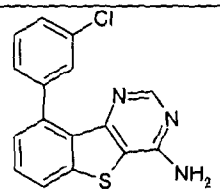
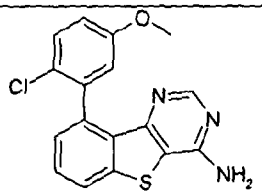
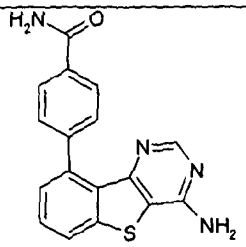
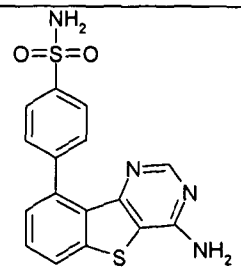
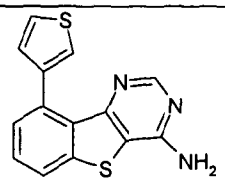
Table 2 Substituted 9-phenyl 4-aminobenzothieno[3,2-d]pyrimidines			
Code	Structure	Reagent used	LCMS
AG-002		3-Chlorophenylboronic acid	rt 8.13, M+H 312
AG-003		2-Chloro-5-methoxyphenyl boronic acid	rt 8.01, M+H 342
AG-004		4-Aminocarbonylphenyl boronic acid	rt 6.42, M+H 321

Table 2 Substituted 9-phenyl 4-aminobenzothieno[3,2-d]pyrimidines			
Code	Structure	Reagent used	LCMS
AG-005		4-Sulfamoylphenylboronic acid, pinacol ester	rt 5.05, M+H 356
AH-014		Thiophen-3-boronic acid	rt 6.99, M+H 284

The following substituted 7-phenyl-4-aminobenzothieno[3,2-d]pyrimidines were synthesised in the same manner as Method 2, using the corresponding boronic acids (listed) in place of phenylboronic acid.

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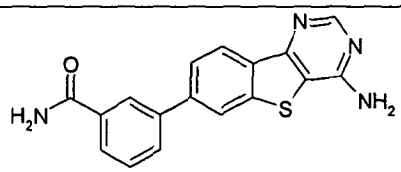
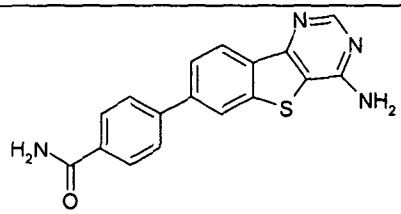
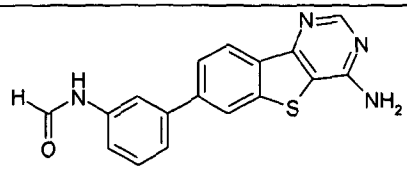
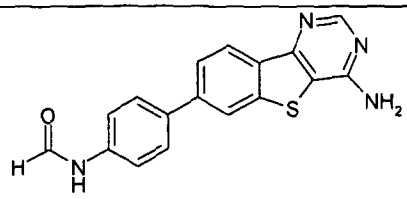
Table 3 Substituted 7-phenyl 4-aminobenzothieno[3,2-d]pyrimidines			
Code	Structure	Reagent used	LCMS
AB-003		3-Aminocarbonylphenyl boronic acid	rt 6.39, M+H 321
AB-008		4-aminocarbonylphenyl boronic acid	rt- 6.33, M+H 321
AC-001		3-Formylaminophenyl boronic acid, pinacol ester	rt 6.67, M+H 321
AC-002		4-Formylaminophenyl boronic acid, pinacol ester	rt 6.52, M+H 321

Table 3
Substituted 7-phenyl 4-aminobenzothieno[3,2-d]pyrimidines

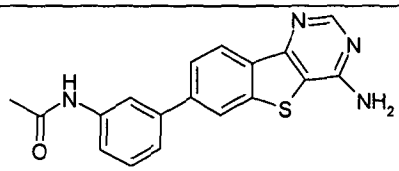
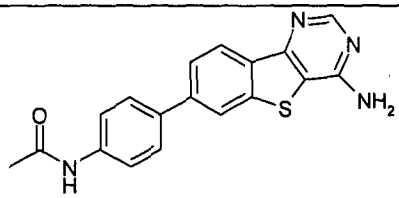
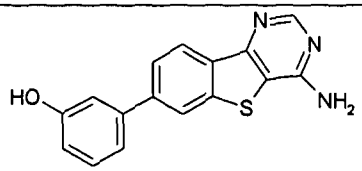
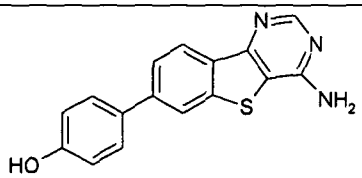
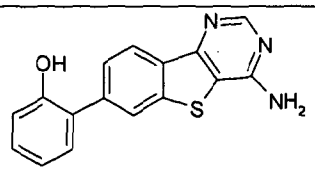
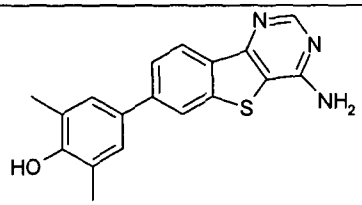
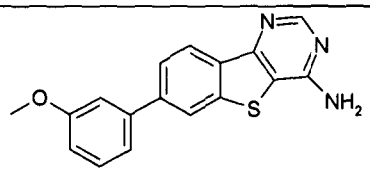
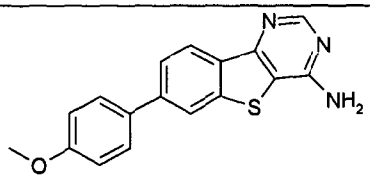
Code	Structure	Reagent used	LCMS
AC-003		3-Acetamidophenylboronic acid	rt 5.64, M+H 335
AC-004		4-Acetamidophenylboronic acid	rt 6.63, M+H 335
AD-001		3-Hydroxyphenylboronic acid	rt 6.78, M+H 294
AD-002		4-Hydroxyphenylboronic acid	rt 5.61, M+H 294
AD-003		2-Hydroxyphenylboronic acid	rt 6.84, M+H 294
AD-004		4-hydroxy-3,5-dimethylphenylboronic acid	rt 6.10, M+H 322
AD-005		3-Methoxy-phenylboronic acid	rt 7.55, M+H 308
AD-006		4-Methoxy-phenylboronic acid	rt 7.41, M+H 308

Table 3
Substituted 7-phenyl 4-aminobenzothieno[3,2-d]pyrimidines

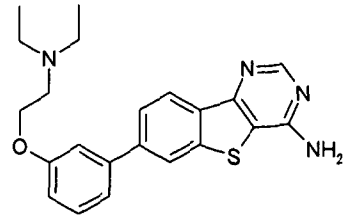
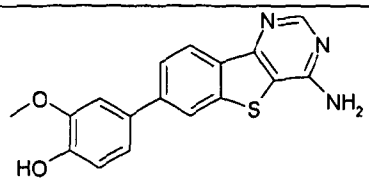
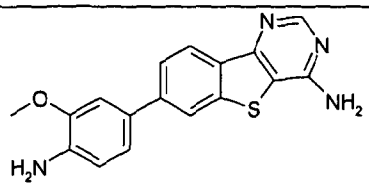
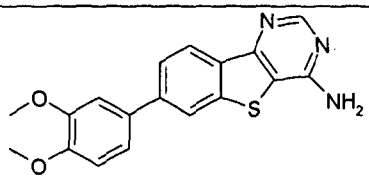
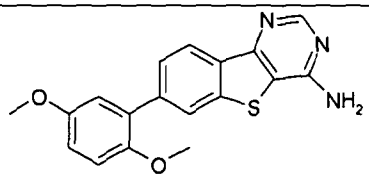
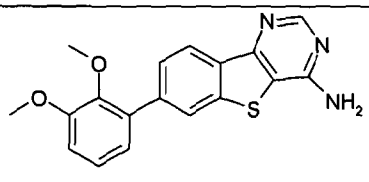
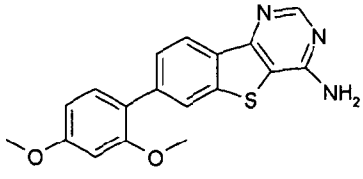
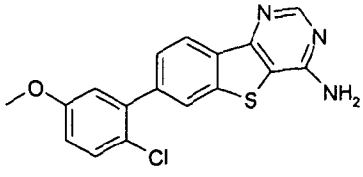
Code	Structure	Reagent used	LCMS
AD-007		3-(2-(Diethylamino) ethoxy)phenylboronic acid, pinacol ester	rt 4.48, M+H 393
AD-008		4-Hydroxy-3-methoxyphenylboronic acid, pinacol ester	rt 6.68, M+H 324
AD-009		4-Amino-3-methoxyphenyl boronic acid, pinacol ester	rt 4.40, M+H 323
AD-010		3,4-Dimethoxyphenyl boronic acid	rt 5.38, M+H 338
AD-011		2,5-Dimethoxyphenyl boronic acid	rt 5.80, M+H 338
AD-012		2,3-Dimethoxyphenyl boronic acid	rt 5.73, M+H 338
AD-013		2,4-Dimethoxyphenyl boronic acid	rt 5.82, M+H 338
AD-014		2-Chloro-5-methoxyphenylboronic acid	rt 7.93, M+H 342

Table 3
Substituted 7-phenyl 4-aminobenzothieno[3,2-d]pyrimidines

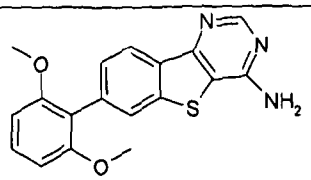
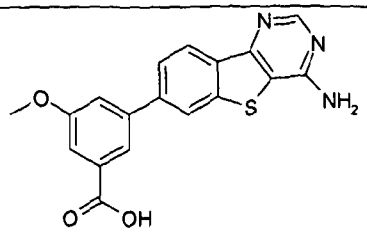
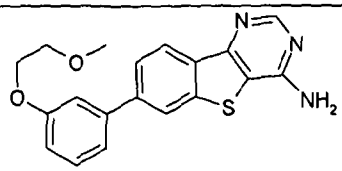
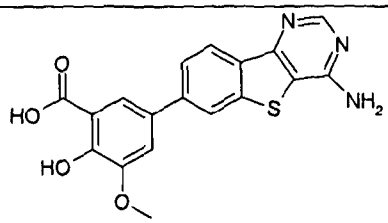
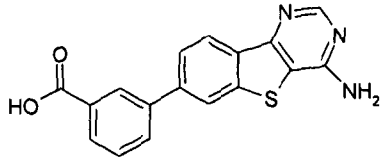
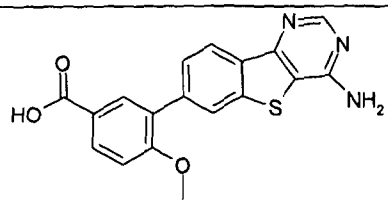
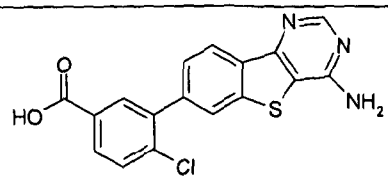
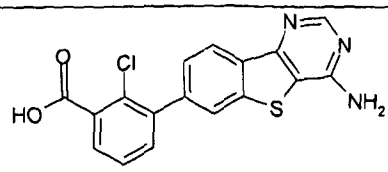
Code	Structure	Reagent used	LCMS
AD-015		2,6-Dimethoxyphenyl boronic acid	rt 5.67, M+H 338
AD-016		3-Carboxy-5-methoxyphenylboronic acid, pinacol ester	rt 7.13, M+H 352
AD-017		3-(2-Methoxyethoxy) phenylboronic acid, pinacol ester	rt 7.30, M+H 352
AE-002		3-Carboxy-4-hydroxy-5-methoxyphenylboronic acid	rt 6.89, M+H 388
AE-003		3-Carboxyphenylboronic acid	rt 6.96, M+H 322
AE-004		3-Carboxy-6-methoxyphenylboronic acid	rt 4.98, M+H 352
AE-005		3-Carboxy-6-chlorophenylboronic acid	rt 7.27, M+H 356
AE-006		3-Carboxy-2-chloro phenylboronic acid	rt 6.96, M+H 356

Table 3
Substituted 7-phenyl 4-aminobenzothieno[3,2-d]pyrimidines

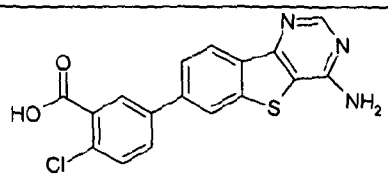
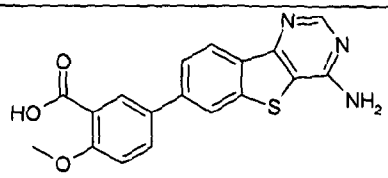
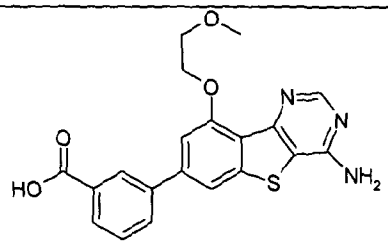
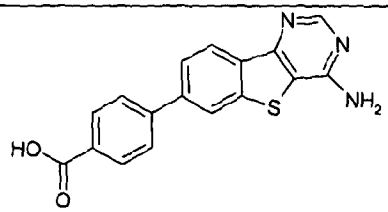
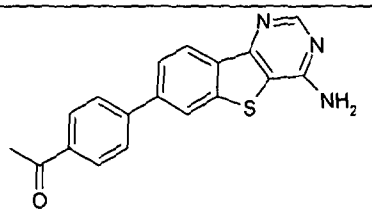
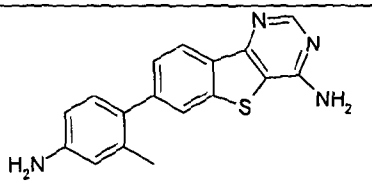
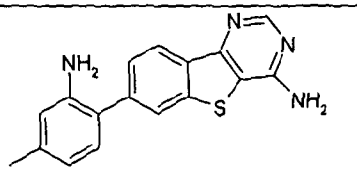
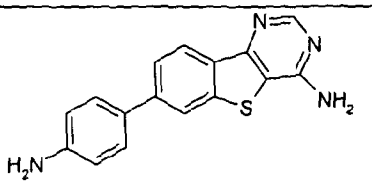
Code	Structure	Reagent used	LCMS
AE-007		3-Carboxy-4-chlorophenylboronic acid	rt 7.13, M+H 356
AE-008		3-Carboxy-4-methoxyphenylboronic acid	rt 6.65, M+H 352
AE-009		3-Carboxyphenylboronic acid	rt 5.50, M+H 396
AE-010		4-Carboxyphenylboronic acid	rt 4.97, M+H 322
AE-011		4-Acetylphenylboronic acid	rt 7.19, M+H 320
AE-012		4-Amino-2-methylphenylboronic acid	rt 5.97, M+H 307
AE-013		2-Amino-4-methyl-phenylboronic acid	rt 6.96, M+H 307
AE-014		2-Aminophenylboronic acid	rt 7.04, M+H 293

Table 3
Substituted 7-phenyl 4-aminobenzothieno[3,2-d]pyrimidines

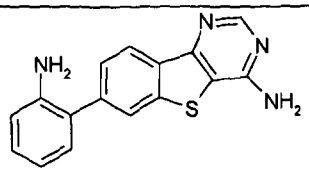
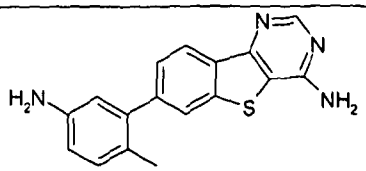
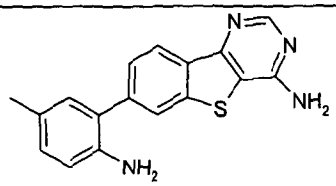
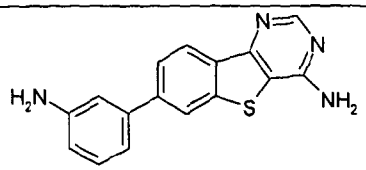
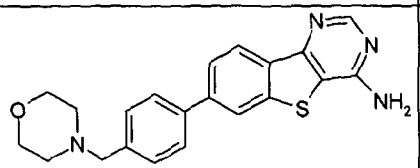
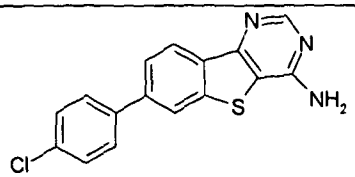
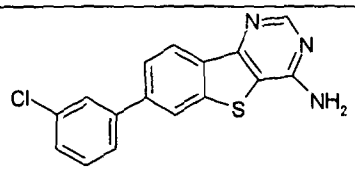
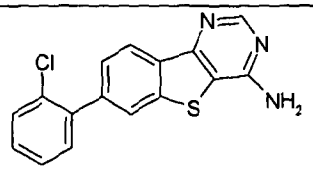
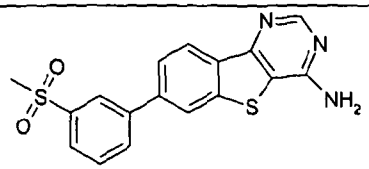
Code	Structure	Reagent used	LCMS
AE-015		2-Amino-phenylboronic acid	rt 6.70, M+H 293
AE-016		3-Amino-6-methylphenylboronic acid	rt 4.25, M+H 307
AE-017		2-Amino-5-methylphenylboronic acid	rt 6.70, M+H 307
AE-018		3-Aminophenylboronic acid	rt 4.42, M+H 293
AE-019		4-(Methylmorpholino) phenylboronic acid, pinacol ester	rt 5.83, M+H 377
AE-020		4-Chlorophenylboronic acid	rt 8.03, M+H 312
AE-021		3-Chlorophenylboronic acid	rt 6.91, M+H 312
AE-022		2-Chlorophenylboronic acid	rt 7.79, M+H 312
AE-024		3-(Methylsulfonyl)phenyl boronic acid	rt 6.92, M+H 356

Table 3
Substituted 7-phenyl 4-aminobenzothieno[3,2-d]pyrimidines

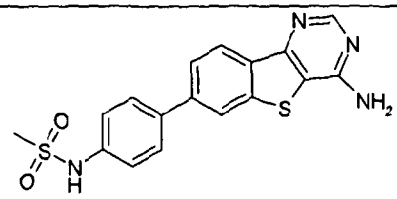
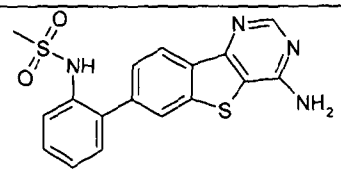
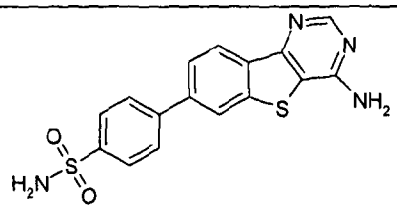
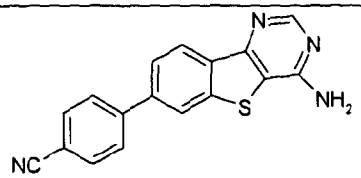
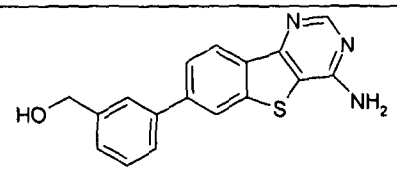
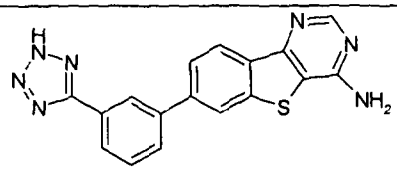
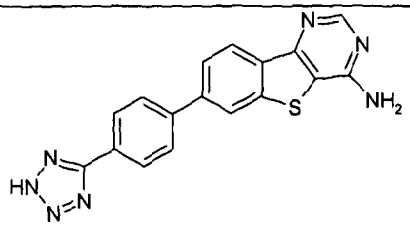
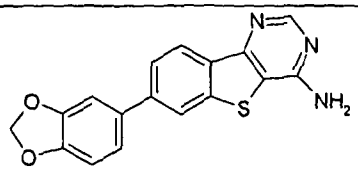
Code	Structure	Reagent used	LCMS
AE-025		[(4-Methylsulfonyl) aminophenyl] boronic acid, pinacol ester	rt 6.72, M+H 371
AE-026		[(2-Methylsulfonyl) aminophenyl] boronic acid, pinacol ester	rt 6.17, M+H 371
AE-027		4-Sulfamoylphenylboronic acid, pinacol ester	rt 6.50, M+H 357
AE-028		4-Cyanophenylboronic acid	rt 7.38, M+H 303
AE-029		3-Hydroxymethyl-phenylboronic acid	rt 6.63, M+H 308
AE-030		3-(Tetrazol-5-yl)phenyl boronic acid	rt 6.99, M+H 346
AE-031		4-(Tetrazol-5-yl)phenyl boronic acid	rt 6.87, M+H 346
AE-034		3,4-(Methylenedioxy)phenyl boronic acid	rt 7.37, M+H 322

Table 3
Substituted 7-phenyl 4-aminobenzothieno[3,2-d]pyrimidines

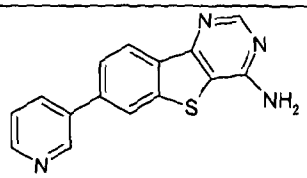
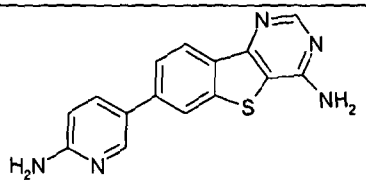
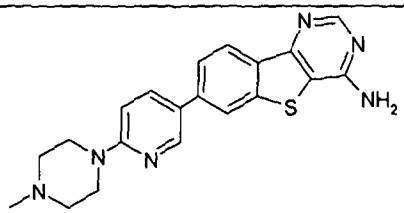
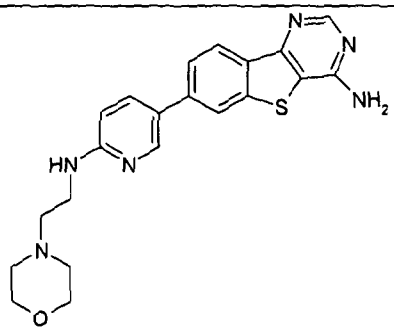
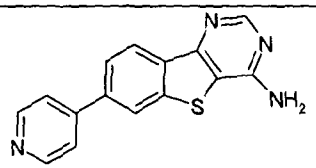
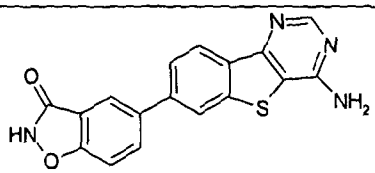
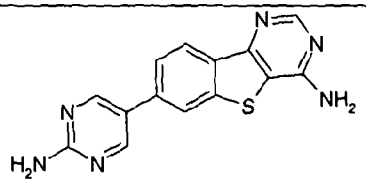
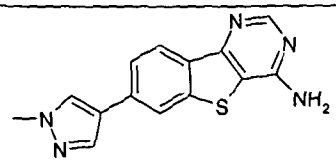
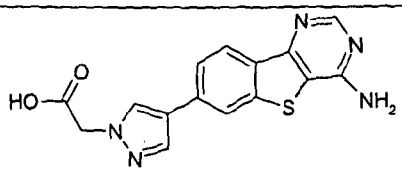
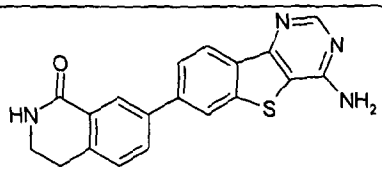
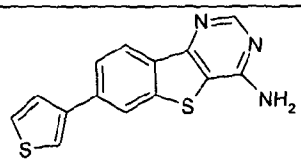
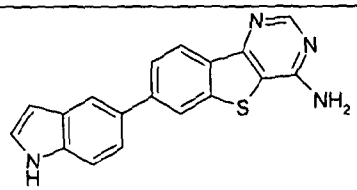
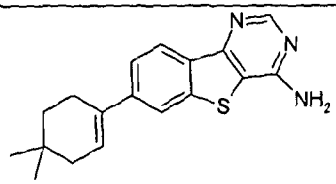
Code	Structure	Reagent used	LCMS
AH-001		Pyridin-3-ylboronic acid	rt 0.90, M+H 279
AH-002		4-Amino-pyridin-3-yl boronic acid	rt 5.57, M+H 294
AH-003		2-(4-Methylpiperazin-1-yl)pyridine-5-boronic acid, pinacol este	rt 5.92, M+H 377
AH-004		6-(2-Morpholinoethyl amino) pyridin-3-yl boronic acid, pinacol ester	rt 5.62, M+H 407
AH-005		Pyridin-4-ylboronic acid	rt 0.90, M+H 279
AH-006		3-Oxo-2,3-dihydro benzo[d]isoxazol-5-ylboronic acid, pinacol ester	rt 6.91, M+H 335
AH-007		2-Aminopyrimidine-5- boronic acid, pinacol ester	rt 5.95, M+H 295

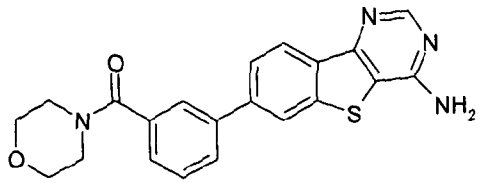
Table 3
Substituted 7-phenyl 4-aminobenzothieno[3,2-d]pyrimidines

Code	Structure	Reagent used	LCMS
AH-008		4-(1-Methyl-1H-pyrazole) boronic acid, pinacol ester	rt 6.30, M+H 282
AH-009		1-(Ethoxycarbonyl methyl)-1H-pyrazole-4-boronic acid, pinacol ester	rt 6.12, M+H 362
AH-012		1-Oxo-1,2,3,4-tetrahydroisoquinolin-7-ylboronic acid, pinacol ester	rt 4.82, M+H 4.82
AH-013		Thiophen-3-boronic acid	rt 7.07, M+H 284
AH-015		5-Indoleboronic acid, pinacol ester	rt 7.20, M+H 317
AJ-01		4,4-dimethylcyclohex-1-enylboronic acid, pinacol ester	rt 8.56, M+H 310

Method 3: Substituted amido 7-phenyl 4-aminobenzothieno[3,2-d]pyrimidine

Synthesis 3A

7-(3-N,N-morpholinylbenzamide) 4-aminobenzothieno[3,2-d] pyrimidine (AB-036)



A mixture of 7-(3-carboxyphenyl)-4-aminobenzothieno[3,2-d]pyrimidine AA-003 (0.09 mmol), diisopropylethylamine (0.42 mmol) and HBTU (0.13 mmol) in N,N-dimethylformamide (0.3 mL), was allowed to stir for 5 min. Morpholine (0.18 mmol)

was added and the solution was allowed to stir for 16 h. Ice-water was added and the precipitate that formed was filtered off, washing with water and dried in a vacuum oven to give the amide as a tanned solid (90%).

LCMS rt 6.66, M+H 391; ^{1}H-NMR (DMSO) δ □8.58 (1H, s), 8.55 (1H, s), 8.37, (1H, s), 7.94-7.42 (7H, m), 3.62 (4H, bs), 2.97 (4H, bs).

The following substituted amido 7-phenyl-4-aminobenzothieno[3,2-d]pyrimidines were synthesised in the same manner as Method 3, using the corresponding amines (listed) in place of morpholine.

Table 4A
Substituted amido 7-phenyl 4-aminobenzothieno[3,2-d]pyrimidines

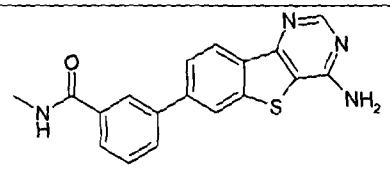
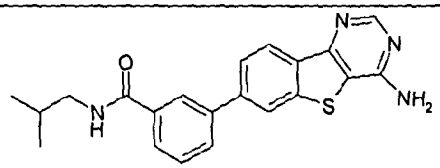
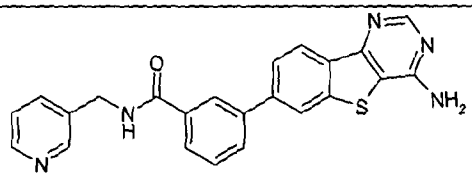
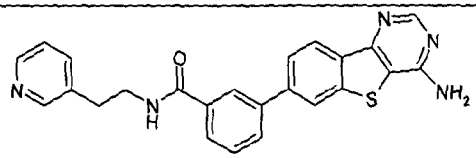
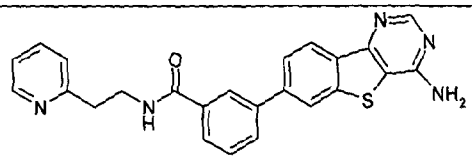
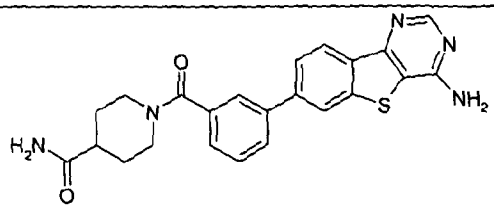
Code	Structure	Reagent used	LCMS
AB-009		N,N-dimethylamine hydrochloride	rt 6.63, M+H 349
AB-010		2-Methylpropan-1-amine	rt 7.34, M+H 377
AB-012		3-(2-Aminomethyl) pyridine	rt 6.19, M+H 412
AB-013		3-(2-Aminoethyl) pyridine	rt 0.22, M+H 426
AB-014		2-(2-Aminoethyl) pyridine	rt 6.11, M+H 426
AB-017		Piperidine-4-carboxamide	rt-6.38, M+H 432

Table 4A

Substituted amido 7-phenyl 4-aminobenzothieno[3,2-d]pyrimidines

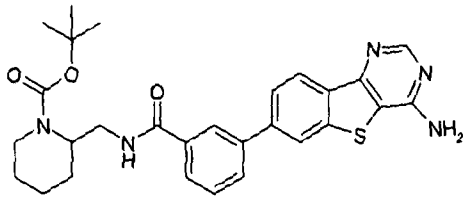
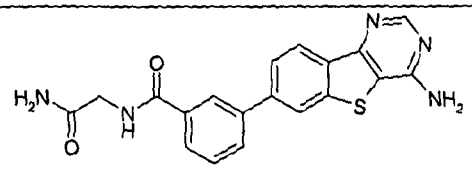
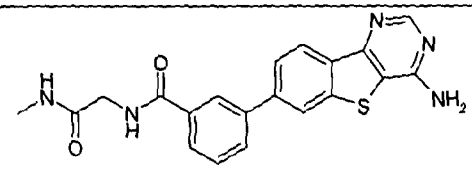
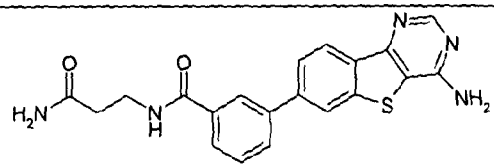
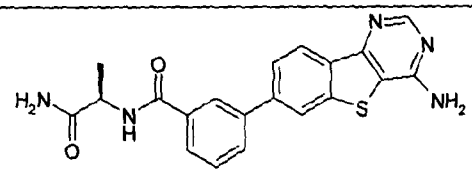
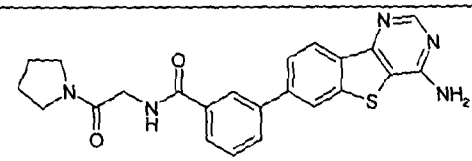
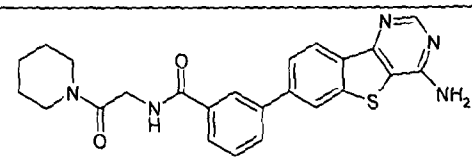
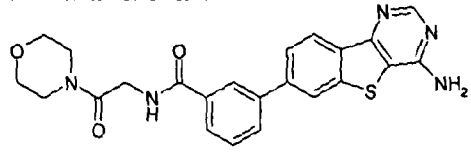
Code	Structure	Reagent used	LCMS
AB-018		tert-Butyl 2-(aminomethyl)piperidine-1-carboxylate hydrochloride	rt- 8.01, M+H 518
AB-019		Glycinamide hydrochloride	rt 6.25, M+H 378
AB-020		2-Amino-N-methylacetamide	rt 6.46, M+H 392
AB-021		3-Aminopropanamide	rt 6.46, 392
AB-024		L-Alaninamide hydrochloride	rt-4.50, M+H 392
AB-025		2-Amino-1-(pyrrolidin-1-yl)ethanone hydrochloride	rt 6.84, M+H 432
AB-026		2-Amino-1-(piperidin-1-yl)ethanone hydrochloride	rt 7.14, M+H 446
AB-027		2-Amino-1-morpholinoethanone hydrochloride	rt 6.50, M+H 448

Table 4A

Substituted amido 7-phenyl 4-aminobenzothieno[3,2-d]pyrimidines

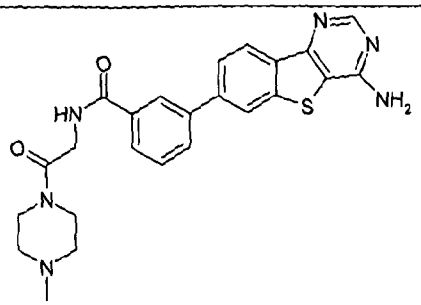
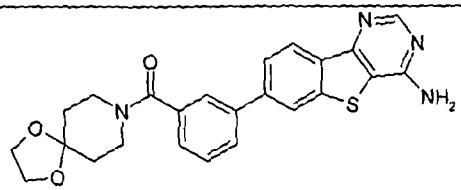
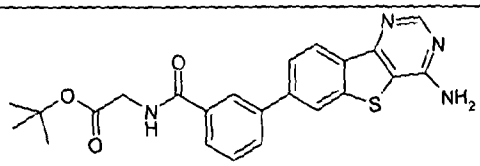
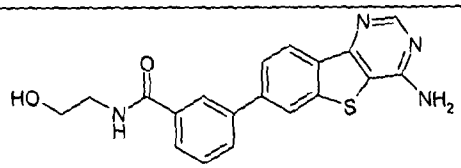
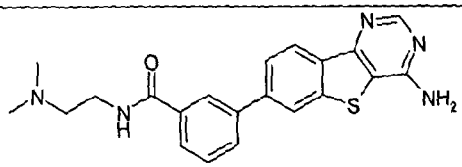
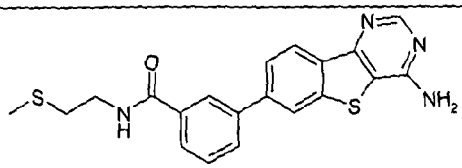
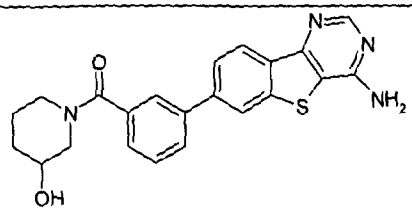
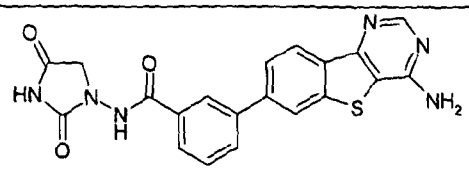
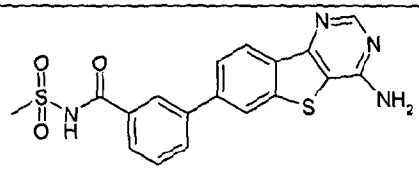
Code	Structure	Reagent used	LCMS
AB-029		2-Amino-1-(4-methylpiperazin-1-yl)ethanone dihydrochloride	rt 5.94, M+H 461
AB-031		1,4-Dioxa-8-azaspiro[4.5]decane	rt- 6.92, M+H 447
AB-032		tert-Butyl glycinate	rt-7.63, M+H 435
AB-033		2-Aminoethanol	rt-0.20, M+H 365
AB-034		N,N-Dimethylethane-1,2-diamine	rt 0.20, M+H 392
AB-035		2-(Methylthio) ethanamine	rt 7.23, M+H 395
AB-037		Piperidin-3-ol	rt- 6.59, M+H 405

Table 4A Substituted amido 7-phenyl 4-aminobenzothieno[3,2-d]pyrimidines			
Code	Structure	Reagent used	LCMS
AE-032		1-Amino imidazolidine-2,4-dione	rt 4.58, M+H 419
AE-033		Methanesulfonamide	rt 6.77, M+H 399

The following substituted amido 7-aryl-4-aminobenzothieno[3,2-d]pyrimidines were synthesised in the same manner as Method 3, using the corresponding amines (listed) in place of morpholine and starting from the appropriate substituted 7-(carboxyaryl)-4-aminobenzothieno[3,2-d]pyrimidine starting material.

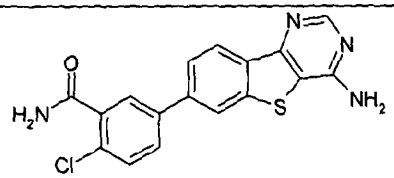
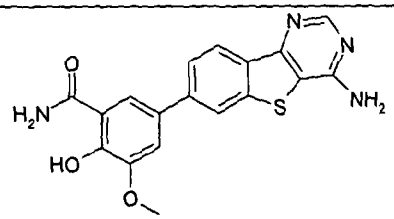
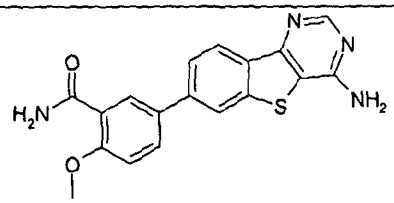
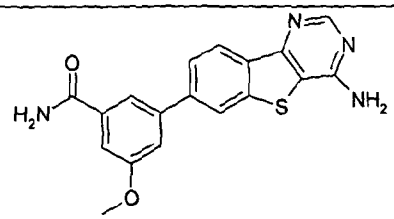
Table 4B Substituted amido 7-aryl 4-aminobenzothieno[3,2-d]pyrimidines				
Code	Structure	Reagents used		LCMS
AB-001		7N Ammonia in methanol	AE-007	rt 6.62, M+H 355
AB-002		7N Ammonia in methanol	AE-002	rt 4.85, M+H 368
AB-004		7N Ammonia in methanol	AE-008	rt 6.6, M+H 351
AB-005		7N Ammonia in methanol	AD-016	rt 6.75, M+H 351

Table 4B

Substituted amido 7-aryl 4-aminobenzothieno[3,2-d]pyrimidines

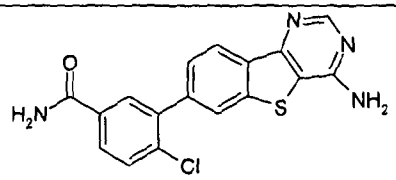
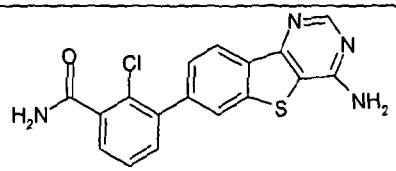
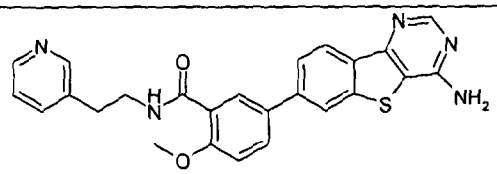
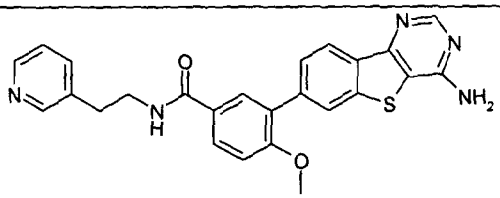
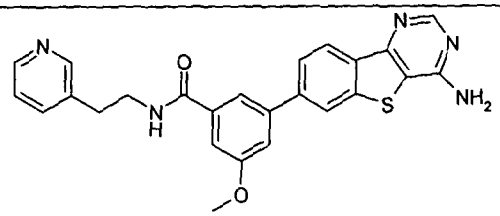
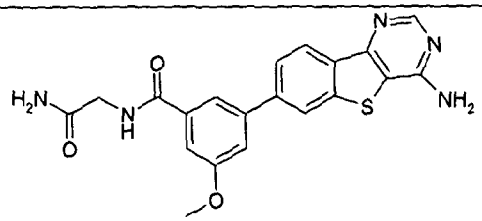
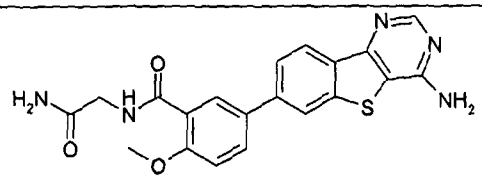
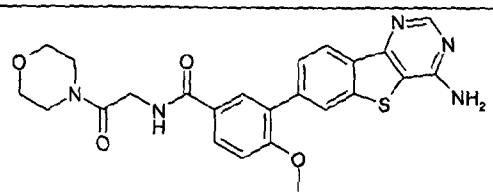
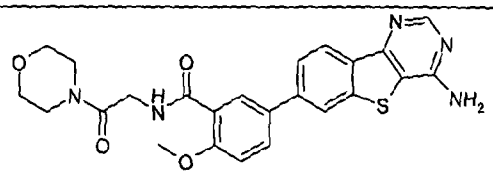
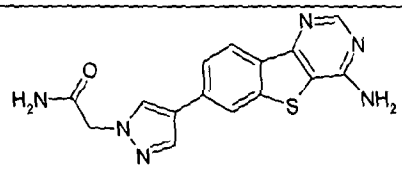
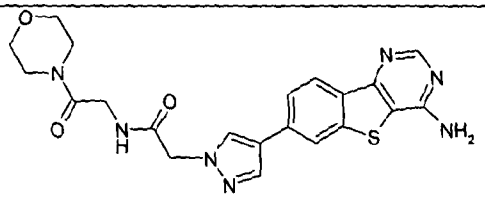
Code	Structure	Reagents used		LCMS
AB-006		7N Ammonia in methanol	AE-005	rt 6.83, M+H 355
AB-007		7N Ammonia in methanol	AE-006	rt 6.33, M+H 355
AB-011		3-(2-Aminoethyl) pyridine	AE-008	rt 4.56, M+H 456
AB-015		3-(2-Aminoethyl) pyridine	AE-004	rt 6.11, M+H 456
AB-016		3-(2-Aminoethyl) pyridine	AD-016	rt 6.51, M+H 478
AB-022		Glycinamide hydrochloride	AD-016	rt 5.87, M+H 408
AB-023		Glycinamide hydrochloride	AE-008	rt 6.56, M+H 408

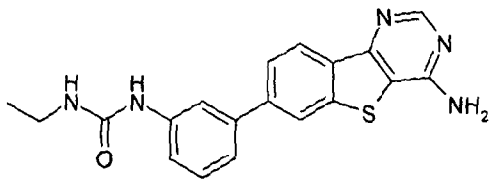
Table 4B
Substituted amido 7-aryl 4-aminobenzothieno[3,2-d]pyrimidines

Code	Structure	Reagents used		LCMS
AB-028		2-Amino-1-morpholino ethanone hydrochloride	AE-004	rt 6.51, M+H 478
AB-030		2-Amino-1-morpholinoethanone hydrochloride	AE-008	rt 6.90, M+H 478
AH-010		7N Ammonia in methanol	AH-009	rt 5.07, M+H 325
AH-011		2-Amino-1-morpholinoethanone hydrochloride	AH-009	rt 6.17, M+H 452

Method 5: Substituted ureido 7-phenyl 4-aminobenzothieno[3,2-d] pyrimidine

Synthesis 5A

7-(3-ethylurea)-4-aminobenzothieno[3,2-d]pyrimidine (AA-003)



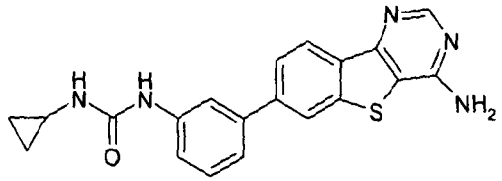
A solution of 7-(3-amino)-4-aminobenzothieno[3,2-d]pyrimidine AE-018 (0.07 mmol) and ethyl isocyanate (1.09 mmol) in anhydrous THF (1 mL) was stirred at 50°C for 16 h. After this time, the solvent was removed in vacuo. The resulting residue was triturated with diethyl ether, and filtered to give the urea as a tanned solid (80%).

LCMS rt 4.86, M+H 363; ^{1}H-NMR (DMSO) δ 8.55 (1H, s), 8.53 (1H, s), 8.36 (1H, s), 8.33 (1H,s), 7.90 (1H, s), 7.81-7.77 (1H, m), 7.54 (2H, bs), 7.38-7.34 (3H, m), 6.18-6.14 (1H, bs), 3.40-3.20 (2H, m), 1.07 (3H, t J 7.2 Hz).

Method 6: Substituted ureido 7-phenyl 4-aminobenzothieno[3,2-d] pyrimidine

Synthesis 6A

7-(3-cyclopropylurea)-4-aminobenzothieno[3,2-d]pyrimidine (AA-032)



A solution of 7-(3-aminophenyl)-4-aminobenzothieno[3,2-d]pyrimidine AE-018 (0.51 mmol), pyridine (1.54 mmol) and phenyl chloroformate (0.59 mmol) in N,N-dimethylformamide (3 mL) containing under nitrogen was stirred at 0°C for 45 min and then warmed to 25°C for 2 h. After this time, water was added and a precipitate formed. This was filtered, washed with water and then oven dried to give the 7-(3-phenylcarbamate)-4-aminobenzothieno[3,2-d]pyrimidine as an olive solid (80%). A solution of the carbamate (0.05 mmol) in 1,4-dioxane (0.5 mL) containing excess cyclopropylamine (6.91 mmol) was stirred at 70°C for 4 h. After this time the solvent and excess amine was removed in vacuo. Diethyl ether was added and the precipitate that resulted was filtered, washing with diethylether, to give the urea as a light brown solid (80%).

LCMS rt 6.86, M+H 376; ^{1}H-NMR (DMSO) δ 8.34 (1H, 8.53), 8.43 (1H, s), 8.37-8.33 (3H, m), 7.93 (1H, s), 7.82-7.78 (1H, m), 7.54 (2H, bs), 7.41-7.35 (3H, m), 6.46 (1H, bs), 2.57-2.54 (1H, m), 0.66-0.64 (2H, m), 0.44-0.42 (2H, m).

The following substituted ureido 7-phenyl-4-aminobenzothieno[3,2-d]pyrimidines were synthesised in the same manner as Method 5, using the corresponding isocyanates (listed) in place of ethyl isocyanate, or in the same manner as Method 6 using the corresponding amines (listed) in place of cyclopropylamine.

Table 5A

Substituted ureido 7-phenyl 4-aminobenzothieno[3,2-d]pyrimidines

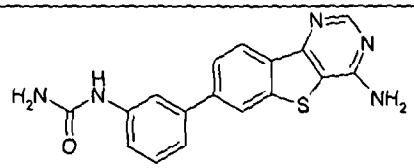
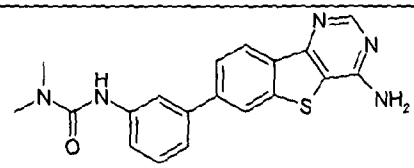
Code	Structure	Reagent used	LCMS
AA-001		Potassium isocyanate	rt 6.45, M+H 336
AA-002		N,N-Dimethylamine	rt 6.57, M+H 363

Table 5A
Substituted ureido 7-phenyl 4-aminobenzothieno[3,2-d]pyrimidines

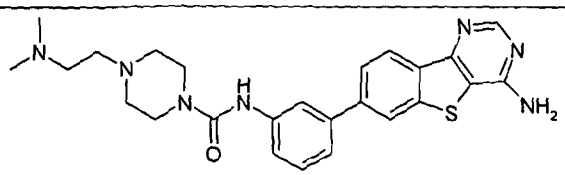
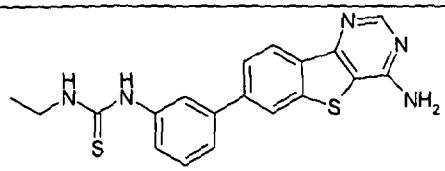
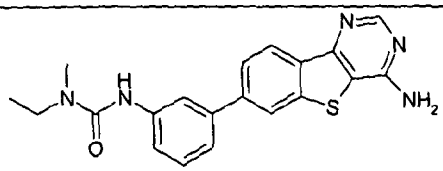
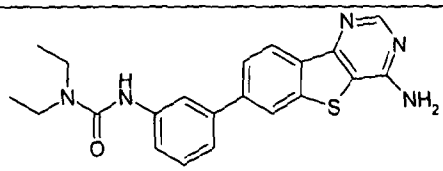
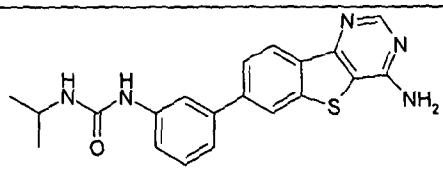
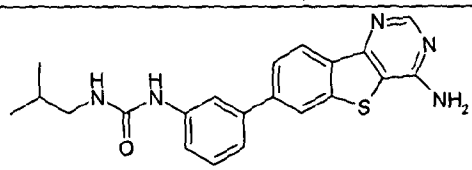
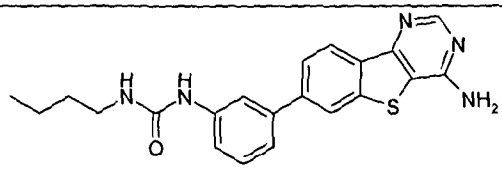
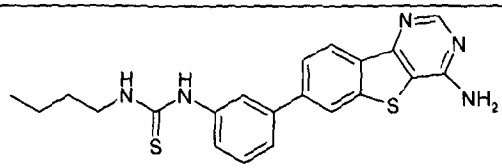
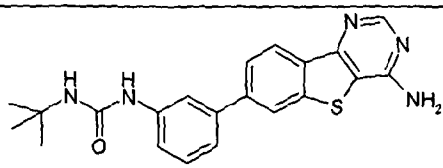
Code	Structure	Reagent used	LCMS
AA-004		N,N-Dimethyl-2-(piperazin-1-yl)ethyl amine	rt 5.83, M+H 476
AA-005		Ethyl isothiocyanate	rt 7.05, M+H 380
AA-014		N,N-Methylethylamine	rt 6.93 M+H 379
AA-015		N,N-*Diethylamine*	rt 7.24 M+H 392
AA-016		Isopropylamine	rt 6.86, M+H 376
AA-017		2-Methylpropyl-amine	rt 6.86, M+H 376
AA-018		1-Butyl isocyanate	rt 7.44, M+H 392
AA-019		1-Butyl isothiocyanate	rt 7.68, M+H 408
AA-020		tert-Butylamine	rt 6.98 M+H 378

Table 5A
Substituted ureido 7-phenyl 4-aminobenzothieno[3,2-d]pyrimidines

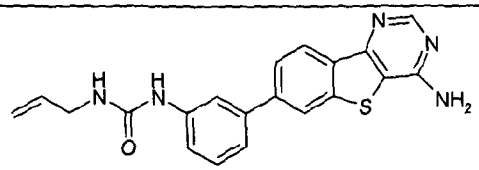
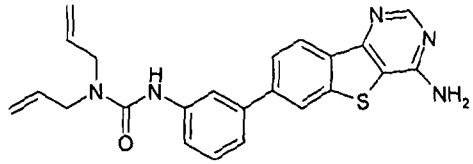
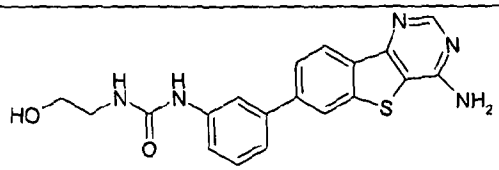
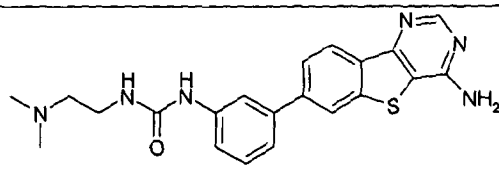
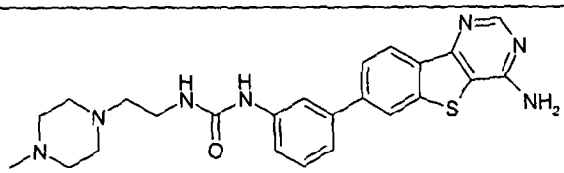
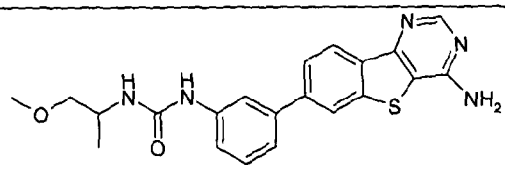
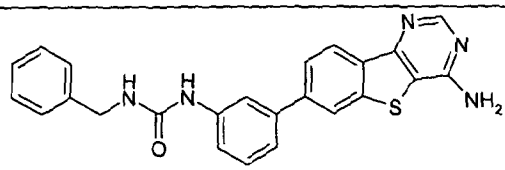
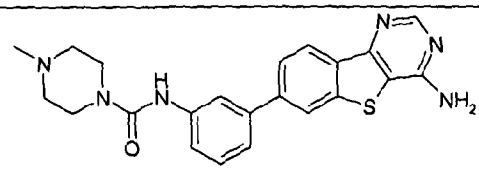
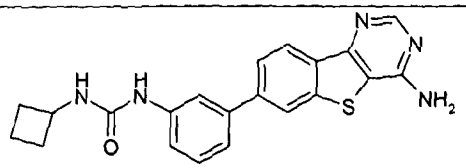
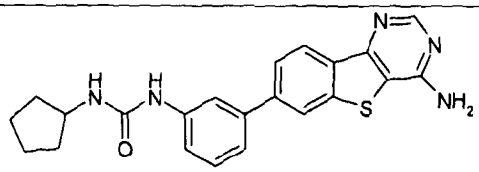
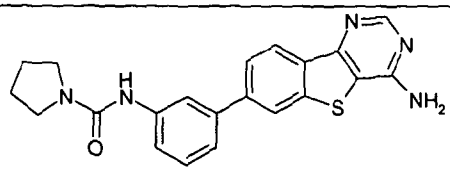
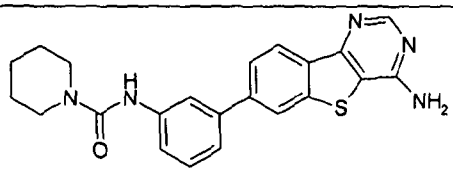
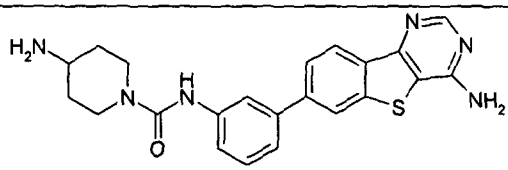
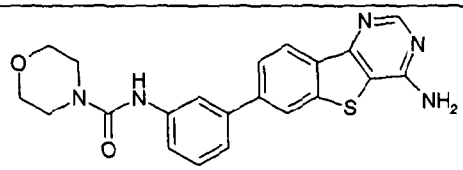
Code	Structure	Reagent used	LCMS
AA-021		Allyl isocyanate	rt 5.20, M+H 376
AA-023		N,N-Diallylamine	rt 7.97, M+H 413
AA-024		1-Aminoethanol	rt 0.20, M+H 380
AA-025		N,N-Dimethylethyl-1,2-diamine	rt 6.32, M+H 407
AA-027		2-(4-Methylpiperazin-1-yl)ethyl amine	rt 6.17, M+H 462
AA-028		1-Methoxypropan-2-amine	rt 6.86, M+H 376
AA-029		Benzyl isocyanate	rt 5.85, M+H 426
AA-030		N-Methyl piperazine	rt 0.20, M+H 419
AA-033		Cyclobutylamine	rt 7.17, M+H 390

Table 5A
Substituted ureido 7-phenyl 4-aminobenzothieno[3,2-d]pyrimidines

Code	Structure	Reagent used	LCMS
AA-034		Cyclopentylamine	rt 5.60, M+H 403
AA-036		Pyrrolidine	rt 7.06, M+H 390
AA-037		Piperidine	rt 7.04 M+H 404
AA-038		4-Amino piperidine	rt 5.87, M+H 419
AA-039		Morpholine	rt 6.59, M+H 406

The following substituted ureido 7-phenyl-4-aminobenzothieno[3,2-d]pyrimidines were synthesised in the same manner as Method 5, using the corresponding isocyanates (listed) in place of ethyl isocyanate, or in the same manner as Method 6 using the corresponding amines (listed) in place of cyclopropylamine, and replacing 7-(3-aminophenyl)-4-aminobenzothieno[3,2-d]pyrimidine (AE-018) with an appropriately substituted analogue.

Table 5B
Substituted ureido 7-phenyl 4-aminobenzothieno[3,2-d]pyrimidines

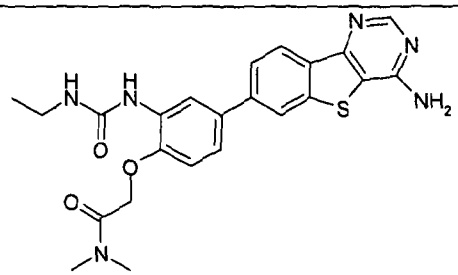
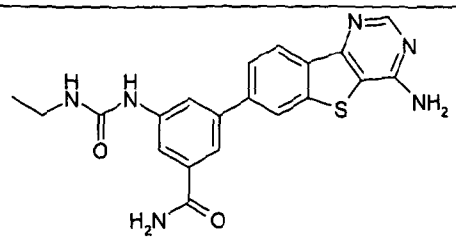
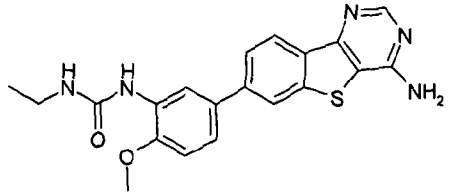
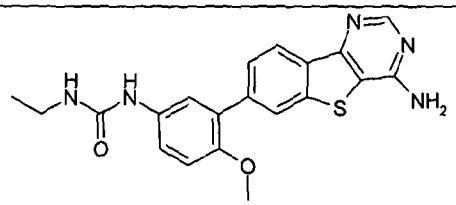
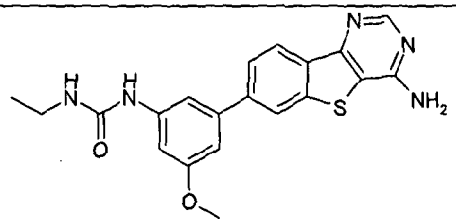
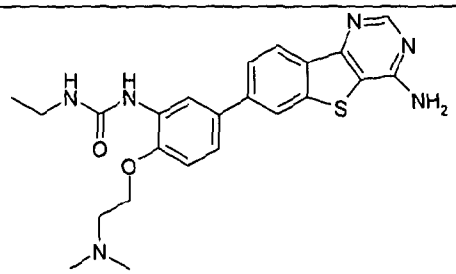
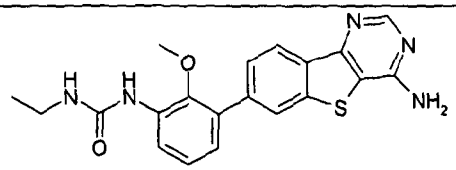
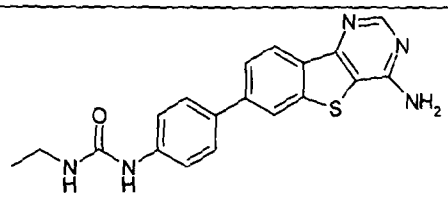
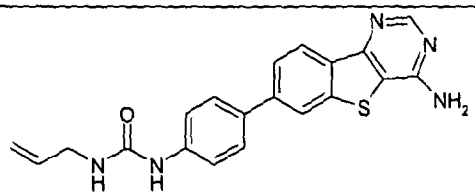
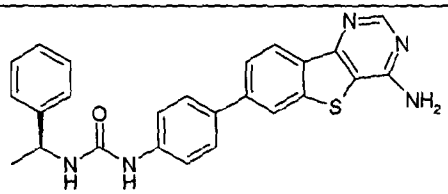
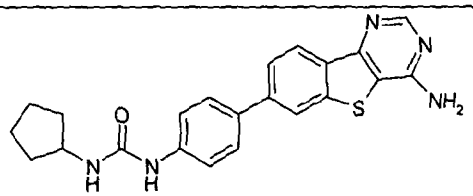
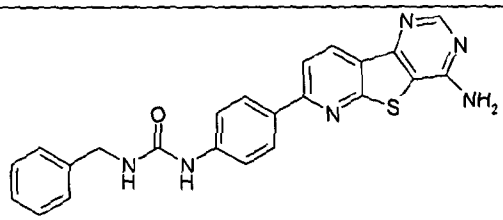
Code	Structure	Reagent used	LCMS
AA-007		Ethyl isocyanate	rt 6.89, M+H 465

Table 5B
Substituted ureido 7-phenyl 4-aminobenzothieno[3,2-d]pyrimidines

Code	Structure	Reagent used	LCMS
AA-008		Ethyl isocyanate	rt 4.13, M+H 407
AA-009		Ethyl isocyanate	rt 7.06, M+H 394
AA-010		Ethyl isocyanate	rt 6.46, M+H 254
AA-011		Ethyl isocyanate	rt 7.03, M+H 394
AA-012		Ethyl isocyanate	rt 5.98, M+H 451
AA-013		Ethyl isocyanate	rt 7.04, M+H 394

The following substituted ureido 7-phenyl-4-aminobenzothieno[3,2-d]pyrimidines were synthesised in the same manner as Method 5, using the corresponding isocyanates (listed) in place of ethyl isocyanate, or in the same manner as Method 6 using the corresponding amines (listed) in place of cyclopropylamine, and replacing *7-(3-aminophenyl)-4-aminobenzothieno[3,2-d]pyrimidine* (AE-018) with 7-(4-aminophenyl)-4-aminobenzothieno[3,2-d]pyrimidine (AE-014).

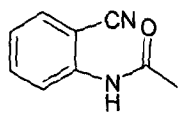
Table 5C
Substituted ureido 7-phenyl 4-aminobenzothieno[3,2-d]pyrimidines

Code	Structure	Reagent used	LCMS
AA-006		Ethyl isocyanate	rt 4.92, M+H 364
AA-022		Allyl isocyanate	rt 5.10, M+H 376
AA-031		(S)-1-Phenyl-ethyl isocyanate	rt 5.97, M+H 440
AA-035		Cyclopentylamine	rt 5.59, M+H 403
BB-002		Benzyl isocyanate	rt 7.50, M+H 426

Method 7: 4-Amino-5H-pyrimido[5,4-b]indole

Synthesis 7A

Preparation of N-(2-cyanophenyl)acetamide

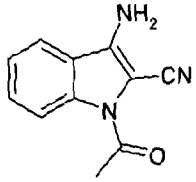


A mixture of anthranilamide (42.3 mmol), acetic anhydride (42.3 mmol) and dimethylamino pyridine (2.1 mmol) in dichloromethane (50 mL) was allowed to stir for 20 h at room temperature. Petroleum ether was added to the reaction mixture. A precipitate formed and was filtered off, washing with petroleum ether to obtain the acetamide as a white solid (88%).

LCMS rt 3.76, M+H 376. ^{1}H-NMR ($CDCl_3$) δ 8.35 (1H, d, J 8.7 Hz), 7.75 (1H, bs), 7.60-7.55 (2H, m), 7.19-7.13 (1H, m), 2.26 (3H, s).

Synthesis 7B

1-acetyl-3-amino-1H-indole-2-carbonitrile

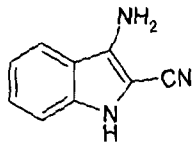


A mixture of N-(2-cyanophenyl)acetamide (28 mmol), chloroacetonitrile (28 mmol) and potassium tert-butoxide (28 mmol) in N,N-dimethylformamide (20 mL) was allowed to stir for 20 h at room temperature. Ice-water was added to the reaction mixture. The mixture was extracted with ethyl acetate (2 x 30 mL). The organic layer was dried ($MgSO_4$) and the organic layer was concentrated in vacuo to obtain an oil. The oil was subjected to silica chromatography gradient eluting with 100% petroleum ether to 60% ethyl acetate /petroleum ether to obtain a pale orange solid (54%).

LCMS rt 5.62, M+H 200. ^{1}H-NMR (DMSO) δ 8.09 (1H, d, J 8.7 Hz), 7.93 (1H, d, J 8.0 Hz), 7.51 (1H, t, J 8.4 Hz), 7.31 (1H, t, J 7.9 Hz), 6.69 (2H, bs), 2.71 (3H, s).

Synthesis 7C

3-amino-1H-indole-2-carbonitrile

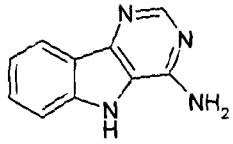


A mixture of 1-acetyl-3-amino-1H-indole-2-carbonitrile (13.6 mmol), and potassium carbonate (27.2 mmol) in a solution of water (20 mL) and ethanol (20 mL) was allowed to reflux for 4 h. Ice-water was added to the reaction mixture. The mixture was extracted with ethyl acetate (2 x 40 mL). The organic layer was dried ($MgSO_4$) and the organic layer was concentrated in vacuo to obtain an oil. The oil was subjected to silica chromatography gradient eluting with 100% dichloromethane to 5% methanol / dichloromethane to obtain a white solid (24%).

LCMS rt 5.62, M+H 158. ^{1}H-NMR (DMSO) δ □10.63 (1h, bs), 7.71 (1H, d, J 8.1 Hz), 7.25-7.14, (2H, m), 6.96-6.90 (1H, m), 5.65 (2H, bs).

Synthesis 7D

4-Amino-5H-pyrimido[5,4-b]indole



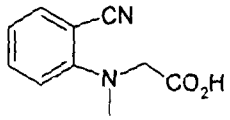
3-Amino-1H-indole-2-carbonitrile was used in a similar process to that in Synthesis 1B.

LCMS rt 2.42, M+H 185. ^{1}H-NMR (DMSO) δ □10.94 (1H, bs), 8.28 (1H, s), 8.05 (1H, d, J 7.9 Hz), 7.61 (1H, d, J 8.3 Hz), 7.49 (1H, t, J 7.0 Hz), 7.20 (1H, t, J 7.1 Hz), 6.89 (2H, bs).

Method 8: 4-Amino5-methyl-5H-pyrimido[5,4-b]indole

Synthesis 8A

2-((2-cyanophenyl)(methyl)amino)acetic acid

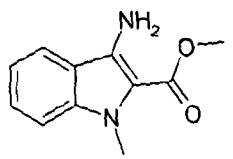


2-Fluoro-benzonitrile (4.13 mmol), sarcosine (4.54 mmol), potassium carbonate (10.0 mmol), and copper acetate (0.41 mmol) in dimethylsulfoxide (4 mL) was allowed to stir at 140°C for 20 h. Ice-water is added, followed by ethyl acetate (10 mL) and the layers were separated. The aqueous layer is then acidified to pH 2 with concentrated hydrochloric acid. The aqueous layer is then extracted with ethyl acetate (2 x 10 mL). The organic layer is dried ($MgSO_4$) and concentrated in vacuo to afford the aniline as an orange oil (89%).

LCMS rt 5.38, M+H 191. ^{1}H-NMR (DMSO) δ 12.70 (1H, bs), 7.44 (1H, dd, J 6.0 and 1.5 Hz), 7.50-7.44 (1H, m), 6.96 (1H, d, J 8.7 Hz), 6.89-6.84 (1H, m), 4.19 (2H, s), 3.06 (3H, s).

Synthesis 8B

Methyl 3-amino-1-methyl-1H-indole-2-carboxylate



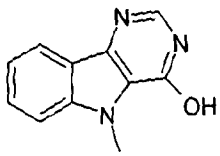
2-((2-Cyanophenyl)(methyl)amino)acetic acid (3.42 mmol) was heated to reflux in thionyl chloride (10 mL) for 30 min. The solution was cooled and evaporated to dryness in vacuo. Anhydrous methanol (10 mL) was added to the resulting residue and allowed the solution was allowed to sit for 5 min. The methanol was then removed in vacuo and the residue dissolved in ethyl acetate (20 mL). The organic solution was then washed with 10% sodium hydrogen carbonate solution (20 mL), dried ($MgSO_4$) and concentrated

under vacuum to afford an oily residue. The residue was dissolved in N,N-dimethylformamide (5 mL) and potassium carbonate (3.42 mmol) was added. This mixture was then heated at 60°C for 24 h. Ice-water was added and the mixture extracted with ethyl acetate (2 x 10 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The resulting residue was subjected to column chromatography eluting with 100% petroleum ether to 40% ethyl acetate/petroleum ether to afford the indole as an oil (53%).

^{1}H-NMR (DMSO) δ □7.81-7.77 (1H, m), 7.31-7.28 (2H, m), 6.95-6.90 (1H, m), 5.88 (2H, bs), 3.81 (3H, s), 3.76 (3H, s).

Synthesis 8C

5-methyl-5H-pyrimido[5,4-b]indol-4-ol

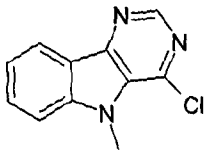


Methyl 3-amino-1-methyl-1H-indole-2-carboxylate was used in a similar process to that in Synthesis 1B.

LCMS rt 5.07, M+H 200. ^{1}H-NMR (DMSO) δ □12.35 (1H, bs), 8.02-7.99 (1H, m), 7.96 (1H, s), 7.67-7.64 (1H, m), 7.56-7.50 (1H, m), 7.29-7.24 (1H, m), 4.15 (3H, s).

Synthesis 8D

4-Chloro-5-methyl-5H-pyrimido[5,4-b]indole

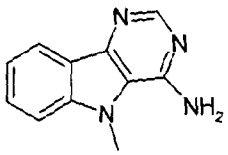


5-Methyl-5H-pyrimido[5,4-b]indol-4-ol was used in a similar process to that in Synthesis 1C.

LCMS rt 6.50, M+H 218. ^{1}H-NMR (DMSO) δ □8.81 (1H, s), 8.28-8.25 (1H, m), 7.85-7.77 (2H, m), 7.43-7.40 (1H, m), 4.18 (3H, s).

Synthesis 8E

4-Amino5-methyl-5H-pyrimido[5,4-b]indole



A suspension of 4-chloro-5-methyl-5H-pyrimido[5,4-b]indole (0.45 mmol) in concentrated ammonium hydroxide (1 mL) and dimethylsulfoxide (3 mL) was heated to 150°C in a

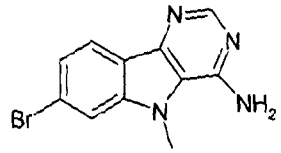
sealed pressure vessel for 20 h. Ice-water was added and the precipitate that resulted was filtered off, washed with water, and dried in a vacuum oven to obtain the amino pyrimidine as a pale-yellow solid (90%).

LCMS rt 5.52, M+H 199.

Method 9: 7-Phenyl-4-amino-5-methyl-5H-pyrimido[5,4-b]indole

Synthesis 9A

7-Bromo-4-amino-5-methyl-5H-pyrimido[5,4-b]indole

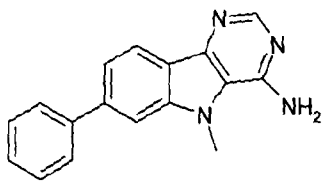


7-Bromo-4-amino-5-methyl-5H-pyrimido[5,4-b]indole was synthesised from 4-bromo-2-fluorobenzonitrile in the same manner as Method 8.

LCMS rt 4.58, M+H 277. ^{1}H-NMR (DMSO) δ □8.27 (1H, s), 7.98-7.97 (2H, m), 7.34 (1H, dd, J 8.10 and 1.8 Hz), 6.96 (2H, bs), 4.05 (3H, s).

Synthesis 9B

7-Phenyl-4-amino-5-methyl-5H-pyrimido[5,4-b]indole (CC-004)

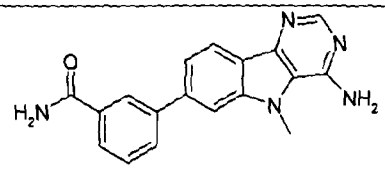
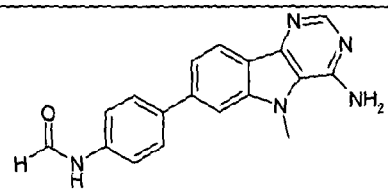
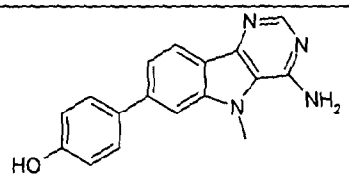


The title compound was synthesised from 7-bromo-4-amino-5-methyl-5H-pyrimido[5,4-b]indole in the same manner as Method 2 (AE-001).

LCMS rt 6.21, M+H 275. ^{1}H-NMR (DMSO) δ □8.28 (1H, s), 8.12 (1H, d, J 8.1 Hz), 7.95 (1H, s), 7.84-7.81 (2H, m), 7.55-7.39 (4H, m), 6.87 (2H, bs).

Substituted 7-phenyl-4-amino-5-methyl-5H-pyrimido[5,4-b]indoles were synthesised from the corresponding boronic acids in the same manner as Method 9 (CC-005).

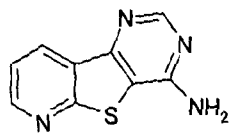
Table 6
Substituted 7-phenyl-4-amino-5-methyl-5H-pyrimido[5,4-b]indoles

Code	Structure	Reagent used	LCMS
CC-001		3-Aminocarbonyl phenylboronic acid	rt 5.97, M+H 318
CC-002		3-Formylaminophenyl boronic acid, pinacol ester	rt 6.05, M+H 318
CC-003		4-Hydroxyphenyl boronic acid	rt 6.05, M+H 291

Method 10: Pyrido[3',2':4:5]thieno[3,2-d]pyrimidine

Synthesis 10A

Pyrido[3',2':4:5]thieno[3,2-d]pyrimidine



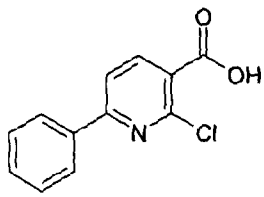
The title compound was synthesised from 2-chloro-3-cyanopyridine in the same manner as in Synthesis 1D.

LCMS rt 2.98, M+H 203. ^{1}H-NMR (DMSO) δ 8.81 (1H, dd, J 4.7 and 1.7 Hz), 8.61 (1H, dd, J 7.9 and 1.7 Hz), 8.54 (1H, s), 7.64-7.60 (3H, m).

Method 11: 7-Phenyl-pyrido[3',2':4:5]thieno[3,2-d]pyrimidine (BB-001)

Synthesis 11A

2-Chloro-6-phenylnicotinic acid



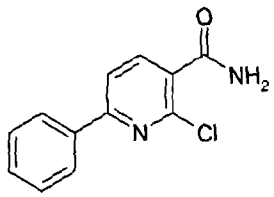
A mixture of 2,6-nicotinic acid (4.4 mmol), phenylboronic acid (4.4 mmol), potassium carbonate (15.5 mmol) and $PdCl_2(PPh_3)_2$ (5 mol %) in a solution of dimethoxyethane

(5 mL), ethanol (5 mL) and water (5 mL) was allowed to reflux for 4 h. The mixture was partitioned between ethyl acetate and water. The layers were then separated. The aqueous layer was then acidified with 2 N hydrochloric acid solution to pH 5 and extracted with ethyl acetate (2 x 20 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo to obtain the acid as a solid (70%).

^{1}H-NMR ($CDCl_3$) δ 8.13 (1H, d, J 8.0 Hz), 8.09-8.05 (2H, m), 7.99 (1H, d, J 8.0 Hz), 7.53-7.47 (3H, m).

Synthesis 11B

2-Chloro-6-phenylnicotinamide

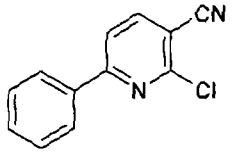


A mixture of 2-chloro-6-phenylnicotinic acid in thionyl chloride was allowed to reflux for 1 h. The reaction mixture was concentrated to dryness in vacuo. The residue was dissolved in dioxane (5 mL) and NH_4OH solution was added. Ice-water was added to the reaction mixture. The precipitate that formed was filtered off, washing with water and dried in a vacuum oven to obtain the amide as a white solid (90%).

^{1}H-NMR ($CDCl_3$) δ 8.07-7.94 (5H, m), 7.73 (1H, bs), 7.54-7.48 (3H, m).

Synthesis 11C

2-Chloro-6-phenylnicotinonitrile

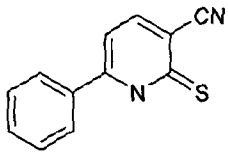


A mixture of 2-chloro-6-phenylnicotinamide in acetic anhydride was allowed to reflux for 2 h. The reaction mixture was concentrated to dryness in vacuo. Ice-water was added to the reaction mixture. The mixture was partitioned between ethyl acetate and 10% sodium hydrogencarbonate solution. The layers were then separated. The organic layer was dried ($MgSO_4$) and the organic layer was concentrated in vacuo to obtain an oil. The oil was subjected to silica chromatography gradient eluting with 10% ethyl acetate / petroleum ether to 50% ethyl acetate / petroleum ether to obtain the nitrile as a white solid (49%).

^{1}H-NMR ($CDCl_3$) δ □8.05-8.00 (2H, m), 7.99 (1H, d, J 8.4 Hz), 7.76 (1H, d, J 8.1 Hz), 7.51-7.49 (3H, m).

Synthesis 11D

6-Phenyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile

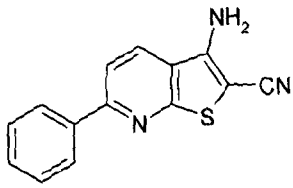


A mixture of 2-chloro-6-phenylnicotinonitrile (0.2 mmol) and sodium hydrosulfide (0.2 mmol) in ethanol (3 mL) was allowed to reflux for 2 h. 10% Citric acid solution was added to the reaction mixture. The precipitate that formed was filtered off, washing with water and dried in a vacuum oven to obtain a bight yellow solid. The solid was suspended between ethyl acetate and 1 N sodium hydroxide solution. The layers were then separated. The aqueous layer was then acidified with 2 N hydrochloric acid solution to pH 5 and the precipitate that formed was filtered off, washing with water and dried in a vacuum oven to obtain the pyrid-2-thione as a bight yellow solid (60%).

^{1}H-NMR (DMSO) δ □8.06 (1H, d, J 7.8 Hz), 7.76-7.73 (2H, m), 7.55-7.52 (2H, m), 7.06 (1H, d, J 7.8 Hz).

Synthesis 11E

3-Amino-6-phenylthieno[2,3-b]pyridine-2-carbonitrile

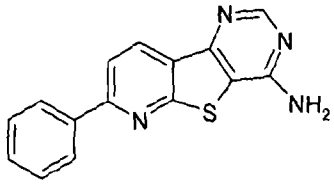


A mixture of 6-phenyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile (0.7 mmol), diisopropylethylamine (0.7 mmol) and chloroacetonitrile (0.7 mmol) in N,N-dimethylformamide (3 mL) was allowed to stir for 1 h at room temperature. Ice-water was added to the reaction mixture. The precipitate that formed was filtered off, washing with water and dried in a vacuum oven to obtain a white solid (the solid was a mixture of acyclic and cyclic product). The solid was dissolved in N,N-dimethylformamide (3 mL) and potassium carbonate (0.7 mmol) was added. The mixture was allowed to stir at 50°C for 8 h. Ice-water was added to the reaction mixture. The precipitate that formed was filtered off, washing with water and dried in a vacuum oven to obtain the thieno pyridine as a white solid (68 %).

^{1}H-NMR (DMSO) δ □8.55 (1H, d, J 8.7 Hz), 8.17-8.14 (2H, m), 8.11 (1H, d, J 8.4 Hz), 7.53-7.50 (3H, m), 7.33 (2H, bs).

Synthesis 11F

7-Phenyl-pyrido[3',2':4:5]thieno[3,2-d]pyrimidine (BB-001)



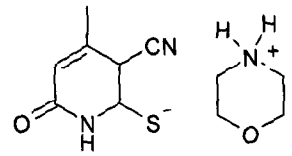
The title compound was synthesised from 3-amino-6-phenylthieno[2,3-b]pyridine-2-carbonitrile in the same manner as Synthesis 1B.

LCMS rt 5.87, M+H 279. ^{1}H-NMR (DMSO) δ □8.66 (1H, d, J 8.1 Hz), 8.52 (1H, s), 8.19-8.15 (3H, m), 7.63 (2H, bs), 7.54-7.52 (2H, m).

Method 12: 7-Morpholino-4-amino-9-methyl-pyrido[3',2':4:5]thieno[3,2-d]pyrimidine (BB-008)

Synthesis 12A

Morpholine 3-cyano-4-methyl-6-oxo-1,2,3,6-tetrahydropyridine-2-thiolate

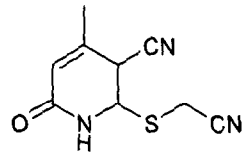


Morpholine (36.3 mmol) is added to a solution of 2-cyanothioacetamide (36.3 mmol) in ethanol (20 mL) and the solution stirred at 25°C for 5 min. Ethyl acetoacetate (36.3 mmol) is added and the solution was then stirred at 25°C for 24 h. Acetone was added to the solution and the precipitate that formed was filtered off washing with acetone to afford the pyridine as a white solid (61%).

^{1}H-NMR (DMSO) δ 5.36 (1H, s), 3.75-3.72 (4H, m), 3.09-3.06 (4H, m), 1.97 (3H, s).

Synthesis 12B

2-(Cyanomethylthio)-4-methyl-6-oxo-1,6-dihydropyridine-3-carbonitrile

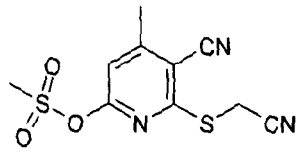


To a solution of morpholine 3-cyano-4-methyl-6-oxo-1,2,3,6-tetrahydropyridine-2-thiolate (23.8 mmol) in N,N-dimethylformamide (15 mL), was added chloroacetonitrile (23.8 mmol). The solution was stirred at 25°C for 1 h and ice-water was added. The precipitate that formed was filtered off, washing with water to give the nitrile as a light brown solid (88%).

LCMS rt 7.25, M+H 206. ^{1}H-NMR (DMSO) δ 6.51 (1H,s), 4.28 (2H, s), 2.36 (3H, s).

Synthesis 12C

5-cyano-6-(cyanomethylthio)-4-methylpyridin-2-yl methanesulfonate

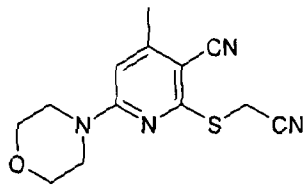


To a solution of 2-(cyanomethylthio)-4-methyl-6-oxo-1,6-dihydropyridine-3-carbonitrile (14.6 mmol) and methanesulfonyl chloride (16.0 mmol) in tetrahydrofuran (15 mL), was added diisopropylethylamine (16.0 mmol). The solution was then stirred at 25°C for 24 h. Water was added and the solution was extracted with ethyl acetate (2 x 40 mL). The organic solvent was dried ($MgSO_4$) and concentrated in vacuo. The residue was triturated with dichloromethane and the precipitate filtered off washing with dichloromethane. The filtrate was concentrated in vacuo to afford the mesylate as a solid (35%).

^{1}H-NMR (DMSO) δ 7.28 (1H, s), 4.36 (2H, s), 3.69 (3H, s), 2.52 (3H, s).

Synthesis 12D

2-(Cyanomethylthio)-4-methyl-6-morpholinonicotinonitrile

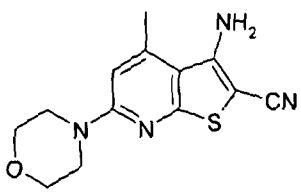


A mixture of 5-cyano-6-(cyanomethylthio)-4-methylpyridin-2-yl methanesulfonate (0.35 mmol), diisopropylethylamine (1.06 mmol), and morpholine (1.06 mmol) in dioxane (4 mL) was stirred at 90°C for 16 h. Ice-water was added and the precipitate that resulted was filtered off, washing water to give the aminopyridine as a solid (70%).

^{1}H-NMR ($CDCl_3$) δ 6.24 (1H,s), 3.86 (2H, s), 3.83-3.80 (4H, m), 3.71-3.68 (4H, m), 2.39 (3H, s).

Synthesis 12E

3-Amino-4-methyl-6-morpholinothieno[2,3-b]pyridine-2-carbonitrile

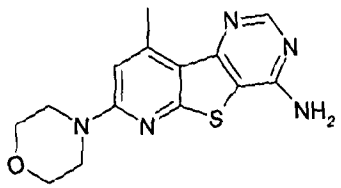


A mixture of 2-(cyanomethylthio)-4-methyl-6-morpholinonicotinonitrile (0.25 mmol), potassium carbonate (0.50 mmol), in N,N-dimethylformamide (2 mL) was heated at 90°C for 2 h. Ice-water was added and the precipitate that resulted was filtered off, washing water and dried in a vacuum oven to give the thienopyridine as a cream coloured solid (92%).

LCMS rt 6.38, M+H 275. ^{1}H-NMR (DMSO) δ □6.39 (1H, s), 3.70 (4H , m), 3.55-3.34 (4H, m), 2.58 (3H, s).

Synthesis 12F

7-Morpholino-4-amino-9-methyl-pyrido[3',2':4:5]thieno[3,2-d]pyrimidine (BB-014)



7-Morpholino-4-amino-9-methyl-pyrido[3',2':4:5]thieno[3,2-d]pyrimidine was synthesised from 3-amino-4-methyl-6-morpholinothieno[2,3-b]pyridine-2-carbonitrile in the same manner as Synthesis 1B.

LCMS rt 6.39, M+H 302. ^{1}H-NMR (DMSO) δ □8.42 (1H, s), 7.19 (2H, bs), 6.84 (1H, s), 3.71-3.69 (4H, m), 3.63-3.61 (4H, m), 2.82 (3H, s).

Substituted 4-amino-9-methyl-pyrido[3',2':4:5]thieno[3,2-d]pyrimidines were synthesised from the corresponding amines in the same manner as Method 12 (AA-022).

Table 7

7-amino 4-amino-9-methyl-pyrido[3',2':4:5]thieno[3,2-d]pyrimidines

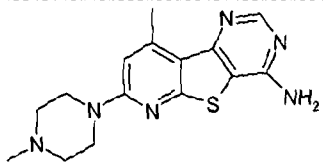
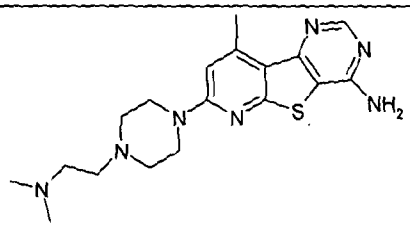
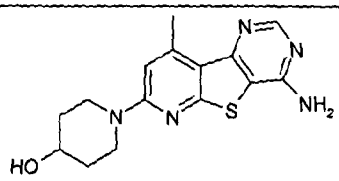
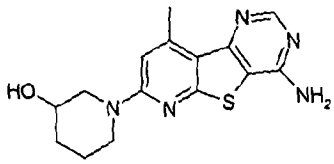
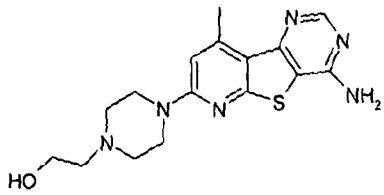
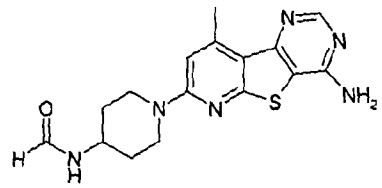
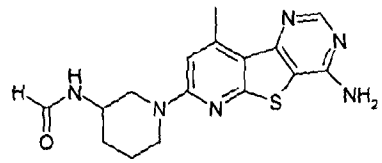
Code	Structure	Reagent used	LCMS
BB-003		N-Methyl piperazine	rt- 5.39, M+H 315
BB-004		N,N-Dimethyl-2-(piperazin-1-yl)ethyl amine	rt- 0.90, M+H 372

Table 7 7-amino 4-amino-9-methyl-pyrido[3',2':4:5]thieno[3,2-d]pyrimidines			
Code	Structure	Reagent used	LCMS
BB-005		4-Hydroxypiperidine	rt- 6.16, M+H 316
BB-006		3-Hydroxypiperidine	rt- 6.26, M+H 316
BB-007		2-(Piperazin-1-yl)ethanol	rt- 5.43, M+H 345
BB-009		4-*N*-Boc-aminopiperidine	rt- 6.17, M+H 343
BB-010		3-*N*-Boc-Aminopiperidine	rt- 6.25, M+H 343

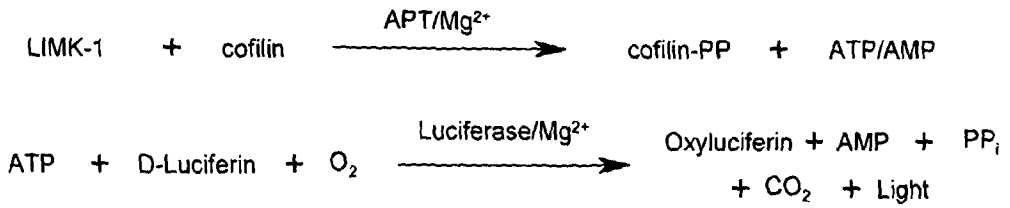
Biological Methods

Assay 1 - LIMK1 (Kinase Domain) Kinase Glo

1. *Introduction*

The serine kinases LIMK-1 and LIMK-2 are kinases which have LIM domains or protein-motifs that are frequently found in cytosolic proteins which interact with the actin cytoskeleton involved in cell division and motility. The purpose of the assay was to screen for inhibitors of LIMK-1 whereby kinase activity was measured by a luminescence ATP detection system in a single-point 384 well screening assay measuring ATP consumption by the kinase-substrate phosphorylation reaction.

The reaction measured was characterized by two steps as outlined below:



In the first step, LIMK-1 catalyses the phosphorylation of its substrate cofilin thereby consuming ATP. The second step involves the detection of the remaining ATP using the Luminescence ATP detection system, Kinase-Glo® (Promega). In the detection reaction, the firefly luciferase enzyme produces light by its reaction with its substrate D-Luciferin and ATP. The light which is produced as a result of the reaction is proportional to the amount of ATP that is present in the initial kinase reaction.

2. Materials and Methods

2.1. Reagents and Materials

LimK-1 and cofilin were supplied by Ora Bernard, St Vincent's Medical Institute. ATP (99% purity) supplied by Sigma Aldrich whilst the Kinase-Glo detection kit was obtained from Promega Corp (Cat #V6714). Common assay buffer reagents such as HEPES, KCl, $MgCl_2$, $MnCl_2$, NaF, $NaVO_4$ and BSA were purchased from Sigma Aldrich. Library compounds were pre-prepared in Matrical 50 µL, V-bottom polypropylene plates. The assay was carried out in PerkinElmer Lifesciences 384 well Proxiplates™ (white, shallow well of 28µl total volume, inverted chimney design) with Matrical deep well plates (Millennium Science) and Axygen open reservoir plates (Proscience) used for automated reagent additions. The MiniTrak IX (PerkinElmer Lifesciences) was used to automate the dilution of compounds, the MultiDrop reagent dispenser (Thermo Corporation) was used to perform all other additions and measurements were detected using the Envision 2103 (PerkinElmer Lifesciences).

2.2. Method

2.2.1. Kinase buffer 1X

20 mM HEPES, pH 7.4
150 mM NaCl
10 mM $MgCl_2$
0.25 mM EGTA
0.01% Triton X-100
0.01% (w/v) ovalbumine
1 mM DTT

All solutions were prepared using MilliQ or a comparable quality of water. The kinase buffer was stored as stock at room temperature except for ovalbumine and DTT added on the day of screening from stock solutions.

2.2.2. Assay Protocol

- 4.9 µL of LimK-1 in kinase buffer (5 ng/reaction).
- + 0.1 µL of compound dilution.
- incubate at RT for 20 min.
- + 5 µL of cofilin (1.9 µg/reaction = 10 µM final concentration) with ATP (10 µM final concentration) in kinase buffer.
- incubate at room temperature for 30 min.
- + 10 µL Kinase-Glo solution.
- incubate at room temperature for 10 min in dark.
- read luminescence.

Automation was used utilized to run the assay. A MultiDrop reagent dispenser added 4.9 µL of LIMK-1 in kinase buffer to all wells except negative control wells. Those were filled with the same volume of assay buffer.

On a separate plate a dilution series was prepared: 10 µL of compounds in DMSO (concentration 10 mM) were dispensed into the wells of column 1 and 12. A MiniTrak program was used to dispense 5 µL DMSO into a new column and mix with 5 µL from the previous one. The remaining columns 23 and 24 were filled with DMSO only.

Using the 384-pintool 100 nL of the dilutions were transferred to the assay plate. Compounds were incubated with the enzyme for at least 20 min to ensure homogenous distribution in the well before 5 µL of cofilin/ATP in kinase buffer was added to all wells (MultiDrop dispenser). Prepared in that way, final concentrations of the compounds ranged between 100 µM and 9.7 nM. The plates were lidded and incubated for 30 min at room temperature.

The plates were de-lidded and 10 µL Kinase-Glo reagent per well were added with a MultiDrop. The plates were lidded again and incubated for further 10 min in the dark to allow for stabilization of the luminescence signal. Afterwards, the plates were read in the EnVision 2103 reader using the program "Ultrasensitive Luminescence". Each well was read for 0.1 sec. Because the Kinase-Glo reagents were sensitive to light, all handlings were done under modest light conditions.

2.2.3. Data Analysis

Data were analysed in Microsoft Excel or IDBS BioBook templates and the quality of the assay results were monitored by determination of the Z'-factor for each assay plate

(Zhang *et al*, J Biomol Screening, 4:67-73, 1999). The results were calculated as percent inhibition of the enzyme by the compound according to the following equation:

$$\%Inhibition = 100 * (1 - \left[\frac{(x - \mu^-)}{(\mu^+ - \mu^-)}\right])$$

where:
x = signal in samples after compound treatment.
μ^- = mean signal of the controls (no compound).
μ^+ = mean signal of the blanks (no LIMK-1).

3. *Appendix*

3.1. Parameters for the PerkinElmer Envision 2103 read program "US Lum"

General:
Program Name: LUM384 for LIMK-1.
Label 1: Ultra sensitive Luminescence.
Plate filter: 384 wells, 16 × 24.
Counting time: 0.1 sec.

Corrections:
Background correction: Yes.

Counting Control:
Measure each sample: 1 time.
Measure each plate: 1 time.
Delay between plate: 0 min.
Plate orientation: Normal.

3.2. Kinase-Glo substrate solution (10x100 ml kit)

Most of the reagent was prepared fresh for each screen run. Any left over solution from previous occasions was stored at -20°C and only thawed once. The substrate solution was prepared according to the supplier's manual, e.g., bringing the solutions to room temperature and reconstituting the lyophilized substrate solution. This was carried out in the dark due to the reagent's sensitivity to light. The reconstituted substrate solution contained a mutant of firefly luciferase and its substrate D-Luciferin which were necessary for the detection of ATP levels after the kinase reaction.

3.3. Automation Protocol

The MiniTrak program "LimK1 pintool addition only" was utilized to run the assay.

Assay 2 - Lim-kinase 1 (LimK-1) Transcreener FP

1. Introduction

This protocol describes a method to quantify the effect of inhibitors of LIMK1. The 384 well format assay is based on the Transcreener FP technology to measure ADP formed during the reaction.

2. Materials and Methods

2.1. Materials

Object	Supplier	Specification
LIMK1	Millipore(Upstate)	Catalog # 14656, N-terminal 6xHis tagged human LimK1, amino acids 285-638
cofilin	CSIRO	human cofilin-2
ATP	Sigma	A7699 (≥99% purity)
Transcreener ADP Assay	BellBrook Labs	Catalog # 3004-10K
Assay plates	PerkinElmer	384w Proxiplate, BLACK, low volume of 28µl, inverted chimney design
Dilution plates	Millennium Science	Matrical plates
Plate seals	Applied Biosystems	MicroAmp Optical Adhesive Film, Catalog # 4311971 (Standard PCR seals won't work with fluorescence polarization)
Dispenser	Thermo Corp.	MultiDrop
Dispensing station	PerkinElmer	Minitrak IX with 100 nl pin tool
Plate reader	PerkinElmer	EnVision 2103, see appendix for configuration

2.2. Solutions:

All solutions were prepared using MilliQ or a comparable quality of water.

LIMK1 assay buffer 1X:

20 mM HEPES, pH 7.4
150 mM NaCl

10 mM MgCl2
0.25 mM EGTA
0.01% Triton X-100

Stored at room temperature.

Added on the day of the assay from 1000X stock solutions:
0.01% (w/v) ovalbumine.
1mM DTT.

ATP stock solution 10 mM:
ATP 10 mM.
HEPES 10 mM.
EDTA 1mM.
titrated to pH 7.00.
single-use aliquots stored at -20°C.

LIMK1 dilution:
LIMK1: 0.8 ng/5 µL will give a final concentration of 1.9 nM during the kinase reaction.
LIMK1 assay buffer 1X.

Substrate dilution:
Cofilin: 1.9 µg/5 µL will give 10 µM final concentration during the kinase reaction.
ATP: 40 µM in dilution to give 20 µM during the kinase reaction.
LIMK1 assay buffer 1X.

Stop & Detect mix:
The concentration of the ADP antibody is dependent on the ATP concentration present due to a limited selectivity.
ADP-antibody: 28.1 µg/mL in the mix.
Tracer: 8 nM.
Dilute in Stop & Detect buffer 1X, contained in the pack as 10X.

2.3. Assay Protocol:

Preparation of dilution series:

a – volume of compound containing solution.
b – volume of diluent.
The Minitrak program for pin tool transfer is optimized to pick up the dilution out of 7.5 µL of DMSO, therefore *b* is usually 7.5 µL. Choose *a* to achieve any desired dilution factor of 1:(*a*+*b*)/*a*.

Protocol:

- into columns 1 and 12 of the dilution plate add *a+b* µl of 10 mM compound stock.
- add *a+b* µl DMSO into columns 23+24.
- the following steps are performed by the Minitrak program 11_pt_titration_P30.
- dilute by aspirating *a* µl from columns 1/12, mixing with *b* µl DMSO, and dispensing the entire volume into columns 2/13.
- continue till columns 11/22.

Assay setup:

- add 5 µL LIMK1 dilution to all wells except Blank and Buffer only.
- transfer 0.1 µl compound dilution into assay plate using Minitrak program Limk1_Pintool_Addition_Only.
- incubate 10 minutes to allow for binding of compounds to enzyme.
- add 5 µl substrate dilution to all wells except Buffer only.
- incubate 60 min at room temperature.
- add 10 µl Stop & Detect mix.
- seal plate with Microamp seal.
- incubate at room temperature 2-4 h (over night is acceptable).
- read fluorescence polarization.

Note for the MultiDrop: prior to all additions flush the MultiDrop cassette with assay buffer containing ovalbumine to minimize loss of the enzyme/ substrate in the tubings.

Data Analysis:

Data was analysed in Microsoft Excel or IDBS BioBook templates and the quality of the assay results was monitored by determination of the Z'-factor for each assay plate (Zhang *et al*, J Biomol Screening, 4:67-73, 1999). The results were calculated as percent inhibition of the enzyme by the compound according to the following equation:

$$\%Inhibition = 100 * (1 - \left[\frac{(x - \mu^-)}{(\mu^+ - \mu^-)} \right])$$

where:
x = signal in samples after compound treatment
μ^- = mean signal of the controls (no compound)
μ^+ = mean signal of the blanks (no LIMK-1)

3. Appendix

3.1. Automation details

The MiniTrak programs "Titration_11pt_P30" and "LimK1_pintool_addition_only" were utilized to run the assay.

3.2. Accessories for the PerkinElmer Envision 2103

Filter set Cy5 FP label (#2100-8380) consisting of:
excitation filter 620/40 nm.
mirror module D658.
emission filters 688/45 nm for S- and P-polarisation.

3.3. Program and Label settings for PerkinElmer Envision 2103

Program Name: FP Transcreener.
Label: Transcreener FP.
Plate layout: 384 wells, 16 × 24.
Background correction: Yes.
Reading mode: Fluorescence polarization.
Calculation: mP value, with blank correction.
Excitation light: 50%.
G factor: 0.63.
Detector gain (1^{st} and 2^{nd}): 800.
Number of flashes: 150.
Number of flashes per A/D conversion: 1.

Assay 3 - LIMK2 (Full Length) Enzyme Binding Assay

1. Reagents

1X Kinase Buffer A: 50 mM HEPES at pH 7.5, 10 mM $MgCl_2$, 1 mM EGTA, 0.01% Brij-35.

Kinase Enzyme: LIM Kinase 2, full length human N-terminal GST-fusion protein (99 kDa) with human His-tagged ROCK2 using baculovirus expression system purchased from Carna Biosciences (Product code 09-106) (Lot # 08CBS-0416 C); Stock concentration = 279 µg/mL. Aliquots stored at -80°C.

LanthaScreen™ Eu Kinase Binding Assay Reagents: Kinase tracer 178 (Product code PV5593) and Eu-anti GST antibody (Product code PV5594) were obtained from Invitrogen. Both reagents were stored at -20°C. Prior to IC50 determinations, a Tracer

Kd experiment was run to optimise the concentration of each new batch of Tracer 178 to use to ensure that the concentration of Tracer selected was near or slightly below Kd to ensure sensitive detection of inhibitors.

2. *Method*

Dry spot 5 µL of compound in 3% DMSO to test wells, or 3% DMSO to blanks and controls into a white polystyrene non-binding surface 384-well low volume microplate (Matrix, product code 4365) using a BioMek Nx. A 15 nM kinase and 6 nM antibody kinase/antibody solution (3 X the desired final assay concentration) was prepared in 1 X Kinase Buffer A. The antibody tube was centrifuged at approximately 10,000 x g for 10 minutes and the desired volume aspirated from the top of the solution to eliminate spurious data points that can arise on occasion due to any particulates in the product. A working solution of tracer 178 was prepared at 3x the final desired concentration in 1 X Buffer A. 5 µL of kinase/antibody solution was added to all test compound wells and positive control wells. An antibody solution containing no LIMK2 kinase was added to the final two columns to give negative control wells. 5 µL of Tracer 178 was added to all wells of the plate and then incubated at room temperature for 60 minutes. Following the incubation period the plate was read on a Tecan Ultra plate reader where two sequential measurements were measured: one at 620 nm for the antibody/donor emission, and the other at 665 nm for the acceptor/tracer emission. The emission ratio is calculated by the ratio of the two fluorescence intensities (acceptor/donor).

3. *Tecan settings*

Measurement 1: Excitation Filter 337 nm, Emission Filter 620 nm, Mirror Dichroic2 (e.g., FI 96), Lag time 100 µs, Integration time 200 µs, optimal Gain, optimal Z-position.

Measurement 2: Excitation Filter 337 nm, Emission Filter 665 nm, Mirror Dichroic2 (e.g., FI 96), Lag time 100 µs, Integration time 200 µs, optimal Gain, optimal Z-position.

Biological Data - Assay 1 - LIMK1 (Kinase Domain) Enzyme Activity Assay

The following compounds were examined using Assay 1:

AA-003, AA-004, AA-006, AA-021, AA-022, AA-024, AA-025, AA-026, AA-027, AA-029, AA-030, AA-031, AA-034, AA-035, AA-038, AA-039, AA-040, AB-003, AB-008, AC-001, AC-002, AC-003, AC-004, AD-001, AD-002, AD-003, AD-004, AD-005, AD-006, AD-008, AD-009, AD-010, AD-011, AD-012, AD-013, AD-014, AD-015, AE-001, AE-003, AE-011, AE-012, AE-013, AE-014, AE-015, AE-016, AE-017, AE-018, AE-020, AE-021, AE-022, AE-023, AE-025, AE-026, AE-027, AE-028, AE-029, AE-034, AF-001, AG-001, AG-002, AG-003, AG-004, AG-005, AH-001, AH-002, AH-003, AH-005, AH-007, AH-008, AH-012,

AH-013, AH-014, AH-015, BB-001, BB-002, BB-003, BB-004, BB-005, BB-006, BB-007, BB-008, BB-009, BB-010, CC-001, CC-002, CC-003, CC-004.

All of these compounds were found to have an IC_{50} of less than 20 μM.

The following compounds were found to have an IC50 of less than 5 μM:

AA-003, AA-004, AA-006, AA-021, AA-022, AA-024, AA-025, AA-026, AA-027, AA-029, AA-030, AA-034, AA-035, AA-038, AA-039, AA-040, AB-003, AB-008, AC-001, AC-002, AC-003, AC-004, AD-001, AD-002, AD-003, AD-004, AD-005, AD-006, AD-008, AD-009, AD-010, AD-011, AD-012, AD-013, AD-014, AD-015, AE-001, AE-003, AE-011, AE-012, AE-013, AE-014, AE-015, AE-016, AE-017, AE-018, AE-021, AE-025, AE-026, AE-027, AE-028, AE-029, AE-034, AG-003, AG-005, AH-001, AH-002, AH-003, AH-005, AH-007, AH-008, AH-012, AH-013, AH-015, BB-001, BB-002, BB-006, BB-008, BB-009, BB-010, CC-001, CC-002, CC-003, CC-004.

The following compounds were found to have an IC50 of less than 0.5 μM:

AA-003, AA-004, AA-006, AA-021, AA-024, AA-025, AA-026, AA-027, AA-029, AA-030, AA-034, AA-038, AA-039, AA-040, AB-003, AB-008, AC-001, AC-002, AC-003, AC-004, AD-001, AD-002, AD-003, AD-005, AD-006, AD-008, AD-009, AD-010, AD-011, AD-013, AE-001, AE-003, AE-011, AE-014, AE-015, AE-017, AE-018, AE-021, AE-025, AE-027, AE-029, AE-034, AH-002, AH-003, AH-007, AH-012, AH-015, CC-001, CC-002, CC-004.

The following compounds were found to have an IC50 of less than 0.2 μM:

AA-003, AA-021, AA-024, AA-029, AA-030, AA-034, AA-038, AA-040, AB-003, AB-008, AC-001, AC-002, AC-004, AD-005, AD-008, AD-009, AE-003, AE-011, AE-014, AE-021, AE-029, AE-034, AH-002, CC-004.

<u>Biological Data - Assay 2 - LIMK1 (Kinase Domain) Enzyme Binding Assay</u>

The following compounds were examined using Assay 2:

AA-001, AA-002, AA-003, AA-005, AA-006, AA-007, AA-008, AA-009, AA-010, AA-011, AA-012, AA-013, AA-014, AA-015, AA-016, AA-017, AA-018, AA-019, AA-020, AA-021, AA-023, AA-028, AA-029, AA-032, AA-033, AA-036, AA-037, AA-038, AA-040, AB-001, AB-002, AB-003, AB-004, AB-005, AB-006, AB-007, AB-009, AB-010, AB-011, AB-012, AB-013, AB-014, AB-015, AB-016, AB-017, AB-018, AB-019, AB-020, AB-021, AB-022, AB-023, AB-024, AB-025, AB-026, AB-027, AB-028, AB-029, AB-030, AB-031, AB-032, AB-033, AB-034, AB-035, AB-036, AB-037, AC-001, AC-002, AD-007, AD-008, AD-009, AD-016, AD-017, AE-001, AE-002, AE-003, AE-004, AE-005, AE-006, AE-007, AE-008,

AE-009, AE-010, AE-019, AE-024, AE-030, AE-031, AE-032, AE-033, AH-003, AH-004, AH-006, AH-009, AH-010, AH-011, AJ-001, BB-009, CC-001, CC-002, CC-003, CC-004.

All of these compounds were found to have an IC_{50} of less than 10 μM.

The following compounds were found to have an IC50 of less than 1 μM:

AA-001, AA-002, AA-003, AA-005, AA-006, AA-007, AA-008, AA-009, AA-010, AA-011, AA-012, AA-013, AA-014, AA-015, AA-016, AA-017, AA-018, AA-019, AA-020, AA-021, AA-023, AA-028, AA-029, AA-032, AA-033, AA-036, AA-037, AA-038, AA-040, AB-001, AB-002, AB-003, AB-004, AB-005, AB-006, AB-007, AB-009, AB-010, AB-011, AB-012, AB-013, AB-014, AB-015, AB-016, AB-017, AB-018, AB-019, AB-020, AB-021, AB-022, AB-023, AB-024, AB-025, AB-026, AB-027, AB-028, AB-029, AB-030, AB-031, AB-032, AB-033, AB-034, AB-035, AB-037, AC-001, AC-002, AD-007, AD-008, AD-009, AD-016, AD-017, AE-001, AE-002, AE-003, AE-004, AE-005, AE-006, AE-019, AE-024, AE-030, AE-031, AE-032, AE-033, AH-003, AH-004, AH-006, AH-009, AH-011, BB-009, CC-001, CC-002, CC-003, CC-004.

The following compounds were found to have an IC50 of less than 0.2 μM:

AA-001, AA-003, AA-005, AA-007, AA-008, AA-009, AA-010, AA-014, AA-015, AA-016, AA-018, AA-020, AA-021, AA-023, AA-028, AA-029, AA-032, AA-033, AA-036, AA-037, AA-038, AA-040, AB-002, AB-003, AB-004, AB-005, AB-010, AB-012, AB-013, AB-014, AB-015, AB-016, AB-019, AB-020, AB-021, AB-022, AB-025, AB-026, AB-027, AB-028, AB-029, AB-034, AB-035, AC-001, AC-002, AD-007, AD-008, AD-009, AE-002, AE-030, AE-031, AE-032, AE-033.

Biological Data - Assay 3 - LIMK2 (Full Length) Enzyme Binding Assay

The following compounds were examined using Assay 3: AA-040 and AB-027.

The IC50 for AA-040 was 0.202 μM.
The IC50 for AA-027 was 0.547 μM.

Biological Data - Selected Compounds

Data for some of the compounds is shown in the following table.

Code	Assay 1 IC_{50} (μM)	Assay 2 IC_{50} (μM)	Assay 3 IC_{50} (μM)
AA-040	0.062	0.155	0.202
AB-003	0.083	0.094	-
AC-001	0.077	0.066	-
AD-009	0.061	0.111	-
AE-003	0.135	0.258	-
AF-001	5.704	-	-
AG-005	2.459	-	-
AH-003	0.418	0.442	-
AJ-001	-	8.011	-
BB-009	0.793	0.859	-
CC-001	0.327	0.433	-

* * *

The foregoing has described the principles, preferred embodiments, and modes of operation of the present invention. However, the invention should not be construed as limited to the particular embodiments discussed. Instead, the above-described embodiments should be regarded as illustrative rather than restrictive, and it should be appreciated that variations may be made in those embodiments by workers skilled in the art without departing from the scope of the present invention.

REFERENCES

A number of patents and publications are cited herein in order to more fully describe and disclose the invention and the state of the art to which the invention pertains. Full citations for these references are provided below. Each of these references is incorporated herein by reference in its entirety into the present disclosure, to the same extent as if each individual reference was specifically and individually indicated to be incorporated by reference.

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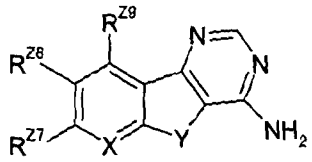
CLAIMS

1. A compound selected from compounds of the following formula, and pharmaceutically acceptable salts, hydrates, and solvates thereof:



wherein:

-X= is independently -CR^{Z6}= or -N=;

-Y- is independently -S-, -NR^{Y}-, or -O-;

-R^{Y} is independently -H or saturated aliphatic C_{1-6}alkyl;

and wherein, if -X= is -CR^{Z6}=, then:

-R^{Z6} is independently -H, -R^{QS}, or -R^{QL};

-R^{Z7} is independently -H, -R^{QS}, or -R^{QL};

-R^{Z8} is independently -H, -R^{QS}, or -R^{QL}; and

-R^{Z9} is independently -H, -R^{QS}, or -R^{QL};

with the proviso that *at least one* of -R^{Z6}, -R^{Z7}, -R^{Z8}, and -R^{Z9} is -R^{QL};

and wherein, if -X= is -N=, then:

-R^{Z7} is independently -H, -R^{QS}, or -R^{QL};

-R^{Z8} is independently -H, -R^{QS}, or -R^{QL}; and

-R^{Z9} is independently -H, -R^{QS}, or -R^{QL};

with the proviso that *at least one* of -R^{Z7}, -R^{Z8}, and -R^{Z9} is -R^{QL};

wherein:

each -R^{QL} is independently -R^{CA}, -R^{HA}, -R^{CC}, or -R^{HC};

wherein:

-R^{CA} is independently phenyl or naphthyl, and is optionally substituted with one or more substituents, -R^{X};

-R^{HA} is independently C_{5-12}heteroaryl, and is optionally substituted with one or more substituents, -R^{X};

-R^{CC} is independently non-aromatic C_{3-7}cycloalkyl or non-aromatic C_{3-7}cycloalkenyl, and is optionally substituted with one or more substituents, -R^{X};

-R^{HC} is independently non-aromatic C_{3-7}heterocyclyl, and is optionally substituted with one or more substituents, -R^{X};

and wherein:

each -R^{QS} is independently -F, -Cl, -Br, -I, -R^S, -CF_3, -OH, -OR^S, -OCF_3, -NH_2, -NHR^S, -$NR^S{}_2$, -NHC(=O)R^S, -NHC(=O)OR^S, -C(=O)OH, -C(=O)OR^S, -C(=O)NH_2, -C(=O)NHR^S, -C(=O)$NR^S{}_2$, -SH, -SR^S, -CN, or -NO_2;

wherein each -R^S is independently saturated aliphatic $C_{1\text{-}8}$alkyl, phenyl, -CH_2-phenyl, -CH_2CH_2-phenyl, or -CH=CH-phenyl, wherein each phenyl is optionally substituted with one or more groups selected from: -F, -Cl, -Br, -I, -R^{SS}, -CF_3, -OH, -OR^{SS}, and -OCF_3, wherein each -R^{SS} is independently saturated aliphatic $C_{1\text{-}4}$alkyl;

and wherein each -R^X is independently selected from -R^{X1} and -R^{X2}, wherein:

each -R^{X1} is independently:

-R^Z,
-F, -Cl, -Br, -I,
-CF_3, -OCF_3,
-OH, -R^{ZL}-OH, -O-R^{ZL}-OH, -NH-R^{ZL}-OH, -NR^Z-R^{ZL}-OH,
-OR^Z, -R^{ZL}-OR^Z, -O-R^{ZL}-OR^Z, -NH-R^{ZL}-OR^Z, -NR^Z-R^{ZL}-OR^Z,
-SH, -SR^Z,
-CN,
-NO_2,
-C(=O)OH, -C(=O)OR^Z,
-C(=O)R^Z,
-NH_2, -NHR^Z, -$NR^Z{}_2$, -R^{NZ},
-R^{ZL}-NH_2, -R^{ZL}-NHR^Z, -R^{ZL}-$NR^Z{}_2$, -R^{ZL}-R^{NZ},
-O-R^{ZL}-NH_2, -O-R^{ZL}-NHR^Z, -O-R^{ZL}-$NR^Z{}_2$, -O-R^{ZL}-R^{NZ},
-NH-R^{ZL}-NH_2, -NH-R^{ZL}-NHR^Z, -NH-R^{ZL}-$NR^Z{}_2$, -NH-R^{ZL}-R^{NZ},
-NR^Z-R^{ZL}-NH_2, -NR^Z-R^{ZL}-NHR^Z, -NR^Z-R^{ZL}-$NR^Z{}_2$, -NR^Z-R^{ZL}-R^{NZ},
-C(=O)NH_2, -C(=O)NHR^Z, -C(=O)$NR^Z{}_2$, -C(=O)R^{NZ},
-R^{ZL}-C(=O)NH_2, -R^{ZL}-C(=O)NHR^Z, -R^{ZL}-C(=O)$NR^Z{}_2$, -R^{ZL}-C(=O)R^{NZ},
-O-R^{ZL}-C(=O)NH_2, -O-R^{ZL}-C(=O)NHR^Z, -O-R^{ZL}-C(=O)$NR^Z{}_2$, -O-R^{ZL}-C(=O)R^{NZ},
-NH-C(=O)R^Z, -NR^Z-C(=O)R^Z,
-NH-C(=O)OH, -NR^Z-C(=O)OH, -NH-C(=O)OR^Z, -NR^Z-C(=O)OR^Z,
-OC(=O)NH_2, -OC(=O)NHR^Z, -OC(=O)$NR^Z{}_2$, -OC(=O)R^{NZ},
-NHC(=O)NH_2, -NHC(=O)NHR^Z, -NHC(=O)$NR^Z{}_2$, -NHC(=O)R^{NZ},
-NR^ZC(=O)NH_2, -NR^ZC(=O)NHR^Z, -NR^ZC(=O)$NR^Z{}_2$, -NR^ZC(=O)R^{NZ},
-$S(=O)_2R^Z$,
-$S(=O)_2NH_2$, -$S(=O)_2NHR^Z$, -$S(=O)_2NR^Z{}_2$, -$S(=O)_2R^{NZ}$,
-NH-$S(=O)_2R^Z$, -NR^Z-$S(=O)_2R^Z$, or
=O;

and additionally, two or more adjacent substituents -R^{X1}, if present, may together form -OCH_2O-, -OCH_2CH_2O-, or -$OCH_2CH_2CH_2O$-;

wherein:

each -R^{ZL}- is independently saturated aliphatic C_{1-4}alkylene;

each -R^{NZ} is independently azetidino, pyrrolidino, piperidino, piperazino, morpholino, azepino, or diazepino, and is optionally substituted with one or more substitutents selected from saturated aliphatic C_{1-4}alkyl;

each -R^{Z} is independently saturated aliphatic C_{1-6}alkyl, phenyl, benzyl, or C_{5-6}heteroaryl, wherein phenyl, benzyl, and C_{5-6}heteroaryl are each optionally substituted with one or more substituents selected from -F, -Cl, -Br, -I, -R^{ZZ}, -CF_3, -OH, -OR^{ZZ}, -OCF_3, -NH_2, -NHR^{ZZ}, -NR^{ZZ}_2, -C(=O)OH, -C(=O)NH_2, -C(=O)NHR^{ZZ}, and -C(=O)NR^{ZZ}_2, wherein each -R^{ZZ} is independently saturated aliphatic C_{1-4}alkyl; and

each -R^{X2} is independently:

-NH-C(=J)-NH_2, -NR^{K1}-C(=J)-NH_2,
-NH-C(=J)-NHR^{K2}, -NR^{K1}-C(=J)-NHR^{K2},
-NH-C(=J)-NR^{K2}_2, -NR^{K1}-C(=J)-NR^{K2}_2,
-NH-C(=J)-$NR^{K3}R^{K4}$, -NR^{K1}-C(=J)-$NR^{K3}R^{K4}$,

-NH-C(=O)H, -NR^{K1}-C(=O)H,
-NH-C(=O)R^{K5}, -NR^{K1}-C(=O)R^{K5},

-C(=O)-NH_2, -C(=O)-NHR^{K2}, -C(=O)-NR^{K2}_2, -C(=O)-$NR^{K3}R^{K4}$,

-OH, or -OR^{K6};

wherein each =J is independently =O or =S;

and wherein each -R^{K1} is independently saturated aliphatic C_{1-4}alkyl;

and wherein each -R^{K2} is independently:

saturated aliphatic C_{1-4}alkyl, aliphatic C_{2-4}alkenyl, or saturated C_{3-6}cycloalkyl;

each optionally substituted with one or more groups independently selected from: -F, -Cl, -Br, -I, -OH, -OR^{A1}, -OCF_3, -SR^{A1}, -S(=O)R^{A1}, -$S(=O)_2R^{A1}$, -NH_2, -NHR^{A1}, -NR^{A1}_2, pyrrolidinyl, piperidinyl, morpholinyl, piperizinyl, -C(=O)OH, -C(=O)OR^{A1}, -OC(=O)R^{A1}, -C(=O)NH_2, -C(=O)NHR^{A1}, -C(=O)NR^{A1}_2, pyrrolidino-C(=O)-, piperidino-C(=O)-, morpholino-C(=O)-, piperizino-C(=O)-, and -R^{A2};

wherein:

each pyrrolidinyl, piperidinyl, morpholinyl, piperizinyl, pyrrolidino, piperidino, morpholino, and piperizino is optionally substituted with one or more

groups independently selected from -F, -R^{A1}, -OH, -OR^{A1}, -NH_2, -NHR^{A1}, -NR^{A1}_2, *pyrrolidino*, *piperidino*, *morpholino*, *piperizino*, -C(=O)OH, -$C(=O)OR^{A1}$, -$C(=O)R^{A1}$, -$C(=O)NH_2$, -$C(=O)NHR^{A1}$, -$C(=O)NR^{A1}_2$, pyrrolidino-C(=O)-, piperidino-C(=O)-, morpholino-C(=O)-, piperizino-C(=O)-, and -OCH_2CH_2O-;

each -R^{A1} *is independently saturated aliphatic* C_{1-4}alkyl; and

each -R^{A2} is independently phenyl, C_{5-6}heteroaryl, or non-aromatic C_{5-7}heterocyclyl;

and wherein each -$NR^{K3}R^{K4}$ is independently:

pyrrolidino, piperidino, morpholino, or piperizino;

each optionally substituted with one or more groups independently selected from -F, -R^{A3}, -OH, -OR^{A3}, -NH_2, -NHR^{A3}, -NR^{A3}_2, pyrrolidino, piperidino, morpholino, piperizino, -C(=O)OH, -$C(=O)OR^{A3}$, -$C(=O)R^{A3}$, -$C(=O)NH_2$, -$C(=O)NHR^{A3}$, -$C(=O)NR^{A3}_2$, pyrrolidino-C(=O)-, piperidino-C(=O)-, morpholino-C(=O)-, piperizino-C(=O)-, and -OCH_2CH_2O-;

wherein each -R^{A3} is independently saturated aliphatic C_{1-4}alkyl, optionally substituted with one or more groups independently selected from -OH, -OR^{A4}, -NH_2, -NHR^{A4}, -NR^{A4}_2, *pyrrolidino*, *piperidino*, *morpholino*, and *piperizino*;

wherein each -R^{A4} is independently saturated aliphatic C_{1-4}alkyl;

and wherein each -R^{K5} *is independently saturated aliphatic* C_{1-4}alkyl, and is optionally substituted with one or more groups independently selected from: -F, -Cl, -Br, -I, -CF_3, -OH, -OR^{A5}, -OCF_3, -NH_2, -NHR^{A5}, and -NR^{A5}_2, wherein each -R^{A5} is independently saturated aliphatic C_{1-4}alkyl;

and wherein each -R^{K6} is independently saturated aliphatic C_{1-4}alkyl, and is optionally substituted with one or more groups independently selected from: -F, -Cl, -Br, -I, -CF_3, -OH, -OR^{A6}, -OCF_3, -NH_2, -NHR^{A6}, and -NR^{A6}_2, wherein each -R^{A6} is independently saturated aliphatic C_{1-4}alkyl;

with the proviso that the compound is <u>not</u> a compound selected from: compounds PP-001 to PP-034, and pharmaceutically acceptable salts, hydrates, and solvates thereof.

2. A compound according to claim 1, wherein -Y- is -S-.

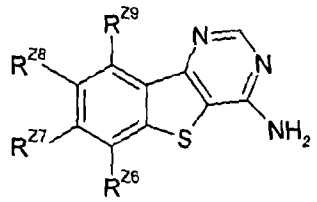
3. A compound according to claim 1, wherein -Y- is -O-.

4. A compound according to claim 1, wherein -Y- is $-NR^{Y}-$.

5. A compound according to any one of claims 1 to 4, wherein -X= is $-CR^{Z6}=$.

6. A compound according to any one of claims 1 to 4, wherein -X= is -N=.

7. A compound according to claim 1, wherein the compound is selected from compounds of the following formula, and pharmaceutically acceptable salts, hydrates, and solvates thereof:

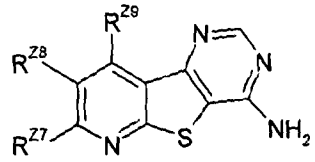


8. A compound according to claim 7, wherein:
$-R^{Z6}$ is independently -H or $-R^{QS}$;
$-R^{Z7}$ is independently $-R^{QL}$;
$-R^{Z8}$ is independently -H or $-R^{QS}$; and
$-R^{Z9}$ is independently -H or $-R^{QS}$.

9. A compound according to claim 7, wherein:
$-R^{Z6}$ is independently -H;
$-R^{Z7}$ is independently $-R^{QL}$;
$-R^{Z8}$ is independently -H; and
$-R^{Z9}$ is independently -H or $-R^{QS}$.

10. A compound according to claim 7, wherein:
$-R^{Z6}$ is independently -H;
$-R^{Z7}$ is independently $-R^{QL}$;
$-R^{Z8}$ is independently -H; and
$-R^{Z9}$ is independently -H.

11. A compound according to claim 1, wherein the compound is selected from compounds of the following formula, and pharmaceutically acceptable salts, hydrates, and solvates thereof:



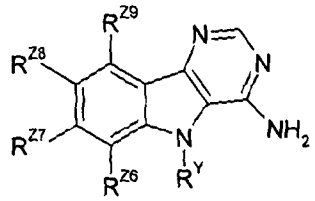
with the proviso that the compound is not a compound selected from: compounds PP-001 to PP-034, and pharmaceutically acceptable salts, hydrates, and solvates thereof.

12. A compound according to claim 11, wherein:
$-R^{Z7}$ is independently $-R^{QL}$;
$-R^{Z8}$ is independently -H or $-R^{QS}$; and
$-R^{Z9}$ is independently -H or $-R^{QS}$.

13. A compound according to claim 11, wherein:
$-R^{Z7}$ is independently $-R^{QL}$;
$-R^{Z8}$ is independently -H; and
$-R^{Z9}$ is independently -H or $-R^{QS}$.

14. A compound according to claim 11, wherein:
$-R^{Z7}$ is independently $-R^{QL}$;
$-R^{Z8}$ is independently -H; and
$-R^{Z9}$ is independently -H.

15. A compound according to claim 1, wherein the compound is selected from compounds of the following formula, and pharmaceutically acceptable salts, hydrates, and solvates thereof:



16. A compound according to claim 15, wherein:
$-R^{Z6}$ is independently -H or $-R^{QS}$;
$-R^{Z7}$ is independently $-R^{QL}$;
$-R^{Z8}$ is independently -H or $-R^{QS}$; and
$-R^{Z9}$ is independently -H or $-R^{QS}$.

17. A compound according to claim 15, wherein:
$-R^{Z6}$ is independently -H;
$-R^{Z7}$ is independently $-R^{QL}$;
$-R^{Z8}$ is independently -H; and
$-R^{Z9}$ is independently -H or $-R^{QS}$.

18. A compound according to claim 15, wherein:
$-R^{Z6}$ is independently -H;
$-R^{Z7}$ is independently $-R^{QL}$;
$-R^{Z8}$ is independently -H; and
$-R^{Z9}$ is independently -H.

19. A compound according to any one of claims 1 to 18, wherein each $-R^{QS}$, if present, is independently -F, -Cl, -Br, -I, $-R^{S}$, $-CF_3$, -OH, $-OR^{S}$, $-OCF_3$, $-NH_2$, $-NHR^{S}$, $-NR^{S}_2$, $-NHC(=O)R^{S}$, $-NHC(=O)OR^{S}$, $-C(=O)OH$, $-C(=O)OR^{S}$, $-C(=O)NH_2$, $-C(=O)NHR^{S}$, or $-C(=O)NR^{S}_2$.

20. A compound according to any one of claims 1 to 18, wherein each $-R^{QS}$, if present, is independently -F, -Cl, -Br, -I, $-R^{S}$, $-CF_3$, -OH, $-OR^{S}$, or $-OCF_3$.

21. A compound according to any one of claims 1 to 18, wherein each $-R^{QS}$, if present, is independently $-R^{S}$.

22. A compound according to any one of claims 1 to 21, wherein each $-R^{S}$, if present, is independently saturated aliphatic C_{1-4}alkyl or phenyl, wherein said phenyl is optionally substituted with one or more groups selected from: -F, -Cl, -Br, -I, $-R^{SSS}$, $-CF_3$, -OH, $-OR^{SSS}$, or $-OCF_3$, wherein each $-R^{SSS}$ is independently saturated aliphatic C_{1-4}alkyl.

23. A compound according to any one of claims 1 to 21, wherein each $-R^{S}$, if present, is independently saturated aliphatic C_{1-4}alkyl or phenyl.

24. A compound according to any one of claims 1 to 21, wherein each $-R^{S}$, if present, is independently -Me, -Et, -nPr, -iPr, -nBu, -iBu, or -tBu.

25. A compound according to any one of claims 1 to 21, wherein each $-R^{S}$, if present, is independently -Me.

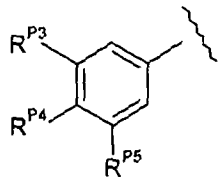
26. A compound according to any one of claims 1 to 25, wherein $-R^{QL}$, or each $-R^{QL}$, is independently $-R^{CA}$ or $-R^{HA}$.

27. A compound according to any one of claims 1 to 25, wherein $-R^{QL}$, or each $-R^{QL}$, is independently $-R^{CA}$.

28. A compound according to any one of claims 1 to 25, wherein $-R^{QL}$, or each $-R^{QL}$, is independently $-R^{HA}$.

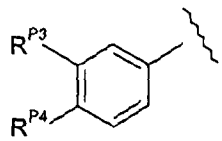
29. A compound according to any one of claims 1 to 28, wherein $-R^{CA}$, if present, or each $-R^{CA}$, if present, is independently phenyl; and is optionally substituted with one or more substituents, $-R^{X}$.

30. A compound according to any one of claims 1 to 28, wherein $-R^{CA}$, if present, or each $-R^{CA}$, if present, is independently:



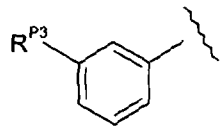
wherein each of $-R^{P3}$, $-R^{P4}$, and $-R^{P5}$ is independently -H or a ring substituent, wherein each ring substituent is independently $-R^{X}$.

31. A compound according to any one of claims 1 to 28, wherein $-R^{CA}$, if present, or each $-R^{CA}$, if present, is independently:



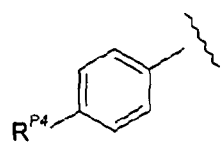
wherein each of $-R^{P3}$ and $-R^{P4}$ is independently -H or a ring substituent, wherein each ring substituent is independently $-R^{X}$.

32. A compound according to any one of claims 1 to 28, wherein $-R^{CA}$, if present, or each $-R^{CA}$, if present, is independently:



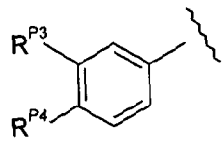
wherein $-R^{P3}$ is independently a ring substituent, wherein the ring substituent is independently $-R^{X}$.

33. A compound according to any one of claims 1 to 28, wherein $-R^{CA}$, if present, or each $-R^{CA}$, if present, is independently:



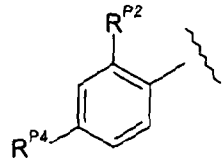
wherein $-R^{P4}$ is independently a ring substituent, wherein the ring substituent is independently $-R^{X}$.

34. A compound according to any one of claims 1 to 28, wherein $-R^{CA}$, if present, or each $-R^{CA}$, if present, is independently:



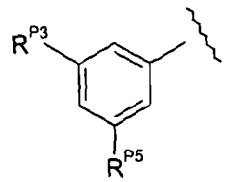
wherein each of $-R^{P3}$ and $-R^{P4}$ is independently a ring substituent, wherein each ring substituent is independently $-R^{X}$.

35. A compound according to any one of claims 1 to 28, wherein $-R^{CA}$, if present, or each $-R^{CA}$, if present, is independently:



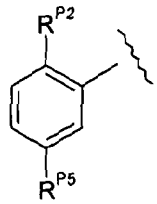
wherein each of $-R^{P2}$ and $-R^{P4}$ is independently -H or a ring substituent, wherein each ring substituent is independently $-R^{X}$.

36. A compound according to any one of claims 1 to 28, wherein $-R^{CA}$, if present, or each $-R^{CA}$, if present, is independently:



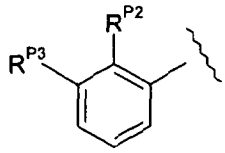
wherein each of $-R^{P3}$ and $-R^{P5}$ is independently a ring substituent, wherein each ring substituent is independently $-R^{X}$.

37. A compound according to any one of claims 1 to 28, wherein $-R^{CA}$, if present, or each $-R^{CA}$, if present, is independently:



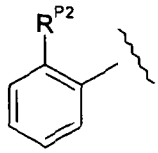
wherein each of $-R^{P2}$ and $-R^{P5}$ is independently a ring substituent, wherein each ring substituent is independently $-R^{X}$.

38. A compound according to any one of claims 1 to 28, wherein $-R^{CA}$, if present, or each $-R^{CA}$, if present, is independently:



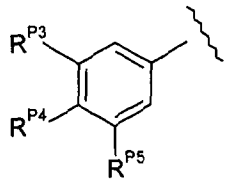
wherein each of $-R^{P2}$ and $-R^{P3}$ is independently a ring substituent, wherein each ring substituent is independently $-R^{X}$.

39. A compound according to any one of claims 1 to 28, wherein $-R^{CA}$, if present, or each $-R^{CA}$, if present, is independently:



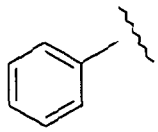
wherein $-R^{P2}$ is independently a ring substituent, wherein the ring substituent is independently $-R^{X}$.

40. A compound according to any one of claims 1 to 28, wherein $-R^{CA}$, if present, or each $-R^{CA}$, if present, is independently:



wherein each of $-R^{P3}$, $-R^{P4}$, and $-R^{P5}$ is independently a ring substituent, wherein each ring substituent is independently $-R^{X}$.

41. A compound according to any one of claims 1 to 28, wherein $-R^{CA}$, if present, or each $-R^{CA}$, if present, is independently:



42. A compound according to any one of claims 1 to 41, wherein $-R^{HA}$, if present, or each $-R^{HA}$, if present, is independently furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, pyridazinyl, and indolyl; and is optionally substituted with one or more substituents, $-R^{X}$.

43. A compound according to any one of claims 1 to 42, wherein:
if exactly one group -R^X is present, then -R^X is -R^{X2}; and
if a plurality of groups -R^X are present, then at least one -R^X is -R^{X2}.

44. A compound according to any one of claims 1 to 42, wherein:
if exactly one group -R^X is present, then -R^X is -R^{X2}; and
if a plurality of groups -R^X are present, then exactly one -R^X is -R^{X2}.

45. A compound according to any one of claims 1 to 42, wherein:
exactly one group -R^X is present, and -R^X is -R^{X2}.

46. A compound according to any one of claims 1 to 42, wherein:
exactly two groups -R^X are present, one -R^X is -R^{X2}, and the other -R^X is -R^{X1}.

47. A compound according to any one of claims 1 to 46, wherein each -R^{X1}, if present, is independently:
-R^Z,
-F, -Cl, -Br, -I,
-CF_3, -OCF_3,
-OH, -R^{ZL}-OH, -O-R^{ZL}-OH,
-OR^Z, -R^{ZL}-OR^Z, -O-R^{ZL}-OR^Z,
-CN,
-NO_2,
-C(=O)OH, -C(=O)OR^Z,
-C(=O)R^Z,
-NH_2, -NHR^Z, -NR^Z_2, -R^{NZ},
-R^{ZL}-NH_2, -R^{ZL}-NHR^Z, -R^{ZL}-NR^Z_2, -R^{ZL}-R^{NZ},
-NH-R^{ZL}-NH_2, -NH-R^{ZL}-NHR^Z, -NH-R^{ZL}-NR^Z_2, -NH-R^{ZL}-R^{NZ},
-C(=O)NH_2, -C(=O)NHR^Z, -C(=O)NR^Z_2, -C(=O)R^{NZ},
-NH-C(=O)R^Z, or -NR^Z-C(=O)R^Z.

48. A compound according to any one of claims 1 to 46, wherein each -R^{X1}, if present, is independently:
-R^Z,
-F, -Cl, -Br, -I,
-CF_3, -OCF_3,
-OH, -R^{ZL}-OH,
-OR^Z, -R^{ZL}-OR^Z,
-CN,
-NO_2,
-C(=O)OH, -C(=O)OR^Z,
-C(=O)R^Z,
-NH_2, -NHR^Z, -NR^Z_2, -R^{NZ},

$-R^{ZL}-NH_2$, $-R^{ZL}-NHR^Z$, $-R^{ZL}-NR^Z_2$, $-R^{ZL}-R^{NZ}$,
$-C(=O)NH_2$, $-C(=O)NHR^Z$, $-C(=O)NR^Z_2$, or
$-NH-C(=O)R^Z$.

49. A compound according to any one of claims 1 to 46, wherein each $-R^{X1}$, if present, is independently: $-R^Z$, -F, -Cl, -Br, -OH, $-OR^Z$, $-C(=O)OH$, $-C(=O)OR^Z$, $-NH_2$, $-NHR^Z$, $-NR^Z_2$, $-R^{NZ}$, $-C(=O)NH_2$, $-C(=O)NHR^Z$, $-C(=O)NR^Z_2$, or $-NH-C(=O)R^Z$.

50. A compound according to any one of claims 1 to 46, wherein each $-R^{X1}$, if present, is independently $-R^Z$, -F, -Cl, -Br, -OH, or $-OR^Z$.

51. A compound according to any one of claims 1 to 50, wherein:

each $-R^{ZL}-$, if present, is independently $-CH_2CH_2-$;

each $-R^{NZ}$, if present, is independently pyrrolidino, piperidino, piperazino, or morpholino, and is optionally substituted with one or more substitutents selected from saturated aliphatic C_{1-4}alkyl; and

each $-R^Z$, if present, is independently saturated aliphatic C_{1-6}alkyl, phenyl, or benzyl.

52. A compound according to any one of claims 1 to 51, wherein each $-R^{X2}$, if present, is independently:
$-NH-C(=J)-NH_2$, $-NR^{K1}-C(=J)-NH_2$,
$-NH-C(=J)-NHR^{K2}$, $-NR^{K1}-C(=J)-NHR^{K2}$,
$-NH-C(=J)-NR^{K2}_2$, $-NR^{K1}-C(=J)-NR^{K2}_2$,
$-NH-C(=J)-NR^{K3}R^{K4}$, or $-NR^{K1}-C(=J)-NR^{K3}R^{K4}$.

53. A compound according to any one of claims 1 to 51, wherein each $-R^{X2}$, if present, is independently:
$-NH-C(=O)-NH_2$, $-NR^{K1}-C(=O)-NH_2$,
$-NH-C(=O)-NHR^{K2}$, $-NR^{K1}-C(=O)-NHR^{K2}$,
$-NH-C(=O)-NR^{K2}_2$, $-NR^{K1}-C(=O)-NR^{K2}_2$,
$-NH-C(=O)-NR^{K3}R^{K4}$, or $-NR^{K1}-C(=O)-NR^{K3}R^{K4}$.

54. A compound according to any one of claims 1 to 51, wherein each $-R^{X2}$, if present, is independently:
$-NH-C(=O)H$, $-NR^{K1}-C(=O)H$,
$-NH-C(=O)R^{K5}$, $-NR^{K1}-C(=O)R^{K5}$,
$-C(=O)-NH_2$, $-C(=O)-NHR^{K2}$, $-C(=O)-NR^{K2}_2$, or $-C(=O)-NR^{K3}R^{K4}$.

55. A compound according to any one of claims 1 to 51, wherein each $-R^{X2}$, if present, is independently: $-NH-C(=O)H$, $-NR^{K1}-C(=O)H$, $-NH-C(=O)R^{K5}$, or $-NR^{K1}-C(=O)R^{K5}$.

56. A compound according to any one of claims 1 to 51, wherein each $-R^{X2}$, if present, is independently: $-C(=O)-NH_2$, $-C(=O)-NHR^{K2}$, $-C(=O)-NR^{K2}_2$, or $-C(=O)-NR^{K3}R^{K4}$.

57. A compound according to any one of claims 1 to 51, wherein each $-R^{X2}$, if present, is independently: -OH or $-OR^{K6}$.

58. A compound according to any one of claims 1 to 57, wherein each $-R^{K1}$, if present, is independently -Me, -Et, -nPr, -iPr, -nBu, -iBu, -sBu, or -tBu.

59. A compound according to any one of claims 1 to 57, wherein each $-R^{K1}$, if present, is independently -Me.

60. A compound according to any one of claims 1 to 59, wherein each $-R^{K2}$, if present, is independently: saturated aliphatic C_{1-4}alkyl, optionally substituted with one or more groups independently selected from: -F, -Cl, -Br, -I, -OH, $-OR^{A1}$, $-OCF_3$, $-SR^{A1}$, $-S(=O)R^{A1}$, $-S(=O)_2R^{A1}$, $-NH_2$, $-NHR^{A1}$, $-NR^{A1}_2$, pyrrolidinyl, piperidinyl, morpholinyl, piperizinyl, -C(=O)OH, $-C(=O)OR^{A1}$, $-OC(=O)R^{A1}$, $-C(=O)NH_2$, $-C(=O)NHR^{A1}$, $-C(=O)NR^{A1}_2$, pyrrolidino-C(=O)-, piperidino-C(=O)-, morpholino-C(=O)-, piperizino-C(=O)-, and $-R^{A2}$.

61. A compound according to any one of claims 1 to 59, wherein each $-R^{K2}$, if present, is independently saturated aliphatic C_{1-4}alkyl.

62. A compound according to any one of claims 1 to 59, wherein each $-R^{K2}$, if present, is independently aliphatic C_{2-4}alkenyl.

63. A compound according to any one of claims 1 to 59, wherein each $-R^{K2}$, if present, is independently saturated C_{3-6}cycloalkyl.

64. A compound according to any one of claims 1 to 63, wherein each $-R^{A1}$, if present, is independently -Me, -Et, -nPr, -iPr, -nBu, -iBu, -sBu, or -tBu.

65. A compound according to any one of claims 1 to 63, wherein each $-R^{A1}$, if present, is independently -Me.

66. A compound according to any one of claims 1 to 65, wherein each $-R^{A2}$, if present, is independently phenyl or C_{5-6}heteroaryl.

67. A compound according to any one of claims 1 to 65, wherein each $-R^{A2}$, if present, is independently phenyl.

68. A compound according to any one of claims 1 to 67, wherein each $-NR^{K3}R^{K4}$, if present, is independently pyrrolidino, piperidino, morpholino, or piperizino.

69. A compound according to any one of claims 1 to 68, wherein each $-R^{A3}$, if present, is independently saturated aliphatic C_{1-4}alkyl.

70. A compound according to any one of claims 1 to 68, wherein each $-R^{A3}$, if present, is independently -Me, -Et, -nPr, -iPr, -nBu, -iBu, -sBu, or -tBu.

71. A compound according to any one of claims 1 to 68, wherein each $-R^{A3}$, if present, is independently -Me.

72. A compound according to any one of claims 1 to 71, wherein each $-R^{A4}$, if present, is independently -Me, -Et, -nPr, -iPr, -nBu, -iBu, -sBu, or -tBu.

73. A compound according to any one of claims 1 to 71, wherein each $-R^{A4}$, if present, is independently -Me.

74. A compound according to any one of claims 1 to 73, wherein each $-R^{K5}$, if present, is independently saturated aliphatic C_{1-4}alkyl, and is optionally substituted with one or more groups independently selected from: -OH, $-OR^{A5}$, $-NH_2$, $-NHR^{A5}$, and $-NR^{A5}{}_2$.

75. A compound according to any one of claims 1 to 73, wherein each $-R^{K5}$, if present, is independently saturated aliphatic C_{1-4}alkyl.

76. A compound according to any one of claims 1 to 75, wherein each $-R^{A5}$, if present, is independently -Me, -Et, -nPr, -iPr, -nBu, -iBu, -sBu, or -tBu.

77. A compound according to any one of claims 1 to 75, wherein each $-R^{A5}$, if present, is independently -Me.

78. A compound according to any one of claims 1 to 77, wherein each $-R^{K6}$, if present, is independently saturated aliphatic C_{1-4}alkyl, and is optionally substituted with one or more groups independently selected from: -OH, $-OR^{A6}$, $-NH_2$, $-NHR^{A6}$, and $-NR^{A6}{}_2$.

79. A compound according to any one of claims 1 to 77, wherein each $-R^{K6}$, if present, is independently saturated aliphatic C_{1-4}alkyl.

80. A compound according to any one of claims 1 to 79, wherein each $-R^{A6}$, if present, is independently -Me, -Et, -nPr, -iPr, -nBu, -iBu, -sBu, or -tBu.

81. A compound according to any one of claims 1 to 79, wherein each $-R^{A6}$, if present, is independently -Me.

82. A compound according to claim 1, selected from the following compounds and pharmaceutically acceptable salts, hydrates, and solvates thereof:

AA-001, AA-002, AA-003, AA-004, AA-005, AA-006, AA-007, AA-008, AA-009, AA-010, AA-011, AA-012, AA-013, AA-014, AA-015, AA-016, AA-017, AA-018, AA-019, AA-020, AA-021, AA-022, AA-023, AA-024, AA-025, AA-026, AA-027, AA-028, AA-029, AA-030, AA-031, AA-032, AA-033, AA-034, AA-035, AA-036, AA-037, AA-038, AA-039,

AB-001, AB-002, AB-003, AB-004, AB-005, AB-006, AB-007, AB-008, AB-009, AB-010, AB-011, AB-012, AB-013, AB-014, AB-015, AB-016, AB-017, AB-018, AB-019, AB-020, AB-021, AB-022, AB-023, AB-024, AB-025, AB-026, AB-027, AB-028, AB-029, AB-030, AB-031, AB-032, AB-033, AB-034, AB-035, AB-036, AB-037,

AC-001, AC-002, AC-003, AC-004,

AD-001, AD-002, AD-003, AD-004, AD-005, AD-006, AD-007, AD-008, AD-009, AD-010, AD-011, AD-012, AD-013, AD-014, AD-015, AD-016, AD-017,

AE-001, AE-002, AE-003, AE-004, AE-005, AE-006, AE-007, AE-008, AE-009, AE-010, AE-011, AE-012, AE-013, AE-014, AE-015, AE-016, AE-017, AE-018, AE-019, AE-020, AE-021, AE-022, AE-023, AE-024, AE-025, AE-026, AE-027, AE-028, AE-029, AE-030, AE-031, AE-032, AE-033, AE-034,

AF-001,

AG-001, AG-002, AG-003, AG-004, AG-005,

AH-001, AH-002, AH-003, AH-004, AH-005, AH-006, AH-007, AH-008, AH-009, AH-010, AH-011, AH-012, AH-013, AH-014, AH-015, and

AJ-001.

83. A compound according to claim 1, selected from the following compounds and pharmaceutically acceptable salts, hydrates, and solvates thereof:

BB-001, BB-002, BB-003, BB-004, BB-005, BB-006, BB-007, BB-008, BB-009, and BB-010.

84. A compound according to claim 1, selected from the following compounds and pharmaceutically acceptable salts, hydrates, and solvates thereof:

CC-001, CC-002, CC-003, and CC-004.

85. A composition comprising a compound according to any one of claims 1 to 84, and a pharmaceutically acceptable carrier, diluent, or excipient.

86. A method of preparing a composition comprising admixing a compound according to any one of claims 1 to 84 and a pharmaceutically acceptable carrier, diluent, or excipient.

87. A compound as defined in any one of claims 1 to 84, *but without the recited proviso regarding compounds PP-001 to PP-034,* for use in a method of treatment of the human or animal body by therapy.

88. A compound as defined in any one of claims 1 to 84, *but without the recited proviso regarding compounds PP-001 to PP-034,* for use in a method of treatment of:

a disease or condition that is mediated by LIM kinase (LIMK);

a disease or condition that is ameliorated by the inhibition of LIM kinase (LIMK) activity;

a proliferative condition;

cancer;

cancer characterised by, or further characterised by, cancer cells which overexpress LIM kinase (LIMK);

solid tumour cancer;

breast cancer; prostate cancer; melanoma; glioma;

vasodilation; hypertension; angina; cerebral vasospasm; ischemia following subarachnoid hemorrhage;

a neurodegenerative disorder;

atherosclerosis;

fibrosis;

inflammatory disease; Crohn's disease; chronic obstructive pulmonary disease (COPD); or

glaucoma.

89. Use of a compound as defined in any one of claims 1 to 84, *but without the recited proviso regarding compounds PP-001 to PP-034,* in the manufacture of a medicament for the treatment of:

a disease or condition that is mediated by LIM kinase (LIMK);

a disease or condition that is ameliorated by the inhibition of LIM kinase (LIMK) activity;

a proliferative condition;

cancer;

cancer characterised by, or further characterised by, cancer cells which overexpress LIM kinase (LIMK);

solid tumour cancer;

breast cancer; prostate cancer; melanoma; glioma;

vasodilation; hypertension; angina; cerebral vasospasm; ischemia following subarachnoid hemorrhage;

a neurodegenerative disorder;

atherosclerosis;

fibrosis;

inflammatory disease; Crohn's disease; chronic obstructive pulmonary disease (COPD); or

glaucoma.

90. A method of inhibiting LIM kinase (LIMK), *in vitro* or *in vivo,* comprising contacting LIMK with an effective amount of a compound as defined in any one of claims 1 to 84, *but without the recited proviso regarding compounds PP-001 to PP-034.*

91. A method of inhibiting LIM kinase (LIMK) activity in a cell, *in vitro* or *in vivo, comprising contacting the cell with an effective amount of a compound as defined* in any one of claims 1 to 84, *but without the recited proviso regarding compounds PP-001 to PP-034.*

92. A method of regulating cell proliferation, inhibiting cell cycle progression, promoting apoptosis, or a combination of one or more these, *in vitro* or *in vivo,* comprising contacting a cell with an effective amount of a compound as defined in any one of claims 1 to 84, *but without the recited proviso regarding compounds PP-001 to PP-034.*

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2012/000280

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D495/04 A61K31/519 A61P25/00 A61P35/00 A61P29/00 A61P3/00
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/035537 A2 (BOEHRINGER INGELHEIM PHARMA [US]; LIU WEIMIN [US]; HICKEY EUGENE RICHA) 21 April 2005 (2005-04-21) page 46; example 1 -----	1-92

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 June 2012	21/06/2012

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2012/000280

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005035537 A2	21-04-2005	CA 2542008 A1	21-04-2005
		EP 1673374 A2	28-06-2006
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		US 2005101601 A1	12-05-2005
		US 2008008720 A1	10-01-2008
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