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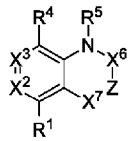
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(54) Title: SMALL MOLECULE STING ANTAGONISTS



(I)

(57) Abstract: The present invention relates to compounds of formula (I). The compounds maybe used to antagonise the Stimulator of Interferon Genes (STING) protein and may thereby treat liver fibrosis, fatty liver disease, non-alcoholic steatohepatitis (NASH), pulmonary fibrosis, lupus, sepsis, rheumatoid arthritis (RA), type I diabetes, STING-associated vasculopathy with onset in infancy (SAVI), Aicardi-Goutieres syndrome (AGS), familial chilblain lupus (FCL), systemic lupus erythematosus (SLE), retinal vasculopathy, neuroinflammation, systemic inflammatory response syndrome, pancreatitis, cardiovascular disease, renal fibrosis, stroke and age-related macular degeneration (AMD).

Small molecule STING antagonists

The present invention relates to small molecule antagonists of the Stimulator of Interferon Genes (STING) protein. Accordingly, the small molecule antagonists may be of use in the treatment of various inflammatory diseases such as fatty liver disease, pulmonary fibrosis, pancreatitis, lupus, and so on. The invention extends to the pharmaceutical compositions of the compounds *per se*, methods of making the compounds and methods of modulating the STING protein using these compounds.

STING (STimulator of INterferon Genes) is an innate signalling molecule that plays a crucial role in mediating an immune response to cytosolic DNA.

The human immune system has evolved to recognize and respond to different types of threats and pathogens to maintain a healthy host. The innate arm of the immune system is mainly responsible for a rapid initial inflammatory response to danger signals associated with cellular or tissue damage from bacteria, viruses and other infectious threats. The innate immune system responds to these damage-associated molecular patterns (DAMPs) or microbial product pathogen-associated molecular patterns (PAMPs) through an array of sentinel proteins called pattern recognition receptors (PRRs) to provide broad and lasting protection to the host against a wide range of threats (P. Broz et. al., *Nat. Revs Immunol.*, **2013**, 13, 551).

The PAMPs and DAMPs are often constituents or replication intermediates of intracellular pathogens. PRRs include Toll-like receptors (TLRs; activated by endosomal nucleic acids), C-type lectin receptors, retinoic acid inducible gene I (RIGI-like receptors; activated by cytosolic RNA), NOD-like receptors (NLRs) and also double stranded DNA sensors (Diebold et. al., *Science*, **2004**, 303, 1529-1531; O. Takeuchi et. al., *Cell*, **2010**, 140, 805; Pichlmair et. al., **2006**, 314, 997). PRRs respond to DAMPs and PAMPs by up-regulating type-1 interferons and cytokines. Free cytosolic nucleic acids (DNA and RNA) are known PAMPs/DAMPs. The main sensor for cytosolic DNA is cGAS (cyclic GMP-AMP synthase). Upon recognition of cytosolic dsDNA, cGAS triggers formation of one specific isomer of the cyclic dinucleotide (CDN) cGAMP, c[G(2',5')pA(3',5')p] (Gao et. al., *Cell*, **2013**, 153, 1094). CDNs are second messenger signalling molecules produced by diverse bacteria and consist of two ribonucleotides that are connected via phosphodiester bonds to make a cyclic structure. CDNs cyclo-di(GMP) (c-diGMP), cyclo-di(AMP) (c-diAMP) and hybrid cyclo-(AMP/GMP) (cGAMP) derivatives (A. Ablasser et. al., *Nature*, **2013**, 498, 380) all bind strongly to the

ER-transmembrane adaptor protein STING (D.L. Burdette et. al., *Nature*, **2011**, 478, 515; H. Ishikawa, *Nature*, **2008**, 455, 674).

STING recognises CDNs through its cytosolic carboxy-terminal domain, which forms a homodimer and adopts a V-shaped binding pocket to bind CDNs (Zhang et. al., *Mol. Cell*, **2013**, 51, 226; G. N. Barber et. al., *Nat. Immunol.*, **2011**, 12, 929). Ligand-induced activation of STING triggers its relocation to the Golgi and a conformational change to facilitate binding to TBK1. TBK1 in turn signals through the transcription factors IRF-3, STAT6 and NF_KB to induce type-I interferons and other cytokines and interferon-stimulated genes (C. Greenhill, *Nat. Revs., Endocrinol.*, **2018**, 14, 192; Y. Li, H.L. Wilson, and E. Kiss-Toth, *J. Inflamm.*, **2017**, 14, 11). Following its activation, STING is rapidly degraded in the normal response.

Excessive activation of STING is associated with a range of monogenic autoinflammatory disorders referred to as interferonopathies (Y.J. Crow and N. Manel, *Nat. Revs. Immunol.*, **2015**, 15, 429-440). Loss of function mutations in the human DNAse Trex1 are associated with elevated levels of cGAMP and autoimmune diseases such as the rare but severe inflammatory disease Aicardi-Goutieres syndrome (AGS), familial chilblain lupus (FCL), systemic lupus erythematosus (SLE) and retinal vasculopathy (Y. Crow et. al., *Hum. Mol. Gen.*, **2009**, 18, R130).

Inhalation of silica particles can result in lung inflammation and pulmonary fibrosis, triggered by lung cell death and release of dsDNA products. Benmerzoug *et. al.* have reported that this increase in circulating dsDNA activates STING and via increased levels of CXCL10 and IFN signalling produces lung inflammation (S. Benmerzoug et. al., *Nat. Comm.*, **2018**, 9, 5226).

Increased cytosolic dsDNA was detected in fibroblast-like synoviocytes (FLS) taken from rheumatoid arthritis (RA) patients with the levels of dsDNA correlating with the severity of rheumatoid synovitis (J. Wang et. al., *Int. Immunopharm.*, **2019**, 76, 105791). These findings indicated that increased dsDNA promoted an inflammatory response via the STING pathway in RA FLS and led to increased expression of STING, suggesting that cytosolic DNA accumulation is an important factor in RA-related inflammation.

Patients with autosomal dominant gain of function mutations in STING have a pediatric autoinflammatory condition called SAVI (STING-associated vasculopathy with onset in infancy), manifest clinically as skin rash, vasculopathy, lupus-like syndromes and pulmonary

fibrosis characterised by aberrant IFN production and systemic inflammation that are associated with high morbidity and mortality (N. Konig, et. al., *Ann. Rheum., Dis.*, **2017**, 76, 468). Characterised mutations in humans include V147L, N154S, V155M and G166E which are all located at the interfacial region between the trans-membrane domain and the ligand binding domain and result in ligand-independent constitutively activated protein. More recently, three other gain of function STING mutations C206Y, R281Q and R284S have been identified at a cluster region that is proposed to promote STING aggregation and disfavour complexation to the C-terminal tail region (H. Konno, et. al., *Cell Rep.* **2018**, 23, 1112 and I. Melki, et. al., J Allergy Clin Immunol. **2017**, 140(2), 543.

A recent report by Habtezion et al. has shown that in mice with acute pancreatitis, STING responds to acinar cell death by detecting DNA from necrotic cells and promotes acute pancreatic inflammation (A. Habtezion et. al., *Gastroenterology*, **2018**, *154*, 1822). STING-knockout mice had less severe acute pancreatitis (less edema, less inflammation) while administering a STING agonist resulted in more severe pancreatitis.

Luo et al. have also shown recently that levels of STING were increased in liver tissues from patients with non-alcoholic fatty liver disease and in mice with a high-fat diet induced hepatic steatosis. Once again, STING-knockout mice developed less severe liver fibrosis and a less acute inflammatory response (X. Luo et.al., *Gastroenterology*, **2018**, *155*, 1971). Elevated cGAMP levels in the peripheral blood mononuclear cells of SLE patients was associated with higher disease scores (J. An et. al., *Arthritis Rheum.*, **2017**, 69, 800) suggesting a link between disease severity in lupus and activation of the STING pathway.

The kidney tubule cells of subjects with fibrosis have been shown to lack mitochondrial transcription factor A (TFAM). Mice lacking tubule TFAM developed severe mitochondrial loss and energy deficit caused by aberrant packaging of mitochondrial DNA and its translocation to the cytosol, where the STING pathway was activated (K.W. Chung, *Cell Metab.*, **2019**, 30, 1). The ensuing cytokine expression and inflammation led to renal fibrosis.

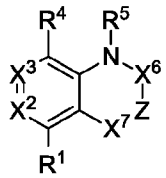
Bennion et. al. have demonstrated that the gain of function mutation N153S knock-in mice showed enhanced susceptibility to viral infection and responded to infection by a murine gamma herpesvirus γHV68 with severe autoinflammation and pulmonary fibrosis (B. Bennion *et. al.*, *J. Virol.*, **2019**, 93, e01806).

Other conditions where excessive immune system activation may be linked to STING pathway activation include systemic inflammatory response syndrome (R.K. Boyapati et. al., *F1000 Res.*, **2017**, 6, 169), cardiovascular disease (K.R. King et. al., *Nat. Med.*, **2017**, 23, 1481), stroke (A.M. Jeffries et. al., *Neurosci. Lett.*, **2017**, 658, 53) and age-related macular degeneration (N. Kerur et. al., *Nat. Med.*, **2018**, 24, 50).

There is therefore a compelling body of evidence that blocking, inhibiting or antagonising the STING pathway could have therapeutic benefit in a number of conditions and disease states. There have been few small molecule antagonists of the STING protein reported, for example by T. Siu et al. (*ACS Med Chem Letts*, **2019**, 10(1), 92) but the compounds described therein reportedly have low cell-based potency. Other reports of STING antagonists include S. Haag et al. (*Nature*, **2018**, 559(7713), 269) and Z. Hong et al. (*PNAS*, 2021, 118(24), e2105465118).

There is therefore a pressing need for improved small molecule blockers of the STING pathway, and in particular for small molecule direct antagonists of the STING protein.
The present invention has arisen from the inventors work in attempting to identify STING protein modulators.

In accordance with a first aspect of the invention, there is provided a compound of formula (**I**):



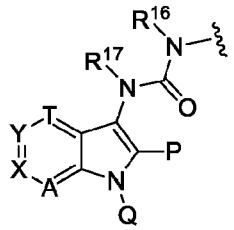
(**I**)

, wherein X^2 is CR^2 and X^3 is CR^3 or N; or X^2 is N and X^3 is CR^3;
X^6 is C=O or CR^7R^8;
Z is CR^9R^{10} or NR^9;
X^7 is S, SO, SO_2, O, NR^{11} or $CR^{11}R^{12}$;
wherein, when Z is CR^9R^{10} then X^7 is S, SO, SO_2, O or NR^{11}, and when Z is NR^9 then X^7 is $CR^{11}R^{12}$;
R^1, R^4, R^7 and R^8 are each independently selected from the group consisting of H, halogen, OR^{13}, CN, $COOR^{13}$, $CONR^{13}R^{14}$, $NR^{13}R^{14}$, $NR^{13}COR^{14}$, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 alkylsulfonyl, optionally substituted mono or bicyclic C_3-C_6 cycloalkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, mono or

bicyclic optionally substituted C_6-C_{12} aryl, mono or bicyclic optionally substituted 5 to 10 membered heteroaryl and optionally substituted mono or bicyclic 3 to 8 membered heterocycle;

R^9 to R^{12} are each independently selected from the group consisting of H, halogen, OR^{13}, CN, $COOR^{13}$, $CONR^{13}R^{14}$, $NR^{13}R^{14}$, $NR^{13}COR^{14}$, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl or optionally substituted C_2-C_6 alkynyl;

one of R^2 and R^3 is:



and, when X^2 is CR^2 and X^3 is CR^3, the other of R^2 and R^3 is selected from the group consisting of H, halogen, OR^{13}, CN, $COOR^{13}$, $CONR^{13}R^{14}$, $NR^{13}R^{14}$, $NR^{13}COR^{14}$, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 alkylsulfonyl, optionally substituted mono or bicyclic C_3-C_6 cycloalkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, mono or bicyclic optionally substituted C_6-C_{12} aryl, mono or bicyclic optionally substituted 5 to 10 membered heteroaryl and optionally substituted mono or bicyclic 3 to 8 membered heterocycle;

A is CR^{19} or N;

X is CR^{20} or N;

Y is CR^{21} or N;

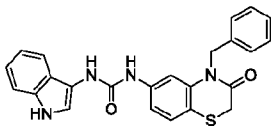
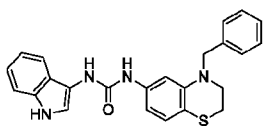
T is CR^{22} or N;

Q is H or optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, $COOR^{13}$, COR^{13} or $CONR^{13}R^{14}$;

P is selected from the group consisting of H, halogen, OR^{13}, CN, $COOR^{13}$, $CONR^{13}R^{14}$, $NR^{13}R^{14}$, $NR^{13}COR^{14}$, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted mono or bicyclic C_3-C_6 cycloalkyl, mono or bicyclic optionally substituted C_6-C_{12} aryl, mono or bicyclic optionally substituted 5 to 10 membered heteroaryl and optionally substituted mono or bicyclic 3 to 8 membered heterocycle;

R^5 is selected from the group consisting of $COOR^{13}$, $CONR^{13}R^{14}$, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 alkylsulfonyl, optionally substituted mono or bicyclic C_3-C_6 cycloalkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, mono or bicyclic optionally substituted C_6-C_{12} aryl, mono or bicyclic optionally substituted 5 to 10 membered heteroaryl, optionally substituted mono or bicyclic 3 to 8 membered heterocycle and L^1-L^2-R^{15};

R^{13} and R^{14} are each independently selected from the group consisting of H, halogen, OH, CN, COOH, $CONH_2$, NH_2, NHCOH, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 alkylsulfonyl, optionally substituted mono or bicyclic C_3-C_6 cycloalkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted C_1-C_6 alkoxy, optionally substituted C_1-C_6 alkoxycarbonyl group, mono or bicyclic optionally substituted C_6-C_{12} aryl, mono or bicyclic optionally substituted 5 to 10 membered heteroaryl, optionally substituted mono or bicyclic 3 to 8 membered heterocycle, optionally substituted aryloxy, optionally substituted heteroaryloxy and optionally substituted heterocyclyloxy;
L^1 is absent or an optionally substituted C_1-C_6 alkylene, an optionally substituted C_2-C_6 alkenylene, an optionally substituted C_2-C_6 alkynylene, O, S, S=O, SO_2 or NR^{18};
L^2 is absent or an optionally substituted C_1-C_6 alkylene, an optionally substituted C_2-C_6 alkenylene, an optionally substituted C_2-C_6 alkynylene, O, S, S=O, SO_2 or NR^{18};
R^{15} is optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted mono or bicyclic C_3-C_6 cycloalkyl, mono or bicyclic optionally substituted C_6-C_{12} aryl, mono or bicyclic optionally substituted 5 to 10 membered heteroaryl or optionally substituted mono or bicyclic 3 to 8 membered heterocycle; and
R^{16} to R^{18} are independently H, an optionally substituted C_1-C_6 alkyl, an optionally substituted C_2-C_6 alkenyl, an optionally substituted C_2-C_6 alkynyl or CN;
R^{19} to R^{22} are independently H, halogen, OR^{13}, CN, $COOR^{13}$, $CONR^{13}R^{14}$, $NR^{13}R^{14}$, $NR^{13}COR^{14}$, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted mono or bicyclic C_3-C_6 cycloalkyl, mono or bicyclic optionally substituted C_6-C_{12} aryl, mono or bicyclic optionally substituted 5 to 10 membered heteroaryl and optionally substituted mono or bicyclic 3 to 8 membered heterocycle;
or a pharmaceutically acceptable complex, salt, solvate, tautomeric form or polymorphic form thereof;

wherein the compound is not  or .

The compounds of formula (**I**) may be used as a medicament.

Hence, in a second aspect, there is provided a compound of formula (**I**), or a pharmaceutically acceptable complex, salt, solvate, tautomeric form or polymorphic form thereof, for use as a medicament.

The inventors have found that compounds of formula (**I**) are useful in modulating the STimulator of INterferon Genes (STING) protein.

Hence, in a third aspect, there is provided a compound of formula (**I**), or a pharmaceutically acceptable complex, salt, solvate, tautomeric form or polymorphic form thereof, for use in modulating the STimulator of INterferon Genes (STING) protein.

Preferably, the compound of formula (**I**) is for use in inhibiting, or inactivating, the STING protein. The compound of formula (**I**) may be for use in inhibiting, or inactivating, STING functional activity as evidenced by a reduction of one or more biological effects selected from the group consisting of cellular interferon β production, cellular levels of interferon-stimulated genes, production of cytokines and phosphorylation of the transcription factors IRF-3 and NF-κB.

By inhibiting the STING protein, it is possible to treat, ameliorate or prevent liver fibrosis, fatty liver disease, pulmonary fibrosis, lupus, rheumatoid arthritis (RA), STING-associated vasculopathy with onset in infancy (SAVI), pancreatitis, cardiovascular disease, non-alcoholic fatty liver disease and renal fibrosis.

By inhibiting the STING protein, it is possible to treat, ameliorate or prevent liver fibrosis, fatty liver disease, non-alcoholic steatohepatitis (NASH), pulmonary fibrosis, lupus, rheumatoid arthritis (RA), STING-associated vasculopathy with onset in infancy (SAVI), Aicardi-Goutieres syndrome (AGS), familial chilblain lupus (FCL), systemic lupus erythematosus (SLE), retinal vasculopathy, neuroinflammation, systemic inflammatory response syndrome, pancreatitis, cardiovascular disease, renal fibrosis, stroke and age-related macular degeneration (AMD).

Accordingly, in a fourth aspect there is provided a compound of formula (**I**), or a pharmaceutically acceptable complex, salt, solvate, tautomeric form or polymorphic form thereof, for use in treating, ameliorating or preventing a disease selected from liver fibrosis, fatty liver disease, non-alcoholic steatohepatitis (NASH), pulmonary fibrosis, lupus, sepsis, rheumatoid arthritis (RA), type I diabetes, STING-associated vasculopathy with onset in infancy (SAVI), Aicardi-Goutieres syndrome (AGS), familial chilblain lupus (FCL), systemic lupus erythematosus (SLE), retinal vasculopathy, neuroinflammation, systemic inflammatory response syndrome, pancreatitis, cardiovascular disease, renal fibrosis, stroke and age-related macular degeneration (AMD).

In a fifth aspect, there is provided a method of modulating the STING protein in a subject, the method comprising administering, to a subject in need of such treatment, a

therapeutically effective amount of a compound of formula (**I**), or a pharmaceutically acceptable complex, salt, solvate, tautomeric form or polymorphic form thereof.

Preferably, the method comprises inhibiting the STING protein.

Preferably, the method is a method of inhibiting, or inactivating, the STING protein.

In a sixth aspect, there is provided a method of treating, ameliorating or preventing a disease selected from liver fibrosis, fatty liver disease, non-alcoholic steatohepatitis (NASH), pulmonary fibrosis, lupus, sepsis, rheumatoid arthritis (RA), type I diabetes, STING-associated vasculopathy with onset in infancy (SAVI), Aicardi-Goutieres syndrome (AGS), familial chilblain lupus (FCL), systemic lupus erythematosus (SLE), retinal vasculopathy, neuroinflammation, systemic inflammatory response syndrome, pancreatitis, cardiovascular disease, renal fibrosis, stroke and age-related macular degeneration (AMD); the method comprising administering, to a subject in need of such treatment, a therapeutically effective amount of a compound of formula (**I**), or a pharmaceutically acceptable complex, salt, solvate, tautomeric form or polymorphic form thereof.

It may be appreciated that the term "preventing" can mean "reducing the likelihood of". In one preferred embodiment, the disease is fibrosis. The fibrosis may be selected from the group consisting of liver fibrosis, pulmonary fibrosis or renal fibrosis. In some embodiments, the fibrosis patient may have upregulated STING expression and /or STING activity in a tissue compared to that of a healthy subject.

In an alternative preferred embodiment, the disease is fatty liver disease. The fatty liver disease may be non-alcoholic (or simple) fatty liver or non-alcoholic steatohepatitis (NASH).

The following definitions are used in connection with the compounds of the present invention unless the context indicates otherwise.

Throughout the description and the claims of this specification the word "comprise" and other forms of the word, such as "comprising" and "comprises," means including but not limited to, and is not intended to exclude for example, other additives, components, integers, or steps.

As used in the description 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 composition" includes mixtures of two or more such compositions.

"Optional" or "optionally" means that the subsequently described event, operation or circumstances can or cannot occur, and that the description includes instances where the event, operation or circumstance occurs and instances where it does not.

The term "alkyl" as used herein, unless otherwise specified, refers to a saturated straight or branched hydrocarbon. In certain embodiments, the alkyl group is a primary, secondary, or tertiary hydrocarbon. In certain embodiments, the alkyl group includes one to six carbon atoms, *i.e.* C_1-C_6 alkyl. C_1-C_6 alkyl includes for example methyl, ethyl, n-propyl (1-propyl) and isopropyl (2-propyl, 1-methylethyl), butyl, pentyl, hexyl, *iso*butyl, *sec*-butyl, *tert*-butyl, *iso*pentyl, *neo*pentyl and *iso*hexyl. An alkyl group can be unsubstituted or substituted with one or more of halogen, OH, optionally substituted C_1-C_6 alkoxy, CN, oxo, $C(O)R^{23}$, $COOR^{23}$, $OC(O)R^{23}$, $CONR^{23}R^{24}$, $NR^{23}R^{24}$, $NR^{23}C(O)R^{24}$, $=NOR^{23}$, SR^{23}, SO_2R^{23}, OSO_2R^{23}, $SO_2NR^{23}R^{24}$, $OP(O)(OR^{23})(OR^{24})$, optionally substituted C_6-C_{12} aryl, optionally substituted 5 to 10 membered heteroaryl, optionally substituted C_3-C_6 cycloalkyl and optionally substituted 3 to 8 membered heterocycle. Accordingly, it will be appreciated that an optionally substituted C_1-C_6 alkyl may be an optionally substituted C_1-C_6 haloalkyl, *i.e.* a C_1-C_6 alkyl substituted with at least one halogen, and optionally further substituted with one or more of OH, optionally substituted C_1-C_6 alkoxy, CN, oxo, $C(O)R^{23}$, $COOR^{23}$, $OC(O)R^{23}$, $CONR^{23}R^{24}$, $NR^{23}R^{24}$, $NR^{23}C(O)R^{24}$, $=NOR^{23}$, SR^{23}, SO_2R^{23}, OSO_2R^{23}, $SO_2NR^{23}R^{24}$, $OP(O)(OR^{23})(OR^{24})$, optionally substituted C_6-C_{12} aryl, optionally substituted 5 to 10 membered heteroaryl, optionally substituted C_3-C_6 cycloalkyl and optionally substituted 3 to 8 membered heterocycle. The optionally substituted C_1-C_6 alkyl may be a polyfluoroalkyl, preferably a C_1-C_3 polyfluoroalkyl.

R^{23} and R^{24} may each independently be selected from the group consisting of H, halogen, OH, CN, COOH, $CONH_2$, NH_2, NHCOH, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 alkylsulfonyl, optionally substituted mono or bicyclic C_3-C_6 cycloalkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted C_1-C_6 alkoxy, optionally substituted C_1-C_6 alkoxycarbonyl group, mono or bicyclic optionally substituted C_6-C_{12} aryl, mono or bicyclic optionally substituted 5 to 10 membered heteroaryl, optionally substituted mono or bicyclic 3 to 8 membered heterocycle, optionally substituted aryloxy, optionally substituted heteroaryloxy and optionally substituted

heterocyclyloxy. R^{23} and R^{24} may each independently be selected from the group consisting of H and halogen.

The term "alkylene", as used herein, unless otherwise specified, refers to a bivalent saturated straight or branched hydrocarbon. In certain embodiments, the alkylene group is a primary, secondary, or tertiary hydrocarbon. In certain embodiments, the alkylene group includes one to six carbon atoms, *i.e.* C_1-C_6 alkylene. C_1-C_6 alkylene includes for example methylene, ethylene, n-propylene and isopropylene, butylene, pentylene, hexylene, *iso*butylene, *sec*-butylene, *tert*-butylene, *iso*pentylene, *neo*pentylene, and *iso*hexylene. An alkylene group can be unsubstituted or substituted with one or more of optionally substituted C_1-C_6 alkyl, halogen, OH, optionally substituted C_1-C_6 alkoxy, CN, oxo, $C(O)R^{23}$, $COOR^{23}$, $OC(O)R^{23}$, $CONR^{23}R^{24}$, $NR^{23}R^{24}$, $NR^{23}C(O)R^{24}$, $=NOR^{23}$, SR^{23}, SO_2R^{23}, OSO_2R^{23}, $SO_2NR^{23}R^{24}$, $OP(O)(OR^{23})(OR^{24})$, optionally substituted C_6-C_{12} aryl, optionally substituted 5 to 10 membered heteroaryl, optionally substituted C_3-C_6 cycloalkyl and optionally substituted 3 to 8 membered heterocycle. Accordingly, it will be appreciated that an optionally substituted C_1-C_6 alkylene may be an optionally substituted C_1-C_6 haloalkylene, *i.e.* a C_1-C_6 alkylene substituted with at least one halogen, and optionally further substituted with one or more of optionally substituted C_1-C_6 alkyl, OH, optionally substituted C_1-C_6 alkoxy, CN, oxo, $C(O)R^{23}$, $COOR^{23}$, $OC(O)R^{23}$, $CONR^{23}R^{24}$, $NR^{23}R^{24}$, $NR^{23}C(O)R^{24}$, $=NOR^{23}$, SR^{23}, SO_2R^{23}, OSO_2R^{23}, $SO_2NR^{23}R^{24}$, $OP(O)(OR^{23})(OR^{24})$, optionally substituted C_6-C_{12} aryl, optionally substituted 5 to 10 membered heteroaryl, optionally substituted C_3-C_6 cycloalkyl and optionally substituted 3 to 8 membered heterocycle. It will be appreciated that an optionally substituted C_1-C_6 alkylene may be an optionally substituted polyfluoroalkylene, preferably a C_1-C_3 polyfluoroalkylene. R^{23} and R^{24} may be as defined above. R^{23} and R^{24} may each independently be selected from the group consisting of H, halogen and optionally substituted C_1-C_6 alkyl.

The term "halo" or "halogen" includes fluoro (-F), chloro (-Cl), bromo (-Br) and iodo (-I). The term "polyfluoroalkyl" may denote a C_1-C_3 alkyl group in which two or more hydrogen atoms are replaced by fluorine atoms. The term may include perfluoroalkyl groups, *i.e.* a C_1-C_3 alkyl group in which all the hydrogen atoms are replaced by fluorine atoms. Accordingly, the term C_1-C_3 polyfluoroalkyl includes, but is not limited to, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, 3,3,3-trifluoropropyl, 2,2,3,3,3-pentafluoropropyl, and 2,2,2-trifluoro-1-(trifluoromethyl)ethyl.

"Alkoxy" refers to the group R^{22}-O-, where R^{22} is an optionally substituted C_1-C_6 alkyl group, an optionally substituted C_3-C_6 cycloalkyl group, an optionally substituted C_2-C_6 alkenyl or

an optionally substituted C_2-C_6 alkynyl. Exemplary C_1-C_6 alkoxy groups include but are not limited to methoxy, ethoxy, n-propoxy (1-propoxy), n-butoxy and *tert*-butoxy. An alkoxy group can be unsubstituted or substituted with one or more of halogen, OH, CN, oxo, $C(O)R^{23}$, $COOR^{23}$, $OC(O)R^{23}$, $CONR^{23}R^{24}$, $NR^{23}R^{24}$, $NR^{23}C(O)R^{24}$, $=NOR^{23}$, SR^{23}, SO_2R^{23}, OSO_2R^{23}, $SO_2NR^{23}R^{24}$, $OP(O)(OR^{23})(OR^{24})$, optionally substituted C_6-C_{12} aryl, optionally substituted 5 to 10 membered heteroaryl, optionally substituted C_3-C_6 cycloalkyl and optionally substituted 3 to 8 membered heterocycle. R^{23} and R^{24} may be as defined above. R^{23} and R^{24} may each independently be selected from the group consisting of H, halogen and optionally substituted C_1-C_6 alkyl.

"Aryl" refers to an aromatic 6 to 12 membered hydrocarbon group. The term includes bicyclic groups where one of the rings is aromatic and the other is not. Examples of a C_6-C_{12} aryl group include, but are not limited to, phenyl, α-naphthyl, β-naphthyl, biphenyl, tetrahydronaphthyl and indanyl. An aryl group can be unsubstituted or substituted with one or more of optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted C_1-C_6 alkoxy, halogen, OH, CN, oxo, $C(O)R^{23}$, $COOR^{23}$, $OC(O)R^{23}$, $CONR^{23}R^{24}$, $NR^{23}R^{24}$, $NR^{23}C(O)R^{24}$, $=NOR^{23}$, SR^{23}, SO_2R^{23}, OSO_2R^{23}, $SO_2NR^{23}R^{24}$, $OP(O)(OR^{23})(OR^{24})$, optionally substituted C_6-C_{12} aryl, optionally substituted 5 to 10 membered heteroaryl, optionally substituted C_3-C_6 cycloalkyl and optionally substituted 3 to 8 membered heterocycle. R^{23} and R^{24} may be as defined above. R^{23} and R^{24} may each independently be selected from the group consisting of H, halogen and optionally substituted C_1-C_6 alkyl.

The term "bicycle" or "bicyclic" as used herein refers to a molecule that features two fused rings, which rings are a cycloalkyl, heterocyclyl, or heteroaryl. In one embodiment, the rings are fused across a bond between two atoms. The bicyclic moiety formed therefrom shares a bond between the rings. In another embodiment, the bicyclic moiety is formed by the fusion of two rings across a sequence of atoms of the rings to form a bridgehead. Similarly, a "bridge" is an unbranched chain of one or more atoms connecting two bridgeheads in a polycyclic compound. In another embodiment, the bicyclic molecule is a "spiro" or "spirocyclic" moiety. The spirocyclic group may be a C_3-C_6 cycloalkyl or a mono or bicyclic 3 to 8 membered heterocycle which is bound through a single carbon atom of the spirocyclic moiety to a single carbon atom of a carbocyclic or heterocyclic moiety. In one embodiment, the spirocyclic group is a cycloalkyl and is bound to another cycloalkyl. In another embodiment, the spirocyclic group is a cycloalkyl and is bound to a heterocyclyl. In a further embodiment, the spirocyclic group is a heterocyclyl and is bound to another heterocyclyl. In still another embodiment, the spirocyclic group is a heterocyclyl and is

bound to a cycloalkyl. A spirocyclic group can be unsubstituted or substituted with one or more of optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted C_1-C_6 alkoxy, halogen, OH, CN, oxo, $C(O)R^{23}$, $COOR^{23}$, $OC(O)R^{23}$, $CONR^{23}R^{24}$, $NR^{23}R^{24}$, $NR^{23}C(O)R^{24}$, $=NOR^{23}$, SR^{23}, SO_2R^{23}, OSO_2R^{23}, $SO_2NR^{23}R^{24}$, $OP(O)(OR^{23})(OR^{24})$, optionally substituted C_6-C_{12} aryl, optionally substituted 5 to 10 membered heteroaryl, optionally substituted C_3-C_6 cycloalkyl and optionally substituted 3 to 8 membered heterocycle. R^{23} and R^{24} may be as defined above. R^{23} and R^{24} may each independently be selected from the group consisting of H, halogen and optionally substituted C_1-C_6 alkyl.

"Cycloalkyl" refers to a non-aromatic, saturated, partially saturated, monocyclic, bicyclic or polycyclic hydrocarbon 3 to 6 membered ring system. Representative examples of a C_3-C_6 cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl. A cycloalkyl group can be unsubstituted or substituted with one or more of optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted C_1-C_6 alkoxy, halogen, OH, CN, oxo, $C(O)R^{23}$, $COOR^{23}$, $OC(O)R^{23}$, $CONR^{23}R^{24}$, $NR^{23}R^{24}$, $NR^{23}C(O)R^{24}$, $=NOR^{23}$, SR^{23}, SO_2R^{23}, OSO_2R^{23}, $SO_2NR^{23}R^{24}$, $OP(O)(OR^{23})(OR^{24})$, optionally substituted C_6-C_{12} aryl, optionally substituted 5 to 10 membered heteroaryl, optionally substituted C_3-C_6 cycloalkyl and optionally substituted 3 to 8 membered heterocycle. R^{23} and R^{24} may be as defined above. R^{23} and R^{24} may each independently be selected from the group consisting of H, halogen and optionally substituted C_1-C_6 alkyl.

"Heteroaryl" refers to a monocyclic or bicyclic aromatic 5 to 10 membered ring system in which at least one ring atom is a heteroatom. The term includes bicyclic groups where one of the rings is aromatic and the other is not. The or each heteroatom may be independently selected from the group consisting of oxygen, sulfur and nitrogen. Examples of 5 to 10 membered heteroaryl groups include furan, thiophene, indole, azaindole, oxazole, thiazole, isoxazole, isothiazole, imidazole, N-methylimidazole, pyridine, pyrimidine, pyrazine, pyrrole, N-methylpyrrole, pyrazole, N-methylpyrazole, 1,3,4-oxadiazole, 1,2,4-triazole, 1- methyl-1,2,4-triazole, 1H-tetrazole, 1-methyltetrazole, benzoxazole, benzothiazole, benzofuran, benzisoxazole, benzimidazole, N-methylbenzimidazole, azabenzimidazole, indazole, quinazoline, quinoline, and isoquinoline. Bicyclic 5 to 10 membered heteroaryl groups include those where a phenyl, pyridine, pyrimidine, pyrazine or pyridazine ring is fused to a 5 or 6-membered monocyclic heteroaryl ring. A heteroaryl group can be unsubstituted or substituted with one or more of optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted C_1-C_6 alkoxy, halogen,

OH, CN, oxo, $C(O)R^{23}$, $COOR^{23}$, $OC(O)R^{23}$, $CONR^{23}R^{24}$, $NR^{23}R^{24}$, $NR^{23}C(O)R^{24}$, $=NOR^{23}$, SR^{23}, SO_2R^{23}, OSO_2R^{23}, $SO_2NR^{23}R^{24}$, $OP(O)(OR^{23})(OR^{24})$, optionally substituted C_6-C_{12} aryl, optionally substituted 5 to 10 membered heteroaryl, optionally substituted C_3-C_6 cycloalkyl and optionally substituted 3 to 8 membered heterocycle. R^{23} and R^{24} may be as defined above. R^{23} and R^{24} may each independently be selected from the group consisting of H, halogen and optionally substituted C_1-C_6 alkyl.

"Heterocycle" or "heterocyclyl" refers to 3 to 8 membered monocyclic, bicyclic or bridged molecules in which at least one ring atom is a heteroatom. The or each heteroatom may be independently selected from the group consisting of oxygen, sulfur and nitrogen. A heterocycle may be saturated or partially saturated. Exemplary 3 to 8 membered heterocycle groups include but are not limited to aziridine, oxirane, oxirene, thiirane, pyrroline, pyrrolidine, dihydrofuran, tetrahydrofuran, dihydrothiophene, tetrahydrothiophene, dithiolane, piperidine, 1,2,3,6-tetrahydropyridine-1-yl, tetrahydropyran, pyran, morpholine, piperazine, thiane, thiine, piperazine, azepane, diazepane and oxazine. A heterocycle group can be unsubstituted or substituted with one or more of optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted C_1-C_6 alkoxy, halogen, OH, CN, oxo, $C(O)R^{23}$, $COOR^{23}$, $OC(O)R^{23}$, $CONR^{23}R^{24}$, $NR^{23}R^{24}$, $NR^{23}C(O)R^{24}$, $=NOR^{23}$, SR^{23}, SO_2R^{23}, OSO_2R^{23}, $SO_2NR^{23}R^{24}$, $OP(O)(OR^{23})(OR^{24})$, optionally substituted C_6-C_{12} aryl, optionally substituted 5 to 10 membered heteroaryl, optionally substituted C_3-C_6 cycloalkyl and optionally substituted 3 to 8 membered heterocycle. R^{23} and R^{24} may be as defined above. R^{23} and R^{24} may each independently be selected from the group consisting of H, halogen and optionally substituted C_1-C_6 alkyl.

"Alkenyl" refers to an olefinically unsaturated hydrocarbon groups which can be unbranched or branched. In certain embodiments, the alkenyl group has 2 to 6 carbons, *i.e.* it is a C_2-C_6 alkenyl. C_2-C_6 alkenyl includes for example vinyl, allyl, propenyl, butenyl, pentenyl and hexenyl. An alkenyl group can be unsubstituted or substituted with one or more of optionally substituted C_2-C_6 alkynyl, optionally substituted C_1-C_6 alkoxy, halogen, OH, CN, oxo, $C(O)R^{23}$, $COOR^{23}$, $OC(O)R^{23}$, $CONR^{23}R^{24}$, $NR^{23}R^{24}$, $NR^{23}C(O)R^{24}$, $=NOR^{23}$, SR^{23}, SO_2R^{23}, OSO_2R^{23}, $SO_2NR^{23}R^{24}$, $OP(O)(OR^{23})(OR^{24})$, optionally substituted C_6-C_{12} aryl, optionally substituted 5 to 10 membered heteroaryl, optionally substituted C_3-C_6 cycloalkyl and optionally substituted 3 to 8 membered heterocycle. R^{23} and R^{24} may be as defined above. R^{23} and R^{24} may each independently be selected from the group consisting of H, halogen and optionally substituted C_1-C_6 alkyl.

"Alkynyl" refers to an acetylenically unsaturated hydrocarbon groups which can be unbranched or branched. In certain embodiments, the alkynyl group has 2 to 6 carbons, *i.e.* it is a C_2-C_6 alkynyl. C_2-C_6 alkynyl includes for example propargyl, propynyl, butynyl, pentynyl and hexynyl. An alkynyl group can be unsubstituted or substituted with one or more of optionally substituted C_2-C_6 alkenyl, optionally substituted C_1-C_6 alkoxy, halogen, OH, CN, oxo, $C(O)R^{23}$, $COOR^{23}$, $OC(O)R^{23}$, $CONR^{23}R^{24}$, $NR^{23}R^{24}$, $NR^{23}C(O)R^{24}$, $=NOR^{23}$, SR^{23}, SO_2R^{23}, OSO_2R^{23}, $SO_2NR^{23}R^{24}$, $OP(O)(OR^{23})(OR^{24})$, optionally substituted C_6-C_{12} aryl, optionally substituted 5 to 10 membered heteroaryl, optionally substituted C_3-C_6 cycloalkyl and optionally substituted 3 to 8 membered heterocycle. R^{23} and R^{24} may be as defined above. R^{23} and R^{24} may each independently be selected from the group consisting of H, halogen and optionally substituted C_1-C_6 alkyl.

The term "alkenylene", as used herein, unless otherwise specified, refers to a bivalent olefinically unsaturated straight or branched hydrocarbon. An alkenylene group may be as defined above in relation the alkenyl group, but with a hydrogen atom removed therefrom to cause the group to be bivalent.

The term "alkynylene", as used herein, unless otherwise specified, refers to a bivalent acetylenically unsaturated straight or branched hydrocarbon. An alkynylene group may be as defined above in relation the alkynyl group, but with a hydrogen atom removed therefrom to cause the group to be bivalent.

"Alkylsulfonyl" refers to the group alkyl-SO_2- where alkyl is an optionally substituted C_1-C_6 alkyl, and is as defined as above.

"Alkoxycarbonyl" refers to the group alkyl-O-C(O)-, where alkyl is an optionally substituted C_1-C_6 alkyl. An alkoxycarbonyl group can be unsubstituted or substituted with one or more of optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted C_1-C_6 alkoxy, halogen, OH, CN, oxo, $C(O)R^{23}$, $COOR^{23}$, $OC(O)R^{23}$, $CONR^{23}R^{24}$, $NR^{23}R^{24}$, $NR^{23}C(O)R^{24}$, $=NOR^{23}$, SR^{23}, SO_2R^{23}, OSO_2R^{23}, $SO_2NR^{23}R^{24}$, $OP(O)(OR^{23})(OR^{24})$, optionally substituted C_6-C_{12} aryl, optionally substituted 5 to 10 membered heteroaryl, optionally substituted C_3-C_6 cycloalkyl and optionally substituted 3 to 8 membered heterocycle.

"Aryloxy" refers to the group Ar-O- where Ar is a mono or bicyclic optionally substituted C_6-C_{12} aryl group, as defined above.

"Heteroaryloxy" refers to the group heteroaryl-O- where the heteroaryl is a mono or bicyclic optionally substituted 5 to 10 membered heteroaryl, and is as defined above.

"Heterocyclyloxy" refers to the group heterocycle-O- where heterocycle is an optionally substituted mono or bicyclic 3 to 8 membered heterocycle, and is as defined as above.

A complex of the compound of formula (**I**) may be understood to be a multi-component complex, wherein the drug and at least one other component are present in stoichiometric or non-stoichiometric amounts. The complex may be other than a salt or solvate. Complexes of this type include clathrates (drug-host inclusion complexes) and co-crystals. The latter are typically defined as crystalline complexes of neutral molecular constituents which are bound together through non-covalent interactions, but could also be a complex of a neutral molecule with a salt. Co-crystals may be prepared by melt crystallisation, by recrystallisation from solvents, or by physically grinding the components together - see *Chem Commun*, 17, 1889-1896, by O. Almarsson and M. J. Zaworotko (**2304**), incorporated herein by reference. For a general review of multi-component complexes, see *J Pharm Sci*, 64 (8), 1269-1288, by Haleblian (August **1975**), incorporated herein by reference.

The term "pharmaceutically acceptable salt" may be understood to refer to any salt of a compound provided herein which retains its biological properties and which is not toxic or otherwise undesirable for pharmaceutical use. Such salts may be derived from a variety of organic and inorganic counter-ions well known in the art. Such salts include, but are not limited to: (1) acid addition salts formed with organic or inorganic acids such as hydrochloric, hydrobromic, sulfuric, nitric, phosphoric, sulfamic, acetic, adepic, aspartic, trifluoroacetic, trichloroacetic, propionic, hexanoic, cyclopentylpropionic, glycolic, glutaric, pyruvic, lactic, malonic, succinic, sorbic, ascorbic, malic, maleic, fumaric, tartaric, citric, benzoic, 3-(4-hydroxybenzoyl)benzoic, picric, cinnamic, mandelic, phthalic, lauric, methanesulfonic, ethanesulfonic, 1,2-ethane-disulfonic, 2-hydroxyethanesulfonic, benzenesulfonic, 4-chlorobenzenesulfonic, 2-naphthalenesulfonic, 4-toluenesulfonic, camphoric, camphorsulfonic, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic, glucoheptonic, 3-phenylpropionic, trimethylacetic, tert-butylacetic, lauryl sulfuric, gluconic, benzoic, glutamic, hydroxynaphthoic, salicylic, stearic, cyclohexylsulfamic, quinic, muconic acid and the like acids; or (2) base addition salts formed when an acidic proton present in the parent compound either (a) is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion or an aluminium ion, or alkali metal or alkaline earth metal hydroxides, such as sodium, potassium, calcium, magnesium, aluminium, lithium, zinc, and barium hydroxide, ammonia or (b) coordinates with an organic base, such as aliphatic, alicyclic, or aromatic organic

amines, such as ammonia, methylamine, dimethylamine, diethylamine, picoline, ethanolamine, diethanolamine, triethanolamine, ethylenediamine, lysine, arginine, ornithine, choline, N,N′-dibenzylethylene-diamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethylamine, N-methylglucamine piperazine, tris(hydroxymethyl)-aminomethane, tetramethylammonium hydroxide, and the like.

Pharmaceutically acceptable salts may include, sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium and the like, and when the compound contains a basic functionality, salts of non-toxic organic or inorganic acids, such as hydrohalides, e.g. hydrochloride, hydrobromide and hydroiodide, carbonate or bicarbonate, sulfate or bisulfate, borate, phosphate, hydrogen phosphate, dihydrogen phosphate, pyroglutamate, saccharate, stearate, sulfamate, nitrate, orotate, oxalate, palmitate, pamoate, acetate, trifluoroacetate, trichloroacetate, propionate, hexanoate, cyclopentylpropionate, glycolate, glutarate, pyruvate, lactate, malonate, succinate, tannate, tartrate, tosylate, sorbate, ascorbate, malate, maleate, fumarate, tartarate, camsylate, citrate, cyclamate, benzoate, isethionate, esylate, formate, 3-(4-hydroxybenzoyl)benzoate, picrate, cinnamate, mandelate, phthalate, laurate, methanesulfonate (mesylate), methylsulphate, naphthylate, 2-napsylate, nicotinate, ethanesulfonate, 1,2-ethane-disulfonate, 2-hydroxyethanesulfonate, benzenesulfonate (besylate), 4-chlorobenzenesulfonate, 2-naphthalenesulfonate, 4-toluenesulfonate, camphorate, camphorsulfonate, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylate, glucoheptonate, 3-phenylpropionate, trimethylacetate, tert-butylacetate, lauryl sulfate, gluceptate, gluconate, glucoronate, hexafluorophosphate, hibenzate, benzoate, glutamate, hydroxynaphthoate, salicylate, stearate, cyclohexylsulfamate, quinate, muconate, xinofoate and the like.

Hemisalts of acids and bases may also be formed, for example, hemisulphate salts.

The skilled person will appreciate that the aforementioned salts include ones wherein the counterion is optically active, for example D-lactate, or racemic, for example DL-tartrate.

For a review on suitable salts, see "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

Pharmaceutically acceptable salts of compounds of formula (**I**) may be prepared by one or more of three methods:

(i) by reacting the compound of formula (**I**) with the desired acid or base;

(ii) by removing an acid- or base-labile protecting group from a suitable precursor of the compound of formula (**I**) using the desired acid or base; or
(iii) by converting one salt of the compound of formula (**I**) to another by reaction with an appropriate acid or base or by means of a suitable ion exchange column.

All three reactions are typically carried out in solution. The resulting salt may precipitate out and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionisation in the resulting salt may vary from completely ionised to almost non-ionised. The term "solvate" may be understood to refer to a compound provided herein or a salt thereof, that further includes a stoichiometric or non-stoichiometric amount of solvent bound by non-covalent intermolecular forces. Where the solvent is water, the solvate is a hydrate. Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, e.g. D_2O, d_6-acetone and d_6-DMSO.

A currently accepted classification system for organic hydrates is one that defines isolated site, channel, or metal-ion coordinated hydrates - see Polymorphism in Pharmaceutical Solids by K. R. Morris (Ed. H. G. Brittain, Marcel Dekker, 1995), incorporated herein by reference. Isolated site hydrates are ones in which the water molecules are isolated from direct contact with each other by intervening organic molecules. In channel hydrates, the water molecules lie in lattice channels where they are next to other water molecules. In metal-ion coordinated hydrates, the water molecules are bonded to the metal ion.

When the solvent or water is tightly bound, the complex will have a well-defined stoichiometry independent of humidity. When, however, the solvent or water is weakly bound, as in channel solvates and hygroscopic compounds, the water/solvent content will be dependent on humidity and drying conditions. In such cases, non-stoichiometry will be the norm.

The compounds of the invention may exist in a continuum of solid states ranging from fully amorphous to fully crystalline, including polymorphs of said crystalline material. The term 'amorphous' refers to a state in which the material lacks long range order at the molecular level and, depending upon temperature, may exhibit the physical properties of a solid or a liquid. Typically such materials do not give distinctive X-ray diffraction patterns and, while exhibiting the properties of a solid, are more formally described as a liquid. Upon heating, a change from solid to liquid properties occurs which is characterised by a change of state, typically second order ('glass transition'). The term 'crystalline' refers to a solid phase in

which the material has a regular ordered internal structure at the molecular level and gives a distinctive X-ray diffraction pattern with defined peaks. Such materials when heated sufficiently will also exhibit the properties of a liquid, but the change from solid to liquid is characterised by a phase change, typically first order ('melting point').

The compounds of the invention may also exist in a mesomorphic state (mesophase or liquid crystal) when subjected to suitable conditions. The mesomorphic state is intermediate between the true crystalline state and the true liquid state (either melt or solution). Mesomorphism arising as the result of a change in temperature is described as 'thermotropic' and that resulting from the addition of a second component, such as water or another solvent, is described as 'lyotropic'. Compounds that have the potential to form lyotropic mesophases are described as 'amphiphilic' and consist of molecules which possess an ionic (such as $-COO^-Na^+$, $-COO^-K^+$, or $-SO_3^-Na^+$) or non-ionic (such as $-N^-N^+(CH_3)_3$) polar head group. For more information, see Crystals and the Polarizing Microscope by N. H. Hartshorne and A. Stuart, 4th Edition (Edward Arnold, 1970), incorporated herein by reference.

Compounds of formula (**I**) may include one or more stereogenic centers and so may exist as optical isomers, such as enantiomers and diastereomers. All such isomers and mixtures thereof are included within the scope of the present invention.

It will be understood that the above compounds may exist as enantiomers and as diastereoisomeric pairs. These isomers also represent further embodiments of the invention. Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC).

Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, an alcohol, or, in the case where the compound of formula (I) contains an acidic or basic moiety, a base or acid such as 1-phenylethylamine or tartaric acid. The resulting diastereomeric mixture may be separated by chromatography and/or fractional crystallization and one or both of the diastereoisomers converted to the corresponding pure enantiomer(s) by means well known to a skilled person.

Chiral compounds of the invention (and chiral precursors thereof) may be obtained in enantiomerically-enriched form using chromatography, typically HPLC, on an asymmetric

resin with a mobile phase consisting of a hydrocarbon, typically heptane or hexane, containing from 0 to 50% by volume of isopropanol, typically from 2% to 20%, and from 0 to 5% by volume of an alkylamine, typically 0.1% diethylamine. Concentration of the eluate affords the enriched mixture.

Mixtures of stereoisomers may be separated by conventional techniques known to those skilled in the art; see, for example, "Stereochemistry of Organic Compounds" by E. L. Eliel and S. H. Wilen (Wiley, New York, 1994).

The term 'STING' refers to STimulator of INterferon Genes, an adaptor protein that is functionally activated by cyclic dinucleotides which leads to the production of interferons and inflammatory cytokines.

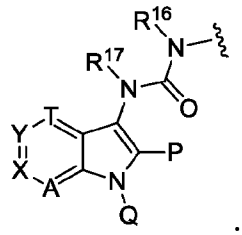
It will be appreciated that an 'antagonist', or 'inhibitor' as it relates to a ligand and STING, comprises a molecule, combination of molecules, or a complex, that inhibits, counteracts, downregulates, and/or desensitizes STING activity. 'Antagonist' encompasses any reagent that inhibits a constitutive activity of STING. A constitutive activity is one that is manifest in the absence of a ligand/STING interaction. 'Antagonist' also encompasses any reagent that inhibits or prevents a stimulated (or regulated) activity of STING.

Preferably, the compound of formula (**I**) is an inhibitor of the STING protein.

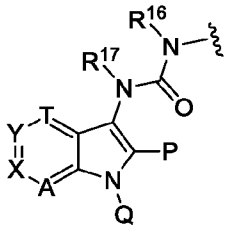
R^1 may be H, halogen, OH, CN, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl or optionally substituted C_2-C_6 alkynyl. R^1 may be H, halogen, OH, CN, C_1-C_3 alkyl, C_2-C_3 alkenyl or C_2-C_3 alkynyl. Preferably, R^1 is H.

It may be appreciated that since X^2 is CR^2 and X^3 is CR^3 or N; or X^2 is N and X^3 is CR^3, at least one of R^2 and R^3 is present in the compound of formula (I). In embodiments where X^2 is CR^2 and X^3 is CR^3 both R^2 and R^3 are present in the compound of formula (I).

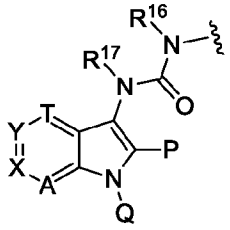
As specified above, one of R^2 and R^3 is:



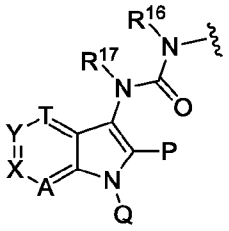
Accordingly, in embodiments where R^2 is present and R^3 absent, R^2 will be



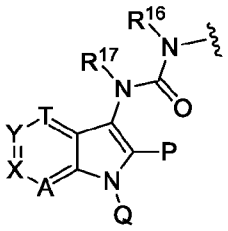
. Conversely, in embodiments where R^2 is absent but R^3 is present, R^3 will



be . Finally, in embodiments where both R^2 and R^3 are present, only one

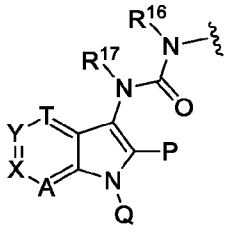


of R^2 and R^3 is .

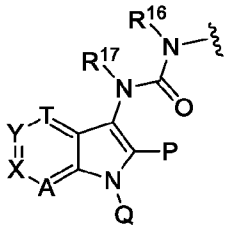
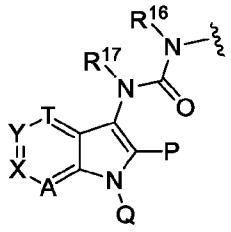


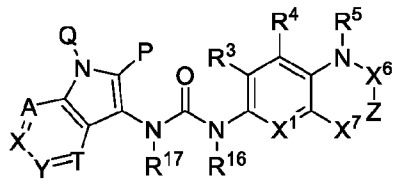
In one embodiment X^2 is N and X^3 is CR^3. In this embodiment, R^3 is .

In an alternative embodiment, X^2 is CR^2 and X^3 is N. In this embodiment, R^2 is

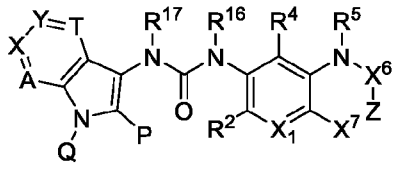


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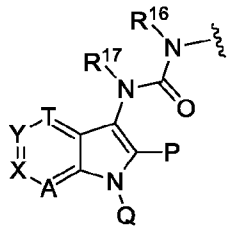
However, in a preferred embodiment, X^2 is CR^2 and X^3 is CR^3. In some embodiments, R^2 is  . In alternative embodiments, R^3 is  . Accordingly, the compound may be a compound of Formula (**Ia**) or Formula (**Ib**):

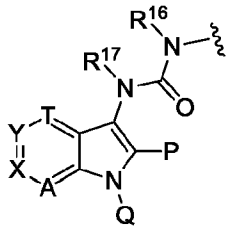
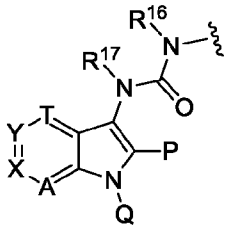


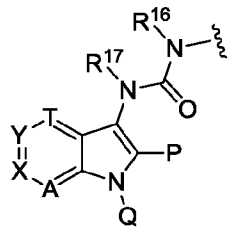
(**Ia**)



(**Ib**)



Preferably, one of R^2 and R^3 is and the other of R^2 and R^3 is H, halogen, OH, CN, $COOR^{13}$, $CONR^{13}R^{14}$, $NR^{13}R^{14}$, $NR^{13}COR^{14}$, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl or optionally substituted C_2-C_6 alkynyl, and R^{13} and R^{14} are each independently selected from the group consisting of H, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_3 alkenyl and optionally substituted C_2-C alkynyl. More preferably, one of R^2 and R^3 is  and the other of R^2 and R^3 is H, halogen, OH, CN, $CONR^{13}R^{14}$, $NR^{13}R^{14}$, C_1-C_3 alkyl, C_2-C_3 alkenyl or C_2-C_3 alkynyl, and R^{13} and R^{14} are each independently selected from the group consisting of H, C_1-C_3 alkyl, C_2-C_3 alkenyl and C_2-C alkynyl. Preferably, one of R^2 and R^3 is  and the other of R^2 and R^3 is



H, bromine or $CONH_2$. In a preferred embodiment, one of R^2 and R^3 is and the other of R^2 and R^3 is H.

R^{16} and R^{17} may independently be H, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl or optionally substituted C_2-C_6 alkynyl. R^{16} and R^{17} may independently be H, C_1-C_3 alkyl, C_2-C_3 alkenyl or C_2-C_3 alkynyl. Preferably, R^{16} and R^{17} are H or methyl. Most preferably, R^{16} and R^{17} are H.

P may be H, halogen, OH, CN, $COOR^{13}$, $CONR^{13}R^{14}$, $NR^{13}R^{14}$, $NR^{13}COR^{14}$, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl or optionally substituted C_2-C_6 alkynyl, and R^{13} and R^{14} are each independently selected from the group consisting of H, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_3 alkenyl and optionally substituted C_2-C alkynyl. Preferably, P is H, halogen, C_1-C_3 alkyl, C_2-C_3 alkenyl or C_2-C_3 alkynyl. In a preferred embodiment, P is H or methyl.

Q may be H, halogen, OH, CN, $COOR^{13}$, $CONR^{13}R^{14}$, $NR^{13}R^{14}$, $NR^{13}COR^{14}$, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl or optionally substituted C_2-C_6 alkynyl, and R^{13} and R^{14} are each independently selected from the group consisting of H, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_3 alkenyl and optionally substituted C_2-C alkynyl. Preferably, Q is H, halogen, C_1-C_3 alkyl, C_2-C_3 alkenyl or C_2-C_3 alkynyl. In a preferred embodiment, Q is H.

At least one of A, X, Y and T may be N. Accordingly, in one embodiment, A is N, X is CR^{20}, Y is CR^{21} and T is CR^{22}. In another embodiment, A is CR^{19}, X is N, Y is CR^{21} and T is CR^{22}. In a further embodiment, A is CR^{19}, X is CR^{20}, Y is N and T is CR^{22}. In a still further embodiment, A is CR^{19}, X is CR^{20}, Y is CR^{21} and T is N.

Alternatively, A may be CR^{19}, X may be CR^{20}, Y may be CR^{21} and T may be CR^{22}.

R^{19} to R^{22} may independently be H, halogen, CN, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_3 alkenyl, optionally substituted C_2-C_3 alkynyl, optionally substituted mono or bicyclic C_3-C_6 cycloalkyl, mono or bicyclic optionally substituted C_6-C_{12} aryl, mono or bicyclic optionally substituted 5 to 10 membered heteroaryl or optionally

substituted mono or bicyclic 3 to 8 membered heterocycle. Preferably, R^{19} to R^{22} are independently H, halogen, CN, C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, mono or bicyclic optionally substituted C_6-C_{12} aryl or mono or bicyclic optionally substituted 5 to 10 membered heteroaryl.

When one or more of R^{19} to R^{22} is halogen, the or each halogen may be fluorine, chlorine, bromine or iodine. Preferably, halogen is fluorine, chlorine or bromine.

When one or more of R^{19} to R^{22} is an optionally substituted aryl, the or each optionally substituted aryl may be optionally substituted phenyl. The or each aryl group may be unsubstituted or substituted with one or more of optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted C_1-C_6 alkoxy, halogen, OH, CN, $C(O)R^{23}$, $COOR^{23}$, $OC(O)R^{23}$, $CONR^{23}R^{24}$, $NR^{23}R^{24}$, $NR^{23}C(O)R^{24}$, $=NOR^{23}$, SR^{23}, SO_2R^{23}, OSO_2R^{23}, $SO_2NR^{23}R^{24}$ or $OP(O)(OR^{23})(OR^{24})$.

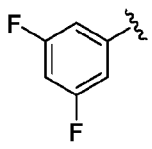
Preferably, the or each aryl group may be unsubstituted or substituted with one or more of optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_3 alkenyl, optionally substituted C_2-C_3 alkynyl, optionally substituted C_1-C_3 alkoxy, halogen, OH, CN, $COOR^{23}$, $CONR^{23}R^{24}$, SO_2R^{23} or OSO_2R^{23}. Preferably R^{23} and R^{24} are independently H, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl or optionally substituted C_2-C_6 alkynyl. More preferably, R^{23} and R^{24} are independently H or methyl. The or each alkyl, alkenyl, alkynyl or alkoxyl may be unsubstituted or substituted with halogen, OH, CN, C_1-C_3 alkoxy or C_3-C_6 cycloalkyl. Accordingly, in a most preferred embodiment, the or each aryl group may be unsubstituted or substituted with one or more of fluorine, chlorine, methyl, ethyl, isopropyl, CHF_2, CF_3, CH_2OH, CH_2CH_2OH, $CH_2CH_2OCH_3$, $CH_2CH(OH)CH_3$, CH_2CH_2CN, OCH_3, OCF_3, cyclopropylmethyl, OH, CN, $CONH_2$ or SO_2CH_3.

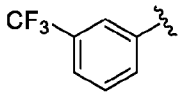
When one or more of R^{19} to R^{22} is an optionally substituted heteroaryl, the or each optionally substituted heteroaryl may be optionally substituted pyrrolyl, optionally substituted pyrazolyl, optionally substituted imidazolyl, optionally substituted 1,2,4-triazolyl, optionally substituted 1,2,3-triazolyl, optionally substituted tetrazolyl, optionally substituted furanyl, optionally substituted thiophenyl, optionally substituted oxazolyl, optionally substituted isooxazolyl, optionally substituted thiazolyl, optionally substituted isothiazolyl, optionally substituted 1,2,5-oxadiazolyl, optionally substituted 1,2,3-oxadiazolyl, optionally substituted 1,2,5-thiadiazolyl, optionally substituted 1,3,4-thiasiazolyl, optionally substituted pyridinyl, optionally substituted pyridazinyl, optionally substituted pyrimidinyl, optionally substituted pyrazinyl, optionally substituted 1,2,4-triazinyl, optionally substituted 1,3,5-triazinyl,

optionally substituted indolinyl, optionally substituted 1H-indolyl, optionally substituted 2H-isoindolyl, optionally substituted indolizinyl, optionally substituted 1H-indazolyl, optionally substituted benzimidazolyl, optionally substituted 4-azaindolyl, optionally substituted 5-azaindolyl, optionally substituted 6-azaindolyl, optionally substituted 7-azaindolyl, optionally substituted benzofuranyl, optionally substituted benzo[b]thiophenyl or optionally substituted 1,3-benzodioxolyl. The or each heteroaryl group may be unsubstituted or substituted with one or more of optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted C_1-C_6 alkoxy, halogen, oxo, OH, CN, $C(O)R^{23}$, $COOR^{23}$, $OC(O)R^{23}$, $CONR^{23}R^{24}$, $NR^{23}R^{24}$, $NR^{23}C(O)R^{24}$, $=NOR^{23}$, SR^{23}, SO_2R^{23}, OSO_2R^{23}, $SO_2NR^{23}R^{24}$ or $OP(O)(OR^{23})(OR^{24})$. Preferably, the or each heteroaryl group may be unsubstituted or substituted with one or more of optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_3 alkenyl, optionally substituted C_2-C_3 alkynyl, optionally substituted C_1-C_3 alkoxy, halogen, oxo, OH, CN, $COOR^{23}$, $CONR^{23}R^{24}$, SO_2R^{23} or OSO_2R^{23}. Preferably R^{23} and R^{24} are independently H, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl or optionally substituted C_2-C_6 alkynyl. More preferably, R^{23} and R^{24} are independently H or methyl. The or each alkyl, alkenyl, alkynyl or alkoxyl may be unsubstituted or substituted with halogen, OH, CN, C_1-C_3 alkoxy or C_3-C_6 cycloalkyl. Accordingly, in a most preferred embodiment, the or each aryl group may be unsubstituted or substituted with one or more of fluorine, chlorine, methyl, ethyl, isopropyl, CHF_2, CF_3, CH_2OH, CH_2CH_2OH, $CH_2CH_2OCH_3$, $CH_2CH(OH)CH_3$, CH_2CH_2CN, OCH_3, OCF_3, cyclopropylmethyl, oxo, OH, CN, $CONH_2$ or SO_2CH_3.

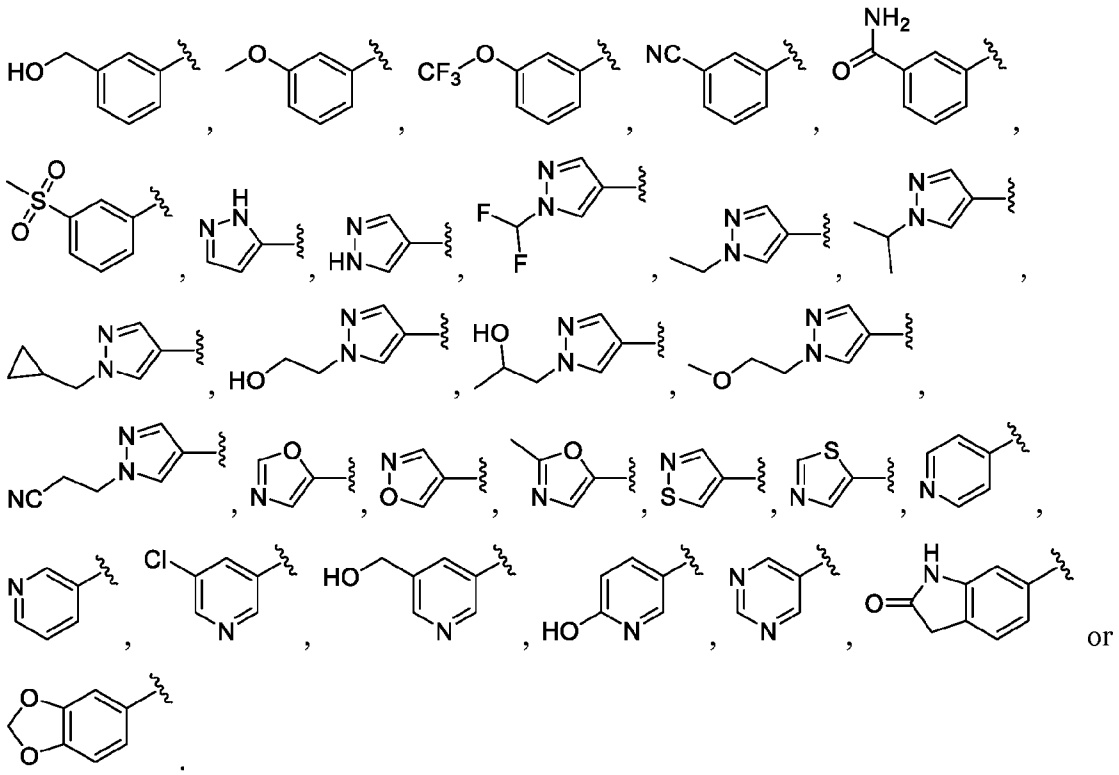
Preferably, R^{19} is H, halogen, CN, C_1-C_3 alkyl, C_2-C_3 alkenyl or C_2-C_3 alkynyl. More preferably, R^{19} is H or fluorine. Most preferably, R^{19} is H.

Preferably, R^{20} is H, halogen, CN, C_1-C_3 alkyl, C_2-C_3 alkenyl or C_2-C_3 alkynyl. More preferably, R^{20} is H or fluorine. Most preferably, R^{19} is H.

Preferably, R^{21} is H, halogen, CN, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_3 alkenyl, optionally substituted C_2-C_3 alkynyl, mono or bicyclic optionally substituted C_6-C_{12} aryl or mono or bicyclic optionally substituted 5 to 10 membered heteroaryl. In some embodiments, R^{21} is H, fluorine, chlorine, bromine, CN, 

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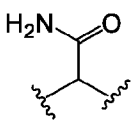
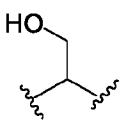
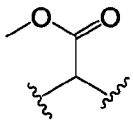
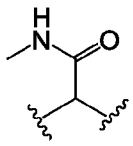
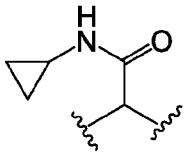


Preferably, R^{22} is H, halogen, CN, C_1-C_3 alkyl, C_2-C_3 alkenyl or C_2-C_3 alkynyl. More preferably, R^{22} is H or fluorine. Most preferably, R^{22} is H.

R^4 may be H, halogen, OH, CN, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl or optionally substituted C_2-C_6 alkynyl. R^4 may be H, halogen, OH, CN, C_1-C_3 alkyl, C_2-C_3 alkenyl or C_2-C_3 alkynyl. Preferably, R^4 is H.

R^5 may be $-L^1$-L^2-R^{15}.

Preferably, L^1 is an optionally substituted C_1-C_3 alkylene, an optionally substituted C_2-C_3 alkenylene or an optionally substituted C_2-C_3 alkynylene. The alkylene, alkenylene or alkynylene may be unsubstituted or substituted with one or more of halogen, OH, CN, $C(O)R^{23}$, $COOR^{23}$, $OC(O)R^{23}$, $CONR^{23}R^{24}$, $NR^{23}R^{24}$, $NR^{23}C(O)R^{24}$, $=NOR^{23}$, SR^{23}, SO_2R^{23}, OSO_2R^{23}, $SO_2NR^{23}R^{24}$ and oxo. R^{23} and R^{24} may be independently be H, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_3 alkenyl, optionally substituted C_2-C_3 alkynyl, optionally substituted mono or bicyclic C_3-C_6 cycloalkyl or optionally substituted mono or bicyclic 3 to 8 membered heterocycle. Preferably, R^{23} and R^{24} are independently H,

methyl or cyclopropyl. Preferably, L^1 is CH_2, CH_2CH_2, CO, , , ,  or . More preferably, L^1 is CH_2 or CO.

Alternatively, L^1 may be absent.

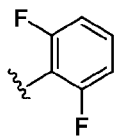
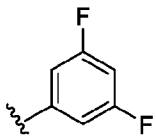
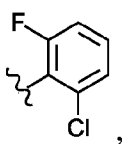
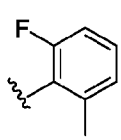
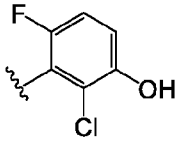
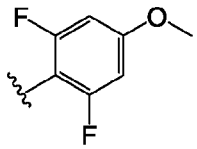
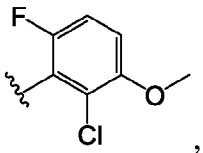
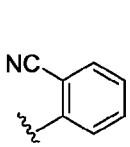
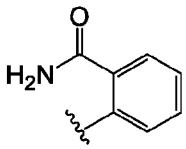
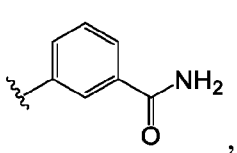
In some embodiments, L^2 is absent.

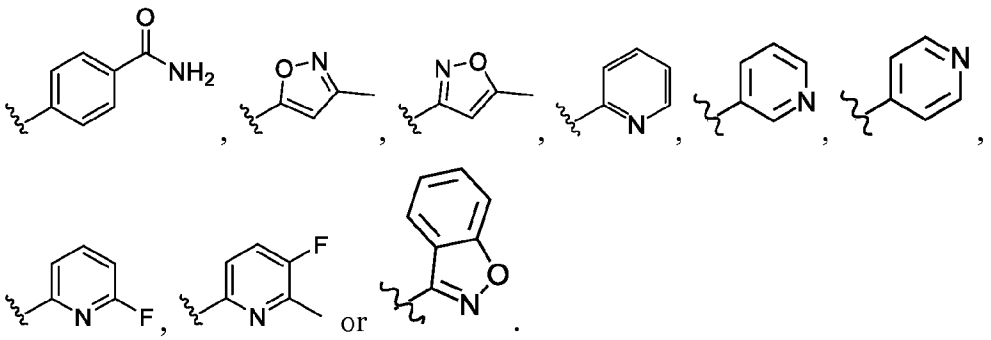
Alternatively, L^2 may be O, S, S=O, SO_2 or NR^{19}. R^{19} may be H, an optionally substituted C_1-C_3 alkyl, an optionally substituted C_2-C_3 alkenyl or an optionally substituted C_2-C_3 alkynyl. Preferably, L^2 is O or S, and most preferably is O.

R^{15} may be optionally substituted mono or bicyclic C_3-C_6 cycloalkyl, mono or bicyclic optionally substituted C_6-C_{12} aryl, mono or bicyclic optionally substituted 5 to 10 membered heteroaryl or optionally substituted mono or bicyclic 3 to 8 membered heterocycle. Preferably, R^{15} is a mono or bicyclic optionally substituted C_6-C_{12} aryl, a mono or bicyclic optionally substituted 5 to 10 membered heteroaryl or optionally substituted mono or bicyclic 3 to 8 membered heterocycle. More preferably, R^{15} is an optionally substituted phenyl or an optionally substituted 5 to 10 membered heteroaryl. Optionally substituted mono or bicyclic C_3-C_6 cycloalkyl may be cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. Mono or bicyclic optionally substituted 5 to 10 membered heteroaryl may be optionally substituted oxazolyl, optionally substituted thiazolyl, optionally substituted isoxazolyl, optionally substituted isothiazolyl, optionally substituted imidazolyl, optionally substituted pyrazolyl, optionally substituted 1,2,3-oxadiazolyl, optionally substituted 1,2,4-oxadiazolyl, optionally substituted 1,2,5-oxadiazolyl, optionally substituted 1,3,4-oxadiazolyl, optionally substituted pyridinyl, optionally substituted pyridazinyl, optionally substituted pyrimidinyl, optionally substituted pyrazinyl, optionally substituted 1H-indolyl, optionally substituted azaindolyl, optionally substituted benzisoxazolyl, optionally substituted 4-azabenzimidazolyl, optionally substituted 5-benzimidazolyl, optionally substituted indazolyl, optionally substituted benzimidazolyl, optionally substituted benzofuranyl, optionally substituted benzo[b]thiophenyl, optionally substituted benzo[d]isoxazolyl, optionally substituted benzo[d]isothiazolyl, optionally substituted imidazo[1,2-a]pyridinyl, optionally substituted quinazolinyl, optionally substituted quinolinyl, optionally substituted

isoquinolinyl, optionally substituted benzothiazole, optionally substituted 1,3-benzodioxolyl, optionally substituted benzofuranyl, optionally substituted 2,1,3-benzothiadiazolyl, optionally substituted 3,4-dihydro-2H,1,4-benzoxazinyl, or optionally substituted benzo-1,4-dioxanyl. Mono or bicyclic 3 to 8 membered heterocycle may be an optionally substituted pyrrolidinyl, optionally substituted tetrahydrofuranyl, optionally substituted tetrahydrothiophenyl, optionally substituted piperidinyl, an optionally substituted piperazinyl, an optionally substituted tetrahydropyranyl, an optionally substituted dioxanyl, an optionally substituted thianyl, an optionally substituted dithianyl or an optionally substituted morpholinyl.

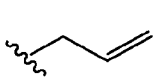
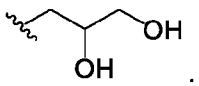
When R^{15} is an aryl, cycloalkyl, heteroaryl or heterocycle the aryl, cycloalkyl, heteroaryl or heterocycle may be unsubstituted or substituted with one or more substituents selected from the group consisting of optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted C_1-C_6 alkoxy, halogen, OH, CN, $C(O)R^{23}$, $COOR^{23}$, $OC(O)R^{23}$, $CONR^{23}R^{24}$, $NR^{23}R^{24}$, $NR^{23}C(O)R^{24}$, $=NOR^{23}$, SR^{23}, SO_2R^{23}, OSO_2R^{23}, $SO_2NR^{23}R^{24}$, $OP(O)(OR^{23})(OR^{24})$, optionally substituted C_6-C_{12} aryl, optionally substituted 5 to 10 membered heteroaryl, optionally substituted C_3-C_6 cycloalkyl and optionally substituted 3 to 8 membered heterocycle. More preferably, when R^{15} is an aryl, cycloalkyl, heteroaryl or heterocycle, the aryl, cycloalkyl, heteroaryl or heterocycle may be unsubstituted or substituted with one or more substituents selected from the group consisting of optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_3 alkenyl, optionally substituted C_2-C_3 alkynyl, optionally substituted C_1-C_3 alkoxy, fluorine, chlorine, OH, CN, $COOR^{23}$ and $CONR^{23}R^{24}$. Preferably R^{23} and R^{24} are independently H, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl or optionally substituted C_2-C_6 alkynyl. More preferably, R^{23} and R^{24} are independently H or methyl. Accordingly, when R^{15} is an aryl, cycloalkyl, heteroaryl or heterocycle, the aryl, cycloalkyl, heteroaryl or heterocycle may be unsubstituted or substituted with one or more substituents selected from the group consisting of methyl, OCH_3, fluorine, chlorine, OH, CH and $CONH_2$.

Accordingly, R^{15} may be phenyl, , , , , , , , , , .



In an alternative embodiment, R^5 is optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl or optionally substituted C_2-C_6 alkynyl. R^5 may be optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_3 alkenyl or optionally substituted C_2-C_3 alkynyl. The alkyl, alkenyl or alkynyl may be unsubstituted or substituted with one or more of halogen, OH, CN and oxo. R^5 may be CH_3 or CH_2CN. Preferably, R^5 is CH_3.

In some embodiments, X^6 is CO.

In alternative embodiments, X^6 is CR^7R^8. R^7 and R^8 may independently be H, halogen, OH, CN, $COOR^{13}$, $CONR^{13}R^{14}$, $NR^{13}R^{14}$, $NR^{13}COR^{14}$, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl or optionally substituted C_2-C_6 alkynyl. R^7 and R^8 may independently be H, halogen, OH, CN, $COOR^{13}$, $CONR^{13}R^{14}$, $NR^{13}R^{14}$, $NR^{13}COR^{14}$, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_3 alkenyl or optionally substituted C_2-C_3 alkynyl. R^{13} and R^{14} are preferably H, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_3 alkenyl or optionally substituted C_2-C_3 alkynyl, and most preferably H. The alkyl, alkenyl or alkynyl may be unsubstituted or substituted with one or more of halogen, OH, oxo, CN, $C(O)R^{20}$, $COOR^{20}$, $OC(O)R^{20}$, $CONR^{20}R^{21}$, $NR^{20}R^{21}$, $NR^{20}C(O)R^{21}$, $=NOR^{20}$, SR^{20}, SO_2R^{20}, OSO_2R^{20}, $SO_2NR^{20}R^{21}$ and $OP(O)(OR^{20})(OR^{21})$. R^{20} and R^{21} may independently be H or methyl. Preferably, R^7 and R^8 are independently H, CN, $CONH_2$, CH_2NH_2, CH_2CH_2OH,  or  . Most preferably, R^7 and R^8 are H.

In one embodiment, Z is CR^9R^{10} and X^7 is S, SO, SO_2, O or NR^{11}. More preferably, X^7 is S, O, SO or NR^{11}. Most preferably, X^7 is S or O. R^9 and R^{10} may independently be H, halogen, OR^{13}, CN, $COOR^{13}$, $CONR^{13}R^{14}$, $NR^{13}R^{14}$, $NR^{13}COR^{14}$, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_3 alkenyl or optionally substituted C_2-C_3 alkynyl. R^{13} and R^{14} may independently be H, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_3 alkenyl or optionally substituted C_2-C_3 alkynyl. The alkyl, alkenyl or alkynyl may be unsubstituted or substituted with one or more of halogen, OH, oxo, CN, $C(O)R^{20}$, $COOR^{20}$, $OC(O)R^{20}$,

$CONR^{20}R^{21}$, $NR^{20}R^{21}$, $NR^{20}C(O)R^{21}$, $=NOR^{20}$, SR^{20}, SO_2R^{20}, OSO_2R^{20}, $SO_2NR^{20}R^{21}$ and $OP(O)(OR^{20})(OR^{21})$. R^{20} and R^{21} may independently be H or methyl. Preferably, R^9 and R^{10} are independently H, methyl, CH_2CONH_2 or CH_2CN. More preferably, R^9 and R^{10} are H. R^{11} may be H, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl or optionally substituted C_2-C_6 alkynyl. R^{11} may be H, C_1-C_3 alkyl, C_2-C_3 alkenyl or C_2-C_3 alkynyl. Preferably, R^{11} is H or methyl.

In an alternative embodiment, Z is NR^9 and X^7 is $CR^{11}R^{12}$. R^9 may be H, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_3 alkenyl or optionally substituted C_2-C_3 alkynyl. Preferably, R^9 is methyl. R^{11} and R^{12} may independently be H, halogen, OH, CN, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl or optionally substituted C_2-C_6 alkynyl. R^{11} and R^{12} may independently be H, halogen, OH, CN, C_1-C_3 alkyl, C_2-C_3 alkenyl or C_2-C_3 alkynyl. Preferably, R^{11} and R^{12} are H or methyl. In embodiments where X^7 is $CR^{11}R^{12}$ and R^{11} and R^{12} are different, the carbon to which R^{11} and R^{12} are bonded defines a chiral centre. The chiral centre may be an *S* or *R* chiral centre. In some embodiments, the chiral centre is an *S* chiral centre.

It will be appreciated that the compounds described herein or a pharmaceutically acceptable salt, solvate, tautomeric form or polymorphic form thereof may be used in a medicament which may be used in a monotherapy (i.e. use of the compound alone), for modulating the STING protein and/or treating, ameliorating or preventing a disease.

Alternatively, the compounds or a pharmaceutically acceptable salt, solvate, tautomeric form or polymorphic form thereof may be used as an adjunct to, or in combination with, known therapies for modulating the STING protein and/or treating, ameliorating or preventing a disease.

The compound of Formula (**I**) may be combined in compositions having a number of different forms depending, in particular, on the manner in which the composition is to be used. Thus, for example, the composition may be in the form of a powder, tablet, capsule, liquid, ointment, cream, gel, hydrogel, aerosol, spray, micellar solution, transdermal patch, liposome suspension or any other suitable form that may be administered to a person or animal in need of treatment. It will be appreciated that the vehicle of medicaments according to the invention should be one which is well-tolerated by the subject to whom it is given.

Medicaments comprising the compounds described herein may be used in a number of ways. Suitable modes of administration include oral, intra-tumoral, parenteral, topical, inhaled/intranasal, rectal/intravaginal, and ocular/aural administration.

Formulations suitable for the aforementioned modes of administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

The compounds of the invention may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the blood stream directly from the mouth. Formulations suitable for oral administration include solid formulations such as tablets, capsules containing particulates, liquids, or powders, lozenges (including liquid-filled), chews, multi- and nano-particulates, gels, solid solution, liposome, films, ovules, sprays, liquid formulations and buccal/mucoadhesive patches.

Liquid formulations include suspensions, solutions, syrups and elixirs. Such formulations may be employed as fillers in soft or hard capsules and typically comprise a carrier, for example, water, ethanol, polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet.

The compounds of the invention may also be used in fast-dissolving, fast-disintegrating dosage forms such as those described in *Expert Opinion in Therapeutic Patents*, 11 (6), 981-986, by Liang and Chen (2001).

For tablet dosage forms, depending on dose, the drug may make up from 1 weight % to 80 weight % of the dosage form, more typically from 5 weight % to 60 weight % of the dosage form. In addition to the drug, tablets generally contain a disintegrant. Examples of disintegrants include sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, crospovidone, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, lower alkyl-substituted hydroxypropyl cellulose, starch, pregelatinised starch and sodium alginate. Generally, the disintegrant will comprise from 1 weight % to 25 weight %, preferably from 5 weight % to 20 weight % of the dosage form.

Binders are generally used to impart cohesive qualities to a tablet formulation. Suitable binders include microcrystalline cellulose, gelatin, sugars, polyethylene glycol, natural and

synthetic gums, polyvinylpyrrolidone, pregelatinised starch, hydroxypropyl cellulose and hydroxypropyl methylcellulose. Tablets may also contain diluents, such as lactose (monohydrate, spray-dried monohydrate, anhydrous and the like), mannitol, xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch and dibasic calcium phosphate dihydrate.

Tablets may also optionally comprise surface active agents, such as sodium lauryl sulfate and polysorbate 80, and glidants such as silicon dioxide and talc. When present, surface active agents may comprise from 0.2 weight % to 5 weight % of the tablet, and glidants may comprise from 0.2 weight % to 1 weight % of the tablet.

Tablets also generally contain lubricants such as magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, and mixtures of magnesium stearate with sodium lauryl sulphate. Lubricants generally comprise from 0.25 weight % to 10 weight %, preferably from 0.5 weight % to 3 weight % of the tablet. Other possible ingredients include anti-oxidants, colourants, flavouring agents, preservatives and taste-masking agents.

Exemplary tablets contain up to about 80% drug, from about 10 weight % to about 90 weight % binder, from about 0 weight % to about 85 weight % diluent, from about 2 weight % to about 10 weight % disintegrant, and from about 0.25 weight % to about 10 weight % lubricant. Tablet blends may be compressed directly or by roller to form tablets. Tablet blends or portions of blends may alternatively be wet-, dry-, or melt-granulated, melt congealed, or extruded before tabletting. The final formulation may comprise one or more layers and may be coated or uncoated; it may even be encapsulated. The formulation of tablets is discussed in "Pharmaceutical Dosage Forms: Tablets", Vol. 1, by H. Lieberman and L. Lachman (Marcel Dekker, New York, 1980).

Suitable modified release formulations for the purposes of the invention are described in US Patent No. 6,106,864. Details of other suitable release technologies such as high energy dispersions and osmotic and coated particles are to be found in "Pharmaceutical Technology On-line", 25(2), 1-14, by Verma et al (2001). The use of chewing gum to achieve controlled release is described in WO 00/35298.

The compounds of the invention may also be administered directly into the blood stream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous. Suitable devices for parenteral

administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water.

The preparation of parenteral formulations under sterile conditions, for example, by lyophilisation, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.

The solubility of compounds of formula (**I**) used in the preparation of parenteral solutions may be increased by the use of appropriate formulation techniques, such as the incorporation of solubility-enhancing agents. Formulations for parenteral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release. Thus compounds of the invention may be formulated as a solid, semi-solid, or thixotropic liquid for administration as an implanted depot providing modified release of the active compound. Examples of such formulations include drug-coated stents and poly(dl-lactic-coglycolic)acid (PGLA) microspheres.

The compounds of the invention may also be administered topically to the skin or mucosa, that is, dermally or transdermally. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibres, bandages and microemulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol. Penetration enhancers may be incorporated - see, for example, J Pharm Sci, 88 (10), 955-958, by Finnin and Morgan (October 1999).

Other means of topical administration include delivery by electroporation, iontophoresis, phonophoresis, sonophoresis and microneedle or needle-free (e.g. Powderject™, Bioject™, etc.) injection.

The compounds of the invention can also be administered intranasally or by inhalation, typically in the form of a dry powder (either alone, as a mixture, for example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with phospholipids, such as phosphatidylcholine) from a dry powder inhaler or as an aerosol spray from a pressurised container, pump, spray, atomiser (preferably an atomiser using electrohydrodynamics to produce a fine mist), or nebuliser, with or without the use of a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. For intranasal use, the powder may comprise a bioadhesive agent, for example, chitosan or cyclodextrin.

The pressurised container, pump, spray, atomizer, or nebuliser contains a solution or suspension of the compound(s) of the invention comprising, for example, ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilising, or extending release of the active, a propellant(s) as solvent and an optional surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

Prior to use in a dry powder or suspension formulation, the drug product is micronised to a size suitable for delivery by inhalation (typically less than 5 microns). This may be achieved by any appropriate comminuting method, such as spiral jet milling, fluid bed jet milling, and supercritical fluid processing to form nanoparticles, high pressure homogenisation, or spray drying.

Capsules (made, for example, from gelatin or hydroxypropylmethylcellulose), blisters and cartridges for use in an inhaler or insufflator may be formulated to contain a powder mix of the compound of the invention, a suitable powder base such as lactose or starch and a performance modifier such as L-leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of the monohydrate, preferably the latter. Other suitable excipients include dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose and trehalose.

A suitable solution formulation for use in an atomiser using electrohydrodynamics to produce a fine mist may contain from 1μg to 20mg of the compound of the invention per actuation and the actuation volume may vary from 1μl to 100μl. A typical formulation may comprise a compound of formula (**I**), propylene glycol, sterile water, ethanol and sodium chloride. Alternative solvents which may be used instead of propylene glycol include glycerol and polyethylene glycol.

Suitable flavours, such as menthol and levomenthol, or sweeteners, such as saccharin or saccharin sodium, may be added to those formulations of the invention intended for inhaled/intranasal administration.

In the case of dry powder inhalers and aerosols, the dosage unit is determined by means of a valve which delivers a metered amount. Units in accordance with the invention are typically arranged to administer a metered dose or "puff" containing from 1μg to 100mg of the compound of formula (**I**). The overall daily dose will typically be in the range 1μg to 200mg which may be administered in a single dose or, more usually, as divided doses throughout the day.

The compounds of the invention may be administered rectally or vaginally, for example, in the form of a suppository, pessary, microbicide, vaginal ring or enema. Cocoa butter is a traditional suppository base, but various alternatives may be used as appropriate.

The compounds of the invention may also be administered directly to the eye or ear, typically in the form of drops of a micronised suspension or solution in isotonic, pH-adjusted, sterile saline. Other formulations suitable for ocular and aural administration include ointments, biodegradable (e.g. absorbable gel sponges, collagen) and non-biodegradable (e.g. silicone) implants, wafers, lenses and particulate or vesicular systems, such as niosomes or liposomes. A polymer such as crossed-linked polyacrylic acid, polyvinylalcohol, hyaluronic acid, a cellulosic polymer, for example, hydroxypropylmethylcellulose, hydroxyethylcellulose, or methyl cellulose, or a heteropolysaccharide polymer, for example, gelan gum, may be incorporated together with a preservative, such as benzalkonium chloride. Such formulations may also be delivered by iontophoresis.

The compounds of the invention may also be administered directly to a site of interest by injection of a solution or suspension containing the active drug substance. The site of interest may be a tumour and the compound may by administer via intratumoral injection. Typical injection solutions are comprised of propylene glycol, sterile water, ethanol and sodium chloride. Alternative solvents which may be used instead of propylene glycol include glycerol and polyethylene glycol.

The compounds of the invention may be combined with soluble macromolecular entities, such as cyclodextrin and suitable derivatives thereof or polyethylene glycol-containing polymers, in order to improve their solubility, dissolution rate, taste-masking, bioavailability and/or stability for use in any of the aforementioned modes of administration.

Drug-cyclodextrin complexes, for example, are found to be generally useful for most dosage forms and administration routes. Both inclusion and non-inclusion complexes may be used. As an alternative to direct complexation with the drug, the cyclodextrin may be used as an auxiliary additive, i.e. as a carrier, diluent, or solubiliser. Most commonly used for these purposes are alpha-, beta- and gamma-cyclodextrins, examples of which may be found in International Patent Applications Nos. WO 91/11172, WO 94/02518 and WO 98/55148.

It will be appreciated that the amount of the compound that is required is determined by its biological activity and bioavailability, which in turn depends on the mode of administration, the physiochemical properties of the compound, and whether it is being used as a monotherapy, or in a combined therapy. The frequency of administration will also be influenced by the half-life of the compound within the subject being treated. Optimal dosages to be administered may be determined by those skilled in the art, and will vary with the particular compound in use, the strength of the pharmaceutical composition, the mode of administration, and the advancement of the disease. Additional factors depending on the particular subject being treated will result in a need to adjust dosages, including subject age, weight, sex, diet, and time of administration.

Generally, for administration to a human, the total daily dose of the compounds of the invention is typically in the range 100μg to 10g, such as 1mg to 1g, for example 10mg to 500mg. For example, oral administration may require a total daily dose of from 25mg to 250mg. The total daily dose may be administered in single or divided doses and may, at the physician's discretion, fall outside of the typical range given herein. These dosages are based on an average human subject having a weight of about 60kg to 70kg. The physician will readily be able to determine doses for subjects whose weight falls outside this range, such as infants and the elderly.

The compound may be administered before, during or after onset of the disease to be treated.

Known procedures, such as those conventionally employed by the pharmaceutical industry (e.g. *in vivo* experimentation, clinical trials, etc.), may be used to form specific formulations comprising the compounds according to the invention and precise therapeutic regimes (such as daily doses of the compounds and the frequency of administration). The inventors believe that they are the first to describe a pharmaceutical composition for treating a disease, based on the use of the compounds of the invention.

Hence, in an seventh aspect of the invention, there is provided a pharmaceutical composition comprising a compound according to the first aspect, or a pharmaceutically acceptable salt, solvate, tautomeric form or polymorphic form thereof, and a pharmaceutically acceptable vehicle.

The invention also provides, in an eighth aspect, a process for making the composition according to the seventh aspect, the process comprising contacting a therapeutically effective amount of a compound of the first aspect, or a pharmaceutically acceptable salt, solvate, tautomeric form or polymorphic form thereof, and a pharmaceutically acceptable vehicle.

A "subject" may be a vertebrate, mammal, or domestic animal. Hence, compounds, compositions and medicaments according to the invention may be used to treat any mammal, for example livestock (e.g. a horse), pets, or may be used in other veterinary applications. Most preferably, however, the subject is a human being.

A "therapeutically effective amount" of compound is any amount which, when administered to a subject, is the amount of drug that is needed to treat the target disease, or produce the desired effect, i.e. inhibit the STING protein.

For example, the therapeutically effective amount of compound used may be from about 0.01 mg to about 800 mg, and preferably from about 0.01 mg to about 500 mg. It is preferred that the amount of compound is an amount from about 0.1 mg to about 250 mg, and most preferably from about 0.1 mg to about 20 mg.

A "pharmaceutically acceptable vehicle" as referred to herein, is any known compound or combination of known compounds that are known to those skilled in the art to be useful in formulating pharmaceutical compositions.

In one embodiment, the pharmaceutically acceptable vehicle may be a solid, and the composition may be in the form of a powder or tablet. A solid pharmaceutically acceptable vehicle may include one or more substances which may also act as flavouring agents, lubricants, solubilisers, suspending agents, dyes, fillers, glidants, compression aids, inert binders, sweeteners, preservatives, dyes, coatings, or tablet-disintegrating agents. The vehicle may also be an encapsulating material. In powders, the vehicle is a finely divided solid that is in admixture with the finely divided active agents (i.e. the compound according to the first aspect) according to the invention. In tablets, the active compound may be mixed

with a vehicle having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active compound. Suitable solid vehicles include, for example calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, polyvinylpyrrolidine, low melting waxes and ion exchange resins. In another embodiment, the pharmaceutical vehicle may be a gel and the composition may be in the form of a cream or the like.

However, the pharmaceutical vehicle may be a liquid, and the pharmaceutical composition is in the form of a solution. Liquid vehicles are used in preparing solutions, suspensions, emulsions, syrups, elixirs and pressurized compositions. The compound according to the invention may be dissolved or suspended in a pharmaceutically acceptable liquid vehicle such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fats. The liquid vehicle can contain other suitable pharmaceutical additives such as solubilisers, emulsifiers, buffers, preservatives, sweeteners, flavouring agents, suspending agents, thickening agents, colours, viscosity regulators, stabilizers or osmo-regulators. Suitable examples of liquid vehicles for oral and parenteral administration include water (partially containing additives as above, e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g. glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration, the vehicle can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid vehicles are useful in sterile liquid form compositions for parenteral administration. The liquid vehicle for pressurized compositions can be a halogenated hydrocarbon or other pharmaceutically acceptable propellant.

Liquid pharmaceutical compositions, which are sterile solutions or suspensions, can be utilized by, for example, intramuscular, intrathecal, epidural, intraperitoneal, intravenous and particularly subcutaneous injection. The compound may be prepared as a sterile solid composition that may be dissolved or suspended at the time of administration using sterile water, saline, or other appropriate sterile injectable medium.

The compound and compositions of the invention may be administered in the form of a sterile solution or suspension containing other solutes or suspending agents (for example, enough saline or glucose to make the solution isotonic), bile salts, acacia, gelatin, sorbitan monoleate, polysorbate 80 (oleate esters of sorbitol and its anhydrides copolymerized with ethylene oxide) and the like. The compounds used according to the invention can also be administered orally either in liquid or solid composition form. Compositions suitable for oral

administration include solid forms, such as pills, capsules, granules, tablets, and powders, and liquid forms, such as solutions, syrups, elixirs, and suspensions. Forms useful for parenteral administration include sterile solutions, emulsions, and suspensions.

It will be known to those skilled in the art that active drug ingredients may be converted into a prodrug, which is a metabolically labile derivative that is converted within the body into the active drug substance. Also included within the scope of the invention are prodrugs which are compounds of formula (**I**) which contain metabolically or hydrolytically labile moieties which in vivo are converted into the active drug of formula (**I**). The processes by which the prodrug is converted into the active drug substance include, but are not limited to, ester or carbonate or carbamate hydrolysis, phosphate ester hydrolysis, *S*-oxidation, *N*-oxidation, dealkylation and metabolic oxidation as described in Beaumont et. al., *Curr. Drug Metab.*, **2003**, 4, 461-485 and Huttenen et. al., *Pharmacol. Revs.*, **2011**, 63, 750-771. Such prodrug derivatives may offer improved solubility, stability or permeability compared to the parent drug substance, or may better allow the drug substance to be administered by an alternative route of administration, for example as an intravenous solution.

Also included within the scope of the invention are soft drugs or antedrugs which are compounds of formula (**I**) which contain metabolically or hydrolytically labile moieties which *in vivo* are converted into inactive derivatives. The processes by which the active drug substance is converted into an inactive derivative include, but are not limited to, ester hydrolysis, *S*-oxidation, *N*-oxidation, dealkylation and metabolic oxidation as described for example in Pearce et al., *Drug Metab. Dispos.*, **2006**, 34, 1035-1040 and B. Testa, Prodrug and Soft Drug Design, in Comprehensive Medicinal Chemistry II, Volume 5, Elsevier, Oxford, 2007, pp. 1009-1041 and Bodor, N. *Chem. Tech.* **1984**, 14, 28–38.

The scope of the invention includes all pharmaceutically acceptable isotopically-labelled compounds of the invention wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number which predominates in nature.

Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as ^{2}H and ^{3}H, carbon, such as ^{11}C, ^{13}C and ^{14}C, chlorine, such as ^{36}Cl, fluorine, such as ^{18}F, iodine, such as ^{123}I and ^{125}I, nitrogen, such as ^{13}N and ^{15}N, oxygen, such as ^{15}O, ^{17}O and ^{18}O, phosphorus, such as ^{32}P, and sulphur, such as ^{35}S.

Certain isotopically-labelled compounds of the invention, for example those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, i.e. ^{3}H, and carbon-14, i.e. ^{14}C, are particularly useful for this

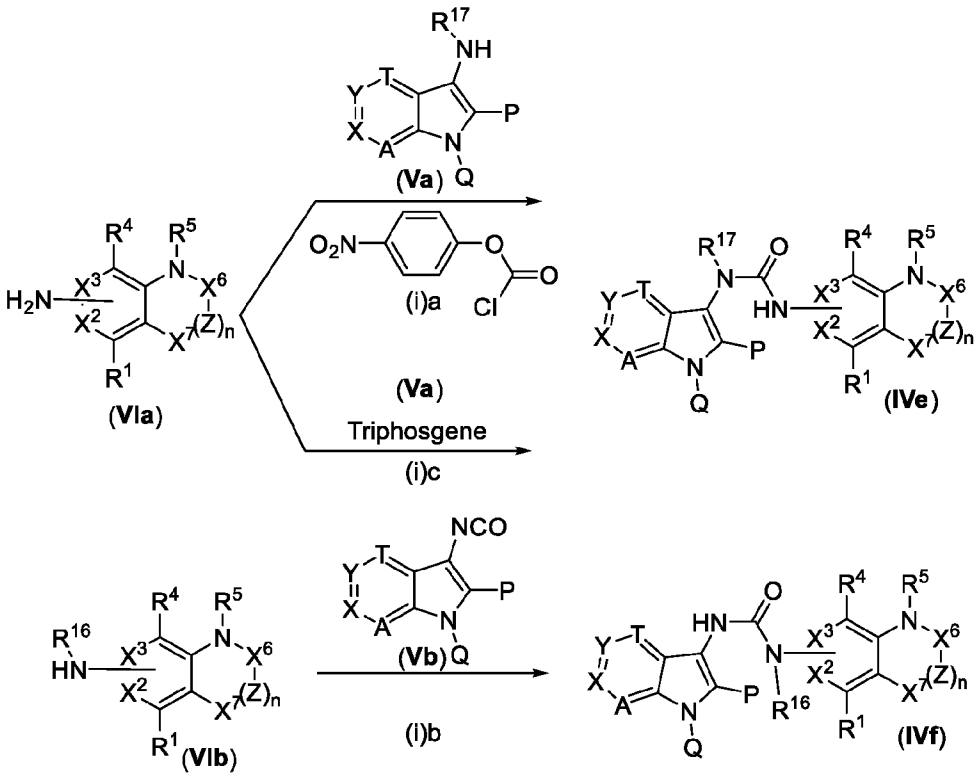
purpose in view of their ease of incorporation and ready means of detection. Substitution with isotopes such as deuterium, i.e. ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced dosage requirements, and hence may be preferred in some circumstances. Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

Isotopically-labelled compounds of formula (**I**) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labelled reagent in place of the non-labelled reagent previously employed.

General Schemes

General Scheme 1

Compounds of formula (**IVe**) and (**IVf**) may be prepared from compounds of formula (**VIa**) and (**VIb**) using a urea bond forming reaction, as shown below.



Typical reaction conditions for the activation of the aromatic amine of the compounds of formula (**VIa**) or (**VIb**) employ 4-nitrophenyl chloroformate or triphosgene to generate an activated intermediate which can be attacked by a suitable nucleophile such as amine (**Va**) to give a urea compound of formula (**IVe**) or (**IVf**). Preferred organic bases include DIPEA or

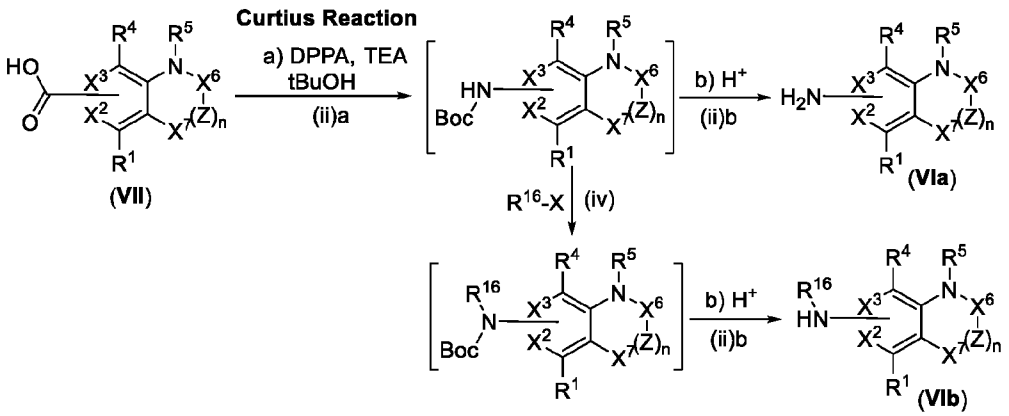
TEA in a suitable organic solvent such as DCM, DMF, DMA or MeCN. The reaction may be shaken or stirred at room temperature.

Alternatively, the compounds of formula (**IVe**) or (**IVf**) can also be prepared with an isocyanate (**Vb**) in a suitable solvent such as THF, DMF or MeCN and a preferred organic base such as TEA or DIPEA. The reaction may be shaken or stirred at room temperature.

Compounds of formula (**V**) and (**VI**) are commercially available or may be synthesized by those skilled in the art. In particular, methods of synthesizing compounds of formula (**VI**) are described in General Schemes 2 to 4.

General Scheme 2

Compounds of formula (**VIa**) and (**VIb**) may be synthesized from compounds of formula (**VII**) using the Curtius reaction, as shown below.

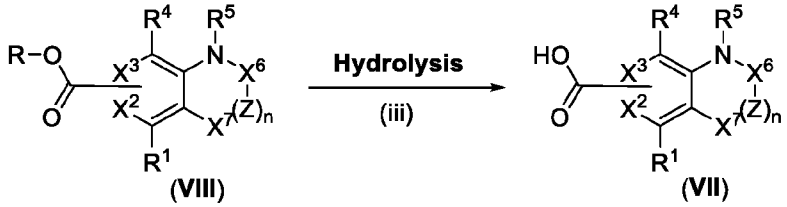


Typical reaction conditions included treating a compound of formula (**VII**) with the reagent diphenylphosphoryl azide (DPPA) and a base such as TEA to produce the corresponding acyl azide which was further refluxed in *t*-butanol to furnish the BOC protected amines as intermediates. The corresponding intermediates either can be de-protected in an acidic environment to give the free amines of formula (**VIa**) or can be first substituted with suitable agents such as R^{16}-X using methods described in General Procedure (iv) then de-protected in an acidic environment to give the N-substituted amines of formula (**VIb**).

Compounds of formula (**VII**) are commercially available or may be synthesized by those skilled in the art. In particular, methods of synthesizing compounds of formula (**VII**) are described in General Schemes 3-4.

General Scheme 3

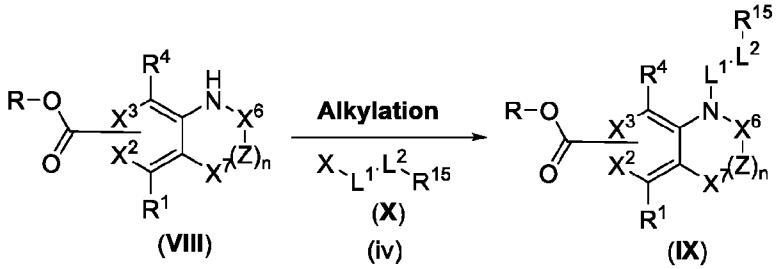
Compounds of formula (**VII**) may be synthesized from esters of formula (**VIII**), where R is methyl, ethyl, benzyl or *tert*-butyl, by a hydrolysis reaction.



The compound of formula (**VIII**) may be reacted with a suitable alkali or base to cause it to undergo hydrolysis and provide a compound of formula (**VII**). The suitable alkali or base may be LiOH, KOH, NaOH or K_2CO_3, and the reaction may be conducted in an aqueous solution.

General Scheme 4

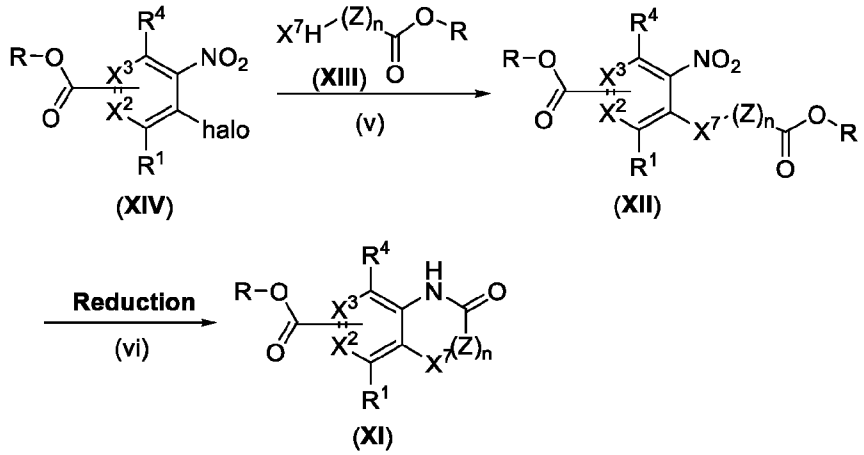
Compounds of formula (**IX**) may be synthesized by those skilled in the art via an alkylation/acylation/sulfonylation reaction with a compound of formula (**VIII**), where X is a leaving group such as an optionally substituted alkylaryl(het), alkyl, aryl(het), cycloalkyl, alkylcycloalkyl halide, triflate or tosylate.



Compounds of formula (**VIII**) may be reacted with compounds of formula (**X**) in the presence of a suitable base such as NaH, K_2CO_3, $NaHCO_3$, Cs_2CO_3 or TEA to furnish compounds of formula (**IX**). Suitable reaction solvents include THF, CAN, DMA and DMF. In some cases we have also used 18-Crown-6.

General Scheme 5

Alternatively, a compound of formula (**XI**) may be prepared in a two-step process, as shown below, from a compound of formula (**XIV**), where R is methyl, ethyl, benzyl or *tert*-butyl.



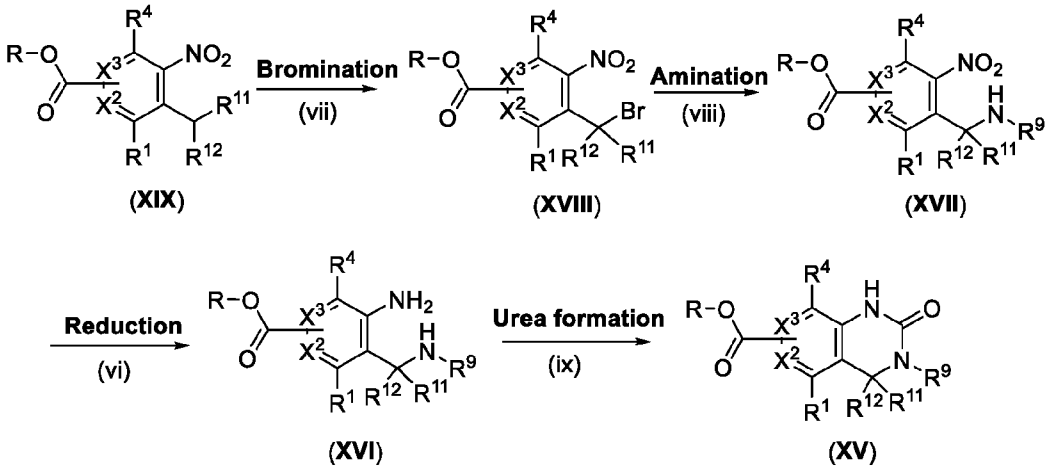
Firstly, compounds of formula (**XIV**) undergo a nucleophilic substitution reaction with a compound of formula (**XIII**), where R is methyl, ethyl, benzyl or *tert*-butyl, to produce a compound of formula (**XII**). The nucleophilic substitution reaction may be conducted in the presence of a mild base, such as DBU, NaH, TEA, DIPEA, K_2CO_3, Cs_2CO_3 or $KHCO_3$. The solvent used may be 1,4-dioxane, acetone, MeCN, THF or DMF.

The nitro group of compounds of formula (**XII**) may then be reduced to an amino group using a suitable reducing agent, such as Fe/AcOH, Zn/HCl, Zn/NH_4Cl, Zn/$HCOONH_4$, $SnCl_2$/HCl or Pd/C/H_2, in a suitable solvent such as EtOH, MeOH or THF. The ensuing amino compounds typically undergo in-situ cyclization resulting in the formation of compounds of formula (**XI**).

It will be appreciated that the compound of formula (**XI**) is a compound of formula (**VIII**) where R^5 is H and X^6 is C=O.

General Scheme 6

A compound of formula (**XV**) may be prepared in a four-step process, as shown below, from a compound of formula (**XIX**), where R is methyl, ethyl, benzyl or *tert*-butyl.

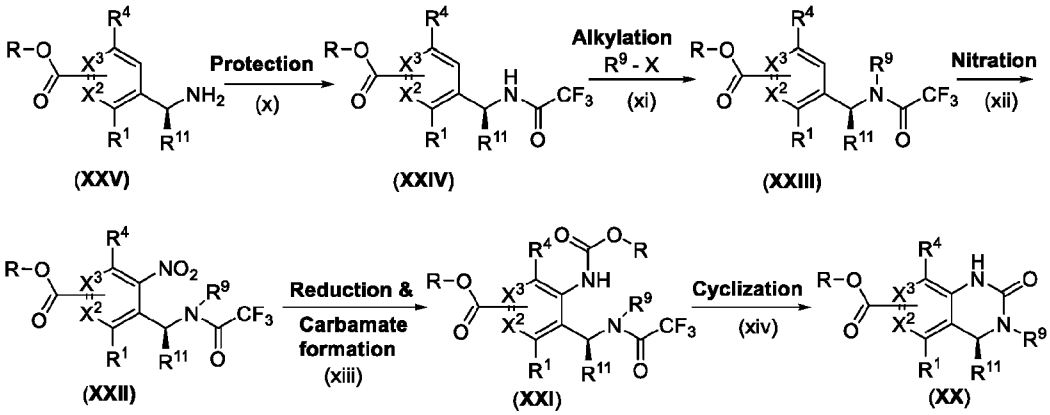


Firstly, the compound of formula (**XIX**) may be brominated, using either Br_2 or a bromine source, such as NBS, to give a compound of formula (**XVIII**). This compound can then be aminated by bromine displacement, using R^9NH_2, to provide a compound of formula (**XVII**). The nitro group on the compound of formula (**XVII**) can then be reduced using suitable reducing agents, for example those described in General Scheme 5, to provide a compound of formula (**XVI**). The compound of formula (**XVI**) may then be reacted with a suitable carbonyl source to provide a compound of formula (**XV**). The carbonyl source may for example be 1,1-carbonyl-diimidazole, phosgene or triphosgene.

It will be appreciated that the compound of formula (**XV**) is a compound of formula (**VIII**) where R^5 is H, X^6 is C=O, Z is NR^9, X^7 is $CR^{11}R^{12}$ and n is 1.

General Scheme 7

A compound of formula (**XX**) may be prepared in a five-step process, as shown below, from a compound of formula (**XXV**), where R is methyl, ethyl, benzyl or *tert*-butyl.



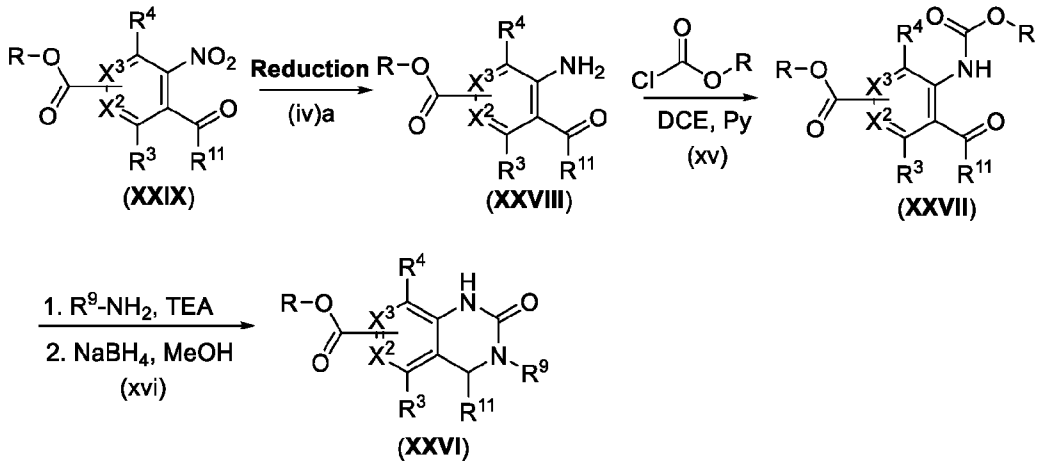
Firstly, the compound of formula (**XXV**) may be protected with a suitable acetyl group using reagents such as TFAA, BOC-anhydride or acetic anhydride to give a compound of formula

(**XXIV**). This compound may be alkylated using a suitable alkyl halide (R^9-X) in the presence of a suitable base such as NaH, K_2CO_3, $KHCO_3$, Cs_2CO_3 or ^{t}BuCOOK/Na to give a compound of formula (**XXIII**). A subsequent nitration reaction may be performed on compounds of formula (**XXIII**) with a nitrating mixture, such as nitric acid and sulfuric acid mixtures, to give a compound of formula (**XXII**). The nitro group on compounds of formula (**XXII**) can then be reduced either by Pd-catalyzed hydrogenation methods or by using the sodium dithionite and TBASH method as described in General Procedure 6b to give the corresponding amino derivative. Further reaction of this amine with an alkyl chloroformate RO(CO)Cl in the presence of a suitable organic or inorganic base such as pyridine or K_2CO_3 provides a compound of formula (**XXI**). This compound may then undergo a cyclization process to give a compound of formula (**XX**) by using a suitable base and solvent combination such as K_2CO_3 and methanol.

It will be appreciated that the compound of formula (**XX**) is a compound of formula (**VIII**) where R^5 is H, X^6 is C=O, Z is NR^9, X^7 is $CH(S)R^{11}$ and n is 1.

General Scheme 8

A compound of formula (**XXVI**) may be prepared in a three-step process, as shown below, from a compound of formula (**XXIX**), where R is methyl, ethyl, benzyl or *tert*-butyl.



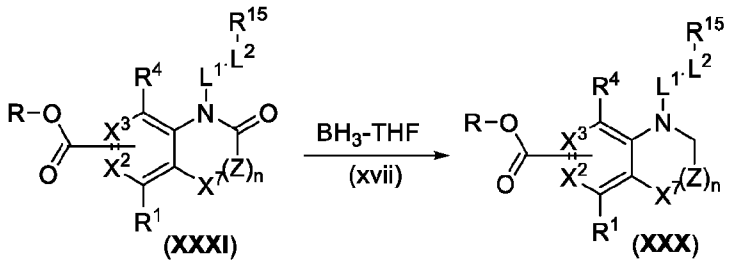
Firstly, the compound of formula (**XXIX**) can be reduced using any of the methods described in General Scheme 5, for example Fe/Zn-AcOH/HCl to convert the nitro group into an amino group and furnish a compound of formula (**XXVIII**). This compound may then form a corresponding carbamate using a suitable chloroformate, in the presence of a suitable organic or inorganic base such as pyridine or K_2CO_3 to provide a compound of formula (**XXVII**). The compound of formula (**XXVII**) can be converted into a cyclized compound of formula (**XXVI**) in a series of reactions such as Schiff base formation with a suitable amine R^9-NH_2 in the presence of an organic base such as TEA or DIPEA followed by

reduction of the resulting imine with a mild reducing agent, for example $Na(AcO)_3BH$, $NaCNBH_3$ or $NaBH_4$ in methanol. The resulting amine typically undergoes spontaneous cyclization in-situ to afford the compound of formula (**XXVI**).

It will be appreciated that the compound of formula (**XXVI**) is a compound of formula (**VIII**) where R^5 is H, X^6 is C=O, Z is NR^9, X^7 is CHR^{11} and n is 1.

General Scheme 9

A compound of formula (**XXX**) may be prepared from a compound of formula (**XXXI**), where R is methyl, ethyl, benzyl or *tert*-butyl.

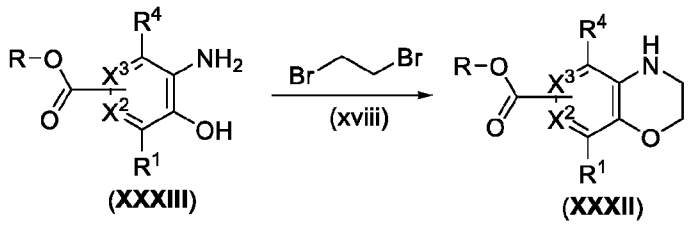


The lactam carbonyl group of a compound of formula (**XXXI**) can be reduced to the corresponding methylene group of a compound of formula (**XXX**) using borane-THF solution in a suitable solvent such as THF, typically at low temperatures.

It will be appreciated that the compound of formula (**XXX**) is a compound of formula (**VIII**) where X^6 is CH_2.

General Scheme 10

A compound of formula (**XXXII**) may be prepared from a compound of formula (**XXXIII**) where R is methyl, ethyl, benzyl or *tert*-butyl.

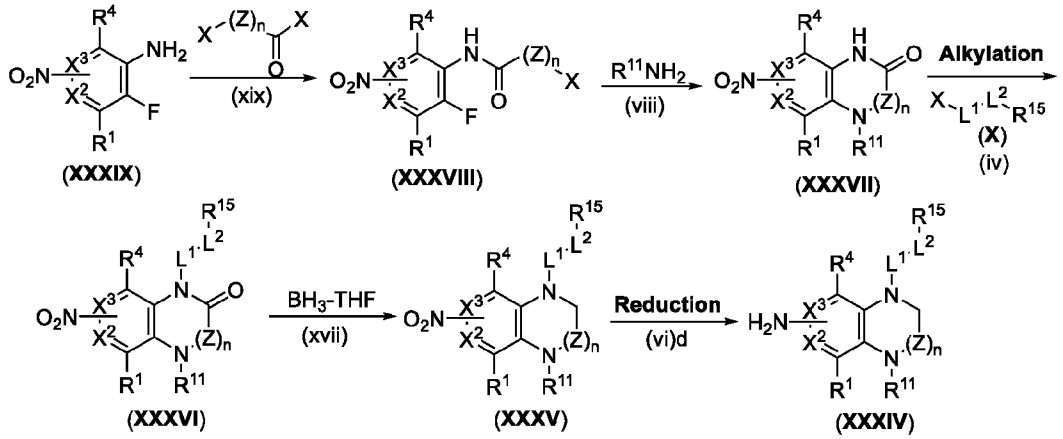


Compounds of formula (**XXXIII**) may undergo cyclization with 1,2-dibromoethane in a basic reaction medium to give a fused-morpholine derivative compound of formula (**XXXII**).

It will be appreciated that the compound of formula (**XXXII**) is a compound of formula (**VIII**) where X^6 and Z are CH_2, and X^7 is O.

General Scheme 11

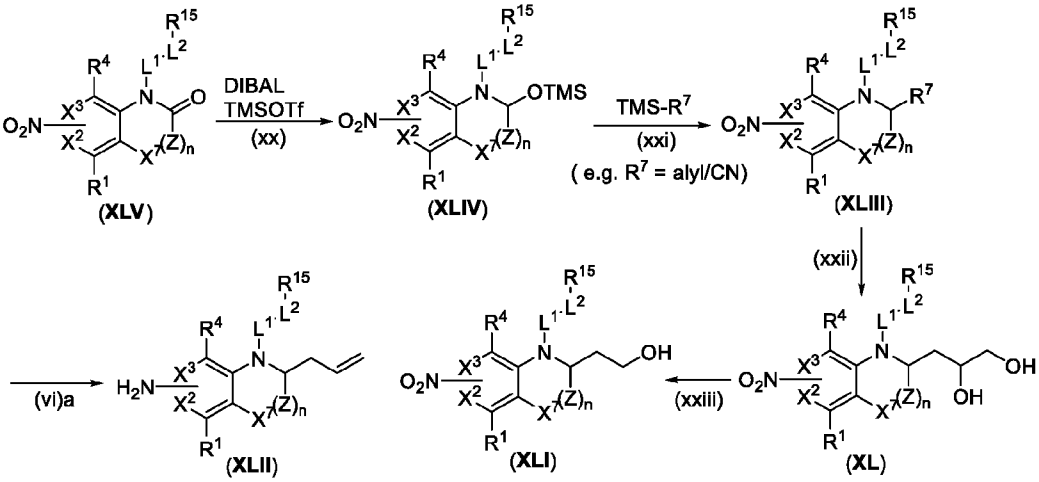
A compound of formula (**XXXIV**) may be prepared from a compound of formula (**XXXIX**) in a sequence of reactions described in the below scheme where X is halogen.



A compound of formula (**XXXIX**) may undergo acylation with a suitable acylating agent in acetone or alcoholic solvents to produce a compound of formula (**XXXVIII**) which can be cyclized in situ after introducing an amine $R^{11}NH_2$ to give a compound of formula (**XXXVII**). The compound of formula (**XXXVII**) may be reacted with compounds of formula (**X**) where X is a suitable leaving group such as halide, tosylate or triflate in the presence of a suitable base such as NaH, $NaHCO_3$ or TEA to furnish compounds of formula (**XXXVI**). Suitable reaction solvents include THF, DMA and DMF. The lactam carbonyl group of a compound of formula (**XXXVI**) can be reduced to the corresponding methylene group of a compound of formula (**XXXV**) using borane-THF solution in a suitable solvent such as THF, typically at low temperatures. The nitro group of compound of formula (**XXXV**) can be reduced to its corresponding amino group of a compound of formula (**XXXIV**) using $NiCl_2.6H_2O$ and sodium borohydride in a polar solvent such as methanol.

General Scheme 12

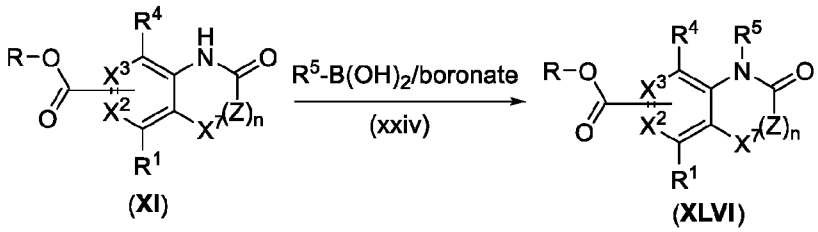
A compound of formula (**XL**), (**XLI**) and (**XLII**) may be prepared from a compound of formula (**XLV**) in a sequence of reactions described in the below scheme.



A compound of formula (**XLV**) may be reduced to the corresponding alcohol with reducing agents such as DIBAL-H and then subsequently converted into a leaving group, for example a silyl ether (OTMS) with TMSOTf to give a compound of formula (**XLIV**). The leaving group can be replaced by a suitable nucleophile to generate a compound of formula (**XLIII**). The suitable nucleophile could be CN or allyl. An allyl containing compound of formula (**XLIII**) can then undergo hydroxylation with OsO_4 to give a compound of formula (**XL**). The compound of formula (**XL**) can be oxidized to the corresponding aldehyde with $NaIO_4$ and then subsequently reduced to the corresponding primary alcohol (**XLI**) with suitable reducing reagents such as $NaBH_4$. The nitro group of a compound of formula (**XLIII**) can also be reduced to the corresponding amine (**XLII**) with a suitable reducing reagent such as Fe/AcOH or Zn/AcOH or Fe/NH_4Cl.

General Scheme 13

A compound of formula (**XLVI**) may be prepared from a compound of formula (**XI**) in the one step reaction described in the below scheme where R is methyl, ethyl, benzyl or *tert*-butyl.

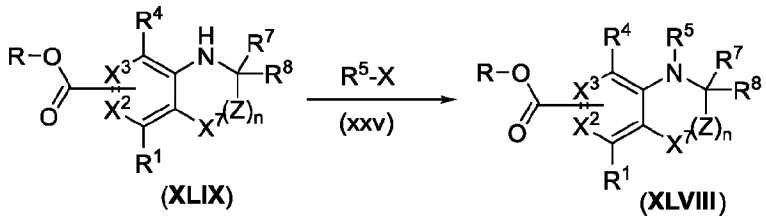


A compound of formula (**XI**) may undergo a Chan-Lam coupling reaction with a suitable boronic acid/boronate ester in the presence of a suitable catalyst and base to give a compound of formula (**XLVI**).

It will be appreciated that the compound of formula (**XLVI**) is a compound of formula (**VIII**) where X^6 is C=O.

General Scheme 14

A compound of formula (**XLVIII**) may be prepared from a compound of formula (**XLIX**) in a one-step reaction described in the below scheme where R is methyl, ethyl, benzyl or *tert*-butyl.

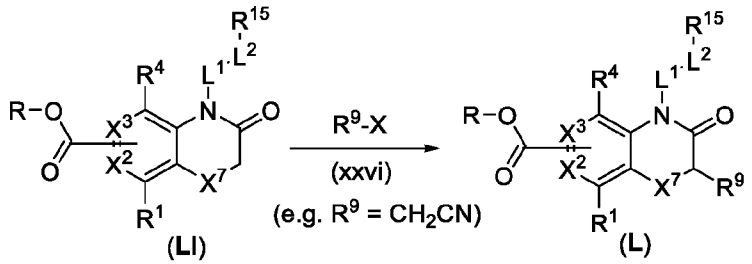


A compound of formula (**XLIX**) may undergo a Buchwald coupling reaction with a suitable aromatic halide (R^5-X) to give a compound of formula (**XLVIII**).

It will be appreciated that the compound of formula (**XLVIII**) is a compound of formula (**VIII**) where X^6 is CR^7R^8.

General Scheme 15

A compound of formula (**L**) may be prepared from a compound of formula (**LI**) in the one step reaction described in the below scheme where R is methyl, ethyl, benzyl or *tert*-butyl.

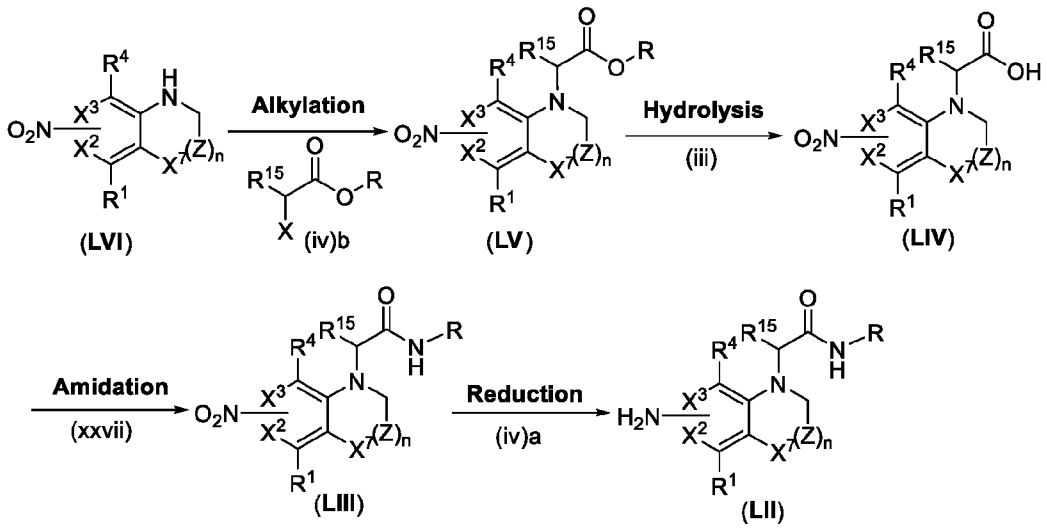


A compound of formula (**LI**) may be treated with a suitable base such as LiHMDS to generate an anion at the most acidic methylene position which can then be alkylated with a suitable electrophile such as XCH_2CN to generate a compound of formula (**L**).

It will be appreciated that the compound of formula (**L**) is a compound of formula (**VIII**) where X^6 is C=O, Z is CHR^9 and n is 1.

General Scheme 16

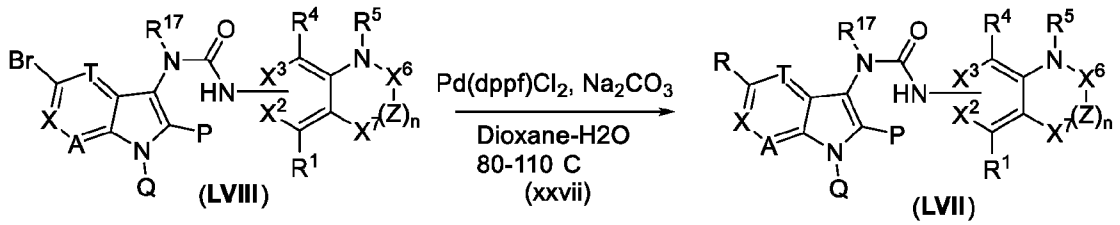
A compound of formula (**LII**) may be prepared from a compound of formula (**LVI**) in a sequence of reactions described in the below scheme where R is methyl, ethyl, benzyl or *tert*-butyl.



Firstly, a compound of formula (**LVI**) may be alkylated with suitable alkylating agents in the presence of a suitable base in a suitable solvent such as ACN, THF or DMF to give a compound of formula (**LV**) which can undergo ester hydrolysis to produce a compound of formula (**LIV**). The acid functional group can then be converted into the corresponding amide under typical amide coupling reaction conditions with a suitable amine to afford the compound of formula (**LIII**). Finally, the nitro group of a compound of formula (**LIII**) may be reduced to the corresponding amine in a compound of formula (**LII**) with suitable reducing reagents.

Library General Scheme 1

Compounds of formula (**LVII**) may be prepared in parallel using library or array techniques from a compound of formula (**LVIII**) by metal catalyzed carbon-carbon bond formation reaction as described in the below scheme.



A compound of formula (**LVII**) may be synthesized by Suzuki-Miyaura cross coupling reaction using required boranic acid or boronate ester in the presence of suitable metal

catalyst and inorganic base in suitable solvent under inert atmosphere at elevated temperature.

General Synthetic Procedures

General Purification and Analytical Methods

All final compounds were purified by either Combi-flash or prep-HPLC purification, and analysed for purity and product identity by UPLC or LCMS according to one of the below conditions.

Prep-HPLC

Preparative HPLC was carried out on a Waters auto purification instrument using a Gemini C18 column (250 x 21.2 mm, 10 µm) operating at ambient temperature with a flow rate of 16.0 – 25.0 mL/min.

Mobile phase 1: A = 0.1% formic acid in water, B = Acetonitrile; Gradient Profile: Mobile phase initial composition of 80% A and 20% B, then to 60% A and 40% B after 3 min., then to 30% A and 70% B after 20 min., then to 5% A and 95% B after 21 min., held at this composition for 1 min. for column washing, then returned to the initial composition for 3 min.

Mobile phase 2: A = 10mM Ammonium Acetate in water, B = Acetonitrile; Gradient Profile: Mobile phase initial composition of 90% A and 10% B, then to 70% A and 30% B after 2 min., then to 20% A and 80% B after 20 min., then to 5% A and 95% B after 21 min., held at this composition for 1 min. for column washing, then returned to the initial composition for 3 min.

LCMS method

General 5 min method: Gemini C18 column (50 x 4.6 mm, 5µm) operating at ambient temperature and a flow rate of 1.2 mL/min. Mobile phase: A = 10 mM Ammonium Acetate in water, B = Acetonitrile; Gradient profile: from 90 % A and 10 % B to 70 % A and 30 B in 1.5 min, and then to 10 % A and 90 % B in 3.0 min, held at this composition for 1.0 min, and finally back to the initial composition for 2.0 min.

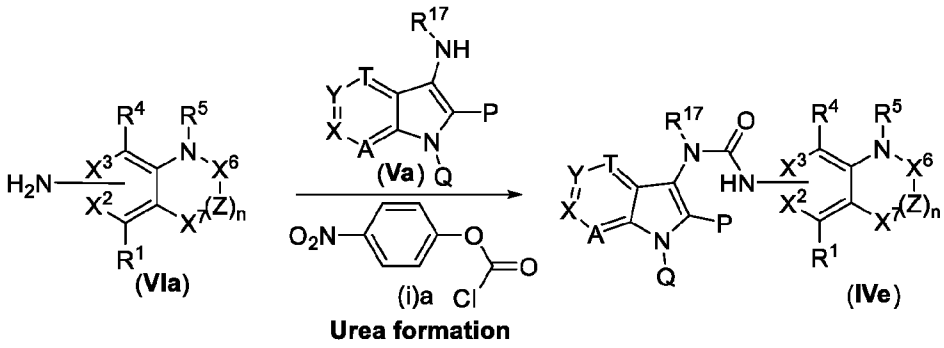
UPLC method

UPLC was carried out on a Waters UPLC using Kinetex EVo C18 column (100 x 2.1 mm, 1.7µm) at ambient temperature and a flow rate of 1.5ml/min.

Mobile phase 1: A = 5 mM Ammonium Acetate in water, B = 5 mM Ammonium Acetate in 90:10 Acetonitrile/water; Gradient profile from 95% A and 5% B to 65% A and 35% B in 2 min., then to 10% A and 90% B in 3.0 min., held at this composition for 2.0 min. and finally back to the initial composition for 6.0 min.

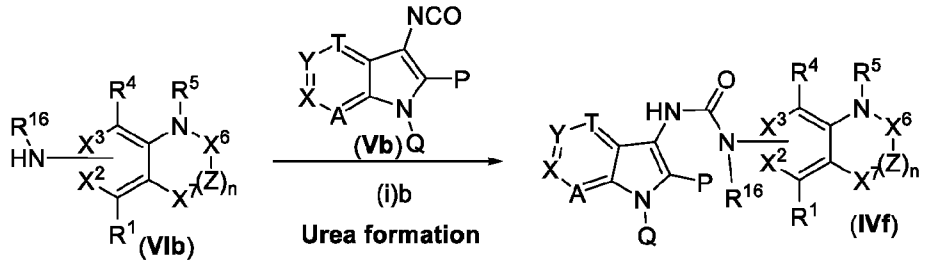
Mobile phase 2: A = 0.05 % formic acid in water, B = Acetonitrile; Gradient profile from 95 % A and 5 % B over 1 min., then 90 % A and 10 % B for 1 min., then 2 % A and 98 % B for 4 min. and then back to the initial composition for 6 min.

General Procedure 1 (Method a)



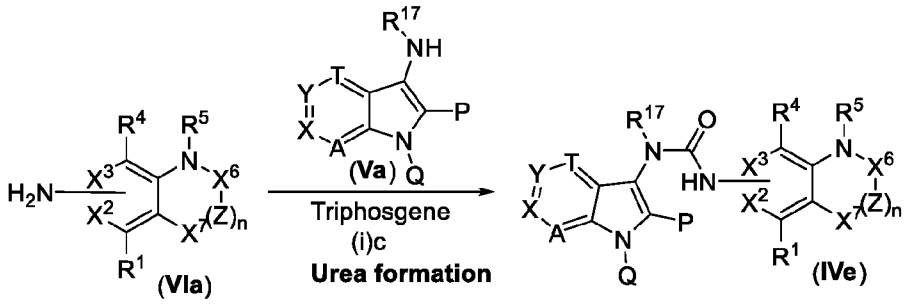
To a stirred solution of an aromatic amine of formula (**VIa**) (1.0 eq.) in a suitable solvent, such as THF, DMF, MeCN or DCM (8 mL/mmol) was added p-nitrophenyl chloroformate (1.2 eq.) at 0-5 °C and the whole stirred at RT for 1-3 h. Then amine (**Va**) (1.1 eq.) and TEA or DIPEA (6 eq.) were added dropwise successively at 0-5 °C and the whole further stirred at RT for 1-5 h. Progress of the reaction was monitored by TLC/LCMS and after completion the reaction mass was diluted with water and extracted with EtOAc. The combined organic layers were washed with a dilute solution of a suitable inorganic base such as $NaHCO_3$ or 1N NaOH followed by 1N HCl and finally with brine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to give a residue which was purified by column chromatography or combi-flash or prep-HPLC to afford a compound of formula (**IVe**) (yield 6-70%) as solids. A similar procedure can be followed to synthesize all urea of formula (**IVe**).

General Procedure 1 (Method b)



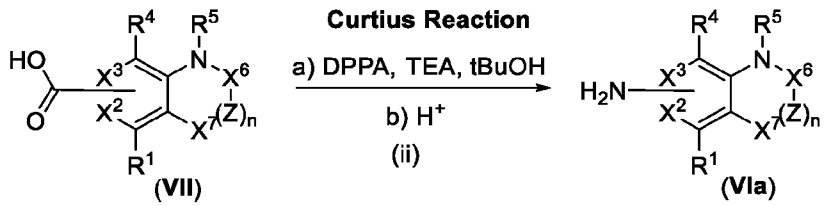
To a stirred solution of an aromatic amine of formula (**VIa**) (1.0 eq.) in a suitable solvent such as THF, DMF, MeCN or DCM (5.5 mL/mmol) was added (**Vb**) (1.08 eq.) followed by TEA (1.08 eq.) at 0-5 °C and the whole stirred for 5-10 min. at the same temperature. The reaction mixture was brought slowly to RT and stirred for 1-2 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to afford a crude solid which was purified by column chromatography or combi-flash or prep-HPLC to afford a compound of formula (**IVe**) (yield 10-70%) as solids. A similar procedure can be followed to synthesize all ureas of formula (**IVe**).

General Procedure 1 (Method c)



To a stirred solution of a compound of formula (**Va**) (1 eq.) in THF (10 mL/mmol) was added triphosgene (0.5 eq.) at 0-5 °C. The combined mixture was stirred at RT for 1 h. Completion of the first stage of the reaction was confirmed by TLC or UPLC-MS before an aromatic amine compound of formula (**VIa**) (1.8 eq.) and TEA (2.5 eq.) were added into the reaction mixture and stirring continued at RT for 1-2 h. Progress of the reaction was monitored by TLC and or UPLC-MS. After completion of the reaction, the solvent was evaporated *in vacuo* to afford the crude material which was purified by column chromatography or prep-HPLC to give a compound of formula (**IVe**) (12-50% yield) as a solid.

General Procedure 2

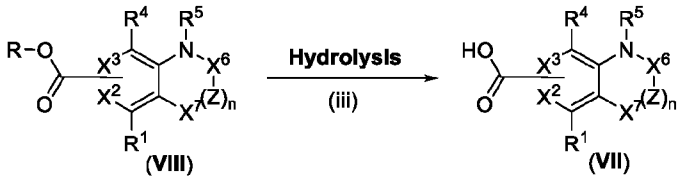


To a stirred solution of a compound of formula (**VII**) (1.0 eq.) in a suitable solvent such as MeCN, THF or DCM (3.5 mL/mmol) under an inert atmosphere was added TEA (1.5 eq.) followed by DPPA (2.0 eq.) at 0-5 °C and the whole stirred for 5-10 min. at the same

temperature. The reaction mixture was then brought to RT and stirred for 4-6 h. Formation of the corresponding acyl azide was confirmed by TLC and UPLC-MS by quenching an aliquot of the reaction mixture with methanol. The solvents were evaporated *in vacuo* and *tert*-butanol (3.5 mL/mmol) added to the resulting residue. This mixture was then refluxed overnight. Completion of the reaction was monitored by TLC and LC-MS, which showed the formation of a BOC-protected amine compound of formula (**VIa**) with complete consumption of the compound of the starting material of formula (**VII**). After completion of the reaction, the solvent was evaporated *in vacuo* to obtain a crude oil which was adsorbed on silica gel and purified by Combi flash to afford the intermediate BOC-protected amine compounds of formula (**VIa**) (40-80% yield) as off white solids.

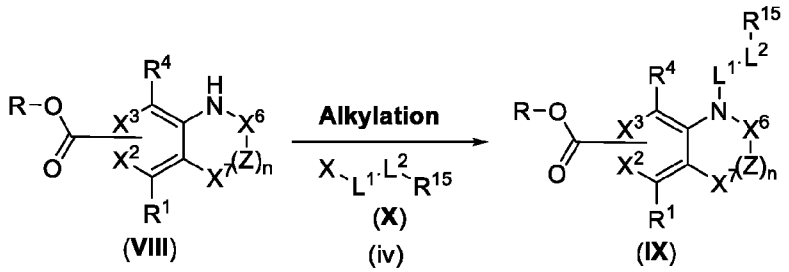
The resulting compound was dissolved in 1,4-dioxane (5.5 mL/mmol) and a solution of 4M HCl in 1,4-dioxane (5.5 mL/mmol) added at 0-5 °C and the whole stirred for 5-10 min. Then the reaction mixture was allowed to warm slowly to room temperature overnight. Completion of the reaction was confirmed by UPLC-MS and after completion the solvent was evaporated *in vacuo*. The resulting crude was then washed with $NaHCO_3$ solution and extracted with EtOAc. The organics were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give compounds of formula (**VIa**) (yield 50-90%) as deep yellow solids.

General Procedure 3



To a stirred solution of ester (**VIII**) (1.0 eq.) in a mixture of MeOH or THF (6.5 mL/mmol) and water (0.8 mL/mmol) was added LiOH, NaOH or KOH (2.0 eq.) at RT and the resulting reaction mixture was stirred at RT for 2-16 h. TLC showed complete consumption of the ester (**VIII**). The solvents were evaporated *in vacuo* and the resulting residue was washed with ether. The residue was then acidified with 1N HCl to pH 5-6, which resulted in the formation of a precipitate, which was filtered and washed with water and then dried by azeotropic distillation or under reduced pressure at 50-60 °C to afford the desired carboxylic acids of formula (**VII**) (70-85% yield) as solids.

General Procedure 4



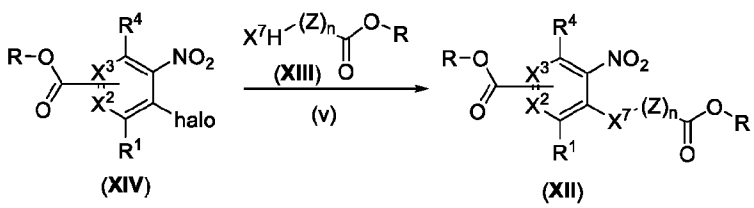
Option A

To a stirred solution of a compound of formula (**VIII**) (1.0 eq.) in DMF or THF or ACN (4 mL/mmol) was added K_2CO_3, Cs_2CO_3, K_2CO_3, Na_2CO_3, NaOH or NaH (1.1 eq.). In the case where NaOH was used, TBAB (0.1 eq.) was also added as a phase transfer catalyst and in the case where K_2CO_3 was used, 18-Crown-6 (0.4 eq.) was also added as a phase transfer catalyst, followed by addition of a compound of formula (**X**) (1.05 eq.) and the mixture allowed to stir at RT for 0.5-1 h. The reaction was monitored by TLC. After completion of the reaction the reaction mixture was quenched with a saturated solution of NH_4Cl, diluted with ice-cold water and extracted with EtOAc or MTBE. The organic layers were washed with brine, dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to afford the crude product which was purified by Combi-flash using mixtures of EtOAc in hexanes as eluent to give compounds of formula (**IX**) (60-80% yield) as colourless oils.

Option B

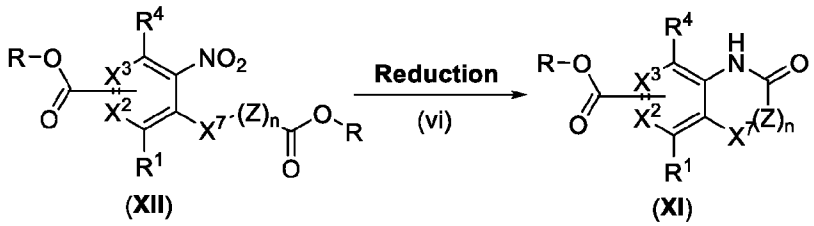
Alternatively, to a stirred solution of a compound of formula (**VIII**) (1,0 eq.) in DCM or MeCN or THF (4 mL/mmol) was added TEA or DIPEA (2.0 eq.) or without the base followed by addition of a compound of formula (**X**) (1.5 eq.) and the whole allowed to stir at RT for 0.5 to 1 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was diluted with water, extracted with EtOAc, and the combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The organic layers were evaporated *in vacuo* to obtain the crude product which was purified by Combi-flash using mixtures of EtOAc in hexanes as eluent to afford compounds of formula (**IX**) (60-80% yield) as colourless oils.

General Procedure 5



To a stirred solution of a compound of formula (**XIV**) (1.0 eq.) and a suitable nucleophile (**XIII**) (1.25 eq.) in a suitable solvent, such as 1,4-dioxane, MeCN, DMF or THF (3 mL/mmol), was added dropwise or portionwise a suitable base such as TEA, DBU, NaH or K_2CO_3 (1.5 eq.) with ice bath cooling and the combined mixture allowed to stir at 0-25 °C for 1-16 h. Progress of the reaction was monitored by TLC or LCMS and on completion of the reaction the mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to dryness. The crude compounds of formula (**XII**) (60-95% yield) obtained as solids were pure enough to be used directly in the next step without any further purification.

General Procedure 6



Option A (Reduction by Fe/Zn-AcOH/HCl/NH4Cl)

To a stirred solution of a compound of formula (**XII**) (1.0 eq.) in EtOH or MeOH (2 mL/mmol) was added a suitable acid, such as AcOH or aq. HCl (3 mL/mmol) followed by iron powder or zinc powder (4.0 eq.) at RT. In some cases NH4Cl was also used as source of hydrogen. The reaction mixture was stirred at 75-85 °C for 1-5 h. The reaction was monitored by TLC or LCMS and after completion the reaction mixture was poured into ice-cold water and filtered through a short celite bed. The filtrate was extracted with EtOAc and then washed with aqueous $NaHCO_3$ and then brine. The collected organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford compounds of formula (**XI**) (60-80% yield) as crude solid, which were used in the next step without any further purification.

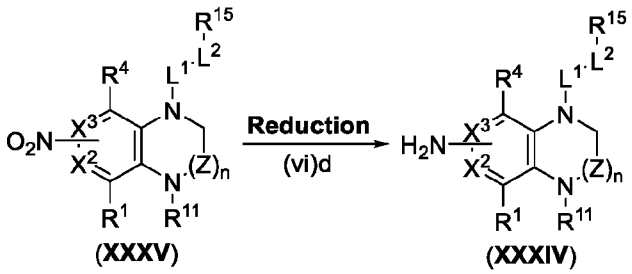
Option B: (Reduction by Sodium dithionate)

To a stirred solution of a compound of formula (**XII**) (1.0 eq.) in a mixture of either MeCN/H_2O or THF/H_2O (12 mL/mmol, 2:1) was added sodium hydrosulphite (8.0 eq.), *tetra*-butyl ammonium hydrosulphate (0.5 eq.) and K_2CO_3 (6.0 eq.) at RT and the mixture then stirred for 1 h. Progress of the reaction was monitored by TLC and or LCMS. After completion of the reaction the solvents were evaporated *in vacuo* to give an oily liquid which was dissolved in 1N HCl and extracted with EtOAc. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The organics were filtered and evaporated *in vacuo* to give a compound of formula (**XI**) (80-90% yield) as solids.

Option C: (Reduction by $Pd/C/H_2$)

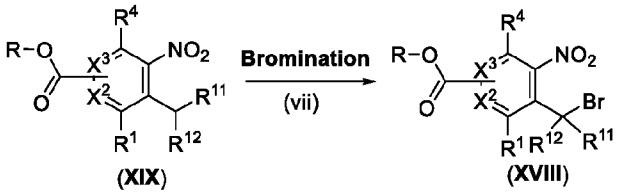
To a stirred solution of a compound of formula (**XII**) (1.0 eq.) in EtOAc, MeOH or EtOH (9.4 mL/mmol, 120 mL) was added 10% Pd-C (50% w/w in water) (77.8 mg/mmol) under an inert atmosphere at room temperature. The reaction mixture was purged with H_2 gas using balloon pressure and then allowed to further stir for 3-5 h at room temperature. The course of the reaction was monitored by TLC and/or LCMS. After completion of the reaction the mixture was diluted with EtOAc, filtered carefully through a bed of celite and washed with EtOAc 4-5 times until the mother liquor showed no compound remaining by TLC. Then the collected organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a compound of formula (**XI**) (80-85 % yield) as semi-solids. The products were pure enough to use in the next step without any further purification.

Option D: (Reduction by $NiCl_2.6H_2O/NaBH_4$)



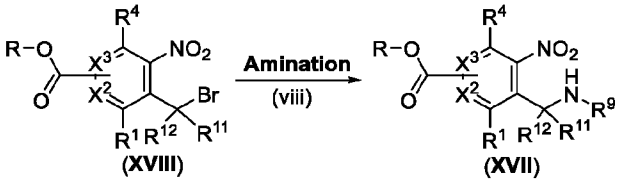
To a stirred solution of a compound of formula (**XXXV**) (1.0 eq.) in MeOH (9 mL/mmol) was added Boc_2O (1.5 eq.) followed by $NiCl_2.6H_2O$ (0.5 eq.) and $NaBH_4$ (2.5 eq.) at 5-10 °C. The combined mixture was then allowed to warm to RT over 3-5 h. Progress of the reaction was monitored by TLC and UPLC-MS which showed formation of the intermediate product. After completion, the reaction mixture was diluted with chilled water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to afford the crude product which was purified by Combi-flash to provide the Boc-protected amine compound (90-96% yield). This material was dissolved in DCM (9 mL/mmol) and TFA (4 mL/mmol) and the whole was stirred at RT for 4-6 h. UPLC-MS showed formation of the desired product. The solvent was evaporated *in vacuo* to give the crude product which was neutralized with aqueous sodium carbonate solution and extracted with EtOAc. The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to afford the compound of formula (**XXXIV**) (80-85% yield) as a semi-solid.

General Procedure 7



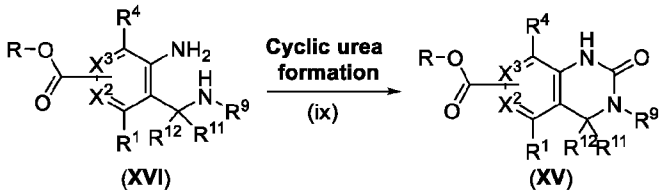
To a stirred solution of a compound of formula (**XIX**) (1.0 eq.) in a suitable solvent such as carbon tetrachloride or trifluoromethylbenzene (100 mL) was added NBS (1.2 eq.) and AIBN or benzoyl peroxide (0.1 eq.). The reaction mixture was heated at 70-100 °C for 12-16 h. After complete consumption of the starting material, the reaction mixture was quenched with a saturated solution of $Na_2S_2O_3$ and extracted with EtOAc. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The crude product obtained after concentration of the organic layer *in vacuo* was purified by column chromatography to afford a compound of formula (**XVIII**) in 30-40% yield.

General Procedure 8



To a stirred solution of a compound of formula (**XVIII**) (1.0 eq.) in a suitable solvent such as THF (5 mL/mmol) was added a suitable amine such as $MeNH_2$, (3 mL/mmol, 2M solution in THF) at RT and the combined mixture was stirred at the same temperature or elevated temperature (60-90 °C) for 10-16 h. After completion of the reaction, the reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed with a saturated brine solution, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford a compound of formula (**XVII**) (60-70% yield) as gummy solids.

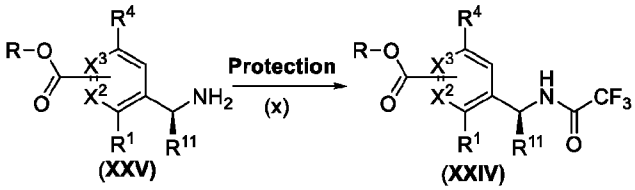
General Procedure 9



To a stirred solution of a compound of formula (**XVI**) (1.0 eq.) in a suitable solvent, such as DCM or THF (5 mL/mmol) was added a suitable carbonyl source equipped with suitable leaving groups, such as 1,1-carbonyl-diimidazole, phosgene or triphosgene (1.1 eq.) followed by a suitable base, such as TEA or DIPEA (3.0 eq.) at 0-5 °C and the reaction mixture was

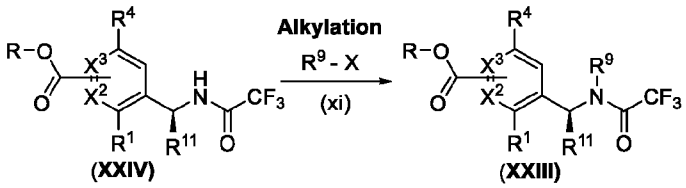
stirred at room temperature under an inert atmosphere for 2-4 h. The reaction mixture was quenched by the addition of a saturated aqueous $NaHCO_3$ solution and extracted with DCM. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to provide a crude residue which was purified by silica gel column chromatography and eluted with 1% MeOH in DCM to afford a compound of formula (**XV**) (20-30% yield) as solids.

General Procedure 10



To a stirred solution of a compound of formula (**XXV**) (1 .0 eq.) in toluene (1.8 mL/mmol) was added TFAA (2.0 eq.) at 10-15 °C dropwise over 20-30 min. and the resulting reaction mixture was stirred at 25-30 °C for 1-5 h. Progress of the reaction was monitored by UPLC-MS. After completion, the reaction mixture was poured into crushed ice and extracted with EtOAc. The combined organic layers were washed successively with a saturated aqueous solution of $NaHCO_3$, brine and then dried over anhydrous Na_2SO_4. The filtered organics were evaporated under reduced pressure to afford compounds of formula (**XXIV**) (85-90% yield) as solids. The products were pure enough to use in the next step without any further purification.

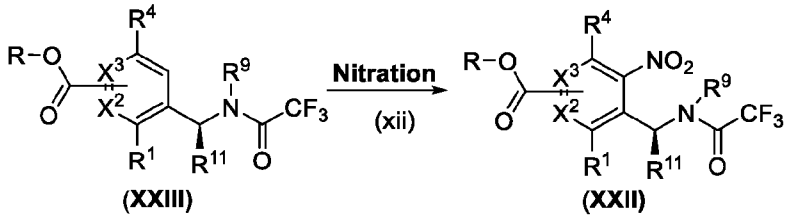
General Procedure 11



To a stirred solution of NaH (1.2 eq., 60% suspension in oil) in DMF (1.65 mL/mmol) was added a mixture of a compound of formula (**XXIV**) (1.0 eq.) and an alkyl or aryl halide (R^9-X) (2.0 eq.) in DMF (1.1 mL/mmol) dropwise using a dropping funnel over 20-30 min. at 10-15 °C and the resulting reaction mixture then stirred for 2 h at 20-25 °C. Completion of the reaction was confirmed by UPLC-MS. The reaction mixture was poured into an ice-water mixture and extracted with EtOAc. The combined organics were washed with 1N HCl, a saturated solution of $NaHCO_3$ and then brine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to afford a compound of formula (**XXIII**)

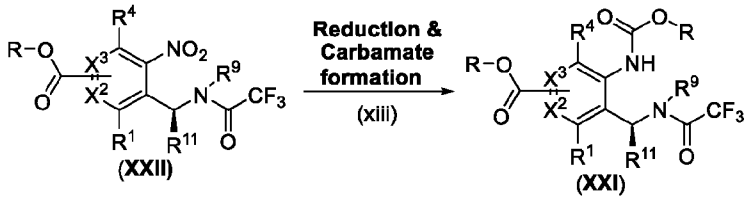
(90-95% yield) as solids. The product was pure enough to use in the next step without any further purification.

General Procedure 12



A compound of formula (**XXIII**) (1.0 eq.) was added into a pre-prepared nitrating mixture of concentrated sulfuric acid (2.17 mL/mmol) and fuming nitric acid (0.73 mL/mmol) portionwise whilst maintaining the internal temperature between 0-5 °C over a period of 30 min. The resulting mixture was stirred at 20-25 °C for 1-2 h. Completion of the reaction was confirmed by UPLC-MS and after consumption of the starting material the reaction mixture was poured into an ice-water mixture and extracted with EtOAc. The combined organics were washed with a saturated solution of $NaHCO_3$ followed by a saturated brine solution, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to afford a compound of formula (**XXII**) (yield 85-95%) as thick oil. The product was pure enough to use in the next step without any further purification.

General Procedure 13



Option A

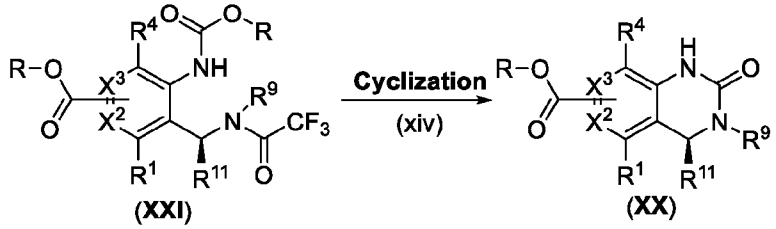
To a stirred solution of a compound of formula (**XXII**) (1.0 eq.) in 1,4-dioxane (3.34 mL/mmol, degassed with nitrogen) was added 10% Pd-C (0.167 g/mmol, 50% w/w in water) under an inert atmosphere and the resulting reaction mixture was stirred under H_2 gas balloon pressure at RT overnight. Progress of the reaction was monitored by TLC and UPLC-MS which showed complete conversion of the nitro group into its corresponding amino group. The balloon was removed and solid K_2CO_3 (1.66 eq.) was added into the reaction vessel followed by the dropwise addition of ethyl chloroformate (1.34 eq.) at RT. The resulting reaction mixture was further stirred overnight. UPLC-MS showed completion of the reaction; the reaction mixture was filtered through a celite bed and the bed was washed with DCM. The filtrate was evaporated *in vacuo* to give a crude product which was dissolved

in EtOAc, washed with water followed by brine, dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to afford a crude product as a thick oil which was purified by trituration with n-hexane and dried to afford a compound of formula (**XXI**) (80-85% yield) as solids.

Option B

To a stirred solution of a compound of formula (**XXII**) (1.0 eq.) in THF (6.68 mL/mmol) was added a solution of K_2CO_3 (6.0 eq.) in water (3 mL/mmol) at 10-15 °C followed by portionwise addition of sodium dithionite (8.0 eq.), TBASH (0.5 eq.) and water (0.4 mL/mmol). The resulting reaction mixture was stirred at RT (20-25 °C) for a further 2-3 h. The reaction was monitored by UPLC-MS and after completion the reaction mixture was left to settle to allow separation of the organic and aqueous layers. The aqueous layer was then extracted with THF. The combined organic layers were dried over anhydrous Na_2SO_4 and then pyridine (0.8 mL/mmol) was added. The mixture was then evaporated at ~40 °C under reduced pressure to afford the crude product which was dissolved in DCM (6.7 mL/mmol) and another portion of pyridine (0.8 mL/mmol) added followed by dropwise addition of ethyl chloroformate (5.0 eq.) at 10-15 °C. The resulting reaction mixture was further stirred at RT for 2-3 h. UPLC-MS showed completion of the reaction. The reaction mixture was diluted with water and allowed to settle to allow separation of the layers. The aqueous layer was washed with DCM and the combined organics were washed with 0.5N HCl, a saturated solution of $NaHCO_3$ and finally with brine. The obtained organic layer was dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to afford the crude product as a yellowish thick oil. The oil was purified by trituration with hexane to give a compound of formula (**XXI**) (85-90% yield) as solids.

General Procedure 14

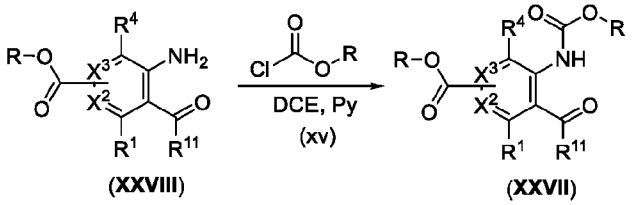


(**XXI**) (**XX**)

To a stirred solution of a compound of formula (**XXI**) (1.0 eq.) in methanol (3.8 mL/mmol) was added K_2CO_3 (2.0 eq.) at RT and the resulting reaction mixture was heated to 60-65 °C for 2-3 h. Progress of the reaction was monitored by UPLC-MS and after completion, the reaction mass was cooled to 5-10°C and acidified with 2N HCl to pH ~3-4. The solvents were evaporated under reduced pressure at 40-45 °C to give the crude product which was dissolved in EtOAc, washed successively with a saturated brine solution, 2N HCl, $NaHCO_3$ solution and finally again with brine, dried over anhydrous Na_2SO_4 and evaporated under

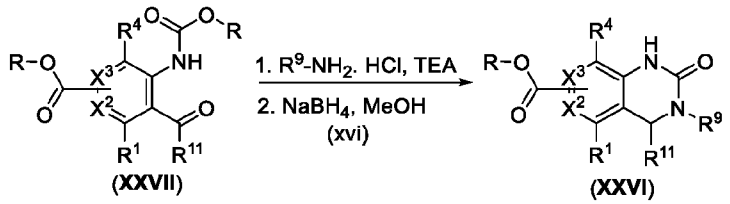
reduced pressure to afford the crude compound as a brownish solid. This was purified by trituration with n-hexane to afford a compound of formula (**XX**) (80-85% yield) as solids.

General Procedure 15



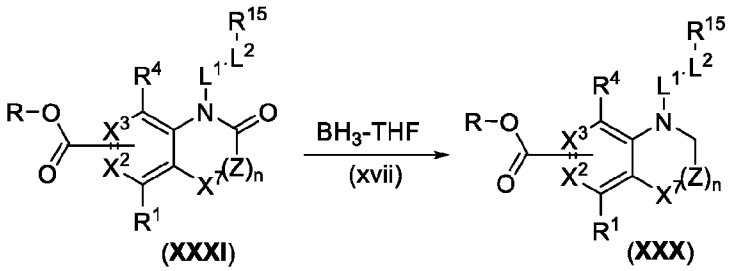
To a stirred solution of a compound of formula (**XXVIII**) (1.0 eq.) in DCE (1.8 mL/mmol) was added pyridine (2.2 eq.) and alkyl(aryl)chloroformate (1.2 eq.) at 0-5 °C and the mixture stirred at RT for 1-2 h. Progress of the reaction was monitored by TLC and LC-MS. Upon completion, the reaction mixture was quenched with 1N HCl solution and extracted with DCM followed by a brine wash. The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford a compound of formula (**XXVII**) (70-75% yield) as solids which were used in the next step without any further purification.

General Procedure 16



To a stirred solution of an amine R^9-NH_2.HCl (1.0 eq.) in MeOH (5 mL/mmol) was added TEA (1.2 eq.) under an inert atmosphere at RT and the whole was stirred for 30 min.. Then, a compound of formula (**XXVII**) (1.0 eq.) was added and stirring was continued for 20-24 h. During this period, the solution became a suspension. $NaBH_4$ (1.5 eq.) was added and the reaction mixture was further stirred for another 20-24 h. Completion of the reaction was monitored by TLC and LC-MS and after completion the reaction mixture was diluted with water and extracted with EtOAc followed by a brine wash. The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford a compound of formula (**XXVI**) as solids.

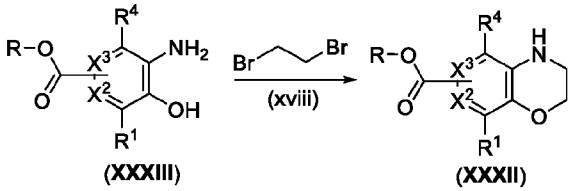
General Procedure 17



(XXXI) (XXX)

A stirred solution of a compound of formula (**XXXI**) (1.0 eq. 0.96 mmol) in THF (5 mL/mmol) was cooled to 0-5 °C and borane-THF complex (1M solution in THF) (10 mL/mmol, 10 eq.) added portionwise. After the addition was complete, the mixture was allowed to warm to RT, and then heated to reflux for 1-2 h. Progress of the reaction was monitored by UPLC-MS which showed formation of a compound of formula (**XXX**). After completion the reaction mixture was diluted with methanol and refluxed for 5-10 min., the solvent was evaporated to give a crude material which was purified by Combi-flash or column chromatography to afford a compound of formula (**XXX**) as colorless oil.

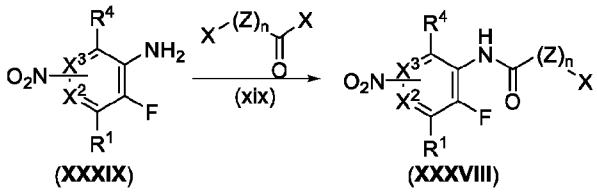
General Procedure 18



(XXXIII) (XXXII)

To a stirred solution of a compound of formula (**XXXIII**) (1.0 eq.) in DMF or THF (1.6 mL/mmol) was added K_2CO_3, Cs_2CO_3, Na_2CO_3, NaOH or NaH (4.0 eq.) at RT and then 1,2-dibromoethane (4.0 eq.) was added and the reaction mass maintained at 80-85 °C for 10-16 h. Progress of the reaction was monitored by TLC and UPLC-MS which showed formation of the desired product. After completion of the reaction, the reaction mixture was diluted with water and extracted with EtOAc. The combined organics were washed with brine, dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to afford a crude material which was purified by Combi-flash to afford compounds of formula (**XXXII**) (50-55% yield) as solids.

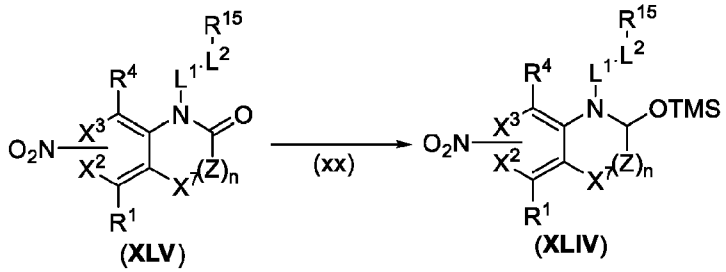
General Procedure 19



(XXXIX) (XXXVIII)

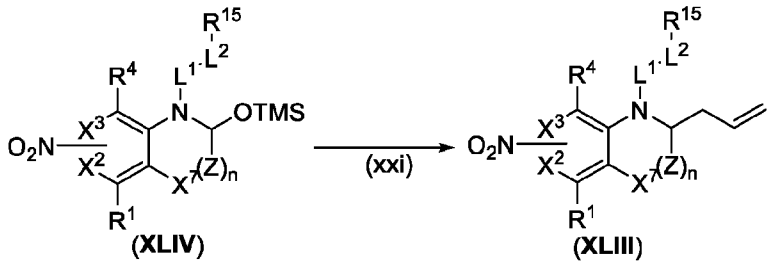
To a stirred solution of a compound of formula (**XXXIX**) (1.0 eq.) in acetone (3.2 mL/mmol) was added a suitable haloacetyl halide (1.3 eq.) at RT and the combined mixture was stirred at RT for 1-2 h. Progress of the reaction was monitored by TLC and UPLC-MS and after completion the reaction mixture was quenched with ice-cold water to give a solid precipitate which was filtered, washed with water and then dried in a vacuum oven to afford a compound of formula (**XXXVIII**) (85-90% yield) as a brownish solid.

General Procedure 20



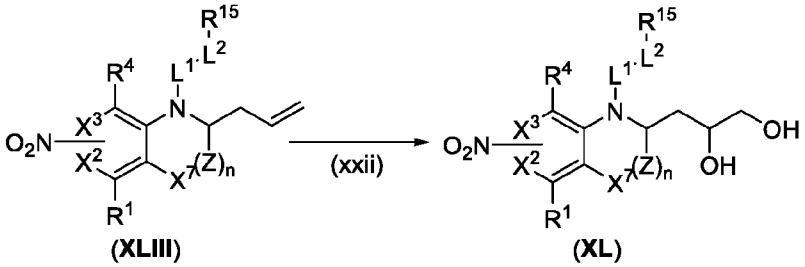
To a stirred solution of a compound of formula (**XLV**) (1.0 eq.) in DCM (10 mL/mmol) was added DIBAL-H (1.5 eq.) at -78 °C under a nitrogen atmosphere. The whole was stirred for 1-2 h at the same temperature and then pyridine (3.5 eq.) and TMSOTf (3.0 eq.) were added to the reaction mixture. The temperature of the reaction was then slowly allowed to rise to 0-5 °C. Progress of the reaction was monitored by TLC and after completion of the reaction, Et_2O (285 mL/mmol) was added and the mixture was filtered. The collected organic layer was then concentrated *in vacuo* to afford compound of formula (**XLIV**) as crude solids.

General Procedure 21



To a stirred solution of a compound of formula (**XLIV**) (1.0 eq.) in DCM (10 mL/mmol) was added allyl-TMS (4.0 eq.) and $BF_3.Et_2O$ (4.0 eq.) at -78 °C under nitrogen. The temperature was then slowly raised to 0-5 °C. Progress of the reaction was checked by UPLC-MS and after completion of the reaction it was quenched with water and extracted with EtOAc. The combined organic layer was collected, dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The crude product was purified by column chromatography to afford the title compounds of formula (**XLIII**) (70-75% yield) as pure solids.

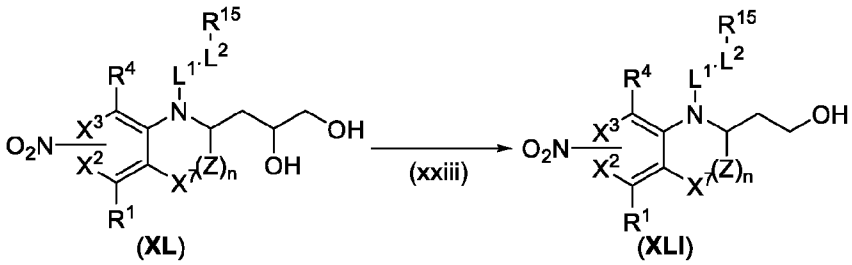
General Procedure 22



(XLIII) (XL)

To a stirred solution of a compound of formula (**XLIII**) (1.0 eq.) in ^{t}BuOH/H_2O solution (12 mL/mmol, 1:1) was added OsO_4 (0.09 eq.) and NMO (1.4 eq.). The resulting reaction mixture was stirred at RT for 10-12 h. Progress of the reaction was checked by LCMS and after completion of the reaction it was further diluted with EtOAc. The organic layer was separated and washed with 10% HCl, water and finally with brine. It was then dried and concentrated *in vacuo* to afford a compound of formula (**XL**) as a crude solid.

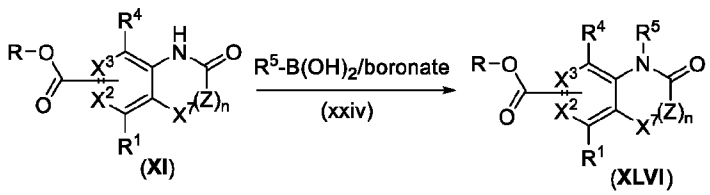
General Procedure 23



(XL) (XLI)

To a stirred solution of a compound of formula (**XL**) (1.0 eq.) in ^{t}BuOH/H_2O solution (12 mL/mmol, 1:1) was added $NaIO_4$ (4.0 eq.) at RT. The resulting reaction mixture was stirred at RT for 10-12 h. Progress of the reaction was checked by LCMS and after completion of the reaction it was diluted with water and extracted with EtOAc. The separated organic layer was dried and concentrated *in vacuo* to afford the crude corresponding aldehyde which was dissolved in methanol (12 mL/mmol) and $NaBH_4$ (2.0 eq.) added at 0-5 ^{o}C. The reaction mixture was further stirred at RT for 1-2 h. After completion of the reaction it was quenched with NH_4Cl solution and extracted with EtOAc. The separated organic layers were dried and concentrated *in vacuo* to afford compound of formula (**XLI**) as crude solids.

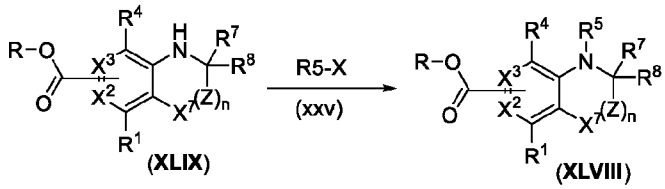
General Procedure 24



(XI) (XLVI)

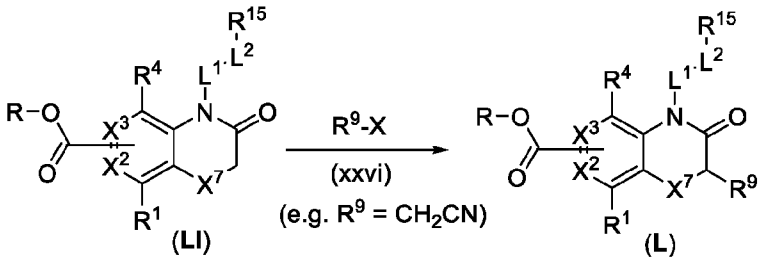
To a stirred solution of a compound of formula (**XI**) (1.0 eq.) in EDC (1.1 mL/mmol) was added R^5-$B(OH)_2$/boronate (1.5 eq.) in EDC or toluene (1.1 mL/mmol), DBU (2.0 eq.) and a solution of Cu(OAc) (2.0 eq.) at RT. The resulting reaction mixture was stirred at RT for 20-24 h. Progress of the reaction was monitored by LCMS and after completion the reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to afford the crude material which was purified by Combi-flash to afford a compound of formula (**XLVI**) (34-40% yield) as a solid.

General Procedure 25



To a stirred solution of a compound of formula (**XLIX**) (1.0 eq.) in toluene or dioxane or EDC (6 mL/mmol) was added R^5-X (where X is a suitable leaving group) (1.5 eq.), cesium carbonate (2.0 eq.) and BINAP (0.2 eq.) at RT. The whole was degassed with nitrogen for 20 min., then $Pd(OAc)_2$ (0.1 eq.) was added into the reaction mixture and stirring continued at 100-110 °C for 20-24 h. Progress of the reaction was monitored by UPLC-MS and after completion the reaction mixture was concentrated *in vacuo* to give a crude material which was purified by column chromatography to afford a compound of formula (**XLVIII**) (30-35% yield) as a solid.

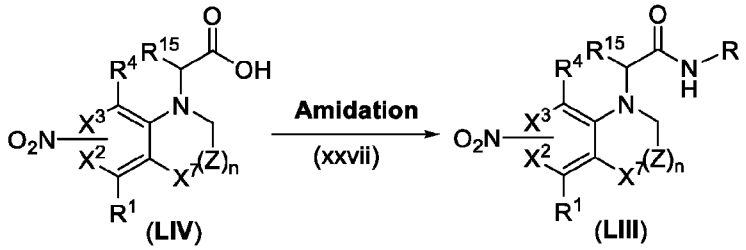
General Procedure 26



To a stirred solution of a compound of formula (**LI**) (1.0 eq.) in dry Et_2O or THF (6 mL/mmol) was added LiHMDS (1.5 eq.) at -78 °C under an inert atmosphere and stirred for 5-10 min. R^9-X e.g. bromoacetonitrile (1.2 eq.) was then added to the reaction mixture and stirring continued for 30 min. at the same temperature. After this time, the reaction mixture was brought slowly to room temperature and stirred for 1-2 h. Progress of the reaction was monitored by UPLC-MS and after completion of the reaction it was quenched with a saturated solution of NH_4Cl and extracted with EtOAc. The combined organic layers were

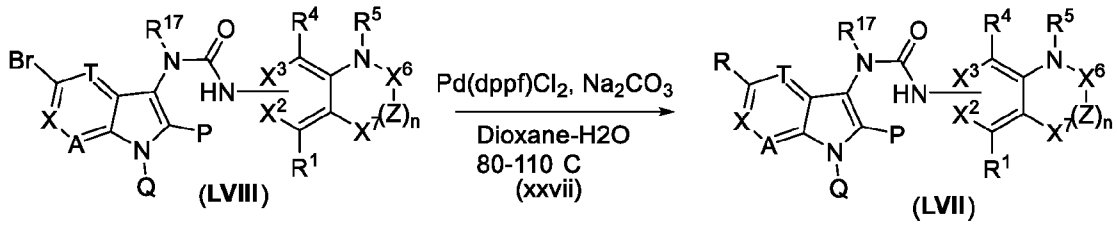
washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude product which was purified by combi-flash to afford a compound of formula (**L**) (45-50% yield) as a solid.

General Procedure 27



To a stirred solution of a compound of formula (**LIV**) (1.0 eq.) in DMF (5.5 mL/mmol) was added an amide coupling reagent such as EDC-HCl (1.5 eq.) and DIPEA (3.0 eq.) at 0-5 °C and the reaction mixture was stirred for 5-10 min. at this temperature. R-NH2 (5.0 eq.) was then added and the reaction mixture was stirred at RT for 10-16 h. After completion of the reaction (monitored by TLC), the solvent was evaporated under reduced pressure to give a residue which was extracted with EtOAc and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to afford the crude product. This crude material was purified by column chromatography to give compounds of formula (**LIII**) (70-75% yield) as solids.

Library General Procedure 28



To a degassed solution of a compound of formula (**LVIII**) (1.0 eq. 100 mg, 0.2 mmol) in a mixture of 1,4-dioxane and water (50 mL/mmol, 9:1) was added suitable boranic acid or boronate ester (1.2 eq.), sodium carbonate (2.0 eq.) and $Pd(dppf)Cl_2$ (0.1 eq.). The whole was heated to 80-110 °C under a N_2 atmosphere for 3-16 h. Completion of the reaction was confirmed by LCMS and TLC. Then the reaction mass was filtered through a celite bed and the filtrate was concentrated under reduced pressure to give the crude product which was purified by combi-flash or prep-HPLC to afford the compounds of formula (**LVII**) (25-15% yield) as an off-white to white solid.

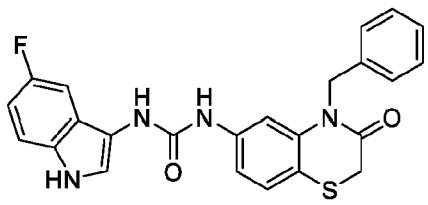
Examples

Nuclear magnetic resonance (NMR) spectra were in all cases consistent with the proposed structures. Characteristic chemical shifts (δ) are given in parts-per-million downfield from tetramethylsilane (for ^{1}H-NMR) and upfield from trichloro-fluoro-methane (for ^{19}F NMR) using conventional abbreviations for designation of major peaks: e.g. s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. The following abbreviations have been used for common solvents: $CDCl_3$, deuterochloroform; d_6-DMSO, deuterodimethylsulphoxide; and CD_3OD, deuteromethanol.

Mass spectra, MS (m/z), were recorded using electrospray ionisation (ESI). Where relevant and unless otherwise stated the m/z data provided are for isotopes ^{19}F, ^{35}Cl, ^{79}Br and ^{127}I. All chemicals, reagents and solvents were purchased from commercial sources and used without further purification. All reactions were performed under an atmosphere of nitrogen unless otherwise noted.

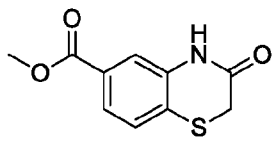
Flash column chromatography was carried out using pre-packed silica gel cartridges in a Combi-Flash platform. Prep-HPLC purification was carried out according to the General purification and analytical methods described above. Thin layer chromatography (TLC) was carried out on Merck silica gel 60 plates (5729). All final compounds were >95% pure as judged by the LCMS or UPLC analysis methods described in the General Purification and Analytical methods above unless otherwise stated.

Example 1: 1-(4-Benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-fluoro-1H-indol-3-yl)urea

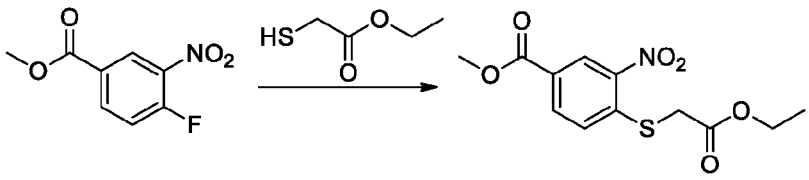


Example 1 was prepared according to the methods described in General Procedures 1-6, and the methods described below.

Preparation 1: Methyl 3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxylate

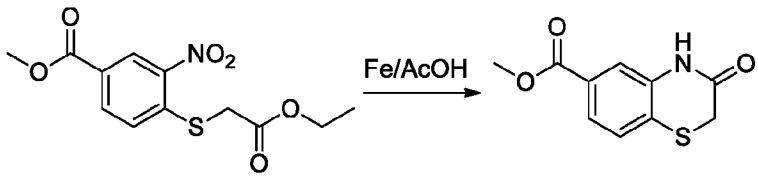


Step 1: Methyl 4-((2-ethoxy-2-oxoethyl)thio)-3-nitrobenzoate



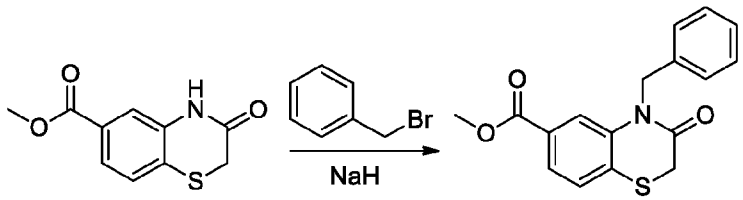
Methyl 4-fluoro-3-nitrobenzoate (10.0 g, 50.2 mmol) was taken up in MeCN (2.0 L) and TEA (7.61 g, 75.38 mmol) was added to the solution. The reaction mixture was cooled to 0-5 °C and ethyl thioglycolate (7.25 g, 62.7 mmol) was added dropwise. The reaction mixture was stirred for 30 min. at ice-cold temperature. It was then diluted with EtOAc and washed with a saturated solution of NH_4Cl and brine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to dryness to give the title compound (14.0 g, 46.82 mmol, 93% yield) as a yellow solid, which was pure enough to be used in the next step without any further purification. LCMS m/z: 300.06 [M+H].

Step 2: Methyl 3-oxo-3,4-dihydro-2*H*-benzo[b-1,4]thiazine-6-carboxylate



To a stirred solution of methyl 4-((2-ethoxy-2-oxoethyl)thio)-3-nitrobenzoate (Step 1) (5.0 g, 16.7 mmol) in acetic acid (50 mL) was added iron powder (3.73 g, 66.8 mmol). The resulting reaction mixture was stirred at 80 °C for 3 h. On completion (monitored by TLC), the reaction was cooled to room temperature and poured onto 1N HCl (250 mL) and then stirred for 1 h. The resulting white precipitate was filtered off and washed with water. The residue obtained was re-dissolved in 5% MeOH in DCM (50 mL) and filtered through a bed of celite. The filtrate was evaporated to dryness *in vacuo* to afford the title compound (3.5 g, 15.6 mmol, 91% yield) as a pale yellow solid. LCMS m/z: 222.05 [M-H].

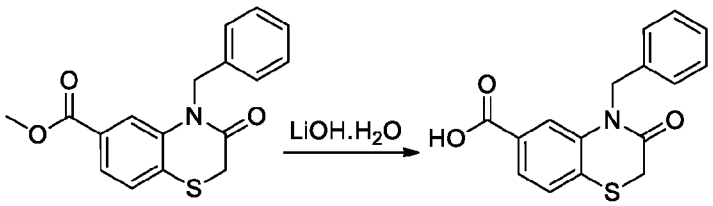
Preparation 2: Methyl 4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxylate



To a stirred solution of methyl 3-oxo-3,4-dihydro-2*H*-benzo[b-1,4]thiazine-6-carboxylate (Preparation 1, Step 2) (5.0 g, 22.2 mmol) in DMF (50 mL) at 0-5 °C was added NaH (0.98 g, 24.4 mmol) portionwise and the whole stirred for another 5-10 min. at the same

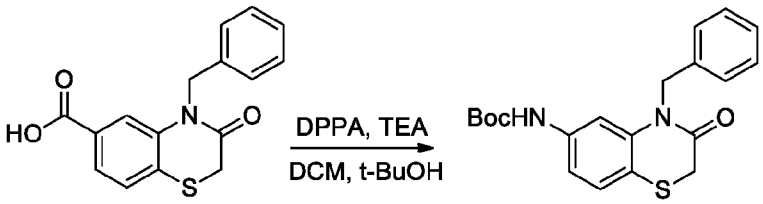
temperature. Then, benzyl bromide (2.8 mL, 23.3 mmol) was added and the reaction mixture was stirred for 1 h. Completion of the reaction was monitored by TLC and LC-MS. After completion, the reaction mixture was quenched with a saturated solution of NH_4Cl and diluted with ice-cold water. The aqueous reaction mixture was extracted with MTBE and washed with brine. The separated organic layer was then dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the title compound (9.0 g) as a crude pale yellow solid which was used in the next step without any further purification. LCMS m/z: 314.16 [M+H].

Preparation 3: 4-Benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxylic acid



To a stirred solution of methyl 4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxylate (Preparation 2) (9.0 g, 28.8 mmol) in a mixture of solvents THF/MeOH/H_2O (160 mL, 2:1:1) was added LiOH.H_2O (4.8 g, 115.2 mmol) at RT and the combined mixture stirred for 2 h at the same temperature. Progress of the reaction was monitored by TLC and LC-MS, showing complete consumption of the starting material. The solvents were evaporated *in vacuo* and the resulting residue was diluted with water and washed with EtOAc. The aqueous layer was collected and acidified with 1N HCl to pH 5-6 to obtain a precipitate which was filtered, collected and dried by azeotropic distillation with MeCN to afford the title compound (5.0 g) as a crude white solid. LCMS m/z: 300.13 [M+H].

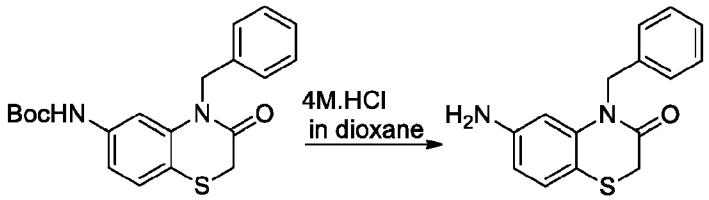
Preparation 4: *tert*-Butyl (4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)carbamate



To a stirred solution of 4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxylic acid (Preparation 3) (4.5 g, 14.4 mmol) in DCM (50 mL) was added TEA (3 mL, 21.6 mmol) under an inert atmosphere at 0-5 °C followed by DPPA (6.3 mL, 28.8 mmol) and stirring then continued for 5 min. at the same temperature. The reaction mixture was brought slowly to room temperature and stirred for 4 h. Formation of the corresponding acyl azide was confirmed by TLC and UPLC-MS by quenching an aliquot of the reaction mixture into

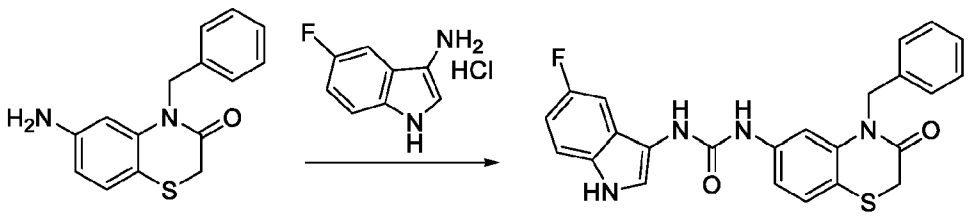
methanol. The solvents were evaporated, *tert*-butanol (50 mL) was added to the reaction mixture and the whole was refluxed overnight. Completion of the reaction was monitored by TLC and LC-MS, which showed formation of the desired product with complete consumption of the starting material. The solvents were evaporated *in vacuo* to obtain a crude oil which was adsorbed onto silica gel and purified by Combi flash to afford the title compound (4.2 g, 80% yield) as an off white solid. LCMS m/z: 317.15 [M+H].

Preparation 5: 6-Amino-4-benzyl-2H-benzo[b][1,4]thiazin-3(4H)-one



To a stirred solution of *tert*-butyl (4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)carbamate (Preparation 4) (1.0 g, 2.7 mmol) in 1,4-dioxane (15 mL) was added HCl (15 mL, 4M HCl solution in 1,4-dioxane) at 0-5 °C and the combined mixture stirred for 5 min. The reaction mixture was then stirred overnight at room temperature. UPLC showed consumption of the starting material. The solvent was evaporated *in vacuo*. The resulting crude residue was then washed with $NaHCO_3$ solution and extracted with EtOAc. It was then evaporated *in vacuo* to give the title compound (750 mg, 90.5% yield) as a deep yellow solid. LCMS m/z: 271.23 [M+H].

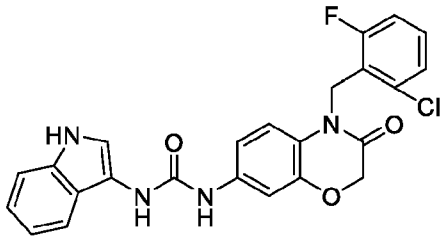
Preparation 6: 1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-fluoro-1H-indol-3-yl)urea (**Example 1**)



To a stirred solution of 6-amino-4-benzyl-2H-benzo[b][1,4]thiazin-3(4H)-one (Preparation 5) (100 mg, 0.37 mmol) in THF (2.5 mL) was added p-nitrophenyl-chloroformate (89.22 mg, 0.44 mmol) at 0-5 °C and the combined mixture was stirred for 5 min. and then allowed to warm slowly to room temperature over 1 h at which point carbamate formation was confirmed by TLC. Then, 6-amino-5-fluoro-indole hydrochloride (69.03 mg, 0.37 mmol) in THF (2.5 mL) was added followed by TEA (0.16 mL, 1.11 mmol) at 0-5 °C and the reaction mixture was stirred at room temperature for a further 1 h. Urea formation was detected by UPLC-MS and TLC and after completion the reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed with 10% sodium

bicarbonate solution, followed by 1N HCl and finally with brine, dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to give the crude product which was purified by prep-HPLC to afford the title compound (22 mg, 14% yield) as a brick red solid. Purity by UPLC: 95.24%; 1H NMR (500 MHz; DMSO-d_6): δ 3.64 (s, 2H), 5.18 (s, 2H), 6.94 (t, J = 8.85 Hz, 1H), 7.20 (t, J= 9.6 Hz, 1H), 7.19-7.25 (m, 4H), 7.30-7.35 (m, 5H), 7.52 (s, 1H), 8.50 (s, 1H), 8.67 (s, 1H), 10.87 (s, 1H); LCMS m/z: 447.16 [M+H].

Example 2: 1-(4-(2-Chloro-6-fluorobenzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1H-indol-3-yl)urea



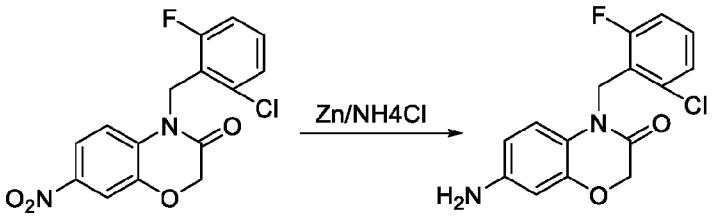
Example 2 was prepared according to General Procedure 1, 4, 6 and the methods described below.

Preparation 7: 4-(2-Chloro-6-fluorobenzyl)-7-nitro-2H-benzo[b][1,4]oxazin-3(4H)-one



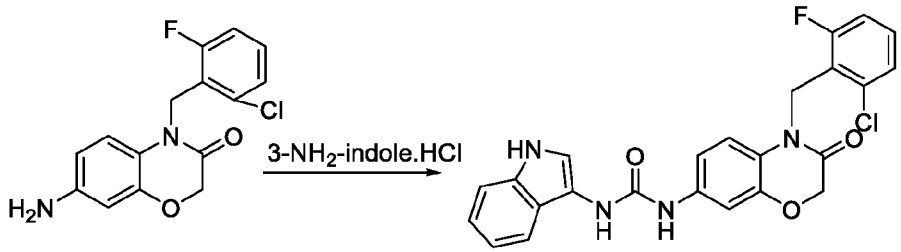
To a stirred solution of commercially available 7-nitro-2H-benzo[b][1,4]oxazin-3(4H)-one (1.0 g, 5.15 mmol) in DMF (10.0 mL) was added Cs_2CO_3 (3.35 g, 10.30 mmol) and 2-chloro-6-fluoro-benzyl bromide (1.06 mL, 7.73 mmol) at room temperature and stirred at the same temperature for 3 h. Progress of the reaction was monitored by LCMS and after completion of the reaction, the reaction mixture was quenched with saturated aqueous sodium bicarbonate solution. The product was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine solution (1 x 30 mL), dried over anhydrous $Na_2SO_4$and filtered. The filtrate was concentrated under reduced pressure to give crude. The crude was purified by Combi-flash chromatography (10-15% EtOAc-Hexane) to afford the title compound (1.0 g, 57.6% yield) as an orange solid. LCMS m/z: 337.1 [M+H]

Preparation 8: 7-Amino-4-(2-chloro-6-fluorobenzyl)-2H-benzo[b][1,4]oxazin-3(4H)-one



To a stirred solution of 4-(2-chloro-6-fluorobenzyl)-7-nitro-2H-benzo[b][1,4]oxazin-3(4H)-one (Preparation 7) (300.0 mg, 0.89 mmol) in acetone/water (4:1 mL) was added ammonium chloride (476.59 mg, 8.91 mmol) and Zn-dust (291.26 mg, 4.45 mmol) at RT. The whole was allowed to stir at room temperature for 10 min. after which time TLC indicated the starting material was consumed and a new polar spot had formed. The reaction mass was filtered through a celite bed and washed with EtOAc. The solvents were then evaporated to obtain the crude material which was purified by Combi flash chromatography using 5% MeOH in DCM as solvent to afford the title compound (180 mg. 65.8% yield) as a yellow solid. LCMS m/z: 307.01 [M+H]

Preparation 9: 1-(4-(2-Chloro-6-fluorobenzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1H-indol-3-yl)urea (**Example 2**)

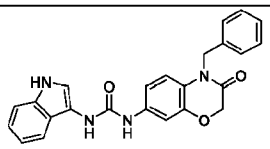
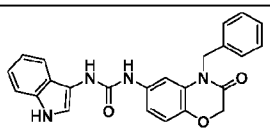
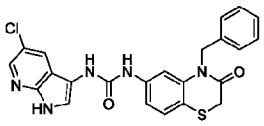
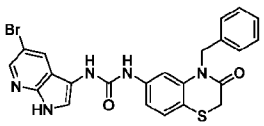
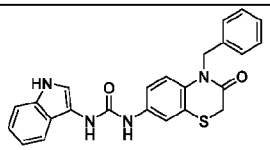
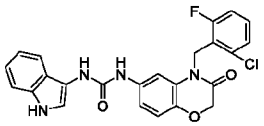
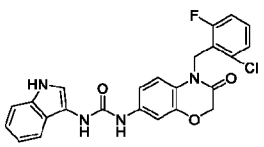


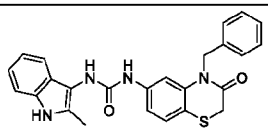
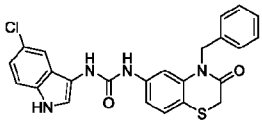
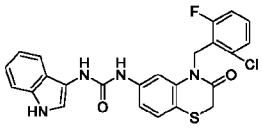
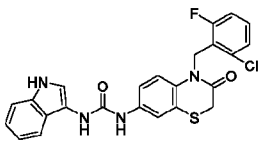
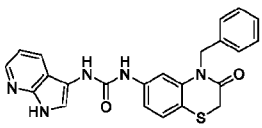
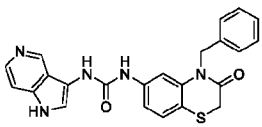
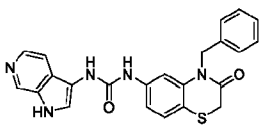
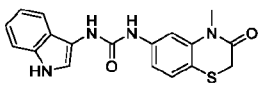
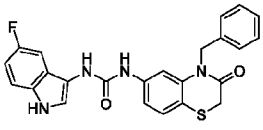
To a stirred solution of 7-amino-4-(2-chloro-6-fluorobenzyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (Preparation 8) (200 mg, 0.65 mmol) in THF (5 mL) was added p-nitrophenyl chloroformate (197 mg, 0.98 mmol) at 0-5 °C and the mixture was stirred at room temperature for 3 h. Then to the reaction mixture were added triethylamine (0.45 mL, 3.26 mmol) and 3-aminoindole hydrochloride (86.1 mg, 0.65 mmol) at room temperature and the resulting mixture was stirred at 70 °C for another 2 h. After completion (monitored by LCMS), the reaction mixture was quenched with water and extracted with EtOAc (2 x 20 mL). The combined organic layer was washed with brine (2 x 20 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude product which was purified by prep HPLC to afford the title compound (20 mg, 6.6% yield) as a brown solid. Purity by HPLC: 97.77%; 1H NMR (400 MHz; DMSO-d_6): δ 4.65 (s, 2H), 5.27 (s, 2H), 6.92-7.01 (m, 3H), 7.08 (t, *J*= 7.12 Hz, 1H), 7.12-7.22 (m, 1H), 7.27 (d, *J* = 2.0 Hz, 1H), 7.31-7.38

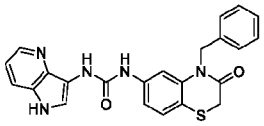
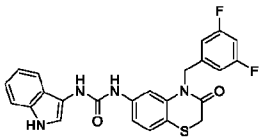
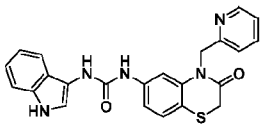
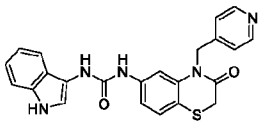
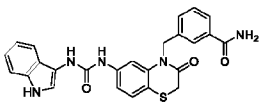
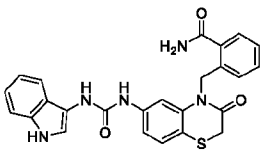
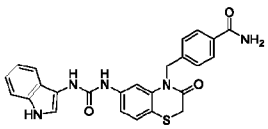
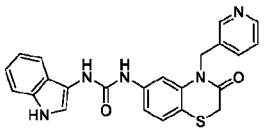
(m, 3H), 7.45 (d, J = 2.32 Hz, 1H), 7.48 (d, J = 7.84 Hz, 1H), 8.43 (s, 1H), 8.54 (s, 1H), 10.71 (s, 1H); LCMS m/z: 465.23 [M+H].

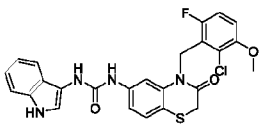
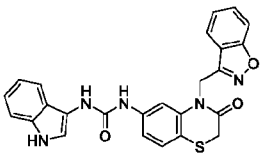
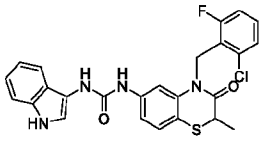
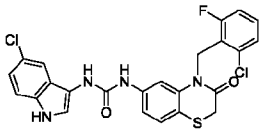
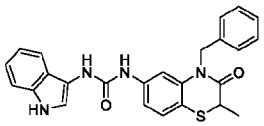
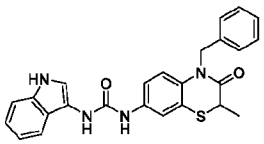
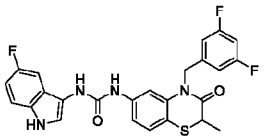
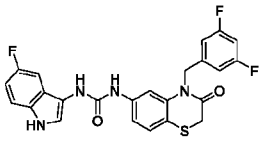
Examples 3-37

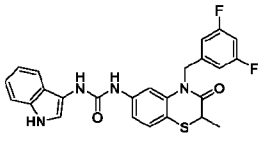
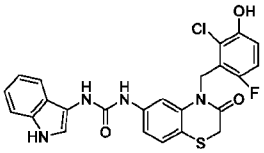
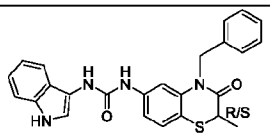
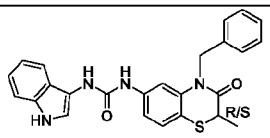
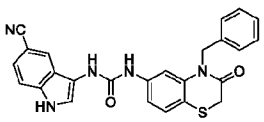
The examples in the table below were prepared according to the above methods used to make Examples 1 and 2 as described in General Procedures 1-6 using the appropriate amines. Purification was as stated in the aforementioned methods

Ex.	Structure	IUPAC Name	LCMS [M+H]	Purity (%)
3		1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1H-indol-3-yl)urea	413.13	94.15
4		1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)-3-(1H-indol-3-yl)urea	413.15	95.07
5		1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)urea	464.14	95.09
6		1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)urea	508.13	98.57
7		1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-7-yl)-3-(1H-indol-3-yl)urea	429.1	93.88
8		1-(4-(2-chloro-6-fluorobenzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)-3-(1H-indol-3-yl)urea	465.19	99.88
2		1-(4-(2-chloro-6-fluorobenzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1H-indol-3-yl)urea	465.23	97.77

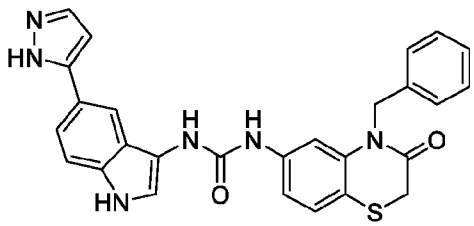
Ex.	Structure	IUPAC Name	LCMS [M+H]	Purity (%)
9		1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(2-methyl-1H-indol-3-yl)urea	443.15	99.19
10		1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-chloro-1H-indol-3-yl)urea	463.1	97.94
11		1-(4-(2-chloro-6-fluorobenzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(1H-indol-3-yl)urea	481.22	95.57
12		1-(4-(2-chloro-6-fluorobenzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-7-yl)-3-(1H-indol-3-yl)urea	481.22	99.72
13		1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(1H-pyrrolo[2,3-b]pyridin-3-yl)urea	530.08	99.81
14		1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(1H-pyrrolo[3,2-c]pyridin-3-yl)urea	430.1	95.7
15		1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(1H-pyrrolo[2,3-c]pyridin-3-yl)urea	430.09	99.28
16		1-(1H-indol-3-yl)-3-(4-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)urea	351.1	97.99
1		1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-fluoro-1H-indol-3-yl)urea	447.16	95.24

Ex.	Structure	IUPAC Name	LCMS [M+H]	Purity (%)
17		1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(1H-pyrrolo[3,2-b]pyridin-3-yl)urea	428.16 (M-H)	97.21
18		1-(4-(3,5-difluorobenzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(1H-indol-3-yl)urea	465.23	99.79
19		1-(1H-indol-3-yl)-3-(3-oxo-4-(pyridin-2-ylmethyl)-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)urea	430.23	97.72
20		1-(1H-indol-3-yl)-3-(3-oxo-4-(pyridin-4-ylmethyl)-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)urea	430.21	93.48
21		3-((6-(3-(1H-indol-3-yl)ureido)-3-oxo-2,3-dihydro-4H-benzo[b][1,4]thiazin-4-yl)methyl)benzamide	472.26	99.4
22		2-((6-(3-(1H-indol-3-yl)ureido)-3-oxo-2,3-dihydro-4H-benzo[b][1,4]thiazin-4-yl)methyl)benzamide	472.26	99.3
23		4-((6-(3-(1H-indol-3-yl)ureido)-3-oxo-2,3-dihydro-4H-benzo[b][1,4]thiazin-4-yl)methyl)benzamide	472.15	98.8
24		1-(1H-indol-3-yl)-3-(3-oxo-4-(pyridin-3-ylmethyl)-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)urea	430.4	99.6

Ex.	Structure	IUPAC Name	LCMS [M+H]	Purity (%)
25		1-(4-(2-chloro-6-fluoro-3-methoxybenzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(1H-indol-3-yl)urea	511.28	99.84
26		1-(4-(benzo[d]isoxazol-3-ylmethyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(1H-indol-3-yl)urea	470.27	99.33
27		1-(4-(2-chloro-6-fluorobenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(1H-indol-3-yl)urea	495.09	95.45
28		1-(5-chloro-1H-indol-3-yl)-3-(4-(2-chloro-6-fluorobenzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)urea	515.04	95.6
29		1-(4-benzyl-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(1H-indol-3-yl)urea	443.11	97.01
30		1-(4-benzyl-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-7-yl)-3-(1H-indol-3-yl)urea	443.15	97.15
31		1-(4-(3,5-difluorobenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-fluoro-1H-indol-3-yl)urea	497.12	97.28
32		1-(4-(3,5-difluorobenzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-fluoro-1H-indol-3-yl)urea	483.15	99.02

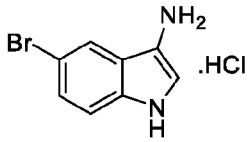
Ex.	Structure	IUPAC Name	LCMS [M+H]	Purity (%)
33		1-(4-(3,5-difluorobenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(1H-indol-3-yl)urea	479.17	99.19
34		1-(4-(2-chloro-6-fluoro-3-hydroxybenzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(1H-indol-3-yl)urea	497.27	98.56
35	 single isomer	1-(4-benzyl-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(1H-indol-3-yl)urea	443.16	97.61
36	 single isomer	1-(4-benzyl-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(1H-indol-3-yl)urea	443.17	95.88
37		1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-cyano-1H-indol-3-yl)urea	454.5	99.63

Example 38: 1-(5-(1H-Pyrazol-5-yl)-1H-indol-3-yl)-3-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)urea

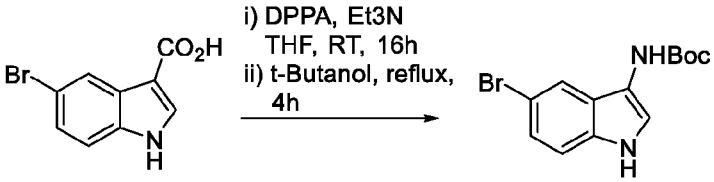


Example 38 was prepared according to General Procedure 1-6, Library General Procedure 28 and the methods described below.

Preparation 12: 5-Bromo-1H-indol-3-amine hydrochloride

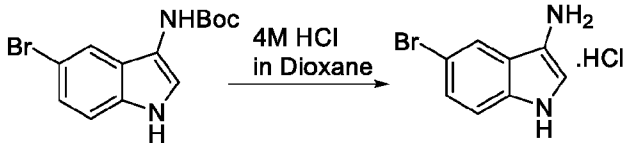


Step-1: *tert*-Butyl (5-bromo-1H-indol-3-yl)carbamate



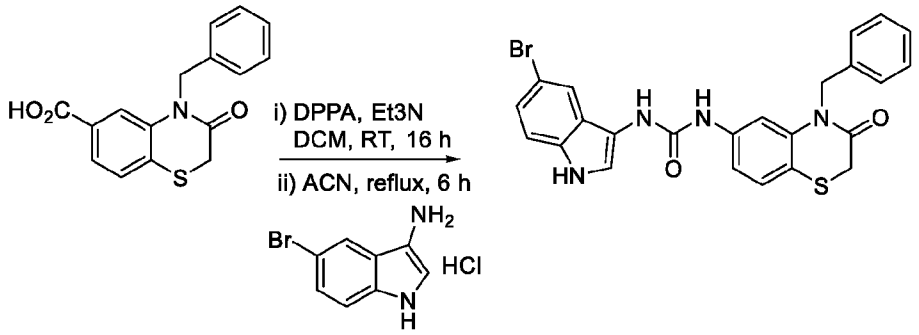
To a stirred solution of commercially available 5-bromo-1H-indole-3-carboxylic acid (5.0 g, 20.83 mmol) in THF (50 mL) were added triethylamine (5.37 mL, 25 mmol) and DPPA (3.48 mL, 25 mmol) at room temperature and the mixture was stirred at the same temperature overnight. After completion of the reaction (monitored by LCMS), the solvent was evaporated under pressure and the resulting reaction mixture was dissolved in t-butanol (50 mL) and refluxed for 5 h. Then, the reaction mixture was concentrated under vacuum and taken up in EtOAc (100 mL). The organic layer was washed with saturated aqueous sodium bicarbonate solution (3 x 100 mL), water (3 x 100 mL), brine (3 x 100 mL), dried over $Na_2SO_4$and concentrated to give the crude product which was purified over silica gel column chromatography to afford the title compound (3.5 g, 79.6% yield) as an off-white solid. LCMS m/z: 311.0 [M+H].

Step-2: 5-Bromo-1H-indol-3-amine hydrochloride



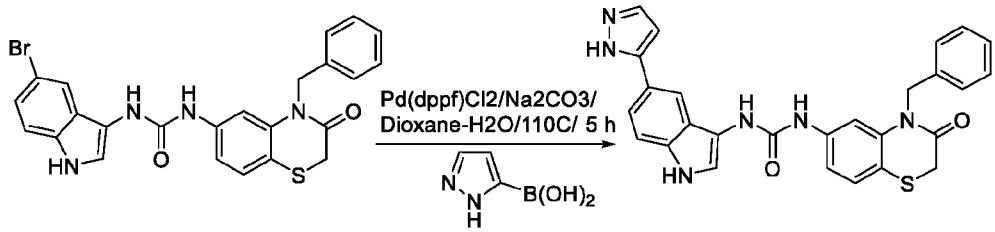
To a solution of tert-butyl (5-bromo-1H-indol-3-yl)carbamate (Preparation 12, Step-1) (3.0 g, 9.64 mmol) in 1,4-dioxane (45 mL) was added 4M HCl in 1,4-dioxane (25 mL) at 0-5 °C dropwise. After completion of the addition, the reaction mixture was stirred at room temperature for 5 h. Progress of the reaction was monitored by LCMS and after completion, the reaction mixture was concentrated under vacuum to obtain a green solid which was triturated with ether-pentane to afford the title compound (3.0 g, as the HCl salt) as a light green solid. LCMS m/z: 211.0 [M+H].

Preparation 13: 1-(4-Benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-bromo-1H-indol-3-yl)urea



To a stirred solution of 4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxylic acid (Preparation 3) (5.0 g, 16.7 mmol) was dissolved in DCM (50 mL) under a N_2 atmosphere. Then triethylamine (3.49 ml, 25.06 mmol) was added followed by diphenylphosphorylazide (7.18 ml, 33.41 mmol) at 0-5 °C. The reaction mixture was stirred at room temperature overnight. After completion of the reaction, the solvent was evaporated to obtain a residue which was dissolved in acetonitrile (50 mL) and 5-bromoindole-3-amine was added (Preparation 12, Step-2) (4.41 g, 33.41 mmol) under a N_2 atmosphere. The resulting reaction mixture was refluxed for 6 h. Progress of the reaction was monitored by LCMS and after completion the reaction mixture was concentrated under vacuum to give the crude product which was purified by silica gel column chromatography to afford the title compound (3.0 g, 41.9% yield) as an off-white solid. LCMS m/z: 505.2 [M+H].

Preparation 14: 1-(5-(1H-Pyrazol-5-yl)-1H-indol-3-yl)-3-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)urea (**Example 38**)

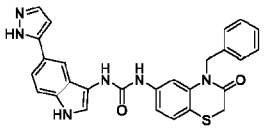
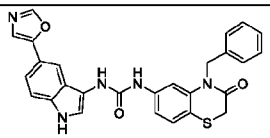
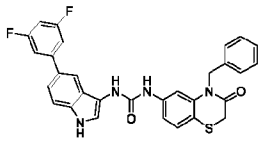
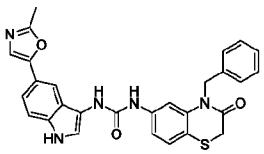
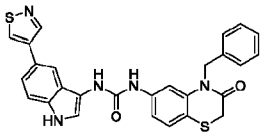
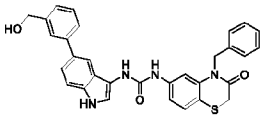


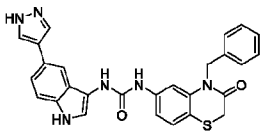
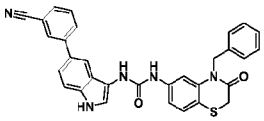
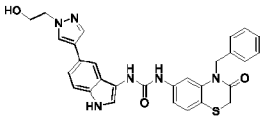
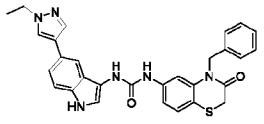
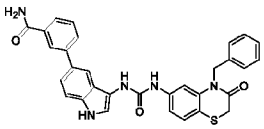
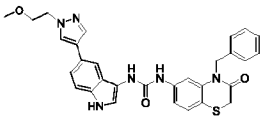
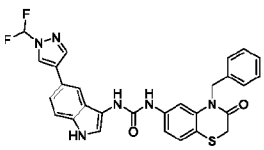
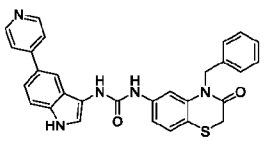
To a degassed solution of 1-(4-Benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-bromo-1H-indol-3-yl)urea (Preparation 13) (100 mg, 0.2 mmol) in a mixture of 1,4-dioxane and water (10 mL, 9:1) were added (1H-pyrazol-5-yl)boronic acid (26.6 mg, 0.24 mmol), sodium carbonate (41.9 mg, 0.4 mmol) and $Pd(dppf)Cl_2$ (14.5 mg, 0.02 mmol) and the whole was heated to 90 °C under a N_2 atmosphere for 3 h. Completion of the reaction was confirmed by LCMS and TLC. Then the reaction mass was filtered through a celite bed and the filtrate was concentrated under reduced pressure to give the crude product which was purified by prep-HPLC to afford the title compound (18 mg, 18.4% yield) as an off-white solid. Purity by HPLC: 99.53%; ^1H NMR (400 MHz; DMSO-d_6): δ 3.63 (s, 2H), 5.18 (s, 2H),

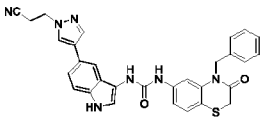
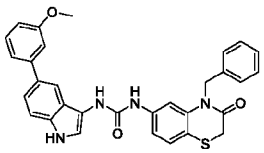
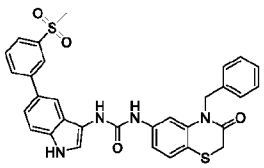
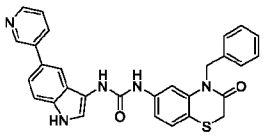
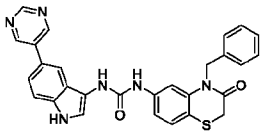
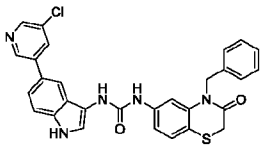
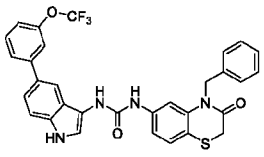
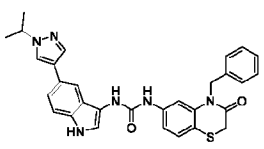
6.60 (s, 2H), 7.23-7.33 (m, 8H), 7.45-7.56 (m, 2H), 7.73-7.74 (m, 1H), 7.97 (bs, 1H), 8.56-8.60 (m, 2H), 10.71 (s, 1H), 12.71 (s, 1H); LCMS m/z: 495.26 [M+H].

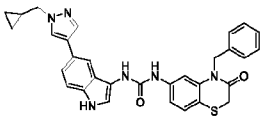
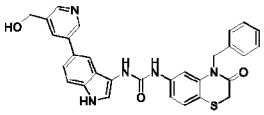
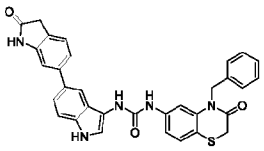
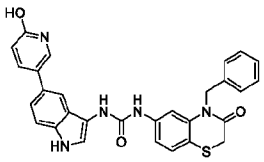
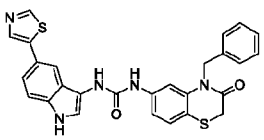
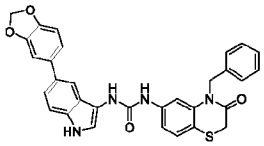
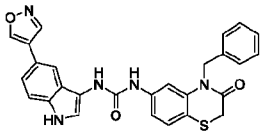
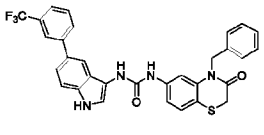
Examples 39-68 and 112

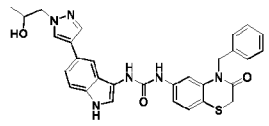
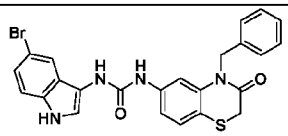
The examples in the table below were prepared according to the above methods used to make Example 38 as described in General Procedures 1-6 and Library General Procedure 28 using the appropriate amines. Purification was as stated in the aforementioned methods

Ex.	Structure	IUPAC Name	LCMS [M+H]	Purity (%)
38		1-(5-(1H-pyrazol-5-yl)-1H-indol-3-yl)-3-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)urea	495.26	99.53
39		1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(oxazol-5-yl)-1H-indol-3-yl)urea	496.26	93.86 By LCMS
40		1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(3,5-difluorophenyl)-1H-indol-3-yl)urea	541.31	91.85 By LCMS
41		1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(2-methyloxazol-5-yl)-1H-indol-3-yl)urea	510.28	94.8 By LCMS
42		1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(isothiazol-4-yl)-1H-indol-3-yl)urea	512.24	99.6 By LCMS
43		1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(3-(hydroxymethyl)phenyl)-1H-indol-3-yl)urea	535.29	100 By LCMS

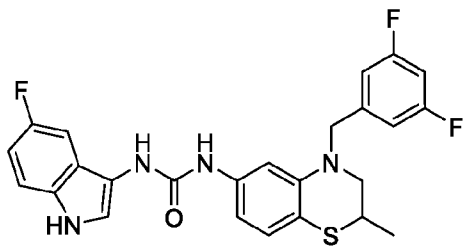
Ex.	Structure	IUPAC Name	LCMS [M+H]	Purity (%)
44		1-(5-(1H-pyrazol-4-yl)-1H-indol-3-yl)-3-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)urea	495.19	100 By LCMS
45		1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(3-cyanophenyl)-1H-indol-3-yl)urea	530.31	90.3 By LCMS
46		1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(1-(2-hydroxyethyl)-1H-pyrazol-4-yl)-1H-indol-3-yl)urea	539.32	98.0 By LCMS
47		1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(1-ethyl-1H-pyrazol-4-yl)-1H-indol-3-yl)urea	523.35	94.5 By LCMS
48		3-(3-(3-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)ureido)-1H-indol-5-yl)benzamide	548.28	97.4 By LCMS
49		1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(1-(2-methoxyethyl)-1H-pyrazol-4-yl)-1H-indol-3-yl)urea	553.31	97.4 By LCMS
50		1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(1-(difluoromethyl)-1H-pyrazol-4-yl)-1H-indol-3-yl)urea	545.31	100 By LCMS
51		1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(pyridin-4-yl)-1H-indol-3-yl)urea	506.31	100 By LCMS

Ex.	Structure	IUPAC Name	LCMS [M+H]	Purity (%)
52		1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(1-(2-cyanoethyl)-1H-pyrazol-4-yl)-1H-indol-3-yl)urea	548.36	100 By LCMS
53		1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(3-methoxyphenyl)-1H-indol-3-yl)urea	535.35	92.16 By LCMS
54		1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(3-(methylsulfonyl)phenyl)-1H-indol-3-yl)urea	583.26	99.57 By LCMS
55		1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(pyridin-3-yl)-1H-indol-3-yl)urea	506.27	99.54 By LCMS
56		1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(pyrimidin-5-yl)-1H-indol-3-yl)urea	507.24	100 By LCMA
57		1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(5-chloropyridin-3-yl)-1H-indol-3-yl)urea	540.22	95.84 By LCMS
58		1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(3-(trifluoromethoxy)phenyl)-1H-indol-3-yl)urea	589.24	98.03
59		1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(1-isopropyl-1H-pyrazol-4-yl)-1H-indol-3-yl)urea	537.31	95.0 By LCMS

Ex.	Structure	IUPAC Name	LCMS [M+H]	Purity (%)
60		1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(1-(cyclopropylmethyl)-1H-pyrazol-4-yl)-1H-indol-3-yl)urea	549.34	97.77 By LCMS
61		1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(5-(hydroxymethyl)pyridin-3-yl)-1H-indol-3-yl)urea	536.34	100 By LCMS
62		1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(2-oxoindolin-6-yl)-1H-indol-3-yl)urea	560.34	95.42 By LCMS
63		1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(6-hydroxypyridin-3-yl)-1H-indol-3-yl)urea	522.32	98.45 By LCMS
64		1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(thiazol-5-yl)-1H-indol-3-yl)urea	512.25	98.78 By LCMS
65		1-(5-(benzo[d][1,3]dioxol-5-yl)-1H-indol-3-yl)-3-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)urea		92.71 By LCMS
66		1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(isoxazol-4-yl)-1H-indol-3-yl)urea	496.35	98.81 By LCMS
67		1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(3-(trifluoromethyl)phenyl)-1H-indol-3-yl)urea	573.12	97.27 By LCMS

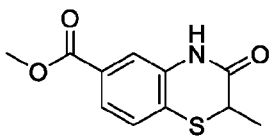
Ex.	Structure	IUPAC Name	LCMS [M+H]	Purity (%)
68		1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(1-(2-hydroxypropyl)-1H-pyrazol-4-yl)-1H-indol-3-yl)urea	553.34	99.42 By LCMS
112		1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-bromo-1H-indol-3-yl)urea	507.21	92.46

Example 69: 1-(4-(3,5-Difluorobenzyl)-2-methyl-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-fluoro-1H-indol-3-yl)urea

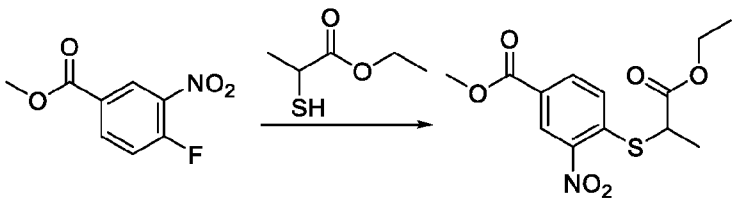


Example 69 was prepared according to General Procedure 1-6, 17 and the methods described below.

Preparation 15: Methyl 2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxylate



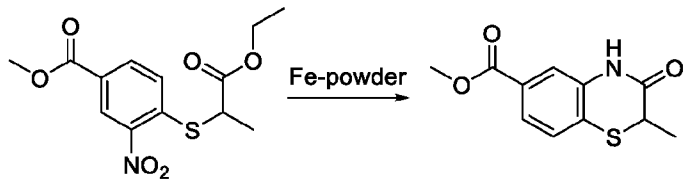
Step-1: Methyl 4-((1-ethoxy-1-oxopropan-2-yl)thio)-3-nitrobenzoate



To a stirred solution of commercially available methyl 4-fluoro-3-nitrobenzoate (8.0 g, 33.72 mmol) in acetonitrile (80 mL) was added TEA (14.5 mL, 101 mmol) and ethyl 2-mercaptopropanoate (6.84 mL, 43.83 mmol) and the whole maintained at RT for 1 h. UPLC showed formation of the desired compound, the solvent was evaporated to afford the crude product which was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and evaporated to afford the title compound (13.0 g)

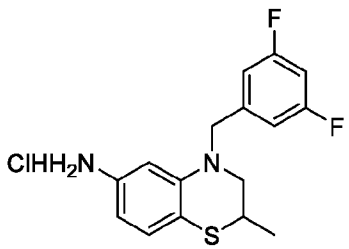
as a pale yellow solid which was used in the next step without any further purification. LCMS m/z: 312 [M+H].

Step-2: Methyl 2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxylate

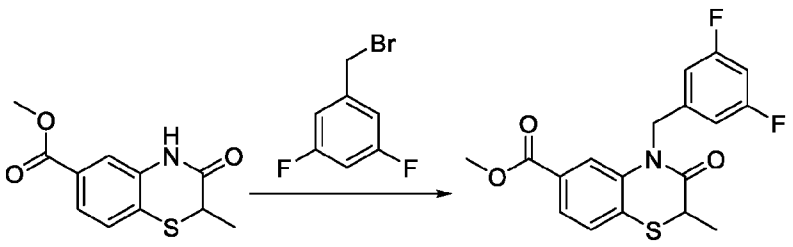


To a stirred solution of methyl 4-((1-ethoxy-1-oxopropan-2-yl)thio)-3-nitrobenzoate (Preparation 15, Step-1) (13.0 g, 41.53 mmol) in AcOH (100 mL) was added Fe-powder (10.79 g, 166.10 mmol) and the whole stirred at 80 °C for 1.5 h. UPLC showed formation of the desired compound, the reaction mass was quenched by puring into ice cold water (600 mL) and the whole stirred for 30 min. The precipitated solid was filtered and washed with cold water, dried in a vacuum oven at 60 °C overnight to afford the title compound (9.8 g) as a faint brown solid which was used in the next step without any further purification. LCMS m/z: 238 [M+H].

Preparation 16: 4-(3,5-Difluorobenzyl)-2-methyl-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-amine hydrochloride



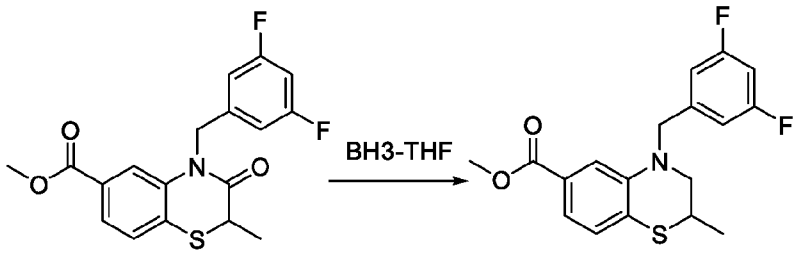
Step-1: Methyl 4-(3,5-difluorobenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxylate



To a stirred solution of methyl 2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxylate (Preparation 15, Step-2) (2.0 g, 8.4 mmol) in DMF (20 mL) was added NaH (371 mg, 9.3 mmol) at 0-5 °C followed by 1-(bromomethyl)-3,5-difluorobenzene (1.13 mL, 8.7

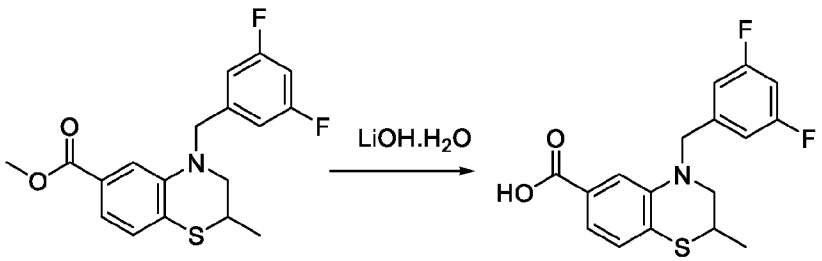
mmol). The resulting reaction mixture was warmed to room temperature and stirred for 2 h. Progress of the reaction was monitored by LC-MS. After completion of the reaction, the reaction mixture was diluted with ice-cold water and extracted with MTBE. The organic layer was then washed with brine solution and concentrated *in vacuo* to give the crude product which was purified by Combi-flash (eluted in 15% EtOAc/hexane) to afford the title compound (3.0 g, 98% yield) as a white solid. LCMS m/z: 364.1 [M+H].

Step-2: Methyl 4-(3,5-difluorobenzyl)-2-methyl-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxylate



BH_3.THF (30 mL, 27 mmol) solution was added to methyl 4-(3,5-difluorobenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxylate (Preparation 16, Step-1) (3.0 g, 8.26 mmol) at 0-5 °C and then was brought to RT slowly and stirred for 4 h. Consumption of the starting material was confirmed by TLC and LC-MS which showed formation of the desired product. After completion of the reaction, the reaction mixture was quenched with methanol,and concentrated *in vacuo* to give a crude residue, which was diluted with water and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and then concentrated in *vacuo* to give a yellow liquid which was purified by Combi-flash (eluted in 12% EtOAc/hexane) to afford the title compound (2.67 g, 93% yield) as a pale yellow solid. LCMS m/z: 439.2 [M+H].

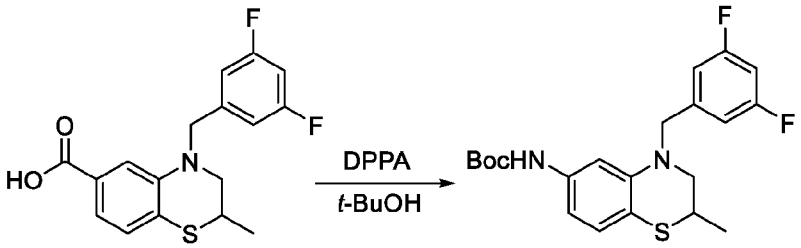
Step-3: 4-(3,5-Difluorobenzyl)-2-methyl-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxylic acid



To a stirred solution of methyl 4-(3,5-difluorobenzyl)-2-methyl-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxylate (Preparation 16, Step-2) (2.67g, 7.65 mmol) in a mixture of solvents THF/MeOH/H_2O (48 mL, 1:1:1) was added LiOH.H_2O (1.28 g, 30.6 mmol). The reaction mixture was then stirred at RT for 16 h. Consumption of the starting material was

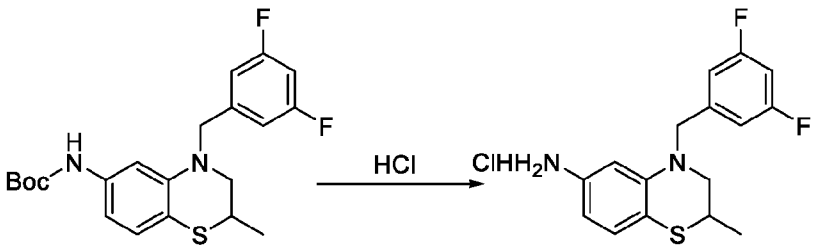
confirmed by TLC and LC-MS. The solvents were evaporated under reduced pressure to give a residue, which was diluted with water and washed with MTBE. The resulting aqueous solution was then neutralized with 2M HCl solution and the desired product was extracted with EtOAc. The organic layer was then concentrated *in vacuo* to afford the title compound (2.2 g, crude) as a white solid. LCMS m/z: 334.1 [M+H].

Step-4: *tert*-Butyl (4-(3,5-difluorobenzyl)-2-methyl-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)carbamate



To a stirred solution of 4-(3,5-difluorobenzyl)-2-methyl-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxylic acid (Preparation 16, Step-3) (2.2 g, 6.57 mmol) in DCM (30 mL) was added TEA (1.37 mL, 9.85 mmol) followed by DPPA (2.1 mL, 9.85 mmol) at 0-5 °C. The resulting reaction mixture was stirred at RT for 2 h. Consumption of the starting material was confirmed by LC-MS. After completion of the reaction, the reaction mixture was concentrated in *vacuo* to give a residue, which was diluted with t-BuOH and further stirred at 90 °C for 5 h. LC-MS showed formation of the desired product. The solvent was evaporated under vacuum to give the crude product which was purified by Combi-flash (eluted in 10% EtOAc/hexane) to afford the title compound (2.0 g, 75% yield) as a pale yellow solid. LCMS m/z: 407.2 [M+H].

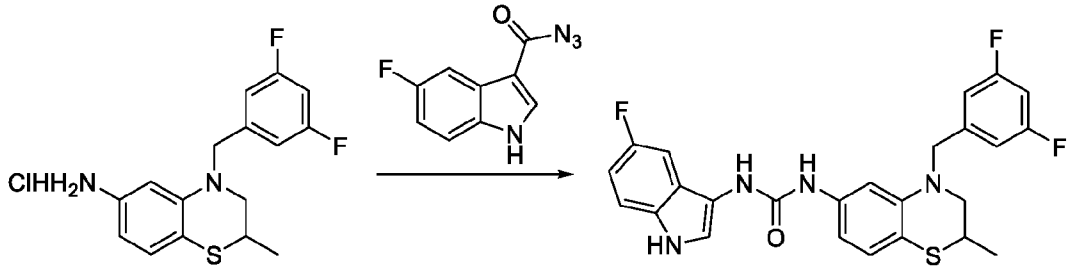
Step-5: 4-(3,5-Difluorobenzyl)-2-methyl-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-amine hydrochloride



To a stirred solution of *tert*-butyl (4-(3,5-difluorobenzyl)-2-methyl-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)carbamate (Preparation 16, Step-4) (600 mg, 1.47 mmol) in 1,4-dioxane (5 mL) was added 1N HCl solution (15 mL) at 0-5 °C. Then, the reaction mixture was stirred at RT for 3 h. Consumption of the starting material was confirmed by LCMS. After completion of the reaction, the reaction mixture was concentrated in *vacuo* to give the crude

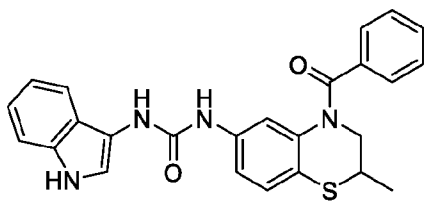
product which was purified by trituration with hexane to afford the title compound (600 mg, crude) as a pale yellow solid. LCMS m/z: 307.1 [M+H].

Preparation 17: 1-(4-(3,5-Difluorobenzyl)-2-methyl-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-fluoro-1H-indol-3-yl)urea (**Example 69**)



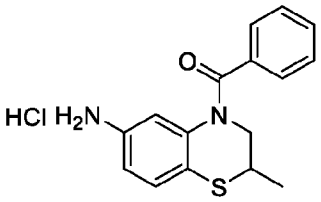
To a stirred solution of 4-(3,5-difluorobenzyl)-2-methyl-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-amine (Preparation 16, Step-5) (600 mg, 1.47 mmol) in toluene (10 mL) was added TEA (0.4 mL, 2.94 mmol) followed by 5-fluoro-1H-indole-3-carbonyl azide (344 mg, 1.68 mmol, synthesized separately from 5-fluoro-1H-indole-3-carboxylic acid using DPPA) as described in Preparation 12, Step-1) at RT. The reaction mixture was stirred at 100 °C for 2 h. Completion of the reaction was confirmed by LC-MS. The reaction mixture was concentrated *in vacuo* to give the crude material which was purified by combi-flash followed by prep-HPLC to afford the title compound (115 mg, 16% yield) as a pale brown solid. Purity by UPLC: 97.61%; ^{1}H NMR (500 MHz; DMSO-d_6): δ 1.30 (d, *J* = 6.4 Hz, 3H), 3.33-3.34 (m, 2H), 3.70-3.72 (m, 1H), 4.56-4.59 (m, 2H), 6.72 (s, 1H), 6.82-6.87 (dd, *J*1 = 8.25 Hz, *J*2 = 19.25 Hz, 2H), 6.93 (t, *J* = 9.15 Hz, 1H), 7.00 (d, *J* = 7.05 Hz, 2H), 7.12 (t, *J* = 9.45 Hz, 1H), 7.17 (d, *J* = 9.75 Hz, 1H), 7. 13-7.34 (m, 1H), 7.49 (s, 1H), 8.28 (d, *J* = 12.55 Hz, 2H), 10.82 (s, 1H); LCMS m/z: 483.15 [M+H].

Example 70: 1-(4-Benzoyl-2-methyl-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(1H-indol-3-yl)urea

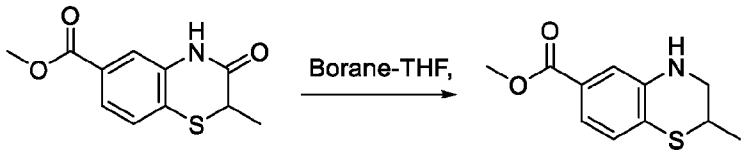


Example 70 was prepared according to General Procedure 1-6, 17 and the methods described below.

Preparation 18: (6-Amino-2-methyl-2,3-dihydro-4H-benzo[b][1,4]thiazin-4-yl)(phenyl)methanone hydrochloride

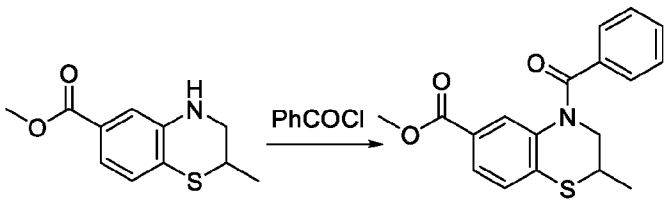


Step-1: Methyl 2-methyl-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxylate



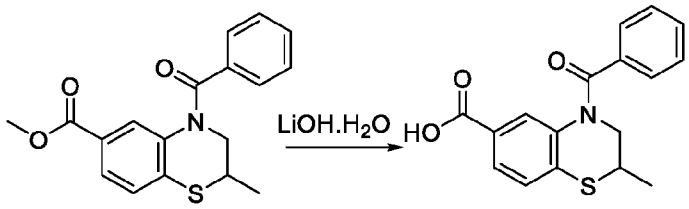
A solution of methyl 2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxylate (Preparation 15, Step-2) (1.0 g, 4.21 mmol) in borane.THF complex (1M solution in THF) (12.6 mL, 12.64 mmol) was stirred at RT for 3 h. Progress of the reaction was monitored by UPLC-MS which showed formation of the desired product and after completion, the reaction mixture was diluted with MeOH (10 mL) and refluxed for 10 min.. Then, the solvent was evaporated *in vacuo* to give a residue which was diluted with water and extracted with EtOAc, the organic layer was washed with brine, dried over anhydrous $Na_2SO_4$and evaporated *in vacuo* to afford the title compound (824 mg, crude) as a pale yellow solid which was used in the next step without any further purification. LCMS m/z: 224 [M+H].

Step-2: Methyl 4-benzoyl-2-methyl-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxylate



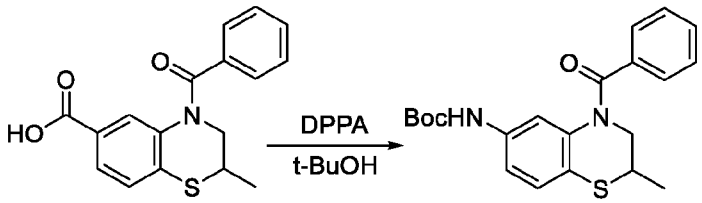
To a stirred solution of methyl 2-methyl-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxylate (Preparation 18, Step-1) (0.824 g, 3.69 mmol) in DCM (10 mL) was added TEA (1.33 mL, 9.23 mmol) and benzoyl chloride (0.55 mL, 3.93 mmol) at RT. The resulting solution was stirred at RT for 1 h, after which time UPLC-MS showed formation of the desired product. The solvent was evaporated *in vacuo* to give the crude material which was purified by Combi-flash (20 g column) to afford the title compound (1.2 g, 99% yield) as a white solid. LCMS m/z: 328 [M+H].

Step-3: 4-Benzoyl-2-methyl-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxylic acid



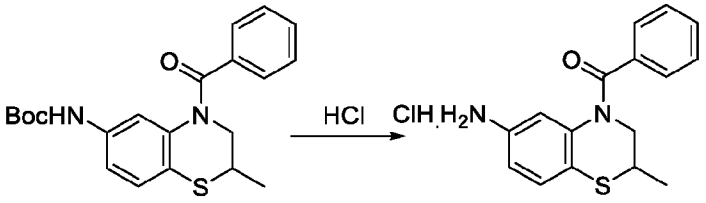
To a stirred solution of methyl 4-benzoyl-2-methyl-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxylate (Preparation 18, Step-2) (1.2 g, 3.67 mmol) in a mixture of solvents MeOH (5 mL), THF (5 mL) and H_2O (10 mL) was added $LiOH.H_2O$ (770 mg, 18.33 mmol) and the whole maintained at RT for 1.5 h. UPLC-MS showed completion of the reaction. Then, the solvents were evaporated *in vacuo* and the aqueous residue was washed with diethyl ether and acidified with 1N HCl. The acidified aqueous part was extracted with EtOAc and the combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$and evaporated under reduced pressure to afford the title compound (1.18 g, crude) as a faint brown solid which was used in the next step without any further purification . LCMS m/z: 314 [M+H].

Step-4: *tert*-Butyl (4-benzoyl-2-methyl-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)carbamate



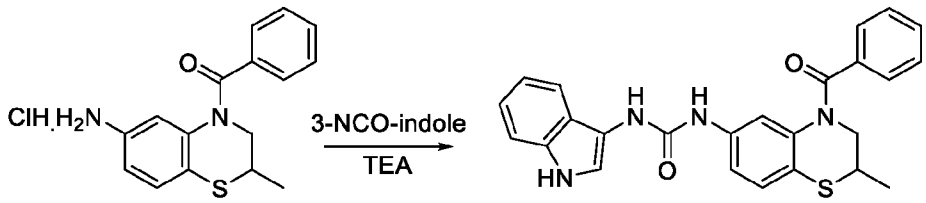
To a stirred solution of 4-benzoyl-2-methyl-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxylic acid (Preparation 18, Step-3) (1.15 g, 3.67 mmol) in DCM (20 mL) was added TEA (0.79 mL, 5.50 mmol) followed by DPPA (1.59 mL,7.34 mmol) at 0-5 °C and the resulting reaction mixture was stirred at RT for 3 h. UPLC-MS showed formation of the desired product. Then, the solvent was evaporated *in vacuo* to afford the corresponding acyl azide intermediate (2.0 g) as a faint brownish oil which was dissolved in t-BuOH (15 mL) and refluxed for 16 h. Progress of the reaction was monitored by UPLC-MS which showed formation of the desired compound. Then, the solvent was evaporated *in vacuo* and the crude was purified by Combi-flash (40 g column) using 25% EtOAc in hexane to afford the title compound (900 mg, 40% yield) as an off-white solid. LCMS m/z: 383 [M+H].

Step-5: (6-Amino-2-methyl-2,3-dihydro-4H-benzo[b][1,4]thiazin-4-yl)(phenyl)methanone hydrochloride



A solution of *tert*-butyl (4-benzoyl-2-methyl-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)carbamate (Preparation 18, Step-4) (900 mg, 2.34 mmol) in 4M HCl in dioxane (15 mL) at 0-5 °C was allowed to warm slowly to RT over 1 h. The reaction was monitored by UPLC-MS and after completion of the reaction, the solvent was evaporated under reduced pressure to give the crude product which was washed with hexane, dried and evaporated *in vacuo* to afford the title compound (770 mg, crude) as a pale yellow solid. The crude material was used in the next step without any further purification. LCMS m/z: 285 [M+H].

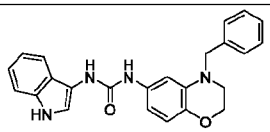
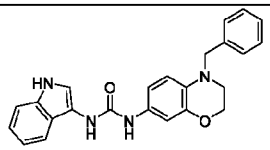
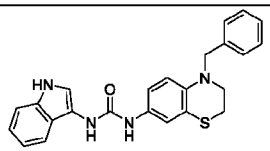
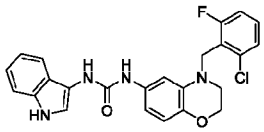
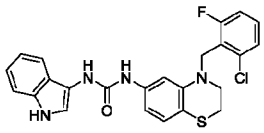
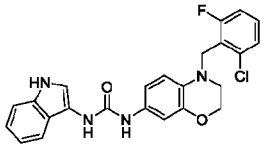
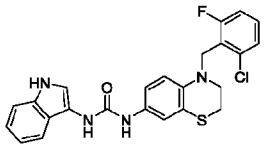
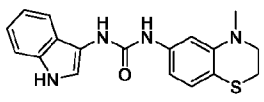
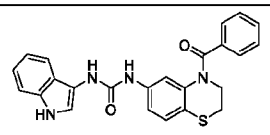
Preparation 19: 1-(4-Benzoyl-2-methyl-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(1H-indol-3-yl)urea (**Example 70**)

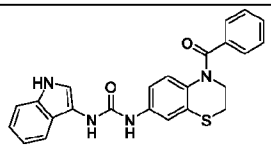
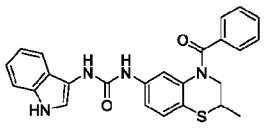
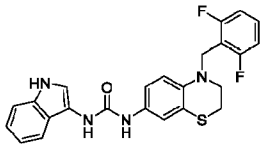
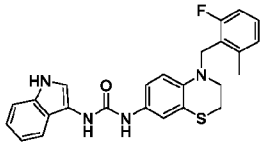
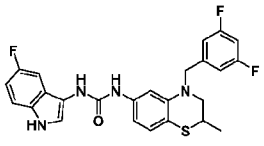
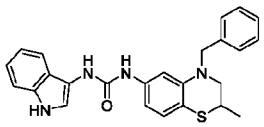
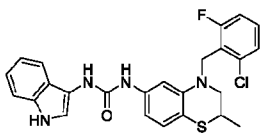
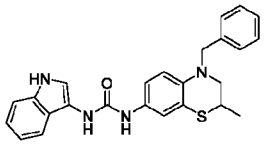


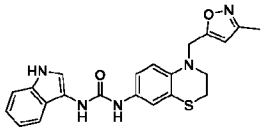
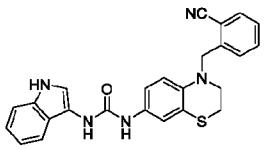
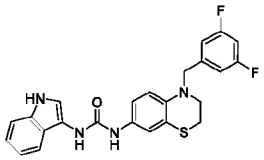
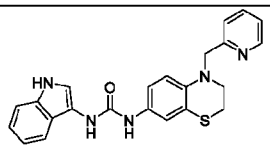
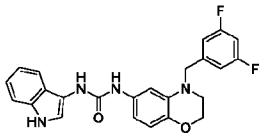
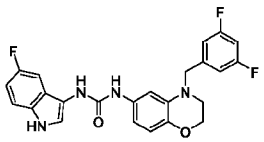
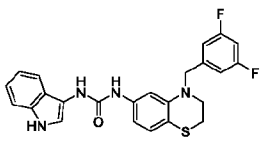
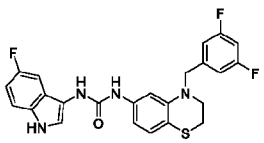
To a stirred solution of (6-amino-2-methyl-2,3-dihydro-4H-benzo[b][1,4]thiazin-4-yl)(phenyl)methanone hydrochloride (Preparation 18, Step-5) (500 mg, 1.56 mmol) in DCM (20 mL) was added 3-NCO-indole (369.54 mg, 2.34 mmol) followed by TEA (0.254 mL, 1.56 mmol) at 0-5 °C. The resulting reaction mixture was stirred at RT for 2.5 h, UPLC-MS showed completion of the reaction. Then, the solvent was evaporated *in vacuo* to give crude material which was purified by Combi -flash (40 g column) using 55% EtOAc in hexane to afford the title compound (300 mg, 44% yield) as a faint brown solid. Purity by UPLC: 98.63%; ^{1}H NMR (400 MHz; DMSO-d_6): δ 1.35 (d, J = 6.4 Hz, 3H), 3.17 (d, J = 6 Hz, 1H), 3.70-3.78 (m, 1H), 4.06-4.13 (m, 1H), 6.86 (s, 1H), 6.97 (t, J = 7.2 Hz, 1H), 7.07 (t, J = 7.2 Hz, 1H), 7.12 (d, J = 8.8 Hz, 1H), 7.24-7.26 (dd, $J1$= 2.0 Hz, $J2$ = 8.8 Hz, 1H), 7.30-7.37 (m, 5H), 7.38-7.42 (m, 3H), 8.26 (s, 1H), 8.31 (s, 1H), 10.67 (s 1H); LCMS m/z: 441.11 [M-H].

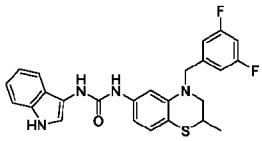
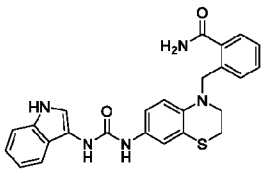
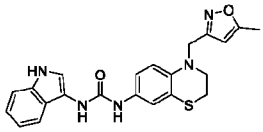
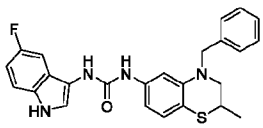
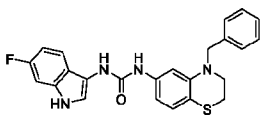
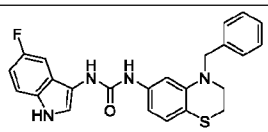
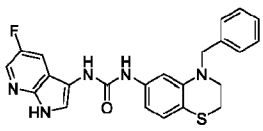
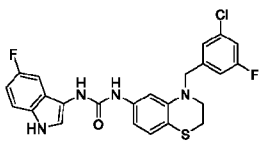
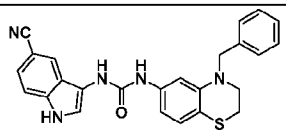
Examples 71-101 and 109-111

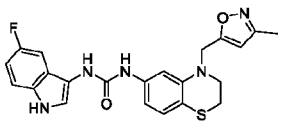
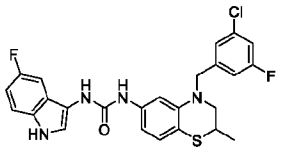
The examples in the table below were prepared according to the above methods used to make Example 69 and 70 as described in General Procedures 1-6 and 17 using the appropriate amine. Purification was as stated in the aforementioned methods.

Ex.	Structure	IUPAC Name	LCMS [M+H]	Purity (%)
71		1-(4-benzyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)-3-(1H-indol-3-yl)urea	399.32	94.14
72		1-(4-benzyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1H-indol-3-yl)urea	399.34	93.23
73		1-(4-benzyl-3,4-dihydro-2H-benzo[b][1,4]thiazin-7-yl)-3-(1H-indol-3-yl)urea	415.30	98.62
74		1-(4-(2-chloro-6-fluorobenzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)-3-(1H-indol-3-yl)urea	451.24	99.61
75		1-(4-(2-chloro-6-fluorobenzyl)-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(1H-indol-3-yl)urea	467.24	97.67
76		1-(4-(2-chloro-6-fluorobenzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1H-indol-3-yl)urea	451.27	96.92
77		1-(4-(2-chloro-6-fluorobenzyl)-3,4-dihydro-2H-benzo[b][1,4]thiazin-7-yl)-3-(1H-indol-3-yl)urea	467.22	99.58
78		1-(1H-indol-3-yl)-3-(4-methyl-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)urea	339.26	99.49
79		1-(4-benzoyl-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(1H-indol-3-yl)urea	429.21	95.45

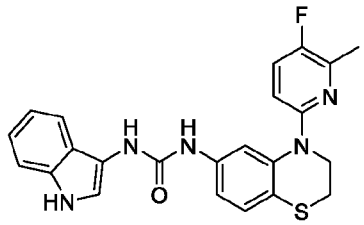
Ex.	Structure	IUPAC Name	LCMS [M+H]	Purity (%)
80		1-(4-benzoyl-3,4-dihydro-2H-benzo[b][1,4]thiazin-7-yl)-3-(1H-indol-3-yl)urea	429.1	95.86
70		1-(4-benzoyl-2-methyl-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(1H-indol-3-yl)urea	441.11 (M-H)	98.63
81		1-(4-(2,6-difluorobenzyl)-3,4-dihydro-2H-benzo[b][1,4]thiazin-7-yl)-3-(1H-indol-3-yl)urea	451.3	93.86
82		1-(4-(2-fluoro-6-methylbenzyl)-3,4-dihydro-2H-benzo[b][1,4]thiazin-7-yl)-3-(1H-indol-3-yl)urea	547.28	99.73
69		1-(4-(3,5-difluorobenzyl)-2-methyl-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-fluoro-1H-indol-3-yl)urea	483.14	97.61
83		1-(4-benzyl-2-methyl-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(1H-indol-3-yl)urea	429.17	99.4
84		1-(4-(2-chloro-6-fluorobenzyl)-2-methyl-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(1H-indol-3-yl)urea	481.12	99.06
85		1-(4-benzyl-2-methyl-3,4-dihydro-2H-benzo[b][1,4]thiazin-7-yl)-3-(1H-indol-3-yl)urea	429.17	97.91

Ex.	Structure	IUPAC Name	LCMS [M+H]	Purity (%)
86		1-(1H-indol-3-yl)-3-(4-((3-methylisoxazol-5-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]thiazin-7-yl)urea	420.12	95.0
87		1-(4-(2-cyanobenzyl)-3,4-dihydro-2H-benzo[b][1,4]thiazin-7-yl)-3-(1H-indol-3-yl)urea	440.3	96.76
88		1-(4-(3,5-difluorobenzyl)-3,4-dihydro-2H-benzo[b][1,4]thiazin-7-yl)-3-(1H-indol-3-yl)urea	451.28	94.62
89		1-(1H-indol-3-yl)-3-(4-(pyridin-2-ylmethyl)-3,4-dihydro-2H-benzo[b][1,4]thiazin-7-yl)urea	416.31	89.09
90		1-(4-(3,5-difluorobenzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)-3-(1H-indol-3-yl)urea	435.20	98.64
91		1-(4-(3,5-difluorobenzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)-3-(5-fluoro-1H-indol-3-yl)urea	453.16	97.93
92		1-(4-(3,5-difluorobenzyl)-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(1H-indol-3-yl)urea	451.17	98.79
93		1-(4-(3,5-difluorobenzyl)-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-fluoro-1H-indol-3-yl)urea	469.16	99.0

Ex.	Structure	IUPAC Name	LCMS [M+H]	Purity (%)
94		1-(4-(3,5-difluorobenzyl)-2-methyl-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(1H-indol-3-yl)urea	465.16	98.05
95		2-((7-(3-(1H-indol-3-yl)ureido)-2,3-dihydro-4H-benzo[b][1,4]thiazin-4-yl)methyl)benzamide	458.28	97.85
96		1-(1H-indol-3-yl)-3-(4-((5-methylisoxazol-3-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]thiazin-7-yl)urea	420.28	98.81
97		1-(4-benzyl-2-methyl-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-fluoro-1H-indol-3-yl)urea	445.23 (M-H)	99.56
98		1-(4-benzyl-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(6-fluoro-1H-indol-3-yl)urea	433.14	99.75
99		1-(4-benzyl-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-fluoro-1H-indol-3-yl)urea	433.16	99.39
100		1-(4-benzyl-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-yl)urea	434.19	99.41
101		1-(4-(3-chloro-5-fluorobenzyl)-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-fluoro-1H-indol-3-yl)urea	485.17	95.35
109		1-(4-benzyl-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-cyano-1H-indol-3-yl)urea	440.1	97.75

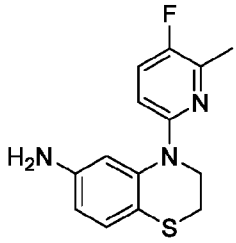
Ex.	Structure	IUPAC Name	LCMS [M+H]	Purity (%)
110		1-(5-fluoro-1H-indol-3-yl)-3-(4-((3-methylisoxazol-5-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)urea	438.1	99.39
111		1-(4-(3-chloro-5-fluorobenzyl)-2-methyl-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-fluoro-1H-indol-3-yl)urea	499.22	97.67

Example 102: 1-(4-(5-Fluoro-6-methylpyridin-2-yl)-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(1H-indol-3-yl)urea

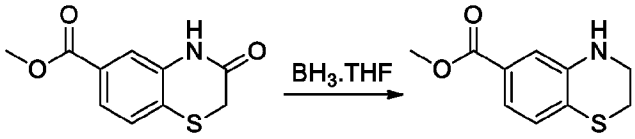


Example 102 was prepared according to General Procedures 1-6, 17, 25 and the methods described below

Preparation 20: 4-(5-Fluoro-6-methylpyridin-2-yl)-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-amine



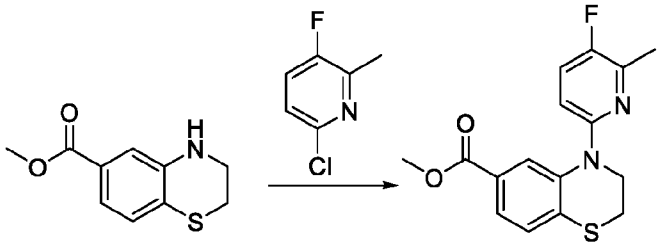
Step 1: Methyl 3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxylate



BH_3.THF (30 mL, 27 mmol) was added to methyl 3-oxo-3,4-dihydro-2*H*-benzo[b-1,4]thiazine-6-carboxylate (Preparation 1, Step 2) (2.0 g, 9.0 mmol) at 0-5 °C with stirring under an inert atmosphere. After the addition was complete, the mixture was brought to RT and stirred for 3 h. Completion of the reaction was confirmed by TLC and UPLC-MS. The

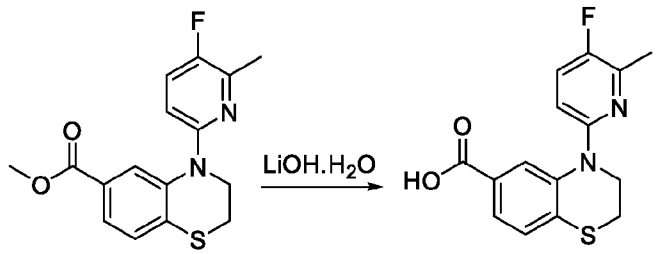
reaction mixture was quenched by adding in portions to methanol in a conical flask and stirring until all effervescence had ceased. Then, the reaction mixture was concentrated *in vacuo* to give a crude material which was mixed with water and extracted with EtOAc. The organic layers were combined, washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (1.8 g) as a pale yellow crude solid. UPLC-MS m/z: 209.9 [M+H].

Step 2: Methyl 4-(5-fluoro-6-methylpyridin-2-yl)-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxylate



To a stirred solution of methyl 3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxylate (Preparation 20, Step-1) (400 mg, 1.9 mmol), 6-chloro-3-fluoro-2-methylpyridine (400 mg, 2.76 mmol), potassium phosphate (1.5 g, 7 mmol) and Xphos (183mg, 0.38mmol) in toluene (10 mL) was degassed with N_2 at RT. Then, $Pd_2(dba)_3$ (94 mg, 0.1 mmol) was added to the solution and the whole was stirred at 110 °C for 16 h. Completion of the reaction was confirmed by LC-MS. Then, the reaction mixture was concentrated *in vacuo* to give crude material, which was purified by column chromatography to afford the title compound (550 mg, 91% yield) as a pale yellow solid. UPLC-MS m/z: 319.1 [M+H].

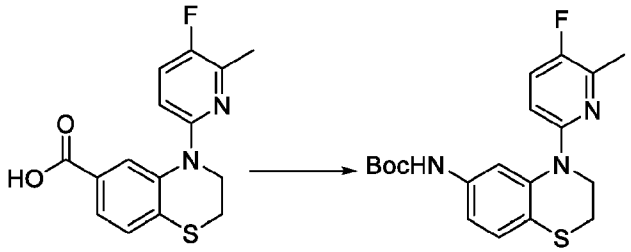
Step 3: 4-(5-Fluoro-6-methylpyridin-2-yl)-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxylic acid



To a stirred solution of methyl 4-(5-fluoro-6-methylpyridin-2-yl)-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxylate (Preparation 20, Step-2) (550 mg, 1.73 mmol) in THF (4 mL) and MeOH (4mL) was added $LiOH.H_2O$ (300 mg, 7.14 mmol). The reaction mixture was then stirred at RT for 16 h. Consumption of the starting material was confirmed by TLC and LC-MS and after completion the solvents were evaporated under reduced pressure to give crude product which was diluted with water and washed with MTBE. The aqueous solution

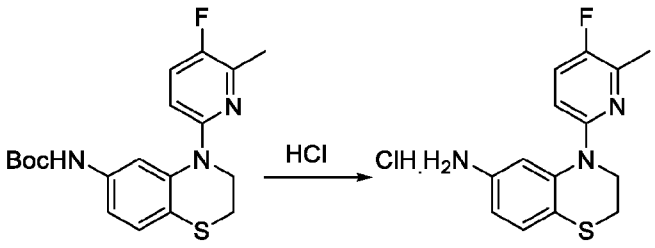
was then neutralized with 2M HCl solution and the product was extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the title compound (400 mg, crude) as a white solid. UPLC-MS m/z: 305.1 [M+H].

Step-4: *tert*-Butyl (4-(5-fluoro-6-methylpyridin-2-yl)-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)carbamate



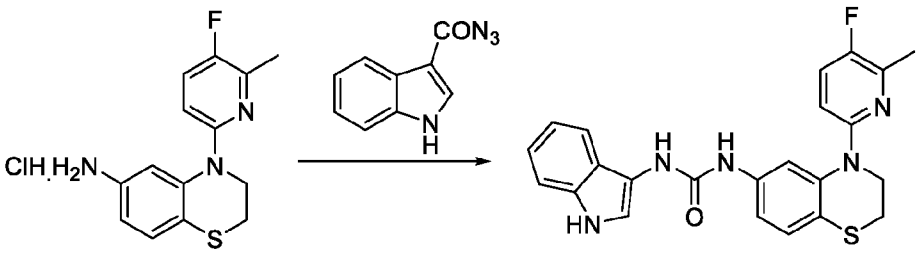
To a stirred solution of 4-(5-fluoro-6-methylpyridin-2-yl)-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxylic acid (Preparation 20, Step-3) (400 mg, 1.3 mmol) in DCM (6 mL) was added TEA (274 µL, 1.97 mmol) and DPPA (335 µL, 1.56mmol) at 0-5 °C. The resulting reaction mixture was allowed to slowly warm to RT over 2 h. Consumption of the starting material was confirmed by LC-MS. After completion of the reaction, the reaction mixture was concentrated *in vacuo* and the obtained residue was diluted with t-BuOH. The resulting reaction mixture was further stirred at 90 °C for 1 h. Progress of the reaction was monitored by LC-MS and after completion, the solvent was concentrated *in vacuo* to give crude material which was purified by Combi-flash to afford the title compound (270 mg, 55% yield) as a pale yellow solid. UPLC-MS m/z: 376.2 [M+H].

Step-5: 4-(5-Fluoro-6-methylpyridin-2-yl)-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-amine hydrochloride



To a stirred solution of *tert*-butyl (4-(5-fluoro-6-methylpyridin-2-yl)-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)carbamate (Preparation 20, Step-4) (270 mg, 0.72 mmol) in dioxane (2 mL) was added 4N HCl solution (6 mL, 24 mmol) at 0-5 °C. Then, the reaction mixture was stirred at RT for 3 h. Consumption of the starting material was confirmed by LC-MS. After completion of the reaction, the reaction mixture was concentrated *in vacuo* to afford the crude which was purified by trituration with hexane to give the title compound (210 mg, crude) as a pale yellow solid. UPLC-MS m/z: 276.1 [M+H].

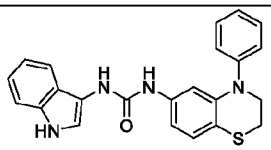
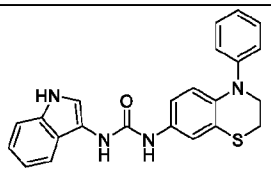
Preparation 21: 1-(4-(5-Fluoro-6-methylpyridin-2-yl)-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(1H-indol-3-yl)urea (**Example 102**)

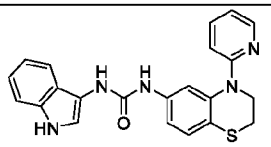
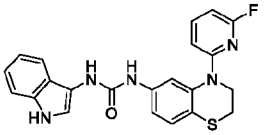
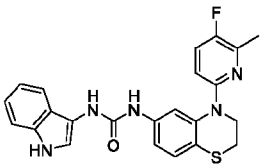


To a stirred solution of 4-(5-fluoro-6-methylpyridin-2-yl)-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-amine hydrochloride (Preparation 20, Step-5) (190 mg, 0.61 mmol) in toluene (4 mL) was added TEA (127 µL, 0.9 mmol) and freshly prepared 1H-indole-3-carbonyl azide (75 mg, 0.4 mmol). The resulting reaction mixture was stirred at 100 °C for 2 h. Completion of the reaction was confirmed by LC-MS. After that, the reaction mixture was concentrated *in vacuo* to give crude material which was purified by Combi-flash followed by prep-HPLC to afford the title compound (15 mg, 9% yield) as a pale yellow solid. Purity by UPLC: 99.22%; 1H NMR (400 MHz; DMSO-d_6): δ 2.37 (s, 3H), 3.09 (d, *J* = 5.4 Hz, 2H), 4.10 (t, *J* = 5.2 Hz, 2H), 6.85-6.88 (dd, *J1* = 2.8 Hz, *J2* = 9.04 Hz, 1H), 6.99 (t, *J* = 7.64 Hz, 1H), 7.05-7.12 (m, 3H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.42-7.49 (m, 4H), 8.36 (s, 1H), 8.55 (s, 1H), 10.69 (s, 1H); UPLC-MS m/z: 434.32 [M+H].

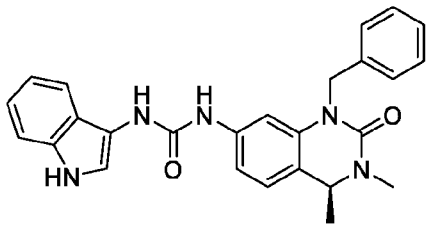
Examples 102-106

The examples in the table below were prepared according to the above methods used to make Example 102 as described in General Procedures 1-6, 17 and 25 using the appropriate amine. Purification was as stated in the aforementioned methods.

Ex.	Structure	IUPAC Name	LCMS [M+H]	Purity (%)
103		1-(1H-indol-3-yl)-3-(4-phenyl-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)urea	401.26	99.3
104		1-(1H-indol-3-yl)-3-(4-phenyl-3,4-dihydro-2H-benzo[b][1,4]thiazin-7-yl)urea	401.09	97.97

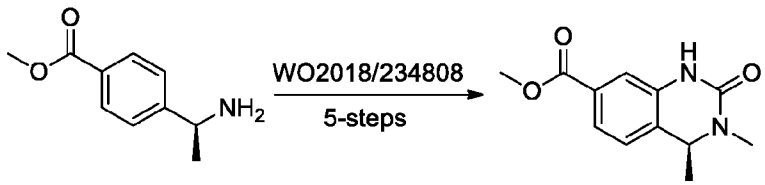
Ex.	Structure	IUPAC Name	LCMS [M+H]	Purity (%)
105		1-(1H-indol-3-yl)-3-(4-(pyridin-2-yl)-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)urea	400.24 (M-H)	99.59
106		1-(4-(6-fluoropyridin-2-yl)-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(1H-indol-3-yl)urea	420.21	99.42
102		1-(4-(5-fluoro-6-methylpyridin-2-yl)-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(1H-indol-3-yl)urea	434.32	99.22

Example 107: (S)-1-(1-Benzyl-3,4-dimethyl-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl)-3-(1H-indol-3-yl)urea



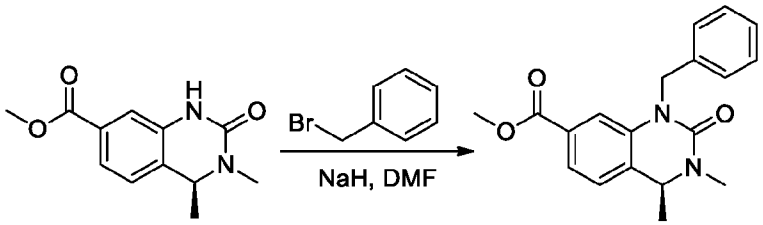
Example 107 was prepared according to the methods described in General Procedures 1-4, 10-14 and the methods described below

Preparation 22: (*S*)-Methyl-3,4-dimethyl-2-oxo-1,2,3,4-tetrahydroquinazoline-7-carboxylate



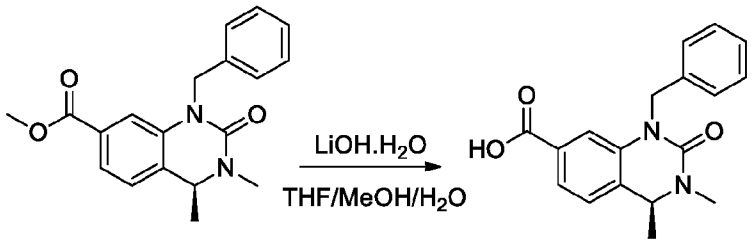
(*S*)-methyl-3,4-dimethyl-2-oxo-1,2,3,4-tetrahydroquinazoline-7-carboxylate was prepared in five steps according to the methods described in patent WO2018/234808.

Preparation 23: (*S*)-Methyl 1-benzyl-3,4-dimethyl-2-oxo-1,2,3,4-tetrahydroquinazoline-7-carboxylate



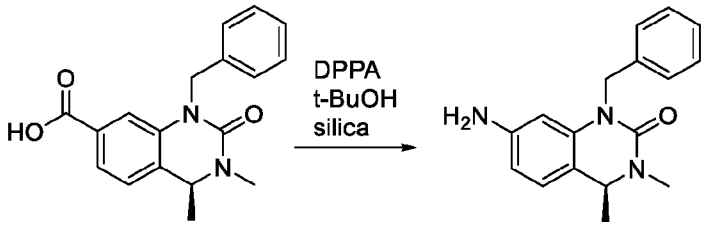
To a stirred solution of (*S*)-methyl-3,4-dimethyl-2-oxo-1,2,3,4-tetrahydroquinazoline-7-carboxylate (Preparation 22) (1.0 g, 4.26 mmol) in DMF (12 mL) was added NaH (187 mg, 4.69 mmol) followed by benzyl bromide (0.53 mL, 4.48 mmol) at 0-5 °C. The combined mixture was stirred at RT for 30 min. TLC showed complete consumption of the starting cyclic urea. Then the reaction mixture was quenched with ice-water to give a precipitate which was filtered, washed with hexane and dried under high vacuum to afford the title compound (1.1 g, 80% yield) as a white solid. LCMS m/z: 325 [M+H].

Preparation 24: (*S*)-1-Benzyl-3,4-dimethyl-2-oxo-1,2,3,4-tetrahydroquinazoline-7-carboxylic acid



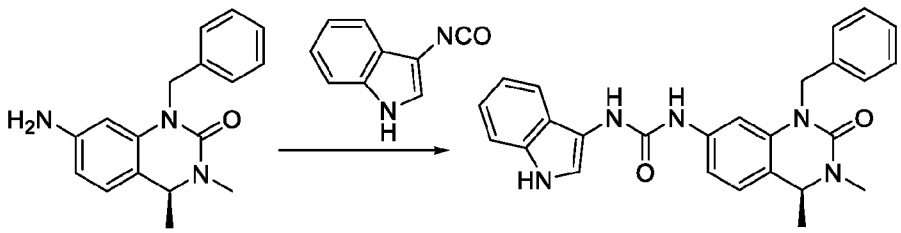
To a stirred solution of (*S*)-methyl 1-benzyl-3,4-dimethyl-2-oxo-1,2,3,4-tetrahydroquinazoline-7-carboxylate (Preparation 23) (0.5 g, 1.54 mmol) in THF (5 mL) and MeOH (2.5 mL) was added a solution of $LiOH.H_2O$ (258 mg, 6.16 mmol) in water (2.5 mL) and the combined mixture stirred at RT for 2 h. TLC showed completion of the reaction. The solvents were evaporated and the residue was diluted with water, washed with MTBE and the aqueous layer acidified with 1N HCl to pH 4-5. The aqueous layer was extracted with EtOAc, washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford the title compound (450 mg, crude) as a white solid. LCMS m/z: 311 [M+H].

Preparation 25: (S)-7-amino-1-benzyl-3,4-dimethyl-3,4-dihydroquinazolin-2(1H)-one



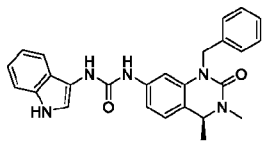
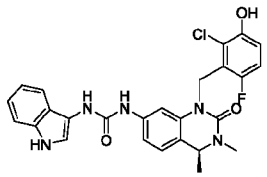
A stirred solution of (*S*)-1-benzyl-3,4-dimethyl-2-oxo-1,2,3,4-tetrahydroquinazoline-7-carboxylic acid (Preparation 24) (0.3 g, 0.97 mmol) in DCM (5 mL) was cooled to 0-5 °C and TEA (0.209 mL, 1.45 mmol) was added in one portion, followed by DPPA (0.419 mL, 1.93 mmol) and the whole was then stirred at RT for 3 h. UPLC-MS showed formation of the desired product. The solvent was evaporated to afford the corresponding acyl azide as intermediate, which was dissolved in t-butanol (10 mL) and refluxed at 100 °C for 24 h. UPLC-MS showed formation of the corresponding Boc-protected amine intermediate. The solvent was evaporated *in vacuo* to give the crude which was purified by Combi-flash and during purification the Boc group was removed to afford the title compound (100 mg, crude) as a white solid which was used in the next step without any further purification. LCMS m/z: 282 [M+H].

Preparation 26: (S)-1-(1-benzyl-3,4-dimethyl-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl)-3-(1H-indol-3-yl)urea (**Example 107**)



To a stirred solution of (*S*)-7-amino-1-benzyl-3,4-dimethyl-3,4-dihydroquinazolin-2(1H)-one (Preparation 25) (100 mg, 0.36 mmol) in THF (5 mL) was added 3-isocyanato-1H-indole (56 mg, 0.36 mmol) at 0-5 °C followed by TEA (0.102 mL, 0.71 mmol) and the whole was maintained at RT for 1 h. UPLC showed completion of the reaction. The reaction mixture was diluted with EtOAc and washed with 10% sodium bicarbonate solution, followed by 1N HCl and finally with brine, dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to afford the crude product which was purified by Combi-flash followed by prep-HPLC to afford the title compound (10 mg, 6.4% yield) as a faint brown solid. Purity by UPLC: 95.09%; 1H NMR (400 MHz; DMSO-d_6): δ 1.19 (d, *J* = 6.25 Hz, 3H), 2.90 (s, 3H), 4.44 (d, *J* = 6.35 Hz, 1H), 4.89-4.92 (m, 1H), 5.04-5.07 (m, 1H), 6.85 (s, 1H), 6.91 (d, J = 7.5 Hz, 1H), 6.95 (d, *J* = 8.15 Hz, 1H), 7.00 (d, *J* = 7.65 Hz, 1H), 7.08 (d, *J* = 8.01 Hz, 1H), 7.1 3-7.17 (m, 3H), 7.24-7.26 (m,

3H), 7.38-7.42 (m, 2H), 8.46 (s, 1H), 8.58 (s, 1H), 10.63 (s, 1H).; UPLC-MS m/z: 440.15 [M+H].

Ex.	Structure	IUPAC Name	LCMS [M+H]	Purity (%)
107		(S)-1-(1-benzyl-3,4-dimethyl-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl)-3-(1H-indol-3-yl)urea	440.15	95.09
108		(S)-1-(1-(2-chloro-6-fluoro-3-hydroxybenzyl)-3,4-dimethyl-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl)-3-(1H-indol-3-yl)urea	506.16 (M-H)	95.77

Biological assay

Reporter gene expression assay in THP-1 cells

THP1-Dual™ cells (Invivogen) were derived from the human THP-1 monocyte cell line by stable integration of two inducible reporter constructs. As a result, THP1-Dual™ cells allow the simultaneous study of the IRF pathway, by assessing the activity of a secreted luciferase (Lucia) and the NF-κB pathway, by monitoring the activity of secreted SEAP. 5 x 10^4 THP1-Dual™ cells were seeded in 384-well plates in growth medium and preincubated with novel compounds for 10 minutes followed by stimulation with 5 μM 2',3'-cGAMP. After 20hr of stimulation the supernatant was removed and the IRF pathway reporter protein was readily measured in the cell culture supernatant using QUANTI-Luc™ (Invivogen), a luciferase detection reagent on a Spectramax i3X luminometer.

In the tables below, IC_{50} value ranges for exemplary compounds are given. The IC_{50} ranges are indicated as "A" for values less than or equal to 1 μM, "B" for values greater than 1 μM and less than or equal to 10 μM, and "C" for values greater than 10 μM.

Activity data

Ex	CRD	THP-1 (HAQ) Activity
3	5137	A
4	5138	A

Ex	CRD	THP-1 (HAQ) Activity
71	5140	A
5	5141	A

Ex	CRD	THP-1 (HAQ) Activity
6	5142	A
72	5167	A
73	5168	A
7	5169	A
8	5184	A
74	5185	A
2	5186	A
9	5191	B
10	5192	A
75	5202	A
11	5203	A
12	5204	A
76	5205	A
13	5210	A
14	5211	B
77	5229	A
107	5235	A
15	5237	A
16	5257	A
78	5258	A
79	5269	A
1	5272	A
17	5276	B
18	5290	A
19	5296	B
20	5297	B
21	5299	B
22	5300	B
23	5301	B
24	5302	B
103	5304	A
25	5309	A
26	5310	A
27	5320	A

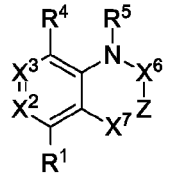
Ex	CRD	THP-1 (HAQ) Activity
38	5330	B
39	5331	A
40	5332	A
28	5333	B
108	5334	B
80	5335	A
104	5336	A
41	5347	B
42	5348	A
43	5349	A
44	5350	B
45	5351	A
46	5352	B
47	5354	A
48	5355	B
49	5356	B
50	5357	A
51	5358	A
52	5359	B
53	5360	A
54	5361	B
55	5362	A
56	5363	A
57	5364	A
58	5365	A
29	5368	A
70	5369	A
30	5370	A
59	5385	A
60	5386	A
81	5387	A
61	5388	B
62	5389	A
82	5390	A

Ex	CRD	THP-1 (HAQ) Activity
63	5391	B
64	5392	A
69	5396	A
83	5397	A
31	5398	A
84	5399	A
85	5400	A
65	5416	A
66	5417	A
67	5418	A
68	5419	B
86	5420	A
87	5421	A
88	5422	A
89	5423	A
90	5425	A
91	5426	A
92	5427	A
93	5428	A
32	5429	A

Ex	CRD	THP-1 (HAQ) Activity
94	5430	A
33	5431	A
95	5432	A
96	5433	A
34	5434	A
35	5435	A
36	5436	A
97	5437	A
105	5438	A
106	5439	A
102	5440	A
37	5456	A
98	5458	A
99	5459	A
100	5460	A
101	5461	A
109	5478	A
110	5506	A
111	5529	A
112	5479	A

Claims

1. A compound of formula (**I**):



(**I**)

, wherein X^2 is CR^2 and X^3 is CR^3 or N; or X^2 is N and X^3 is CR^3;

X^6 is C=O or CR^7R^8;

Z is CR^9R^{10} or NR^9;

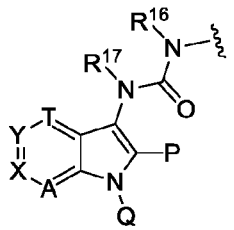
X^7 is S, SO, SO_2, O, NR^{11} or $CR^{11}R^{12}$;

wherein, when Z is CR^9R^{10} then X^7 is S, SO, SO_2, O or NR^{11}, and when Z is NR^9 then X^7 is $CR^{11}R^{12}$;

R^1, R^4, R^7 and R^8 are each independently selected from the group consisting of H, halogen, OR^{13}, CN, $COOR^{13}$, $CONR^{13}R^{14}$, $NR^{13}R^{14}$, $NR^{13}COR^{14}$, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 alkylsulfonyl, optionally substituted mono or bicyclic C_3-C_6 cycloalkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, mono or bicyclic optionally substituted C_6-C_{12} aryl, mono or bicyclic optionally substituted 5 to 10 membered heteroaryl and optionally substituted mono or bicyclic 3 to 8 membered heterocycle;

R^9 to R^{12} are each independently selected from the group consisting of H, halogen, OR^{13}, CN, $COOR^{13}$, $CONR^{13}R^{14}$, $NR^{13}R^{14}$, $NR^{13}COR^{14}$, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl or optionally substituted C_2-C_6 alkynyl;

one of R^2 and R^3 is;



and, when X^2 is CR^2 and X^3 is CR^3, the other of R^2 and R^3 is selected from the group consisting of H, halogen, OR^{13}, CN, $COOR^{13}$, $CONR^{13}R^{14}$, $NR^{13}R^{14}$, $NR^{13}COR^{14}$, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 alkylsulfonyl, optionally substituted mono or bicyclic C_3-C_6 cycloalkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, mono or bicyclic optionally substituted C_6-C_{12} aryl, mono or

bicyclic optionally substituted 5 to 10 membered heteroaryl and optionally substituted mono or bicyclic 3 to 8 membered heterocycle;

A is CR^{19} or N;

X is CR^{20} or N;

Y is CR^{21} or N;

T is CR^{22} or N;

Q is H or optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, $COOR^{13}$, COR^{13} or $CONR^{13}R^{14}$;

P is selected from the group consisting of H, halogen, OR^{13}, CN, $COOR^{13}$, $CONR^{13}R^{14}$, $NR^{13}R^{14}$, $NR^{13}COR^{14}$, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted mono or bicyclic C_3-C_6 cycloalkyl, mono or bicyclic optionally substituted C_6-C_{12} aryl, mono or bicyclic optionally substituted 5 to 10 membered heteroaryl and optionally substituted mono or bicyclic 3 to 8 membered heterocycle;

R^5 is selected from the group consisting of $COOR^{13}$, $CONR^{13}R^{14}$, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 alkylsulfonyl, optionally substituted mono or bicyclic C_3-C_6 cycloalkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, mono or bicyclic optionally substituted C_6-C_{12} aryl, mono or bicyclic optionally substituted 5 to 10 membered heteroaryl, optionally substituted mono or bicyclic 3 to 8 membered heterocycle and $-L^1-L^2-R^{15}$;

R^{13} and R^{14} are each independently selected from the group consisting of H, halogen, OH, CN, COOH, $CONH_2$, NH_2, NHCOH, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 alkylsulfonyl, optionally substituted mono or bicyclic C_3-C_6 cycloalkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted C_1-C_6 alkoxy, optionally substituted C_1-C_6 alkoxycarbonyl group, mono or bicyclic optionally substituted C_6-C_{12} aryl, mono or bicyclic optionally substituted 5 to 10 membered heteroaryl, optionally substituted mono or bicyclic 3 to 8 membered heterocycle, optionally substituted aryloxy, optionally substituted heteroaryloxy and optionally substituted heterocyclyloxy;

L^1 is absent or an optionally substituted C_1-C_6 alkylene, an optionally substituted C_2-C_6 alkenylene, an optionally substituted C_2-C_6 alkynylene, O, S, S=O, SO_2 or NR^{18};

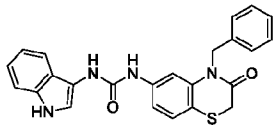
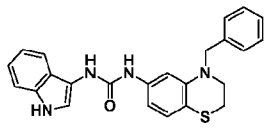
L^2 is absent or an optionally substituted C_1-C_6 alkylene, an optionally substituted C_2-C_6 alkenylene, an optionally substituted C_2-C_6 alkynylene, O, S, S=O, SO_2 or NR^{18};

R^{15} is optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted mono or bicyclic C_3-C_6 cycloalkyl, mono or bicyclic optionally

substituted C_6-C_{12} aryl, mono or bicyclic optionally substituted 5 to 10 membered heteroaryl or optionally substituted mono or bicyclic 3 to 8 membered heterocycle; and R^{16} to R^{18} are independently H, an optionally substituted C_1-C_6 alkyl, an optionally substituted C_2-C_6 alkenyl, an optionally substituted C_2-C_6 alkynyl or CN;

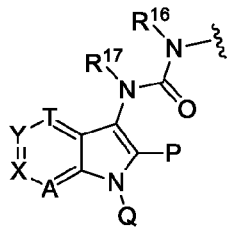
R^{19} to R^{22} are independently H, halogen, OR^{13}, CN, $COOR^{13}$, $CONR^{13}R^{14}$, $NR^{13}R^{14}$, $NR^{13}COR^{14}$, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted mono or bicyclic C_3-C_6 cycloalkyl, mono or bicyclic optionally substituted C_6-C_{12} aryl, mono or bicyclic optionally substituted 5 to 10 membered heteroaryl and optionally substituted mono or bicyclic 3 to 8 membered heterocycle;

or a pharmaceutically acceptable complex, salt, solvate, tautomeric form or polymorphic form thereof;

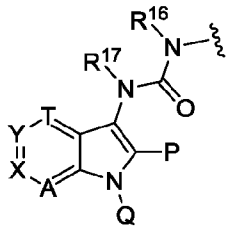
wherein the compound is not  or .

2. The compound of claim 1, wherein R^1 is H, halogen, OH, CN, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl or optionally substituted C_2-C_6 alkynyl.

3. The compound of claim 1 or claim 2, wherein X^2 is CR^2 and X^3 is CR^3.



4. The compound of claim 3, wherein one of R^2 and R^3 and the other of R^2 and R^3 is H, halogen, OH, CN, $COOR^{13}$, $CONR^{13}R^{14}$, $NR^{13}R^{14}$, $NR^{13}COR^{14}$, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl or optionally substituted C_2-C_6 alkynyl, and R^{13} and R^{14} are each independently selected from the group consisting of H, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_3 alkenyl and optionally substituted C_2-C alkynyl.



5. The compound of claim 4, wherein one of R^2 and R^3 is and the other of R^2 and R^3 is H, halogen, OH, CN, $CONR^{13}R^{14}$, $NR^{13}R^{14}$, C_1-C_3 alkyl, C_2-C_3 alkenyl or C_2-C_3 alkynyl, and R^{13} and R^{14} are each independently selected from the group consisting of H, C_1-C_3 alkyl, C_2-C_3 alkenyl and C_2-C alkynyl.

6. The compound of any preceding claim, wherein R^{16} and R^{17} are independently be H, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl or optionally substituted C_2-C_6 alkynyl.

7. The compound of any preceding claim, wherein P is H, halogen, OH, CN, $COOR^{13}$, $CONR^{13}R^{14}$, $NR^{13}R^{14}$, $NR^{13}COR^{14}$, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl or optionally substituted C_2-C_6 alkynyl, and R^{13} and R^{14} are each independently selected from the group consisting of H, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_3 alkenyl and optionally substituted C_2-C alkynyl.

8. The compound of any preceding claim, wherein Q is H, halogen, OH, CN, $COOR^{13}$, $CONR^{13}R^{14}$, $NR^{13}R^{14}$, $NR^{13}COR^{14}$, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl or optionally substituted C_2-C_6 alkynyl, and R^{13} and R^{14} are each independently selected from the group consisting of H, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_3 alkenyl and optionally substituted C_2-C alkynyl.

9. The compound of any preceding claim, wherein:
- A is N, X is CR^{20}, Y is CR^{21} and T is CR^{22};
- A is CR^{19}, X is N, Y is CR^{21} and T is CR^{22};
- A is CR^{19}, X is CR^{20}, Y is N and T is CR^{22}; or
- A is CR^{19}, X is CR^{20}, Y is CR^{21} and T is N.

10. The compound of any one of claims 1 to 8, wherein A is CR^{19}, X is CR^{20}, Y is CR^{21} and T is CR^{22}.

11. The compound of any preceding claim, wherein R^{19} to R^{22} are independently H, halogen, CN, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_3 alkenyl, optionally substituted C_2-C_3 alkynyl, optionally substituted mono or bicyclic C_3-C_6 cycloalkyl, mono or bicyclic optionally substituted C_6-C_{12} aryl, mono or bicyclic optionally substituted 5 to 10 membered heteroaryl or optionally substituted mono or bicyclic 3 to 8 membered heterocycle.

12. The compound of any preceding claim, wherein R^4 is H, halogen, OH, CN, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl or optionally substituted C_2-C_6 alkynyl.

13. The compound of any preceding claim, wherein R^5 is $-L^1$-L^2-R^{15}.

14. The compound of claim 13, wherein L^1 is an optionally substituted C_1-C_3 alkylene, an optionally substituted C_2-C_3 alkenylene, an optionally substituted C_2-C_3 alkynylene or is absent.

15. The compound of claim 13 or claim 14, wherein L^2 is absent or is O, S, S=O, SO_2 or NR^{19}.

16. The compound of any one of claims 13 to 15, wherein R^{15} is optionally substituted mono or bicyclic C_3-C_6 cycloalkyl, mono or bicyclic optionally substituted C_6-C_{12} aryl, mono or bicyclic optionally substituted 5 to 10 membered heteroaryl or optionally substituted mono or bicyclic 3 to 8 membered heterocycle.

17. The compound of any one of claims 1 to 12, wherein R^5 is optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl or optionally substituted C_2-C_6 alkynyl.

18. The compound of any preceding claim, wherein X^6 is CO.

19. The compound of any one claims 1 to 17, wherein X^6 is CR^7R^8 and R^7 and R^8 are independently H, halogen, OH, CN, $COOR^{13}$, $CONR^{13}R^{14}$, $NR^{13}R^{14}$, $NR^{13}COR^{14}$, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl or optionally substituted C_2-C_6 alkynyl.

20. The compound of any preceding claim, wherein:

Z is CR^9R^{10};

X^7 is S, O, SO or NR^{11};

R^9 and R^{10} are independently H, halogen, OR^{13}, CN, $COOR^{13}$, $CONR^{13}R^{14}$, $NR^{13}R^{14}$, $NR^{13}COR^{14}$, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_3 alkenyl or optionally substituted C_2-C_3 alkynyl; and

R^{11} is H, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_3 alkenyl or optionally substituted C_2-C_3 alkynyl.

21. The compound of any one of claims 1 to 19, wherein:

Z is NR^9;

X^7 is $CR^{11}R^{12}$;

R^9 is H, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_3 alkenyl or optionally substituted C_2-C_3 alkynyl;

R^{11} is H, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_3 alkenyl or optionally substituted C_2-C_3 alkynyl; and

R^{12} is H, halogen, OH, CN, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl or optionally substituted C_2-C_6 alkynyl.

22. The compound of claim 1, wherein the compound is:

1-(4-Benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-fluoro-1H-indol-3-yl)urea;

1-(4-(2-Chloro-6-fluorobenzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1H-indol-3-yl)urea;

1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1H-indol-3-yl)urea;

1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)-3-(1H-indol-3-yl)urea;

1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)urea;

1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)urea;

1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-7-yl)-3-(1H-indol-3-yl)urea;

1-(4-(2-chloro-6-fluorobenzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)-3-(1H-indol-3-yl)urea;

1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(2-methyl-1H-indol-3-yl)urea;

1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-chloro-1H-indol-3-yl)urea;

1-(4-(2-chloro-6-fluorobenzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(1H-indol-3-yl)urea;
1-(4-(2-chloro-6-fluorobenzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-7-yl)-3-(1H-indol-3-yl)urea;
1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(1H-pyrrolo[2,3-b]pyridin-3-yl)urea;
1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(1H-pyrrolo[3,2-c]pyridin-3-yl)urea;
1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(1H-pyrrolo[2,3-c]pyridin-3-yl)urea;
1-(1H-indol-3-yl)-3-(4-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)urea;
1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(1H-pyrrolo[3,2-b]pyridin-3-yl)urea;
1-(4-(3,5-difluorobenzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(1H-indol-3-yl)urea;
1-(1H-indol-3-yl)-3-(3-oxo-4-(pyridin-2-ylmethyl)-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)urea;
1-(1H-indol-3-yl)-3-(3-oxo-4-(pyridin-4-ylmethyl)-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)urea;
3-((6-(3-(1H-indol-3-yl)ureido)-3-oxo-2,3-dihydro-4H-benzo[b][1,4]thiazin-4-yl)methyl)benzamide;
2-((6-(3-(1H-indol-3-yl)ureido)-3-oxo-2,3-dihydro-4H-benzo[b][1,4]thiazin-4-yl)methyl)benzamide;
4-((6-(3-(1H-indol-3-yl)ureido)-3-oxo-2,3-dihydro-4H-benzo[b][1,4]thiazin-4-yl)methyl)benzamide;
1-(1H-indol-3-yl)-3-(3-oxo-4-(pyridin-3-ylmethyl)-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)urea;
1-(4-(2-chloro-6-fluoro-3-methoxybenzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(1H-indol-3-yl)urea;
1-(4-(benzo[d]isoxazol-3-ylmethyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(1H-indol-3-yl)urea;
1-(4-(2-chloro-6-fluorobenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(1H-indol-3-yl)urea;
1-(5-chloro-1H-indol-3-yl)-3-(4-(2-chloro-6-fluorobenzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)urea;

1-(4-benzyl-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(1H-indol-3-yl)urea;
1-(4-benzyl-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-7-yl)-3-(1H-indol-3-yl)urea;
1-(4-(3,5-difluorobenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-fluoro-1H-indol-3-yl)urea;
1-(4-(3,5-difluorobenzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-fluoro-1H-indol-3-yl)urea;
1-(4-(3,5-difluorobenzyl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(1H-indol-3-yl)urea;
1-(4-(2-chloro-6-fluoro-3-hydroxybenzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(1H-indol-3-yl)urea;
1-(4-benzyl-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(1H-indol-3-yl)urea;
1-(4-benzyl-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(1H-indol-3-yl)urea;
1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-cyano-1H-indol-3-yl)urea;
1-(5-(1H-Pyrazol-5-yl)-1H-indol-3-yl)-3-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)urea;
1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(oxazol-5-yl)-1H-indol-3-yl)urea;
1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(3,5-difluorophenyl)-1H-indol-3-yl)urea;
1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(2-methyloxazol-5-yl)-1H-indol-3-yl)urea;
1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(isothiazol-4-yl)-1H-indol-3-yl)urea;
1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(3-(hydroxymethyl)phenyl)-1H-indol-3-yl)urea;
1-(5-(1H-pyrazol-4-yl)-1H-indol-3-yl)-3-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)urea;
1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(3-cyanophenyl)-1H-indol-3-yl)urea;
1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(1-(2-hydroxyethyl)-1H-pyrazol-4-yl)-1H-indol-3-yl)urea;

1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(1-ethyl-1H-pyrazol-4-yl)-1H-indol-3-yl)urea;
3-(3-(3-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)ureido)-1H-indol-5-yl)benzamide;
1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(1-(2-methoxyethyl)-1H-pyrazol-4-yl)-1H-indol-3-yl)urea;
1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(1-(difluoromethyl)-1H-pyrazol-4-yl)-1H-indol-3-yl)urea;
1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(pyridin-4-yl)-1H-indol-3-yl)urea;
1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(1-(2-cyanoethyl)-1H-pyrazol-4-yl)-1H-indol-3-yl)urea;
1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(3-methoxyphenyl)-1H-indol-3-yl)urea;
1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(3-(methylsulfonyl)phenyl)-1H-indol-3-yl)urea;
1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(pyridin-3-yl)-1H-indol-3-yl)urea;
1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(pyrimidin-5-yl)-1H-indol-3-yl)urea;
1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(5-chloropyridin-3-yl)-1H-indol-3-yl)urea;
1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(3-(trifluoromethoxy)phenyl)-1H-indol-3-yl)urea;
1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(1-isopropyl-1H-pyrazol-4-yl)-1H-indol-3-yl)urea;
1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(1-(cyclopropylmethyl)-1H-pyrazol-4-yl)-1H-indol-3-yl)urea;
1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(5-(hydroxymethyl)pyridin-3-yl)-1H-indol-3-yl)urea;
1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(2-oxoindolin-6-yl)-1H-indol-3-yl)urea;
1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(6-hydroxypyridin-3-yl)-1H-indol-3-yl)urea;
1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(thiazol-5-yl)-1H-indol-3-yl)urea;

1-(5-(benzo[d][1,3]dioxol-5-yl)-1H-indol-3-yl)-3-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)urea;
1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(isoxazol-4-yl)-1H-indol-3-yl)urea;
1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(3-(trifluoromethyl)phenyl)-1H-indol-3-yl)urea;
1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-(1-(2-hydroxypropyl)-1H-pyrazol-4-yl)-1H-indol-3-yl)urea;
1-(4-(3,5-Difluorobenzyl)-2-methyl-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-fluoro-1H-indol-3-yl)urea;
1-(4-Benzoyl-2-methyl-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(1H-indol-3-yl)urea;
1-(4-benzyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)-3-(1H-indol-3-yl)urea;
1-(4-benzyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1H-indol-3-yl)urea;
1-(4-benzyl-3,4-dihydro-2H-benzo[b][1,4]thiazin-7-yl)-3-(1H-indol-3-yl)urea;
1-(4-(2-chloro-6-fluorobenzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)-3-(1H-indol-3-yl)urea;
1-(4-(2-chloro-6-fluorobenzyl)-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(1H-indol-3-yl)urea;
1-(4-(2-chloro-6-fluorobenzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-3-(1H-indol-3-yl)urea;
1-(4-(2-chloro-6-fluorobenzyl)-3,4-dihydro-2H-benzo[b][1,4]thiazin-7-yl)-3-(1H-indol-3-yl)urea;
1-(1H-indol-3-yl)-3-(4-methyl-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)urea;
1-(4-benzoyl-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(1H-indol-3-yl)urea;
1-(4-benzoyl-3,4-dihydro-2H-benzo[b][1,4]thiazin-7-yl)-3-(1H-indol-3-yl)urea;
1-(4-(2,6-difluorobenzyl)-3,4-dihydro-2H-benzo[b][1,4]thiazin-7-yl)-3-(1H-indol-3-yl)urea;
1-(4-(2-fluoro-6-methylbenzyl)-3,4-dihydro-2H-benzo[b][1,4]thiazin-7-yl)-3-(1H-indol-3-yl)urea;
1-(4-benzyl-2-methyl-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(1H-indol-3-yl)urea;
1-(4-(2-chloro-6-fluorobenzyl)-2-methyl-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(1H-indol-3-yl)urea;
1-(4-benzyl-2-methyl-3,4-dihydro-2H-benzo[b][1,4]thiazin-7-yl)-3-(1H-indol-3-yl)urea;

1-(1H-indol-3-yl)-3-(4-((3-methylisoxazol-5-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]thiazin-7-yl)urea;
1-(4-(2-cyanobenzyl)-3,4-dihydro-2H-benzo[b][1,4]thiazin-7-yl)-3-(1H-indol-3-yl)urea;
1-(4-(3,5-difluorobenzyl)-3,4-dihydro-2H-benzo[b][1,4]thiazin-7-yl)-3-(1H-indol-3-yl)urea;
1-(1H-indol-3-yl)-3-(4-(pyridin-2-ylmethyl)-3,4-dihydro-2H-benzo[b][1,4]thiazin-7-yl)urea;
1-(4-(3,5-difluorobenzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)-3-(1H-indol-3-yl)urea;
1-(4-(3,5-difluorobenzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)-3-(5-fluoro-1H-indol-3-yl)urea;
1-(4-(3,5-difluorobenzyl)-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(1H-indol-3-yl)urea;
1-(4-(3,5-difluorobenzyl)-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-fluoro-1H-indol-3-yl)urea;
1-(4-(3,5-difluorobenzyl)-2-methyl-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(1H-indol-3-yl)urea;
2-((7-(3-(1H-indol-3-yl)ureido)-2,3-dihydro-4H-benzo[b][1,4]thiazin-4-yl)methyl)benzamide;
1-(1H-indol-3-yl)-3-(4-((5-methylisoxazol-3-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]thiazin-7-yl)urea;
1-(4-benzyl-2-methyl-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-fluoro-1H-indol-3-yl)urea;
1-(4-benzyl-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(6-fluoro-1H-indol-3-yl)urea;
1-(4-benzyl-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-fluoro-1H-indol-3-yl)urea;
1-(4-benzyl-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-yl)urea;
1-(4-(3-chloro-5-fluorobenzyl)-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-fluoro-1H-indol-3-yl)urea;
1-(4-(5-Fluoro-6-methylpyridin-2-yl)-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(1H-indol-3-yl)urea;
1-(1H-indol-3-yl)-3-(4-phenyl-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)urea;
1-(1H-indol-3-yl)-3-(4-phenyl-3,4-dihydro-2H-benzo[b][1,4]thiazin-7-yl)urea;
1-(1H-indol-3-yl)-3-(4-(pyridin-2-yl)-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)urea;
1-(4-(6-fluoropyridin-2-yl)-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(1H-indol-3-yl)urea;

(S)-1-(1-Benzyl-3,4-dimethyl-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl)-3-(1H-indol-3-yl)urea;
(S)-1-(1-(2-chloro-6-fluoro-3-hydroxybenzyl)-3,4-dimethyl-2-oxo-1,2,3,4-tetrahydroquinazolin-7-yl)-3-(1H-indol-3-yl)urea;
1-(4-benzyl-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-cyano-1H-indol-3-yl)urea;
1-(5-fluoro-1H-indol-3-yl)-3-(4-((3-methylisoxazol-5-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)urea;
1-(4-(3-chloro-5-fluorobenzyl)-2-methyl-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-fluoro-1H-indol-3-yl)urea; or
1-(4-benzyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-6-yl)-3-(5-bromo-1H-indol-3-yl)urea.

23. A pharmaceutical composition comprising a compound according to any preceding claim, or a pharmaceutically acceptable salt, solvate, tautomeric form or polymorphic form thereof, and a pharmaceutically acceptable vehicle.

24. A compound of formula (**I**), as defined by any one of claims 1 to 22, or a pharmaceutically acceptable complex, salt, solvate, tautomeric form or polymorphic form thereof, or a pharmaceutical composition as defined by claim 23, for use as a medicament.

25. A compound of formula (**I**), as defined by any one of claims 1 to 22, or a pharmaceutically acceptable complex, salt, solvate, tautomeric form or polymorphic form thereof, or a pharmaceutical composition as defined by claim 23, for use in modulating the STimulator of INterferon Genes (STING) protein.

26. A compound of formula (**I**), as defined by any one of claims 1 to 22, or a pharmaceutically acceptable complex, salt, solvate, tautomeric form or polymorphic form thereof, or a pharmaceutical composition as defined by claim 23, for use in treating, ameliorating or preventing a disease selected from liver fibrosis, fatty liver disease, non-alcoholic steatohepatitis (NASH), pulmonary fibrosis, lupus, sepsis, rheumatoid arthritis (RA), type I diabetes, STING-associated vasculopathy with onset in infancy (SAVI), Aicardi-Goutieres syndrome (AGS), familial chilblain lupus (FCL), systemic lupus erythematosus (SLE), retinal vasculopathy, neuroinflammation, systemic inflammatory response syndrome, pancreatitis, cardiovascular disease, renal fibrosis, stroke and age-related macular degeneration (AMD).