



(11) **EP 2 942 349 A1**

(12) **EUROPEAN PATENT APPLICATION**

(43) Date of publication:  
**11.11.2015 Bulletin 2015/46**

(21) Application number: **15166821.7**

(22) Date of filing: **23.12.2005**

(51) Int Cl.:  
**C07D 401/04** <sup>(2006.01)</sup> **C07D 401/14** <sup>(2006.01)</sup>  
**A61K 31/17** <sup>(2006.01)</sup> **A61K 31/47** <sup>(2006.01)</sup>  
**A61K 31/4155** <sup>(2006.01)</sup> **A61P 35/00** <sup>(2006.01)</sup>  
**A61P 29/00** <sup>(2006.01)</sup>

(84) Designated Contracting States:  
**AT BE BG CH CY CZ DE DK EE ES FI FR GB GR  
HU IE IS IT LI LT LU LV MC NL PL PT RO SE SI  
SK TR**

(30) Priority: **23.12.2004 US 639087 P**  
**23.12.2004 US 638986 P**  
**23.12.2004 US 638987 P**  
**23.12.2004 US 638968 P**

(62) Document number(s) of the earlier application(s) in  
accordance with Art. 76 EPC:  
**05855777.8 / 1 835 934**

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Remarks:

This application was filed on 07-05-2015 as a  
divisional application to the application mentioned  
under INID code 62.

(54) **ENZYME MODULATORS AND TREATMENTS**

(57) Novel compounds and methods of using those  
compounds for the treatment of inflammatory conditions,  
hyperproliferative diseases, cancer, and diseases char-  
acterized by hypervascularization are provided. In a pre-  
ferred embodiment, modulation of the activation state of

p38 kinase protein ab1 kinase protein, bcr-ab1 kinase  
protein, braf kinase protein, VEGFR kinase protein, or  
PDGFR kinase protein comprises the step of contacting  
said kinase protein with the novel compounds.

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**Description****Cross-Reference to Related Applications**

- 5 [0001] This application claims the benefit of: (1) Provisional Application SN 60/639,087 filed December 23, 2004; (2) Provisional Application SN 60/638,986, filed December 23, 2004; (3) Provisional Application SN 60/638,987, filed December 23, 2004; (4) Provisional Application SN 60/638,968, filed December 23, 2004.

**Enzyme Modulators for treatment of cancers and hyperproliferative diseases**

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**Field of the Invention**

- 15 [0002] The present invention relates to novel kinase inhibitors and modulator compounds useful for the treatment of various diseases. More particularly, the invention is concerned with such compounds, kinase/compound adducts, methods of treating diseases, and methods of synthesis of the compounds. Preferably, the compounds are useful for the modulation of kinase activity of C-Abl, c-Kit, VEGFR, PDGFR, Raf and P38 kinases and disease polymorphs thereof.

**Background of the invention**

- 20 [0003] Several members of the protein kinase family have been clearly implicated in the pathogenesis of various proliferative diseases and thus represent important targets for treatment of these diseases. Some of the proliferative diseases relevant to this invention include cancer, rheumatoid arthritis, atherosclerosis, and retinopathies. Important examples of kinases which have been shown to cause or contribute to the pathogenesis of these diseases include C-Abl kinase and the oncogenic fusion protein BCR-Abl kinase; PDGF receptor kinase; VEGF receptor kinases; MAP kinase p38 $\alpha$ ; and the RAF kinase family.

- 25 [0004] C-Abl kinase is an important non-receptor tyrosine kinase involved in cell signal transduction. This ubiquitously expressed kinase--- upon activation by upstream signaling factors including growth factors, oxidative stress, integrin stimulation, and ionizing radiation---localizes to the cell plasma membrane, the cell nucleus, and other cellular compartments including the actin cytoskeleton (Van Etten, Trends Cell Biol. (1999) 9: 179). There are two normal isoforms of Abl kinase: Abl-1A and Abl-1B. The N-terminal half of c-Abl kinase is important for autoinhibition of the kinase domain catalytic activity (Pluk et al, Cell (2002) 108: 247). Details of the mechanistic aspects of this autoinhibition have recently been disclosed (Nagar et al, Cell (2003) 112: 859). The N-terminal myristoyl amino acid residue of Abl-1B has been shown to intramolecularly occupy a hydrophobic pocket formed from alpha-helices in the C-lobe of the kinase domain. Such intramolecular binding induces a novel binding area for intramolecular docking of the SH2 domain and the SH3 domain onto the kinase domain, thereby distorting and inhibiting the catalytic activity of the kinase. Thus, an intricate intramolecular negative regulation of the kinase activity is brought about by these N-terminal regions of c-Abl kinase. An aberrant dysregulated form of c-Abl is formed from a chromosomal translocation event, referred to as the Philadelphia chromosome (P.C. Nowell et al, Science (1960) 132: 1497; J.D. Rowley, Nature (1973) 243: 290). This abnormal chromosomal translocation leads aberrant gene fusion between the Abl kinase gene and the breakpoint cluster region (BCR) gene, thus encoding an aberrant protein called Bcr-Abl (G. Q. Daley et al, Science (1990) 247: 824; M. L. Gishizky et al, Proc. Natl. Acad. Sci. USA (1993) 90: 3755; S. Li et al, J. Exp. Med. (1999) 189: 1399). the Bcr-Abl fusion protein does not include the regulatory myristoylation site (B. Nagar et al, Cell (2003) 112: 859) and as a result functions as an oncoprotein which causes chronic myeloid leukemia (CML). CML is a malignancy of pluripotent hematopoietic stem cells. The p210 form of Bcr-Abl is seen in 95% of patients with CML, and in 20% of patients with acute lymphocytic leukemia. A p185 form has also been disclosed and has been linked to being causative of up to 10% of patients with acute lymphocytic leukemia.

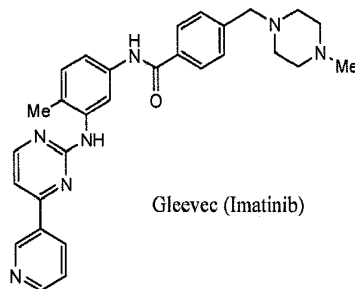
- 30 [0005] Growth factor receptor kinases contribute to the growth and metastasis of tumors by stimulating the proliferation of endothelial cells, fibroblasts, smooth muscle cells, and matrix proteins. Conditions such as hypoxia can induce tumor cells to secrete growth factors which subsequently result in the growth of new blood vessels to support the tumor. These growth factors include platelet derived growth factor (PDGF) and transforming growth factor-beta (TGF-beta), which subsequently stimulate secretion of other growth factors including vascular endothelial growth factor (VEGF), fibroblast growth factor, and epidermal growth factor (EGF). The formation of new blood vessels, which is known as angiogenesis, also provides the tumor with a route to metastasize to remote secondary sites. Inhibiting angiogenic factors that support stromal growth has been proposed as a useful therapy for treating cancers (R.M. Shaheen et al, Cancer Research (1999) 59: 5412; R.M. Shaheen et al, Cancer Research (2001) 61: 1464). Mutations of the PDGF receptor have also been identified which constitutively active in absence of growth factor. VEGF can also stimulate the formation of new lymphatic vessels through direct action on the so-called VEGF-3 receptor, providing yet another pathway for tumor metastasis. Among the three known VEGF receptors, in particular the so-called VEGFR2 (otherwise known as the kinase

insert domain-containing receptor tyrosine kinase or KDR) has been demonstrated to be responsible for the role of VEGF in tumor angiogenesis.

**[0006]** A major signaling pathway downstream of cell surface growth factor receptor activation is the Ras-RAF-MEK-ERK-MAP kinase pathway (Peyssonnaud, C. et al, Biol. Cell (2001) 93: 53-62, Cancers arise when mutations occur in one or more of the proteins involved in this signaling cascade. Cell proliferation and differentiation become dysregulated and cell survival mechanisms are activated which allow unregulated cancer cells to override protective programmed cell death surveillance. Mutations in the p21-Ras protein have been shown to be a major cause of dysregulation of this signaling pathway, leading to the development of human cancers. P21-Ras mutations have been identified in approximately 30% of human cancers (Bolton et al, Ann. Rep. Med. Chem. (1994) 29: 165-174). Cancer-causing mutations in the P21-Ras protein lead to a constitutively active signaling cascade, causing unregulated activation of the downstream components of the RAF-MEK-ERK-MAP kinase pathway (Magnuson et al., Semin.Cancer Biol. (1994) 5: 247-253). The three RAF kinases which participate in this signaling cascade are known as ARAF, BRAF, and CRAF (Peyssonnaud, C. et al, Biol. Cell (2001) 93: 53-62; Avruch, J., Recent Prog. Horm. Res. (2001) 56: 127-155; Kolch, W., Biochem. J. (2000) 351: 289-305). These RAF kinase isoforms are all activated by Ras, and thus are activated in cancers that result from mutated and upregulated p21-Ras protein activity. In addition to activation of this signaling cascade at the initial p21-Ras protein level, mutations have also been found in BRAF kinase which results in activation of the cascade downstream from p21-Ras (Davies, H., et al, Nature (2002) 417: 949-954). A dominant single site mutation at position 599 in the BRAF kinase was shown to be particularly aggressive and linked to approximately 80% of the observed human malignant melanomas. This mutation substitutes the negatively charged amino acid glutamic acid for the normally occurring neutral amino acid valine. This single site mutation is sufficient to render the mutated BRAF kinase constitutively active, resulting in signaling pathway dysregulation and human cancer. Hence small molecule inhibitors of BRAF kinase are a rational approach to the treatment of human malignancy, whether the signaling mutation is at the level of the upstream p21-Ras protein or at the level of BRAF kinase.

**[0007]** The MAP kinase p38 $\alpha$  has recently been identified as an important mechanistic target for the treatment of inflammatory diseases. Inhibition of the MAP kinase p38-*alpha* has been demonstrated to result in the suppression the production and release the proinflammatory mediators TNF- $\alpha$ , IL-1  $\beta$ , IL-6, IL-8 and other proinflammatory cytokines (Chen, Z. et al, Chem. Rev. (2001) 101: 2449). Recently, p38-*alpha* kinase has been implicated in the regulation of tissue factor expression in monocytes, suggesting a role for inhibition of p38-*alpha* kinase in the treatment of thrombotic disorders and atherosclerosis (Chu, A.J., et al, J. Surg. Res. (2001) 101: 85-90; Eto, M., et al, Circulation (2002) 105: 1756-1759). The p38-*alpha* kinase has also been shown to be involved in thrombin-induced proinflammatory conditions (V. Marin, et al, Blood, August 1, 2001, 98: 667-673). Validation of this approach has been achieved by the successful application of various protein therapeutic agents for the treatment of severe chronic inflammatory disease. Monoclonal antibodies to TNF have shown effectiveness in the treatment of rheumatoid arthritis, ulcerative colitis, and Crohn's disease (Rankin, E.C.C., et al, British J. Rheum. (1997) 35: 334-342; Stack, W.A., et al, Lancet (1997) 349: 521-524). Enbrel (etanercept), a soluble TNF receptor, has been developed by Immunex, Inc., and marketed currently by Amgen for the treatment of rheumatoid arthritis (Brower et al, Nature Biotechnology (1997) 15: 1240; Pugsley, M.K., Curr. Opin. Invest. Drugs (2001) 2: 1725). Ro 45-2081, a recombinant soluble TNF- $\alpha$  receptor chimeric protein, has also shown effectiveness in the treatment of the acute phase of lung injury and in animal models of allergic lung disease (Renzetti, et al, Inflamm Res. (1997) 46: S143). Remicade (infliximab) is a monoclonal TNF- $\alpha$  antibody that has shown effectiveness in the treatment of rheumatoid arthritis and Crohn's disease (Bondeson, J. et al, Int. J. Clin. Pract. (2001) 55: 211).

**[0008]** Importantly, small molecule inhibitors of kinase activity have been shown to produce therapeutic benefit as anticipated. The most important example thus far is Gleevec (Imatinib), which is an inhibitor of BCR-Abl kinase (J. Zimmermann et al, WO 99/03854; N. von Bubnoff et al, Cancer Research (2003) 63: 6395; B. J. Druker et al, Nature Medicine (1996) 2: 561; J. Zimmermann et al, Bioorganic and Medicinal Chemistry Letters (1997) 7: 187). Gleevec has been shown to produce clinical remissions in CML patients. However, resistance to the effects of Gleevec have often been encountered (M. E. Gorre et al, Science (2001) 293: 876). Over 17 mutations of Bcr-Abl kinase have been associated with Gleevec resistance (N. von Bubnoff et al, Lancet (2002) 359: 487; S. Branford et al, Blood (2002) 99: 3472; C. Roche-Lestienne et al, Blood (2002) 100: 1014; N.P. Shah et al, Cancer Cell (2002) 2: 117; A. Hochhaus et al, Leukemia (2002) 16: 2190; H.K. Al-Ali et al, Hematology (2004) 5: 55). These mutations are primarily found in the kinase active site domain of Bcr-Abl, and frequently occur in regions proximal to the ATP binding pocket.



**[0009]** The majority of small molecule kinase inhibitors that have been reported have been shown to bind in one of three ways. Most of the reported inhibitors interact with the ATP binding domain of the active site and exert their effects by competing with ATP for occupancy. Other inhibitors have been shown to bind to a separate hydrophobic region of the protein known as the "DFG-in-conformation" pocket, and still others have been shown to bind to both the ATP domain and the "DFG-in-conformation" pocket. Examples specific to inhibitors of RAF kinases can be found in Lowinger et al, Current Pharmaceutical Design (2002) 8: 2269-2278; Dumas, J. et al., Current Opinion in Drug Discovery & Development (2004) 7: 600-616; Dumas, J. et al, WO 2003068223 A1 (2003); Dumas, J., et al, WO 9932455 A1 (1999), and Wan, P.T.C., et al, Cell (2004) 116: 855-867

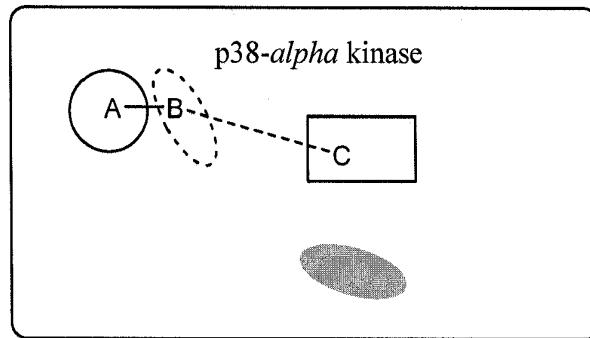
Physiologically, kinases are regulated by a common activation/deactivation mechanism wherein a specific activation loop sequence of the kinase protein binds into a specific pocket on the same protein which is referred to as the switch control pocket. Such binding occurs when specific amino acid residues of the activation loop are modified for example by phosphorylation, oxidation, or nitrosylation. The binding of the activation loop into the switch pocket results in a conformational change of the protein into its active form (Huse, M. and Kuriyan, J. Cell (109) 275-282.)

#### Summary of the Invention

**[0010]** The present invention describes novel potent and selective inhibitors of CAbI kinase, VEGFR2/KDR kinase, and BRAF kinase. The compounds of this invention inhibit kinase activity in a novel way by binding into the "switch pocket" remote from the ATP-cofactor pocket with or without concomitant binding into the "DFG-in-conformation" pocket. X-ray structures determined from small molecule/BRAF co-crystals have confirmed this novel mode of binding to the kinase by the compounds of this present invention, and illustrate the novel features of this binding mode when compared to inhibitors which anchor or bind into the ATP pocket of BRAF kinase. The novel inhibitors of the present invention in some cases also exhibit a preference for inhibiting the oncogenic mutant form of a kinase (V599E-BRAF) and a sparing of normal wild-type kinase that lack the cancer-causing mutation, wherein the oncogenic mutation is a modification of a critical binding amino acid residue of the switch control pocket. An example of this profile has been identified for BRAF, wherein mutation of the valine 599 residue to a glutamic acid residue results in an oncogenic form of BRAF and for which it has been found that compounds of this invention inhibit the oncogenic mutant form of BRAF but not the wild type BRAF. This desirable feature of inhibitor selectivity enables the use of a BRAF inhibitor to treat mammalian cancer caused by mutant V559E BRAF kinase, while sparing the normal wildtype BRAF kinase present in non-cancerous cells. Enhanced safety and selectivity realized from this "wild-type kinase-sparing" provides safer inhibitors that target the cancer-causing forms of BRAF kinase.

**[0011]** Figures 1 and 2 further illustrates the novel binding interaction for the compounds of this invention with kinases. In Figure 1, the known interactions of kinase inhibitors reported previously are defined as directed to a combination of the ATP binding domain, an adjacent binding area known as the ATP binding domain hinge region, and in some cases a third domain known as the "DFG-in conformation" kinase pocket.

Figure 1. Illustration of the kinase binding domains of known kinase inhibitors



represents the kinase ATP binding domain



represents the kinase ATP binding domain hinge region



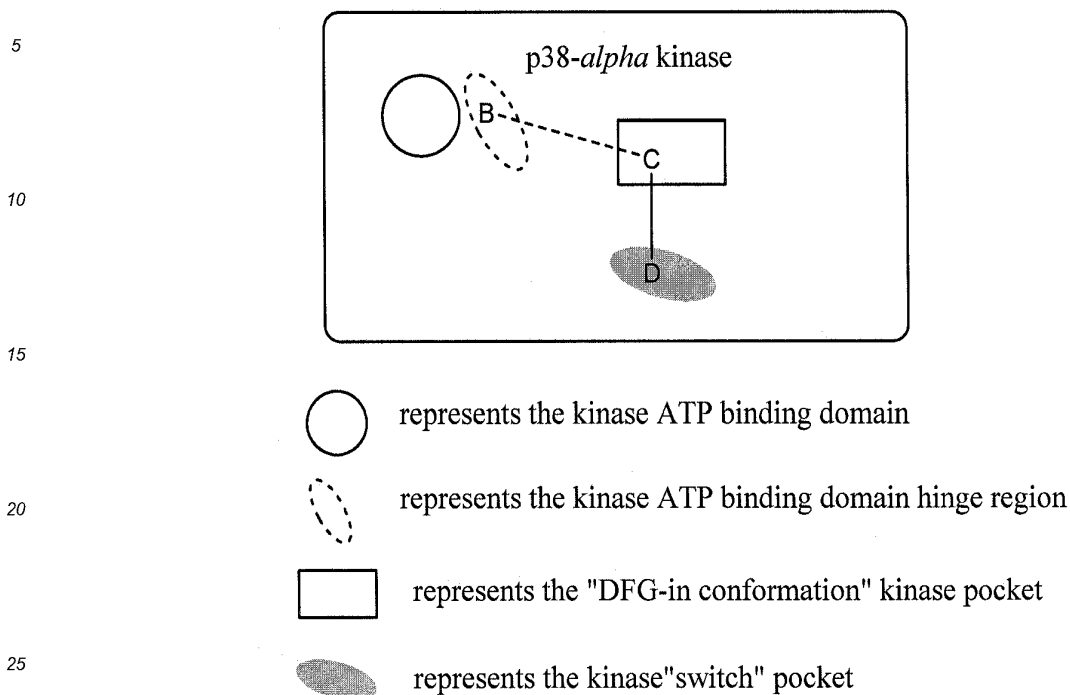
represents the "DFG-in conformation" kinase pocket



represents the kinase "switch" pocket

**[0012]** The binding modality of the compounds of this invention is illustrated in Figure 2. The unique feature is the necessary engagement of another binding domain within the kinase referred to as the switch pocket. Compounds of this invention uniquely and necessarily bind within the switch pocket, and optionally the "DFG-in conformation" domain, and optionally to the ATP binding domain hinge region. This unique binding modality confers upon compounds of this invention a novel mechanism to modulate kinase activity as well as significant advantages over previously described kinase inhibitors in achieving a therapeutically important degree of selectivity for the preferred target over inhibitors which occupy the ATP binding domain. The novel binding modality of the compounds of this invention also avoids mutations within the ATP binding domain which commonly confer resistance to inhibition by compounds which require interaction with the ATP binding domain.

Figure 2. Illustration of the binding modality for compounds of this invention to kinases



[0013] Compounds of the present invention find utility in the treatment of mammalian cancers and especially human cancers including but not limited to malignant melanoma, colorectal cancer, ovarian cancer, papillary thyroid carcinoma, non small cell lung cancer, and mesothelioma. Compounds of the present invention also find utility in the treatment of rheumatoid arthritis and retinopathies including diabetic retinal neuropathy and macular degeneration.

#### Description of the Preferred Embodiments

[0014] The following descriptions refer to various compounds and moieties thereof. Generally, the following definitions apply to these descriptions, with the understanding that in some instances the descriptions are further limited. However, as broadly defined, the following definitions apply.

Carbocyclyl refers to monocyclic saturated carbon rings taken from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptanyl;

Aryl refers to monocyclic or fused bicyclic ring systems characterized by delocalized  $\pi$  electrons (aromaticity) shared among the ring carbon atoms of at least one carbocyclic ring; preferred aryl rings are taken from phenyl, naphthyl, tetrahydronaphthyl, indenyl, and indanyl;

Heteroaryl refers to monocyclic or fused bicyclic ring systems characterized by delocalized  $\pi$  electrons (aromaticity) shared among the ring carbon or heteroatoms including nitrogen, oxygen, or sulfur of at least one carbocyclic or heterocyclic ring; heteroaryl rings are taken from, but not limited to, pyrrolyl, furyl, thienyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, imidazolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, indolyl, isoindolyl, isoindolinyl, indazolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzothiazolonyl, benzoxazolyl, benzoxazolonyl, benzisoxazolyl, benzisothiazolyl, benzimidazolyl, benzimidazolonyl, benzotriazolyl, imidazopyridinyl, dihydropurinonyl, pyrrolopyrimidinyl, purinyl, pyrazolopyridinyl, pyrazolopyrimidinyl, phthalimidyl, phthalimidinyl, pyrazinylpyridinyl, pyridinopyrimidinyl, pyrimidinopyrimidinyl, cinnolinyl, quinoxalinyl, quinazolinyl, quinoliny, isoquinoliny, phthalazinyl, benzodioxyl, indoliny, benzisothiazoline-1,1,3-trionyl, dihydroquinoliny, tetrahydroquinoliny, dihydroisoquinoliny, tetrahydroisoquinoliny, benzoazepiny, benzodiazepiny, benzoxapiny, or benzoxazepiny;

Heterocyclyl refers to monocyclic rings containing carbon and heteroatoms taken from oxygen, nitrogen, or sulfur

and wherein there is not delocalized  $\pi$  electrons (aromaticity) shared among the ring carbon or heteroatoms; heterocyclyl rings include, but are not limited to, oxetanyl, azetadiny, tetrahydrofuranyl, pyrrolidinyl, oxazolinyl, oxazolidinyl, pyranyl, thiopyranyl, tetrahydropyranyl, dioxalanyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, azepinyl, oxepinyl, diazepinyl, tropanyl, homotropanyl;

Poly-aryl refers to two or more monocyclic or fused bicyclic ring systems characterized by delocalized  $\pi$  electrons (aromaticity) shared among the ring carbon atoms of at least one carbocyclic ring wherein the rings contained therein are optionally linked together.

**[0015]** Poly-heteroaryl refers to two or more monocyclic or fused bicyclic systems characterized by delocalized  $\pi$  electrons (aromaticity) shared among the ring carbon or heteroatoms including nitrogen, oxygen, or sulfur of at least one carbocyclic or heterocyclic ring wherein the rings contained therein are optionally linked together, wherein at least one of the monocyclic or fused bicyclic rings of the poly-heteroaryl system is taken from heteroaryl as defined broadly above and the other rings are taken from either aryl, heteroaryl, or heterocyclyl as defined broadly above;

**[0016]** Poly-heterocyclyl refers to two or more monocyclic or fused bicyclic ring systems containing carbon and heteroatoms taken from oxygen, nitrogen, or sulfur and wherein there is not delocalized  $\pi$  electrons (aromaticity) shared among the ring carbon or heteroatoms wherein the rings contained therein are optionally linked, wherein at least one of the monocyclic or fused bicyclic rings of the poly-heteroaryl system is taken from heterocyclyl as defined broadly above and the other rings are taken from either aryl, heteroaryl, or heterocyclyl as defined broadly above;

**[0017]** Lower alkyl refers to straight or branched chain C1-C6alkyls;

**[0018]** Substituted in connection with a moiety refers to the fact that a further substituent may be attached to the moiety to any acceptable location on the moiety.

**[0019]** The term salts embraces pharmaceutically acceptable salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically-acceptable. Suitable pharmaceutically-acceptable acid addition salts may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclyl, carboxylic and sulfonic classes of organic acids, example of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, stearic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, cyclohexylaminosulfonic, algenic, (3-hydroxybutyric, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of Formula I include metallic salts and organic salts. More preferred metallic salts include, but are not limited to appropriate alkali metal (group Ia) salts, alkaline earth metal (group IIa) salts and other physiological acceptable metals. Such salts can be made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc. Preferred organic salts can be made from tertiary amines and quaternary ammonium salts, including in part, tromethamine, diethylamine, N,N'-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine.

**[0020]** The term prodrug refers to derivatives of active compounds which revert *in vivo* into the active form. For example, a carboxylic acid form of an active drug may be esterified to create a prodrug, and the ester is subsequently converted *in vivo* to revert to the carboxylic acid form. See Ettmayer et. al, J. Med. Chem, 2004, 47(10), 2393-2404 and Lorenzi et. al, J. Pharm. Exp. Therapeutics, 2005, 883-8900 for reviews.

#### Protein definitions

**[0021]** PGDF refers to platelet-derived growth factor; PGDFR refers to platelet-derived growth factor receptor; VEGF refers to vascular endothelial growth factor; VEGFR refers to vascular endothelial growth factor receptor; MAP kinase refers to mitogen-activated protein kinase; BCR refers to breakpoint cluster region; CML refers to chronic myeloid leukemia; TGF-beta refers to transforming growth factor beta; EGF refers to epidermal growth factor; KDR refers to kinase insert domain-containing receptor; TNF refers to tumor necrosis factor; ATP refers to adenosine triphosphate; DFG-in-conformation refers to the tripeptide sequence aspartylphenylalanylglucyl in the kinase protein sequence; V599E refers to the mutational replacement of valine 599 of BRAF kinase by glutamic acid; FGFR refers to fibroblast growth factor receptor; TrkA refers to tyrosine receptor kinase type A and neurotrophic tyrosine kinase type 1 (NTRK1); TrkB refers to tyrosine receptor kinase type B and neurotrophic tyrosine kinase type 2 (NTRK2); EPHA1, EPHA2, EPHA3, EPHA4, EPHA5, EPHA6, EPHA7, EPHA8, EPHA9, EPHA10, EPHB1, EPHB2, EPHB3, EPHB4, EPHB5, EPHB6, EPHB7, and EPHB8 refers to members of the ephrin receptor subfamily of the receptor tyrosine kinases.

## 1. First aspect of the invention - C-Abl Kinase Modulator Compounds, Methods, Preparations and Adducts

## 1.1 Generally -A2 Bicyclic Compounds

5 [0022] The invention includes compounds of the formula



15 wherein A2 is selected from the group consisting of bicyclic fused aryl, bicyclic fused heteroaryl, and bicyclic fused heterocyclyl rings, each A2 moiety presenting a proximal ring bonded with A1 and a distal ring attached to the proximal ring, and either the distal ring has a heteroatom in the ring structure thereof and/or the distal ring has Z2 or Z3 substituents;

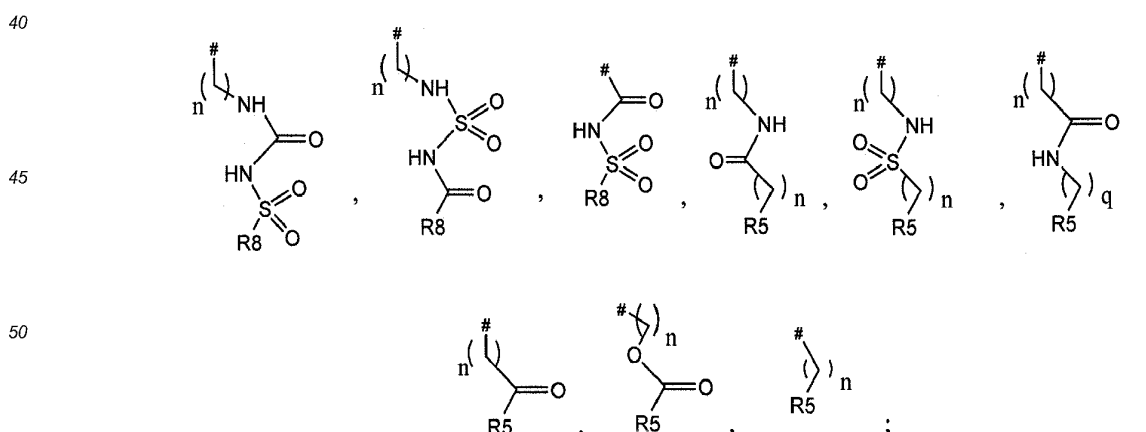
20 A1 is selected from the group consisting of R2'- and R7-substituted phenyl, pyridyl, or pyrimidinyl, R2-substituted monocyclic 5-membered ring heteroaryl, and R2'-substituted monocyclic heterocyclyl moieties;

W and Y are CHR<sub>4</sub>, NR<sub>3</sub>, or O and wherein W and Y are not simultaneously O;

25 X is O, S, or NR<sub>3</sub>;

30 D comprises a member of the group consisting of Z5- or Z6-substituted mono- and poly-aryl, of Z5- or Z6-substituted mono- and poly-heteroaryl, of Z5- or Z6-substituted mono- and poly-heterocyclyl, of Z5- or Z6-substituted mono- and poly-arylalkyl, of Z5- or Z6-substituted mono- and poly-aryl branched alkyl, of Z5- or Z6-substituted mono- and poly-heteroarylalkyl, of Z5- or Z6-substituted mono- and poly-heteroaryl branched alkyl, of Z5- or Z6-substituted mono- and poly-heterocyclylalkyl, of Z5- or Z6-substituted mono- and poly-heterocyclyl branched alkyl, alkyl, and carbocyclyl moieties;

35 each Z2 is independently and individually selected from the group consisting of hydroxyl, hydroxyC1-C6alkyl, cyano, (R<sub>3</sub>)<sub>2</sub>N-, (R<sub>4</sub>)<sub>2</sub>N-, (R<sub>4</sub>)<sub>2</sub>NC1-C6alkyl, (R<sub>4</sub>)<sub>2</sub>NC2-C6alkylN(R<sub>4</sub>)-(CH<sub>2</sub>)<sub>n</sub>, (R<sub>4</sub>)<sub>2</sub>NC2-C6alkylO-(CH<sub>2</sub>)<sub>n</sub>, (R<sub>3</sub>)<sub>2</sub>N-C(=O)-, (R<sub>4</sub>)<sub>2</sub>N-C(=O)-, (R<sub>4</sub>)<sub>2</sub>N-CO-C1-C6alkyl, carboxyl, carboxyC1-C6alkyl, C1-C6alkoxycarbonyl, C1-C6alkoxycarbonylC1-C6alkyl, (R<sub>3</sub>)<sub>2</sub>NSO<sub>2</sub>, (R<sub>4</sub>)<sub>2</sub>NSO<sub>2</sub>, -SO<sub>2</sub>R<sub>5</sub>-, -(CH<sub>2</sub>)<sub>n</sub>N(R<sub>4</sub>)C(O)R<sub>8</sub>, =O, =NOH, =N(OR<sub>6</sub>), heteroarylC1-C6alkyl, heterocyclylC1-C6alkyl heteroaryloxyC1-C6alkyl, heterocycliloxyC1-C6alkyl, arylaminoC1-C6alkyl, heteroarylaminoC1-C6alkyl, heterocyclylaminoC1-C6alkyl, or moieties of the formulae



55 wherein the symbol (#) indicates the point of attachment of the Z2 moiety to the A2 ring of formula I;

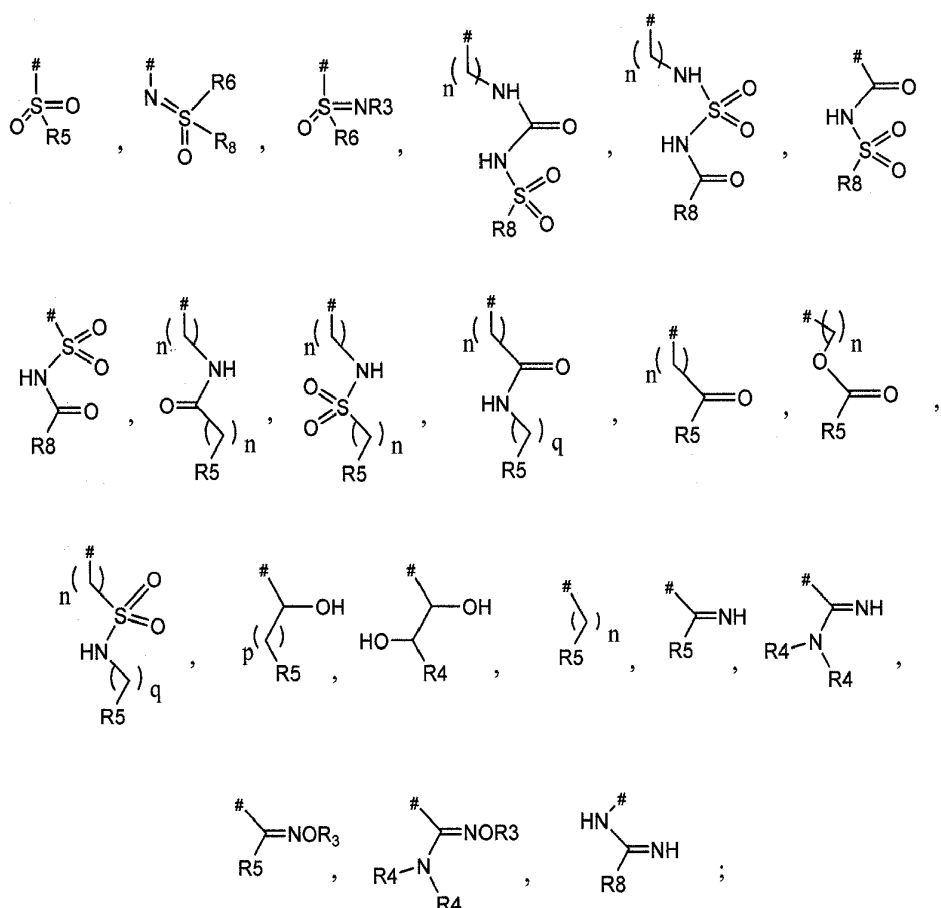
in the event that Z2 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;



wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z2 may cyclize to form a C3-C7 heterocycl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z2 may cyclize to form a C3-C7 heterocycl ring;

each Z3 is independently and individually selected from the group consisting of H, C1-C6alkyl, hydroxyl, hydroxyl-C6alkyl, cyano, C1-C6alkoxy, C1-C6alkoxyC1-C6alkyl, halogen, CF<sub>3</sub>, (R<sub>3</sub>)<sub>2</sub>N-, (R<sub>4</sub>)<sub>2</sub>N-, (R<sub>4</sub>)<sub>2</sub>NC1-C6alkyl, (R<sub>4</sub>)<sub>2</sub>NC2-C6alkylN(R<sub>4</sub>)-(CH<sub>2</sub>)<sub>n</sub>, (R<sub>4</sub>)<sub>2</sub>NC2-C6alkylO-(CH<sub>2</sub>)<sub>n</sub>, -R8C(=O)-, (R<sub>4</sub>)<sub>2</sub>N-CO-C1-C6alkyl, carboxyl, carboxylC1-C6alkyl, C1-C6alkoxycarbonyl, C1-C6alkoxycarbonylC1-C6alkyl, (R<sub>3</sub>)<sub>2</sub>NSO<sub>2</sub>, -SO<sub>2</sub>R<sub>3</sub>, SOR<sub>3</sub>, (R<sub>4</sub>)<sub>2</sub>NSO<sub>2</sub>, -SO<sub>2</sub>R<sub>4</sub>, -SOR<sub>4</sub>, -(CH<sub>2</sub>)<sub>n</sub>N(R<sub>4</sub>)C(O)R<sub>8</sub>, -C(=NOH)R<sub>6</sub>, -C(=NOR<sub>3</sub>)R<sub>6</sub>, heteroaryl, heterocycl, heteroarylC1-C6alkyl, heterocyclC1-C6alkyl heteroaryloxy, heterocyclloxy, heteroaryloxyC1-C6alkyl, heterocyclloxyC1-C6alkyl, arylamino, heteroarylamino, heterocycllamino, arylaminoC1-C6alkyl, heteroarylaminoC1-C6alkyl, heterocycllaminoC1-C6alkyl, or moieties of the formulae



wherein the symbol (#) indicates the point of attachment of the Z3 moiety to the A2 ring of formula I;

in the event that Z3 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z3 may cyclize to form a C3-C7 heterocycl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched

C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z3 may cyclize to form a C3-C7 heterocyclyl ring;

each Z5 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, halogen, fluoroalkyl, cyano, hydroxyl, alkoxy, oxo, aminocarbonyl, carbonylamino, aminosulfonyl, sulfonylamino, -N(R<sub>3</sub>)<sub>2</sub>, -O-(CH<sub>2</sub>)<sub>q</sub>-N(R<sub>4</sub>)<sub>2</sub>, -N(R<sub>3</sub>)-(CH<sub>2</sub>)<sub>q</sub>-N(R<sub>4</sub>)<sub>2</sub>, -R<sub>5</sub>, -O-(CH<sub>2</sub>)<sub>q</sub>-O-Alkyl, -O-(CH<sub>2</sub>)<sub>q</sub>-N(R<sub>4</sub>)<sub>2</sub>, -N(R<sub>3</sub>)-(CH<sub>2</sub>)<sub>q</sub>-O-Alkyl, -N(R<sub>3</sub>)-(CH<sub>2</sub>)<sub>q</sub>-N(R<sub>4</sub>)<sub>2</sub>, -O-(CH<sub>2</sub>)<sub>q</sub>-R<sub>5</sub>, and -N(R<sub>3</sub>)-(CH<sub>2</sub>)<sub>q</sub>-R<sub>5</sub>;

wherein two R<sub>3</sub> moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z5 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R<sub>4</sub> moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z5 may cyclize to form a C3-C7 heterocyclyl ring;

each Z6 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, hydroxyl, C1-C6alkoxy, (R<sub>3</sub>)<sub>2</sub>N-, -N(R<sub>3</sub>)COR<sub>8</sub>, (R<sub>4</sub>)<sub>2</sub>N-, -R<sub>5</sub>, -N(R<sub>4</sub>)COR<sub>8</sub>, -N(R<sub>3</sub>)SO<sub>2</sub>R<sub>6</sub>-, -CON(R<sub>3</sub>)<sub>2</sub>, -CON(R<sub>4</sub>)<sub>2</sub>, -COR<sub>5</sub>, -SO<sub>2</sub>NHR<sub>4</sub>, heteroaryl, heterocyclyl, heteroaryloxy, heterocyclyloxy, arylamino, heteroarylamino, and heterocyclylamino;

wherein two R<sub>3</sub> moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z6 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R<sub>4</sub> moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z6 may cyclize to form a C3-C7 heterocyclyl ring;

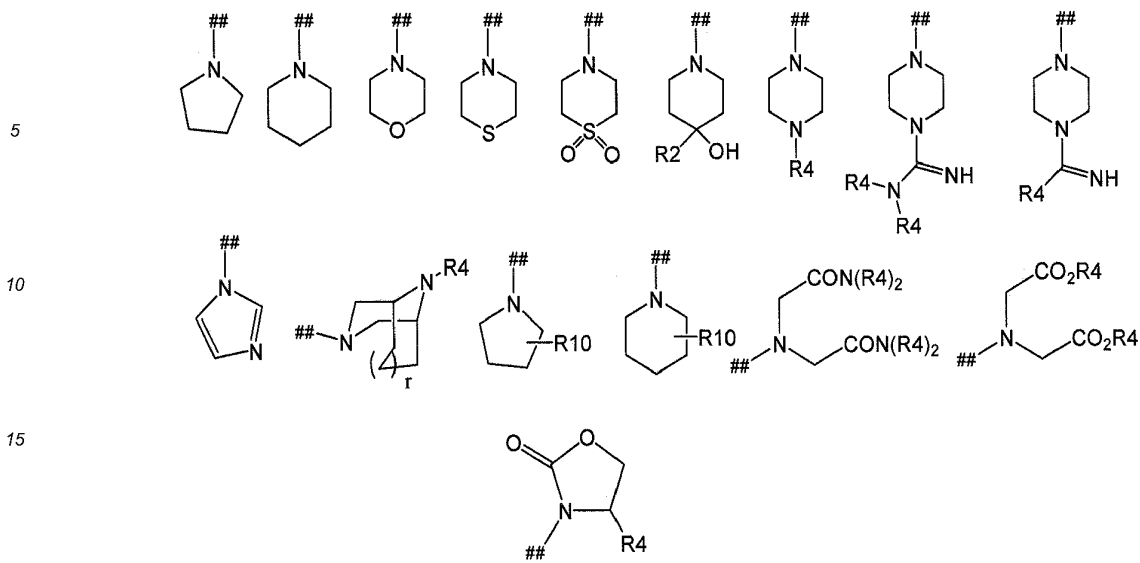
each R<sub>2</sub> is selected from the group consisting of alkyl, branched alkyl, fluoroalkyl, wherein the alkyl group is partially or fully fluorinated, and R<sub>19</sub> substituted C3-C8carbocyclyl wherein R<sub>19</sub> is H, and C1-C6alkyl;

each R<sub>2</sub>' is selected from the group consisting of halogen and R<sub>2</sub>;

each R<sub>3</sub> is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, C3-C7carbocyclyl, or phenyl;

each R<sub>4</sub> is selected from the group consisting of H, C1-C6alkyl, hydroxyC1-C6 alkyl, dihydroxyC1-C6alkyl, C1-C6alkoxyC1-C6alkyl, branched C3-C7alkyl, branched hydroxyC1-C6 alkyl, branched C1-C6alkoxyC1-C6alkyl, branched dihydroxyC1-C6alkyl, carbocyclyl, hydroxyl substituted carbocyclyl, alkoxy substituted carbocyclyl, dihydroxy substituted carbocyclyl, phenyl, heteroaryl, heterocyclyl, phenylC1-C6alkyl, heteroarylC1-C6alkyl, and heterocyclylC1-C6alkyl;

each R<sub>5</sub> is independently and individually selected from the group consisting of



and wherein the symbol (##) is the point of attachment to respective R8, R10, Z2, or Z3, moieties containing a R5 moiety;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R5 may cyclize to form a C3-C7 heterocyclyl ring;

each R6 is independently and individually selected from the group consisting of C1-C6alkyl, branched C3-C7alkyl, carbocyclyl, phenyl, heteroaryl, and heterocyclyl;

each R7 is selected from the group consisting of H, halogen, C1-C3fluoroalkyl wherein the alkyl moiety is partially or fully fluorinated, C1-C3alkyl, cyclopropyl, cyano, or C1-C3alkoxy;

each R8 is independently and individually selected from the group consisting of C1-C6alkyl, branched C3-C7alkyl, fluoroalkyl wherein the alkyl moiety is partially or fully fluorinated, carbocyclyl, phenyl, C1-C6phenylalkyl, heteroaryl or heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, OH, C1-C6alkoxy, N(R3)2, N(R4)2, or R5;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of R8 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R8 may cyclize to form a C3-C7 heterocyclyl ring;

each R10 is independently and individually selected from the group consisting of CO2H, CO2C1-C6alkyl, CO-N(R4)2, OH, C1-C6alkoxy, -N(R4)2;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R10 may cyclize to form a C3-C7 heterocyclyl ring;

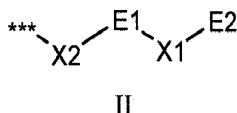
and n is 0-4; p is 1-4; q is 2-6; r is 0 or 1;

and tautomers, diastereomers, geometric isomers, enantiomers, hydrates, prodrugs and salts of any of the foregoing.

## 1.1.1 Preferred D Moieties

## 1.1.1a

5 [0023] Preferably, the compounds of formula I above contain D moieties of the formula



wherein E1 is selected from the group consisting cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyrrolidinyl, piperidinyl, phenyl, thienyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, pyrrolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, furyl, imidazolyl, pyridyl, pyrimidinyl and naphthyl;

15 wherein the symbol (\*\*\*) is the point of attachment to the Y group of formula I;

X1 is selected from the group consisting of O, S, NR<sub>3</sub>, -C(=O)-, -O-(CH<sub>2</sub>)<sub>n</sub>-, -S-(CH<sub>2</sub>)<sub>n</sub>-, -NR<sub>3</sub>-(CH<sub>2</sub>)<sub>n</sub>-, -O-(CH<sub>2</sub>)<sub>q</sub>-O-, -O-(CH<sub>2</sub>)<sub>q</sub>-NR<sub>3</sub>-, -N(R<sub>3</sub>)-(CH<sub>2</sub>)<sub>q</sub>-N(R<sub>3</sub>)-, -(CH<sub>2</sub>)<sub>n</sub>-N(R<sub>4</sub>)-C(=O)-, -(CH<sub>2</sub>)<sub>n</sub>-N(R<sub>4</sub>)-C(=O)(CH<sub>2</sub>)<sub>n</sub>-, - (CH<sub>2</sub>)<sub>n</sub>-CO-N(R<sub>4</sub>)-, -(CH<sub>2</sub>)<sub>p</sub>-, C2-C5alkenyl, C2-C5alkynyl, C3-C6cycloalkyl, and a direct bond wherein the E1 ring and the E2 ring are directly linked by a covalent bond;

and wherein the carbon atoms of -(CH<sub>2</sub>)<sub>n</sub>-, -(CH<sub>2</sub>)<sub>q</sub>-, (CH<sub>2</sub>)<sub>p</sub>-, C2-C5alkenyl, and C2-C5alkynyl moieties of X1 may be further substituted by one or more C1-C6alkyl;

25 X2 is selected from the group consisting of C1-C6 alkyl, C3-C6 branched alkyl, or a direct bond wherein E1 is directly linked to the Y group of formula I;

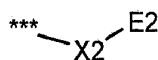
and wherein the carbon atoms of -(CH<sub>2</sub>)<sub>n</sub>-, -(CH<sub>2</sub>)<sub>q</sub>-, -(CH<sub>2</sub>)<sub>p</sub>-, C2-C5alkenyl, and C2-C5alkynyl of X2 can be further substituted by one or more C1-C6alkyl;

and E2 is selected from the group comprising cyclopentyl, cyclohexyl, phenyl, naphthyl, pyrrolyl, furyl, thienyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, imidazolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, fused bicyclic rings selected from the group comprising indolyl, isoindolyl, isoindolinyl, isoindolonyl, indazolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzothiazolonyl, benzoxazolyl, benzoxazolonyl, benzisoxazolyl, benzisothiazolyl, benzimidazolyl, benzimidazolonyl, benztriazolyl, imidazopyridinyl, imidazopyrimidinyl, imidazonopyrimidinyl, dihydropurinonyl, pyrrolopyrimidinyl, purinyl, pyrazolopyrimidinyl, pyrazolopyrimidinyl, isoxazolopyrimidinyl, isothiazolopyrimidinyl, furylopyrimidinyl, thienopyrimidinyl, phthalimidyl, phthalimidinyl, pyrazinylpyridinyl, pyridinopyrimidinyl, pyrimidinopyrimidinyl, cinnolinyl, quinoxalinyl, quinazolinyl, quinolinyl, isoquinolinyl, phthalazinyl, benzodioxyl, indolinyl, benzisothiazoline-1,1,3-trionyl, dihydroquinolinyl, tetrahydroquinolinyl, dihydroisoquinolinyl, tetrahydroisoquinolinyl, benzoazepinyl, benzodiazepinyl, benzoxapinyl, benzoxazepinyl, non-fused bicyclic rings comprising pyridylpyrimidinyl, pyrimidinylpyrimidinyl, oxazolylpyrimidinyl, thiazolylpyrimidinyl, imidazolylpyrimidinyl, isoxazolylpyrimidinyl, isothiazolylpyrimidinyl, pyrazolylpyrimidinyl, triazolylpyrimidinyl, oxadiazolylpyrimidinyl, thiadiazolylpyrimidinyl, morpholinylpyrimidinyl, dioxothiomorpholinylpyrimidinyl, thiomorpholinylpyrimidinyl, and heterocyclis selected from the group comprising oxetanyl, azetadinyl, tetrahydrofuranyl, pyrrolidinyl, oxazolanyl, oxazolidinyl, imidazolonyl, pyranal, thiopyranal, tetrahydropyranal, dioxalanyl, piperidinyl, morpholinyl, thiomorpholinyl, dioxothiomorpholinyl, piperazinyl, azepinyl, oxepinyl, diazepinyl, tropinyl, and homotropinyl;

50 and n is 0-4; p is 1-4; q is 2-6.

## 1.1.1b

[0024] Additional preferred D moieties comprise carbocyclis and a moiety of the formula



X2 is selected from the group consisting of C1-C6 alkyl, C3-C6 branched alkyl, or a direct bond wherein E2 is directly linked to the Y group of formula I.

1.1.1c

5

**[0025]** More preferred D moieties from 1.1.1b comprise the compounds of Formula III wherein the E2 ring is selected from the group comprising cyclopentyl, cyclohexyl, phenyl, naphthyl, pyrrolyl, furyl, thienyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, imidazolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, fused bicyclic rings selected from the group comprising indolyl, isoindolyl, isoindolinyl, isoindolonyl, indazolyl, benzofuranyl, benzothieryl, benzothiazolyl, benzothiazolonyl, benzoxazolyl, benzoxazolonyl, benzisoxazolyl, benzisothiazolyl, benzimidazolyl, benzimidazolonyl, benztriazolyl, imidazopyridinyl, imidazopyrimidinyl, imidazonopyrimidinyl, dihydropurinonyl, pyrrolopyrimidinyl, purinyl, pyrazolopyridinyl, pyrazolopyrimidinyl, isoxazolopyrimidinyl, isothiazolopyrimidinyl, furylopyrimidinyl, thienopyrimidinyl, phthalimidyl, phthalimidinyl, pyrazinylpyridinyl, pyridinopyrimidinyl, pyrimidinopyrimidinyl, cinnolyl, quinoxalyl, quinazolyl, quinolyl, isoquinolyl, phthalazyl, benzodioxyl, indolyl, benzisothiazoline-1,1,3-trionyl, dihydroquinolyl, tetrahydroquinolyl, dihydroisoquinolyl, tetrahydroisoquinolyl, benzazepinyl, benzodiazepinyl, benzoxapinyl, benzoxazepinyl, non-fused bicyclic rings comprising pyridylpyrimidinyl pyrimidinylpyrimidinyl, oxazolylpyrimidinyl, thiazolylpyrimidinyl, imidazolylpyrimidinyl, isoxazolylpyrimidinyl, isothiazolylpyrimidinyl, pyrazolylpyrimidinyl, triazolylpyrimidinyl, oxadiazolylpyrimidinyl, thiadiazolylpyrimidinyl, morpholinylpyrimidinyl, dioxothiomorpholinylpyrimidinyl, thiomorpholinylpyrimidinyl, and heterocyclyls selected from the group comprising oxetanyl, azetadanyl, tetrahydrofuranyl, pyrrolidinyl, oxazolyl, oxazolidinyl, imidazolonyl, pyranyl, thiopyranyl, tetrahydropyranyl, dioxalyl, piperidinyl, morpholyl, thiomorpholyl, dioxothiomorpholyl, piperazyl, azepinyl, oxepinyl, diazepinyl, tropanyl, and homotropanyl.

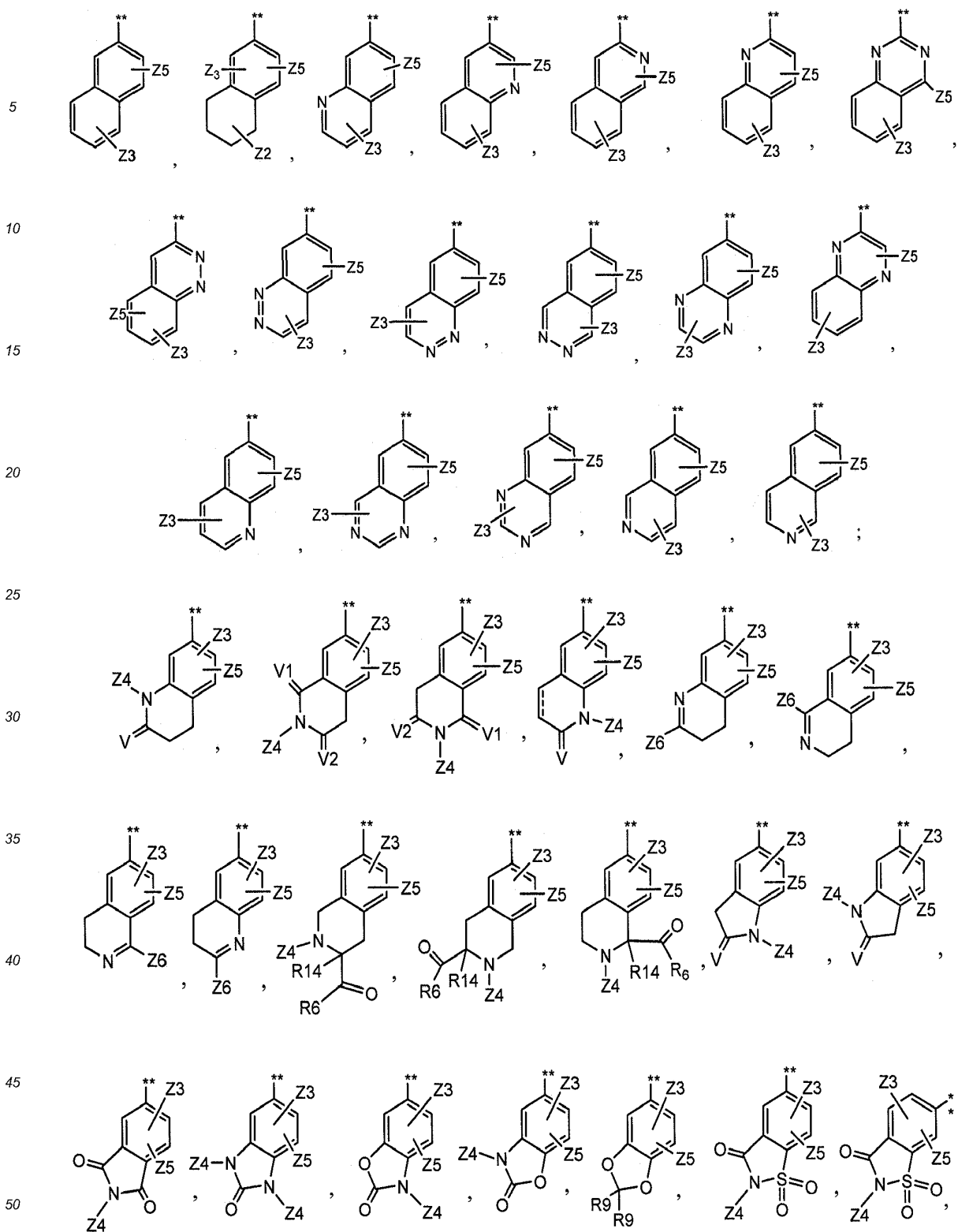
### 1.1.2 Preferred A2 Moieties

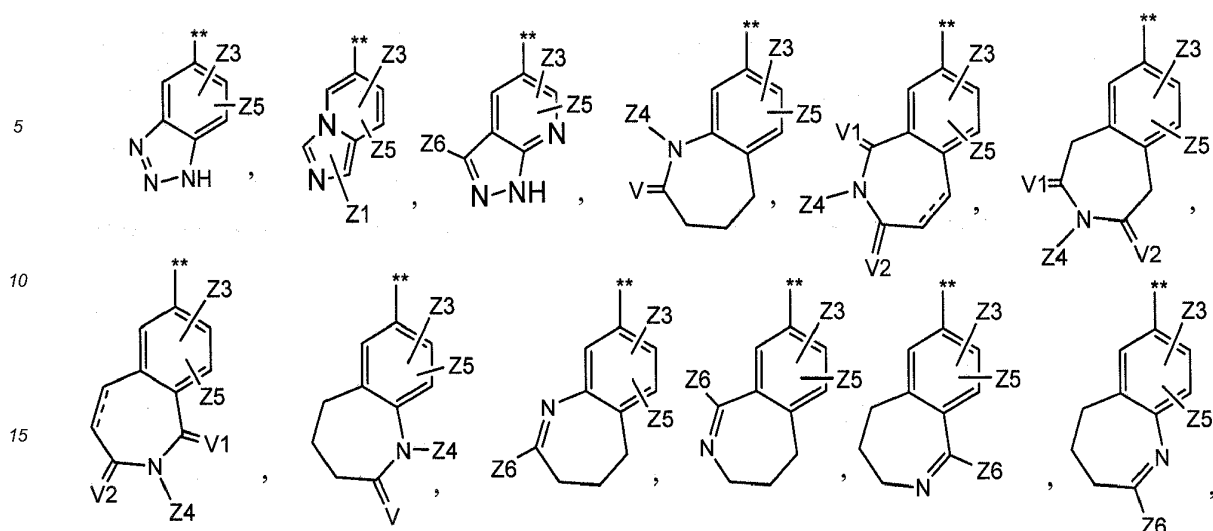
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1.1.2a

**[0026]** Preferred A2 moieties of Formula I are selected from the group consisting of







and wherein the symbol (\*\*) is the point of attachment to the A1 ring of formula I;

and wherein  $\text{---}$  indicates either a saturated or an unsaturated bond;

wherein each Z3 and Z5 may be independently attached to either of the rings making up the foregoing bicyclic structures;

each R9 is independently and individually selected from the group consisting of H, F, C1-C6alkyl, branched C4-C7alkyl, carbocyclyl, phenyl, phenyl C1-C6alkyl, heterocyclyl and heterocyclylC1-C6alkyl;

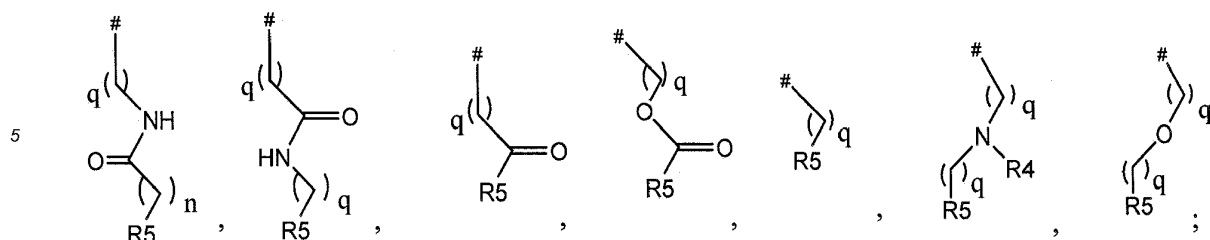
each R13 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, carbocyclyl, hydroxyC2-C7alkyl, C1-C6alkoxyC2-C7alkyl, (R4)<sub>2</sub>N-CO, (R4)<sub>2</sub>N-CO-C1-C6alkyl, carboxyC1-C6alkyl, C1-C6alkoxycarbonyl, C1-C6alkoxycarbonylC1-C6alkyl, (R4)<sub>2</sub>N-C2-C6alkyl, (R4)<sub>2</sub>N-C2-C6alkylN(R4)-(CH<sub>2</sub>)<sub>q</sub>, R5-C2-C6alkylN(R4)-(CH<sub>2</sub>)<sub>q</sub>, (R4)<sub>2</sub>N-C2-C6alkylO-(CH<sub>2</sub>)<sub>q</sub>, R5-C2-C6alkylO-(CH<sub>2</sub>)<sub>q</sub>, -(CH<sub>2</sub>)<sub>q</sub>N(R4)C(O)R8, aryl, arylC1-C6alkyl, heteroaryl, heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, aryloxyC2-C6alkyl, heteroaryloxyC2-C6alkyl, heterocyclyloxyC2-C6alkyl, arylaminoC2-C6alkyl, heteroarylaminoC2-C6alkyl, and heterocyclylaminoC2-C6alkyl;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R13 may cyclize to form a C3-C7 heterocyclyl ring;

each R14 is independently and respectively selected from the group consisting of H and C1-C6alkyl;

V, V1, and V2 are each independently and respectively selected from the group consisting of O and H<sub>2</sub>;

each Z4 is a substituent attached to a ring nitrogen and is independently and individually selected from the group consisting of H, C1-C6alkyl, hydroxyC2-C6alkyl, C1-C6alkoxyC2-C6alkyl, (R4)<sub>2</sub>N-C2-C6alkyl, (R4)<sub>2</sub>N-C2-C6alkylN(R4)-C2-C6alkyl, (R4)<sub>2</sub>N-C2-C6alkyl-O-C2-C6alkyl, (R4)<sub>2</sub>N-CO-C2-C6alkyl, carboxyC2-C6alkyl, C1-C6alkoxycarbonylC2-C6alkyl, -C2-C6alkylN(R4)C(O)R8, R8-C(=NR3)-, -SO<sub>2</sub>R8, -COR8, heteroaryl, heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl heteroaryloxyC2-C6alkyl, heterocyclyloxyC2-C6alkyl, arylaminoC2-C6alkyl, heteroarylaminoC2-C6alkyl, heterocyclylaminoC2-C6alkyl, and moieties of the formulae



10 wherein the symbol (#) indicates the point of attachment of the Z4 moiety to the A2 ring for formula I;

in the event that Z4 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

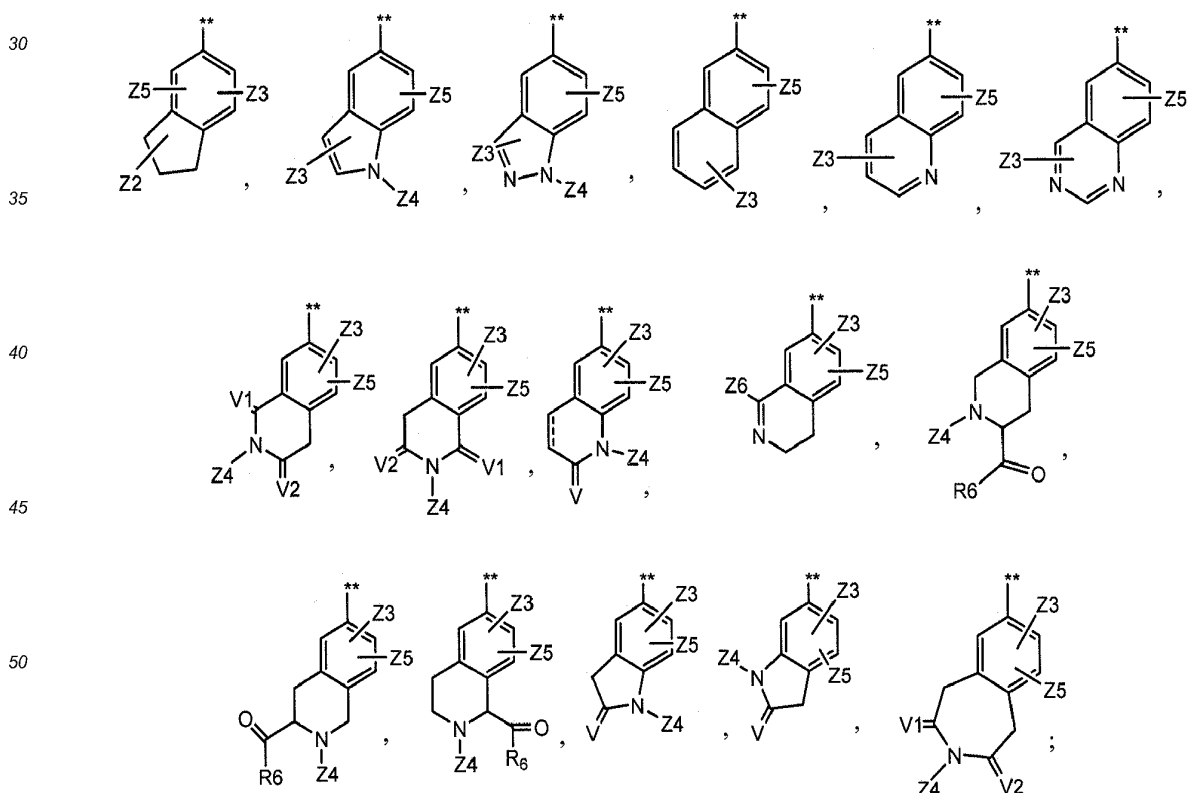
15 wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z4 may cyclize to form a C3-C7 heterocyclyl ring;

20 wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z4 may cyclize to form a C3-C7 heterocyclyl ring;

and n is 0-4; p is 1-4; q is 2-6; r is 0 or 1; v is 1 or 2.

25 1.1.2b

[0027] More preferred A2 moieties are selected from the group consisting of



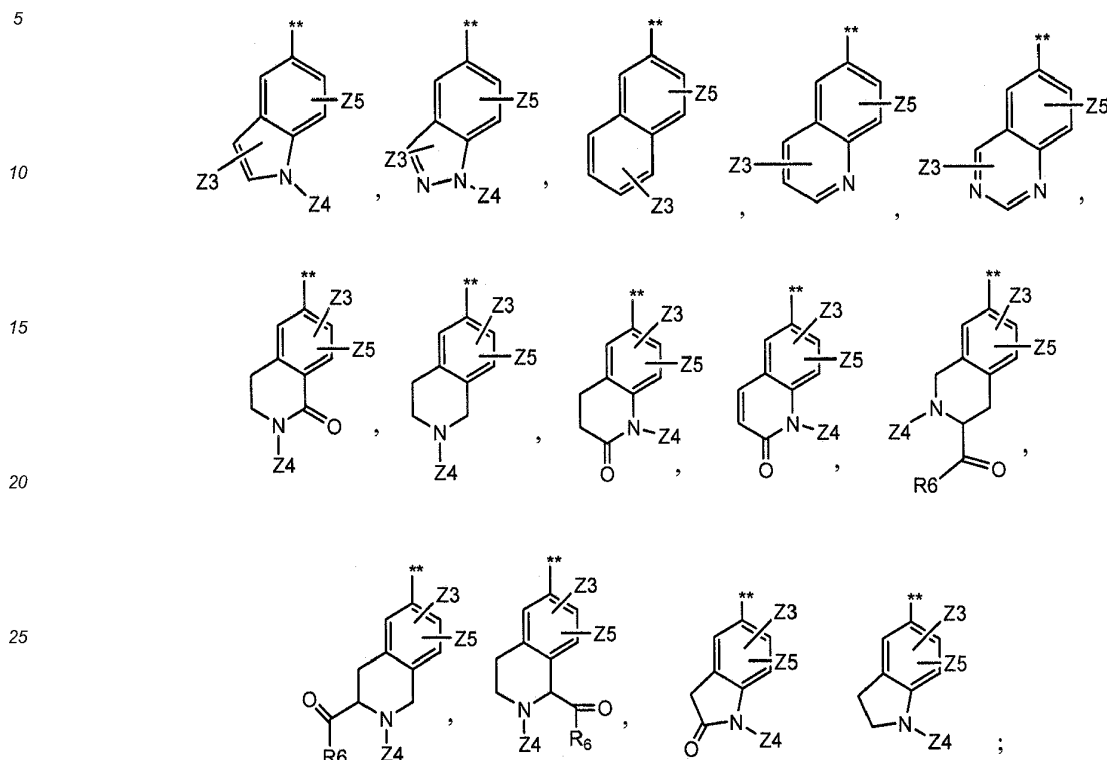
and wherein the symbol (\*\*) is the point of attachment to the A1 ring for formula I;

wherein each Z3 and Z5 is independently attached to either aryl or heteroaryl ring of the A2 bicyclic ring.



## 1.1.2c

**[0028]** Still more preferred A2 moieties are selected from the group consisting of



and wherein the symbol (\*\*) is the point of attachment to the A1 ring of formula I;  
wherein each Z3 and Z5 is independently attached to either aryl or heteroaryl ring of the A2 bicyclic ring.

## 1.1.3 Preferred Classes of Compounds

## 1.1.3a

**[0029]** Compounds as defined in 1.1.1a wherein the A2 group is defined in 1.1.2a.

## 1.1.3b

**[0030]** Compounds as defined in 1.1.3a wherein the A2 group is defined in 1.1.2b.

## 1.1.3c

**[0031]** Compounds as defined in 1.1.3a wherein the A2 group is defined in 1.1.2c.

## 1.1.3d

**[0032]** Compounds as defined in 1.1.1b wherein the A2 group is defined in 1.1.2a.

## 1.1.3e

**[0033]** Compounds as defined in 1.1.3c wherein the A2 group is defined in 1.1.2b.

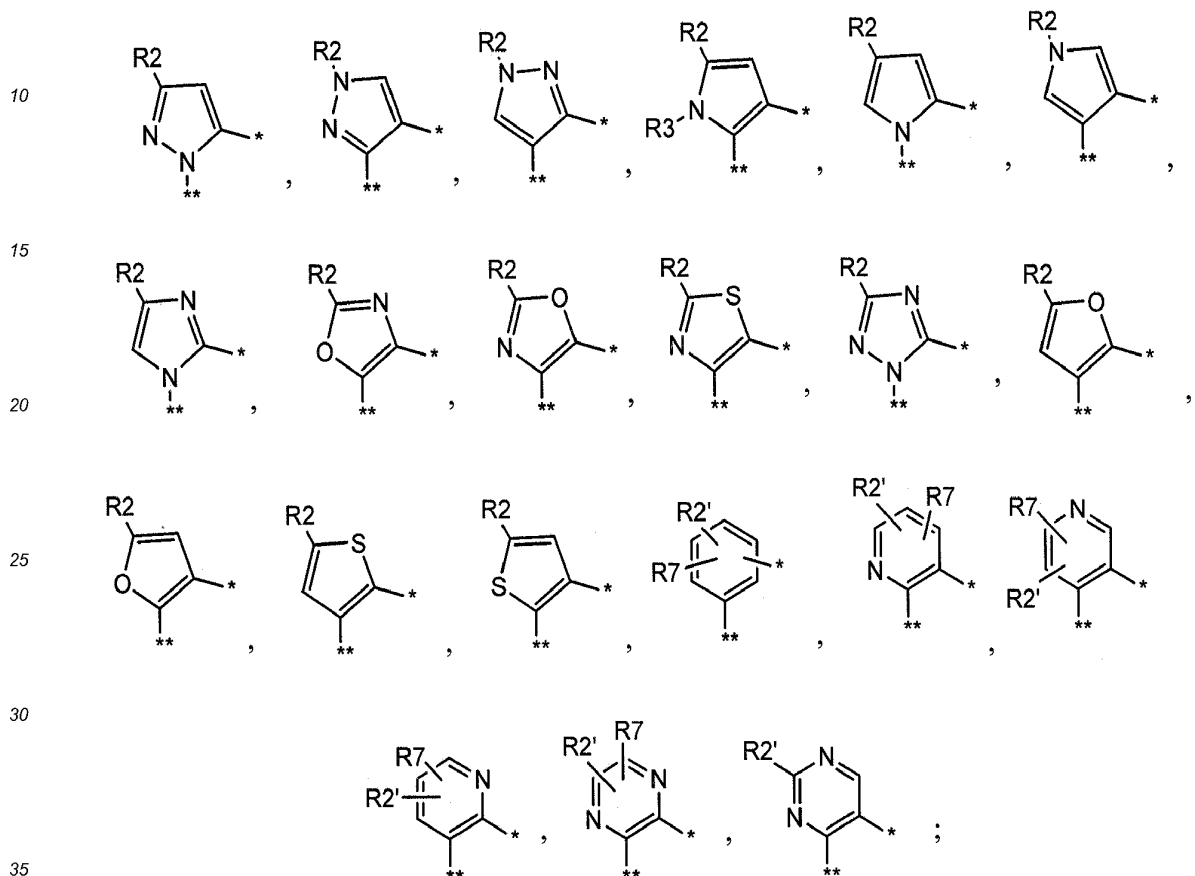
## 1.1.3f

**[0034]** Compounds as defined in 1.1.3c wherein the A2 group is defined in 1.1.2c.

## 1.1.4 Preferred A1 Moieties

## 1.1.4a

5 [0035] A1 moieties are selected from the group consisting of

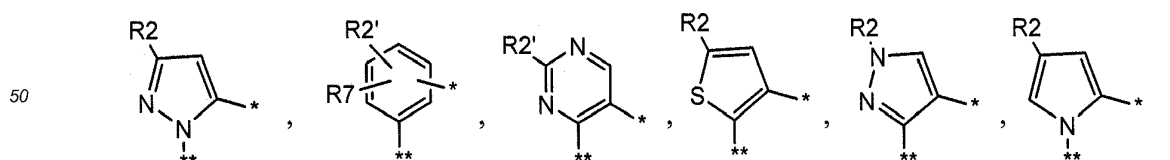


wherein the symbol (\*) denotes the attachment to the W moiety of formula I and the symbol (\*\*) denotes the attachment to the A2 moiety of formula I;

40 each R7 is selected from the group consisting of halogen, C1-C3fluoroalkyl wherein the alkyl moiety is partially or fully fluorinated, C1-C3alkyl, cyclopropyl, cyano, or C1-C3alkoxy.

## 1.1.4b

45 [0036] Preferred A1 moieties are selected from the group consisting of



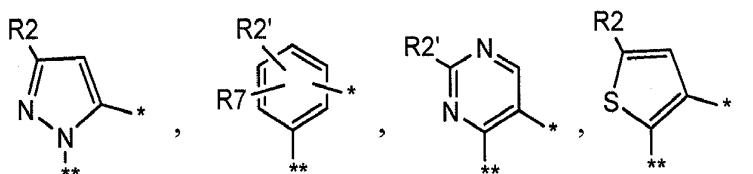
55 wherein the symbol (\*) denotes the attachment to the W moiety of formula I and the symbol (\*\*) denotes the attachment to the A2 moiety of formula I.

## 1.1.4c

**[0037]** Still more preferred A1 moieties are selected from the group consisting of

5

10



wherein the symbol (\*) denotes the attachment to the W moiety of formula I and the symbol (\*\*) denotes the attachment to the A2 moiety of formula I.

15

## 1.1.5 Preferred W and Y Moieties

## 1.1.5a

20

**[0038]** (1) W and Y are each NH, and X=O; (2) W=NH, Y=CHR<sup>4</sup> and X=O; or (3) W=CHR<sup>4</sup>, Y=NH, and X=O.

## 1.1.5b

**[0039]** W and Y are each NH and X=O.

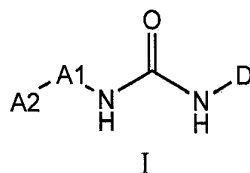
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## 1.1. 6 Further Preferred Compounds

## 1.1.6a

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**[0040]** Further preferred compounds are of the formula

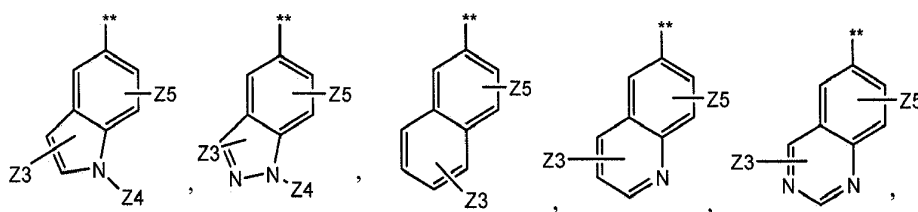


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wherein A2 is selected from the group consisting of

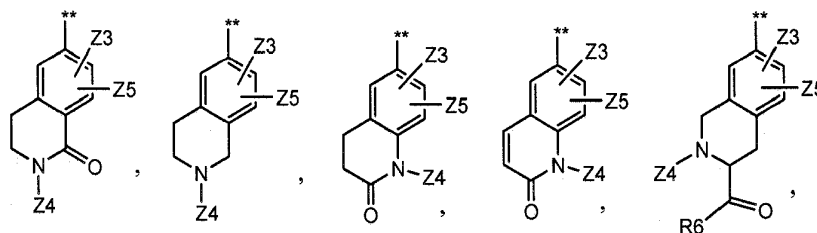
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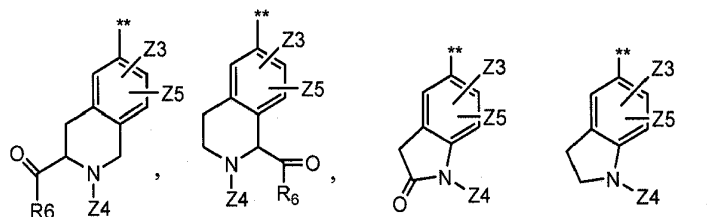


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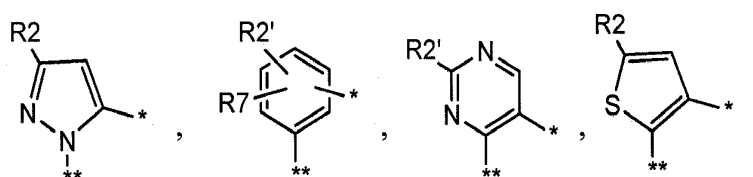
wherein each Z3 and Z5 is independently attached to either aryl or heteroaryl ring of the A2 bicyclic ring;

wherein the symbol (\*\*) denotes the attachment to the A1 moiety of formula I;

A1 is selected from the group consisting of

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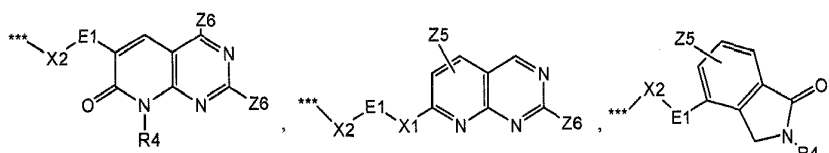
wherein the symbol (\*) denotes the attachment to the W moiety of formula I and the symbol (\*\*) denotes the attachment to the A2 moiety of formula I;

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X is O, S, or NR3;

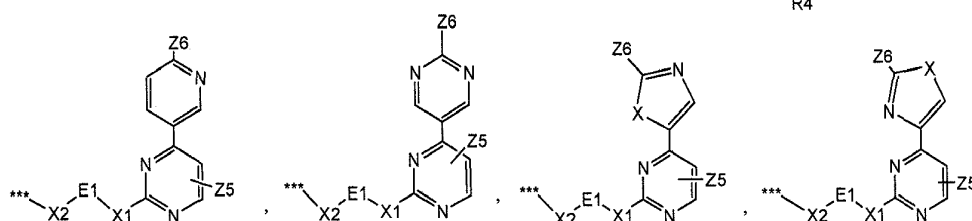
D is selected from the group consisting of 2,3-dichlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 3-cyanophenyl, 2,3-difluorophenyl, 2,4-difluorophenyl, 3,4-difluorophenyl, 2,5-difluorophenyl, 3,5-difluorophenyl, 2,3,5-trifluorophenyl, 2,4,5-trifluorophenyl, 2,3,4-trifluorophenyl, 3,4,5-trifluorophenyl, 4-cyanophenyl, 3-fluoro-5-cyanophenyl, 3-(R8SO<sub>2</sub>)-phenyl, 3-(hydroxyC1-C3alkyl)-phenyl, 3-(R3O-N=C(R6))-phenyl, 3-phenoxyphenyl, 4-phenoxyphenyl,

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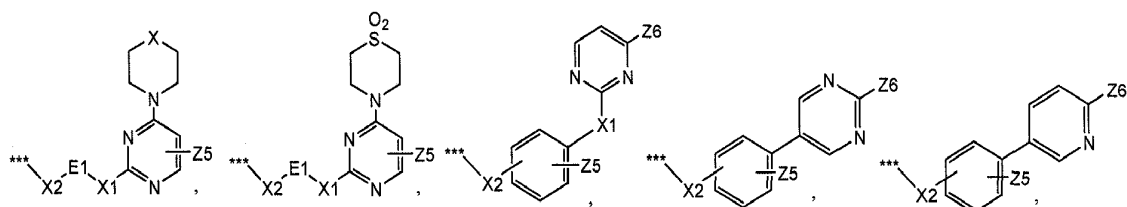


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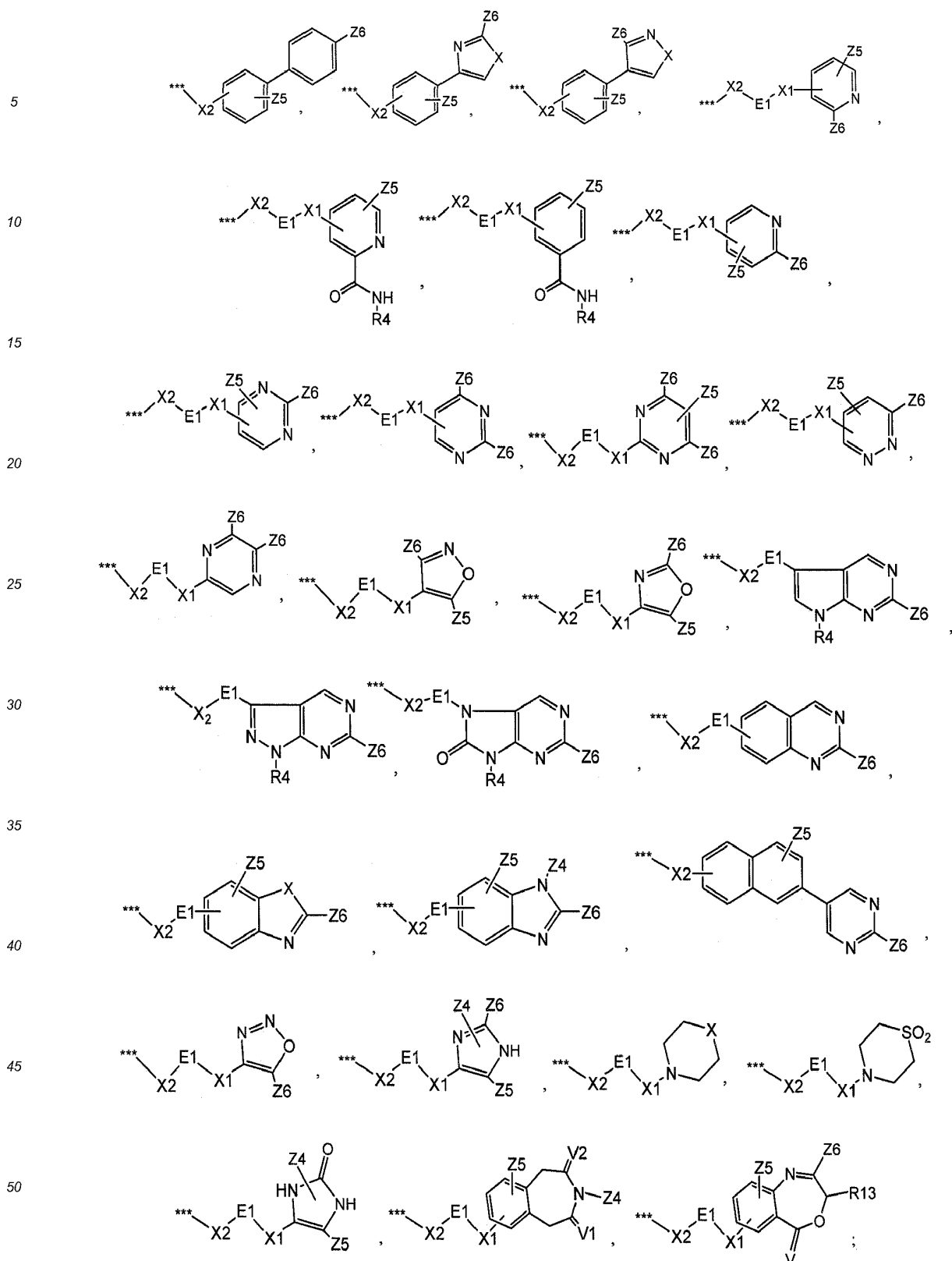
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55 wherein E1 is selected from the group consisting cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyrrolidinyl, piperidinyl, phenyl, thienyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, pyrrolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, furyl, imidazolyl, pyridyl, pyrimidinyl and naphthyl;

X1 is selected from the group consisting of O, S, NR3, -C(=O)-, -O-(CH<sub>2</sub>)<sub>n</sub>-, -S-(CH<sub>2</sub>)<sub>n</sub>-, -NR3-(CH<sub>2</sub>)<sub>n</sub>-, -O-(CH<sub>2</sub>)<sub>q</sub>-O-, -O-(CH<sub>2</sub>)<sub>q</sub>-NR3-, -N(R3)-(CH<sub>2</sub>)<sub>q</sub>-N(R3)-, -(CH<sub>2</sub>)<sub>n</sub>-N(R4)-C(=O)-, -(CH<sub>2</sub>)<sub>n</sub>-N(R4)-C(=O)(CH<sub>2</sub>)<sub>n</sub>-, -(CH<sub>2</sub>)<sub>n</sub>-CO-N(R4)-, -(CH<sub>2</sub>)<sub>p</sub>-, C2-C5alkenyl, C2-C5alkynyl, C3-C6cycloalkyl, and a direct bond wherein the E1 ring and the E2 ring are directly linked by a covalent bond;

and wherein the carbon atoms of -(CH<sub>2</sub>)<sub>n</sub>-, -(CH<sub>2</sub>)<sub>q</sub>-, (CH<sub>2</sub>)<sub>p</sub>-, C2-C5alkenyl, and C2-C5alkynyl moieties of X1 may be further substituted by one or more C1-C6alkyl;

X2 is selected from the group consisting of C1-C6 alkyl, C3-C6 branched alkyl, or a direct bond wherein E1 is directly linked to the Y group of formula I;

and wherein the carbon atoms of -(CH<sub>2</sub>)<sub>n</sub>-, -(CH<sub>2</sub>)<sub>q</sub>-, -(CH<sub>2</sub>)<sub>p</sub>-, C2-C5alkenyl, and C2-C5alkynyl of X2 can be further substituted by one or more C1-C6alkyl;

each R2 is selected from the group consisting of alkyl, branched alkyl, fluoroalkyl, wherein the alkyl group is partially or fully fluorinated, and R19 substituted C3-C8carbocyclyl wherein R19 is H, and Cl-C6alkyl;

each R2' is selected from the group consisting of halogen and R2;

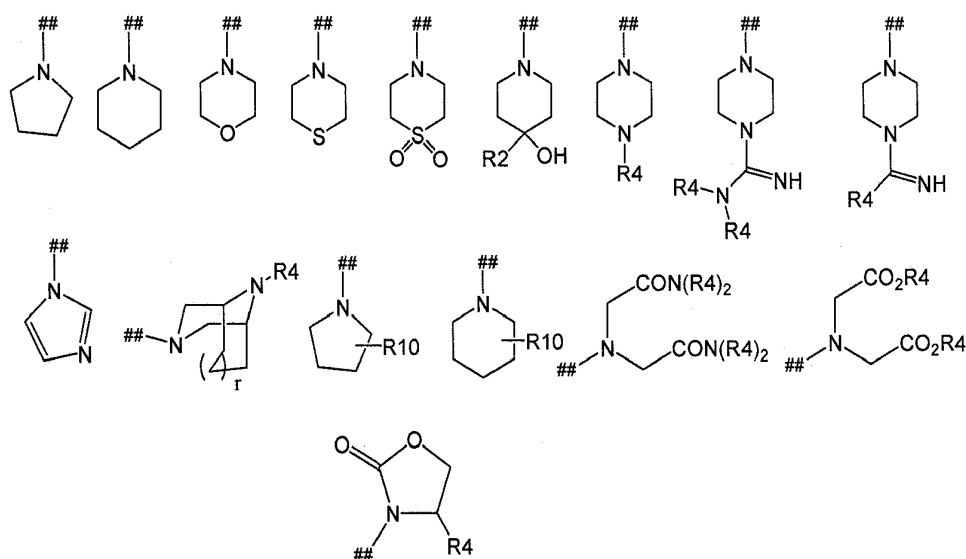
each R3 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, C3-C7carbocyclyl, or phenyl;

wherein two R3 moieties independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C7alkyl are attached to the same nitrogen heteroatom, the two R3 moieties may cyclize to form a C3-C7 heterocycl ring;

each R4 is selected from the group consisting of H, C1-C6alkyl, hydroxyC1-C6 alkyl, dihydroxyC1-C6alkyl, C1-C6alkoxyC1-C6alkyl, branched C3-C7alkyl, branched hydroxyC1-C6 alkyl, branched C1-C6alkoxyC1-C6alkyl, branched dihydroxyC1-C6alkyl, carbocyclyl, hydroxyl substituted carbocyclyl, alkoxy substituted carbocyclyl, dihydroxy substituted carbocyclyl, phenyl, heteroaryl, heterocyclyl, phenylC1-C6alkyl, heteroarylC1-C6alkyl, and heterocyclylC1-C6alkyl;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom may cyclize to form a C3-C7 heterocycl ring;

each R5 is independently and individually selected from the group consisting of



and wherein the symbol (##) is the point of attachment to respective R8, R10, R13, Z2, Z3, Z4, Z5, or A2 ring moieties containing a R5 moiety;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R5 may cyclize to form a C3-C7 heterocyclyl ring;

wherein each R6 is independently and individually selected from the group consisting of C1-C6alkyl, branched C3-C7alkyl, carbocyclyl, phenyl, heteroaryl, and heterocyclyl;

each R7 is selected from the group consisting of H, halogen, C1-C3fluoroalkyl wherein the alkyl moiety is partially or fully fluorinated, C1-C3alkyl, cyclopropyl, cyano, or C1-C3alkoxy;

each R8 is independently and individually selected from the group consisting of C1-C6alkyl, branched C3-C7alkyl, fluoroalkyl wherein the alkyl moiety is partially or fully fluorinated, carbocyclyl, phenyl, C1-C6phenylalkyl, heteroaryl or heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl OH, C1-C6alkoxy, N(R3)<sub>2</sub>, N(R4)<sub>2</sub>, or R5;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of R8 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R8 may cyclize to form a C3-C7 heterocyclyl ring;

each R10 is independently and individually selected from the group consisting of CO<sub>2</sub>H, CO<sub>2</sub>C1-C6alkyl, CO-N(R4)<sub>2</sub>, OH, C1-C6alkoxy, -N(R4)<sub>2</sub>;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R10 may cyclize to form a C3-C7 heterocyclyl ring;

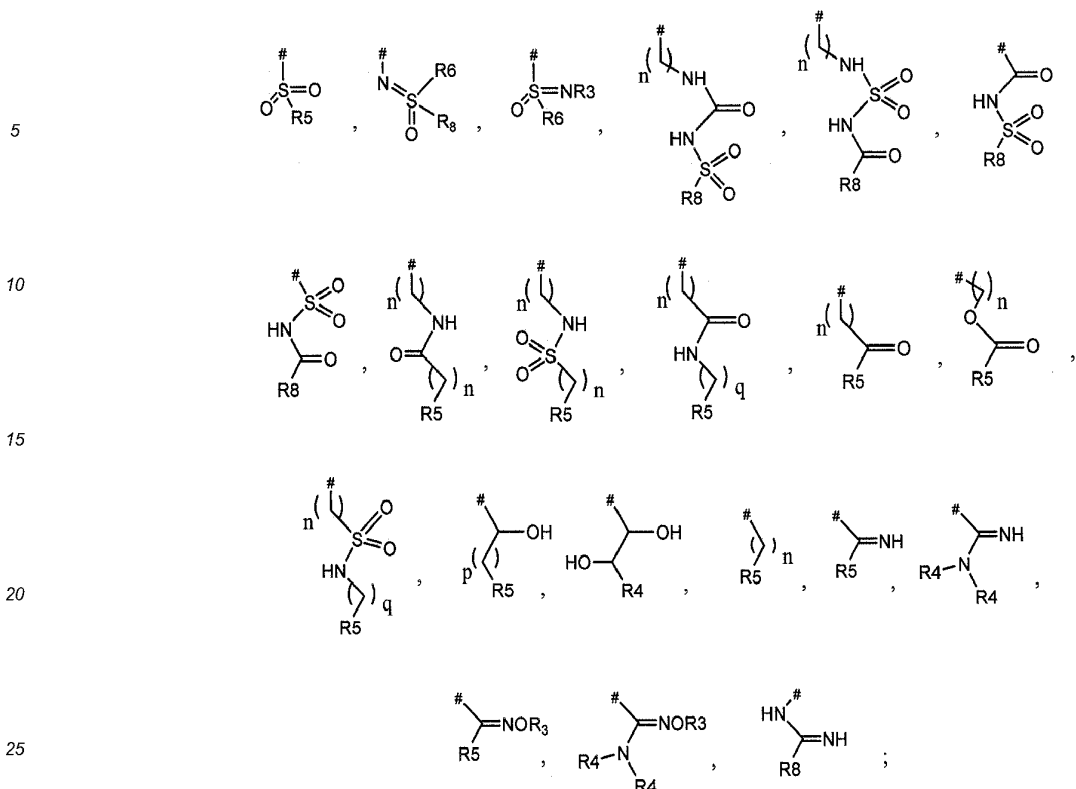
each R13 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, carbocyclyl, hydroxyC2-C7alkyl, C1-C6alkoxyC2-C7alkyl, (R4)<sub>2</sub>N-CO, (R4)<sub>2</sub>N-CO-C1-C6alkyl, carboxyC1-C6alkyl, C1-C6alkoxycarbonyl, C1-C6alkoxycarbonylC1-C6alkyl, (R4)<sub>2</sub>N-C2-C6alkyl, (R4)<sub>2</sub>N-C2-C6alkylN(R4)-(CH<sub>2</sub>)<sub>q</sub>, R5-C2-C6alkylN(R4)-(CH<sub>2</sub>)<sub>q</sub>, (R4)<sub>2</sub>N-C2-C6alkylO-(CH<sub>2</sub>)<sub>q</sub>, R5-C2-C6alkyl-O-(CH<sub>2</sub>)<sub>q</sub>, -(CH<sub>2</sub>)<sub>q</sub>N(R4)C(O)R8, aryl, arylC1-C6alkyl, heteroaryl, heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, aryloxyC2-C6alkyl, heteroaryloxyC2-C6alkyl, heterocycliloxyC2-C6alkyl, arylaminoC2-C6alkyl, heteroarylaminoC2-C6alkyl, and heterocyclylaminoC2-C6alkyl;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R13 may cyclize to form a C3-C7 heterocyclyl ring;

each R14 is independently and respectively selected from the group consisting of H and C1-C6alkyl;

V, V1, and V2 are each independently and respectively selected from the group consisting of O and H<sub>2</sub>;

each Z3 is independently and individually selected from the group consisting of H, C1-C6alkyl, hydroxyl, hydroxyC1-C6alkyl, cyano, C1-C6alkoxy, C1-C6alkoxyC1-C6alkyl, halogen, CF<sub>3</sub>, (R3)<sub>2</sub>N-, (R4)<sub>2</sub>N-, (R4)<sub>2</sub>NC1-C6alkyl, (R4)<sub>2</sub>NC2-C6alkylN(R4)-(CH<sub>2</sub>)<sub>n</sub>, (R4)<sub>2</sub>NC2-C6alkylO-(CH<sub>2</sub>)<sub>n</sub>, R8CO-, (R4)<sub>2</sub>N-CO-C1-C6alkyl, carboxyl, carboxyC1-C6alkyl, C1-C6alkoxycarbonyl, C1-C6alkoxycarbonylC1-C6alkyl, (R3)<sub>2</sub>NSO<sub>2</sub>, -SO<sub>2</sub>R3, SOR3, (R4)<sub>2</sub>NSO<sub>2</sub>, -SO<sub>2</sub>R4, -SOR4, -(CH<sub>2</sub>)<sub>n</sub>N(R4)C(O)R8, -C=(NOH)R6, -C=(NOR3)R6, heteroaryl, heterocyclyl, heteroarylC1-C6alkyl, heterocyclylC1-C6alkyl heteroaryloxy, heterocycliloxy, heteroaryloxyC1-C6alkyl, heterocycliloxyC1-C6alkyl, arylamino, heteroarylamino, heterocyclylamino, arylaminoC1-C6alkyl, heteroarylaminoC1-C6alkyl, heterocyclylaminoC1-C6alkyl, or moieties of the formulae



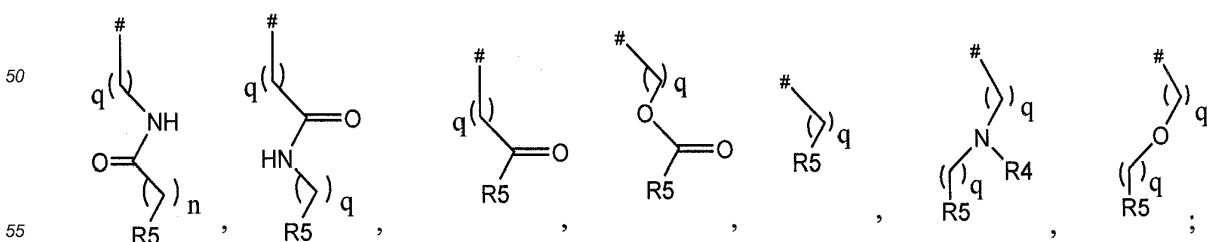
wherein the symbol (#) indicates the point of attachment of the Z3 moiety to the A2 ring of formula I;

in the event that Z3 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z3 may cyclize to form a C3-C7 heterocycl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z3 may cyclize to form a C3-C7 heterocycl ring;

each Z4 is a substituent attached to a ring nitrogen and is independently and individually selected from the group consisting of H, C1-C6alkyl, hydroxyC2-C6alkyl, C1-C6alkoxyC2-C6alkyl, (R4)<sub>2</sub>N-C2-C6alkyl, (R4)<sub>2</sub>N-C2-C6alkylN(R4)-C2-C6alkyl, (R4)<sub>2</sub>N-C2-C6alkyl-O-C2-C6alkyl, (R4)<sub>2</sub>N-CO-C2-C6alkyl, carboxyC2-C6alkyl, C1-C6alkoxycarbonylC2-C6alkyl, -C2-C6alkylN(R4)C(O)R8, R8-C(=NR3)-, -SO<sub>2</sub>R8, -COR8, heteroaryl, heteroarylC1-C6alkyl, heterocycl, heterocyclC1-C6alkyl, heteroarylOxyC2-C6alkyl, heterocyclOxyC2-C6alkyl, arylaminoC2-C6alkyl, heteroarylaminoC2-C6alkyl, heterocyclaminoC2-C6alkyl, and moieties of the formulae



wherein the symbol (#) indicates the point of attachment of the Z4 moiety to the A2 ring for formula I;



in the event that Z4 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z4 may cyclize to form a C3-C7 heterocycl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z4 may cyclize to form a C3-C7 heterocycl ring;

Z5 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, halogen, fluoroalkyl, cyano, hydroxyl, alkoxy, oxo, aminocarbonyl, carbonylamino, aminosulfonyl, sulfonylamino, -N(R3)<sub>2</sub>, -O-(CH<sub>2</sub>)<sub>q</sub>-N(R4)<sub>2</sub>, -N(R3)-(CH<sub>2</sub>)<sub>q</sub>-N(R4)<sub>2</sub>, -R5, -O-(CH<sub>2</sub>)<sub>q</sub>-O-Alkyl, -O-(CH<sub>2</sub>)<sub>q</sub>-N(R4)<sub>2</sub>, -N(R3)-(CH<sub>2</sub>)<sub>q</sub>-O-Alkyl, -N(R3)-(CH<sub>2</sub>)<sub>q</sub>-N(R4)<sub>2</sub>, -O-(CH<sub>2</sub>)<sub>q</sub>-R5, and -N(R3)-(CH<sub>2</sub>)<sub>q</sub>-R5;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z5 may cyclize to form a C3-C7 heterocycl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z5 may cyclize to form a C3-C7 heterocycl ring;

Each Z6 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, hydroxyl, C1-C6alkoxy, (R3)<sub>2</sub>N-, -N(R3)COR8, (R4)<sub>2</sub>N-, -R5, -N(R4)COR8, -N(R3)SO<sub>2</sub>R6-, -CON(R3)<sub>2</sub>, -CON(R4)<sub>2</sub>, -COR5, -SO<sub>2</sub>NHR4, heteroaryl, heterocycl, heteroaryloxy, heterocyclloxy, arylamino, heteroarylamino, and heterocycllamino;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z6 may cyclize to form a C3-C7 heterocycl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z6 may cyclize to form a C3-C7 heterocycl ring;

and n is 0-4; p is 1-4; q is 2-6; r is 0 or 1; v is 1 or 2;

and tautomers, diastereomers, geometric isomers, enantiomers, hydrates, prodrugs and salts of any of the foregoing.

#### 1.1.6b

**[0041]** The following specific compounds are most preferred:

1-(3-t-butyl-1-(1-(methanesulfonylureidoamidomethyl)naphthalen-3-yl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(1-(4-(2-amino-2-oxoethyl)naphthalen-2-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(4-(hydroxymethyl)naphthalen-2-yl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(1-(4-(2-aminoethyl)naphthalen-2-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, (3S)-6-(3-t-butyl-5-(3-(2,3-dichlorophenyl)ureido)-1H-pyrazol-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, 6-(3-t-butyl-5-(3-(2,3-dichlorophenyl)ureido)-1H-pyrazol-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, 1-(1-(4-(2-amino-2-oxoethyl)naphthalen-2-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(2,3,4-trifluorophenyl)urea, 1-(3-t-butyl-1-(4-(hydroxymethyl)naphthalen-2-yl)-1H-pyrazol-5-yl)-3-(2,4,5-trifluorophenyl)urea, 1-(1-(4-(2-amino-2-oxoethyl)naphthalen-2-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(2,4,5-trifluorophenyl)urea, 1-(3-t-butyl-1-(4-(2-(2,3-dihydroxypropylamino)-2-oxoethyl)naphthalen-2-yl)-1H-pyrazol-5-yl)-3-(2,4,5-trifluorophenyl)urea, 1-(3-t-butyl-1-(4-((1-amino-1-oxo-methylamino)methyl)naphthalen-2-yl)-1H-pyrazol-5-yl)-3-(2,4,5-trifluorophenyl)urea, 1-(3-t-butyl-1-(1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(2,4,5-trifluorophenyl)urea, 1-(1-(4-(2-amino-2-oxoethyl)naphthalen-2-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(2,3,5-

trifluorophenyl)urea, 1-(3-t-butyl-1-(4-(2-(2,3-dihydroxypropylamino)-2-oxoethyl)naphthalen-2-yl)-1H-pyrazol-5-yl)-3-(2,3,5-trifluorophenyl)urea, 1-(3-t-butyl-1-(4-(hydroxymethyl)naphthalen-2-yl)-1H-pyrazol-5-yl)-3-(2,3,5-trifluorophenyl)urea, 1-(1-(4-(aminomethyl)naphthalen-2-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(2,3,5-trifluorophenyl)urea, 1-(3-t-butyl-1-(4-((1-amino-1-oxo-methylamino)methyl)naphthalen-2-yl)-1H-pyrazol-5-yl)-3-(2,3,5-trifluorophenyl)urea, 1-(3-t-butyl-1-(4-(hydroxymethyl)naphthalen-2-yl)-1H-pyrazol-5-yl)-3-(3,4,5-trifluorophenyl)urea, 1-(3-t-butyl-1-(4-(2-(2,3-dihydroxypropylamino)-2-oxoethyl)naphthalen-2-yl)-1H-pyrazol-5-yl)-3-(3,4,5-trifluorophenyl)urea, 1-(3-t-butyl-1-(4-(hydroxymethyl)naphthalen-2-yl)-1H-pyrazol-5-yl)-3-(3,5-difluorophenyl)urea, 1-(1-(4-(2-amino-2-oxoethyl)naphthalen-2-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(3,5-difluorophenyl)urea, 1-(1-(4-(2-amino-2-oxoethyl)naphthalen-2-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(2,5-difluorophenyl)urea, 1-(3-t-butyl-1-(4-(2-(1,3-dihydroxypropan-2-ylamino)-2-oxoethyl)naphthalen-2-yl)-1H-pyrazol-5-yl)-3-(2,5-difluorophenyl)urea, 1-(1-(4-(aminomethyl)naphthalen-2-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(3-cyanophenyl)urea, 1-(3-t-butyl-1-(1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-cyanophenyl)urea, 1-(3-t-butyl-1-(1H-indol-5-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, 1-(3-t-butyl-1-(indolin-5-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, 1-(1-(4-(2-amino-2-oxoethyl)naphthalen-2-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, 1-(3-t-butyl-1-(4-(2-(2,3-dihydroxypropylamino)-2-oxoethyl)naphthalen-2-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, 1-(3-t-butyl-1-(4-(hydroxymethyl)naphthalen-2-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, 1-(1-(4-(aminomethyl)naphthalen-2-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, 1-(3-t-butyl-1-(1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, 1-(3-t-butyl-1-(1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(5-chloropyridin-3-yloxy)phenyl)urea, 6-(3-t-butyl-5-(3-(3-(pyridin-3-yloxy)phenyl)ureido)-1H-pyrazol-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, 1-(3-t-butyl-1-(3-carbamoyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, 1-(3-t-butyl-1-(3-(methylcarbamoyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, 1-(3-t-butyl-1-(1-(methylcarbamoyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, 1-(3-t-butyl-1-(2-oxo-1,2-dihydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, 1-(3-t-butyl-1-(quinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, 1-(3-cyclopentyl-1-(2-oxo-1,2-dihydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, 1-(3-t-butyl-1-(1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea, 1-(3-t-butyl-1-(2-oxo-1,2-dihydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea, 1-(3-t-butyl-1-(2-(piperazin-1-yl)quinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea, 1-(1-(2-(2-aminoethylamino)quinolin-6-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea, 1-(3-cyclopentyl-1-(2-oxo-1,2-dihydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea, 1-(3-t-butyl-1-(2-(dimethylamino)quinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea, 1-(3-t-butyl-1-(2-((R)-3-(dimethylamino)pyrrolidin-1-yl)quinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea, 1-(1-(2-aminoquinolin-6-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea, 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1-(3-t-butyl-1-(3-carbamoyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-6-yl)phenyl)urea, 1-(3-t-butyl-1-(1-(methylsulfonyl)indolin-5-yl)-1H-pyrazol-5-yl)-3-(3-(8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-6-yl)phenyl)urea, 1-(3-t-butyl-1-(1H-indol-5-yl)-1H-pyrazol-5-yl)-3-(3-(8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-6-yl)phenyl)urea, 1-(3-t-butyl-1-(2-(piperazin-1-yl)quinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-6-yl)phenyl)urea, 1-(3-t-butyl-1-(1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenyl)urea, 1-(3-t-butyl-1-(2-(piperazin-1-yl)quinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenyl)urea

### 1.1.7 Methods

#### 1.1.7a Methods of Protein Modulation

**[0042]** The invention includes methods of modulating kinase activity of a variety of kinases, e.g. C-Abl kinase, BCR-Abl kinase. The kinases may be wildtype kinases, oncogenic forms thereof, aberrant fusion proteins thereof or polymorphs

of any of the foregoing. The method comprises the step of contacting the kinase species with compounds of the invention and especially those set forth in sections 1.1 and 1.1.6a. The kinase species may be activated or unactivated, and the species may be modulated by phosphorylations, sulfation, fatty acid acylations glycosylations, nitrosylation, cystinylation (i.e. proximal cysteine residues in the kinase react with each other to form a disulfide bond) or oxidation. The kinase activity may be selected from the group consisting of catalysis of phospho transfer reactions, kinase cellular localization, and recruitment of other proteins into signaling complexes through modulation of kinase conformation.

**[0043]** The methods of the invention may also involve the step of inducing, synergizing, or promoting the binding of a second modulator compound of said kinase, especially C-Abl kinase or BCR-Abl kinase, to form a ternary adduct, such co-incident binding resulting in enhanced biological modulation of the kinase when compared to the biological modulation of the protein affected by either of said compounds alone. The second compound may interact at a substrate, co-factor or regulatory site on the kinase, with the second site being distinct from the site of interaction of the first compound. For example, the second site may be an ATP co-factor site. The second compounds may be taken from the group consisting of N-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide (Gleevec); N-(2-chloro-6-methylphenyl)-2-(6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-ylamino)thiazole-5-carboxamide (BMS-354825); 6-(2,6-dichlorophenyl)-2-(3-(hydroxymethyl)phenylamino)-8-methylpyrido[2,3-d]pyrimidin-7(8H)-one (PD 166326); 6-(2,6-dichlorophenyl)-8-methyl-2-(3-(methylthio)phenylamino)pyrido[2,3-d]pyrimidin-7(8H)-one (PD 173955); 6-(2,6-dichlorophenyl)-2-(4-fluoro-3-methylphenylamino)-8-methylpyrido[2,3-d]pyrimidin-7(8H)-one (PD 180970); 6-(2,6-dichlorophenyl)-2-(4-ethoxyphenylamino)-8-methylpyrido[2,3-d]pyrimidin-7(8H)-one (PD 173958); 6-(2,6-dichlorophenyl)-2-(4-fluorophenylamino)-8-methylpyrido[2,3-d]pyrimidin-7(8H)-one (PD 173956); 6-(2,6-dichlorophenyl)-2-(4-(2-(diethylamino)ethoxy)phenylamino)-8-methylpyrido[2,3-d]pyrimidin-7(8H)-one (PD 166285); 2-(4-(2-aminoethoxy)phenylamino)-6-(2,6-dichlorophenyl)-8-methylpyrido[2,3-d]pyrimidin-7(8H)-one; N-(3-(6-(2,6-dichlorophenyl)-8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-ylamino)phenyl)acetamide (SKI DV-MO16); 2-(4-aminophenylamino)-6-(2,6-dichlorophenyl)-8-methylpyrido[2,3-d]pyrimidin-7(8H)-one (SKI DV 1-10); 6-(2,6-dichlorophenyl)-2-(3-hydroxyphenylamino)-8-methylpyrido[2,3-d]pyrimidin-7(8H)-one (SKI DV2-89); 2-(3-aminophenylamino)-6-(2,6-dichlorophenyl)-8-methylpyrido[2,3-d]pyrimidin-7(8H)-one (SKI DV 2-43); N-(4-(6-(2,6-dichlorophenyl)-8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-ylamino)phenyl)acetamide (SKI DV-M017); 6-(2,6-dichlorophenyl)-2-(4-hydroxyphenylamino)-8-methylpyrido[2,3-d]pyrimidin-7(8H)-one (SKI DV-M017); 6-(2,6-dichlorophenyl)-2-(3-ethylphenylamino)-8-methylpyrido[2,3-d]pyrimidin-7(8H)-one (SKI DV 2 87).

#### 1.1.7b Treatment Methods

**[0044]** The methods of the invention also include treating individuals suffering from a condition selected from the group consisting of cancer and hyperproliferative diseases. These methods comprise administering to such individuals compounds of the invention, and especially those of section 1.1 and 1.1.6a. Exemplary conditions include chronic myelogenous leukemia, acute lymphocytic leukemia, gastrointestinal stromal tumors, and hypereosinophilic syndrome. The administration method is not critical, and may be from the group consisting of oral, parenteral, inhalation, and subcutaneous.

#### 1.1.8 Pharmaceutical Preparations

**[0045]** The compounds of the invention, especially those of 1.1 and 1.1.6a may form a part of a pharmaceutical composition by combining one or more such compounds with a pharmaceutically acceptable carrier. Additionally, the compositions may include an additive selected from the group consisting of adjuvants, excipients, diluents, and stabilizers.

#### 1.1.9 Kinase/Compound Adducts

**[0046]** The invention also provides adducts in the form of compounds of the invention bound with a species of kinase such as a wild-type kinase, oncogenic forms thereof, aberrant fusion proteins thereof and polymorphs of any of the foregoing. The compounds are advantageously selected from the groups defined in sections 1.1 and 1.1.6a.

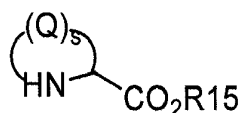
#### 5. Fifth aspect of the invention - Compound Synthesis

**[0047]** Recently, Cu(II)-catalyzed cross coupling reactions have been described for Cu(II) catalyzed cross coupling reactions of aryl or heteroaryl metal reactants with NH-containing heterocycles. These methods have been described by P.Y.S. Lam et al, Tetrahedron Letters (1998) 39: 2941, P.Y.S. Lam et al, Journal of the American Chemical Society (2000) 122: 7600; D. M. T. Chan et al, Tetrahedron Letters (2003) 44: 3863; D. M. T. Chan et al, Tetrahedron Letters (1998) 39: 2933; D. A. Evans et al, Tetrahedron Letters (1998) 39: 2937.

## 5.1 Novel Syntheses

[0048] The present invention further provides novel methods for synthesizing the useful compounds. Broadly speaking, the synthesis method comprises the steps:

providing a ring compound of the formula



wherein s is 3 or 4,

the ring compound has two double bonds and one reactable ring NH moiety,

Q is independently and individually selected from the group consisting of N and CR<sub>2</sub>, and

R<sub>15</sub> is selected from the group consisting of lower alkyl, branched lower alkyl, benzyl, substituted benzyl, or other suitable carboxylic acid protecting group;

each R<sub>2</sub> is selected from the group consisting of C<sub>1</sub>-C<sub>6</sub>alkyl, branched C<sub>3</sub>-C<sub>7</sub>alkyl, carbocyclyl, C<sub>1</sub>-C<sub>6</sub>fluoroalkyl wherein the alkyl group is partially or fully fluorinated;

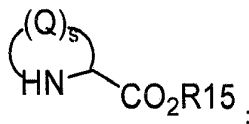
reacting said ring compound with a compound of the formula



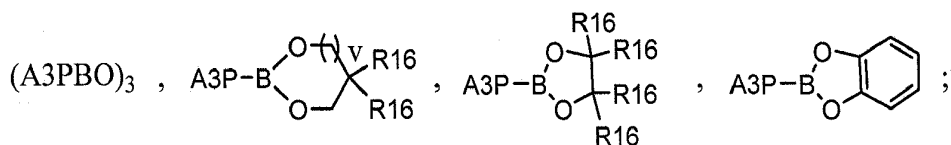
[0049] In the presence of a transition metal catalyst;

wherein A3P is a protected form of A<sub>3</sub>;

wherein A<sub>3</sub> comprises a member of the group consisting of mono- and poly-aryl, mono- and poly-heteroaryl, mono- and poly-heterocyclyl moieties, P is a protective group wherein A<sub>3</sub> is chemically protected so as not to interfere with the reaction of A3P-M with

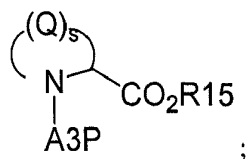


wherein A3P-M is taken from the group consisting of A3P-B(OH)<sub>2</sub>, -A3P-B(OR<sub>16</sub>)<sub>2</sub>, -A3P-B(R<sub>17</sub>)<sub>3</sub>M<sub>2</sub>, -A3P-Si(R<sub>18</sub>)<sub>3</sub>, or A3P-Sn(R<sub>16</sub>)<sub>3</sub>, wherein R<sub>16</sub> is taken from lower alkyl or branched lower alkyl, R<sub>17</sub> is halogen, R<sub>18</sub> is lower alkoxy, and M<sub>2</sub> is Li, K, or Na, and from the formulae,



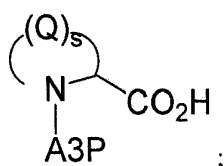
wherein v is 1 or 2;

said reaction generating an intermediate compound of the formula



converting said intermediate compound to the carboxylic acid form thereof

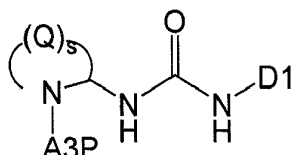
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subjecting said carboxylic acid to a Curtius rearrangement in the presence of a compound of formula D1-NH<sub>2</sub>, to yield a compound of the formula

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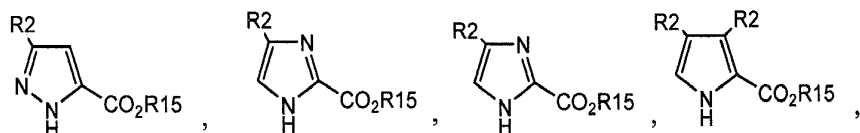


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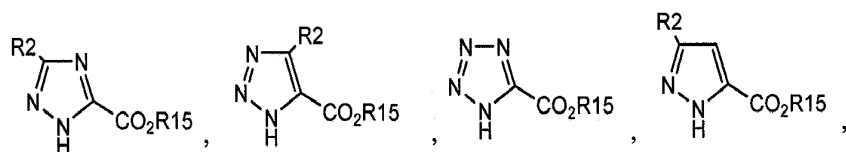
where D1 is selected from the group consisting of mono- and poly-aryl, mono- and poly-heteroaryl, mono- and poly-heterocycl.

**[0050]** Preferably, first step of the method involves using a ring compound taken from the group consisting of

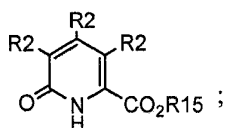
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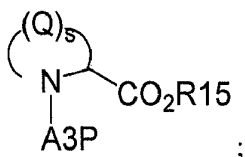
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A3P-M is taken from A3P-B(OH)<sub>2</sub>, A3P-B(OR16)<sub>2</sub>, or boroxines (A3PBO)<sub>3</sub>; said reaction generating an intermediate compound of the formula

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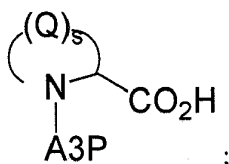


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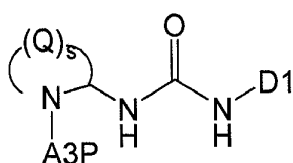
and being catalyzed by a copper(II) catalyst, in an inert solvent taken from the group consisting of dichloromethane, dichloroethane, and N-methylpyrrolidinone, in the presence of a base taken from the group consisting of triethylamine and pyridine, at temperatures ranging from ambient to about 130°C, wherein the reaction is exposed to an atmosphere containing oxygen;

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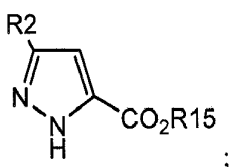
**[0051]** Converting said intermediate compound to the carboxylic acid form thereof



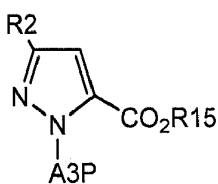
and subjecting said acid form compound to a Curtius rearrangement in the presence of a compound of formula D1-NH<sub>2</sub>, such rearrangement mediated by the use of diphenylphosphoryl azide in an inert solvent taken from the group consisting of toluene, tetrahydrofuran, and dimethoxyethane, and in the presence of a base taken from the group consisting of triethylamine, pyridine, and di-iso-propylethylamine, at temperatures ranging from 80°C to 110°C to yield a desired compound of the formula



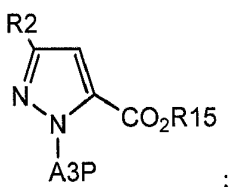
Still more preferably, the starting ring compound is selected from the group consisting of



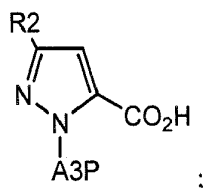
A3P-M is taken from A3P-B(OH)<sub>2</sub>, A3P-B(OR15)<sub>2</sub>, or boroxines (A3PBO)<sub>3</sub>; said reaction generating an intermediate compound of the formula



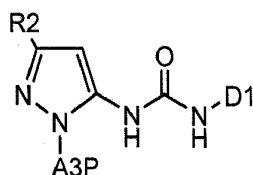
said catalyst comprising copper(II) acetate, said reaction being carried in an inert solvent, selected from the group consisting of dichloromethane, dichloroethane, and N-methylpyrrolidinone, in the presence of a base from the group consisting of triethylamine and pyridine, and in the presence of 4 angstrom sieves at ambient temperature, wherein the reaction is exposed to air, to generate an intermediate compound of the formula



converting said intermediate compound to the carboxylic acid form thereof



subjecting said carboxylic acid form intermediate to a Curtius rearrangement in the presence of a compound of formula D1-NH<sub>2</sub>, such rearrangement mediated by the use of diphenylphosphoryl azide in an inert solvent taken from the group consisting of toluene, and in the presence of triethylamine at temperatures ranging from 80°C to 110°C to yield a desired compound of the formula.

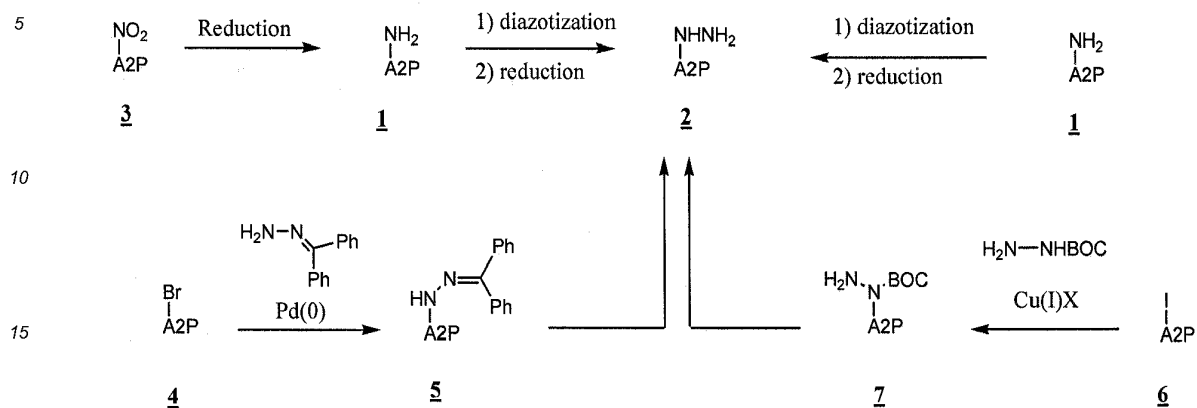


## 5.2 Other syntheses

**[0052]** The preparation of intermediates containing A1 rings and their subsequent conversion into compounds of Formula I is illustrated in the following schemes. Throughout this specification, A2P refers to a protected form of A2, as defined above, wherein the Z1, Z2, Z3, or Z4 moieties or heteroatoms attached to A2 are suitably protected to allow their use in multi-step chemistry.

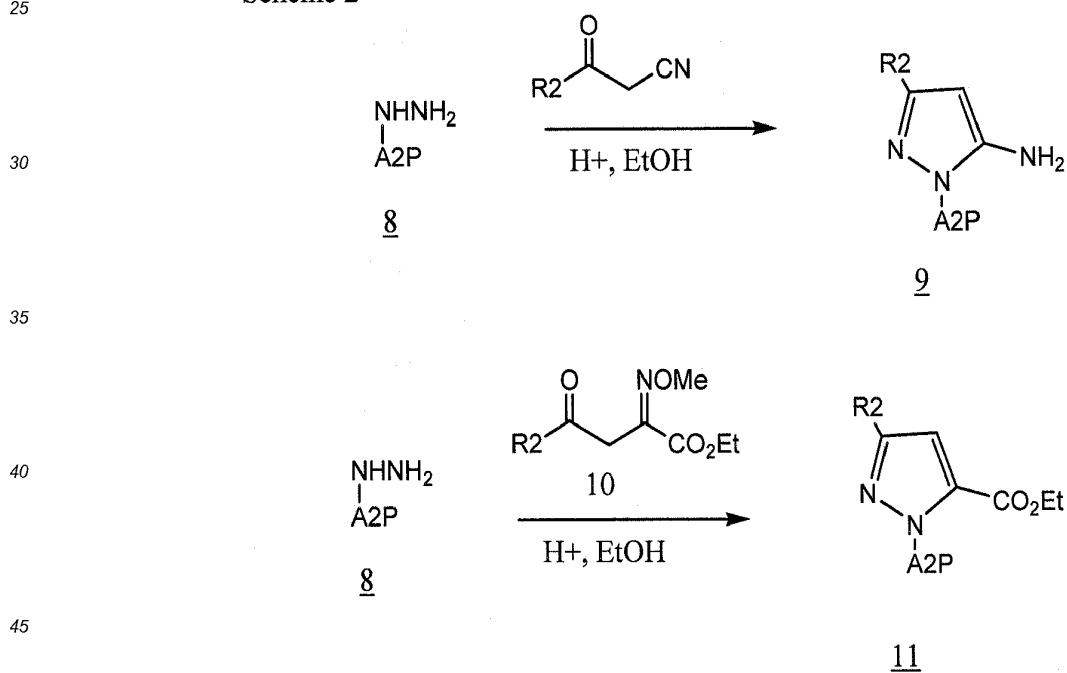
**[0053]** The preparation of intermediates wherein A1 is taken from pyrazolyl A1-1 is illustrated in Schemes 1 through 4. Scheme 1 illustrates the preparation of hydrazines 2. If the amine precursors 1 are readily available, they are converted to the hydrazines 2 by a diazotization/reduction sequence. Preferred conditions react 1 with NaNO<sub>2</sub> in aqueous HCl to form the diazonium salt at about 0°C in aqueous solvent or an aqueous/organic cosolvent. The diazonium salt is not isolated, but directly reduced by reaction with SnCl<sub>2</sub>·2H<sub>2</sub>O under acidic conditions, preferably aqueous HCl at between about 0°C and room temperature. The hydrazines 2 are isolated as the HCl addition salts. If the amine precursors 1 are not directly available, they can be formed from the nitro-substituted A2P precursors 3 by reduction, preferably with iron/HCl, SnCl<sub>2</sub>·2H<sub>2</sub>O, or catalytic hydrogenation, to give the requisite amines 1. Conversion to the hydrazines 2 is accomplished as described above. Alternatively, reaction of the aryl or heteroaryl bromides 4 with benzophenone hydrazone and a palladium catalyst, preferably with Pd(OAc)<sub>2</sub> and DPPF as ligand, can afford the protected hydrazines 5, which are deprotected under acidic conditions, preferably *p*-toluenesulfonic acid or ethanolic HCl, to give rise to the desired hydrazines 2 (Hartwig, J.F., et al, Angew. Chem. Int. Ed. (1998) 37: 2090; Haddad, N., et al, Tetrahedron Letters (2002) 43: 2171-2173). Alternatively, reaction of the aryl or heteroaryl iodides 6 with *t*-butylcarbazate and a copper (I) catalyst, preferably CuI in DMF at about 80°C with Cs<sub>2</sub>CO<sub>3</sub> base and a ligand such as 1,10-phenanthroline, can afford the BOC-protected hydrazines 7, which are converted to the desired hydrazines 2 by treatment with acid (M. Woltor et al, Organic Letters (2001) 3: 3803-3805).

Scheme 1



[0054] Preparation of pyrazoles 9 and 11 are illustrated in Scheme 2. Reaction of hydrazines 8 with *beta*-ketonitriles in an alcoholic solvent, preferably EtOH, and an acid catalyst, preferably HCl or p-toluenesulfonic acid, at about 80°C gives aminopyrazoles 9. Analogous treatment of hydrazines 8 with the ethyl 2-(methoxyimino)-4-oxobutanoates 10 affords the pyrazole ethyl esters 11 (Lam, P.Y.S., et al, Journal of Medicinal Chemistry (2003) 46: 4405-4418).

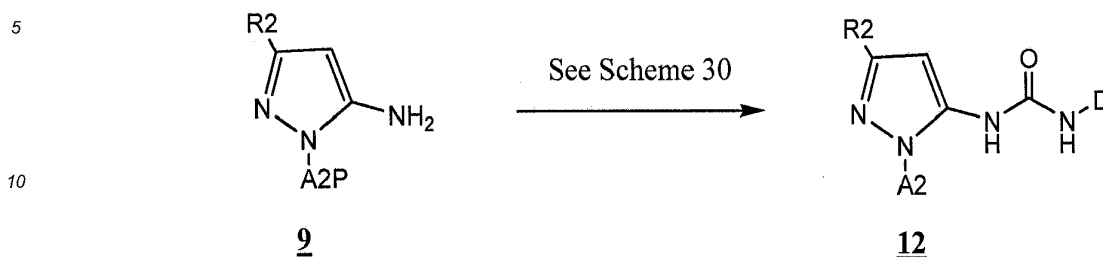
Scheme 2



[0055] The aminopyrazoles 9 are converted into the desired pyrazole ureas 12 of Formula I (see Scheme 3) by methods described in Scheme 30 for the conversion of the aminothiophene into ureas of Formula I.



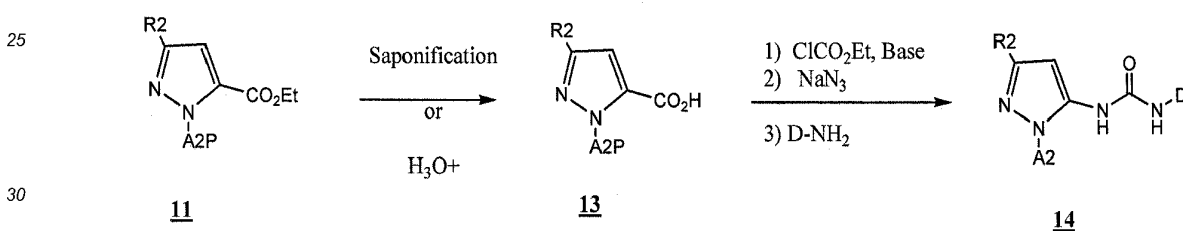
Scheme 3



15 [0056] Alternatively, pyrazole ureas of Formula I can be formed from the pyrazole ethyl esters 11 by a sequence illustrated in Scheme 4. Conversion of esters 11 to the carboxylic acids 13 is accomplished by saponification or by treatment with aqueous acid. Curtius-type rearrangement of 13, preferably by treatment with ethyl chloroformate and base, preferably triethylamine, in an organic solvent, preferably THF at about 0°C, and then forming the acyl azide by reaction with sodium azide, and quenching of the *in situ* rearranged isocyanate with D-NH<sub>2</sub> gives rise to the desired pyrazole ureas 14 of Formula I (El Haddad, M. et al, Journal of Heterocyclic Chemistry (2000) 37: 1247-1252).

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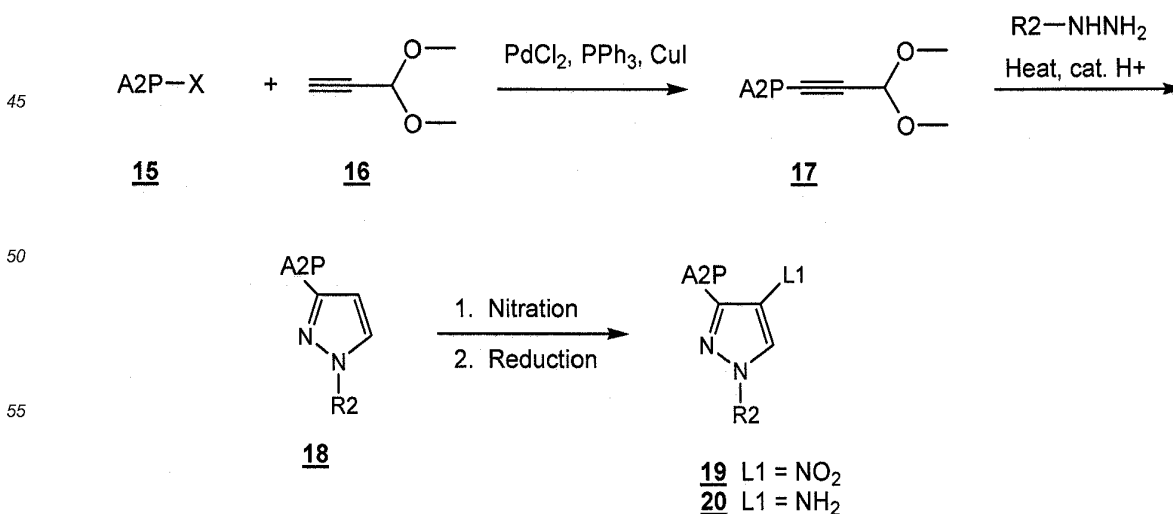
Scheme 4



35 [0057] The synthesis of pyrazoles of formula I wherein A1 is A1-2 is exemplified in Scheme 5. Aryl halide 15 (bromo or iodo (preferred)) is reacted with acetylene 16 [CAS 22537-06-0] under standard palladium cross-coupling conditions to yield 17. As described by Coispeau et. al (Bull. Chem. Soc. France, 1970, 689-696), 17 reacts monosubstituted hydrazines in the presence of catalytic mineral acid to yield pyrazole 18, which is readily nitrated under standard conditions at the 4-position to yield 19. Catalytic hydrogenation or reduction utilizing iron/HCl or tin (II) chloride of 19 yields 20, which can be coupled and deprotected as shown in Scheme 6 to yield urea 21.

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Scheme 5



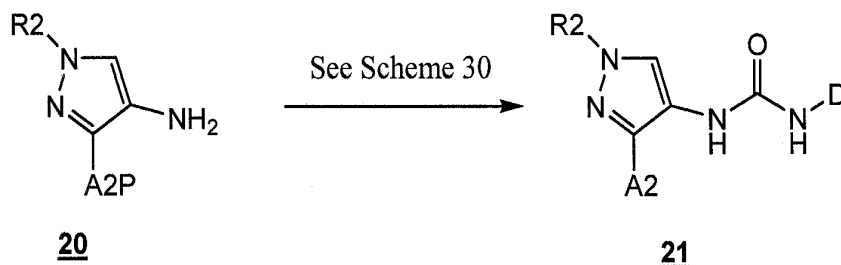
[0058] The aminopyrazoles 20 are converted into the desired pyrazole ureas 21 of Formula I by methods described in Scheme 30.

Scheme 6

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[0059] The synthesis of pyrazoles of formula I wherein A1 is A1-3 is exemplified in Scheme 7. Substituted pyrazole 22 is preferentially halogenated (brominated or iodinated) at the 4-position to yield 23 (see: Bull. Chem. Soc. France, 1967, 328 and J. Gen. Chem. USSR, 1963, 33, 503). Coupling of 23 with boronic acid 24 under standard conditions yields 25, which is nitrated at the 3-position under standard conditions to yield 26. Catalytic hydrogenation or reduction of 26 utilizing iron/HCl or tin (II) chloride yields amine 27 that can be elaborated to deprotected urea 28 of Formula I using the same strategies as outlined in Scheme 30.

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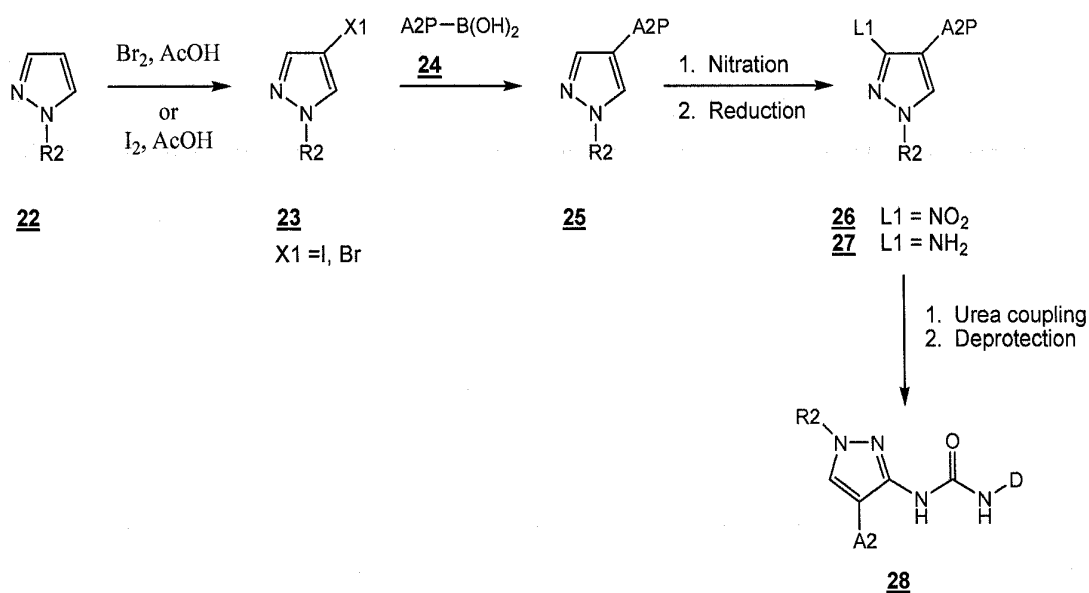
Scheme 7

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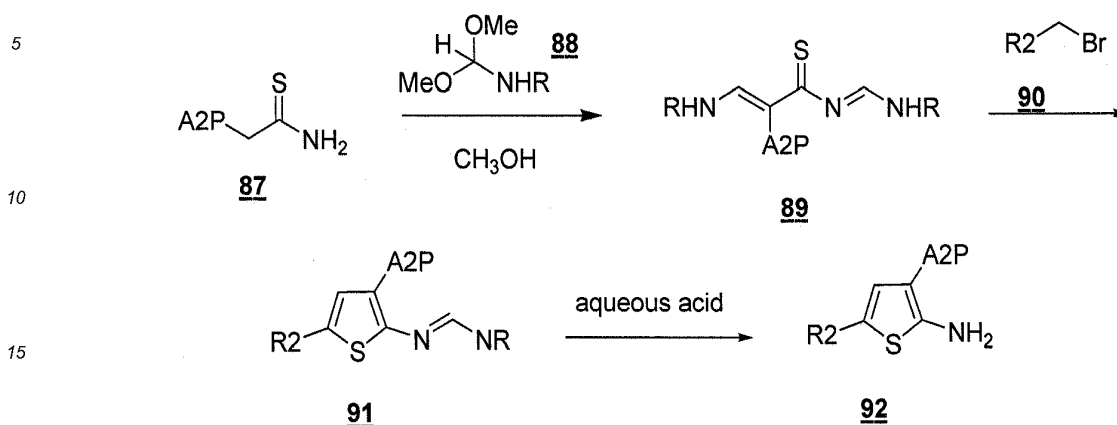


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[0060] The preparation of compounds of Formula I wherein A1 is A1-14 is illustrated in schemes 26 and 27. Scheme 26 illustrates the preparation of 4,5-disubstituted 2-aminothiophenes 92 according to methods reported by Knoll *et al* (Knoll, A. *et al*, Synthesis (1984) 51-53; Knoll, A. *et al*, J. Prakt.Chem. (1985), 327: 463-470). The compound 87 is reacted with an excess of formamide derivatives 88 in methanol to afford N-(3-aminothioacryloyl)-formamidines 89. A mixture of substituted N-(3-aminothioacryloyl)-formamidines, 89 and substituted bromides, 90 in a protic solvent, such as methanol or ethanol, is heated, preferably at a reflux temperature. The product thiophene-imines, 91 are treated with aqueous acid to obtain the thiophene-amines 92.

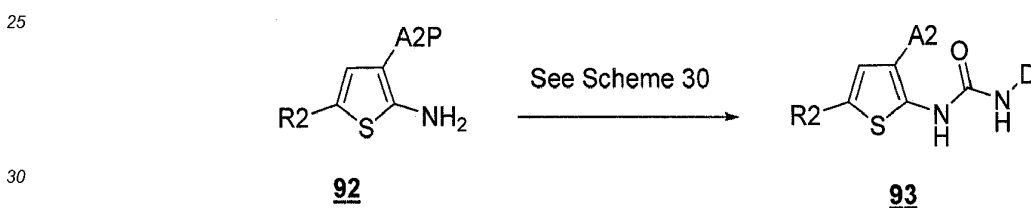
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Scheme 26



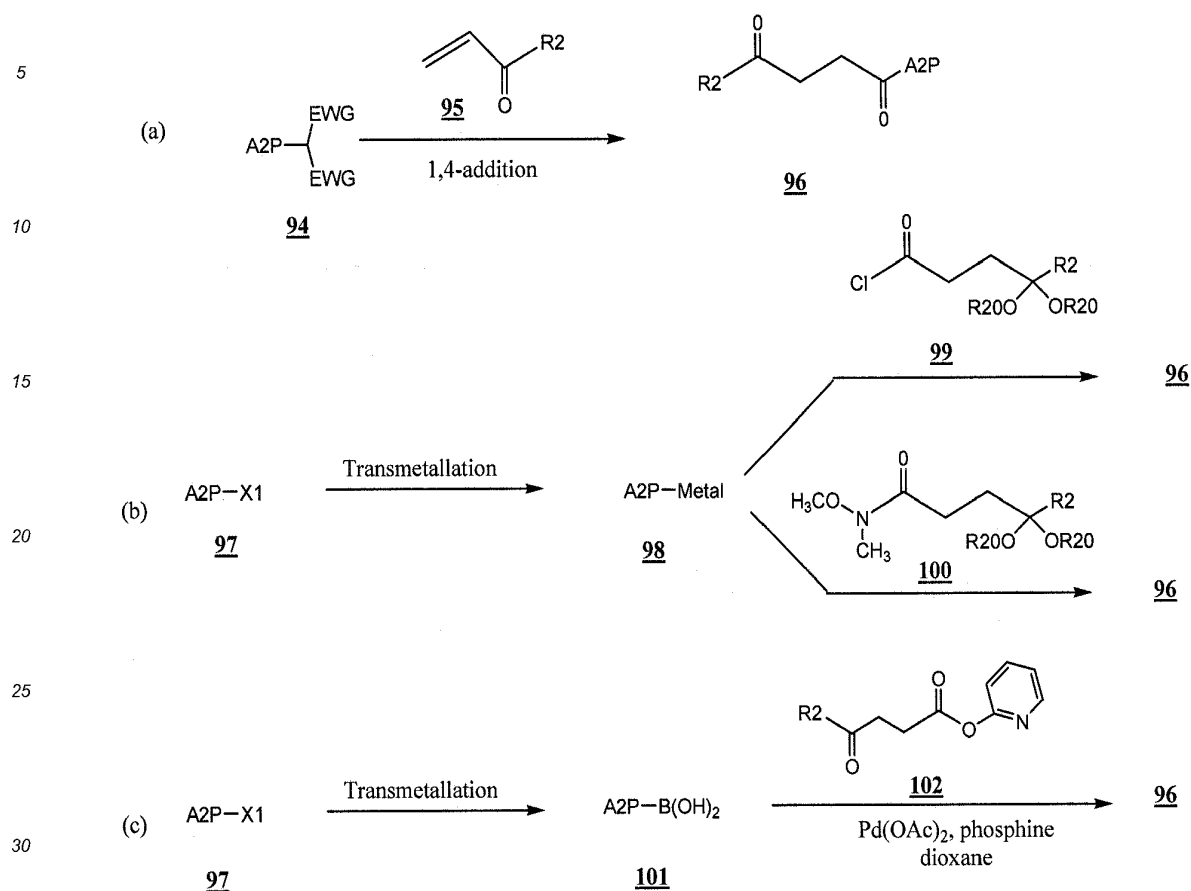
[0061] The aminothiophenes **92** are converted into the desired thiophenyl ureas of Formula I by methods described in Scheme 30.

Scheme 27



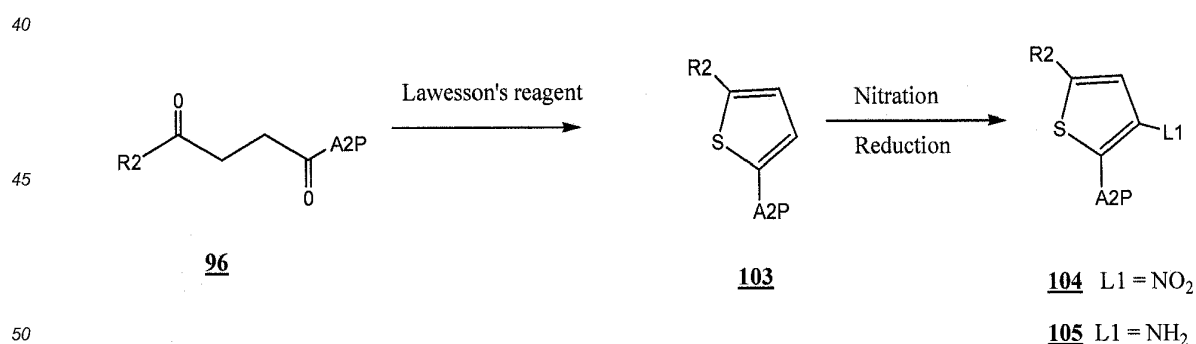
[0062] Scheme 28 illustrates the preparation of 1,4-dicarbonyl starting materials **96** for the preparation of compounds of Formula I, wherein A1 is A1-13. One preferred method utilizes a 1,4-conjugate addition procedure, Scheme 28 (a), to transform **94** to **96** by reaction with the unsaturated ketone **95** in the presence of a suitable base such as a lithium, sodium, or potassium amide or hydride base. Another preferred method, Scheme 28 (b), makes use of a transmetallation reaction, converting **97**, wherein X1 is halogen, to an organometallic species **98** wherein the metal is magnesium, nickel, or cadmium. *In situ* reaction of **98** with acid chloride **99** gives rise to the 1,4-dicarbonyl species **96** after acid-catalyzed removal of the ketal protecting group. Alternative reaction of **98** wherein the metal is lithium with the Weinreb amide **100** also affords **96** after acid-catalyzed removal of the ketal protecting group. A third preferred method, illustrated in Scheme 28 (c), makes use of a palladium-catalyzed reaction between the readily available boronic acid **101** and a suitable 2-pyridyl ester **102** as reported by Chatani et al (Organic Letters (2004) 6: 3597-3599).

Scheme 28



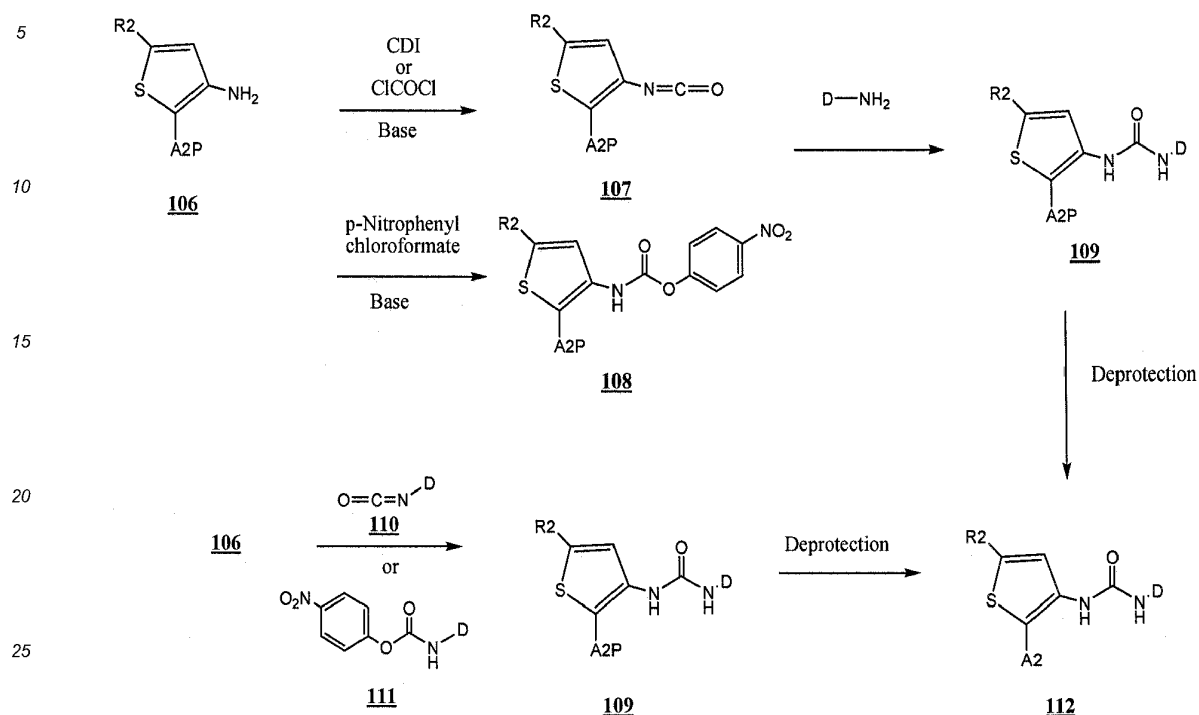
[0063] The 1,4-dicarbonyl starting materials 96 are reacted with Lawesson's reagent in a suitable solvent such as THF or toluene to afford thiophene 103. Nitration of 103 affords 104, which is reduced with iron/HCl, tin (II) chloride, or catalytic hydrogenation conditions to give the 3-aminothiophene intermediates 105 (Scheme 29).

Scheme 29



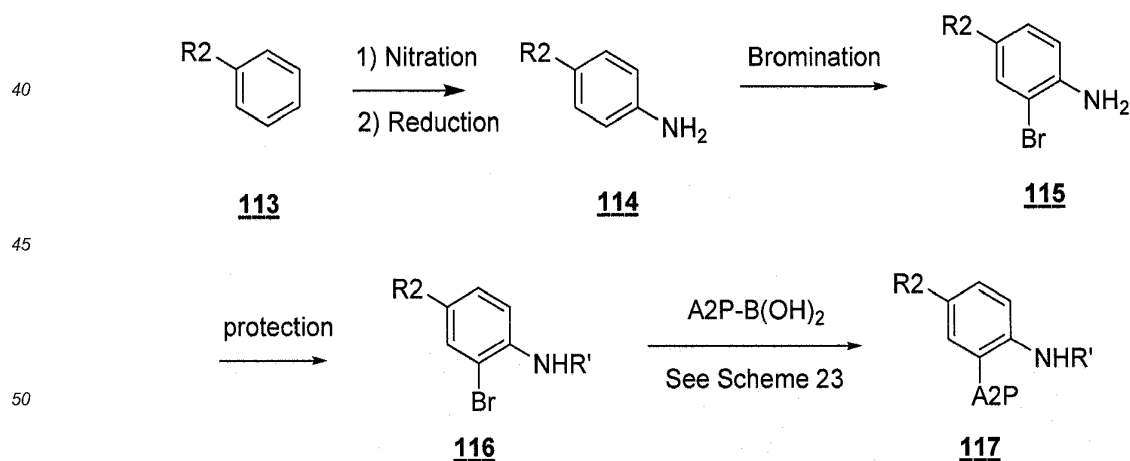
[0064] The preparation of compounds of Formula I are illustrated in Scheme 30. The aminothiophenes 106 are reacted with carbonyl diimidazole (CDI) or phosgene CO(Cl)<sub>2</sub> to give isocyanates 107. Alternatively, 106 can be reacted with p-nitrophenyl chloroformate to give the p-nitrophenylcarbamates 108 as synthetic equivalents to isocyanates 107. Reaction of isocyanates 107, or the corresponding p-nitrophenylcarbamates 108, with readily available amines D-NH<sub>2</sub> affords ureas 109. Alternatively, 106 is reacted with isocyanates 110 or the p-nitrophenylcarbamates 111 to give ureas 109. Removal of the A2P protecting groups from 109 affords the desired compounds of Formula 112.

Scheme 30



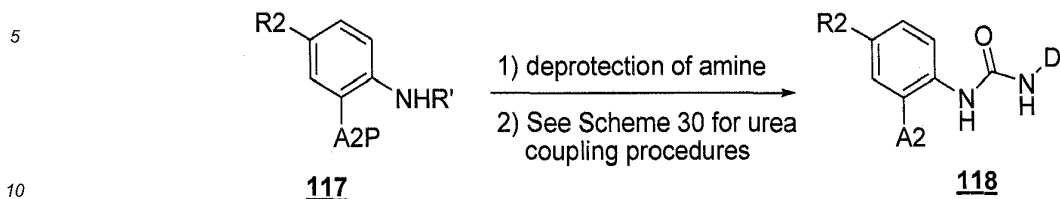
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 [0065] The preparation of compounds of Formula I wherein A1 is A1-16 is illustrated in Schemes 31 and 32. Scheme 31 illustrates the preparation of 2,4-disubstituted N-protected-anilines 117. The commercially available starting materials 113 are converted to 4-substituted anilines 114 by nitration, followed by reduction with iron/HCl, tin (II) chloride, or catalytic hydrogenation conditions. The reaction of 4-substituted anilines 114 with bromine in acetic acid gives 2-brominated anilines 115. The amino groups of 115 are protected to allow their use in Suzuki coupling reactions to obtain 117.

Scheme 31



55  
 [0066] The Suzuki coupled intermediates 117 are converted into the desired phenyl ureas 118 of Formula I by methods described in Scheme 30.

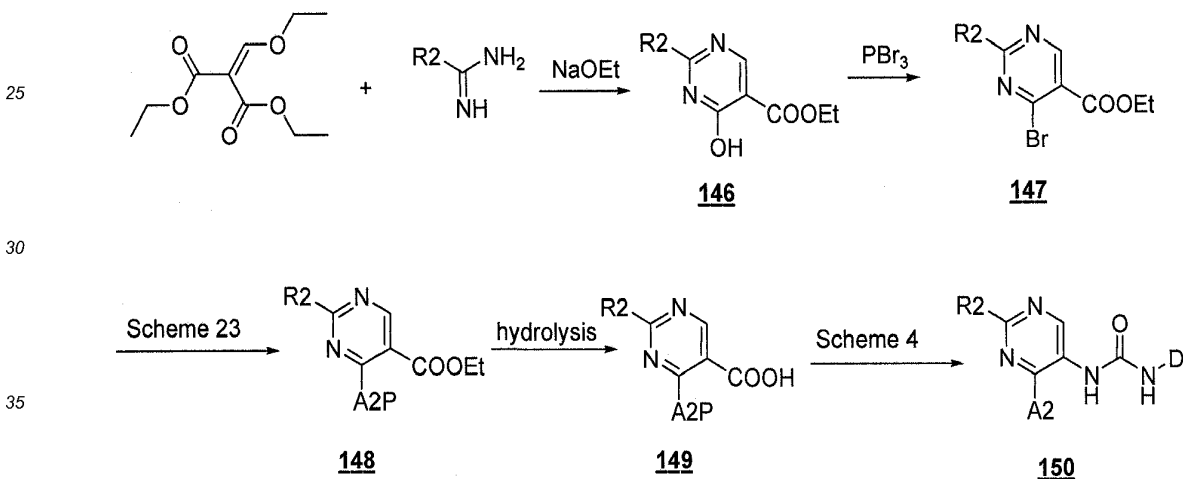
Scheme 32



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**[0067]** Synthesis of compounds of Formula I wherein A1 is A1-21 is described in Scheme 40. As reported by Palanki et al (J. Med. Chem. 2000, 43, 3995-4004) diethyl ethoxymethylenemalonate and trialkylacetamidine are heated with sodium ethoxide to provide pyrimidines **146**. The hydroxyl groups of **146** are converted to the bromides by reaction with  $\text{PBr}_3$  to afford bromopyrimidines **147**. Intermediates **147** are converted to **148** using Suzuki cross-coupling methods illustrated above in Scheme 23. The ester functionalities of **148** are hydrolyzed to acids **149**, which are utilized in a Curtius rearrangement reaction sequence in the presence of amines  $\text{D-NH}_2$  using methods reported above in Scheme 4, to give the desired ureas **150** of Formula I.

Scheme 40

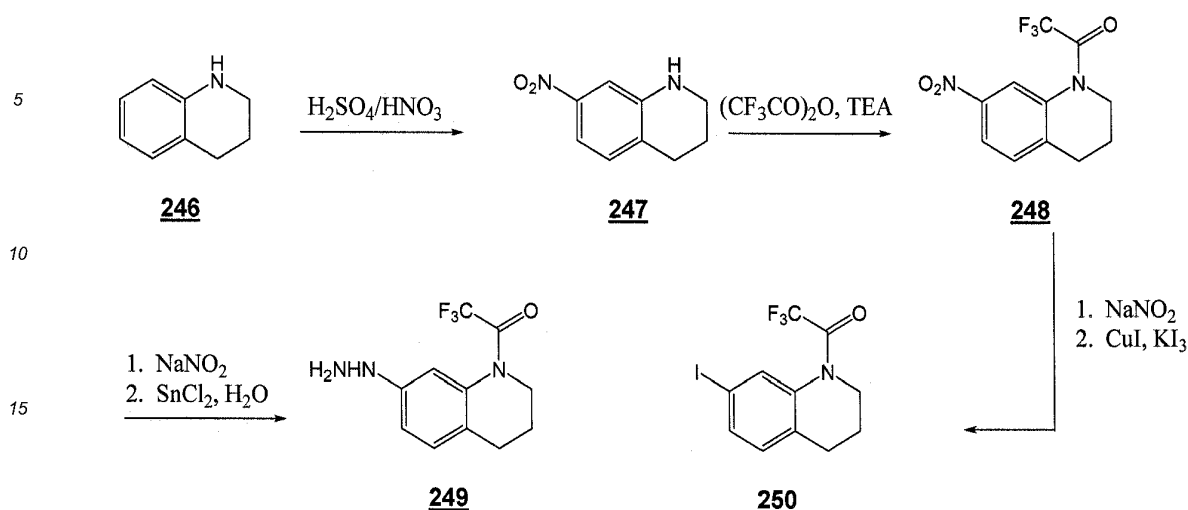
A2-77 V=H<sub>2</sub>

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**[0068]** The synthesis of compounds of Formula I wherein A2 is A2-77 is shown in Scheme 53. Nitration of commercially available tetrahydroisoquinoline (**246**) by the action of  $\text{H}_2\text{SO}_4$  and  $\text{HNO}_3$  affords 7-nitrotetrahydroisoquinoline **247** (see WO 03/0999284). Protection of **247** as its trifluoroacetamide yields **248**, and conversion of the nitro group to the corresponding hydrazine by (a) reduction of the nitro group, (b) oxidation of the resulting amino group to the diazonium with  $\text{NaNO}_2$ , and (c) reduction of the diazonium with  $\text{SnCl}_2$  or  $\text{FeCl}_3$  yields **249**, which corresponds to the protected form of intermediate A2-77 containing hydrazines ( $\text{V}=\text{H}_2$ ). In the case where the corresponding halide is required, conversion of the amine **248** to the diazonium salt, and Sandmeyer displacement with  $\text{CuI}$  and  $\text{KI}_3$  iodine (see Harrington and Hegedus, J. Org. Chem. 1984, 49(15), 2657-2662) results in iodide **250**.

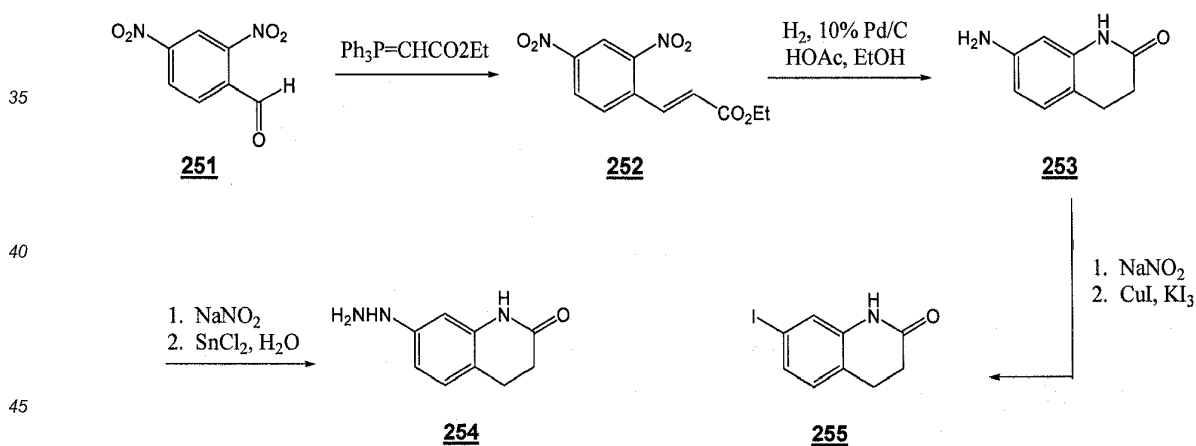
Scheme 53



## A2-77 V=O

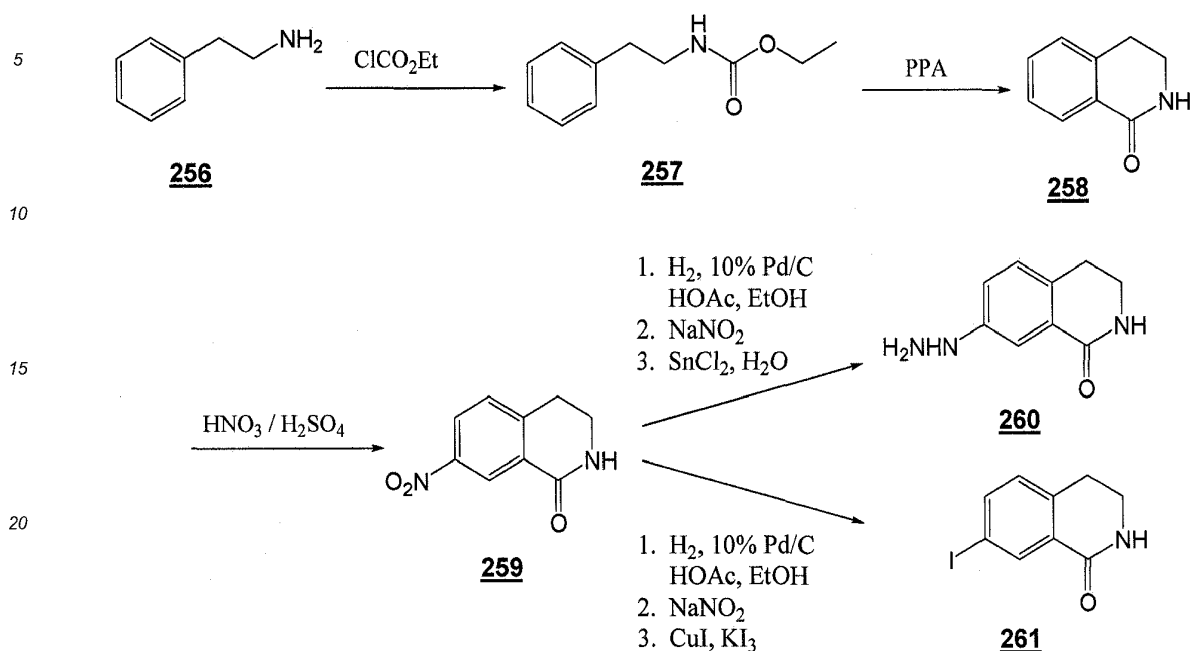
[0069] Synthesis of intermediates containing A2-77 (V=O) is shown in Scheme 54. Utilizing the procedure published by Doherty et. al (see WO 03/0999284), Wittig homologation of commercially available 2,4-dinitrobenzaldehyde (**251**) with ethyl (triphenylphosphoranylidene)-acetate results in propenoate **252**. Catalytic hydrogenation in the presence of glacial acetic acid and ethanol results in the target 1H-quinolin-2-one **253** which, utilizing the same oxidation/reduction sequence as shown in Scheme 53 results in hydrazine **254** (R15, V=O) and iodide (**255**). At the conclusion of the synthesis that utilizes **254** or **255**, reduction of the amide with LAH under standard conditions provides an optional synthesis of intermediates containing A2-77 (V=H<sub>2</sub>).

Scheme 54

A2-78 V1=O, V2 = H<sub>2</sub>

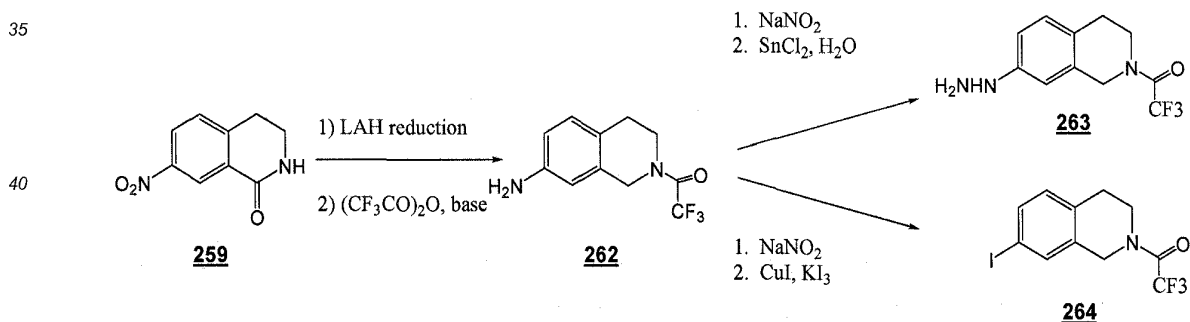
[0070] The synthesis of intermediates containing A2-78 (V1 = O, V2 = H<sub>2</sub>) is shown in Scheme 55. Commercially available phenethylamine **256** is converted to the carbamate **257**, and then cyclized utilizing polyphosphoric acid (PPA) to give the tetrahydroisoquinolone **258**. **258** is nitrated under standard conditions to give **259**, which is either converted to hydrazine **260** or iodide **261** using methodology outlined in Scheme 53.

Scheme 55

**A2-78 V1 AND V2 = H<sub>2</sub>**

[0071] The synthesis of intermediates containing A2-78, wherein V1 and V2 are H<sub>2</sub>, is shown in Scheme 56. Reduction of **259** with LAH affords the amino-substituted tetra-hydroisoquinoline which is selectively protected at the ring nitrogen by reaction with trifluoroacetic anhydride and base, preferably triethylamine. Aniline **262** is then converted into the hydrazine **263** or the iodide **264** using methodology outlined in Scheme 54.

Scheme 56

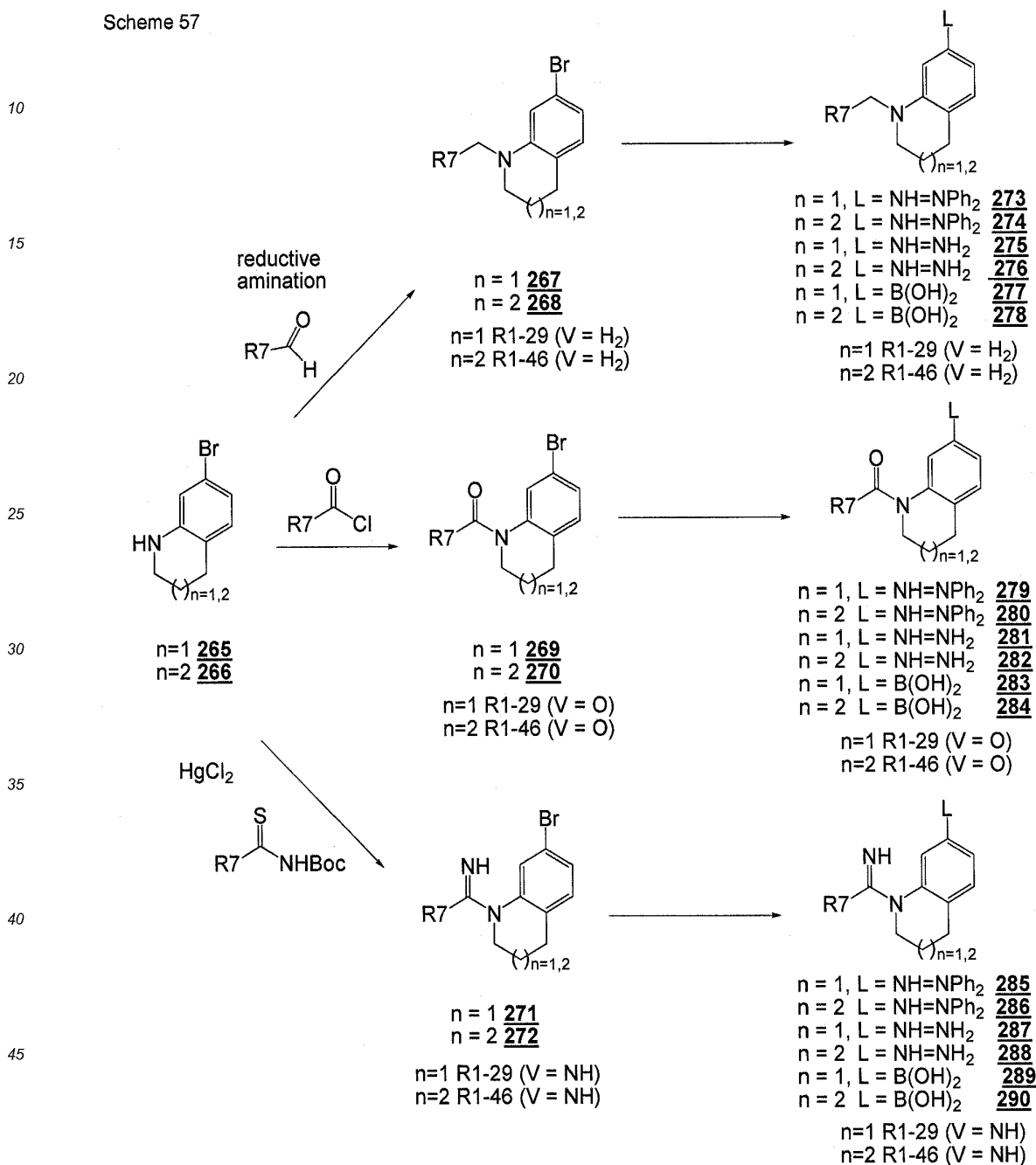
**A2-77 AND A2-98 V = H<sub>2</sub>**

[0072] The preparation of intermediates containing A2-77 and A2-98 wherein V is H<sub>2</sub> is illustrated in Scheme 57. In these schemes, R7 is a suitable moiety that conforms to the generic definition of Z4 or a protected form of such moiety. Compounds **267** and **268** are prepared by reductive alkylation of **265** or **266** with an appropriate aldehyde and sodium triacetoxyborohydride as the reducing agent. **269** and **270** are synthesized from **265** or **266** by simple amide formation using an acid chloride and base, preferably triethylamine or pyridine. **271** and **272** are synthesized by amidine or guanidine formation utilizing a thioamide or a thiourea, respectively. Intermediates **273**, **274**, **279**, **280**, **285** and **286** are prepared by palladium-catalyzed bromide substitution with benzophenone hydrazone as described by Haddad et al. (Tetrahedron Lett. 2002, 43, 2171-2173). **273**, **274**, **279**, **280**, **285** and **286** are either directly implemented by reaction with a suitable A1-containing intermediate, or, if required, first hydrolyzed to hydrazines **275**, **276**, **281**, **282**, **287** and **288**, respectively, under acidic conditions. The bromide functionalities in **267** to **272** are substituted by boronic acid affording **277**, **278**, **283**, **284**, **289** and **290**, respectively. After suitably protecting the amidine or guanidine substructure, the bromide



is transformed into an organometallic species such as a grignard compound, and subsequently reacted with trimethyl borate to afford 277, 278, 283, 284, 289 and 290 after acid hydrolysis. In cases where R7 functionalities prohibit the use of organometallic reagents, the boronic acids are mildly formed from the bromides by utilizing a procedure employing bis(pinacolato)diboron and Pd(dppf).

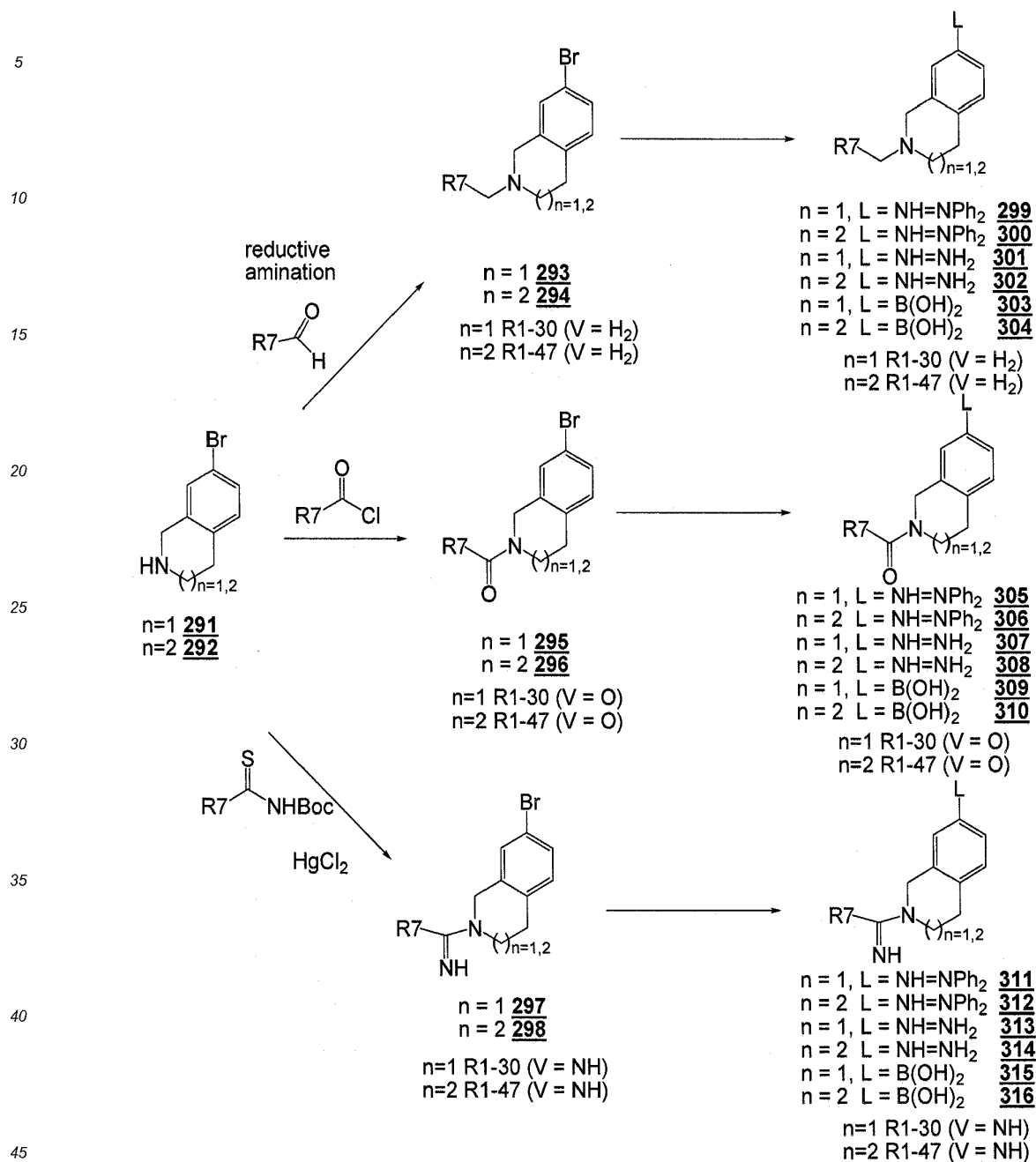
Scheme 57



#### A2-78 and A2-99, V1 AND V2 = H<sub>2</sub>

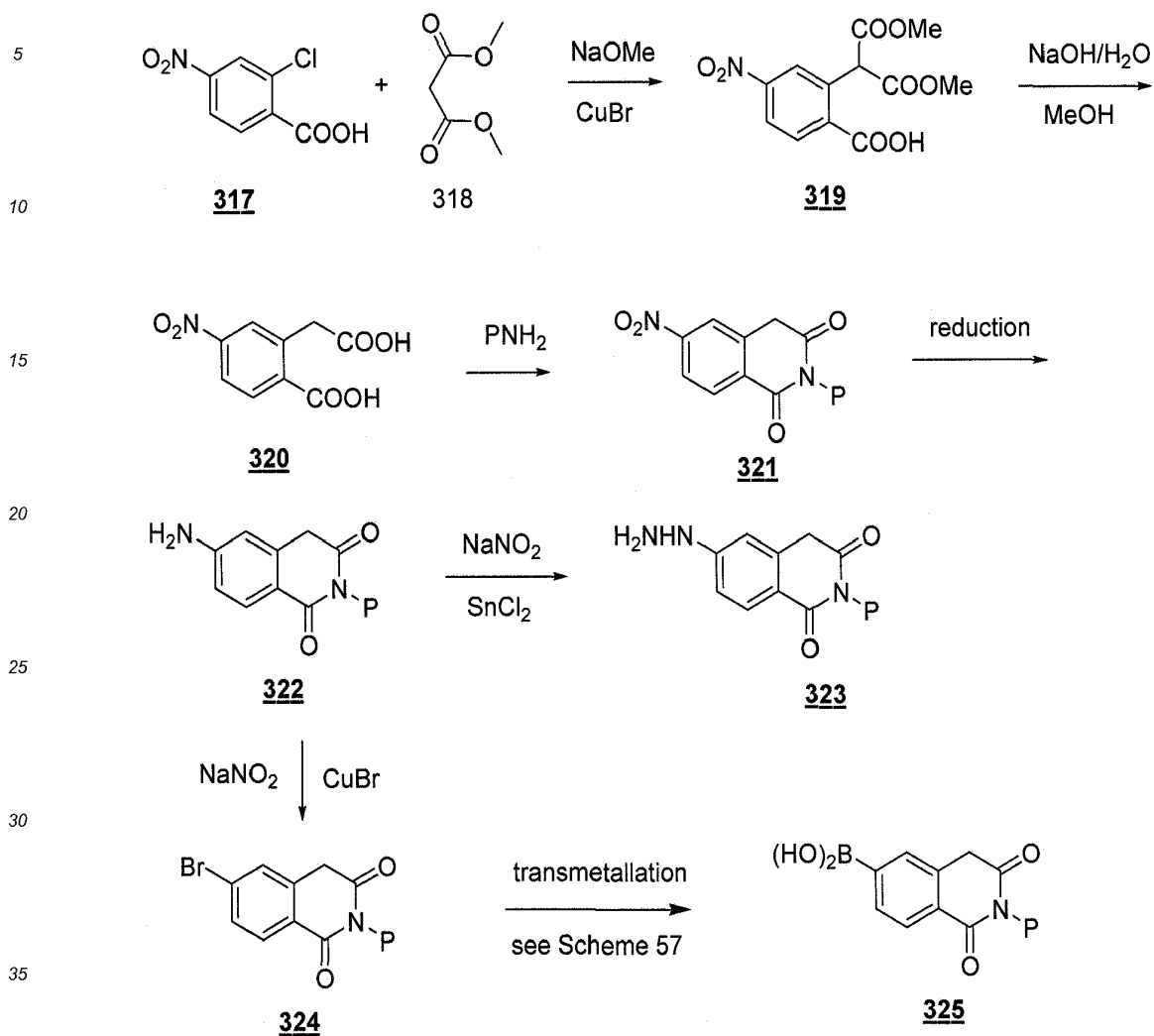
[0073] The preparation of intermediates containing A2-78 or A2-99 wherein V1 and V2 are H<sub>2</sub> is illustrated in Scheme 58. 291 and 292 are converted to intermediates 293 to 316 using methods described above in Scheme 57.

Scheme 58

**A2-79, V1 AND V2 = O**

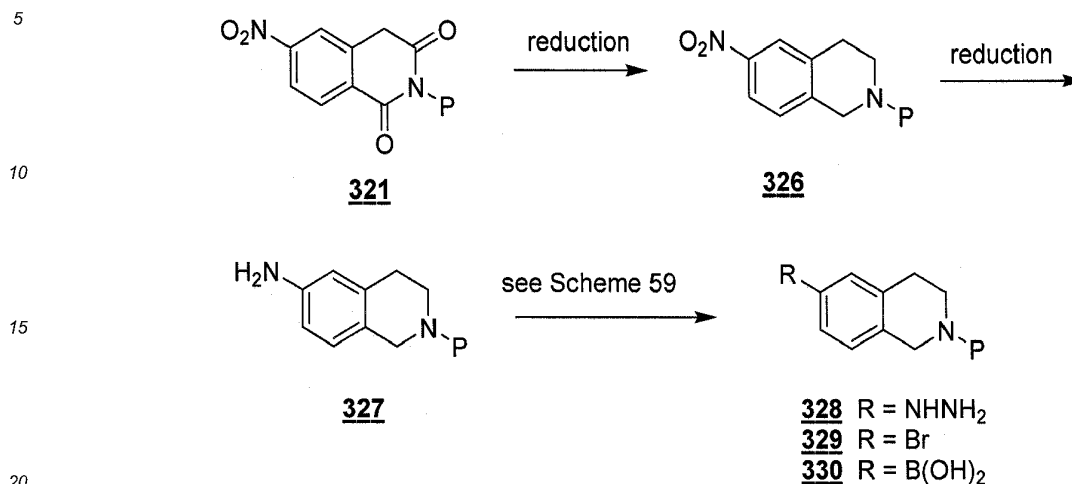
[0074] The synthesis of intermediates containing A2-79 wherein V1 and V2 are O is shown in Scheme 59. The commercially available starting material 2-chloro-4-nitrobenzoic acid **317** is reacted with dimethyl malonate **318**, NaOMe, and catalytic amount of Cu(I)Br to give **319** using conditions described by Quallich, G. J. et al (Quallich, G. J. et al, J. Org. Chem. (1998), 63: 4116-4119). The diester **319** is converted into diacid **320** under basic hydrolytic conditions. The diacid **320** is reacted with a primary amine containing a standard amine protecting group (such as benzyl) at about 115 °C to afford the ring closure product **321**. Reduction of **321** under catalytic hydrogenation conditions gives **322**. The dione **322** is converted into the hydrazine (**323**), bromide (**324**) or boronic acid (**325**) using standard conditions or those conditions described above in Scheme 47.

Scheme 59

A2-79, V1 AND V2 = H<sub>2</sub>

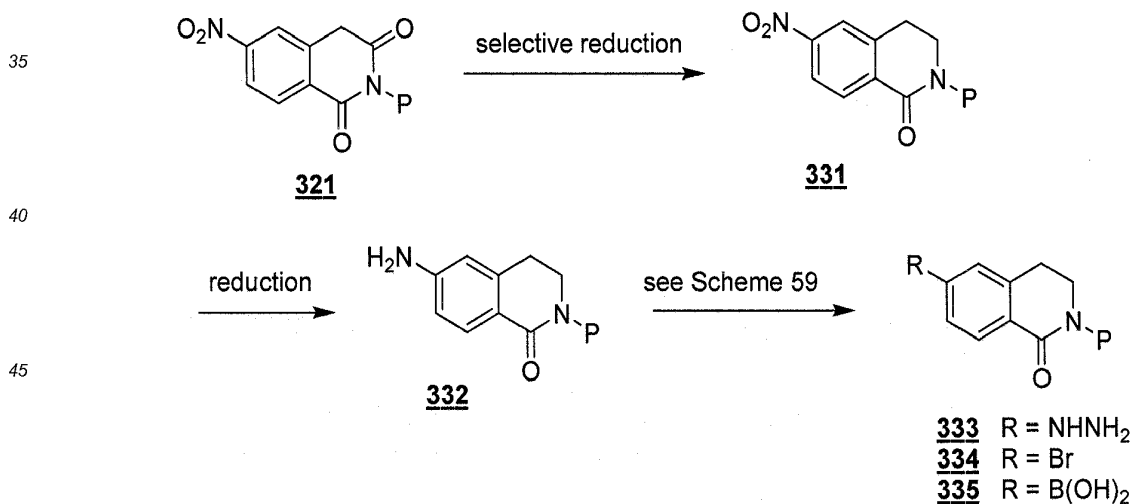
**[0075]** The synthesis of intermediates containing A2-79 wherein V1 and V2 are H<sub>2</sub> is shown in Scheme 60. Reduction of **321** (from Scheme 59) with NaBH<sub>4</sub> in the presence of BF<sub>3</sub>OEt<sub>2</sub> yields the tetrahydroisoquinoline **326**. Subsequent reduction of the nitro functionality of **326** under catalytic hydrogenation conditions gives **327**. Intermediate **327** is converted to the hydrazine **328**, bromide **329** or boronic acid **330** using the methodology described in Scheme 59.

Scheme 60

**A2-79 V1 = O, V2 = H<sub>2</sub>**

[0076] The synthesis of intermediates containing A2-79 wherein V1 is O and V2 is H<sub>2</sub> is shown in Scheme 61. The selective reduction of **321** wherein P is a standard amine protecting group (from Scheme 59) with NaBH<sub>4</sub> in the presence of TFA gives the lactam **331** (Snow, R. J. et al, J. Org. Chem., (2002), 45:3394-3405). Reduction of the nitro functionality of **331** under catalytic hydrogenation conditions yields amine **332**. Intermediate **332** is converted into the hydrazine **333**, bromide **334** or boronic acid **335** using the methodology outlined in Scheme 59.

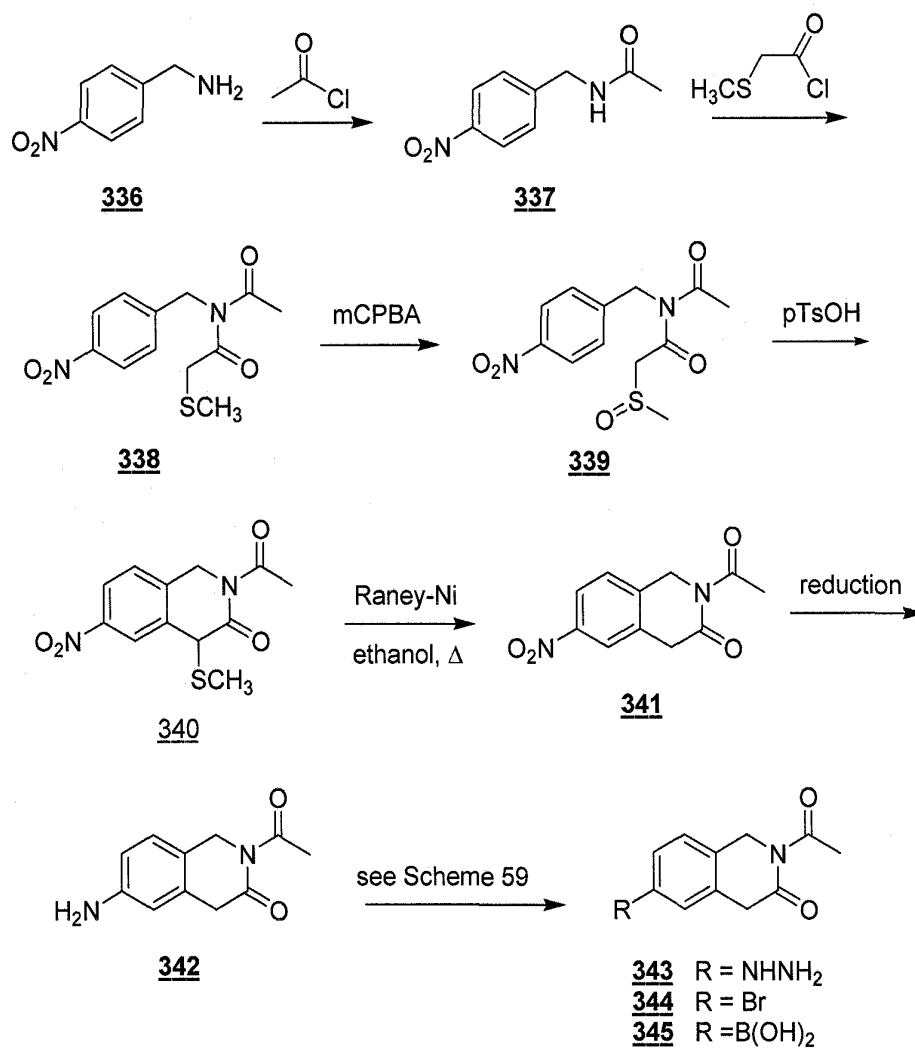
Scheme 61

**A2-79, V1 = H<sub>2</sub>, V2 = O**

[0077] The synthesis of intermediates containing A2-79 wherein V1 is H<sub>2</sub> and V2 is O is shown in Scheme 62, utilizing methods reported by Tamura, Y. et al (Synthesis 1981, 534-537). The commercially available starting material 4-nitrobenzylamine **336** is protected with acetyl chloride to yield **337**. Intermediate **337** is treated with  $\alpha$ -(methylthio)-acetyl chloride to give **338**. Oxidation of **338** with 3-chloroperbenzoic acid gives the sulfoxide **339**. Treatment of sulfoxide **339** with p-TsOH yields the lactam **340**. Lactam **340** reacts with Raney Ni to afford the dihydroisoquinolinone **341**. Reduction of the nitro functionality of **341** under catalytic hydrogenation conditions affords amine **342**. Intermediate **342** is converted

into the hydrazine 343, bromide 344 or boronic acid 345 using the methodology outlined in Scheme 59.

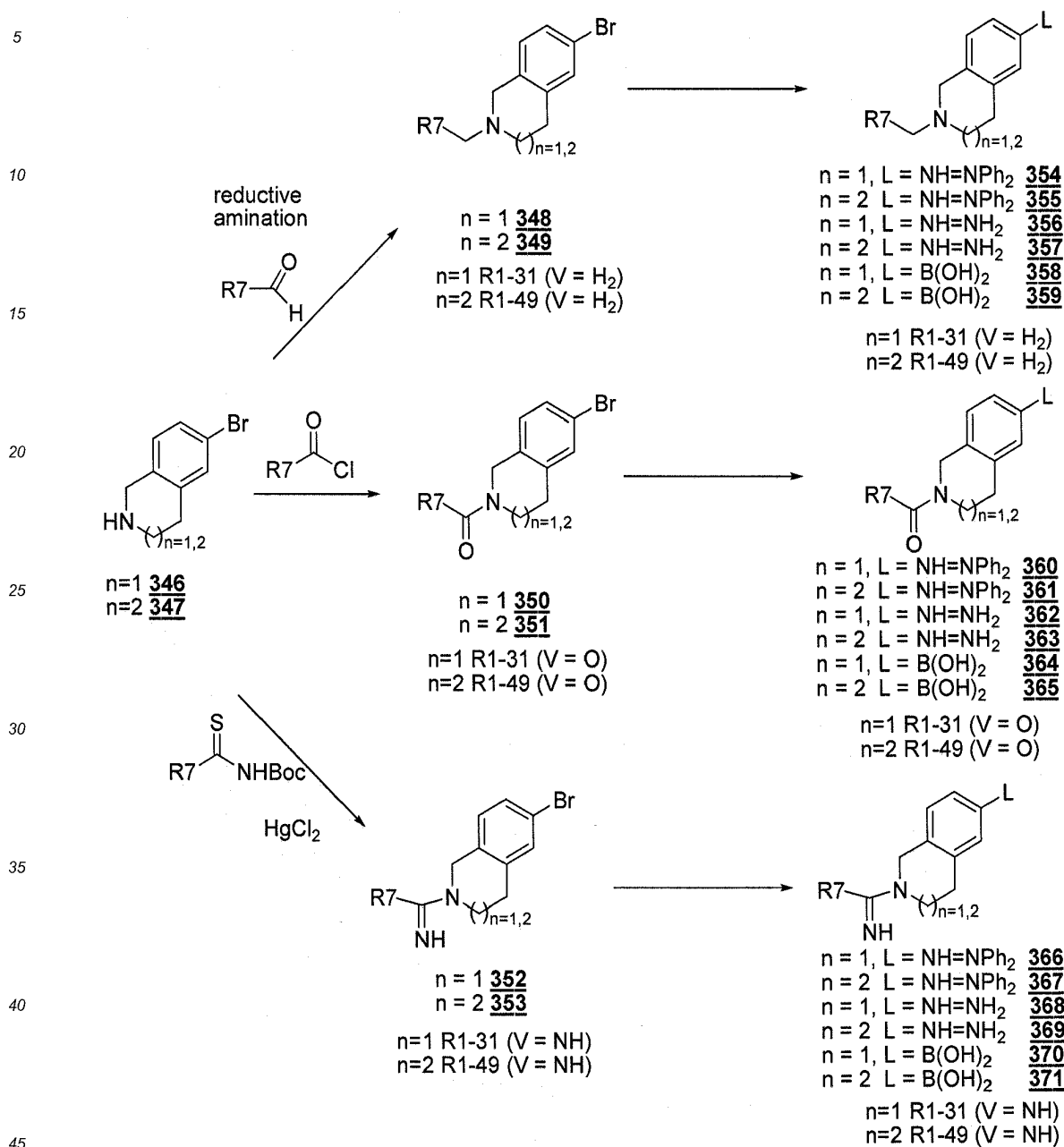
Scheme 62



**A2-79 AND A2-101, V1 AND V2 = H<sub>2</sub>**

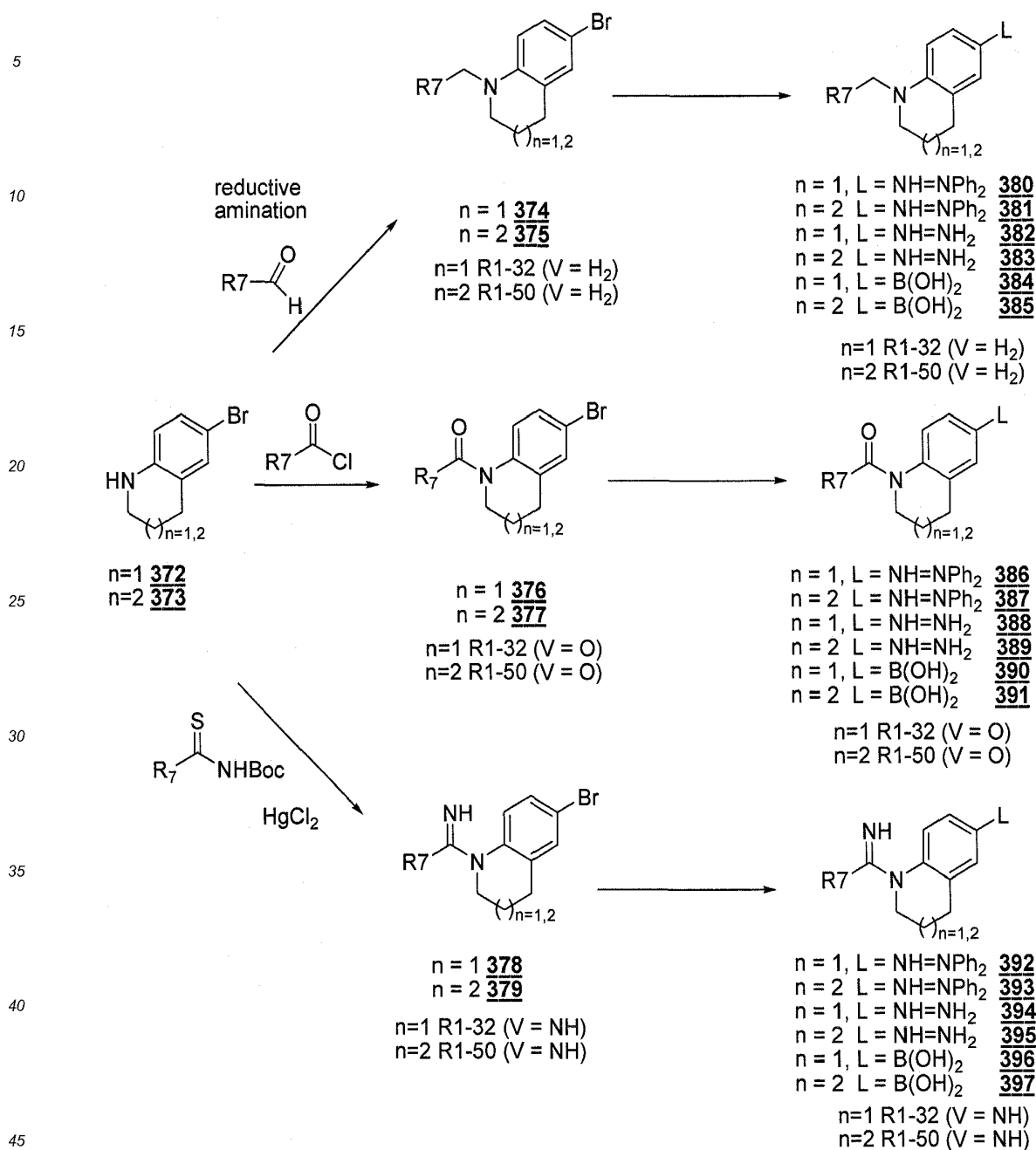
**[0078]** The preparation of intermediates containing A2-79 or A2-101 wherein V1 and V2 are H<sub>2</sub> is illustrated in Scheme 63. 346 and 347 are converted to intermediates 348 to 371 using methods described above in Scheme 57.

Scheme 63

**A2-80 AND A2-102 V = H<sub>2</sub>**

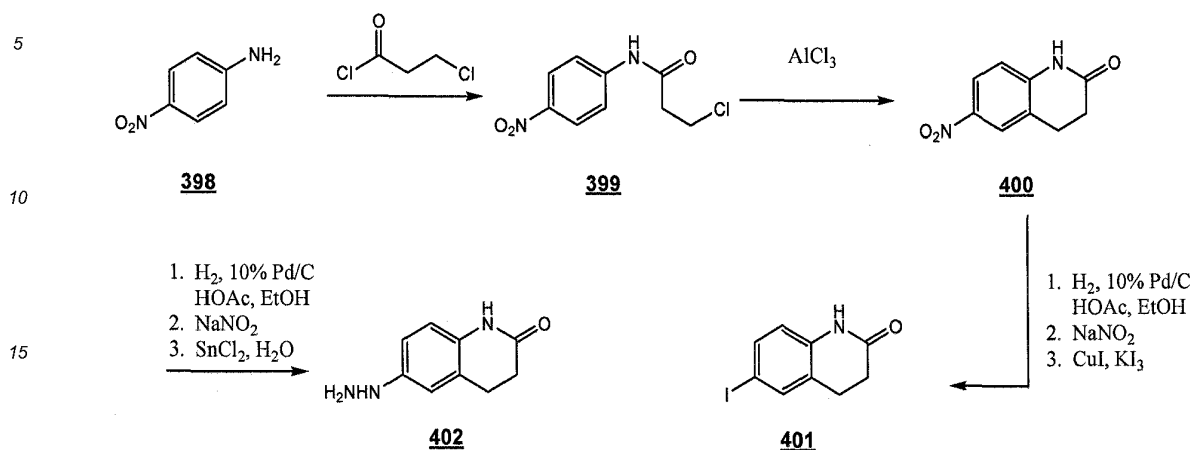
[0079] The preparation of intermediates containing A2-80 or A2-102 wherein V is H<sub>2</sub> is illustrated in Scheme 64. 372 and 373 are converted to intermediates 374 to 397 using methods described above in Scheme 57.

Scheme 64

**A2-80  $V=O$** 

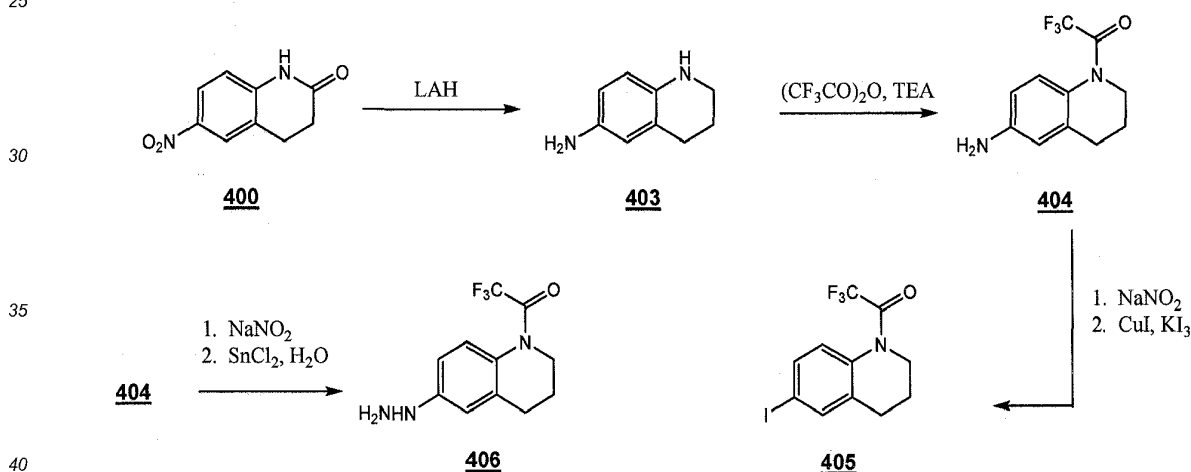
[0080] The synthesis of intermediates containing A2-80 ( $V=O$ ) is shown in Scheme 65. Acylation of 4-nitroaniline 398, and Friedel-Crafts alkylation by the action of  $\text{AlCl}_3$  results in 400 (see Zhang et. al Huaxue Yanjiu Yu Yingyong, 2002, 14(5), 618-619; Zhang et. al Huaxue Yanjiu Yu Yingyong, 2003, 17(5), 534-529). Elaboration of the nitro group in 400 to the hydrazine 401 ( $R18, V=O$ ) and the iodide 402 ( $R18, V=O$ ) proceeds under the same conditions outlined in Schemes 53 and 54. At the conclusion of the synthesis that utilizes 401 or 402, reduction of the amide with LAH under standard conditions yields intermediates A2-80 ( $V=H_2$ ).

Scheme 65



20 **[0081]** Alternatively, **400** can be reduced with LAH to yield **403** and subsequently protected as the trifluoroacetamide (**404**), which is converted to the hydrazine (**405**, R18, V=H2) or iodide (**406**, R18, V=H2) (Scheme 66) using the same methodology outlined in Scheme 53.

Scheme 66



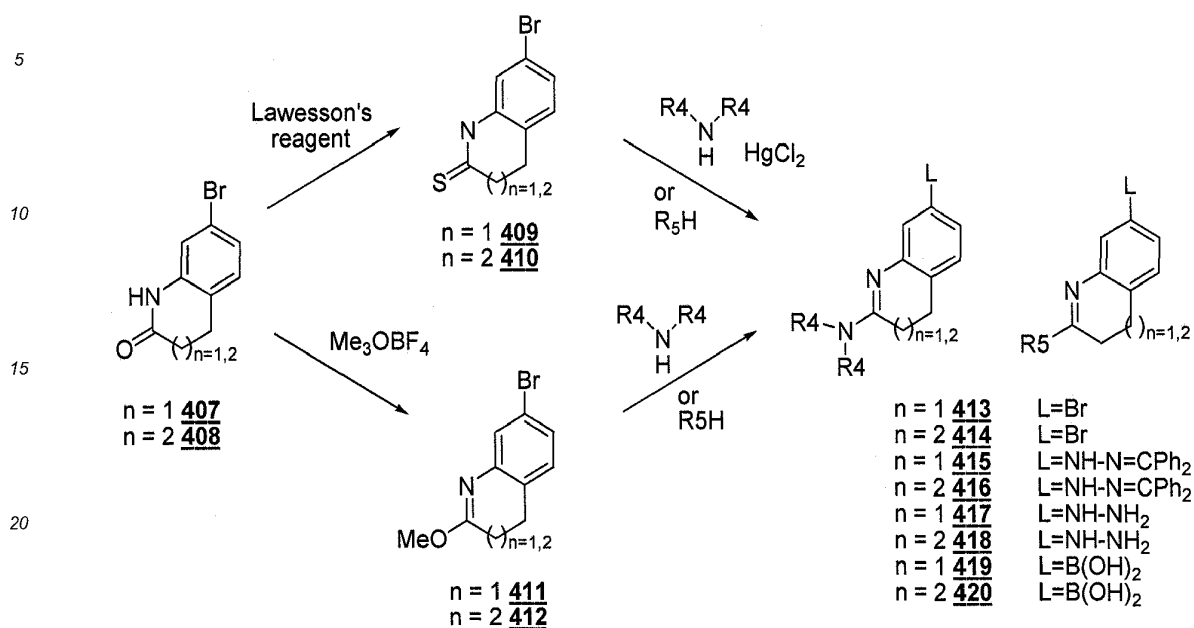
## A2-81 and A2-103

45 **[0082]** The preparation of intermediates containing A2-81 and A2-103 is illustrated in Scheme 67. **407** and **408** (see Scheme 54) are activated either by transformation into the corresponding thiolactams **409** and **410** using Lawesson's reagent in dioxane or by transformation into imino ester **411** and **412** using trimethyloxonium tetrafluoroborate. The displacement reaction with a primary amine (if one R<sub>4</sub> is H) or a secondary amine affords amidines **413** and **414** when heated in a suitable solvent such as methanol or dioxane. From the thiolactam, displacement is supported by addition of mercury chloride. Structures **415** and **416** can be obtained when the bromide is reacted with benzophenone hydrazone under palladium catalysis as described by Haddad et al. (Tetrahedron Lett. 2002, 43, 2171-2173). **415** and **416** can either be directly implemented for reaction with a suitable A1 intermediate or, if required, first hydrolyzed to hydrazines **417** and **418** under acidic conditions. The bromide in **413** and **414** can be substituted by a boronic acid affording **419** and **420**. After suitably protecting the amidine substructure, the bromide is transformed into an organometallic species such as a grignard compound and subsequently reacted with trimethyl borate to afford **419** and **420** after acid hydrolysis.

50 In cases where R<sub>4</sub> or R<sub>5</sub> prohibits the use of organometallic reagents, the boronic acid can be mildly introduced with bis(pinacolato)diboron and Pd(dppf).



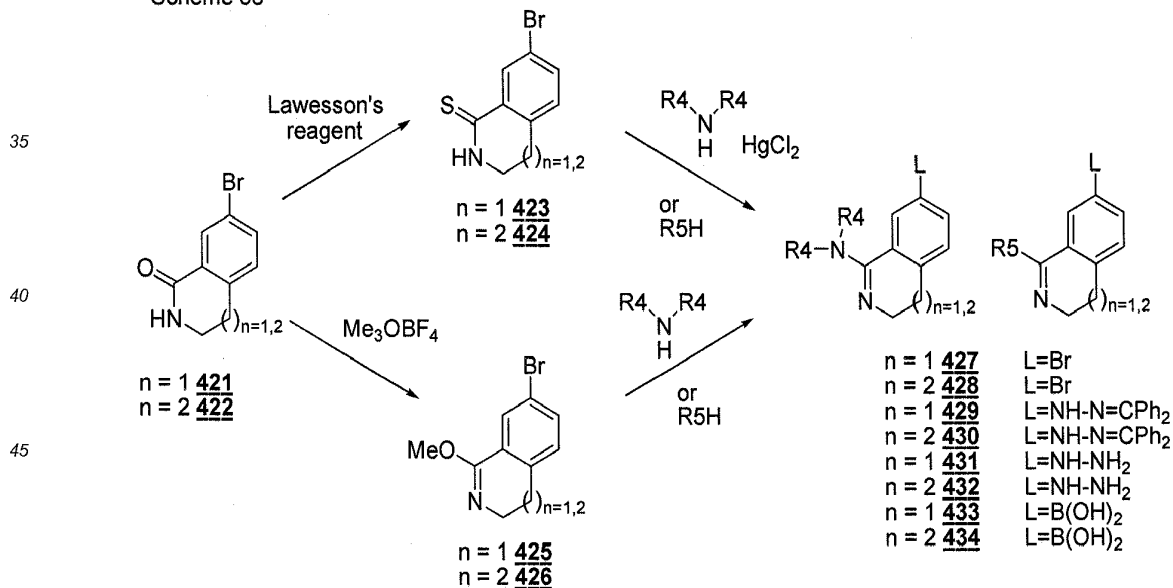
Scheme 67



## A2-82 and A2-104

[0083] The preparation of intermediates containing A2-82 or A2-104 is illustrated in Scheme 68. 421 and 422 (Scheme 55) are converted to intermediates 423 to 434 utilizing the methods described above in Scheme 67.

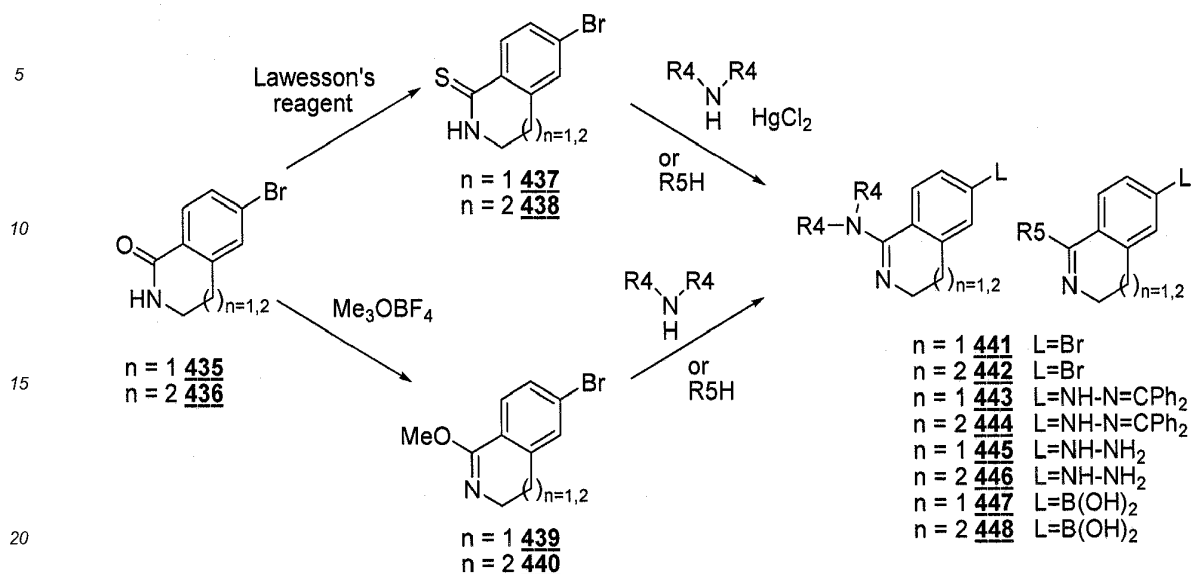
Scheme 68



## A2-83 and A2-105

[0084] The preparation of intermediates containing A2-83 or A2-105 is illustrated in Scheme 69. 435 and 436 are converted into intermediates 437 to 448 using methods described above in Scheme 67.

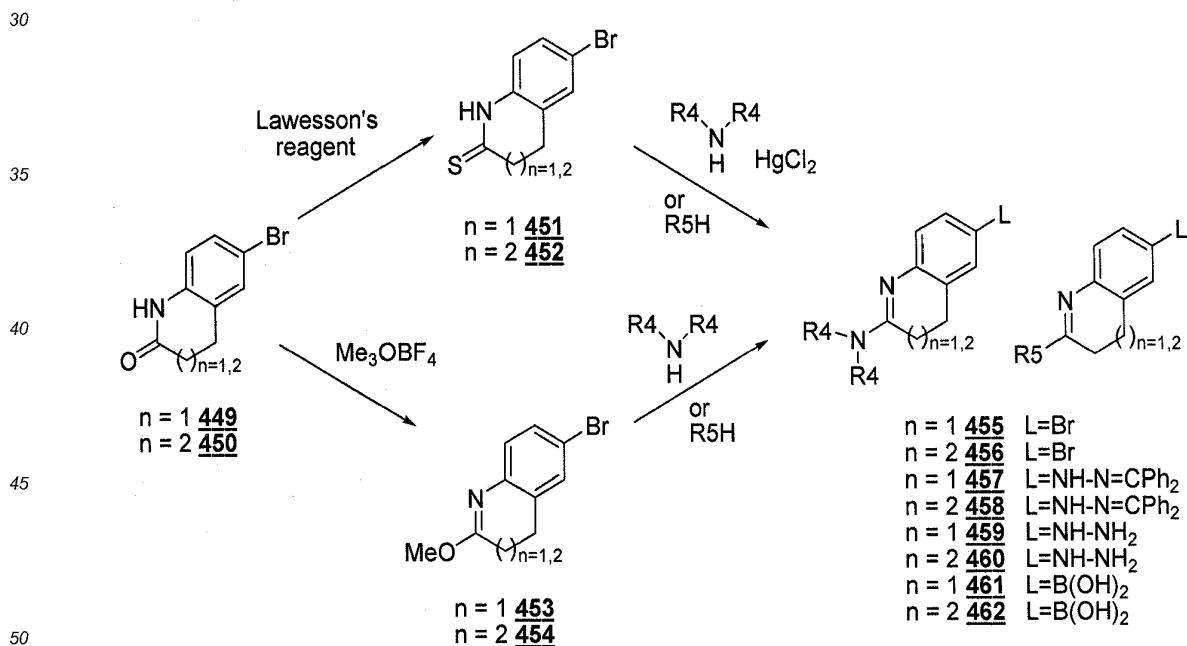
Scheme 69



## A2-84 and A2-106

25 [0085] The preparation of intermediates containing A2-84 or A2-106 is illustrated in Scheme 70. 449 and 450 are converted into intermediates 451 to 462 using methods described above in Scheme 67.

Scheme 70

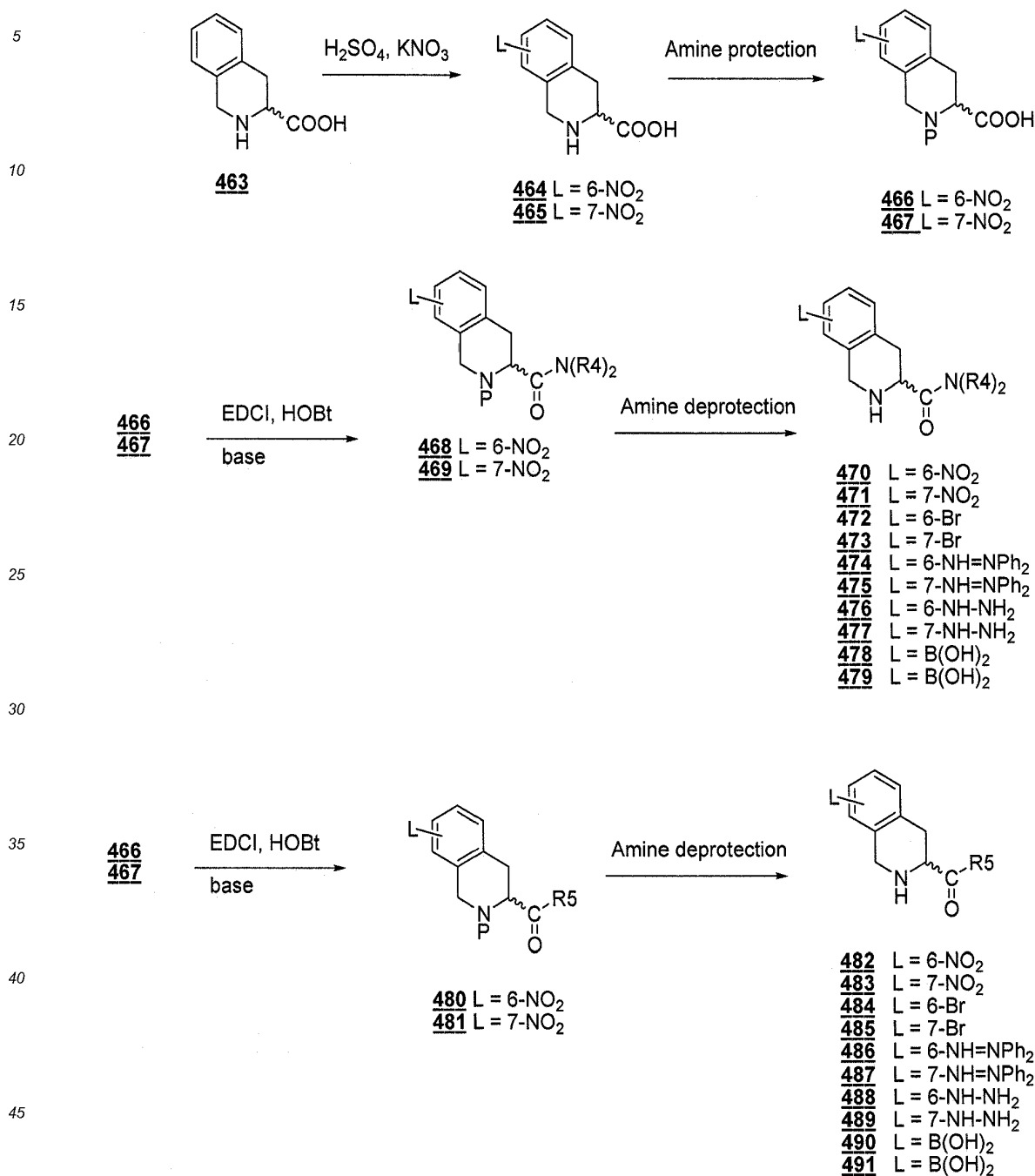


## A2-85 AND A2-86

55 [0086] The preparation of intermediates containing A2-85 or Ar-86 is illustrated in Scheme 71. 463 (1,2,3,4-tetrahydroisquinoline-3-carboxylic acid) is commercially available in each enantiomeric form and as a racemic mixture. Nitration of 463 with sulfuric acid and potassium nitrate gives a mixture of 6- and 7- nitrated compounds 464 and 465. According to the literature (Bioorg. Med. Chem. Lett. 2002, 10, 3529-3544), these compounds are separated from each other by derivative crystallization. N-protection with a standard amine protecting group gives 466 and 467, respectively. Amide

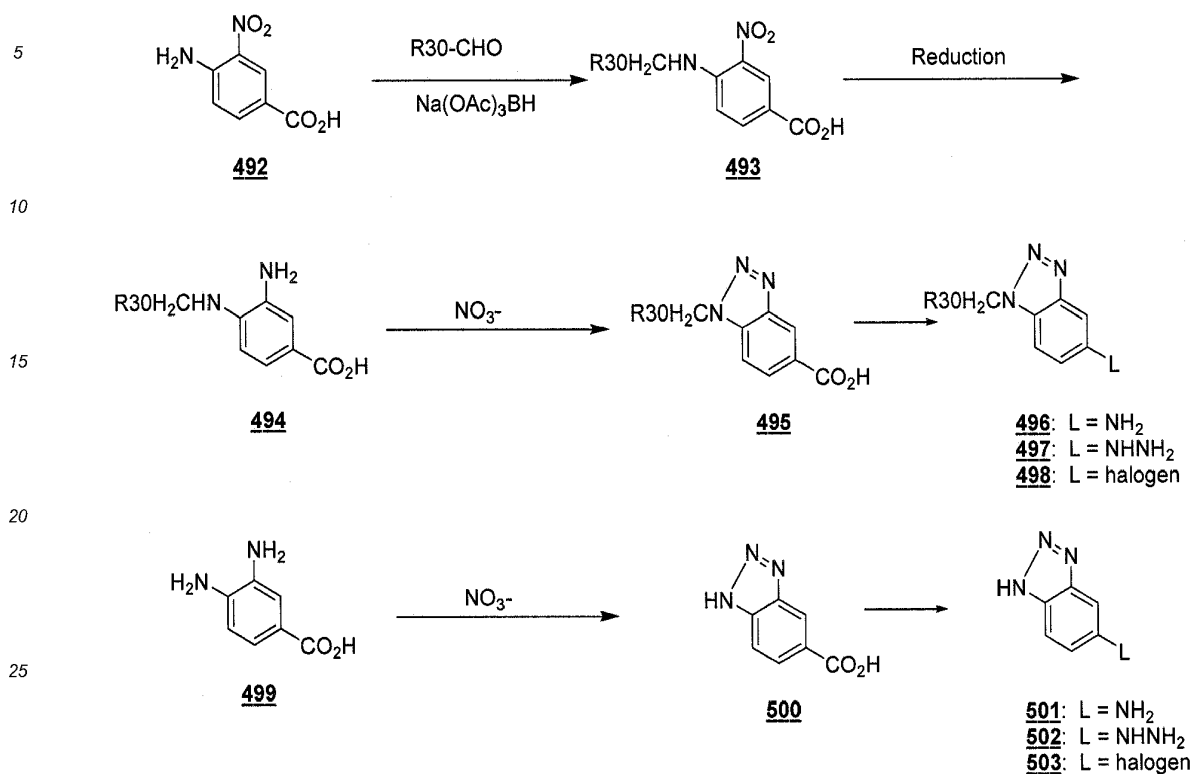
formation by reacting 466 or 467 with amines  $\text{HN(R}_4)_2$  or  $\text{HR}_5$  (fix scheme 71) by employing an acid-activating reagent, preferably EDCI/HOBt in the presence of base, preferably triethylamine, afford amides 468, 469, 480 and 481. Deprotection of the amine protecting group gives rise to nitro compounds 470, 471, 482 and 483. The bromides 472, 473, 484 and 485 are obtained by hydrogenation of the nitro group and subsequent Sandmeyer reaction via a diazotization/CuBr reaction sequence. 474, 475, 486 and 487 are prepared by palladium-catalyzed bromide substitution with benzophenone hydrazone as described by Haddad et al. (Tetrahedron Lett. 2002, 43, 2171-2173). 474, 475, 486 and 487 are either directly implemented by reaction with a suitable A1-containing intermediate, or, if required, first hydrolyzed to hydrazines 476, 477, 488 and 489, respectively, under acidic conditions. The bromide functionalities in 470, 471, 482 and 483 are substituted by a boronic acid affording 478, 479, 490 and 491. The bromide is transformed into an organometallic species such as a grignard compound and subsequently reacted with trimethyl borate to afford 478, 479, 490 and 491 after acid hydrolysis. In cases where R4 or R5 functionalities prohibit the use of organometallic reagents, the boronic acids are mildly formed from the bromides by utilizing a procedure employing bis(pinacolato)diboron and Pd(dppf).

Scheme 71

**A2-95**

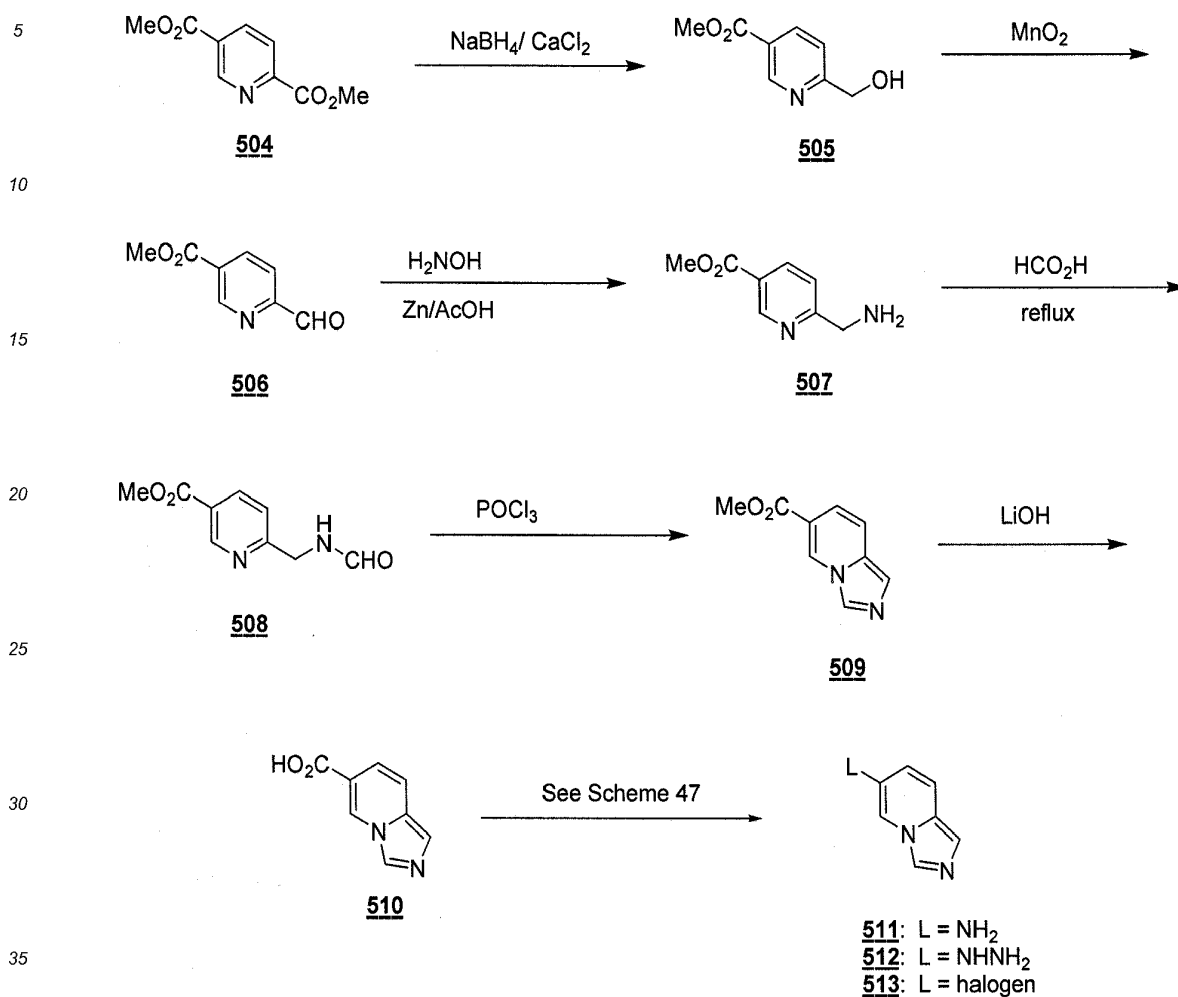
[0087] The synthesis of intermediates containing A2-95 is illustrated in Scheme 72. Commercially available substituted benzoic acid **492** is optionally subjected to a reductive amination reaction employing readily available aldehydes R30-CHO and sodium triacetoxyborohydride to give **493**. Reduction of the nitro functionalities of **492** or **493** afford the amines **494** and **499**. Conversion of **494** or **499** to the benzotriazoles **495** or **500**, respectively, is effected by treatment with NO<sub>3</sub> anion as described in WO 04/041274. Conversion of **495** or **500** to substituted amines **496** or **501**, hydrazines **497** or **502**, or halides **498** or **503** is accomplished using conditions described in Scheme 47.

Scheme 72

**A2-96**

**[0088]** The synthesis of intermediates containing A2-96 is illustrated in Scheme 73. Commercially available pyridine diester **504** is reacted with sodium borohydride/calcium chloride to give the selective reduction product **505** (P. Potier et al. Tetrahedron 1975, 31, 419-422). Oxidation of the alcohol functionality of **505**, preferably with MnO<sub>2</sub>, gives aldehyde **506**. Oxime formation, followed by reduction with zinc/acetic acid, gives pyridinemethanamine **507** (M. Ohta et al. Chem. Pharm. Bull. 1996, 44 (5), 991-999). Intermediate **507** is converted to its formamide **508**, which is subjected to cyclodehydration with POCl<sub>3</sub> to give the imidazopyridine ester **509** (Q. Li et al. Bioorg. Med. Chem. Lett. (2002) 12, 465-469). Hydrolysis of the ester **509** affords acid **510**. Acid **510** is converted to the amine **511**, hydrazine **512**, or halide **513** using conditions described in Scheme 47.

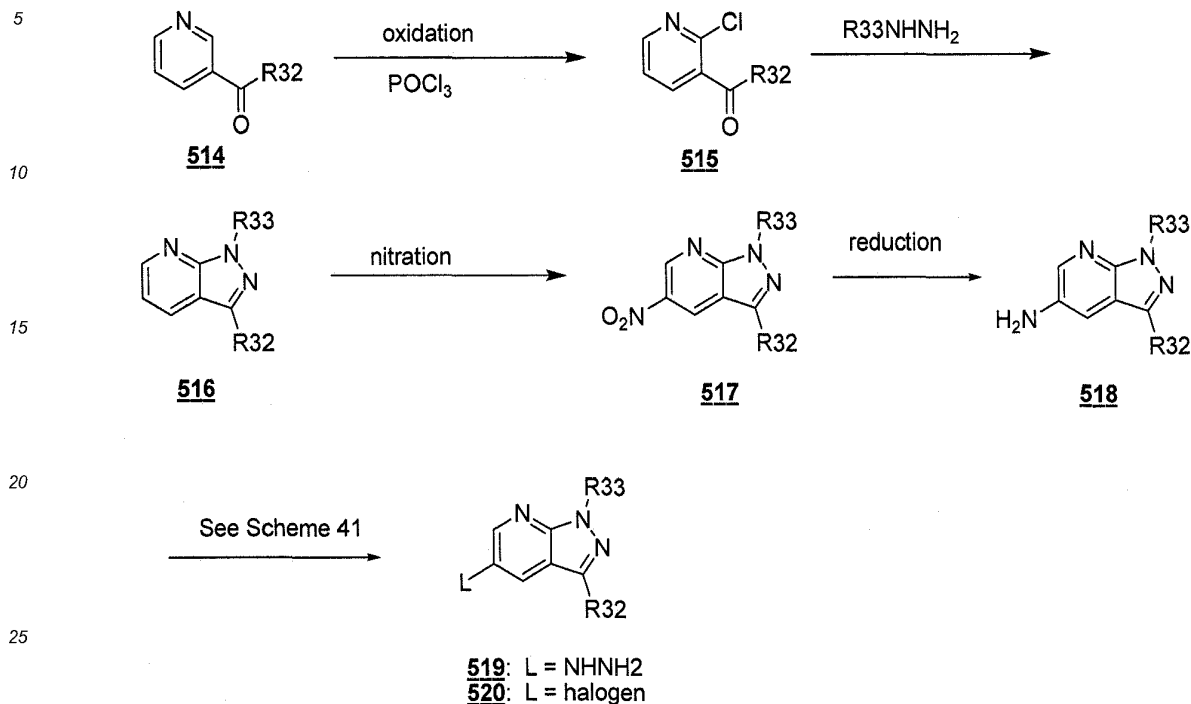
Scheme 73



## A2-97

[0089] The synthesis of intermediates containing A2-97 is illustrated in Scheme 74. Readily available 3-acylpyridines 514, wherein R32 is a substituent which conforms to the definition of a protected or unprotected Z1 moiety, are converted to the 2-chloropyridines 515 as reported in Can. J. Chem. (1988) 66: 420-428. Displacement of the chloro substituent in 515 with various hydrazines, wherein R33 conforms to the definition of a protected or unprotected Z4 moiety, followed by *in situ* cyclization, gives pyrazolylpyridines 516. Nitration of 516 under standard conditions gives 517, which are subjected to reduction to afford the amino-substituted pyrazolylpyridines 518. Conversion of 518 to hydrazines 519 or halides 520 is effected as described in Scheme 41.

Scheme 74



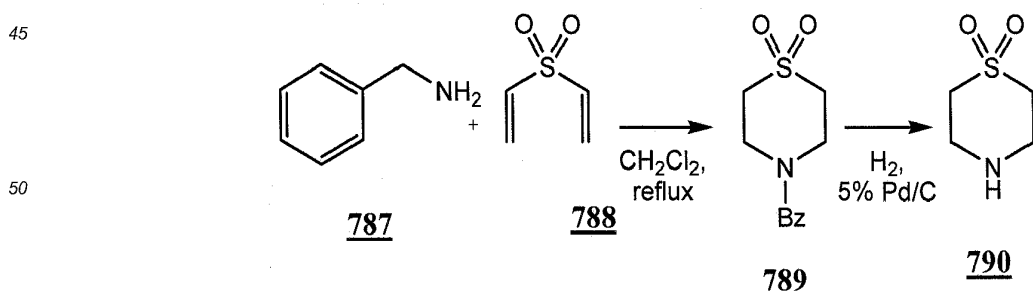
### III. Synthesis of other intermediates

#### Synthesis of R5 intermediates

**[0090]** When R5 is pyrrolidine (R5-1) [CAS 123-75-1], piperidine (R5-2) [CAS 110-98-4], azepine [CAS 11-49-9], morpholine (R5-3) [CAS 110-91-8] or thiomorpholine (R5-4) [CAS 123-90-0], these materials are purchased from a number of commercial sources. When R5 is 2-substituted pyrrolidine (R5-12), 2-substituted piperidine (R5-13), HN(CH<sub>2</sub>CON(R<sub>4</sub>))<sub>2</sub> (R5-14), HN(CH<sub>2</sub>CO<sub>2</sub>R<sub>4</sub>)<sub>2</sub> (R5-15), or 4-substituted oxazolidinone (R5-16), these are prepared from commercially available precursors using standard methods and performed by one of ordinary skill in the art.

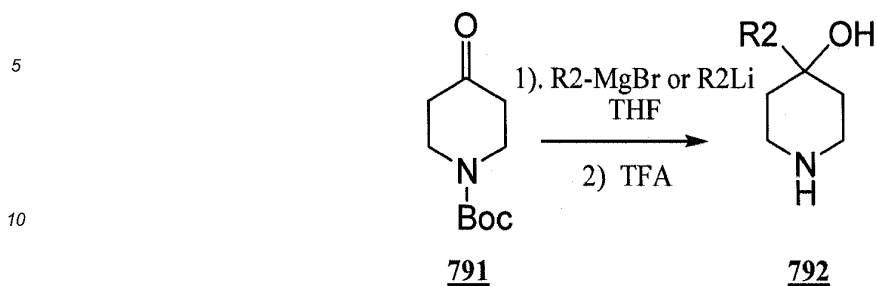
**[0091]** When R5 is thiomorpholinsulphone (R5-5) [790, CAS 39093-93-1], the synthesis is shown in Scheme 114. Benzylamine **787** and divinylsulphone **788** are reacted together in refluxing methylenechloride to yield benzyl-protected thiomorpholinesulphone **789**, which upon hydrogenation yields **790**.

Scheme 114



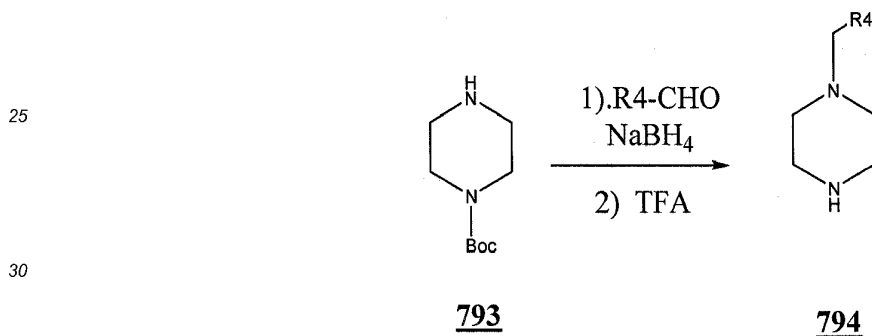
**[0092]** When R5 is 4-alkyl-4-piperdinol (R5-6), the synthesis proceeds as shown in Scheme 115. Commercially available N-Boc-4-piperdone is reacted with the requisite Grignard or alkyl lithium reagent to yield N-Boc-4-alkyl-4-piperdinol **791**, which is readily deprotected to yield species of type **792**.

Scheme 115



15 **[0093]** When  $R_5$  is 4-N-alkylpiperazine ( $R_5\text{-7}$ ), the synthesis proceeds as shown in Scheme 116. Commercially available N-Boc-piperazine is reacted with a suitable aldehyde under reductive amination conditions followed by deprotection to yield species of type **794**. When  $R_4$ =phenyl [CAS 92-54-6], the synthesis proceeds as published by Bloomer *et al* (see BioOrg. Med. Chem. Lett., 2001, 11(14), 1925).

Scheme 116

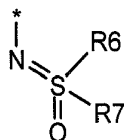


#### Synthesis of Z1, Z2, and Z4 intermediates

35 **[0094]** The syntheses of five-membered heterocycle intermediates Z1, Z2, and Z4 corresponding to Z1-1 through Z1-21, Z2-1 through Z2-21, and Z4-1 through Z4-21 are performed as described in U.S. Continuation-In-Part Application: ANTI-INFLAMMATORY MEDICAMENTS; Docket No. 34477CIP, attached by reference herein.

#### Synthesis of sulfoximes

40 **[0095]** The Syntheses of sulfoxime moieties



50 is accomplished using the method reported by Cho, G. Y., et al, Organic Letters (2004) 6: 3293-3296.

#### General methods

55 **[0096]** General method A: To a stirring suspension of the starting pyrazole amine (0.5mmol, 1.0 eq) in dry THF (2.0 ml) was added pyridine (5.0 mmol, 10.0 eq). The resulting slurry was stirred at RT for 1h, treated with the appropriate isocyanate (1.0 mmol, 2.0 eq) and stirred overnight at RT. The reaction was diluted with EtOAc and 1M HCl (10 ml) and the layers separated. The aqueous was extracted with EtOAc (2x), and the combined organic extracts were washed with  $\text{H}_2\text{O}$  (1x), satd.  $\text{NaHCO}_3$  (1x) and brine (2x), dried ( $\text{MgSO}_4$ ), filtered, concentrated, and purified via column chro-



matography to yield the target compound.

**[0097] General method B:** A solution of the starting pyrazole amine (0.5 mmol, 1.0 eq), triethylamine (2.0 eq) and CDI (2.0 eq) in DMF (5.0 mL) was stirred at RT for 6h. The appropriate amine (1.0 mmol, 2 eq) was added and the solution was stirred at RT for 5h, then poured into H<sub>2</sub>O (50 mL). The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x50 mL) and the combined organic extracts were washed with 1N HCl, brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, concentrated and purified by preparative TLC to afford the target compound.

**[0098] General method C:** To a stirred solution of the starting ester (0.23 mmol, 1.0 eq) in THF (5 mL) was added LiAlH<sub>4</sub> powder (18 mg, 0.5 mmol) portionwise at 0 °C under N<sub>2</sub>. The mixture was stirred at RT for 2h, quenched with H<sub>2</sub>O, and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated to yield the crude product, which was purified either by preparative TLC or column chromatography to afford the target compound.

**[0099] General method D:** To a solution of the starting pyrazole amine (1 eq) in EtOAc were added 2,2,2-trichloroethylchloroformate (1.1 eq) and saturated NaHCO<sub>3</sub> (2-3 eq) at 0 °C. After stirring for 3h at RT, the layers were separated and the aqueous layer extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under vacuum to yield the crude TROC carbamate of the pyrazole amine. To the carbamate (1 eq) in DMSO were added diisopropylethylamine (2 eq), the appropriate amine (2 eq) and the mixture was stirred at 60 °C for 16h or until all the starting carbamate was consumed. Water was added to the mixture and the product was extracted with EtOAc (2x25 mL). The combined organic extracts were washed with brine solution, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to yield crude product, which was purified by column chromatography to yield the target compound.

**[0100] General method E:** A mixture of the starting ester (1 eq) in an aqueous solution of LiOH (2N, 5 mL) and THF (10 mL) was stirred overnight at RT. After removal of the organic solvent, the mixture was extracted with Et<sub>2</sub>O. The aqueous layer was then acidified with 2N HCl to pH 4 and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated to give the crude product, which was purified by reverse phase chromatography to afford the target acid.

**[0101] General method F:** To the starting Boc-protected amine dissolved in EtOAc (5 mL) was added 3N HCl/EtOAc (6 mL). The solution was stirred at RT for 3h. The solid was filtered and dried under vacuum to obtain the target amine as the HCl salt.

**[0102] General method G:** To the starting trifluoroacetamide protected amine dissolved in MeOH (2 mL) was added 2N sodium hydroxide solution (2 mL) and the resulting mixture was stirred at RT for 5 h. The solution was further basified with 2N NaOH (20 mL) and the mixture was extracted with ether (3x20 mL) and subsequently with 1-butanol (3x20 mL). The combined butanol extracts were concentrated and dried to yield the deprotected amine. **General method H:** To a suspension of the amine (150 mg, 0.67 mmol) in EtOAc (2 mL) was added aqueous 1N NaOH. The reaction mixture was cooled to 0 °C and treated with isopropenyl chloroformate (0.1 mL, 0.94 mmol) over 30 sec. The reaction mixture was stirred 15 min at 0 °C and 1h at RT. The reaction was poured into THF-EtOAc (1:1; 40 mL) and washed with H<sub>2</sub>O (2x10 mL) and brine (2x10 mL). The organics were dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated and the residue purified via column chromatography to provide the target (prop-1-en-2-yl)carbamate.

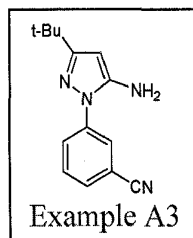
**[0103] General method I:** PyBop (0.11 g, 0.22 mmol) was added to a solution of a starting acid (typically 0.2 mmol) in DMF (1 mL) and was stirred for 5 min at RT. To this mixture was added the appropriate amine (either neat or 1mL of 0.5 M dioxane solution) and the resulting solution stirred for 5h and was followed by the addition of 3M HCl (2mL), water (15 mL) and the aqueous extracted with EtOAc (2x20 mL). The combined organic extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, concentrated and purified via column chromatography to yield the amide.

**[0104] General method J:** To a solution of a starting acid (typically 0.21 mmol) in DMF (2 mL) was added NH<sub>4</sub>Cl (56 mg, 1 mmol) or the appropriate amine, i-Pr<sub>2</sub>NEt (110 mg, 0.84 mmol), EDC (60 mg, 0.31 mmol) and HOBt (48 mg, 0.31 mmol). The mixture was stirred at RT for 6h, then diluted with EtOAc (30 mL). The organic extracts were washed with water (2x25 mL) and brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to afford the target amide.

**[0105] General method K:** To a stirring suspension of a starting acid (typically 0.11 mmol), and the appropriate amine (1.5 eq, either neat or in a 0.5 M dioxane solution) and TBTU (1.5 eq) in DMF (1.1 mL) was added i-Pr<sub>2</sub>NEt (5.0 eq). The resulting solution was stirred at RT overnight and was then diluted with H<sub>2</sub>O (11 mL) and extracted with EtOAc (3x). The combined organics were washed with 1M HCl (1x), satd Na<sub>2</sub>CO<sub>3</sub> (2x), dried (MgSO<sub>4</sub>), filtered and evaporation to provided the target amide.

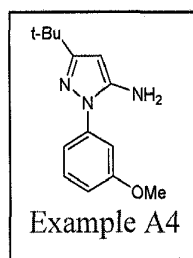
**[0106] General method L:** NaH (2.3 g of a 60% dispersion, 57 mmol) was activated by washing with hexanes (3x15 mL). THF (20 mL) was added and heated to 80 °C. At this point a solution of the appropriate ester (19 mmol) and MeCN (0.91 g, 21 mmol) in THF (40 mL) was added slowly via syringe. After stirring about 30 min a vigorous reaction was observed and soon the color of the reaction turned to dark blue and it was stirred for 10 more min. The reaction mixture was then poured into a biphasic mixture of ice cold 5% HCl (100 mL) and EtOAc (100 mL). The organic layer was separated and aqueous layer was extracted with EtOAc (1x50 mL). The combined organic extracts were washed with brine, dried (MgSO<sub>4</sub>) and concentrated to afford the desired 3-oxo-3-substituted-propanenitrile which was used as is in the next reaction.

**[0107]** General method M: To a suspension of the appropriate aniline (1.05 g, 6.95 mmol) in conc. HCl (3 mL) was added a solution of NaNO<sub>2</sub> (0.57 g, 8.34 mmol) in H<sub>2</sub>O (3 mL) at 0 °C slowly. After stirring for 1h, to the mixture was added SnCl<sub>2</sub>·2H<sub>2</sub>O (2.98 g, 14 mmol) dissolved in conc. HCl (3 mL) at such a rate that the temperature of the mixture was not allowed to cross 5 °C. After stirring for 2h, a solution of the appropriate 3-oxo-3-substituted-propanenitrile (8 mmol; general method L or commercially available) in EtOH (10 mL) was added and the mixture was heated at 60 °C for 16h. The mixture was cooled to RT and the solvent was removed under vacuum. The residue was basified with solid NaHCO<sub>3</sub> and the product was extracted with ethyl acetate (2x50 mL). The combined organic extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under vacuum to yield the desired pyrazole amine.

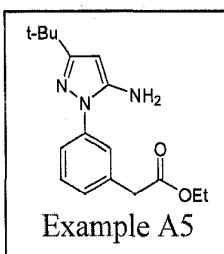


To a solution of Example A1 (14.4 g, 50 mmol) and formamide (4.5 g, 0.1 mol) in DMF (50 mL) was added NaOMe (5.4 g 0.1 mol) at RT. The mixture was stirred at 100 °C for 2h, concentrated and the residue dissolved in EtOAc (150 mL). The organic layer was washed with H<sub>2</sub>O and brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and purified by column chromatography to afford 3-(5-amino-3-*t*-butyl-1*H*-pyrazol-1-yl)benzamide (6 g, 48 % yield).

**[0108]** A solution of 3-(5-amino-3-*t*-butyl-1*H*-pyrazol-1-yl)benzamide (5.2 g, 20 mmol) in SOCl<sub>2</sub> (50 mL) was heated at reflux for 6h. After removal of the solvent, the residue was dissolved in EtOAc (100 mL). The organic layer was washed with saturated NaHCO<sub>3</sub> and brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and purified by column chromatography to afford 3-(5-amino-3-*t*-butyl-1*H*-pyrazol-1-yl)benzonitrile (3.5 g, 73% yield).



To a solution of commercially available 3-methoxyphenylhydrazine hydrochloride (1.0 g, 5.7 mmol) in toluene (5 mL) was added commercially available pivaloylacetone nitrile (0.70 g, 5.5 mmol). The reaction mixture was heated at reflux for 5h, filtered and washed with hexane to obtain 3-*t*-butyl-1-(3-methoxyphenyl)-1*H*-pyrazol-5-amine (1.22 g, 89% yield) as its hydrochloride salt as a pale yellow solid which was used without further purification. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.35 (t, *J* = 8.4 Hz, 1H), 7.04 (t, *J* = 2.1 Hz, 1H), 7.00 (dd, *J* = 1.5 and 7.5 Hz, 1H), 6.95 (dd, *J* = 2.1 and 8.4 Hz, 1H), 5.90 (brs, 2H), 5.83 (s, 1H), 3.81 (s, 3H), 1.89 (s, 9H); MS (EI) *m/z*: 246 (M+H<sup>+</sup>).



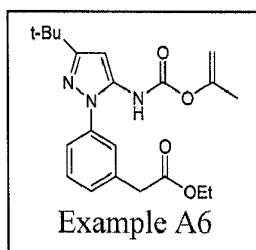
A mixture of 1-(3-nitrophenyl)ethanone (82.5 g, 0.5 mol), *p*-TsOH (3 g) and sulfur (32 g, 1.0 mol) in morpholine (100 mL) was heated at reflux for 3h. After removal of the solvent, the residue was dissolved in dioxane (100 mL). The mixture was treated with conc. HCl (100 mL) and then heated at reflux for 5h. After removal of the solvent, the residue was

extracted with EtOAc (3x150 mL). The combined organic extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated. The residue was dissolved in EtOH (250 mL) and SOCl<sub>2</sub> (50 mL) and heated at reflux for 2h. After removal of the solvent, the residue was extracted with EtOAc (3x150 mL). The combined organic extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, concentrated and purified via column chromatography to afford ethyl (3-nitrophenyl)acetate (40 g). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 8.17 (s, 1H), 8.11 (d, *J* = 7.2 Hz, 1H), 7.72 (d, *J* = 7.2 Hz, 1H), 7.61 (t, *J* = 7.8 Hz, 1H), 4.08 (q, *J* = 7.2 Hz, 2H), 3.87 (s, 2H), 1.17 (t, *J* = 7.2 Hz, 3H).

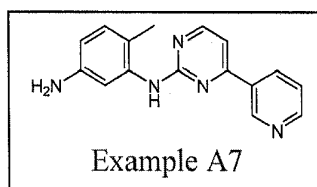
**[0109]** A mixture of ethyl (3-nitrophenyl)acetate (21 g, 0.1 mol) and 10% Pd/C (2 g) in MeOH (300 mL) was stirred at RT under H<sub>2</sub> 40 (psi) for 2h. The reaction mixture was filtered and the filtrate was concentrated to afford ethyl (3-aminophenyl)acetate (17 g). MS (ESI) *m/z*: 180 (M+H<sup>+</sup>).

**[0110]** To a suspension of (3-aminophenyl)acetic acid (17 g, 94 mmol) in conc. HCl (50 mL) was added dropwise a solution of NaNO<sub>2</sub> (6.8 g, 0.1 mol) in H<sub>2</sub>O at 0 °C. The mixture was stirred for 1h, after which a solution of SnCl<sub>2</sub>·2H<sub>2</sub>O (45 g, 0.2 mol) in conc. HCl was added dropwise at such a rate that the reaction mixture never rose above 5 °C. The resulted mixture was stirred for 2h. The precipitate was collected by suction, and washed with Et<sub>2</sub>O to afford ethyl (3-hydrazinophenyl)acetate (15 g). MS (ESI) *m/z*: 195 (M+H<sup>+</sup>).

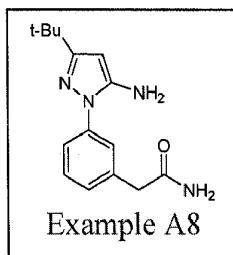
**[0111]** A solution of ethyl (3-hydrazinophenyl)acetate (15 g, 65 mmol) and 4,4-dimethyl-3-oxopentanenitrile (12.5 g, 0.1 mol) in EtOH (100 mL) containing conc. HCl (25 mL) was heated at reflux overnight. After removal of the solvent, the residue was washed with Et<sub>2</sub>O to afford ethyl 2-(3-(5-amino-3-*t*-butyl-1*H*-pyrazol-1-yl)phenyl)acetate (18 g). MS (ESI) *m/z*: 302 (M+H<sup>+</sup>).



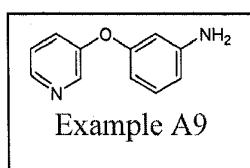
Using general method H, Example A5 (1.08 g, 3.18 mmol) was transformed to ethyl 2-(3-(3-*t*-butyl-5-((prop-1-en-2-yloxy)carbonyl)-1*H*-pyrazol-1-yl)phenyl)acetate (1.23 g, 100 % yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.50-7.32 (m, 4H), 6.80-6.48 (brs, 1H), 4.81 (brs, 1H), 4.75 (s, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.70 (s, 2H), 1.98 (brs, 3H), 1.36 (s, 9H), 1.29 (t, *J* = 7.1 Hz, 3H); MS (ESI) *m/z*: 386.2 (M+H<sup>+</sup>).



To a solution of N-(3-amino-4-methylphenyl)acetamide (5 g, 25 mmol, commercially available) in DMF (5 mL) was added 2-chloro-4-(pyridin-3-yl)pyrimidine (4 g, 35 mmol, commercially available) and KI (0.5 g, 3 mmol). After stirring at 100 °C overnight, the reaction mixture was cooled to 10 °C, quenched with H<sub>2</sub>O, (100mL), extracted with CH<sub>2</sub>Cl<sub>2</sub> (2x100 mL) and the combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. The residue was dissolved in conc. HCl (10 mL), stirred at 80 °C for 2h, and then concentrated to yield 6-methyl-N<sup>1</sup>-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-diamine hydrochloride (4.5 g, 65% yield) as the HCl salt. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.93-7.96 (m, 2H), 7.50-7.47 (m, 1H), 7.47-7.41 (m, 5H), 7.25-7.27 (m, 2H), 2.21(s, 3H); MS (ESI) *m/e*: 277 (M+H<sup>+</sup>).

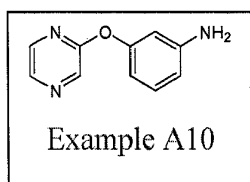


To a solution of Example A5 (6.0 g, 20 mmol) and formamide (1.8 g, 40 mmol) in DMF (20 mL) was added NaOMe (2.1 g, 40 mmol) at RT. The mixture was heated at reflux for 1h, concentrated and the residue was purified via column chromatography to afford 2-[3-(5-amino-3-tert-butyl-1H-pyrazol-1-yl)phenyl]acetamide (2.0 g, 40% yield). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 7.44-7.31 (m, 4H), 7.11 (m, 1H), 6.87 (brs, 1H), 5.33 (s, 1H), 5.12 (s, 2H), 3.38 (s, 2H), 1.17 (s, 9H); MS (ESI) *m/z*: 273 (M+H<sup>+</sup>).



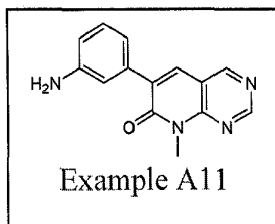
To a solution of 3-hydroxypyridine (5.01 g, 52.7 mmol) in DMSO (60 mL) was added NaH (1.39 g, 57.9 mmol, 2.31 g of 60% suspended in oil) and stirred for 30 min at RT. To the slurry was added 1-fluoro-3-nitrobenzene (9.66 g, 68.5 mmol) and mixture was heated to 80 °C for 72h. The mixture was poured into satd NH<sub>4</sub>Cl solution (200 mL), and extracted with EtOAc (3x125 mL). The combined organic extracts were washed with H<sub>2</sub>O (75 mL), brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to yield a crude residue which was purified by column chromatography afford (4.43 g, 39% yield) pure 3-(3-nitrophenoxy)pyridine as a syrup. <sup>1</sup>H NMR (400 MHz, Acetone-*d*<sub>6</sub>): δ 8.49-8.47 (m, 2H), 8.07-8.05 (m, 1H), 7.85 (t, *J* = 2.4 Hz, 1H), 7.74 (t, *J* = 8.4 Hz, 1H), 7.58-7.53 (m, 2H), 7.51-7.47 (m, 1H); MS (ESI) *m/z*: 217.0 (M+H<sup>+</sup>).

**[0112]** To a solution of 3-(3-nitrophenoxy)pyridine (4.43 g, 20.5 mmol) in EtOAc (50 mL) was added PtO<sub>2</sub> (0.4g) and the mixture was stirred at RT overnight under H<sub>2</sub> (1 atm). The mixture was filtered through Celite®, the Celite® washed with EtOAc (2x20 mL) and the combined filtrates concentrated to yield (3.77 g, 99% yield) pure 3-(pyridin-3-yloxy)benzenamine as a syrup. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.34-8.32 (m, 2H), 7.40-7.39 (m, 2H), 7.02 (t, *J* = 8.0 Hz, 1H), 6.37-6.35 (m, 1H), 6.02-6.14 (m, 2H), 5.28 (brs, 2H); MS (ESI) *m/z*: 187.0 (M+H<sup>+</sup>).



To a solution of 3-nitrophenol (0.151 g, 0.733 mmol) in DMSO (5 mL) was added NaH (35 mg of a 60% dispersion, 0.88 mmol) at 0 °C under Ar atmosphere. After stirring for 30 min, 2-iodopyrazine (0.133 mg, 0.953 mmol) was added and mixture heated to 85 °C for 4h. To the mixture was added satd. NH<sub>4</sub>Cl solution (25 mL) and the product extracted with EtOAc (2x25 mL). The combined organic extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to yield a crude residue which was purified by column chromatography to afford (97 mg, 61% yield) 2-(3-nitrophenoxy)pyrazine as a white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.53 (brs, 1H), 8.38 (d, *J* = 2.4 Hz, 1H), 8.16- 8.09 (m, 3H), 7.63 (t, *J* = 8.0 Hz, 1H), 7.57-7.54 (m, 1H); MS (ESI) *m/z*: 218.0 (M+H<sup>+</sup>).

**[0113]** To a solution of 2-(3-nitrophenoxy)pyrazine (97 mg, 0.45 mmol) in EtOAc (10 mL) was added PtO<sub>2</sub> (10 mg) and the mixture was stirred for 4h under H<sub>2</sub> (1 atm). The mixture was filtered through Celite® and the Celite® was washed with EtOAc (2x5 mL). The combined filtrates were concentrated to yield (78 mg, 93%) 3-(pyrazi-yloxy)benzenamine as a solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.44 (d, *J* = 1.6 Hz, 1H), 8.35 (d, *J* = 2.4 Hz, 1H), 8.23-8.22 (m, 1H), 7.04 (t, *J* = 8.0 Hz, 1H), 6.43 (dd, *J* = 8.0 Hz, and 2.0 Hz, 1H), 6.31 (t, *J* = 2.0 Hz, 1H), 6.26 (dd, *J* = 8.0 Hz, 2.0 Hz, 1H), 5.27 (brs, 2H); MS (ESI) *m/z*: 188.1 (M+H<sup>+</sup>).



5

10 To a solution of 2-ethoxymethylenemalononic acid diethyl ester (59.0 g, 273 mmol) in EtOH (300 mL) was added 2-methyl-  
isothiourea (41.5 g, 150 mmol) in an ice-H<sub>2</sub>O bath. An EtOHic solution of EtONa (2M, 300 mL) was added dropwise  
maintaining the reaction temperature under 5 °C. The mixture was warmed to RT and stirred for 3h. After standing  
overnight, the solvent was removed under reduced pressure and the residue was dissolved in H<sub>2</sub>O (800 mL) at 0 °C.  
The solution was acidified to pH 3 with conc. HCl and the precipitate collected by filtration and air-dried to yield 4-hydroxy-  
2-methylsulfanyl-pyrimidine-5-carboxylic acid ethyl ester as a white solid (50.8 g, 87.6% yield). <sup>1</sup>H NMR (400 MHz,  
DMSO-*d*<sub>6</sub>): δ 8.48 (s, 1H), 4.20 (q, *J* = 9.6 Hz, 2H), 2.51 (s, 3H), 1.23 (t, *J* = 9.6 Hz, 3H).

15 **[0114]** A mixture of 4-hydroxy-2-(methylsulfanyl)pyrimidine-5-carboxylic acid ethyl ester (50 g, 0.234 mmol), POCl<sub>3</sub>  
(110 mL, 1.17 mmol) and diethylaniline (70 mL, 0.28 mmol) was refluxed for 5h. The solvent was removed under vacuum  
and the residue was dissolved in ice H<sub>2</sub>O and cautiously neutralized with aqueous NaHCO<sub>3</sub>. After extraction with EtOAc  
(3x400 mL), the organic extracts were combined, dried and concentrated to give 4-chloro-2-(methylsulfanyl)pyrimidine-  
5-carboxylic acid ethyl ester as a yellow solid (42 g, 77% yield). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.92 (s, 1H), 4.41 (q, *J* =  
7.2 Hz, 2H), 1.40 (t, *J* = 7.2 Hz, 3H).

20 **[0115]** To a solution of 4-chloro-2-(methylsulfanyl)pyrimidine-5-carboxylic acid ethyl ester (42 g, 0.181 mol) in EtOH  
(400 mL) was added MeNH<sub>2</sub> (12.3 g, 0.398 mmol) in EtOH (100 mL) at 0 °C and the mixture stirred for 3h. The mixture  
was concentrated to remove most of the solvent and then partitioned between H<sub>2</sub>O (200 mL) and CH<sub>2</sub>Cl<sub>2</sub> (500 mL). The  
organic layer was washed with brine, dried and concentrated to give 4-(methylamino)-2-(methylsulfanyl)pyrimidine-5-  
carboxylic acid ethyl ester as a white solid (36.0 g, 88% yield). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.59 (s, 1H), 8.18 (brs,  
1H), 4.31 (q, *J* = 7.2 Hz, 2H), 3.05 (d, *J* = 4.8 Hz, 3H), 2.52 (s, 3H), 1.34 (t, *J* = 7.2 Hz, 3H).

30 **[0116]** To a solution of 4-(methylamino)-2-(methylsulfanyl)pyrimidine-5-carboxylic acid ethyl ester (30 g, 132 mmol)  
in THF (300 mL) was added LiAlH<sub>4</sub> powder (7.5 g, 198 mmol) at RT. After 1h, the reaction was carefully quenched with  
H<sub>2</sub>O (10 mL) and 10% NaOH (7 mL). The mixture was stirred for 1h and then filtered. The filtrate was concentrated to  
give crude (4-(methylamino)-2-(methylthio)pyrimidin-5-yl)methanol (22.0 g, 90% yield), which was used in the next  
reaction without further purification. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 7.79 (s, 1H), 6.79 (m, 1H), 5.04 (t, *J* = 5.4 Hz, 1H),  
4.27 (d, *J* = 5.4 Hz, 2H), 2.83 (d, *J* = 4.8 Hz, 3H), 2.40 (s, 3H).

35 **[0117]** A mixture of (4-(methylamino)-2-(methylthio)pyrimidin-5-yl)methanol (22.0 g, 119 mmol) and MnO<sub>2</sub> (44 g, 714  
mmol) in CHCl<sub>3</sub> (300 mL) was stirred at RT for 3h. The reaction was filtered and the filtrate concentrated to give 4-(meth-  
ylamino)-2-(methylsulfanyl)pyrimidine-5-carbaldehyde as a pale solid (20 g, 92% yield). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  
δ 9.71 (s, 1H), 8.60 (brs, 1H), 8.49 (s, 1H), 2.96 (d, *J* = 4.8 Hz, 3H), 2.48 (s, 3H).

40 **[0118]** To a solution of 4-(methylamino)-2-(methylsulfanyl)pyrimidine-5-carbaldehyde (10.0 g, 55 mmol) and (3-nitro-  
phenyl)acetonitrile (10.5 g, 65 mmol) in DMF (150 mL) was added K<sub>2</sub>CO<sub>3</sub> (38 g, 275 mmol) at RT. The mixture was  
stirred at 100 °C for 18h. After cooling, the reaction was diluted with DMF (50 mL) and filtered. The filtrate was concentrated  
to give crude 8-methyl-2-(methylsulfanyl)-6-(3-nitrophenyl)-8H-pyrido[2,3-*d*]pyrimidin-7-ylideneamine (9.0 g, 50% yield)  
which was used in the next reaction without further purification.

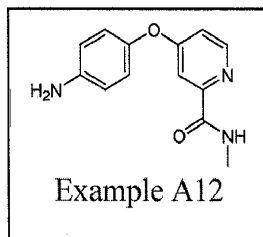
45 **[0119]** A solution of 8-methyl-2-(methylsulfanyl)-6-(3-nitrophenyl)-8H-pyrido[2,3-*d*]pyrimidin-7-ylideneamine (9.0 g,  
crude product) in Ac<sub>2</sub>O (100 mL) was refluxed for 20 min. The mixture was concentrated to give a brown solid. The solid  
was then dissolved in conc. HCl (50 mL) and heated for 30 min. The reaction mixture was cooled and filtered to give a  
brown solid, which was purified by reverse phase chromatography to give 8-methyl-(2-methylsulfanyl)-6-(3-nitrophenyl)-  
8H-pyrido[2,3-*d*]pyrimidin-7-one as a white solid (1.1 g, 21% yied, two steps). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 8.95 (s,  
1H), 8.60 (m, 1H), 8.34 (s, 1H), 8.25 (d, *J* = 5.4 Hz, 1H), 8.16 (d, *J* = 5.1 Hz, 1H), 7.75 (t, *J* = 5.4 Hz, 1H), 3.68 (t, *J* =  
5.4 Hz, 3H), 2.62 (s, 3H).

50 **[0120]** To a solution of 8-methyl-2-(methylsulfanyl)-6-(3-nitrophenyl)-8H-pyrido[2,3-*d*]pyrimidin-7-one (1.0 g, 3 mmol)  
in EtOH (10 mL) was added Raney® nickel (5 g) and the mixture refluxed for 3h. After cooling, the reaction was filtered  
and the filtrate concentrated to give 8-methyl-6-(3-nitrophenyl)-8H-pyrido[2,3-*d*]pyrimidin-7-one (0.35 g, 41% yield),  
which was used in the next reaction without further purification.

55 **[0121]** To a solution of 8-methyl-6-(3-nitrophenyl)-8H-pyrido[2,3-*d*]pyrimidin-7-one (0.35 g, 1.2 mmol) in EtOH (10 mL)  
was added Pd (0.2 g). The mixture was stirred under an atmosphere of H<sub>2</sub> (30 psi) for 1.5h. After removal of the catalyst  
by filtration, the solvent was evaporated under vacuum to give 6-(3-aminophenyl)-8-methyl-8H-pyrido[2,3-*d*]pyrimidin-  
7-one (150 mg, 50% yield) as a white solid. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 9.08 (d, *J* = 4.2 Hz, 1H), 8.18 (s, 1H), 7.85

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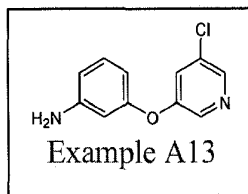
(m, 1H), 7.80 (d,  $J = 5.4$  Hz, 1H), 7.64 (t,  $J = 7.8$  Hz, 1H), 7.43 (d,  $J = 5.4$  Hz, 1H), 3.85 (s, 3H).



To stirred anhydrous DMF (25 mL) was slowly added  $\text{SOCl}_2$  (125 mL) at such a rate that the reaction temperature was maintained at 40-50 °C. Pyridine-2-carboxylic acid (25 g, 0.2 mol) was added in portions over 30 min and the resulting mixture was heated at reflux for 16h during which time a yellow solid precipitated. After cooling to RT, the mixture was diluted with toluene (80 mL) and concentrated. This process was repeated three times. The resulting dry residue was washed with toluene and dried under reduced pressure to yield 4-chloro-pyridine-2-carbonyl chloride (27.6 g, 79%), which was used in the next step without purification.

**[0122]** To a solution of 4-chloro-pyridine-2-carbonyl chloride (27.6 g, 0.16 mol) in anhydrous THF (100 mL) at 0 °C was added dropwise a solution of  $\text{MeNH}_2$  in EtOH. The resulting mixture was stirred at 3 °C for 4h. The reaction mixture was concentrated under reduced pressure to yield a solid, which was suspended in EtOAc and filtered. The filtrate was washed with brine (2x100mL), dried and concentrated to yield 4-chloro-N-methylpicolinamide as a yellow solid (16.4 g, 60% yield).  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  8.78 (d,  $J = 7.2$  Hz, 1H), 8.54 (d,  $J = 7.2$  Hz, 1H), 7.95 (s, 1H), 7.67-7.65 (m, 1H), 2.79 (d,  $J = 4.8$  Hz, 3H); MS (ESI)  $m/z$ : 171 ( $\text{M}+\text{H}^+$ ).

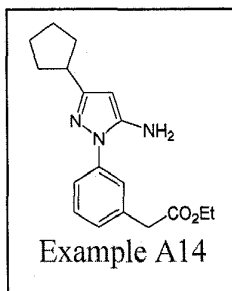
**[0123]** A solution of 4-aminophenol (9.6 g, 88 mmol) in anhydrous DMF (100mL) was treated with NaH (5.28 g of a 60% dispersion, 132 mmol), and the reddish-brown mixture was stirred at RT for 2h. The contents were treated with 4-chloro-N-methylpicolinamide (15 g, 88 mmol) and  $\text{K}_2\text{CO}_3$  (6.5 g, 44 mmol) and heated at 80 °C for 8h. The mixture was cooled to RT and partitioned between EtOAc and brine. The aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine (2x 50 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated to afford 4-(4-amino-phenoxy)pyridine-2-carboxylic acid methylamide (15 g, 71% yield).  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  8.71 (d,  $J = 1.8$  Hz, 1H), 8.43 (d,  $J = 5.7$  Hz, 1H), 7.32 (d,  $J = 2.7$  Hz, 1H), 7.06-7.03 (m, 1H), 6.76 (dd,  $J = 8.7$  Hz, 4H), 5.15 (s, 2H), 2.76 (d,  $J = 4.8$  Hz, 3H); MS (ESI)  $m/z$ : 244 ( $\text{M}+\text{H}^+$ ).



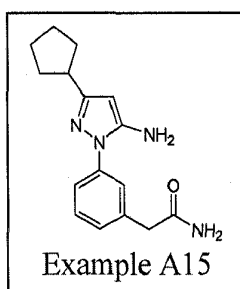
A solution of 5-chloro-3-hydroxypyridine (0.45 g, 3.5 mmol) and NaH (0.15 g of 60% dispersion, 3.83 mmol) in DMSO (10 mL) was stirred at RT for 30 min and then treated with 1-fluoro-3-nitrobenzene (0.69 g, 4.9 mmol). The mixture was heated at 120 °C for 24h, cooled to RT, quenched with satd.  $\text{NH}_4\text{Cl}$  (50 mL), and extracted with EtOAc (3x 25 mL). The combined organic extracts were washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated to yield a crude residue which was purified via column chromatography using to yield 3-chloro-5-(3-nitrophenoxy)pyridine (0.2 g, 23% yield) as a yellow solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.46 (d,  $J = 2.0$  Hz, 1H), 8.35 (d,  $J = 2.0$  Hz, 1H), 8.09 (dd,  $J = 8.4$  Hz, 2.0 Hz, 1H), 7.89 (t,  $J = 2.0$  Hz, 1H), 7.60 (t,  $J = 8.0$  Hz, 1H), 7.41-7.39 (m, 2H); MS (ESI)  $m/z$ : 251.0 ( $\text{M}+\text{H}^+$ ).

**[0124]** To a solution of 3-chloro-5-(3-nitrophenoxy)pyridine (0.2 g, 0.8 mmol) in EtOAc (10 mL) was added  $\text{PtO}_2$  (0.02 g) and the mixture was stirred for 4h under  $\text{H}_2$  (1 atm). It was then filtered through a Celite® pad and washed with EtOAc (2x5 mL). The combined organic extracts were concentrated to afford 3-(5-chloropyridin-3-yloxy)benzenamine (0.165 g, 93% yield) which was used without further purification.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  8.39 (d,  $J = 2.0$  Hz, 1H), 8.31 (d,  $J = 2.8$  Hz, 1H), 7.54-7.53 (m, 1H), 7.05 (t,  $J = 8.0$  Hz, 1H), 6.42-6.39 (m, 1H), 6.25-6.19 (m, 2H), 5.33 (brs, 2H); MS (ESI)  $m/z$ : 221.0 ( $\text{M}+\text{H}^+$ ).

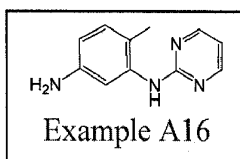
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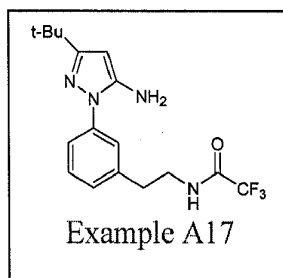
To a mixture of (3-aminophenyl)acetic acid ethyl ester (15 g, 84 mmol) in conc. HCl (20 mL) was added sodium nitrite (6 g, 87 mmol) aqueous solution dropwise under ice-salt bath. The resulting mixture was stirred at 0 °C for 30 min and then added a solution of SnCl<sub>2</sub>·2H<sub>2</sub>O (38 g, 168 mmol) in conc. HCl dropwise also at such a rate that the reaction mixture never rose above 5 °C. After the addition was completed, the mixture was stirred for another 2 h at room temperature. The precipitate was collected by suction and washed with ethyl ether to afford (3-Hydrazinophenyl)acetic acid ethyl ester hydrochloride (17 g, 88%) as a brown solid. MS (ESI) m/z: 195 (M+H<sup>+</sup>). A solution of (3-hydrazinophenyl)acetic acid ethyl ester hydrochloride (17 g, 74 mmol) and 3-cyclopentyl-3-oxopropionitrile (12.2 g, 88.8 mol) in alcohol (150 mL) containing conc. HCl (10 mL) was heated to reflux overnight. After removed of the solvent, the precipitate was collected by suction and washed with ethyl ether to afford the crude product, which was purified by column chromatography to afford [3-(5-amino-3-cyclopentylpyrazol-1-yl)phenyl]acetic acid ethyl ester hydrochloride (8.8 g, 34% yield) as a yellow solid. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 7.40-7.66 (m, 4H), 5.68 (s, 1H), 4.05 (q, *J* = 7.2 Hz, 2H), 3.75 (s, 2H), 3.00-3.08 (m, 1H), 1.98-2.00 (m, 2H), 1.58-1.70 (m, 6H), 1.17 (t, *J* = 7.2 Hz, 3H); MS (ESI) m/z: 314 (M+H<sup>+</sup>).



A mixture of Example A14 (0.600 g, 1.7 mmol, 1.0) and 7N NH<sub>3</sub> in MeOH (9.8 ml, 69 mmol, 40 eq) was heated in a sealed screw-cap vial at 60 °C for 36h. More 7N NH<sub>3</sub> in MeOH (9.8 ml, 69 mmol, 40 eq) was added and the reaction heated at 60 °C 24h. The solution was concentrated to a purple residue of 2-((3-(5-amino-3-cyclopentyl-1H-pyrazol-1-yl)phenyl)amino)propanamide. MS (ESI) m/z: 285.2 (M+H<sup>+</sup>).



To a solution of N-(3-amino-4-methylphenyl)acetamide (5g, 25 mmol) in DMF (5 mL) was added 2-chloropyrimidine (3.8g, 33 mmol) and KI (0.5g). The reaction was stirred at 100 °C overnight, cooled to 10 °C and added to H<sub>2</sub>O (100mL). The resulting mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2x100 mL). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under vacuum. The residue was dissolved in conc. HCl (10 mL), stirred at 80°C for 2h and concentrated under vacuum to yield 6-methyl-N<sup>1</sup>-(pyrimidin-2-yl)benzene-1,3-diamine hydrochloride (3.75g, 75% yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 8.36 (dd, *J* = 15.2, 4.8 Hz, 2H), 7.46 (d, *J* = 2.4 Hz, 1H), 6.97 (d, *J* = 8.0 Hz, 1H), 7.26 (s, 1H), 6.67 (t, *J* = 4.8 Hz, 1H), 6.39 (dd, *J* = 8.0, 2.4, Hz, 1H), 2.20 (s, 3H); MS (ESI) m/e: 201 (M+H<sup>+</sup>).



To a stirring solution of 3-nitrophenylacetic acid (10.4 g, 57.3 mmol) in MeOH (250 ml) at RT was added HCl gas until saturation was achieved. The resulting solution was stirred at 70 °C for 1h. The reaction was cooled and concentrated under reduced pressure. The semisolid residue was dissolved in Et<sub>2</sub>O, washed with H<sub>2</sub>O (2x), satd. NaHCO<sub>3</sub> (2x), brine (1x) and dried (MgSO<sub>4</sub>). Filtration and evaporation provided methyl 2-(3-nitrophenyl)acetate as a low-melting solid (10.7 g, 96% yield), which was used without further purification. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.14-8.04 (m, 2H), 7.64-7.58 (m, 1H), 7.47 (brt, *J* = 8.10 Hz, 1H), 3.72 (s, 2H), 3.68 (s, 3H); MS (ESI) *m/z*: 196.0 (M+H<sup>+</sup>).

**[0125]** Methyl 2-(3-nitrophenyl)acetate (9.6 g, 49 mmol) was treated with conc. NH<sub>4</sub>OH (24 ml, 172 mmol). The suspension was stirred briskly at RT until complete, then chilled thoroughly in an ice bath. The solids were collected by filtration, rinsed sparingly with ice H<sub>2</sub>O and dried to yield pure 2-(3-nitrophenyl)acetamide as an off-white solid (7.47 g, 84% yield). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 8.18-8.02 (m, 2H), 7.75-7.70 (m, 1H), 7.61-7.57 (m, 3H), 7.00 (brs, 1H), 3.58 (s, 3H); MS (ESI) *m/z*: 181.0 (M+H<sup>+</sup>).

**[0126]** To a stirring solution of BH<sub>3</sub>-THF (3.5 ml, 3.5 mmol, 1.0M) was added a solution of 2-(3-nitrophenyl)acetamide (0.25 g, 1.4 mmol) in THF (7.0 mL) at RT. The resulting solution was stirred at RT until the gas evolution had subsided and then heated at 70 °C overnight. The cooled reaction was quenched carefully with 3M HCl (2 ml) and heated again at 70 °C to complete the quench. The reaction was cooled to RT and concentrated to a white solid, which was dissolved in 3M NaOH (pH 14) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (4x). The organics were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated to provide 0.20 g (87% yield) of crude product as an oil, which was purified by precipitation from CH<sub>2</sub>Cl<sub>2</sub> and 3M HCl/EtOAc (0.26 ml, 0.78 mmol) to yield 2-(3-nitrophenyl)ethanamine as the HCl salt as an off-white solid (0.164 g). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 8.18-8.15 (m, 1H), 8.13-8.04 (m, 1H), 8.02 (brs, 3H), 7.76-7.74 (m, 1H), 7.65 (brt, *J* = 7.8 Hz), 3.17-3.08 (m, 2H), 3.06-3.00 (m, 2H); MS (ESI) *m/z*: 167.0 (M+H<sup>+</sup>).

**[0127]** To a stirring suspension of 2-(3-nitrophenyl)ethanamine hydrochloride (0.164 g, 0.81 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (8 ml) at RT was added *i*-Pr<sub>2</sub>NEt (0.42 ml, 2.43 mmol). The reaction was stirred at RT until the solids were dissolved, cooled thoroughly in an ice bath and TFAA (0.14 mL, 1.01 mmol) was added dropwise. The resulting yellow solution was stirred overnight with slow warming to RT. The reaction mixture was washed with ice H<sub>2</sub>O (2x) and dried (MgSO<sub>4</sub>). Filtration and evaporation provided N-(3-nitrophenethyl)-2,2,2-trifluoroacetamide (0.215 g, 101% yield) as an oil that solidified on standing. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.17-8.14 (m, 1H), 8.11-8.10 (m, 1H), 7.58-7.52 (m, 2H), 6.4 (brs, 1H), 3.70 (q, *J* = 6.0 Hz, 2H), 3.06 (t, *J* = 6.0 Hz, 2H).

**[0128]** To a solution of N-(3-nitrophenethyl)-2,2,2-trifluoroacetamide (0.05 g, 34.5 mmol) in MeOH (125 ml) at RT was added 10% Pd/C (50% H<sub>2</sub>O wet) (3.67 g, 1.73 mmol). The resulting suspension was placed under H<sub>2</sub> (3 atm) at RT overnight. The reaction was filtered through Celite® and the cake rinsed with MeOH. The filtrate was concentrated to provide N-(3-aminophenethyl)-2,2,2-trifluoroacetamide as an oil (7.83 g, 98% yield). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.16-7.12 (m, 1H), 6.62-6.58 (m, 2H), 6.54-6.53 (m, 1H), 6.34 (brs, 1H), 3.61 (q, *J* = 6.40 Hz, 2H), 2.80 (t, *J* = 6.40 Hz, 2H), 2.68 (brs, 2H); MS (ESI) *m/z*: 233.3 (M+H<sup>+</sup>).

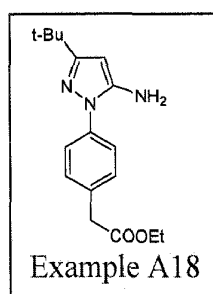
**[0129]** To a stirring solution of N-(3-aminophenethyl)-2,2,2-trifluoroacetamide (7.83 g, 33.7 mmol) in EtOAc (80 ml) at RT was added 3N HCl/EtOAc (12.4 ml, 37.1 mmol). Solids precipitated almost immediately. The resulting suspension was cooled in ice 1 h. The solids were collected by filtration, rinsed with EtOAc and dried on the filter. There was obtained pure N-(3-aminophenethyl)-2,2,2-trifluoroacetamide hydrochloride free of less polar impurities as a pale tan solid (7.94 g, 88% yield). <sup>1</sup>H NMR 300 MHz, (DMSO-*d*<sub>6</sub>): δ 10.3 (brs, 3H), 9.61 (t, *J* = 5.32 Hz, 1H), 7.43-7.39 (m, 1H), 7.25-7.23 (m, 2H), 3.42 (q, *J* = 6.6 Hz, 2H), 2.84 (t, *J* = 6.6 Hz, 2H).

**[0130]** N-(3-aminophenethyl)-2,2,2-trifluoroacetamide hydrochloride (0.27 g, 1.0 mmol) was suspended in 6M HCl (2.0 mL) and cooled thoroughly in an ice bath. This was rapidly stirred while a solution of NaNO<sub>2</sub> (73 mg) in H<sub>2</sub>O (1.0 mL) was added slowly. The mixture was stirred at 0-5 °C for 45 min and was then treated with SnCl<sub>2</sub>·2H<sub>2</sub>O (1.3 g, 5.8 mmol) in 6N HCl (4.0 mL). The resulting suspension was stirred at 0-5 °C for 3h and then carefully quenched with 3N NaOH (15 mL) to pH 7-8. The mixture was diluted with Et<sub>2</sub>O, filtered through Celite® and the filter cake was washed with H<sub>2</sub>O and Et<sub>2</sub>O. The layers of the biphasic filtrate were separated and the aqueous extracted with Et<sub>2</sub>O (2x). The combined organics extracts were washed with brine (1x), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and evaporated to provided N-(3-hydrazinophenethyl)-2,2,2-trifluoroacetamide as a pale yellow oil (0.18 g, 72% yield), which was used without further

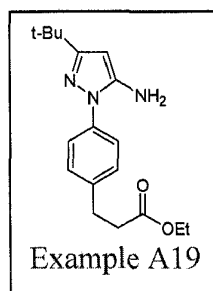


purification. MS (ESI)  $m/z$ : 248.0 ( $M+H^+$ ).

**[0131]** To a stirring solution of *N*-(3-hydrazinophenethyl)-2,2,2-trifluoroacetamide (0.18 g, 0.73 mmol) in absolute EtOH (5 ml) at RT was added pivaloylacetonitrile (0.11 g, 0.87 mmol) and saturated HCl/EtOH (3 drops from a pipet). The resulting solution was stirred at 75-80 °C overnight, then cooled to RT and concentrated. The residue was dissolved in Et<sub>2</sub>O and washed with saturated. NaHCO<sub>3</sub>. The aqueous was extracted with Et<sub>2</sub>O (1x). The combined organics were washed with brine (1x), dried (MgSO<sub>4</sub>), filtered, concentrated and purified via flash chromatography to provide *N*-[3-(5-amino-3-*t*-butyl-1*H*-pyrazol-1-yl)phenethyl]-2,2,2-trifluoroacetamide as an orange glass (0.18 g, 70% yield). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.47-7.46 (m, 2H), 7.43-7.39 (m, 1H), 7.14-7.12 (m, 1H), 5.51 (s, 1H), 3.67 (q,  $J$  = 6.6 Hz, 2H), 2.95 (t,  $J$  = 6.6 Hz, 2H), 1.33 (s, 9H); MS (ESI)  $m/z$ : 355.2 ( $M+H^+$ ).



Using general method M, (4-aminophenyl)acetic acid (20 g, 0.13 mol) was converted to ethyl 2-(4-(3-*t*-butyl-5-amino-1*H*-pyrazol-1-yl)phenyl)acetate (22.5 g, 57.5% yield). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 7.55-7.45 (m, 4H), 5.61 (s, 1H), 4.08 (q,  $J$  = 6.9 Hz, 2H), 3.77 (s, 2H), 1.27 (s, 9H), 1.19 (t,  $J$  = 6.9 Hz, 3H); MS (ESI)  $m/z$ : 302 ( $M+H^+$ ).

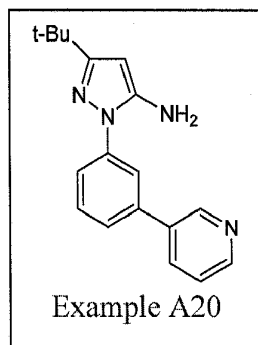


To a solution of 4-nitrobenzaldehyde (15.1 g, 0.1 mol) in CH<sub>2</sub>Cl<sub>2</sub> (200 mL) was added dropwise (triphenylphosphanylidene)acetic acid ethyl ester (34.8 g, 0.1 mol) in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) at 0 °C. After the addition was completed, the resulting mixture was stirred for 2h. After removal the solvent under reduced pressure, the residue was purified by column chromatography to afford 3-(4-nitrophenyl)acrylic acid ethyl ester (16.5 g, 74.6% yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.25 (d,  $J$  = 8.8 Hz, 2H), 7.71 (d,  $J$  = 16.0 Hz, 1H), 7.67 (d,  $J$  = 8.8 Hz, 2H), 6.55 (d,  $J$  = 16.0 Hz, 2H), 4.29 (q,  $J$  = 7.2 Hz, 2H), 1.34 (t,  $J$  = 7.2 Hz, 3H).

**[0132]** A mixture of 3-(4-nitrophenyl)acrylic acid ethyl ester (16.5 g, 74.6 mmol) and Pd/C (1.65 g) in MeOH (200 mL) was stirred under 40 psi of H<sub>2</sub> at RT for 2h. After filtration over Celite® and removal of the solvent, 14 g of 3-(4-aminophenyl)propionic acid ethyl ester was obtained. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 6.98 (d,  $J$  = 8.0 Hz, 2H), 6.61 (d,  $J$  = 8.4 Hz, 1H), 4.12 (q,  $J$  = 7.2 Hz, 2H), 2.84 (t,  $J$  = 8.0 Hz, 2H), 2.55 (t,  $J$  = 7.6 Hz, 2H), 1.23 (t,  $J$  = 7.2 Hz, 3H). MS (ESI):  $m/z$ : 194 ( $M+H^+$ ).

**[0133]** To a solution of 3-(4-aminophenyl)propionic acid ethyl ester (14 g, 72.5 mmol) in conc. HCl (200 mL) was added aqueous (10 mL) NaNO<sub>2</sub> (5 g, 72.5 mmol) at 0 °C and the resulting mixture was stirred for 1h. A solution of SnCl<sub>2</sub>·2H<sub>2</sub>O (33 g, 145 mmol) in conc. HCl (150 mL) was then added at 0 °C. The reaction solution was stirred for an additional 2h at RT. The precipitate was filtered and washed with EtOH and Et<sub>2</sub>O to yield 3-(4-hydrazinophenyl)propionic acid ethyl ester as a white solid, which was used for the next reaction without further purification. MS (ESI):  $m/z$ : 209 ( $M+H^+$ ).

**[0134]** A mixture of 3-(4-hydrazinophenyl)propionic acid ethyl ester (13 g, 53.3 mmol) and 4,4-dimethyl-3-oxopentenenitrile (6.9 g, 55 mol) in EtOH (150 mL) was heated at reflux overnight. The reaction solution was evaporated under vacuum. The residue was purified by column chromatography to yield ethyl 3-(4-(3-*t*-butyl-5-amino-1*H*-pyrazol-1-yl)phenyl)propanoate (14.3 g, 85% yield) as a white solid. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 7.44 (d,  $J$  = 8.4 Hz, 2H), 7.27 (d,  $J$  = 8.7 Hz, 2H), 5.34 (s, 1H), 5.11 (s, 2H), 4.04 (q,  $J$  = 7.2 Hz, 2H), 2.86 (t,  $J$  = 7.5 Hz, 2H), 2.61 (t,  $J$  = 7.5 Hz, 2H), 1.19 (s, 9H), 1.15 (t,  $J$  = 7.2 Hz, 3H); MS (ESI)  $m/z$ : 316 ( $M+H^+$ ).



POCl<sub>3</sub> (26 g, 0.18 mol) was added over 1 h to anhydrous DMF (66 g) while keeping the temperature at 15-20 °C. After the solution had stirred at RT for 1h, 3-nitrophenyl acetic acid (10 g, 0.06 mol) was added. The solution was heated to 85 °C and stirred for 18h. The solution was cooled to RT and poured onto 160 g of ice with vigorous stirring. A solution of sodium perchlorate (11 g, 0.09 mol) in H<sub>2</sub>O was added, and a crystalline precipitate formed over 10 min. The precipitate was filtered, washed with H<sub>2</sub>O, and dried in vacuo at 50 °C to yield a tan power (E)-N-[3-(dimethylamino)-2-(3-nitrophenyl)-2-propenylidene]-N-methylmethanaminium monoperchlorate (12 g, 58% yield). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): 8.23 (d, *J* = 7.5 Hz, 1H), 8.12 (s, 1H), 7.75-7.64 (m, 4H), 3.22 (s, 3H), 2.39 (s, 6H); MS (ESI) *m/z*: 349 (M+H<sup>+</sup>).

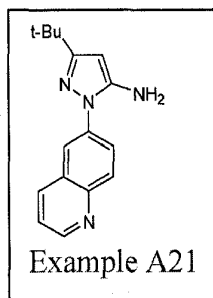
**[0135]** A solution of the material from the previous reaction (12 g, 32 mmol) dissolved in DMF (600 mL) were added *t*-butyl cyanoacetate (5 mL, 35 mmol) and Et<sub>3</sub>N (4.9 mL, 35 mmol). The solution was stirred at RT for 18h and then partitioned between H<sub>2</sub>O and. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x500 mL), the combined organic layers were dried (MgSO<sub>4</sub>), concentrated and the yellow residue was purified by column to yield 2-cyano-5-dimethylamino-4-(3-nitrophenyl)penta-2,4-dienoic acid *t*-butyl ester (9 g, 82% yield). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): 8.9-8.23 (m, 1H), 8.05 (s, 1H), 7.72 (s, 1H), 7.50-7.55 (m, 2H), 7.05 (s, 1H), 2.81 (brs, 6H), 1.44 (s, 9H); MS (ESI) *m/z*: 344 (M+H<sup>+</sup>).

**[0136]** To a solution of the material from the previous reaction (9 g, 26 mmol) in acetic acid (150 mL) was added gaseous HCl at a moderate rate for 15 min at RT. The solution was stirred at RT for 18h and then partitioned between H<sub>2</sub>O and CH<sub>2</sub>Cl<sub>2</sub>. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x250 mL), the combined organic layers were dried (MgSO<sub>4</sub>), concentrated and the yellow residue was purified by column to yield 2-chloro-5-(3-nitrophenyl)pyridine (3.5 g, 55% yield). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 8.65 (s, 1H), 8.42 (s, 1H), 8.29 (d, *J* = 7.8 Hz, 1H), 7.92-7.86 (m, 2H), 7.68 (t, *J* = 7.8 Hz, 1H), 7.49 (d, *J* = 7.8 Hz, 1H).

**[0137]** To a solution of the material from the previous reaction (5 g, 21 mmol) in MeOH (50 mL) was added Raney-Ni and the mixture stirred at RT under a atmosphere of H<sub>2</sub> for 5h. After the Raney-Ni was filtered, the filtrate was concentrated to yield 3-(6-chloro-pyridin-3-yl)phenylamine (3.8 g, 89% yield). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 8.55 (d, *J* = 2.4 Hz, 1H), 7.97 (dd, *J* = 8.4 Hz, and 2.4 Hz, 1H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.10 (t, *J* = 7.8 Hz, 1H), 6.82-6.76 (m, 2H), 6.60 (d, *J* = 7.8 Hz, 1H), 6.22 (d, 2H); MS (ESI) *m/z*: 205 (M+H<sup>+</sup>).

**[0138]** To a solution of the material from the previous reaction (3.5 g, 17 mmol) in conc. HCl (6 mL) was added an aqueous solution (2 mL) of NaNO<sub>2</sub> (1.21 g, 17 mmol) at 0 °C and the resulting mixture was stirred for 1h. A solution of SnCl<sub>2</sub>·2H<sub>2</sub>O (8.0 g, 36 mmol) in conc. HCl (7.5 mL) was then added at 0 °C. The reaction solution was stirred for an additional 2h at RT. The precipitate was filtered and washed with EtOH and ether to give [3-(6-chloropyridin-3-yl)phenyl]hydrazine hydrochloride as a white solid, which was used for the next reaction without further purification. MS (ESI) *m/z*: 220 (M+H<sup>+</sup>).

**[0139]** A mixture of the material from the previous reaction and 4,4-dimethyl-3-oxo-pentanenitrile (2.18 g, 35 mol) in EtOH (25 mL) was heated at reflux overnight. The reaction solution was concentrated and the residue purified by column chromatography to give 5-*t*-butyl-2-[3-(6-chloropyridin-3-yl)-phenyl]-2H-pyrazol-3-ylamine (3.7 g, 60% yield, two steps). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 8.71 (d, *J* = 1.8 Hz, 1H), 8.17 (d, *J* = 6.3 Hz, 1H), 7.94 (s, 1H), 7.92 (s, 1H), 7.78 (t, *J* = 6.3 Hz, 1H), 7.65 (d, *J* = 6.0 Hz, 1H), 7.57 (d, *J* = 6.3 Hz, 1H), 5.80 (s, 1H), 1.39 (s, 9H); MS (ESI) *m/z*: 327 (M+H<sup>+</sup>).



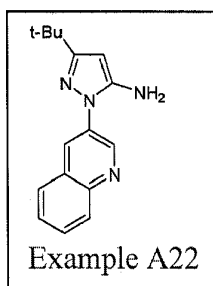
To a solution of quinolin-6-ylamine (5 g, 35 mmol) in conc. HCl (12 mL) was added dropwise an aqueous solution (4 mL) of  $\text{NaNO}_2$  (2.42 g, 35 mmol) at 0 °C. The resulting mixture was stirred for 1h and then treated dropwise with a solution of  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$  (15.8 g, 70 mmol) in conc. HCl (15 mL) at 0 °C. The reaction mixture was stirred for 2h at RT. The precipitate was collected and washed with EtOH and  $\text{Et}_2\text{O}$  to yield 1-(quinolin-6-yl)hydrazine hydrochloride as a yellow powder (4.3 g, 77% yield), which was used for the next reaction without further purification.

**[0140]** A mixture of 1-(quinolin-6-yl)hydrazine hydrochloride (4.0 g, 20.5 mmol) and 4,4-dimethyl-3-oxo-pentanenitrile (3.6 g, 30 mol) in EtOH (50 mL) and conc. HCl (5 mL) was heated at reflux overnight. After removal of the solvent, the residue was purified by column chromatography to yield 3-t-butyl-1-(quinolin-6-yl)-1H-pyrazol-5-amine (2.8 g, 51% yield).  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  8.84 (d,  $J$  = 4.2 Hz, 1H), 8.37 (d,  $J$  = 7.5 Hz, 1H), 8.09 (s, 1H), 8.04 (s, 2H), 7.52 (m, 1H), 5.46 (s, 1H), 5.40 (brs, 2H), 1.29 (s, 9H).

#### General Experimental for Example 55:

**[0141]** A solution of Example A21 and the appropriate isocyanate or aniline was converted to the target compound using the general method indicated.

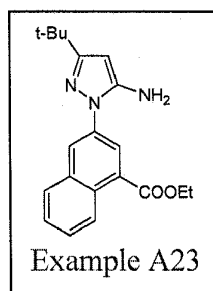
| Example           | Name                                                                                                                                 | MS (EI)<br>( $\text{M}+\text{H}^+$ ) | $^1\text{H}$ NMR (300 MHz/400 MHz, $\text{DMSO}-d_6$ )                                                                                                                                                                                                                                          |
|-------------------|--------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>Example 55</p> | 1-(3-t-butyl-1-(quinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea HCl salt<br><br>62 mg, 55 % yield General method D | 551.2                                | $\delta$ 9.43 (brs, 1H), 9.07 (brs, 1H), 8.81 (brs, 1H), 8.71 (brs, 1H), 8.48 (m, 1H), 8.44 (m, 1H), 8.30 (m, 1H), 8.23 (m, 1H), 8.08 (m, 1H), 7.78 (m, 1H), 7.58 (m, 2H), 7.30 (m, 1H), 7.10 (dd, $J$ = 1.6, and 8.4 Hz, 1H), 6.70 (dd, $J$ = 2.4, and 8.4 Hz, 1H), 6.43 (s, 1H), 1.31 (s, 9H) |



To a solution of quinolin-3-ylamine (5 g, 35 mmol) in conc. HCl (12 mL) was added dropwise an aqueous solution (4 mL) of  $\text{NaNO}_2$  (2.42 g, 35 mmol) at 0 °C. The resulting mixture was stirred for 1h, and then treated with a solution of  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$  (15.8 g, 70 mmol) in conc. HCl (15 mL). The reaction solution was stirred for an additional 2h at RT. The precipitate was filtered and washed with EtOH and ether to yield 1-(quinolin-3-yl)hydrazine hydrochloride (4.5 g, 81% yield), which was used in the next reaction without further purification.

**[0142]** A mixture of 1-(quinolin-3-yl)hydrazine hydrochloride (4 g, 20.5 mmol) and 4,4-dimethyl-3-oxo-pentanenitrile

(3.6 g, 30 mol) in EtOH (50 mL) and conc. HCl (5 mL) was heated at reflux overnight. After removal of the solvent, the residue was purified by column chromatography to yield 3-t-butyl-1-(quinolin-3-yl)-1*H*-pyrazol-5-amine (3.0 g, 55% yield). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 9.16 (d, *J* = 2.4 Hz, 1H), 8.44 (d, *J* = 2.4 Hz, 1H), 8.03 (s, 1H), 8.00 (s, 1H), 7.72 (t, *J* = 7.2 Hz, 1H), 7.64 (t, *J* = 7.2 Hz, 1H), 5.72 (s, 1H), 5.45 (s, 3H), 1.23 (s, 9H).



To a solution of 1,8-naphthalic anhydride (25 g, 0.13 mol) in conc. H<sub>2</sub>SO<sub>4</sub> (100 mL) was added dropwise a solution of conc. HNO<sub>3</sub> (7.85 g, 0.13 mol) in conc. H<sub>2</sub>SO<sub>4</sub> (25 mL) at 0 °C. After the addition was complete, the resulting mixture was allowed to warm to RT, stirred for 90 min and then poured into ice-H<sub>2</sub>O. The solid was filtered by suction, washed with H<sub>2</sub>O, and re-crystallized from glacial AcOH to yield 3-nitro-1,8-naphthalic anhydride (24.5 g). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 9.11 (s, 1H), 9.06 (s, 1H), 8.58 (d, *J* = 7.5 Hz, 1H), 8.43 (d, *J* = 7.8 Hz, 1H), 7.82 (t, *J* = 7.8 Hz, 1H).

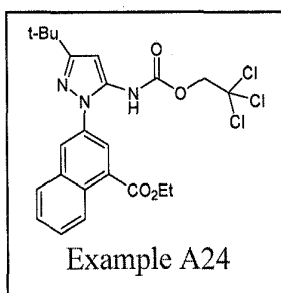
**[0143]** To a solution of 3-nitro-1,8-naphthalic anhydride (21.8 g, 89.7 mmol) in H<sub>2</sub>O (550 mL) containing 14.4 g of NaOH was added a solution of yellow HgO (25.1 g) in a mixture of H<sub>2</sub>O (75 mL) and glacial AcOH (25 mL). After reflux for 4 days, the reaction mixture was cooled and filtered to afford the mercurated product, which was then refluxed in 700 mL of 5N HCl for 3h. The cream-colored precipitate was filtered, washed with cold H<sub>2</sub>O, dried, and recrystallized from hot glacial AcOH to yield 3-nitronaphthalene-1-carboxylic acid (12 g). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 13.7 (brs, 1H), 9.18 (s, 1H), 8.93 (d, *J* = 8.4 Hz, 1H), 8.70 (s, 1H), 7.88 (t, *J* = 7.8 Hz, 1H), 7.76 (t, *J* = 6.9 Hz, 1H).

**[0144]** To a solution of 3-nitronaphthalene-1-carboxylic acid (4.34 g, 20 mmol) in EtOH (50 mL) was added SOCl<sub>2</sub> (3.70 mL, 30 mmol) at 0 °C. The mixture was heated at reflux for 2h and then concentrated. The residue was recrystallized from EtOH to yield ethyl 3-nitronaphthalene-1-carboxylate (4.2 g). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 9.16 (s, 1H), 8.77 (d, *J* = 8.7 Hz, 1H), 8.62 (s, 1H), 8.34 (d, *J* = 8.1 Hz, 1H), 7.87 (t, *J* = 7.2 Hz, 1H), 7.75 (t, *J* = 7.2 Hz, 1H), 4.43 (q, *J* = 7.2 Hz, 2H), 1.38 (t, *J* = 7.2 Hz, 3H).

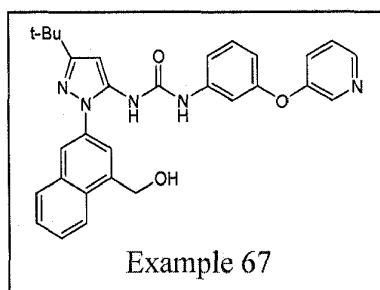
**[0145]** A mixture of 3-nitronaphthalene-1-carboxylic acid ethyl ester (2.45 g, 10 mmol) and Pd/C (0.3 g) in EtOH (20 mL) was stirred overnight at RT under 35 psi of H<sub>2</sub>. After filtration, the filtrate was concentrated to yield ethyl 3-aminonaphthalene-1-carboxylate (2.04 g). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 8.63 (m, 1H), 7.93-7.97 (m, 2H), 7.84 (s, 1H), 7.54-7.57 (m, 2H), 4.39 (q, *J* = 7.2 Hz, 2H), 1.35 (t, *J* = 7.2 Hz, 3H).

**[0146]** To a solution of 3-aminonaphthalene-1-carboxylic acid ethyl ester (2 g, 9.3 mmol) in conc. HCl (2 mL) was added dropwise an aqueous solution of NaNO<sub>2</sub> (0.63 g, 9.3 mmol) at 0 °C. The resulted mixture was stirred for 1h and then treated dropwise with a solution of SnCl<sub>2</sub>·2H<sub>2</sub>O (4.2 g, 18.6 mmol) in conc. HCl (10 mL) at 0 °C. The reaction mixture was stirred for 2h at RT. precipitate was collected and washed with EtOH and Et<sub>2</sub>O to yield ethyl 3-hydrazinonaphthalene-1-carboxylate hydrochloride as a white solid (1.5 g), which was used for the next reaction without further purification.

**[0147]** A mixture of 3-hydrazinonaphthalene-1-carboxylic acid ethyl ester hydrochloride (1.5 g, 5.6 mmol) and 4,4-dimethyl-3-oxopentanenitrile (875 mg, 7.0 mmol) in EtOH (50 mL) and conc. HCl (5 mL) was heated at reflux overnight. After removal of the solvent, the residue was purified by column chromatography to yield ethyl 3-(5-amino-3-t-butyl-1*H*-pyrazol-1-yl)-1-naphthoate (1.8 g, 95% yield). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 8.74 (d, *J* = 6.3 Hz, 1H), 8.47 (s, 1H), 8.24 (s, 1H), 8.15 (d, *J* = 6.0 Hz, 1H), 7.76 (t, *J* = 5.7 Hz, 1H), 7.71 (t, *J* = 5.7 Hz, 1H), 5.68 (s, 1H), 4.44 (q, *J* = 5.4 Hz, 2H), 1.37 (t, *J* = 5.4 Hz, 3H), 1.30 (s, 9H).

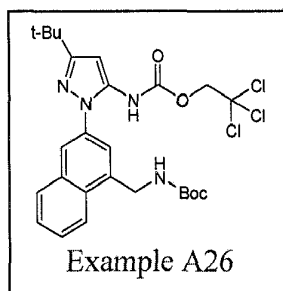


In EtOAc (25 mL) at RT was stirred Example A23 (1.20 g, 3.21 mmol), to this was added saturated  $\text{NaHCO}_3$  (20 mL). The mixture was stirred for 20 min and then treated dropwise with  $\text{Troc-Cl}$  (0.66 mL). The mixture was stirred vigorously overnight at RT, then diluted with EtOAc (50 mL) and  $\text{H}_2\text{O}$  (50 mL). The organic phase was separated, washed with 5% citric acid (50 mL), brine (50 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated yield an oil. This oil was dissolved in hexane (15 mL), warmed to reflux and then cooled to precipitate. The solids were collected by filtration and dried at  $65^\circ\text{C}$  under reduced pressure to yield 885 mg of ethyl 3-(3-t-butyl-5-((2,2,2-trichloroethoxy)carbonylamino)-1*H*-pyrazol-1-yl)-1-naphthoate. This material was used without further purification.

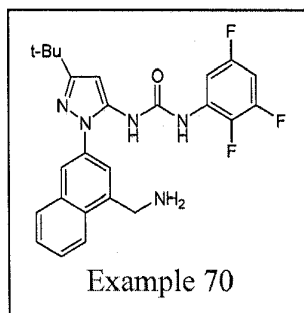


Using general method D, Example A24 (130 mg, 0.24 mmol) and Example A9 (35 mg, 0.234 mmol) were combined to yield 3-(3-t-butyl-5-(3-(3-(pyridin-3-yloxy)phenyl)ureido)-1*H*-pyrazol-1-yl)-1-naphthoate (122 mg, 91% yield).

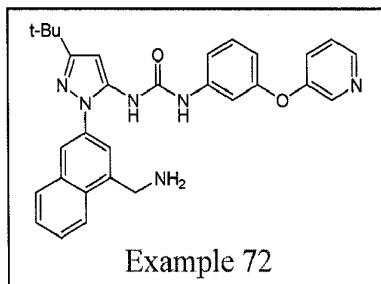
**[0148]** Using general method C, 3-(3-t-butyl-5-(3-(3-(pyridin-3-yloxy)phenyl)ureido)-1*H*-pyrazol-1-yl)-1-naphthoate (52 mg, 0.203 mmol) was reduced to yield 1-(3-t-butyl-1-(4-(hydroxymethyl)naphthalen-2-yl)-1*H*-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea (24 mg, 21% yield).  $^1\text{H-NMR}$  (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  1.30 (s, 9H), 5.03 (s, 2H), 6.41 (s, 1H), 6.67 (d, 1H), 7.07 (d, 1H), 7.24-7.30 (m, 2H), 7.43-7.45 (m, 2H), 7.59-7.61 (m, 2H), 7.71 (s, 1H), 7.95 (s, 1H), 8.00-8.10 (m, 2H), 8.36-8.39 (m, 2H), 8.49 (s, 1H), 9.15 (s, 1H); MS (ESI)  $m/z$ : 508.3 ( $\text{M}+\text{H}^+$ ).



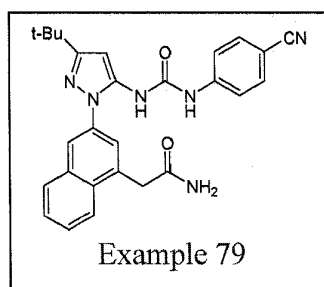
Using general method C, Example A25 (2.0 g, 6.0 mmol) was reduced to yield 1-(4-(aminomethyl)naphthalen-2-yl)-3-t-butyl-1*H*-pyrazol-5-amine, which was immediately protected as the Boc-amine under standard conditions to yield crude t-butyl (3-(5-amino-3-t-butyl-1*H*-pyrazol-1-yl)naphthalen-1-yl)methylcarbamate (3.1 g) which was used without further purification. Using general method D, this crude material (3.1 g, 7.9 mmol) was transformed to yield the desired product as a tan-colored foam (5.1 g, 114% yield).  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.11 (brd,  $J = 7.6$  Hz, 1H), 7.92 (dd,  $J = 2.0$ , and 7.2 Hz, 1H), 7.85 (d,  $J = 2.0$  Hz, 1H), 7.93 (m, 3H), 6.89 (bs, 1H), 6.50 (brs, 1H), 4.94 (brs, 1H), 4.86 (d,  $J = 4.0$  Hz, 2H), 4.84 (s, 2H), 1.49 (s, 9H), 1.40 (s, 9H); MS (EI)  $m/z$ : 569.0 ( $\text{M} + \text{H}^+$ ).



Using general method D, Example A26 (1.0g, 1.75 mmol), and 2,3,5-trifluoroaniline (0.31 g, 2.11 mmol) were combined to yield t-butyl (3-(3-t-butyl-5-(3-(2,3,5-trifluorophenyl)ureido)-1*H*-pyrazol-1-yl)naphthalen-1-yl)methylcarbamate. LC-MS (EI) *m/z*: 568.2 (*M*+*H*<sup>+</sup>). To this material, dissolved in EtOAc (5 mL) was added 3*N* HCl/EtOAc (5.85 mL). The solution was stirred at room temperature for 3h. The solid was filtered and dried under vacuum to obtain 1-(1-(4-(aminomethyl)naphthalen-2-yl)-3-t-butyl-1*H*-pyrazol-5-yl)-3-(2,3,5-trifluorophenyl)urea HCl salt as a white solid (0.31 g, 38% yield). <sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.49 (brs, 1H), 9.29 (brs, 1H), 8.42 (brs, 2H), 8.22 (d, *J* = 7.2 Hz, 1H), 8.18 (brs, 1H), 8.12 (dd, *J* = 2.4, and 6.8 Hz, 1H), 7.83 (m, 2H), 7.69 (m, 2H), 7.12 (m, 1H), 6.50 (s, 1H), 4.64 (q, *J* = 6.0 Hz, 2H), 1.32 (s, 9H); LC-MS (EI) *m/z*: 468.2 (*M*+*H*<sup>+</sup>).



Using the same procedure as for Example 70, Example A26 and Example A9 were combined to yield 1-(1-(4-(aminomethyl)naphthalen-2-yl)-3-t-butyl-1*H*-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea (87 mg, 86% yield). <sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.45 (m, 4H), 8.19 (m, 2H), 8.11 (m, 1H), 7.88 (m, 1H), 7.68 (m, 1H), 7.0-7.6 (m, 5H), 6.68 (m, 1H), 6.44 (s, 1H), 4.64 (q, *J* = 6.0 Hz, 2H), 1.33 (s, 9H); LC-MS (EI) *m/z*: 507.2 (*M* + *H*<sup>+</sup>).



In DMSO (2 mL) was placed Example A28 (120 mg, 0.266 mmol), 4-aminobenzonitrile (31 mg, 0.266 mmol) and *i*-Pr<sub>2</sub>NEt base (34 mg, 0.266 mmol). The mixture was stirred overnight at 65 °C, cooled to RT and diluted with H<sub>2</sub>O (20 mL). The mixture was diluted with EtOAc (20 mL) and the organic phase separated, washed with 5% citric acid (20 mL), brine (20 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to yield methyl 2-(3-(3-t-butyl-5-(3-(4-cyanophenyl)ureido)-1*H*-pyrazol-1-yl)naphthalen-1-yl)acetate as an oil (115 mg, 102% yield). This material was used directly in the next reaction without purification.

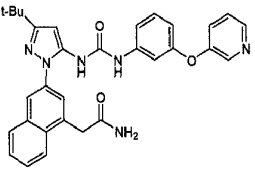
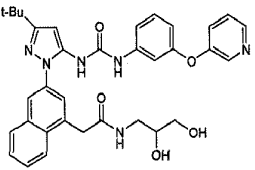
**[0149]** Using general method E, the above ester (115 mg, 0.239 mmol) was saponified to yield 2-(3-(3-t-butyl-5-(3-(4-cyanophenyl)ureido)-1*H*-pyrazol-1-yl)naphthalen-1-yl)-acetic acid as a foam (81mg, 73% yield). This material was used directly in the next reaction without purification.

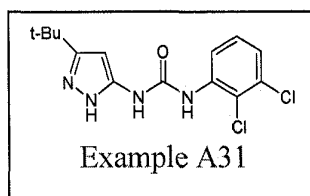
**[0150]** In DMF (1 mL) was placed the above acid (81 mg, 0.20 mmol), HOBt (31 mg, 0.2 mmol) and EDC (50 mg, 0.2 mmol). The mixture was stirred for 15 min and treated with a solution of 0.5*M* NH<sub>3</sub> in dioxane (1 mL, 0.5 mmol) and stirred overnight at RT. Additional EDC (30 mg) and 0.5*M* NH<sub>3</sub> in dioxane (1 mL, 0.5 mmol) were added and the reaction stirred until all starting material was consumed.. The reaction mixture was diluted with EtOAc (15 mL) and 1*N* HCl (10 mL). The organic phase was separated, washed with 5% citric acid (10 mL), satd. NaHCO<sub>3</sub> (10 mL), brine (10 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated, and purified to yield 1-(1-(4-(2-amino-2-oxoethyl)naphthalen-2-yl)-3-t-butyl-1*H*-pyrazol-5-yl)-3-(4-cyanophenyl)urea (17 mg, 21% yield). <sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 1.31 (s, 9H), 3.95 (s, 2H), 6.46 (s, 1H), 7.05 (s, 1H), 7.53-7.71 (m, 8H), 7.95-8.02 (m, 2H), 8.13-8.16 (m, 1H), 8.70 (s, 1H), 9.50 (s, 1H); MS (ESI) *m/z*: 467.3 (*M*+*H*<sup>+</sup>).

General Experimental for Examples 86 and 97:

**[0151]** The following compounds were prepared using the appropriate aniline and the same procedures as for Example

79. For Example 97, 1-amino-2,3-dihydroxypropane was used in place of ammonia.

| Example                                                                                                          | Name                                                                                                                                                          | MS (EI)<br>(M+H <sup>+</sup> ) | <sup>1</sup> H NMR (400 MHz, DMSO-<br><i>d</i> <sub>6</sub> )                                                                                                                                                                                                                                                                      |
|------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <div>  <p>Example 86</p> </div> | <p>1-(1-(4-(2-amino-2-oxoethyl)naphthalen-2-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea hydrochloride</p> <p>69 mg, 46% yield</p>        | 535.2                          | <p>1.30 (s, 9H), 3.95 (s, 2H), 6.40 (s, 1H), 6.75 (d, 1H), 7.04 (brs, 1H), 7.10-7.12 (m, 1H), 7.31-7.40 (m, 2H), 7.57-7.64 (m, 4H), 7.76-7.79 (m, 1H), 7.86-7.89 (m, 1H), 7.99-8.02 (m, 2H), 8.12-8.15 (m, 1H), 8.53-8.55 (m, 1H), 8.62 (m, 1H), 8.83 (s, 1H), 9.57 (s, 1H)</p>                                                    |
| <div>  <p>Example 97</p> </div> | <p>1-(3-t-butyl-1-(4-(2-(2,3-dihydroxypropylamino)-2-oxoethyl)naphthalen-2-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea</p> <p>61 mg, 36% yield</p> | 609.2                          | <p>1.30 (s, 9H), 2.97-3.02 (m, 1H), 3.19-3.29 (m, 3H), 3.48-3.50 (m, 1H), 4.02 (s, 2H), 6.40 (s, 1H), 6.72-6.75 (m, 1H), 7.09-7.12 (m, 1H), 7.30-7.38 (m, 2H), 7.57-7.64 (m, 3H), 7.70-7.73 (m, 1H), 7.78-7.80 (m, 1H), 7.97-8.02 (m, 2H), 8.15-8.18 (m, 1H), 8.23-8.26 (m, 1H), 8.51-8.59 (m, 2H), 8.75 (s, 1H), 9.46 (s, 1H)</p> |



To a solution of 2,3-dichloroaniline (0.200 g, 1.23 mmol) in EtOAc (5 mL) was added NaOH (1M, 2 mL, 2 mmol) and Troc-Cl (0.262 g, 1.23 mmol) and the resulting mixture was stirred overnight. Water (50 mL) was added and the mixture was extracted with EtOAc (3x100 mL), dried (MgSO<sub>4</sub>), concentrated and purified via column chromatography to yield 2,2,2-trichloroethyl-2,3-dichlorophenylcarbamate (408 mg, 98%) as a yellow foam. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.11 (d, *J* = 6.4 Hz, 1H), 7.43 (brs, 1H), 7.25-7.22 (m, 2H), 4.86 (s, 2H); MS (EI) *m/z*: 335.8 (M+H<sup>+</sup>).

**[0152]** A solution of 2,2,2-trichloroethyl-2,3-dichlorophenylcarbamate (0.400 g, 1.19 mmol) and 3-amino-5-t-butylpyrazole (0.165 g, 1.19 mmol) in DMF (1 mL) was stirred at 80 °C overnight. Water (50 mL) was added and the mixture was extracted with EtOAc (3x100 mL), dried (MgSO<sub>4</sub>), concentrated and purified via column chromatography to yield 1-(3-t-butyl-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea (230 mg, 59% yield) as a pink foam. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.26 (d, *J* = 6.8 Hz, 1H), 7.20-7.14 (m, 2H), 5.85 (brs, 1H), 1.34 (s, 9H), amine and urea protons not visible; MS (EI) *m/z*: 327.0 (M+H<sup>+</sup>).

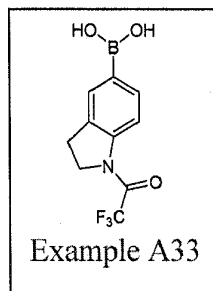




Hz, 1H), 7.24 (t,  $J = 1.6$  Hz, 1H), 7.13 (dd,  $J = 2.0$ , and 8.4 Hz, 1H), 7.05 (dd,  $J = 0.8$ , and 8.4 Hz, 1H), 6.67 (dd,  $J = 2.0$ , and 8.0 Hz, 1H), 6.53 (t,  $J = 2.0$  Hz, 1H), 6.33 (s, 1H), 1.27 (s, 9H); LC-MS (EI)  $m/z$ : 467.3 ( $M+H^+$ ).

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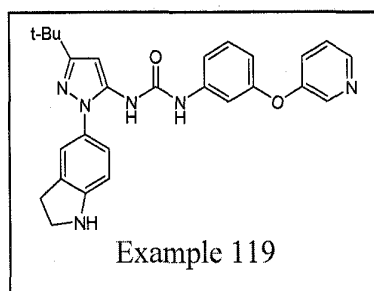
15 To a solution of 5-bromoindoline (1.00 g, 5.05 mmol) in  $CH_2Cl_2$  (20 mL) was added  $Et_3N$  (0.7 mL, 0.51 g, 5.05 mmol). Trifluoroacetic anhydride (0.7 mL, 1.06 g, 5.05 mmol) was added dropwise into the reaction mixture and the resulting solution was stirred at RT for 4h. Water (20 mL) was added and the mixture was extracted with  $CH_2Cl_2$  (3x100 mL). The organic layer was dried ( $Na_2SO_4$ ), concentrated and dried under vacuum to yield (1.42 g, 96% yield) as a yellow solid.  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  8.11 (d,  $J = 9.6$  Hz, 1H), 7.41 (m, 2H), 4.32 (t,  $J = 8.4$  Hz, 2H), 3.28 (t,  $J = 8.4$  Hz, 2H); LC-MS (EI)  $m/z$ : 294.0 ( $M+H^+$ ), 296 ( $M+3H^+$ ).

20 **[0154]** To a solution of 1-(5-bromoindolin-1-yl)-2,2,2-trifluoroethanone (0.70 g, 2.4 mmol) in DMF (10 mL) were added sequentially KOAc (0.70 g, 7.1 mmol), pinacoldiboron (0.91 g, 3.6 mmol) and  $PdCl_2(dppf)$  (98 mg, 0.12 mmol). After flushing the reaction vessel with  $N_2$ , the reaction mixture was sealed and heated at 80 °C for 3h. The reaction mixture was partitioned between  $H_2O$  and EtOAc. The combined organic extracts were washed with brine, dried ( $Na_2SO_4$ ), concentrated and purified via column chromatography to yield 2,2,2-trifluoro-1-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indolin-1-yl)ethanone (0.84 g, 100%) as a yellow solid.  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  8.20 (d,  $J = 7.6$  Hz, 1H), 7.75 (d,  $J = 7.6$  Hz, 1H), 7.72 (s, 1H), 4.30 (t,  $J = 8.4$  Hz, 2H), 3.27 (t,  $J = 8.4$  Hz, 2H), 1.37 (s, 12H); LC-MS (EI)  $m/z$ : 342.3 ( $M+H^+$ ).

25 **[0155]** To a solution of 2,2,2-trifluoro-1-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indolin-1-yl)ethanone (0.7 g, 2.1 mmol) in THF/ $H_2O$  (4/1, 15 mL) was added  $NaIO_4$  (1.4 g, 6.4 mmol). The reaction mixture was stirred at RT for 30 min and then treated with 2N HCl (18 mL). After stirring at RT for 3h, the reaction mixture was filtered and washed with THF. The filtrate was concentrated and the residue triturated with EtOAc (1 mL) to yield 1-(2,2,2-trifluoroacetyl)indolin-6-ylboronic acid (0.45g, 81% yield).  $^1H$  NMR (400 MHz,  $DMSO-d_6$ ):  $\delta$  8.04 (s, 2H), 8.01 (d,  $J = 8.0$  Hz, 1H), 7.75 (brs, 1H), 7.72 (d,  $J = 8.4$  Hz, 1H), 4.29 (t,  $J = 8.0$  Hz, 2H), 3.27 (t,  $J = 8.0$  Hz, 2H); LC-MS (EI)  $m/z$ : 260.0 ( $M+H^+$ ).

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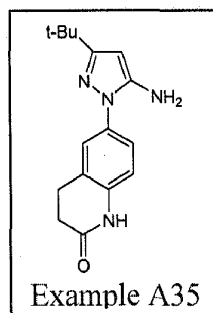


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Using the same procedure as for Example 115, Example A33 and Example A32 were combined to yield 1-(3-(3-(pyridin-3-yloxy)phenyl)urea)-1-(indolin-5-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea (20 mg, 11% yield) as the HCl salt.  $^1H$  NMR (400 MHz,  $DMSO-d_6$ ):  $\delta$  9.62 (s, 1H), 8.74 (s, 1H), 8.56 (brm, 2H), 7.70 (m, 2H), 7.53 (brs, 1H), 7.42 (brd,  $J = 8.0$  Hz, 1H), 7.34 (m, 2H), 7.13 (brd,  $J = 7.6$  Hz, 1H), 7.12 (brm, 1H), 6.72 (dd,  $J = 6.8$  Hz, 1H), 6.34 (s, 1H), 3.72 (brt,  $J = 7.2$  Hz, 2H), 3.22 (brt,  $J = 7.2$  Hz, 2H), 1.26 (s, 9H); LC-MS (EI)  $m/z$ : 469.2 ( $M+H^+$ ).

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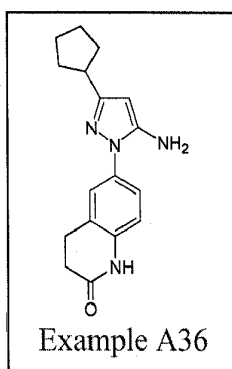
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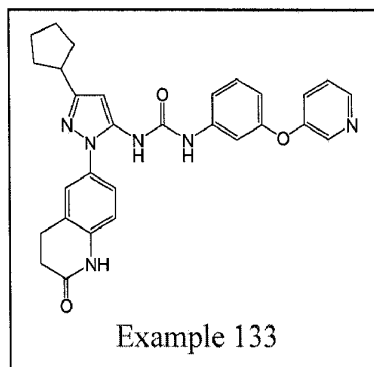
To a solution of hydrocarbostyryl (9.00 g, 61.2 mmol) in conc.  $\text{H}_2\text{SO}_4$  (180 mL) cooled to  $-10^\circ\text{C}$  was slowly added  $\text{H}_2\text{O}$  (45 mL), followed by  $\text{HNO}_3$  (65%, 4.5 mL). The yellow solution was stirred at  $-10^\circ\text{C}$  for 10 min and then carefully quenched at  $-10^\circ\text{C}$  with  $\text{H}_2\text{O}$  (500 mL). The precipitated yellow solid was filtered off, washed with  $\text{H}_2\text{O}$  and dried in vacuo to yield 1,2-dihydro-6-nitroisoquinolin-3(4H)-one (10.3 g, 88% yield).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.35 (brs, 1H), 8.12-8.09 (m, 2H), 6.95-6.92 (m, 1H), 3.10 (t,  $J = 7.6$  Hz, 2H), 2.73 (t,  $J = 7.8$  Hz, 2H); MS (ESI)  $m/z$ : 193.0 ( $\text{M}+\text{H}^+$ ).

**[0156]** To a suspension of 1,2-dihydro-6-nitroisoquinolin-3(4H)-one (10.3 g, 53.6 mmol) in MeOH (150 mL) was added 10% Pd/C (1.14 g, 1.07 mmol) and the mixture was stirred overnight under  $\text{H}_2$  (1 atm). After filtration, the filtrate was concentrated and the residue was suspended in acetone, filtered and precipitated with conc. HCl (10 mL). The resulting precipitate was collected, washed with  $\text{H}_2\text{O}$  and acetone and recrystallized from MeOH/ $\text{H}_2\text{O}$  to yield 6-amino-1,2-dihydroisoquinolin-3(4H)-one as a grey solid (6.7 g, 63 % yield).  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.22 (d,  $J = 2.0$  Hz, 1H), 7.20 (dd,  $J = 8.4$ , and 2.4 Hz, 1H), 6.98 (d,  $J = 8.4$  Hz, 1H), 3.01 (t,  $J = 7.6$  Hz, 2H), 2.59 (t,  $J = 7.6$  Hz, 2H); MS (ESI)  $m/z$ : 163.0 ( $\text{M}+\text{H}^+$ ).

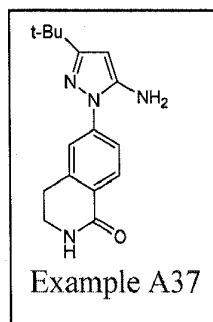
**[0157]** To a suspension of 6-amino-1,2-dihydroisoquinolin-3(4H)-one (4.00 g, 20.1 mmol) in 2M HCl (40 mL) at  $-10^\circ\text{C}$  was added solid  $\text{NaNO}_2$  (1.39 g, 20.1 mmol) causing all solids to dissolve. The mixture was stirred at  $-10^\circ\text{C}$  for 30 min and then solid  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$  (9.09 g, 40.3 mmol) was added at  $-10^\circ\text{C}$ . The mixture was allowed to warm to RT over a period of 30 min and then stirred for 2h. Ethanol (160 mL) and pivaloylacetonitrile (2.52 g, 20.1 mmol) were added and the solution was heated at reflux overnight under Ar atm. The EtOH was removed under reduced pressure,  $\text{H}_2\text{O}$  (200 mL) was added, and the mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (3x200 mL), dried ( $\text{MgSO}_4$ ), concentrated and purified via column chromatography to yield 6-(3-(tert-butyl)-5-amino-1H-pyrazol-1-yl)-1,2-dihydroisoquinolin-3(4H)-one (1.98 g, 35% yield).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.82 (brs, 1H), 7.40 (brs, 1H), 7.35 (dd,  $J = 8.4$ , and 2.4 Hz, 1H), 6.80 (d,  $J = 8.8$  Hz, 1H), 5.52 (s, 1H), 3.67 (brs, 2H), 3.01 (t,  $J = 7.8$  Hz, 2H), 2.65 (t,  $J = 7.4$  Hz, 2H), 1.30 (s, 9H); MS (ESI)  $m/z$ : 285.2 ( $\text{M}+\text{H}^+$ ).



6-Hydrazinyl-3,4-dihydroquinolin-2(1H)-one (1.00g, 4.68 mmol, available from Example A35) was dissolved in EtOH (10 mL) and 3-cyclopentyl-3-oxopropanenitrile (0.706 g, 5.15 mmol) was added. The reaction mixture was heated at  $80^\circ\text{C}$  for 22h. The reaction mixture was concentrated and the residue was suspended in EtOAc (30 mL) and treated slowly with satd.  $\text{Na}_2\text{CO}_3$  (30 mL). The solution was extracted with EtOAc (3x), and the combined organics were washed  $\text{H}_2\text{O}$  and dried ( $\text{Na}_2\text{SO}_4$ ), filtered, concentrated and dried to yield 6-(5-amino-3-cyclopentyl-1H-pyrazol-1-yl)-3,4-dihydroquinolin-2(1H)-one (1.2 g, 87% yield) which was used without further purification. LC-MS (EI)  $m/z$ : 297.2 ( $\text{M}+\text{H}^+$ ).



Using general method D, Example A36 (0.15 g, 0.32 mmol) and Example A9 (70 mg, 0.38 mmol) were combined to yield 1-(3-cyclopentyl-1-(2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea (60 mg, 28% yield, 2 steps) as an off-white solid HCl salt.  $^1\text{H-NMR}$ (DMSO- $d_6$ ):  $\delta$  10.3 (s, 1H), 9.41 (s, 1H), 8.56 (bs, 1H), 8.52 (s, 1H), 8.51 (bs, 1H), 7.71 (m, 2H), 7.33 (m, 2H), 7.25 (dd,  $J$  = 2.4, and 8.8 Hz, 1H), 7.12 (dd,  $J$  = 1.6, and 8.0 Hz, 1H), 6.95 (d,  $J$  = 8.0 Hz, 1H), 6.73 (dd,  $J$  = 2.0, and 8.0 Hz, 1H), 6.26 (s, 1H), 2.98 (m, 1H), 2.93 (t,  $J$  = 7.6 Hz, 2H), 2.47 (t,  $J$  = 7.6 Hz, 2H), 1.95 (m, 2H), 1.64 (m, 6H); LC-MS (EI)  $m/z$ : 509.2 ( $M + H^+$ ).



To an ice-cold solution of 2-(3-methoxyphenyl)-1-ethanamine (5.00 g, 33.1 mmol) and  $\text{Et}_3\text{N}$  (5.10 mL, 37.0 mmol) in  $\text{CH}_2\text{Cl}_2$  (100 mL) was added ethyl chloroformate (3.50 mL, 33.4 mmol). The resulting solution was allowed to warm to RT and was stirred for 2h. Water (100 mL) was added and the mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (3x50 mL), dried ( $\text{MgSO}_4$ ) and concentrated to yield ethyl 3-methoxyphenethylcarbamate (7.32g, 99% yield) as a pale yellow oil.  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.22 (t,  $J$  = 7.8 Hz, 1H), 6.78 (d,  $J$  = 8.0 Hz, 1H), 6.77 (d,  $J$  = 8.0 Hz, 1H), 6.74 (s, 1H), 4.65 (brs, 1H), 4.11 (q,  $J$  = 7.2 Hz, 2H), 3.80 (s, 3H), 3.44 (q,  $J$  = 6.4 Hz, 2H), 2.79 (t,  $J$  = 7.0 Hz, 2H), 1.23 (t,  $J$  = 7.0 Hz, 3H); MS (ESI)  $m/z$ : 224.2 ( $M+H^+$ ).

**[0158]** A mixture of ethyl 3-methoxyphenethylcarbamate (7.32 g, 32.8 mmol) and polyphosphoric acid (30 g) was heated at 120  $^\circ\text{C}$  for 2h after which  $\text{H}_2\text{O}$  (100 mL) was added and the mixture was cooled to RT. The mixture was extracted with  $\text{EtOAc}$  (6x100 mL), dried ( $\text{MgSO}_4$ ) and concentrated to yield crude 6-methoxy-3,4-dihydroisoquinolin-1(2H)-one (8.0 g, 138%) as a sticky gum.  $^1\text{H NMR}$  (400 MHz, acetone- $d_6$ ):  $\delta$  7.88 (d,  $J$  = 8.4 Hz, 1H), 7.04 (brs, 1H), 6.87 (dd,  $J$  = 8.4, and 2.4 Hz, 1H), 6.82 (d,  $J$  = 2.4 Hz, 1H), 3.84 (s, 3H), 3.49 (t,  $J$  = 6.4 Hz, 2H), 2.94 (t,  $J$  = 6.2 Hz, 2H); MS (ESI)  $m/z$ : 178.0 ( $M+H^+$ ).

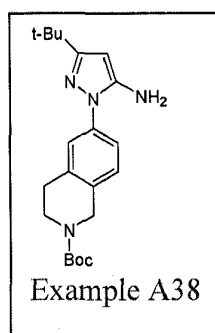
**[0159]** A mixture of 6-methoxy-3,4-dihydroisoquinolin-1(2H)-one (6.40 g, 35.6 mmol) and pyridinium hydrochloride (41.1g, 356 mmol) was heated at 200  $^\circ\text{C}$  for 3h. Water was added (200 mL) and the mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (3x200 mL), dried ( $\text{MgSO}_4$ ) and concentrated to yield 6-hydroxy-3,4-dihydroisoquinolin-1(2H)-one (1.60g, 39%, 2 steps) as a yellow solid.  $^1\text{H NMR}$  (400 Mhz, acetone- $d_6$ ):  $\delta$  8.91 (brs, 1H), 7.81 (d,  $J$  = 8.4 Hz, 1H), 7.40 (brs, 1H), 6.77 (d,  $J$  = 8.4 Hz, 1H), 6.70 (s, 1H), 3.47 (dt,  $J$  = 6.8, and 3.2 Hz, 2H), 2.88 (t,  $J$  = 6.6 Hz, 2H); MS (ESI)  $m/z$ : 164.0 ( $M+H^+$ ).

**[0160]** To a suspension of 6-hydroxy-3,4-dihydroisoquinolin-1(2H)-one (1.60 g, 9.81 mmol) and  $\text{Et}_3\text{N}$  (1.37 mL, 9.992 mmol) in  $\text{CH}_2\text{Cl}_2$  (100 mL) was added triflic chloride (1.65 g, 9.81 mmol). After 2h of stirring,  $\text{H}_2\text{O}$  (100 mL) was added and the mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (3x100 mL), dried ( $\text{MgSO}_4$ ), concentrated and purified via column chromatography to yield 1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl trifluoromethanesulfonate (1.70 mg, 59% yield) as a colorless solid.  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.19 (d,  $J$  = 8.4 Hz, 1H), 7.27 (dd,  $J$  = 8.4, and 2.4 Hz, 1H), 7.19 (d,  $J$  = 2.4 Hz, 1H), 6.58 (brs, 1H), 3.64 (dt,  $J$  = 6.8, and 2.4 Hz, 2H), 3.08 (t,  $J$  = 6.6 Hz, 2H); MS (ESI)  $m/z$ : 296.0 ( $M+H^+$ ).

**[0161]** To a suspension of 1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl trifluoromethanesulfonate (1.70 g, 5.76 mmol),

benzophenone hydrazone (1.36 g, 6.91 mmol), Cs<sub>2</sub>CO<sub>3</sub> (2.81 g, 8.64 mmol) and DPPF (0.048 g, 0.086 mmol) in degassed PhMe (40 mL) was added Pd(OAc)<sub>2</sub> (0.013 g, 0.058 mmol) and the resulting mixture was stirred at RT for 30 min and then heated at 90 °C. After 16h, the mixture was cooled to RT, H<sub>2</sub>O (50 mL) was added and the mixture was extracted with EtOAc (3x50 mL), dried (MgSO<sub>4</sub>), concentrated and purified via column chromatography to yield 6-(2-(diphenylmethylene)hydrazinyl)-3,4-dihydroisoquinolin-1(2H)-one (980 mg, 50% yield). <sup>1</sup>H NMR (400 MHz, acetone-*d*<sub>6</sub>): δ 8.69 (brs, 1H), 7.79 (d, *J* = 9.2 Hz, 1H), 7.63-7.54 (m, 5H), 7.37-7.31 (m, 5H), 7.11-7.08 (m, 2H), 6.67 (brs, 1H), 3.47 (dt, *J* = 7.2, and 3.2 Hz, 2H), 2.90 (t, *J* = 6.6 Hz, 2H); MS (ESI) *m/z*: 342.0 (M+H<sup>+</sup>).

**[0162]** A solution of 6-(2-(diphenylmethylene)hydrazinyl)-3,4-dihydroisoquinolin-1(2H)-one (0.980 g, 2.87 mmol), pivaloylacetonitrile (0.539 g, 4.31 mmol) and *p*-TsOH (4.04 g, 28.8 mmol) in EtOH (20 mL) was heated at reflux overnight. The reaction was cooled and H<sub>2</sub>O was added (20 mL). The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x50 mL), dried (MgSO<sub>4</sub>), concentrated and recrystallized to yield 6-(5-amino-3-*t*-butyl-1*H*-pyrazol-1-yl)-3,4-dihydroisoquinolin-1(2H)-one (387 mg, 48% yield). Purification of the mother liquors via column chromatography yielded an additional 330 mg (40%) of 6-(5-amino-3-*t*-butyl-1*H*-pyrazol-1-yl)-3,4-dihydroisoquinolin-1(2H)-one. <sup>1</sup>H NMR (400 MHz, acetone-*d*<sub>6</sub>): δ 7.99 (d, *J* = 8.4 Hz, 1H), 7.65 (dd, *J* = 8.4, and 2.0 Hz, 1), 7.60 (s, 1H), 6.99 (brs, 1H), 5.53 (s, 1H), 4.92 (brs, 2H), 3.55 (dt, *J* = 6.8, and 2.8 Hz, 2H), 3.02 (t, *J* = 6.4 Hz, 2H), 1.25 (s, 9H); MS (ESI) *m/z*: 28



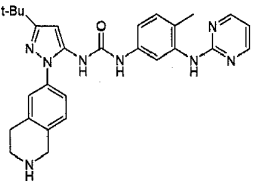
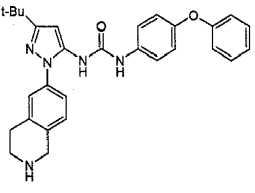
Using general method C, Example A37 (0.200 g, 0.703 mmol) was reduced to 3-*t*-butyl-1-(1,2,3,4-tetrahydroisoquinolin-6-yl)-1*H*-pyrazol-5-amine which was used without further purification. MS (ESI) *m/z*: 446.3 (M+H<sup>+</sup>), 271.3 (M+2H<sup>+</sup>).

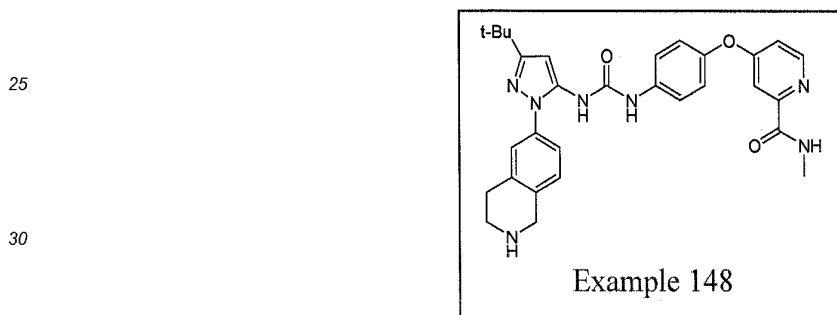
**[0163]** To a solution of 3-*t*-butyl-1-(1,2,3,4-tetrahydroisoquinolin-6-yl)-1*H*-pyrazol-5-amine in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) was added Boc anhydride (0.154 g, 0.703 mmol) and the solution was stirred at RT for 30 min. Evaporation and column chromatography yielded *t*-butyl 6-(5-amino-3-*t*-butyl-1*H*-pyrazol-1-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (154 mg, 59% yield, 2 steps) as a yellow oil. <sup>1</sup>H NMR (400 MHz, acetone-*d*<sub>6</sub>): δ 7.44-7.39 (m, 2H), 7.21 (d, *J* = 7.6 Hz, 1H), 5.47 (s, 1H), 4.76 (brs, 2H), 4.56 (brs, 2H), 3.64 (t, *J* = 5.8 Hz, 2H), 2.85 (t, *J* = 6.0 Hz, 2H), 1.46 (s, 9H), 1.24 (s, 9H); MS (ESI) *m/z*: 371.2 (M+H<sup>+</sup>).

**[0164]** Starting with Example A38, the following compounds were made using either general method A or D and deprotection using general method F. Yields are reported over two (general method A) or three (general method D) steps starting from Example A38.

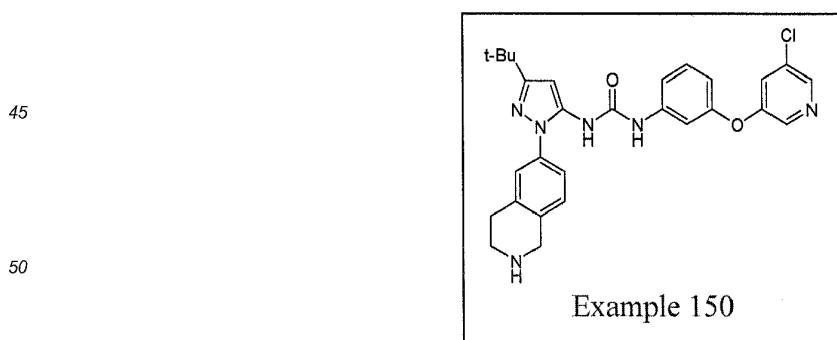
| Example                                        | Name                                                                                                           | MS (EI) (M+H <sup>+</sup> ) | <sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD)                                                                                                                                                                                                                                                                                                                                                |
|------------------------------------------------|----------------------------------------------------------------------------------------------------------------|-----------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p style="text-align: center;">Example 140</p> | 1-(3- <i>t</i> -butyl-1-(1,2,3,4-tetrahydroisoquinolin-6-yl)-1 <i>H</i> -pyrazol-5-yl)-3-(3-phenoxyphenyl)urea | 482.3                       | δ 7.54-7.52 (m, 2H), 7.47 (d, <i>J</i> = 8.8 Hz, 1H), 7.37-7.33 (m, 2H), 7.24 (t, <i>J</i> = 8.2 Hz, 1H), 7.19 (t, <i>J</i> = 2.0 Hz, 1H), 7.12 (t, <i>J</i> = 7.4 Hz, 1H), 7.06 (dd, <i>J</i> = 8.0, and 1.2 Hz, 1H), 7.00-6.97 (m, 2H), 6.67 (s, 1H), 6.65 (dd, <i>J</i> = 8.4, and 2.4 Hz, 1H), 4.47 (s, 2H), 3.56 (t, <i>J</i> = 6.4 Hz, 2H), 3.23 (t, <i>J</i> = 6.2 Hz, 2H), 1.39 (s, 9H) |
|                                                | 54 mg, 84% yield                                                                                               |                             |                                                                                                                                                                                                                                                                                                                                                                                                 |

(continued)

| Example                                                                                                           | Name                                                                                                                                                             | MS (EI)<br>(M+H <sup>+</sup> ) | <sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD)                                                                                                                                                                                                                                                                                                                                                             |
|-------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <div>  <p>Example 142</p> </div> | <div> <p>1-(3-t-butyl-1-(1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-methyl-3-(pyrimidin-2-ylamino)phenyl)-urea</p> <p>53 mg, 84% yield</p> </div> | 497.2                          | <div> <p><math>\delta</math> 8.59 (d, <math>J</math> = 4.8 Hz, 2H), 7.66 (d, <math>J</math> = 2.4 Hz, 1H), 7.51-7.44 (m, 3H), 7.35 (d, <math>J</math> = 8.4 Hz, 1H), 7.30 (dd, <math>J</math> = 8.0, and 2.0 Hz, 1H), 7.10 (t, <math>J</math> = 5.6 Hz, 1H), 6.60 (s, 1H), 4.47 (s, 2H), 3.56 (t, <math>J</math> = 6.4 Hz, 2H), 3.24 (t, <math>J</math> = 6.4 Hz, 2H), 2.25 (s, 3H), 1.37 (s, 9H)</p> </div> |
| <div>  <p>Example 143</p> </div> | <div> <p>1-(3-t-butyl-1-(1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-phenoxyphenyl)-urea</p> <p>45 mg, 70% yield</p> </div>                        | 482.2                          | <div> <p><math>\delta</math> 7.57-7.50 (m, 3H), 7.40 (d, <math>J</math> = 9.2 Hz, 2H), 7.33 (t, <math>J</math> = 8.8 Hz, 2H), 7.08 (t, <math>J</math> = 7.6 Hz, 1H), 6.95-6.93 (m, 4H), 6.76 (s, 1H), 4.50 (s, 2H), 3.58 (t, <math>J</math> = 6.4 Hz, 2H), 3.26 (t, <math>J</math> = 6.2 Hz, 2H), 1.41 (s, 9H)</p> </div>                                                                                    |



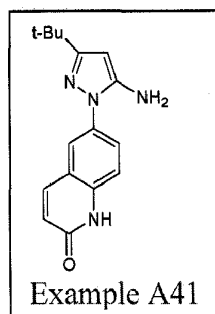
Using general method D, Example A38 (0.08 g, 0.15 mmol) and Example A12 (0.04 g, 0.16 mmol) were combined and the product deprotected using general method F to yield 1-(3-t-butyl-1-(1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea (54 mg, 52% yield, 3 steps) as the HCl salt. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  9.78 (s, 1H), 9.55 (brs, 2H), 8.87 (brs, 2H), 8.52 (d,  $J$  = 5.6 Hz, 1H), 7.55-7.43 (m, 5H), 7.39-7.34 (m, 2H), 7.16-7.14 (m, 2H), 6.35 (s, 1H), 4.30 (brs, 2H), 3.39-3.37 (m, 2H), 3.12-3.09 (m, 2H), 2.78 (d,  $J$  = 5.6 Hz, 3H), 1.28 (s, 9H); MS (ESI) *m/z*: 540.3 (M+H<sup>+</sup>).



Using general method D, Example A38 (0.1 g, 0.22 mmol) and Example A13 (0.037 g, 0.15 mmol) were combined and the product deprotected using general method F to yield 1-(1-(3-(2-amino-2-oxoethyl)phenyl)-3-t-butyl-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea 1-(3-t-butyl-1-(1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(5-chloropyridin-3-yloxy)phenyl)urea (27 mg, 51%, 2 steps) as the HCl salt. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$

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9.77 (s, 1H), 9.49 (brs, 2H), 8.83 (s, 1H), 8.43 (d,  $J = 1.6$  Hz, 1H), 8.33 (d,  $J = 2.0$  Hz, 1H), 7.63-7.62 (m, 1H), 7.43-7.41 (m, 2H), 7.34-7.29 (m, 3H), 7.15-7.13 (m, 1H), 6.72 (dd,  $J = 8.0$  Hz, 2.0 Hz, 1H), 6.32 (s, 1H), 4.29 (brs, 2H), 3.38-3.35 (m, 2H), 3.08 (t,  $J = 6.0$  Hz, 2H), 1.26 (s, 9H); MS (ESI)  $m/z$ : 517.3 ( $M+H^+$ ).

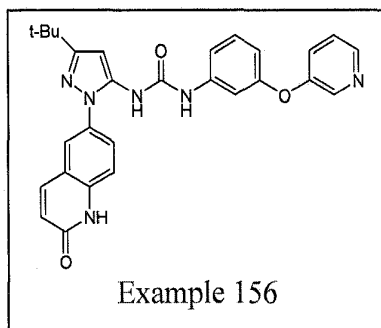


To a solution of hydrocarbostyryl (7.8 g, 0.53 mol) in conc.  $H_2SO_4$  (200 mL) was slowly added  $H_2O$  (50 mL) at  $-10^\circ C$ . Conc.  $HNO_3$  (70%, 4.0 mL) was added dropwise at  $-10^\circ C$ . The yellow solution was stirred at  $-10^\circ C$  for 10 min and then carefully quenched with ice  $H_2O$  (500 mL). The precipitated yellow solid was filtered, washed with  $H_2O$  and dried under vacuum to obtain 6-nitro-3,4-dihydroquinolin-2(1H)-one (7.9 g, 78% yield).  $^1H$  NMR (400 Mhz,  $CDCl_3$ ):  $\delta$  9.28 (s, 1H), 8.12 (m, 2H), 6.95 (d,  $J = 9.2$  Hz, 1H), 3.12 (t,  $J = 7.2$  Hz, 2H), 2.75 (d,  $J = 7.2$  Hz, 2H).

**[0165]** To a solution of 6-nitro-3,4-dihydroquinolin-2(1H)-one (0.46 g, 2.4 mmol) and NBS (0.53 g, 3.0 mmol) in  $CHCl_3$  (20 mL) was added benzoyl peroxide (cat. amount) at RT. The mixture was refluxed at  $80^\circ C$  for 3h. More NBS (0.25 g) was added and the reaction mixture was refluxed at  $80^\circ C$  for 1h. The solvent was evaporated and the residue was dissolved in EtOH. The solid was filtered, washed with EtOH and dried under vacuum to obtain 6-nitroquinolin-2-ol as a pale yellow solid (0.36 g, 79% yield).  $^1H$  NMR (400 MHz,  $DMSO-d_6$ ):  $\delta$  8.71 (d,  $J = 2.0$  Hz, 1H), 8.34 (dd,  $J = 2.8$ , and 9.2 Hz, 1H), 8.14 (d,  $J = 9.6$  Hz, 1H), 7.44 (d,  $J = 9.2$  Hz, 1H), 6.68 (dd,  $J = 1.6$ , and 9.6 Hz, 1H). LC-MS (EI)  $m/z$ : 191.0 ( $M+H^+$ ).

**[0166]** A mixture of 6-nitroquinolin-2-ol and  $PtO_2$  (20 mg) in EtOH (30 mL) was stirred under  $H_2$  (1 atm) for 20h. More  $PtO_2$  (10 mg) was added and was stirred under  $H_2$  (1 atm) for 2 days. The solution was filtered and washed with MeOH and  $CHCl_3$ . The solvent was evaporated and the residue was dried under vacuum to obtain 6-aminoquinolin-2(1H)-one as a yellow solid (0.28 g, 92% yield). LC-MS (EI)  $m/z$ : 161.0 ( $M+H^+$ ).

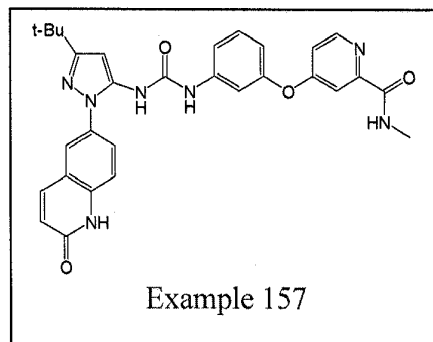
**[0167]** To a solution of 6-aminoquinolin-2(1H)-one in conc. HCl (1.5 mL) was added an aqueous solution (0.75 mL) of  $NaNO_2$  dropwise at  $0^\circ C$ . The reaction mixture was stirred at  $0^\circ C$  for 1h, and then added a solution of  $SnCl_2 \cdot 2H_2O$  in conc. HCl (0.75 mL) dropwise at  $0^\circ C$ . The reaction mixture was allowed to reach RT over a period of 30 min and then stirred for additional 2h. The reaction mixture was diluted with EtOH. The mixture was filtered to remove some solids and then pivaloylacetone nitrile was added into the solution. The reaction mixture was heated at  $80^\circ C$  for 16h. The reaction mixture was evaporated and the residue was suspended in ethyl acetate (30 mL) and treated slowly with satd.  $Na_2CO_3$  (30 mL). The solution was extracted with EtOAc (3x). The combined organics were washed  $H_2O$  and dried ( $Na_2SO_4$ ). Filtration, evaporation, and drying under vacuum provided crude 6-(5-amino-3-*t*-butyl-1H-pyrazol-1-yl)quinolin-2(1H)-one which was used as is in the next reaction. LC-MS (EI)  $m/z$ : 283.0 ( $M+H^+$ ).



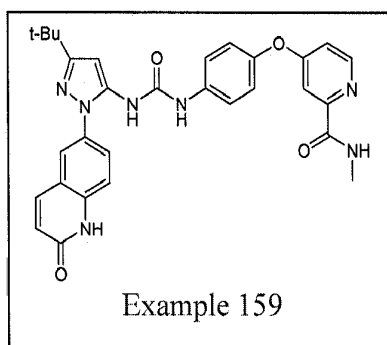
Using general method D, Example A41 (50 mg, 0.18 mmol) and Example A9 (34 mg, 0.18 mmol) were combined to yield 1-(3-*t*-butyl-1-(2-oxo-1,2-dihydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea as an off-white solid (34 mg, 45 % yield).  $^1H$  NMR ( $DMSO-d_6$ ):  $\delta$  9.01 (s, 1H), 8.40 (s, 1H), 8.37 (m, 2H), 7.98 (d,  $J = 9.6$  Hz, 1H), 7.82

## EP 2 942 349 A1

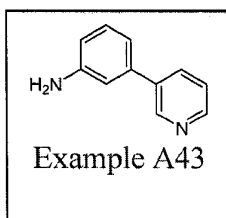
(d,  $J = 2.4$  Hz, 1H), 7.61 (dd,  $J = 2.4$ , and 8.8 Hz, 1H), 7.43 (m, 3H), 7.29 (t,  $J = 8.0$  Hz, 1H), 7.24 (t,  $J = 2.4$  Hz, 1H), 7.08 (dd,  $J = 1.6$ , and 8.4 Hz, 1H), 6.70 (dd,  $J = 2.4$ , and 8.4 Hz, 1H), 6.58 (dd,  $J = 2.0$ , and 10.0 Hz, 1H), 6.36 (s, 1H), 1.27 (s, 9H); LC-MS (EI)  $m/z$ : 495.2 ( $M + H^+$ ).



Using general method D, Example A41 (0.090 g, 0.20 mmol, 1.0 eq) and Example A12 (0.053 g, 0.22 mmol, 1.10 eq) and  $i\text{-Pr}_2\text{NEt}$  (0.044 ml, 0.25 mmol, 1.25 eq) were combined to yield 1-(3-t-butyl-1-(2-oxo-1,2-dihydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea (11.2 mg, 10% yield, 2 steps).  $^1\text{H}$  NMR (acetone- $d_6$ ): 9.04 (s, 1H), 8.49-8.48 (m, 1H), 8.44 (s, 1H), 8.35 (brs, 1H), 7.96-7.94 (m, 1H), 7.87-7.86 (m, 1H), 7.76-7.73 (m, 1H), 7.65-7.64 (m, 1H), 7.59-7.58 (m, 1H), 7.47-7.39 (m, 2H), 7.31-7.29 (m, 1H), 7.31-7.29 (m, 1H), 7.14-7.12 (m, 1H), 6.85-6.82 (m, 1H), 6.55 (s, 1H), 6/52 (s, 1H), 2.94 (s, 3H), 1.33 (s, 9H); MS (ESI)  $m/z$ : 552.2 ( $M+H^+$ ).



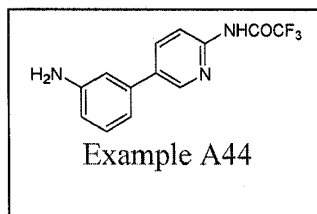
Using general method D, Example A41 (0.081 g, 0.19 mmol) and Example A12 (0.05 g, 0.21 mmol) were combined to afford 1-(3-t-butyl-1-(2-oxo-1,2-dihydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea (0.04 g, 60%, 2 steps) as a white solid HCl salt.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  9.48 (s, 1H), 8.89 (s, 1H), 8.72 (s, 1H), 8.52 (d,  $J = 5.6$  Hz, 1H), 8.01 (d,  $J = 9.6$  Hz, 1H), 7.88 (s, 1H), 7.66 (dd,  $J = 8.8$  Hz, 2.0 Hz, 1H), 7.53 (d,  $J = 8.8$  Hz, 2H), 7.47-7.43 (m, 3H), 7.18-7.13 (m, 3H), 6.59 (d,  $J = 9.6$  Hz, 1H), 6.37 (s, 1H), 2.79 (d,  $J = 4.8$  Hz, 3H), 1.29 (s, 9H); MS (ESI)  $m/z$ : 552.2 ( $M+H^+$ ).



To a degassed solution of 1-iodo-3-nitrobenzene (0.35 g, 1.4 mmol) in DME (5 mL) was added  $\text{Pd}(\text{PPh}_3)_4$  (0.08 g, 10% mol). After stirring for 5 min, 3-pyridylboronic acid (0.2 g, 1.65 mmol) and 2M  $\text{Na}_2\text{CO}_3$  (1 mL) solution were added. After refluxing for 16h under an Ar atmosphere, the reaction mixture was poured into  $\text{H}_2\text{O}$  (15 mL) and extracted with EtOAc (2x30 mL). The combined organic extracts were washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ), concentrated and purified via column chromatography to yield 3-(3-nitrophenyl)pyridine (0.22 g, 78%) as a white solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  8.94 (brs, 1H), 8.73

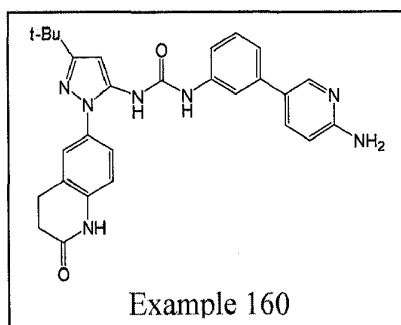
(brs, 1H), 8.48 (t,  $J = 1.6$  Hz, 1H), 8.32 - 8.29 (m, 1H), 7.98 - 7.93 (m, 2H), 7.72 - 7.68 (m, 1H), 7.48 (brs, 1H); Exact mass: 200.0, Found: 201.0 ( $M+1$ )<sup>+</sup>.

**[0168]** To a solution of 3-(3-nitrophenyl)pyridine (0.22 g, 1.1 mmol) in EtOAc (10 mL) was added  $PtO_2$  (0.025 g, 10% mol) and the mixture was stirred for 4h under  $H_2$  (1 atm). It was filtered through Celite® and the combined filtrates were concentrated to yield 3-(pyridin-3-yl)benzenamine (0.175 g, 94%) as a semi solid which was used without further purification. <sup>1</sup>H NMR (DMSO- $d_6$ ):  $\delta$  8.77 (d,  $J = 2.0$  Hz, 1H), 8.53 (dd,  $J = 8.8$  Hz, 1.6 Hz, 1H), 7.57-7.52 (m, 1H), 7.46-7.43 (m, 1H), 7.13 (t,  $J = 8.0$  Hz, 1H), 6.86 - 6.80 (m, 2H), 6.63 - 6.60 (m, 1H), 5.23 (s, 2H); Exact mass: 170.0, Found: 171.0 ( $M+1$ )<sup>+</sup>.



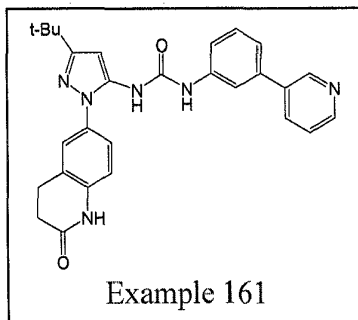
Using the same procedure as for Example A43, 5-iodo-2-aminopyridine (0.31 g, 1.4 mmol) and 3-nitrophenylboronic acid (0.28 g, 1.7 mmol) were combined to yield 5-(3-nitrophenyl)pyridin-2-amine (0.18 g, 60%) as a white solid. <sup>1</sup>H NMR (DMSO- $d_6$ ):  $\delta$  8.37 (d,  $J = 2.4$  Hz, 1H), 8.34 (t,  $J = 2.0$  Hz, 1H), 8.11 - 8.04 (m, 2H), 7.83 (dd,  $J = 8.0$  Hz, 2.4 Hz, 1H), 7.68 (t,  $J = 8.0$  Hz, 1H), 6.55 (dd,  $J = 8.4$  Hz, 0.8 Hz, 1H), 6.26 (s, 2H); Exact mass: 215.0, Found: 216.0 ( $M+1$ )<sup>+</sup>.

**[0169]** To a solution of 5-(3-nitrophenyl)pyridin-2-amine (0.17 g, 0.8 mmol) in  $CH_2Cl_2$  (10 mL) was added pyridine (0.12 g, 1.6 mmol) and TFAA (0.2 g, 0.9 mmol). After stirring for 1h at RT, 3M HCl (20 mL) was added to the reaction and the product was extracted with  $CH_2Cl_2$  (2x20 mL). The combined organic extracts were washed with satd.  $NaHCO_3$  solution (1x25 mL) and brine, then dried ( $Na_2SO_4$ ) and concentrated to yield a solid. This solid was dissolved in EtOAc, and  $PtO_2$  was added to this mixture which was stirred under  $H_2$  (1 atm) for 4h. The mixture was filtered through Celite®, and the combined filtrates were concentrated to yield N-(5-(3-aminophenyl)pyridin-2-yl)-2,2,2-trifluoroacetamide (0.21 g, 95%) as a solid which was used without further purification. <sup>1</sup>H NMR (DMSO- $d_6$ ):  $\delta$  8.65 (d,  $J = 2.4$  Hz, 1H), 8.11 - 8.09 (m, 1H), 8.03 - 8.01 (m, 1H), 7.16 (t,  $J = 8.0$  Hz, 1H), 6.92-6.88 (m, 2H), 6.66 - 6.64 (m, 1H); Exact mass: 281.1, Found: 282.3 ( $M+1$ )<sup>+</sup>.

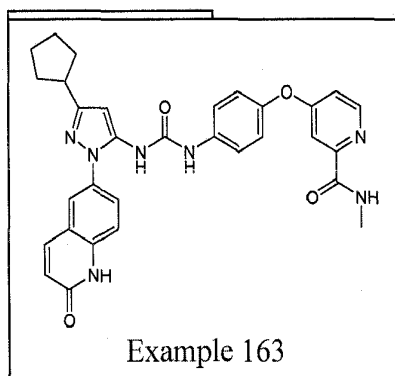


Using general procedure D, Example A35 (0.09 g, 0.2 mmol) and Example A44 (0.05 g, 0.20 mmol) were combined and deprotected using general method G to yield 1-(3-(6-aminopyridin-3-yl)phenyl)-3-(3-t-butyl-1-(2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-1H-pyrazol-5-yl)urea (47 mg, 45% yield) as a solid. <sup>1</sup>H NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  10.27 (s, 1H), 9.40 (s, 1H), 8.58 (s, 1H), 8.23-8.21 (m, 2H), 8.11 (brs, 1H), 7.77 (s, 1H), 7.38-7.33 (m, 2H), 7.28-7.24 (m, 2H), 7.10 (d,  $J = 0.8$  Hz, 1H), 6.97 (d,  $J = 0.8$  Hz, 1H), 6.35 (s, 1H), 2.95 (t,  $J = 6.4$  Hz, 2H), 1.27 (s, 9H); MS (ESI)  $m/z$ : 496.3 ( $M+H$ )<sup>+</sup>.

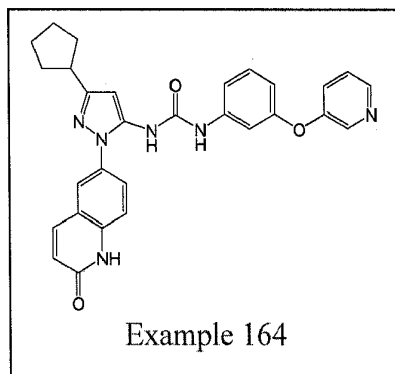




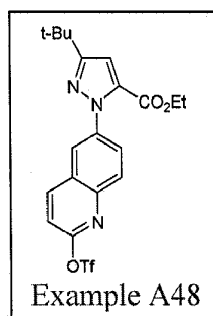
Using general method D, Example A35 (0.09 g, 0.2 mmol) and Example A43 (0.034 g, 0.2 mmol) were combined to yield 1-(3-t-butyl-1-(2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yl)phenyl)urea (76 mg, 74%) as a white solid as the HCl salt. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 10.27 (s, 1H), 9.70-9.67 (m, 1H), 9.16 (s, 1H), 8.89 (s, 1H), 8.77 (brs, 2H), 8.11-8.08 (m, 1H), 7.95 (s, 1H), 7.47 (s, 2H), 7.35 (s, 1H), 7.29 (d, *J* = 8.4 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 6.36 (s, 1H), 2.95 (t, *J* = 7.6 Hz, 2H), 1.27 (s, 9H); MS (ESI) *m/z*: 481.2 (M+H<sup>+</sup>).



To a suspension of 6-aminoquinolin-2(1H)-one (0.72 g, 4.5 mmol, see Example A41) in conc. HCl (5 mL) was slowly added NaNO<sub>2</sub> (0.43 g, 6.3 mmol) solution in H<sub>2</sub>O (5 mL) at 0 °C. After stirring for 1h, SnCl<sub>2</sub>·2H<sub>2</sub>O (2.0 g, 9.0 mmol), dissolved in conc. HCl (7 mL), was slowly added at such a rate that the temperature of the mixture did not rise above 5 °C. After stirring for 2h, the resultant solid was filtered, dried, and suspended in EtOH. To this were added 3-cyclopentyl-3-oxopropanenitrile (0.68 g, 4.9 mmol) and a few drops of HCl and the mixture was heated at 80 °C for 16h. The solution was concentrated, dissolved in satd. NaHCO<sub>3</sub> solution and the product was extracted with EtOAc (2x30 mL). The combined organic extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated and the resultant solid triturated with toluene (10 mL) and filtered to yield 6-(5-amino-3-cyclopentyl-1H-pyrazol-1-yl)quinolin-2(1H)-one (0.75 g, 57% yield) as a solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 7.95 (d, *J* = 10.0 Hz, 1H), 7.81 (d, *J* = 2.4 Hz, 1H), 7.68 (dd, *J* = 8.8 Hz, 2.0 Hz, 1H), 7.35 (d, *J* = 8.8 Hz, 1H), 6.54 (d, *J* = 8.8 Hz, 1H), 5.32 (s, 1H), 5.24 (brs, 2H), 2.92-2.84 (m, 1H), 1.94-1.86 (m, 2H), 1.73-1.57 (m, 6H); MS (ESI) *m/z*: 295.2 (M+H<sup>+</sup>). Using general method D, Example A45 (0.075 g, 0.16 mmol) and Example A12 (0.04 g, 0.16 mmol) were combined to yield 1-(3-cyclopentyl-1-(2-oxo-1,2-dihydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea (0.038 g, 31% yield, 2 steps) as a solid HCl salt. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.59 (brs, 1H), 8.88 (brs, 1H), 8.81 (s, 1H), 8.51 (d, *J* = 6.0 Hz, 1H), 8.01 (d, *J* = 9.6 Hz, 1H), 7.89 (d, *J* = 2.4 Hz, 1H), 7.67 (dd, *J* = 8.8 Hz, 2.0 Hz, 1H), 7.54-7.42 (m, 4H), 7.17-7.13 (m, 3H), 7.58 (d, *J* = 9.6 Hz, 1H), 6.33 (s, 1H), 3.06-2.98 (m, 1H), 2.78 (d, *J* = 6.0 Hz, 3H), 1.99-1.94 (m, 2H), 1.72-1.59 (m, 6H); MS (ESI) *m/z*: 564.3 (M+H<sup>+</sup>).



Using general method D, Example A45 (0.075 g, 0.16 mmol) and Example A9 (0.03 g, 0.16 mmol) were combined to yield 1-(3-cyclopentyl-1-(2-oxo-1,2-dihydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea (0.07 g, 52%, 2 steps) as a solid.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.63-9.61 (m, 1H), 8.80-8.79 (m, 1H), 8.65-8.64 (m, 1H), 8.57-8.56 (m, 1H), 7.98 (d,  $J$  = 10.0 Hz, 1H), 7.93-7.90 (m, 1H), 7.86 (d,  $J$  = 4.4 Hz, 1H), 7.83-7.79 (m, 1H), 7.64 (dd,  $J$  = 8.8 Hz, 2.0 Hz, 1H), 7.42-7.38 (m, 2H), 7.34 (t,  $J$  = 8.0 Hz, 1H), 7.15-7.13 (m, 1H), 6.76 (dd,  $J$  = 8.0 Hz, 2.0 Hz, 1H), 6.57 (d,  $J$  = 10.0 Hz, 1H), 6.29 (s, 1H), 3.04-2.97 (m, 1H), 1.98-1.93 (m, 2H), 1.72-1.60 (m, 6H); MS (ESI)  $m/z$ : 507.2 ( $\text{M}+\text{H}^+$ ).



To a solution of commercially available 6-bromo-1,2,3,4-tetrahydro-2-quinolinone (5.0 g, 22 mmol) and NBS (4.9 g, 27 mmol) in  $\text{CHCl}_3$  (80 mL) was added a catalytic portion of benzoyl peroxide at RT. The mixture was refluxed at 80 °C for 3h, after which additional NBS (2.0 g) was added and the reaction refluxed overnight at 80 °C. Additional NBS (0.9 g) was added into the reaction mixture which was refluxed at 80 °C for 5h. The solid was filtered, washed with EtOH and dried to yield 6-bromoquinolin-2(1H)-one (4.35 g, 88% yield) as a pale yellow solid.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  7.93 (d,  $J$  = 2.8 Hz, 1H), 7.88 (d,  $J$  = 9.6 Hz, 1H), 7.64 (dd,  $J$  = 2.0, and 8.8 Hz, 1H), 7.25 (d,  $J$  = 8.8 Hz, 1H), 6.55 (dd,  $J$  = 2.0, and 9.6 Hz, 1H); LC-MS (EI)  $m/z$ : 224.0 ( $\text{M}+\text{H}^+$ ).

**[0170]** 6-Bromoquinolin-2(1H)-one (4.0 g, 18 mmol), 4-methoxybenzyl chloride (3.6 g, 23 mmol), and tetrabutylammonium bromide (1.2 g, 3.6 mmol) were dissolved in PhMe (200 mL) and then KOH (powder, 1.8 g, 32 mmol) was added into the reaction mixture. The reaction mixture was stirred at RT for 4h, then poured into  $\text{H}_2\text{O}$  and extracted with EtOAc (3x50 mL). The organic layer was washed with  $\text{H}_2\text{O}$ , dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated. Trituration with hexane, followed by collection of the solids yielded 1-(4-methoxybenzyl)-6-bromoquinolin-2(1H)-one (5.4 g, 87% yield) as a yellow solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.70 (d,  $J$  = 2.4 Hz, 1H), 7.66 (d,  $J$  = 9.6 Hz, 1H), 7.52 (dd,  $J$  = 2.0, and 8.8 Hz, 1H), 7.19 (d,  $J$  = 9.2 Hz, 1H), 7.16 (d,  $J$  = 8.8 Hz, 2H), 6.85 (d,  $J$  = 8.8 Hz, 2H), 6.83 (d,  $J$  = 9.4 Hz, 1H), 5.48 (brs, 2H), 3.78 (s, 3H), 1.36 (s, 12H); LC-MS (EI)  $m/z$ : 344.0 ( $\text{M}+\text{H}^+$ ).

**[0171]** Potassium acetate (54.3 g, 44 mmol), pinacol diboron (5.5 g, 22 mmol) and  $\text{PdCl}_2(\text{dppf})$  (0.60 mg, 0.73 mmol) were added sequentially to a solution 1-(4-methoxybenzyl)-6-bromoquinolin-2(1H)-one (5.0 g, 15 mmol) in DMF (70 mL). After flushing with  $\text{N}_2$ , the reaction vessel was sealed and heated at 80 °C for 14h and then partitioned between  $\text{H}_2\text{O}$  and EtOAc. The combined organic extracts were washed with brine, dried ( $\text{MgSO}_4$ ) concentrated and purified via column chromatography to yield 1-(4-methoxybenzyl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinolin-2(1H)-one (38 g, 67% yield) as a yellow solid.  $^1\text{H}$  NMR (400 MHz,  $\text{EDCl}_3$ ):  $\delta$  8.04 (brs, 1H), 7.86 (dd,  $J$  = 1.2, and 8.4 Hz, 1H), 7.76 (d,  $J$  = 9.6 Hz, 1H), 7.32 (d,  $J$  = 9.2 Hz, 1H), 7.17 (d,  $J$  = 8.4 Hz, 2H), 6.83 (d,  $J$  = 8.8 Hz, 2H), 6.80 (d,  $J$  = 9.6 Hz, 1H), 5.52 (brs, 2H), 3.77 (s, 3H), 1.36 (s, 12H); LC-MS (EI)  $m/z$ : 392.3 ( $\text{M}+\text{H}^+$ ).

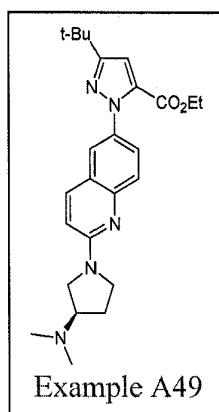
**[0172]** Sodium periodate (5.9 g, 28 mmol) was added to a solution of 1-(4-methoxybenzyl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinolin-2(1H)-one (3.6 g, 9.2 mmol) in THF/ $\text{H}_2\text{O}$  (4/1, 40 mL). The reaction mixture was stirred

at RT for 30 min, after which 2N HCl (9.2 mL) was added and the solution was then stirred at RT for 3h. The solution was extracted with EtOAc (3x50 mL) and the organic layer was dried (MgSO<sub>4</sub>), and concentrated to yield crude 1-(4-methoxybenzyl)-2-oxo-1,2-dihydroquinolin-6-ylboronic acid (2.6 g, 90% yield) which was used without further purification. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.10 (brs, 1H), 7.96 (d, *J* = 9.2 Hz, 1H), 7.88 (dd, *J* = 1.6, and 8.8 Hz, 1H), 7.39 (d, *J* = 9.2 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 6.69 (d, *J* = 9.6 Hz, 1H), 5.45 (brs, 2H), 3.69 (s, 3H); LC-MS (EI) *m/z*: 310.0 (M+H<sup>+</sup>).

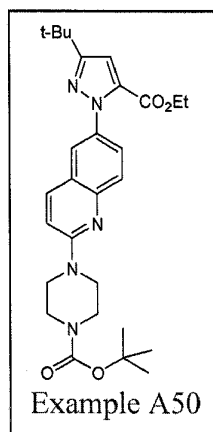
**[0173]** 1-(4-Methoxybenzyl)-2-oxo-1,2-dihydroquinolin-6-ylboronic acid (1.8 g, 5.8 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (120 mL) and pyridine (10 mL) with molecular sieves (activated, 4A) and the solution was kept overnight at RT. Commercially available ethyl 3-*t*-butyl-1*H*-pyrazole-5-carboxylate (1.2 g, 5.8 mmol), Cu(OAc)<sub>2</sub> (1.1 g, 5.8 mmol) and molecular sieves (4Å activated, powder) were added to the boronic acid solution and the reaction mixture was stirred open to the air at RT for 3 days. The reaction mixture was filtered through a pad of Celite®, and the filtrate was evaporated under reduced pressure and purified by silica gel column chromatography to yield ethyl 1-(1-(4-methoxybenzyl)-2-oxo-1,2-dihydroquinolin-6-yl)-3-*t*-butyl-1*H*-pyrazole-5-carboxylate (2.5 g, 94% yield). LC-MS (EI) *m/z*: 460.3 (M+H<sup>+</sup>).

**[0174]** A solution of ethyl 1-(1-(4-methoxybenzyl)-2-oxo-1,2-dihydroquinolin-6-yl)-3-*t*-butyl-1*H*-pyrazole-5-carboxylate (1.5 g, 3.3 mmol) in TFA (25 mL) was heated in a sealed tube at 100 °C for 7h. The mixture was cooled, concentrated and purified by silica gel column chromatography to yield ethyl 3-*t*-butyl-1-(2-oxo-1,2-dihydroquinolin-6-yl)-1*H*-pyrazole-5-carboxylate (1.0 g, 90% yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.95 (d, *J* = 9.6 Hz, 1H), 7.77 (d, *J* = 2.0 Hz, 1H), 7.66 (dd, *J* = 2.4, and 8.4 Hz, 1H), 7.46 (d, *J* = 8.8 Hz, 1H), 6.94 (s, 1H), 6.82 (d, *J* = 9.2 Hz, 1H). LC-MS (EI) *m/z*: 340.3 (M+H<sup>+</sup>).

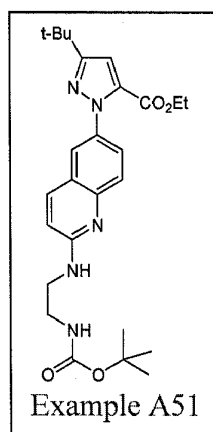
**[0175]** To a stirred suspension of ethyl 3-*t*-butyl-1-(2-oxo-1,2-dihydroquinolin-6-yl)-1*H*-pyrazole-5-carboxylate (1.0 g, 2.95 mmol) and Et<sub>3</sub>N (0.45 g, 4.45 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (30 mL) was added triflic anhydride (1.66 g, 5.9 mmol) at -78 °C and then maintained at this temperature for 30 min. The reaction was allowed to warm to RT over a period 1.5h, then quenched by pouring onto ice. The organic layer was washed with 10% NaOH, extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x50 mL), washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated and purified by column chromatography to yield ethyl 3-*t*-butyl-1-(2-(trifluoromethylsulfonyloxy)quinolin-6-yl)-1*H*-pyrazole-5-carboxylate (1.3 g, 94% yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.40 (d, *J* = 8.8 Hz, 1H), 8.12 (d, *J* = 9.2 Hz, 1H), 8.04 (d, *J* = 2.0 Hz, 1H), 7.90 (dd, *J* = 2.4 and 9.2 Hz, 1H), 7.31 (d, *J* = 8.8 Hz, 1H), 6.99 (s, 1H), 4.28 (q, *J* = 7.2 Hz, 2H), 1.41 (s, 9H), 1.30 (t, *J* = 7.2 Hz, 3H); LC-MS (EI) *m/z*: 472.0 (M+H<sup>+</sup>).



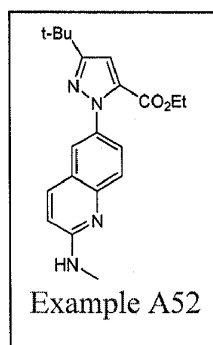
To a solution of Example A48 (0.10 g, 0.21 mmol) in DMSO (1 mL) was added (R)-N,N-dimethylpyrrolidin-3-amine (0.055 g, 0.47 mmol). The reaction mixture was heated at 40 °C for 1h. Ethyl acetate was added and the resulting solution was washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure to yield ethyl 3-*t*-butyl-1-(2-((R)-3-(dimethylamino)pyrrolidin-1-yl)quinolin-6-yl)-1*H*-pyrazole-5-carboxylate (88 mg, 95% yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.89 (d, *J* = 8.8 Hz, 1H), 7.75 (d, *J* = 8.8 Hz, 1H), 7.69 (d, *J* = 2.0 Hz, 1H), 7.56 (dd, *J* = 2.0 and 8.4 Hz, 1H), 6.92 (s, 1H), 6.76 (d, *J* = 9.2 Hz, 1H), 4.21 (q, *J* = 7.6 Hz, 2H), 4.03 (m, 1H), 3.88 (m, 1H), 3.60 (m, 1H), 3.49 (m, 1H), 2.98 (m, 1H), 2.63 (s, 6H), 2.33 (m, 1H), 2.04 (m, 1H), 1.40 (s, 9H), 1.21 (t, *J* = 7.6 Hz, 3H); LC-MS (EI) *m/z*: 436.2 (M+H<sup>+</sup>).



Using the same procedure as for Example A49, Example A48 (0.2 g, 0.42 mmol) and t-butyl piperazine-1-carboxylate (0.17 g, 0.93 mmol) were combined to yield t-butyl 4-(6-(5-amino-3-t-butyl-1H-pyrazol-1-yl)quinolin-2-yl)piperazine-1-carboxylate (210 mg, 98% yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.94 (d, *J* = 8.8 Hz, 1H), 7.74 (d, *J* = 8.8 Hz, 1H), 7.71 (d, *J* = 2.4 Hz, 1H), 7.58 (dd, *J* = 2.4 and 8.8 Hz, 1H), 7.01 (d, *J* = 9.2 Hz, 1H), 6.92 (s, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 3.77 (m, 4H), 3.61 (m, 4H), 2.64 (s, 6H), 1.52 (s, 9H), 2.33 (m, 1H), 1.40 (s, 9H), 1.22 (t, *J* = 7.6 Hz, 3H); LC-MS (EI) *m/z*: 508.3 (M+H<sup>+</sup>).

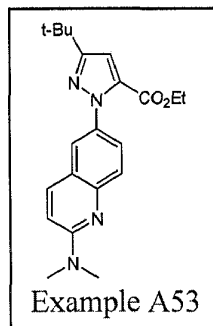


Using the same procedure as for Example A49, Example A48 (0.20 g, 0.42 mmol) and t-butyl 2-aminoethylcarbamate (0.15 g, 0.93 mmol) were combined to yield ethyl 1-(2-(2-(t-butoxycarbonyl)ethylamino)quinolin-6-yl)-3-t-butyl-1H-pyrazole-5-carboxylate (0.20 mg, 98% yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.85 (d, *J* = 9.2 Hz, 1H), 7.75 (d, *J* = 8.8 Hz, 1H), 7.70 (d, *J* = 2.4 Hz, 1H), 7.59 (dd, *J* = 2.4 and 8.8 Hz, 1H), 6.93 (s, 1H), 6.73 (m, 1H), 5.57 (brs, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 3.70 (brq, *J* = 5.2 Hz, 2H), 3.45 (brq, *J* = 5.2 Hz, 2H), 1.45 (s, 9H), 1.40 (s, 9H), 1.24 (t, *J* = 7.2 Hz, 3H); LC-MS (EI) *m/z*: 482.2 (M+H<sup>+</sup>).

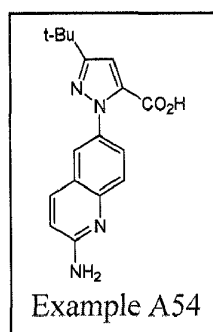


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Using the same procedure as for Example A49, Example A48 (0.20 g, 0.42 mmol) and MeNH<sub>2</sub>·HCl (0.043 g, 0.64 mmol) were combined to yield ethyl 3-*t*-butyl-1-(2-(dimethylamino)quinolin-6-yl)-1*H*-pyrazole-5-carboxylate (82 mg, 55% yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.90 (d, *J* = 9.2 Hz, 1H), 7.68 (d, *J* = 2.8 Hz, 1H), 7.53 (d, *J* = 9.2 Hz, 1H), 7.46 (dd, *J* = 2.0, and 8.8 Hz, 1H), 7.17 (q, *J* = 4.8 Hz, 1H), 6.98 (s, 1H), 6.80 (d, *J* = 8.8 Hz, 1H), 2.92 (d, *J* = 4.8 Hz, 1H), 1.32 (s, 9H); LC-MS (EI) *m/z*: 353.2 (M+H<sup>+</sup>).

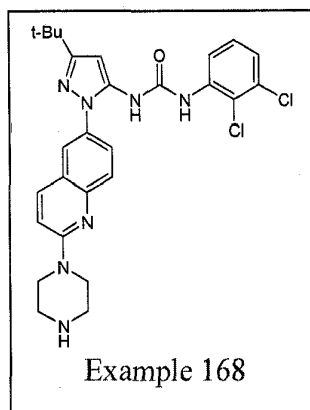


Using the same procedure as for Example A49, Example A48 (0.20 g, 0.42 mmol) and Me<sub>2</sub>NH·HCl (0.026 g, 0.32 mmol) were combined to yield ethyl 3-*t*-butyl-1-(2-(dimethylamino)quinolin-6-yl)-1*H*-pyrazole-5-carboxylate (82 mg, 55% yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.04 (s, 1H), 7.88 (m, 1H), 7.73 (m, 1H), 7.68 (brs, 1H), 7.57 (m, 1H), 6.94 (d, *J* = 8.8 Hz, 1H), 6.92 (s, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 2.98 (s, 3H), 2.90 (s, 3H), 1.40 (s, 9H), 1.21 (t, *J* = 7.2 Hz, 3H); LC-MS (EI) *m/z*: 367.3 (M+H<sup>+</sup>).



Using the same procedure as for Example A49, Example A48 (0.15 g, 0.42 mmol) and 4-methoxybenzylamine (0.13 g, 0.93 mmol) were combined to yield ethyl 1-(2-(4-methoxybenzylamino)quinolin-6-yl)-3-*t*-butyl-1*H*-pyrazole-5-carboxylate (150 mg, 77%). LC-MS (EI) *m/z*: 459.2 (M+H<sup>+</sup>).

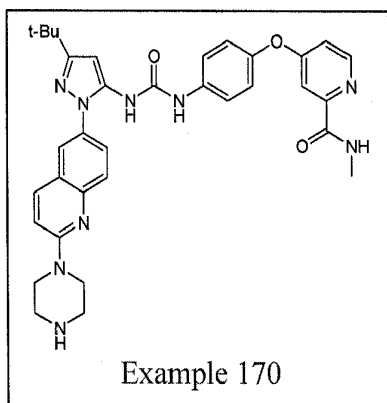
**[0176]** Using general method E, this material was saponified to yield 1-(2-(4-methoxybenzylamino)quinolin-6-yl)-3-*t*-butyl-1*H*-pyrazole-5-carboxylic acid in quantitative yield. A solution of this material in TFA (25 mL) was heated in sealed tube at 100 °C for 7h. The mixture was cooled, concentrated and purified by silica gel column chromatography to yield 1-(2-aminoquinolin-6-yl)-3-*t*-butyl-1*H*-pyrazole-5-carboxylic acid (0.1 g, 99% yield). LC-MS (EI) *m/z*: 311.2 (M+H<sup>+</sup>).



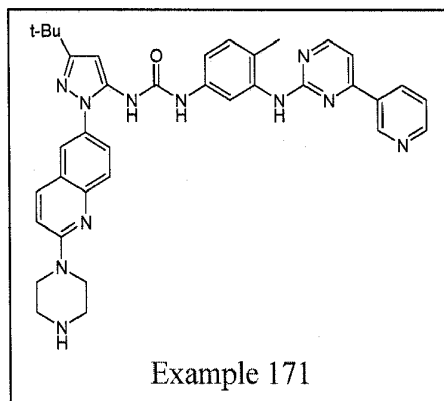
To a solution of Example A50 (0.21 g, 0.41 mmol) in a mix of EtOH:dioxane:H<sub>2</sub>O (1:1:1) (1 mL) was added LiOH (40 mg, 1.7 mmol). The mixture was stirred overnight at RT then diluted with EtOAc (50 mL) and 5% citric acid (50 mL). The organic phase was separated, washed with brine (20 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated and dried to yield 1-(2-(4-(t-butoxycarbonyl)piperazin-1-yl)quinolin-6-yl)-3-t-butyl-1H-pyrazole-5-carboxylic acid as a yellow solid in quantitative yield. LC-MS (EI) m/z: 480.2 (M+H<sup>+</sup>).

**[0177]** To a solution of 1-(2-(4-(t-butoxycarbonyl)piperazin-1-yl)quinolin-6-yl)-3-t-butyl-1H-pyrazole-5-carboxylic acid (0.1 g, 0.21 mmol) in toluene (2 mL) was added Et<sub>3</sub>N (0.032 mL, 0.23 mmol) and 2,3-dichloroaniline (84 mg, 0.52 mmol). The reaction mixture was stirred at RT and DPPA (63 mg, 0.23 mmol) was added. The reaction mixture was heated at 100 °C for 2h, cooled, quenched with H<sub>2</sub>O, and extracted with EtOAc (3x50 mL). The organic extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated and purified by column chromatography to yield t-butyl 4-(6-(3-t-butyl-5-(3-(2,3-dichlorophenyl)ureido)-1H-pyrazol-1-yl)quinolin-2-yl)piperazine-1-carboxylate (0.11 g, 83% yield). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.26 (s, 1H), 8.77 (s, 1H), 8.17 (d, *J* = 9.6 Hz, 1H), 8.07 (dd, *J* = 3.2, and 6.8 Hz, 1H), 7.87 (d, *J* = 2.0 Hz, 1H), 7.68 (m, 2H), 7.31 (m, 3H), 6.42 (s, 1H), 3.74 (m, 4H), 3.47 (m, 4H), 1.44 (s, 9H), 1.30 (s, 9H); LC-MS (EI) m/z: 638.3 (M+H<sup>+</sup>).

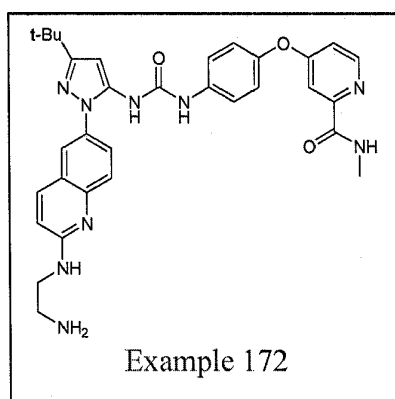
**[0178]** The material from the previous reaction (0.11 g, 0.17 mmol) was dissolved in EtOAc, 3M HCl/EtOAc (2 mL) was added and the solution was stirred at RT for 5h. The solution was concentrated and the residue was dissolved in H<sub>2</sub>O/CH<sub>3</sub>CN (1:1, 4 mL) and lyophilized to obtain 1-(3-t-butyl-1-(2-(piperazin-1-yl)quinolin-6-yl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea (65 mg, 66% yield) as a white solid HCl salt. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.55 (brs, 1H), 9.37 (brs, 2H), 8.89 (s, 1H), 8.40 (brd, *J* = 7.6 Hz, 1H), 8.07 (brs, 1H), 8.00 (m, 2H), 7.87 (m, 1H), 7.53 (brd, *J* = 8.4 Hz, 1H), 7.29 (d, *J* = 4.8 Hz, 2H), 6.42 (s, 1H), 4.10 (m, 4H), 3.29 (m, 4H), 1.30 (s, 9H); LC-MS (EI) m/z: 538.3 (M+H<sup>+</sup>).



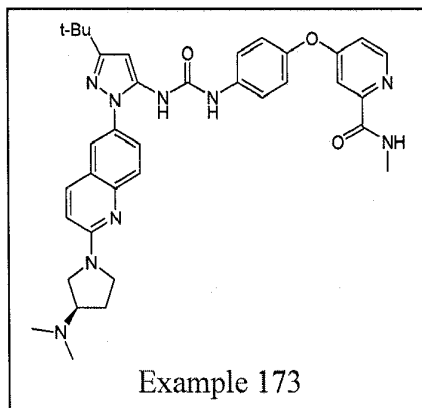
Using the same procedure as for Example 168, Example A50 (0.10 g, 0.21 mmol) and Example A12 (0.13 g, 0.52 mmol) were combined to yield 1-(3-t-butyl-1-(2-(piperazin-1-yl)quinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea (90 mg, 59% yield, 3 steps) as an off-white solid HCl salt. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.33 (brs, 1H), 9.02 (brs, 2H), 8.78 (m, 2H), 8.63 (brs, 1H), 8.50 (d, *J* = 5.6 Hz, 1H), 8.30 (m, 1H), 7.94 (m, 1H), 7.80 (m, 1H), 7.52 (m, 2H), 7.45 (m, 1H), 7.36 (d, *J* = 2.4 Hz, 1H), 7.13 (m, 2H), 6.41 (s, 1H), 4.01 (m, 4H), 3.27 (m, 4H), 2.78 (d, *J* = 4.8 Hz, 3H), 1.31 (s, 9H); LC-MS (EI) m/z: 620.2 (M+H<sup>+</sup>).



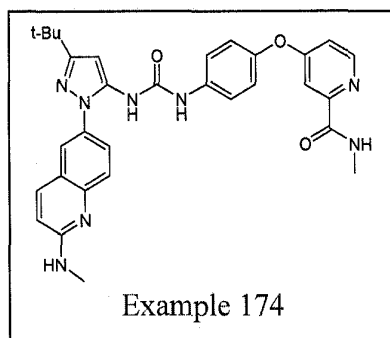
Using the same procedure as for Example 168, Example A50 (0.10 g, 0.21 mmol), and Example A7 (0.14 g, 0.52 mmol) were combined to yield 1-(3-t-butyl-1-(2-(piperazin-1-yl)quinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenyl)urea (94 mg, 57% yield, 3 steps) as the HCl salt.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.36 (brm, 1H), 9.27 (brm, 1H), 8.99 (brs, 1H), 8.82 (brd,  $J = 4.8$  Hz, 1H), 8.78 (brm, 1H), 8.56 (d,  $J = 5.2$  Hz, 1H), 8.37 (brd,  $J = 9.2$  Hz, 1H), 8.04 (brs, 1H), 7.95 (brm, 1H), 7.83 (m, 1H), 7.76 (brm, 1H), 7.49 (m, 2H), 7.11 (d,  $J = 8.8$  Hz, 1H), 7.06 (dd,  $J = 2.0$  and 8.4 Hz, 2H), 6.41 (s, 1H), 4.14 (brm, 4H), 3.28 (brm, 4H), 3.15 (brd,  $J = 4.8$  Hz, 3H), 2.18 (s, 3H), 1.32 (s, 9H); LC-MS (EI)  $m/z$ : 654.3 ( $\text{M}+\text{H}^+$ ).



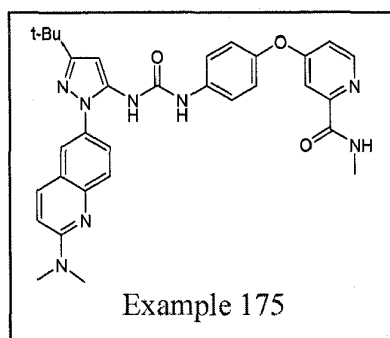
Using the same procedure as for Example 168, Example A51 (0.10 g, 0.21 mmol) and Example A12 (0.11 g, 0.44 mmol) were combined to yield 1-(1-(2-(2-aminoethylamino)quinolin-6-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea (100 mg, 75% yield, 3 steps) as a pale yellow solid HCl salt.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.51 (brs, 1H), 8.80 (brs, 1H), 8.78 (m, 1H), 8.50 (d,  $J = 6.0$  Hz, 1H), 8.39 (m, 1H), 8.15 (m, 3H), 7.98 (m, 1H), 7.52 (m, 2H), 7.36 (d,  $J = 2.8$  Hz, 1H), 7.21 (m, 1H), 7.14 (m, 3H), 6.42 (s, 1H), 3.92 (m, 2H), 3.18 (m, 2H), 2.78 (d,  $J = 4.8$  Hz, 3H), 1.31 (s, 9H); LC-MS (EI)  $m/z$ : 594.2 ( $\text{M}+\text{H}^+$ ).



Using the same procedure as for Example 168, Example A49 (0.08 g, 0.21 mmol) and Example A12 (0.13 g, 0.52 mmol) were combined to yield 1-(3-t-butyl-1-(2-((R)-3-(dimethylamino)pyrrolidin-1-yl)quinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea (30 mg, 20% yield) as a yellow solid HCl salt.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.38 (s, 1H), 8.77 (m, 2H), 7.35 (d,  $J = 2.8$  Hz, 1H), 7.14 (m, 3H), 6.41 (s, 1H), 4.15 (brs, 1H), 4.06 (brs, 1H), 3.95 (brs, 1H), 3.64 (brs, 1H), 2.87 (brt,  $J = 5.6$  Hz, 6H), 2.78 (d,  $J = 4.8$  Hz, 3H), 1.31 (s, 9H); LC-MS (EI)  $m/z$ : 648.2 ( $\text{M} + \text{H}^+$ ).



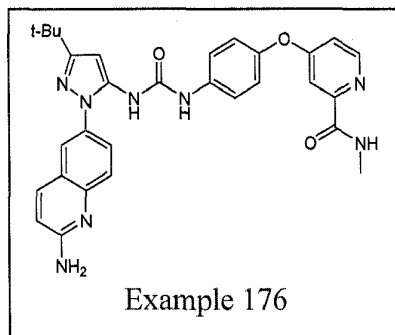
Using the same procedure as for Example 168, Example A52 (0.04 g, 0.11 mmol) and Example A12 (0.07 g, 0.27 mmol) were combined to yield 1-(3-t-butyl-1-(2-(methylamino)quinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea (53 mg, 74% yield) as the HCl salt.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.87 (brm, 1H), 9.38 (brs, 1H), 8.78 (brm, 1H), 8.74 (s, 1H), 8.50 (d,  $J = 5.6$  Hz, 1H), 8.35 (brd,  $J = 9.2$  Hz, 1H), 8.13 (brs, 1H), 8.11 (brm, 1H), 7.97 (dd,  $J = 2.0$ , and  $9.2$  Hz, 1H), 7.52 (d,  $J = 8.8$  Hz, 2H), 7.34 (d,  $J = 2.8$  Hz, 1H), 7.14 (m, 3H), 6.42 (s, 1H), 3.15 (brd,  $J = 4.8$  Hz, 3H), 2.78 (d,  $J = 5.2$  Hz, 3H), 1.31 (s, 9H); LC-MS (EI)  $m/z$ : 565.3 ( $\text{M} + \text{H}^+$ ).



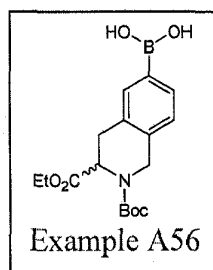
Using the same procedure as for Example 168, Example A53 (0.08, 0.21 mmol) and Example A12 (0.13 g, 0.52 mmol) were combined to yield 1-(3-t-butyl-1-(2-(dimethylamino)quinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea (61mg, 51% yield) as a pale yellow solid HCl salt.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.30 (brs, 1H), 8.78 (q,  $J = 4.4$  Hz, 1H), 8.69 (brs, 1H), 8.50 (d,  $J = 5.6$  Hz, 1H), 8.15 (m, 2H), 7.98 (m, 1H), 7.52 (m, 2H), 7.34 (d,



$J = 2.4$  Hz, 1H), 7.14 (m, 3H), 6.42 (s, 1H), 3.38 (brs, 6H), 2.78 (d,  $J = 4.8$  Hz, 3H), 1.31 (s, 9H); LC-MS (EI)  $m/z$ : 579.2 ( $M+H^+$ ).



Using the same procedure as for Example 168, Example A54 (0.085 g, 0.27 mmol) and Example A12 (0.10 g, 0.41 mmol) were combined to yield 1-(1-(2-aminoquinolin-6-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea (48 mg, 33% yield) as the HCl salt.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.59 (brs, 1H), 9.20 (brs, 1H), 8.90 (brs, 1H), 8.79 (q,  $J = 4.4$  Hz, 1H), 8.50 (d,  $J = 5.6$  Hz, 1H), 8.48 (d,  $J = 9.2$  Hz, 1H), 8.17 (d,  $J = 2.4$  Hz, 1H), 7.97 (dd,  $J = 2.0$ , and 8.8 Hz, 1H), 7.84 (d,  $J = 8.8$  Hz, 1H), 7.52 (m, 2H), 7.37 (m, 3H), 7.17 (m, 4H), 6.41 (s, 1H), 2.78 (d,  $J = 4.4$  Hz, 3H), 1.31 (s, 9H); LC-MS (EI)  $m/z$ : 551.2 ( $M+H^+$ ).



To a suspension of DL-m-tyrosine (5.00 g, 11.0 mmol) in 0.05 N HCl (50 mL) was added 37% aq. formaldehyde (5.00 mL, 5.2 g, 64.0 mmol) and the resulting slurry was heated at 90 °C for 1h and then cooled to RT. The mixture was filtered and the resulting solid was washed with  $\text{H}_2\text{O}$  and acetone and dried in vacuo to yield 6-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (3.31 g, 52% yield) as an off-white solid. MS (EI)  $m/z$ : 194.0 ( $M+H^+$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.03 (d,  $J = 8.0$  Hz, 1H), 6.69 (dd,  $J = 8.8$ , and 2.4 Hz, 1H), 7.00 (s, 1H), 4.28-4.19 (m, 2H), 3.80 (dd,  $J = 11.6$ , and 5.2 Hz, 1H), 3.31-3.27 (m, 1H), 3.05 (dd,  $J = 16.8$ , and 11.2 Hz, 1H), acid, hydroxy and amine protons not visible.

**[0179]** Acetyl chloride (30 mL, 33 g, 422 mmol) was added carefully to ice-cold anhydrous EtOH and the resulting solution was stirred at RT for 10 min. 6-Hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (3.30 g, 14 mmol) was added and the mixture was stirred at 50 °C for 5 h. The solvent was evaporated and the residue was dried under vacuum to yield ethyl 6-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (4.35 g, crude yield > 100%) as a yellow solid. MS expected 222.1 found 222.0.  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.06 (d,  $J = 8.4$  Hz, 1H), 6.74 (dd,  $J = 8.0$ , and 2.4 Hz, 1H), 6.69 (d,  $J = 2.4$  Hz, 1H), 4.44-4.29 (m, 5H), 3.35 (dd,  $J = 17.2$ , and 5.2 Hz, 1H), 3.15 (dd,  $J = 17.2$ , and 11.6 Hz, 1H), 1.35 (t,  $J = 7.2$  Hz, 3H).

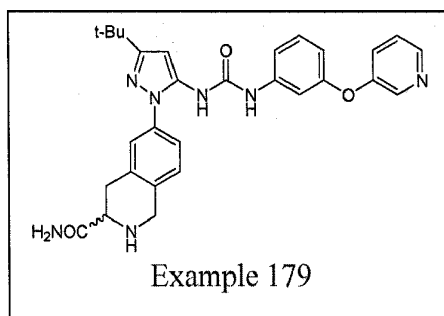
**[0180]** To a solution of the material from the previous reaction (3.70 g, 14.4 mmol) and  $\text{Et}_3\text{N}$  (6.00 mL, 4.36 g, 43.1 mmol) in  $\text{CH}_2\text{Cl}_2$  (100 mL) was added Boc anhydride (3.76 g, 17.2 mmol) at RT and the resulting mixture was stirred for 1h. Water (100 mL) was added and the mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 100 mL), dried ( $\text{MgSO}_4$ ), and concentrated under vacuum to yield 2-t-butyl 3-ethyl 6-hydroxy-3,4-dihydroisoquinoline-2,3(1H)-dicarboxylate (5.80 g, crude yield > 100%) as a light brown foam. MS (EI)  $m/z$ : 344.3 ( $M+\text{Na}^+$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) shows rotameric mixture.

**[0181]** To a solution of material from the previous reaction (4.61 g, 14.3 mmol) in  $\text{CH}_2\text{Cl}_2$  (100 mL) at RT was added  $\text{Et}_3\text{N}$  (3.00 mL, 2.18 g, 21.5 mmol) and triflic chloride (2.29 mL, 3.63 g, 21.5 mmol) and the resulting solution was stirred at RT for 1 h. Water (100 mL) was added and the mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (3x100 mL), dried ( $\text{MgSO}_4$ ), concentrated and purified by column chromatography to yield 2-t-butyl 3-ethyl 6-(trifluoromethylsulfonyloxy)-3,4-dihydroisoquinoline-2,3(1H)-dicarboxylate (6.30 g, 97% yield, 3 steps) as a white wax-like solid. MS (EI)  $m/z$ : 476.0 ( $M+\text{Na}^+$ ).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) shows rotameric mixture.

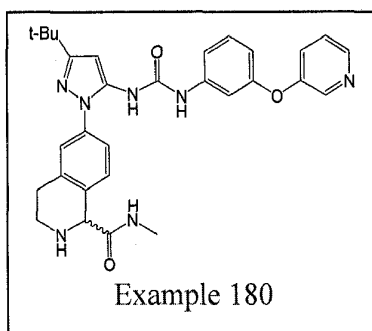
**[0182]** To a degassed solution of the material from the previous reaction (3.270 g, 7.21 mmol), bis(pinacolato)diboron (2.75 g, 0.662 mmol), and KOAc (2.12 g, 21.6 mmol) in DMF (10 mL) was added PdCl<sub>2</sub>(dppf)<sub>2</sub> (0.2945 g, 0.361 mmol) and the resulting mixture was stirred at 80 °C overnight. Water (100 mL) was added and the mixture was extracted with EtOAc (3x100 mL), dried (MgSO<sub>4</sub>), concentrated and purified by column chromatography to yield 2-t-butyl 3-ethyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroisoquinoline-2,3(1*H*)-dicarboxylate (2.77g, 89%) as a colorless oil. MS (EI) m/z: 454.2 (M+Na<sup>+</sup>).

**[0183]** To a solution of the material from the previous reaction (0.105 g, 0.243 mmol) in THF/H<sub>2</sub>O (4:1) (2 mL) was added NaIO<sub>4</sub> (0.160 g, 0.730 mmol) and the thick mixture was stirred for 30 min. Hydrochloric acid (2N, 0.24 mL, 0.48 mmol) was added and the resulting solution was stirred at RT overnight. Water (30 mL) was added and the mixture was extracted with EtOAc (3x100 mL), dried (MgSO<sub>4</sub>), concentrated and dried under vacuum to yield 2-(t-butoxycarbonyl)-3-(ethoxycarbonyl)-1,2,3,4-tetrahydroisoquinolin-6-ylboronic acid (66 mg, 78%) of the crude boronic acid as an orange-yellow solid. MS (EI) m/z: 372.3 (M+Na<sup>+</sup>). This material was used without further purification.



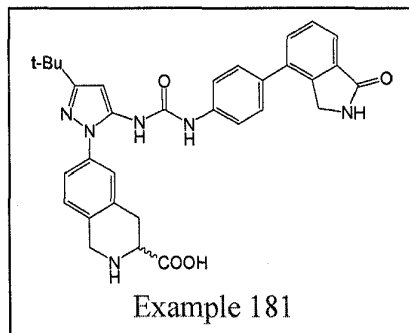
To a solution of Example A32 (0.025 g, 0.071 mmol), Example A56 (0.064 g, 0.180 mmol) and pyridine (0.011 g, 0.14 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was added Cu(OAc)<sub>2</sub> (0.019 g, 0.11 mmol) and the resulting green solution was stirred at RT open to air for 72h, replacing evaporated solvent as needed. Water (20 mL) was added and the mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x20 mL), dried (MgSO<sub>4</sub>), concentrated and purified by column chromatography to yield 2-t-butyl 3-ethyl 6-(3-t-butyl-5-(3-(3-(pyridin-3-yloxy)phenyl)ureido)-1*H*-pyrazol-1-yl)-3,4-dihydroisoquinoline-2,3(1*H*)-dicarboxylate (13 mg, 28% yield) as a yellow oil. MS (EI) m/z: 655.2 (M+H<sup>+</sup>).

**[0184]** A solution of the material from the previous reaction (0.013 g, 0.020 mmol) in 2N HCl in EtOH (5 mL) was stirred overnight. The solvent was evaporated and the residue was dissolved in 7N NH<sub>3</sub>/MeOH and the solution was stirred in a sealed vessel at 60 °C overnight. The solvent was evaporated and the residue was purified by reverse phase chromatography. Basic reextraction and acidification with HCl yielded 1-(3-t-butyl-1-(3-carbamoyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-1*H*-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea (7 mg, 59% yield) as an off-white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ 8.66 (d, *J* = 2.8 Hz, 1H), 8.59 (d, *J* = 5.6 Hz, 1H), 8.21 (ddd, *J* = 8.8, 2.4, and 1.2 Hz, 1H), 8.04 (dd, *J* = 8.4, and 5.4 Hz, 1H), 7.58 (t, *J* = 2.2 Hz, 1H), 7.52 (s, 1H), 7.50 (d, *J* = 1.6 Hz, 1H), 7.45 (d, *J* = 10.0 Hz, 1H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.19 (ddd, *J* = 8.0, 1.8, and 0.8 Hz, 1H), 6.89 (ddd, *J* = 8.0, 2.4, and 1.2 Hz, 1H), 6.50 (s, 1H), 4.54 (d, *J* = 16.0 Hz, 1H), 4.49 (d, *J* = 16.0 Hz, 1H), 4.29 (dd, *J* = 12.0, and 5.0 Hz, 1H), 3.54 (dd, *J* = 17.2, and 4.8 Hz, 1H), 1.36 (s, 9H), one proton is buried under the MeOH peak; MS (EI) m/z: 526.2 (M+H<sup>+</sup>).



Using the same procedure as for Example 179, 2-t-butyl 3-ethyl 6-(3-t-butyl-5-(3-(3-(pyridin-3-yloxy)phenyl)ureido)-1*H*-pyrazol-1-yl)-3,4-dihydroisoquinoline-2,3(1*H*)-dicarboxylate (0.053 g, 0.081 mmol), available from Example 188) in

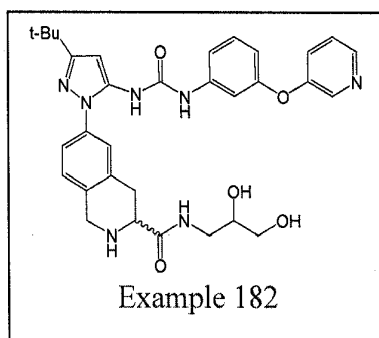
3N hydrochloric acid in MeOH (10.0 mL) was stirred at RT for 1 h. The solvent was evaporated and the residue was dissolved in 8N MeNH<sub>2</sub>/MeOH (3 mL) and the solution was stirred in a sealed vessel at 50 °C overnight. The solvent was evaporated and the residue was purified by reverse phase chromatography and coevaporated with THF/4N HCl to yield 1-(3-t-butyl-1-(1-(methylcarbamoyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea (43 mg, 87% yield) as a yellow solid. <sup>1</sup>H-NMR (MeOH-d<sub>4</sub>): δ 8.66 (d, 1H, J = 2.4 Hz), 8.59 (d, 1H, J = 5.6 Hz), 8.22 (ddd, 1H, J = 9.2, 2.4, 1.2 Hz), 8.05 (dd, 1H, J = 8.0, 6.0 Hz), 7.60-7.54 (m, 4H), 7.42 (t, 1H, J = 8.0 Hz), 7.20 (dd, 1H, J = 7.6, 1.2 Hz), 6.90 (dd, 1H, J = 8.4, 2.0 Hz), 6.53 (s, 1H), 5.23 (s, 1H), 3.80-3.74 (m, 1H), 3.56-3.49 (m, 1H), 3.26-3.14 (m, 2H), 2.88 (s, 3H). 1.36 (s, 9H). MS expected 540.3 found 540.3



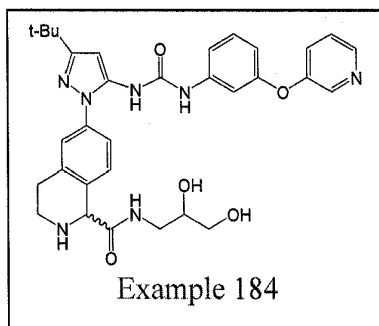
To a solution of 4-(4-aminophenyl)isoindolin-1-one (0.327 g, 1.46 mmol, made according to literature procedures) in EtOAc (5 mL) was added NaOH (2N, 2 mL, 4 mmol) and Troc-Cl (0.618 g, 2.92 mmol) and the resulting mixture was stirred at RT for 6h. Water (20 mL) was added and the mixture was extracted with EtOAc (3x20 mL), dried (MgSO<sub>4</sub>) and concentrated. The residue was dissolved in DMF (2 mL) to which was added 5-amino-3-t-butylpyrazole (0.831 g, 5.97 mmol, made according to literature procedures) and i-Pr<sub>2</sub>NEt (0.406 g, 2.92 mmol) and the solution was stirred at 90 °C overnight. Water (100 mL) was added and the mixture was extracted with EtOAc (3x100 mL), dried (MgSO<sub>4</sub>) and concentrated. Addition of CH<sub>2</sub>Cl<sub>2</sub> to the residue resulted in precipitation of the product. The product was collected and dried to yield 1-(3-t-butyl-1H-pyrazol-5-yl)-3-(4-(1-oxoisoindolin-4-yl)phenyl)urea (270 mg, 48% yield) as a light brown powder. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 9.31 (s, br, 1H), 8.95 (s, br, 1H), 8.65 (s, br, 1H), 7.65-7.63 (m, 2H), 7.58-7.52 (m, 5H), 6.00 (s, br, 1H), 4.51 (s, 2H), 1.25 (s, 9H), one NH is not visible. MS expected 390.2 found 390.2.

**[0185]** To a solution of the material from the previous reaction (0.200 g, 0.514 mmol) and Example A54 (0.179 g, 0.514 mmol) in DMF (2 mL) was added pyridine (0.122 g, 1.54 mmol) and Cu(OAc)<sub>2</sub> (0.140 g, 0.770 mmol) and the resulting solution was stirred under a balloon of air at RT for 96h. Water (20 mL) was added and the mixture was extracted with EtOAc (3x20 mL), dried (MgSO<sub>4</sub>), concentrated and purified by column chromatography to yield 2-t-butyl 3-ethyl 6-(3-t-butyl-5-(3-(4-(1-oxoisoindolin-4-yl)phenyl)ureido)-1H-pyrazol-1-yl)-3,4-dihydroisoquinoline-2,3(1H)-dicarboxylate (50 mg, 14%) as a yellow powder. MS expected 693.3 found 693.2.

**[0186]** A solution of the material from the previous reaction (0.025 g, 0.036 mmol) in 3N HCl/MeOH was stirred at RT for 1 h. The solvent was evaporated and the residue was dried in vacuo. The residue was dissolved in THF (3 mL) and 2N NaOH (2 mL) was added. MeOH was added until the mixture became homogenous. After 1 h, the mixture was acidified with conc. HCl, concentrated and purified by reverse phase chromatography to yield 6-(3-t-butyl-5-(3-(4-(1-oxoisoindolin-4-yl)phenyl)ureido)-1H-pyrazol-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (16 mg, 74%) as a white solid. <sup>1</sup>H-NMR (MeOH-d<sub>4</sub>): δ 7.79 (d, 1H, J = 7.2 Hz), 7.66-7.48 (m, 9H), 6.63 (s, 1H), 4.62-4.47 (m, 5H), 3.61 (dd, 1H, J = 17.6, 4.8 Hz), 3.38-3.31 (m, 1H), 1.40 (s, 9H). MS expected 565.3 found 565.3.

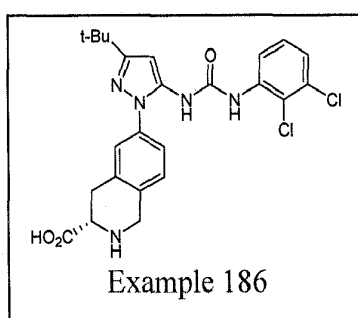


Using the same method as for Example 184, a solution of methyl 6-(3-*t*-butyl-5-(3-(3-(pyridin-3-yloxy)phenyl)ureido)-1*H*-pyrazol-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (0.017 g, 0.026 mmol, available in Example 179) in 3*N* HCl in MeOH (2 mL) was stirred at RT overnight. The solvent was evaporated and the residue was dissolved in MeOH (0.5 mL). 3-Amino-1,2-dihydroxypropane (0.200 g, 2.20 mmol) was added and the solution was kept at RT overnight. The mixture was directly loaded on to a reverse phase column and purified to yield 1-(1-(3-((2,3-dihydroxypropyl)carbamoyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)-3-*t*-butyl-1*H*-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea (16 mg, 97% yield) as a yellow solid. <sup>1</sup>H-NMR (MeOH-*d*<sub>4</sub>): δ 8.66 (s, 1H), 8.60 (d, 1H, *J* = 5.6 Hz), 8.23-8.20 (m, 1H), 8.05 (dd, 1H, *J* = 8.8, 5.6 Hz), 7.57 (t, 1H, *J* = 2.0 Hz), 7.52-7.40 (m, 4H), 7.23 (d, 1H, *J* = 8.4 Hz), 6.89 (dd, 1H, *J* = 7.6, 1.6 Hz), 6.54 (s, 1H), 4.56 (d, 1H, *J* = 16.8 Hz), 4.51 (d, 1H, *J* = 16.8 Hz), 4.29 (dd, 1H, *J* = 12.0, 4.4 Hz), 3.78-3.72 (m, 1H), 3.54-3.45 (m, 5H), 1.36 (s, 9H), one proton is buried under the MeOH peak, urea, amide, amine and hydroxy protons not visible. MS expected 600.3 found 600.2

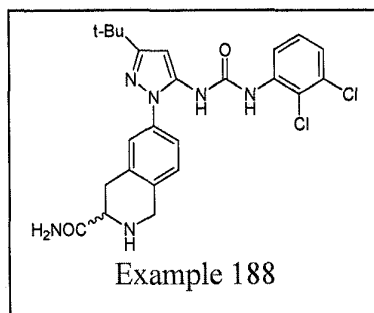


Using the same procedure as for Example 179, 2-*t*-butyl 3-ethyl 6-(3-*t*-butyl-5-(3-(3-(pyridin-3-yloxy)phenyl)ureido)-1*H*-pyrazol-1-yl)-3,4-dihydroisoquinoline-2,3(1*H*)-dicarboxylate (0.029 g, 0.044 mmol), available from experimental 184) in 3*N* hydrochloric acid in MeOH (10.0 mL) was stirred at RT for 1 h. The solvent was evaporated and the residue was dissolved in 3-amino-1,2-dihydroxypropane (0.200 g, 2.2 mmol) in MeOH (0.5 mL) and the solution was stirred at RT for 2 d. The solvent was evaporated and the residue was purified by reverse phase chromatography and coevaporated with THF/4*N* HCl to yield 1-(1-(1-((2,3-dihydroxypropyl)carbamoyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)-3-*t*-butyl-1*H*-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea (24 mg, 81% yield) as a pale yellow solid. <sup>1</sup>H-NMR (MeOH-*d*<sub>4</sub>): δ 8.68 (d, 1H, *J* = 3.2 Hz), 8.60 (d, 1H, *J* = 7.6 Hz), 8.23 (ddd, 1H, *J* = 8.8, 2.6, 1.0 Hz), 8.06 (dd, 1H, *J* = 8.4, 1.4 Hz), 7.70 (dd, 1H, *J* = 9.0, 1.8 Hz), 7.58-7.54 (m, 3H), 7.42 (t, 1H, *J* = 8.0 Hz), 7.22 (dt, 1H, *J* = 8.4, 1.0 Hz), 6.90 (dd, 1H, *J* = 6.8, 1.6 Hz), 6.58 (d, 1H, *J* = 1.2 Hz), 5.29 (s, 1H), 3.84-3.63 (m, 2H), 3.63-3.51 (m, 5H), 3.30-2.87 (m, 2H), 1.37 (s, 9H), urea, amine, hydroxy and amide protons not visible.

**[0187]** MS expected 600.3 found 600.2.

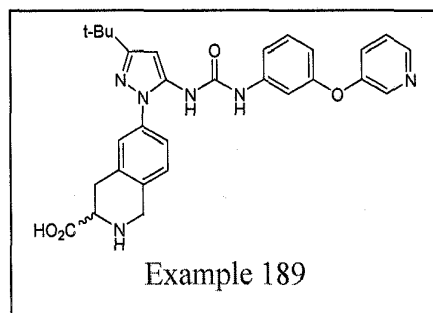


Using general method G, followed by general method E, (3*S*)-methyl 6-(3-*t*-butyl-5-(3-(2,3-dichlorophenyl)ureido)-1*H*-pyrazol-1-yl)-2-(2,2,2-trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate from Example A42 (0.080 g, 0.13 mmol) was deprotected and lyophilized to yield (3*S*)-6-(3-*t*-butyl-5-(3-(2,3-dichlorophenyl)ureido)-1*H*-pyrazol-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (42 mg, 60% yield) as an off-white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ 7.98 (t, *J* = 4.8 Hz, 1H), 7.49 (s, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.24 (d, *J* = 4.8 Hz, 1H), 7.24 (d, *J* = 4.8 Hz, 1H), 6.42 (s, 1H), 4.55 (d, *J* = 16.4 Hz, 1H), 4.48 (d, *J* = 16.4 Hz, 1H), 4.41 (dd, *J* = 10.8, and 4.8 Hz, 1H), 3.56 (dd, *J* = 17.6, and 4.4 Hz, 1H), 1.35 (s, 9H), one aliphatic proton is buried under the MeOH peak; MS (EI) *m/z*: 504.0 (*M*+*H*<sup>+</sup>).

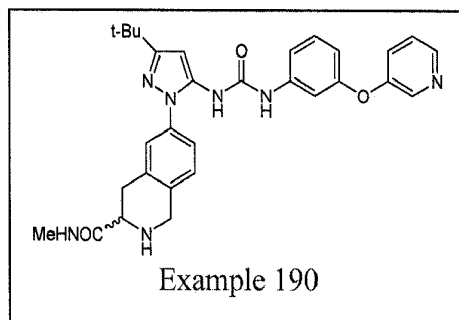


To a solution of Example A31 (0.066 g, 0.200 mmol), Example A56 (0.070 g, 0.200 mmol) and pyridine (0.032 g, 0.401 mmol) in  $\text{CH}_2\text{Cl}_2$  (2 mL) was added copper(II)-acetate (0.055 g, 0.301 mmol) and the resulting green solution was stirred at RT open to air for 96h, replacing evaporated solvent as needed.  $\text{H}_2\text{O}$  was added (20 mL) and the mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (3x20 mL), EtOAc (3x100 mL), dried ( $\text{MgSO}_4$ ), concentrated and purified via reverse phase column chromatography to yield 2-t-butyl 3-ethyl 6-(3-t-butyl-5-(3-(2,3-dichlorophenyl)ureido)-1H-pyrazol-1-yl)-3,4-dihydroisoquinoline-2,3(1H)-dicarboxylate (50 mg, 40%) as an off-white solid. MS (EI)  $m/z$ : 630.2 ( $\text{M}+\text{H}^+$ ).

**[0188]** A solution of the material from the previous reaction (0.040 g, 0.063 mmol) in 7N ammonia in MeOH (3 mL, 21 mmol) was heated at 70 °C for 8h. The solvent was evaporated and the residue was purified by reverse phase chromatography to yield 1-(3-t-butyl-1-(3-carbamoyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea (17 mg, 50% yield) as an off-white solid.  $^1\text{H}$  NMR (400 Mhz,  $\text{CD}_3\text{OD}$ ):  $\delta$  8.03 (t,  $J$  = 4.8 Hz, 1H), 7.56-7.54 (m, 2H), 7.49 (d,  $J$  = 8.8 Hz, 1H), 7.26-7.25 (m, 2H), 6.61 (s, 1H), 4.57 (d,  $J$  = 16.8 Hz, 1H), 4.51 (d,  $J$  = 16.4 Hz, 1H), 4.30 (dd,  $J$  = 12.0, and 4.6 Hz, 1H), 3.54 (dd,  $J$  = 17.6, and 4.8 Hz, 1H), 1.38 (s, 9H), one proton is buried under the MeOH peak, urea, amide and amine protons not visible; MS (EI)  $m/z$ : 501.2 ( $\text{M}+\text{H}^+$ ).



A solution of 2-t-butyl 3-ethyl 6-(3-t-butyl-5-(3-(3-(pyridin-3-yloxy)phenyl)ureido)-1H-pyrazol-1-yl)-3,4-dihydroisoquinoline-2,3(1H)-dicarboxylate (available from Example 179, 0.102 g, 0.160 mmol) in 3N HCl in MeOH (5 mL) was stirred for 1h. The solvent was evaporated. The residue was dissolved in THF (2 mL). 2N NaOH was added (2 mL) and then MeOH until homogenous. The solution was stirred at RT for 1h. The solvents were evaporated, the residue was purified by reverse phase chromatography followed by coevaporation with THF/HCl to yield 6-(3-t-butyl-5-(3-(3-(pyridin-3-yloxy)phenyl)ureido)-1H-pyrazol-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (20 mg, 100%) as a white solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  8.66 (d,  $J$  = 2.8 Hz, 1H), 8.59 (d,  $J$  = 5.2 Hz, 1H), 8.22 (ddd,  $J$  = 9.2, 2.8, and 0.8 Hz, 1H), 8.05 (dd,  $J$  = 8.8, 5.6 Hz, 1H), 7.58 (t,  $J$  = 2.0 Hz, 1H), 7.54-7.46 (m, 3H), 7.42 (t,  $J$  = 8.2 Hz, 1H), 7.21 (d,  $J$  = 8.0 Hz, 1H), 6.89 (dd,  $J$  = 8.4, and 2.4 Hz, 1H), 6.57 (s, 1H), 6.59 (d,  $J$  = 16.0 Hz, 1H), 4.51 (d,  $J$  = 16.0 Hz, 1H), 4.49 (dd,  $J$  = 11.2, and 5.2 Hz, 1H), 3.60 (dd,  $J$  = 18.0, and 4.8 Hz, 1H), 1.37 (s, 9H), acid, amine and urea protons not visible, one proton is buried under the MeOH peak; MS (EI)  $m/z$ : 527.2 ( $\text{M}+\text{H}^+$ ).



A solution of 2-t-butyl 3-ethyl 6-(3-t-butyl-5-(3-(3-(pyridin-3-yloxy)phenyl)ureido)-1H-pyrazol-1-yl)-3,4-dihydroisoquinoline-2,3(1H)-dicarboxylate (available from Example 179, 0.102 g, 0.160 mmol) in 3N HCl in MeOH (5 mL) was stirred for 1h. The solvent was evaporated and the residue was redissolved in 8N methylamine in EtOH and stirred at RT overnight. The solvent was evaporated, the residue was purified by reverse phase chromatography and coevaporation with THF/HCl to yield 1-(3-t-butyl-1-(3-(methylcarbamoyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea (20 mg, 92% yield) as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ 8.67 (d, *J* = 2.8 Hz, 1H), 8.60 (d, *J* = 5.6 Hz, 1H), 8.23 (ddd, *J* = 8.8, 2.8, and 1.0 Hz, 1H), 8.06 (dd, *J* = 8.8, and 5.6 Hz, 1H), 7.58 (t, *J* = 2.2 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 2H), 7.43 (t, *J* = 8.2 Hz, 1H), 7.26 (dd, *J* = 8.0, and 1.6 Hz, 1H), 6.90 (ddd, *J* = 8.4, 2.0, and 0.8 Hz, 1H), 6.64 (s, 1H), 4.56 (d, *J* = 16.4 Hz, 1H), 4.52 (d, *J* = 16.4 Hz, 1H), 4.28 (dd, *J* = 11.6, and 4.8 Hz, 1H), 3.50 (dd, *J* = 17.2, and 4.8 Hz, 1H), 2.86 (s, 3H), 1.38 (s, 9H), amide, urea and amine protons not visible, one proton is buried under the MeOH peak, methylamide protons split due to rotation barrier; MS (EI) *m/z*: 540.3 (M+H<sup>+</sup>).

#### General Experimental for Example 277

**[0189]** A solution of Example A20 and the appropriate isocyanate (general method A) or the appropriate aniline (general method D) were combined to yield the indicated compound.

| Example                                        | Name                                                                                                      | MS (EI)<br>(M+H <sup>+</sup> ) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> )                                                                                                                                                                                                                                                                                                                                       |
|------------------------------------------------|-----------------------------------------------------------------------------------------------------------|--------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p style="text-align: center;">Example 277</p> | 1-(3-t-butyl-1-(3-(pyridin-3-yl)phenyl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea<br>0.80 g, 40% | 505.2                          | 9.80 (s, 1H), 9.33 (s, 1H), 8.96 (s, 1H), 8.85 (d, <i>J</i> = 5.2 Hz, 1H), 8.81 (d, <i>J</i> = 8.0 Hz, 1H), 8.54 (d, <i>J</i> = 1.6 Hz, 1H), 8.49 (d, <i>J</i> = 4.4 Hz, 1H), 8.00 (m, 2H), 7.86 (d, <i>J</i> = 6.8 Hz, 1H), 7.69 (m, 4H), 7.35 (s, 1H), 7.31 (d, <i>J</i> = 8.4, 1H), 7.13 (d, <i>J</i> = 8.0 Hz, 1H), 6.72 (bd, <i>J</i> = 7.6 Hz, 1H), 6.40 (s, 1H), 1.29 (s, 9H); LC-MS (EI) |

#### General Experimental for Example 325

**[0190]** A solution of Example A35 and the appropriate isocyanate (general method A) or the appropriate aniline (general method D) were combined to yield the indicated compound.

| Example                                        | Name                                                                                                                                      | MS (EI)<br>(M+H <sup>+</sup> ) | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> )                                                                                    |
|------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| <p style="text-align: center;">Example 325</p> | 1-(3-t-butyl-1-(2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-phenoxyphenyl)urea.<br><br>50 mg, 42% yield General method A | 496.3                          | 1.24 (s, 9H), 2.46-2.50 (m, 2H), 2.92-2.95 (m, 2H), 6.31 (s, 1H), 6.61 (d, 1H), 6.95-7.41 (m, 11H), 8.29 (s, 1H), 9.09 (s, 1H), 10.27 (s, 1H) |

## Abl Kinase Assay

## Assay A1

5 **[0191]** The activity of Abl kinase was determined by following the production of ADP from the kinase reaction through coupling with the pyruvate kinase/lactate dehydrogenase system (e.g., Schindler, et al. Science (2000) 289, 1938-1942). In this assay, the oxidation of NADH (thus the decrease at  $A_{340nm}$ ) was continuously monitored spectrophotometrically. The reaction mixture (100  $\mu$ l) contained Abl kinase (1.9 nM, nominal concentration), peptide substrate (EAIYAAPFAKKK, 0.2 mM), pyruvate kinase (3.5 units), lactate dehydrogenase (5.5 units), phosphoenolpyruvate (1 mM), and NADH (0.28 mM) in 60 mM Tris buffer containing 0.13 % octyl-glucoside, 13 mM  $MgCl_2$  and 3.5 % DMSO at pH 7.5. The reaction was initiated by adding ATP (0.2 mM, final concentration). The absorption at 340 nm was continuously monitored for 3h at 30 °C on a Polarstar Optima plate reader (BMG). The reaction rate was calculated using the 1h to 2h time frame. Percent inhibition was obtained by comparison of reaction rate with that of a control (i.e. with no test compound).  $IC_{50}$  values were calculated from a series of percent inhibition values determined at a range of inhibitor concentrations using software routines as implemented in the GraphPad Prism software package.

## Assay A2

20 **[0192]** Abl kinase assay A2 is the same as for assay A1 except that (1) a nominal concentration of 1.1 nM of enzyme was employed (2) the reaction was pre-incubated at 30 °C for 2h prior to initiation with ATP (3) 0.5 mM ATP (final concentration) was used to initiate the reaction.

Abl protein sequence used for screening:

25 SPNYDKWEMERTDITMKHKLGGGQYGEVYEGVWKKYSLTVAVKTLKEDTMEVEEFLKEAAVMKEIKHPNLVQLLGVC  
TREPPFYIITEFMTYGNLLDYLRECNRQEVNAVLLYMATQISSAMEYLEKKNFIHRDLAARNCLVGENHLVKVADF  
GLSRLMTGDTYTAHAGAKFPIKWTAPESLAYNKFSSIKSDVWAFGVLLWEIATYGMSPYPGIDLSQVYELLEKDYRME  
RPEGCPEKVYELMRACWQWNPSPDRPSFAEIHQAFETMFQESSISDEVEKELGK

## 30 KDR Kinase Assay

## Assay K1

35 **[0193]** The activity of KDR kinase was determined by following the production of ADP from the kinase reaction through coupling with the pyruvate kinase/lactate dehydrogenase system (e.g., Schindler, et al. Science (2000) 289, 1938-1942). In this assay, the oxidation of NADH (thus the decrease at  $A_{340nm}$ ) was continuously monitored spectrophotometrically. The reaction mixture (100  $\mu$ l) contained KDR (1.5 nM to 7.1 nM, nominal concentration), polyE<sub>4</sub>Y (1 mg/ml), pyruvate kinase (3.5 units), lactate dehydrogenase (5.5 units), phosphoenolpyruvate (1 mM), and NADH (0.28 mM) in 60 mM Tris buffer containing 0.13 % octyl-glucoside, 13 mM  $MgCl_2$ , 6.8 mM DTT, and 3.5 % DMSO at pH 7.5. The reaction was initiated by adding ATP (0.2 mM, final concentration). The absorption at 340 nm was continuously monitored for 3h at 30 °C on a Polarstar Optima plate reader (BMG). The reaction rate was calculated using the 1h to 2h time frame. Percent inhibition was obtained by comparison of reaction rate with that of a control (i.e. with no test compound).  $IC_{50}$  values were calculated from a series of percent inhibition values determined at a range of inhibitor concentrations using software routines as implemented in the GraphPad Prism software package.

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## Assay K2

50 **[0194]** KDR kinase assay K2 is the same as for assay K1 except that (1) a nominal concentration of 2.1 nM of enzyme was employed (2) the reaction was pre-incubated at 30 °C for 2h prior to initiation with ATP (3) 1.0 mM ATP (final concentration) was used to initiate the reaction.

KDR protein sequence used for screening:

55 DPDELPLDEHCERLPYDASKWEFPRDRLKLGKPLGRGAFGQVIEADAFGIDKTATCRTVAVKMLKEGATHSEHRALM  
SELKILIHIGHHLNVVNLLGACTKPGGPLMVIVEFCKFGNLSTYLRSKRNEFVYPYKVAPEDLYKDFTLEHLICYSF  
QVAKGMEFLASRKCIHRDLAARNILLSEKNVVKICDFGLARDIYKDPDYVRKGDARLPLKWMAPETIFDRVYTIQSD  
VWSFGVLLWEIFSLGASPYPGVKIDEEFCRRLKEGTRMRAPDYTTPEMYQTMDCWHGEPSPQRPTFSELVEHLGNLL  
QANAQQD

**B-Raf(V599E) Kinase Assay**

## Assay B1

5 **[0195]** The activity of B-Raf(V599E) kinase was determined by following the formation of ADP from the reaction through coupling with the pyruvate kinase/lactate dehydrogenase system (e.g., Schindler, et al. Science (2000) 289, 1938-1942). In this assay, the oxidation of NADH (thus the decrease at  $A_{340nm}$ ) was continuously monitored spectrophotometrically. The reaction mixture (100  $\mu$ l) contained B-Raf(V599E) kinase (0.34 nM nominal concentration, construct 1), unphosphorylated, full-length MEK1 (42 nM),  $MgCl_2$  (13 mM), pyruvate kinase (3.5 units), lactate dehydrogenase (5.5 units),  
 10 phosphoenolpyruvate (1 mM), and NADH (0.28 mM), in 60 mM Tris buffer, containing 0.13% octyl-glucoside and 3.5 % DMSO concentration at pH 7.5. The test compounds were incubated with the reaction mixture at 30 °C for 2h. The reaction was initiated by adding ATP (0.2 mM, final concentration). The absorption at 340 nm was continuously monitored for 3h at 30 °C on a Polarstar Optima plate reader (BMG). The reaction rate was calculated using the 1.5h to 2.5h time frame. Percent inhibition was obtained by comparison of reaction rate with that of a control (i.e. with no test compound).  
 15  $IC_{50}$  values were calculated from a series of percent inhibition values determined at a range of inhibitor concentrations using software routines as implemented in the GraphPad Prism software package.

## Assay B2

20 **[0196]** Same as assay B1 except that (1) construct 2 was employed at a nominal concentration of 2 nM (2) the reaction was pre-incubated at 30 °C for 1h prior to initiation with ATP (3) a reading time frame of 0.5h to 1.5 h.

B-Raf(V599E) construct 1 protein sequence used for screening:

25 KSPGQREKSSSSSEDRNRMKTLGRRDSSDDWEIPDGQITVGQRIGSGSFGTVYKGKWHGDVAVKMLNVTAPTQQQLQAFKNEVGVLKTRHVNILLFMGYSTKPKQLAIVTQWCEGSSLYHHLHIIETKFEMIKLIDIAQTAQGM DY LHAKSI  
 30 IHRDLKSNNIFLHEDLTVKIGDFGLATEKSRWSGSHQFEQLSGSILWMAPEVIRMQDKNPYSFQSDVYAFGIVLYELMTGQLPYSNINNRDQIIIFMVGRGYLSPDL SKVRSNCPKAMKRLMAECLKKRDERPLFPQILASIELLARS LPKIHR  
 SASEPSLN RAGFQTEDFS LYACASPKTP IQAGGYGAFPVH

B-Raf(V599E) construct 2 protein sequence used for screening:

35 EDRNRMKTLGRRDSSDDWEIPDGQITVGQRIGSGSFGTVYKGKWHGDVAVKMLNVTAPTQQQLQAFKNEVGVLKTRHVNILLFMGYSTKPKQLAIVTQWCEGSSLYHHLHIIETKFEMIKLIDIAQTAQGM DY LHAKSI  
 40 IHRDLKSNNIFLHEDLTVKIGDFGLATEKSRWSGSHQFEQLSGSILWMAPEVIRMQDKNPYSFQSDVYAFGIVLYELMTGQLPYSNINNRDQIIIFMVGRGYLSPDL SKVRSNCPKAMKRLMAECLKKR DERPLFPQILASIELLARS LPKIHR

40 MEK1 protein sequence used for screening:

45 MELKDDDFEKISELGAGNGGVVFKVSHKPSGLVMARKLIHLEIKPAIRNQIIRELQVLHECN SPYIVGFYGA FYSDGEI  
 SICMEHMDGGSLDQVLKAGRIPEQILGKVSIAVIKGLTYLREKHKIMHRDVKPSNILVNSRGEIKLCDFGVSGQLIDS  
 50 MANSFVGTRSYMSPERLQGTHYSVQSDIWSMGLSLVEMAVGRYP I PPD AKELELMFGCQVEGDAAETPPRPRT PGRPL  
 SSGMDSRPPMAIFELLDYIVNEPPPKLP SGVFSLEFQDFVNKCLIKNPAERADLQQLMVHAFIKRSDAEEVD FAGWLC  
 STIGLNQ PSTPTHAAGV

**P-38  $\alpha$  Kinase Assay**

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## Assay P1

**[0197]** The activity of phosphorylated p-38- $\alpha$  kinase was determined by following the formation of ADP from the kinase reaction through coupling with the pyruvate kinase/lactate dehydrogenase system (e.g., Schindler, et al. Science  
 55 (2000) 289, 1938-1942). In this assay, the oxidation of NADH (thus the decrease at  $A_{340nm}$ ) was continuously measured spectrophotometrically. The reaction mixture (100  $\mu$ l) contained phosphorylated p-38  $\alpha$  kinase (7.1-9 nM nominal concentration), peptide substrate (IPTSPITTTYFFKKK-OH, 0.2 mM),  $MgCl_2$  (13 mM), pyruvate kinase (3.5 units), lactate dehydrogenase (5.5 units), phosphoenolpyruvate (1 mM), and NADH (0.28 mM) in 60 mM Tris buffer at pH 7.5,



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containing 130  $\mu$ M *n*-Dodecyl-B-D-maltopyranoside and 3.5 % DMSO concentration. The test compounds were incubated with the reaction mixture at 30 °C for 2h before the addition of ATP (0.3 mM final concentration). The absorption at 340 nm was monitored continuously for up to 3h at 30 °C on Polarstar Optima plate reader (BMG). The reaction rate was calculated using the time frame from 1.5h to 2.5h. Percent inhibition was obtained by comparison of reaction rate with that of a control (i.e. with no test compound). IC<sub>50</sub> values were calculated from a series of percent inhibition values determined at a range of inhibitor concentrations using software routines as implemented in the GraphPad Prism software package.

### Assay P2

**[0198]** Same as assay P1 except that (1) the reaction was not pre-incubated. P38-alpha protein sequence used for screening:

MSQERPTFYRQELNKTIEWEPERYQNLSPVSGAYGSVCAAFDTKTGLRVAVKKLSRPFQSIIHAKRTYRELRLKKH  
MKHENVIGLLDVFTPARSLEEFNDVYLVTHLMGADLNNIVKQKLTDDHVQFLIYQILRGLKYIHSADIIHRDLKPS  
NLAVNEDCELKILDGFLARHTTDEMTGYVATRWYRAPEIMLNWMHYNQTVDIWSVGCIMAELLTGRTLFPGTDHINQ  
LQQIMRLTGTPPAYLINRMPSHEARNYIQSLTQMPKMFANVFIGNPLAVDLLKMLVLDSDKRITAAQALAHAYF  
AQYHDPDDEFPVADPYDQSFESRDLLIDEWKSLTYDEVISFVPPPLDQEEMES

Abl Kinase Assay Data

| Example | Abl Data       | Method |
|---------|----------------|--------|
| 5       | 0.0035         | A2     |
| 67      | 0.001          | A2     |
| 72      | 0.002          | A2     |
| 86      | 0.001          | A2     |
| 97      | 0.0015         | A2     |
| 116     | 0.0066         | A2     |
| 119     | 0.012          | A2     |
| 133     | 0.048          | A2     |
| 140     | 0.12           | A1     |
| 142     | 0.17           | A1     |
| 143     | 0.25           | A1     |
| 148     | 0.0012         | A2     |
| 150     | 0.0013         | A2     |
| 156     | 0.005          | A2     |
| 157     | 0.031          | A2     |
| 159     | 0.0023         | A2     |
| 160     | 14.9           | A2     |
| 161     | 3% @ 1 $\mu$ M | A2     |
| 163     | 0.0063         | A2     |
| 164     | 0.033          | A2     |
| 168     | 1.1            | A2     |
| 170     | 0.0018         | A2     |
| 171     | 0.0040         | A2     |

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(continued)

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| <u>Example</u> | <u>Abl Data</u> | <u>Method</u> |
|----------------|-----------------|---------------|
| 172            | 0.0019          | A2            |
| 173            | 0.0042          | A2            |
| 174            | 0.0018          | A2            |
| 175            | 0.0015          | A2            |
| 176            | 0.0028          | A2            |
| 179            | 0.003           | A2            |
| 180            | 0.009           | A2            |
| 182            | 0.0034          | A2            |
| 184            | 0.010           | A2            |
| 188            | 0.11            | A1            |
| 189            | 0.003           | A2            |
| 190            | 0.004           | A2            |
| 277            | 0.029           | A2            |

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## KDR Kinase Assay Data

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| <u>Example</u> | <u>KDR Data</u> | <u>Method</u> |
|----------------|-----------------|---------------|
| 55             | 0.0040          | K2            |
| 72             | 0.0085          | K2            |
| 116            | 0.0050          | K2            |
| 119            | 0.018           | K1            |
| 140            | 2.3             | K1            |
| 143            | 0.94            | K1            |
| 156            | 0.0032          | K2            |
| 179            | 0.0064          | K2            |
| 180            | 0.0078          | K2            |
| 188            | 0.15            | K2            |
| 189            | 0.023           | K1            |
| 190            | 0.0081          | K2            |
| 277            | 0.010           | K2            |

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## BRaf Kinase Assay Data

| <u>Example</u> | <u>B-Raf Data</u> | <u>Method</u> |
|----------------|-------------------|---------------|
| 55             | 0.0054            | B1            |
| 67             | 0.0048            | B1            |
| 72             | 0.0044            | B1            |
| 86             | 0.179             | B2            |
| 97             | 0.0072            | B1            |

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(continued)

| <u>Example</u> | <u>B-Raf Data</u> | <u>Method</u> |
|----------------|-------------------|---------------|
| 116            | 0.0059            | B1            |
| 119            | 0.0091            | B1            |
| 140            | 0.0046            | B1            |
| 142            | 0.035             | B1            |
| 143            | 0.014             | B1            |
| 148            | 0.031             | B1            |
| 150            | 0.0047            | B1            |
| 156            | 0.0041            | B1            |
| 157            | 0.040             | B2            |
| 159            | 0.014             | B1            |
| 163            | 0.018             | B1            |
| 168            | 0.030             | B1            |
| 170            | 0.040             | B1            |
| 172            | 0.029             | B1            |
| 173            | 0.063             | B1            |
| 174            | 0.245             | B2            |
| 175            | 0.030             | B1            |
| 176            | 0.044             | B2            |
| 179            | 0.017             | B1            |
| 180            | 0.011             | B1            |
| 188            | 0.0058            | B1            |
| 189            | 0.918             | B2            |
| 277            | 0.011             | B1            |
| 325            | 0.0045            | B1            |

## P38 Kinase Assay Data

| <u>Example</u> | <u>P-38 Data</u> | <u>method</u> |
|----------------|------------------|---------------|
| 55             | 0.13             | P1            |
| 67             | 0.035            | P1            |
| 86             | 0.024            | P1            |
| 97             | 0.025            | P1            |
| 119            | 0.060            | P1            |
| 159            | 0.072            | P1            |
| 175            | 0.16             | P1            |
| 179            | 0.096            | P1            |
| 180            | 0.065            | P1            |
| 188            | 0.017            | P1            |

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(continued)

| <u>Example</u> | <u>P-38 Data</u> | <u>method</u> |
|----------------|------------------|---------------|
| 190            | 0.078            | P1            |
| 277            | 0.18             | P1            |

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## SEQUENCE LISTING

<110> Deciphera Pharmaceuticals, LLC  
 5 <120> Enzyme Modulators and Treatments  
 <130> 218-008T1  
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 35 40 45  
 Thr Met Glu Val Glu Glu Phe Leu Lys Glu Ala Ala Val Met Lys Glu  
 45 50 55 60  
 Ile Lys His Pro Asn Leu Val Gln Leu Leu Gly Val Cys Thr Arg Glu  
 50 65 70 75 80  
 Pro Pro Phe Tyr Ile Ile Thr Glu Phe Met Thr Tyr Gly Asn Leu Leu  
 85 90 95  
 55 Asp Tyr Leu Arg Glu Cys Asn Arg Gln Glu Val Asn Ala Val Val Leu  
 100 105 110

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Leu Tyr Met Ala Thr Gln Ile Ser Ser Ala Met Glu Tyr Leu Glu Lys  
115 120 125

5 Lys Asn Phe Ile His Arg Asp Leu Ala Ala Arg Asn Cys Leu Val Gly  
130 135 140

10 Glu Asn His Leu Val Lys Val Ala Asp Phe Gly Leu Ser Arg Leu Met  
145 150 155 160

Thr Gly Asp Thr Tyr Thr Ala His Ala Gly Ala Lys Phe Pro Ile Lys  
165 170 175

15 Trp Thr Ala Pro Glu Ser Leu Ala Tyr Asn Lys Phe Ser Ile Lys Ser  
180 185 190

20 Asp Val Trp Ala Phe Gly Val Leu Leu Trp Glu Ile Ala Thr Tyr Gly  
195 200 205

25 Met Ser Pro Tyr Pro Gly Ile Asp Leu Ser Gln Val Tyr Glu Leu Leu  
210 215 220

Glu Lys Asp Tyr Arg Met Glu Arg Pro Glu Gly Cys Pro Glu Lys Val  
225 230 235 240

30 Tyr Glu Leu Met Arg Ala Cys Trp Gln Trp Asn Pro Ser Asp Arg Pro  
245 250 255

35 Ser Phe Ala Glu Ile His Gln Ala Phe Glu Thr Met Phe Gln Glu Ser  
260 265 270

Ser Ile Ser Asp Glu Val Glu Lys Glu Leu Gly Lys  
275 280

40

<210> 2  
<211> 315  
<212> PRT  
<213> Homo sapiens

45

<400> 2

50 Asp Pro Asp Glu Leu Pro Leu Asp Glu His Cys Glu Arg Leu Pro Tyr  
1 5 10 15

Asp Ala Ser Lys Trp Glu Phe Pro Arg Asp Arg Leu Lys Leu Gly Lys  
20 25 30

55 Pro Leu Gly Arg Gly Ala Phe Gly Gln Val Ile Glu Ala Asp Ala Phe  
35 40 45

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|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
|    | Gly | Ile | Asp | Lys | Thr | Ala | Thr | Cys | Arg | Thr | Val | Ala | Val | Lys | Met | Leu |  |
|    | 50  |     |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |  |
| 5  | Lys | Glu | Gly | Ala | Thr | His | Ser | Glu | His | Arg | Ala | Leu | Met | Ser | Glu | Leu |  |
|    | 65  |     |     |     |     | 70  |     |     |     | 75  |     |     |     |     |     | 80  |  |
|    | Lys | Ile | Leu | Ile | His | Ile | Gly | His | His | Leu | Asn | Val | Val | Asn | Leu | Leu |  |
| 10 |     |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |  |
|    | Gly | Ala | Cys | Thr | Lys | Pro | Gly | Gly | Pro | Leu | Met | Val | Ile | Val | Glu | Phe |  |
|    |     |     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |  |
| 15 | Cys | Lys | Phe | Gly | Asn | Leu | Ser | Thr | Tyr | Leu | Arg | Ser | Lys | Arg | Asn | Glu |  |
|    |     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |  |
|    | Phe | Val | Pro | Tyr | Lys | Val | Ala | Pro | Glu | Asp | Leu | Tyr | Lys | Asp | Phe | Leu |  |
| 20 |     |     |     |     |     |     | 130 |     |     |     |     | 140 |     |     |     |     |  |
|    | Thr | Leu | Glu | His | Leu | Ile | Cys | Tyr | Ser | Phe | Gln | Val | Ala | Lys | Gly | Met |  |
| 25 |     |     |     |     |     | 145 |     |     |     |     | 150 |     |     | 155 |     | 160 |  |
|    | Glu | Phe | Leu | Ala | Ser | Arg | Lys | Cys | Ile | His | Arg | Asp | Leu | Ala | Ala | Arg |  |
|    |     |     |     |     | 165 |     |     |     |     | 170 |     |     |     |     | 175 |     |  |
| 30 | Asn | Ile | Leu | Leu | Ser | Glu | Lys | Asn | Val | Val | Lys | Ile | Cys | Asp | Phe | Gly |  |
|    |     |     |     |     |     | 180 |     |     | 185 |     |     |     |     | 190 |     |     |  |
|    | Leu | Ala | Arg | Asp | Ile | Tyr | Lys | Asp | Pro | Asp | Tyr | Val | Arg | Lys | Gly | Asp |  |
| 35 |     |     |     |     |     |     |     | 195 |     |     |     |     | 200 |     | 205 |     |  |
|    | Ala | Arg | Leu | Pro | Leu | Lys | Trp | Met | Ala | Pro | Glu | Thr | Ile | Phe | Asp | Arg |  |
|    |     |     |     |     |     |     | 210 |     |     |     |     | 215 |     |     | 220 |     |  |
| 40 | Val | Tyr | Thr | Ile | Gln | Ser | Asp | Val | Trp | Ser | Phe | Gly | Val | Leu | Leu | Trp |  |
|    |     |     |     |     |     | 225 |     |     |     |     | 230 |     | 235 |     |     | 240 |  |
|    | Glu | Ile | Phe | Ser | Leu | Gly | Ala | Ser | Pro | Tyr | Pro | Gly | Val | Lys | Ile | Asp |  |
| 45 |     |     |     |     |     | 245 |     |     |     | 250 |     |     |     |     | 255 |     |  |
|    | Glu | Glu | Phe | Cys | Arg | Arg | Leu | Lys | Glu | Gly | Thr | Arg | Met | Arg | Ala | Pro |  |
| 50 |     |     |     |     |     | 260 |     |     | 265 |     |     |     |     | 270 |     |     |  |
|    | Asp | Tyr | Thr | Thr | Pro | Glu | Met | Tyr | Gln | Thr | Met | Leu | Asp | Cys | Trp | His |  |
|    |     |     |     |     |     | 275 |     |     | 280 |     |     |     | 285 |     |     |     |  |
| 55 | Gly | Glu | Pro | Ser | Gln | Arg | Pro | Thr | Phe | Ser | Glu | Leu | Val | Glu | His | Leu |  |

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|    |                                                                 |     |     |    |     |
|----|-----------------------------------------------------------------|-----|-----|----|-----|
|    | 290                                                             |     | 295 |    | 300 |
| 5  | Gly Asn Leu Leu Gln Ala Asn Ala Gln Gln Asp                     |     |     |    |     |
|    | 305                                                             |     | 310 |    | 315 |
| 10 | <210> 3                                                         |     |     |    |     |
|    | <211> 348                                                       |     |     |    |     |
|    | <212> PRT                                                       |     |     |    |     |
|    | <213> Homo sapiens                                              |     |     |    |     |
|    | <400> 3                                                         |     |     |    |     |
| 15 | Lys Ser Pro Gly Gln Arg Glu Arg Lys Ser Ser Ser Ser Ser Glu Asp |     |     |    |     |
|    | 1                                                               | 5   |     | 10 | 15  |
| 20 | Arg Asn Arg Met Lys Thr Leu Gly Arg Arg Asp Ser Ser Asp Asp Trp |     |     |    |     |
|    |                                                                 | 20  | 25  |    | 30  |
|    | Glu Ile Pro Asp Gly Gln Ile Thr Val Gly Gln Arg Ile Gly Ser Gly |     |     |    |     |
|    |                                                                 | 35  | 40  |    | 45  |
| 25 | Ser Phe Gly Thr Val Tyr Lys Gly Lys Trp His Gly Asp Val Ala Val |     |     |    |     |
|    | 50                                                              |     | 55  |    | 60  |
| 30 | Lys Met Leu Asn Val Thr Ala Pro Thr Pro Gln Gln Leu Gln Ala Phe |     |     |    |     |
|    | 65                                                              |     | 70  |    | 75  |
|    | Lys Asn Glu Val Gly Val Leu Arg Lys Thr Arg His Val Asn Ile Leu |     |     |    |     |
|    |                                                                 | 85  | 90  |    | 95  |
| 35 | Leu Phe Met Gly Tyr Ser Thr Lys Pro Gln Leu Ala Ile Val Thr Gln |     |     |    |     |
|    |                                                                 | 100 | 105 |    | 110 |
| 40 | Trp Cys Glu Gly Ser Ser Leu Tyr His His Leu His Ile Ile Glu Thr |     |     |    |     |
|    |                                                                 | 115 | 120 |    | 125 |
|    | Lys Phe Glu Met Ile Lys Leu Ile Asp Ile Ala Arg Gln Thr Ala Gln |     |     |    |     |
|    | 130                                                             |     | 135 |    | 140 |
| 45 | Gly Met Asp Tyr Leu His Ala Lys Ser Ile Ile His Arg Asp Leu Lys |     |     |    |     |
|    | 145                                                             |     | 150 |    | 155 |
| 50 | Ser Asn Asn Ile Phe Leu His Glu Asp Leu Thr Val Lys Ile Gly Asp |     |     |    |     |
|    |                                                                 | 165 | 170 |    | 175 |
|    | Phe Gly Leu Ala Thr Glu Lys Ser Arg Trp Ser Gly Ser His Gln Phe |     |     |    |     |
|    |                                                                 | 180 | 185 |    | 190 |
| 55 | Glu Gln Leu Ser Gly Ser Ile Leu Trp Met Ala Pro Glu Val Ile Arg |     |     |    |     |



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|    | 195                                                                                | 200 | 205 |
|----|------------------------------------------------------------------------------------|-----|-----|
| 5  | Met Gln Asp Lys Asn Pro Tyr Ser Phe Gln Ser Asp Val Tyr Ala Phe<br>210 215 220     |     |     |
|    | Gly Ile Val Leu Tyr Glu Leu Met Thr Gly Gln Leu Pro Tyr Ser Asn<br>225 230 235 240 |     |     |
| 10 | Ile Asn Asn Arg Asp Gln Ile Ile Phe Met Val Gly Arg Gly Tyr Leu<br>245 250 255     |     |     |
| 15 | Ser Pro Asp Leu Ser Lys Val Arg Ser Asn Cys Pro Lys Ala Met Lys<br>260 265 270     |     |     |
|    | Arg Leu Met Ala Glu Cys Leu Lys Lys Lys Arg Asp Glu Arg Pro Leu<br>275 280 285     |     |     |
| 20 | Phe Pro Gln Ile Leu Ala Ser Ile Glu Leu Leu Ala Arg Ser Leu Pro<br>290 295 300     |     |     |
| 25 | Lys Ile His Arg Ser Ala Ser Glu Pro Ser Leu Asn Arg Ala Gly Phe<br>305 310 315 320 |     |     |
| 30 | Gln Thr Glu Asp Phe Ser Leu Tyr Ala Cys Ala Ser Pro Lys Thr Pro<br>325 330 335     |     |     |
|    | Ile Gln Ala Gly Gly Tyr Gly Ala Phe Pro Val His<br>340 345                         |     |     |
| 35 | <210> 4<br><211> 294<br><212> PRT<br><213> Homo sapiens                            |     |     |
| 40 | <400> 4                                                                            |     |     |
|    | Glu Asp Arg Asn Arg Met Lys Thr Leu Gly Arg Arg Asp Ser Ser Asp<br>1 5 10 15       |     |     |
| 45 | Asp Trp Glu Ile Pro Asp Gly Gln Ile Thr Val Gly Gln Arg Ile Gly<br>20 25 30        |     |     |
| 50 | Ser Gly Ser Phe Gly Thr Val Tyr Lys Gly Lys Trp His Gly Asp Val<br>35 40 45        |     |     |
|    | Ala Val Lys Met Leu Asn Val Thr Ala Pro Thr Pro Gln Gln Leu Gln<br>50 55 60        |     |     |
| 55 | Ala Phe Lys Asn Glu Val Gly Val Leu Arg Lys Thr Arg His Val Asn                    |     |     |

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|    | 65    |              | 70  |     | 75  |     | 80  |     |     |     |     |     |     |     |     |     |
|----|-------|--------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| 5  | Ile   | Leu          | Leu | Phe | Met | Gly | Tyr | Ser | Thr | Lys | Pro | Gln | Leu | Ala | Ile | Val |
|    |       |              |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |
| 10 | Thr   | Gln          | Trp | Cys | Glu | Gly | Ser | Ser | Leu | Tyr | His | His | Leu | His | Ile | Ile |
|    |       |              |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |
| 15 | Glu   | Thr          | Lys | Phe | Glu | Met | Ile | Lys | Leu | Ile | Asp | Ile | Ala | Arg | Gln | Thr |
|    |       |              | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |
| 20 | Ala   | Gln          | Gly | Met | Asp | Tyr | Leu | His | Ala | Lys | Ser | Ile | Ile | His | Arg | Asp |
|    |       | 130          |     |     |     |     | 135 |     |     |     |     | 140 |     |     |     |     |
| 25 | Leu   | Lys          | Ser | Asn | Asn | Ile | Phe | Leu | His | Glu | Asp | Leu | Thr | Val | Lys | Ile |
|    | 145   |              |     |     |     | 150 |     |     |     |     | 155 |     |     |     | 160 |     |
| 30 | Gly   | Asp          | Phe | Gly | Leu | Ala | Thr | Glu | Lys | Ser | Arg | Trp | Ser | Gly | Ser | His |
|    |       |              |     |     | 165 |     |     |     |     | 170 |     |     |     |     | 175 |     |
| 35 | Gln   | Phe          | Glu | Gln | Leu | Ser | Gly | Ser | Ile | Leu | Trp | Met | Ala | Pro | Glu | Val |
|    |       |              |     | 180 |     |     |     |     | 185 |     |     |     |     | 190 |     |     |
| 40 | Ile   | Arg          | Met | Gln | Asp | Lys | Asn | Pro | Tyr | Ser | Phe | Gln | Ser | Asp | Val | Tyr |
|    |       |              | 195 |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |
| 45 | Ala   | Phe          | Gly | Ile | Val | Leu | Tyr | Glu | Leu | Met | Thr | Gly | Gln | Leu | Pro | Tyr |
|    |       | 210          |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |
| 50 | Ser   | Asn          | Ile | Asn | Asn | Arg | Asp | Gln | Ile | Ile | Phe | Met | Val | Gly | Arg | Gly |
|    | 225   |              |     |     |     | 230 |     |     |     |     | 235 |     |     |     | 240 |     |
| 55 | Tyr   | Leu          | Ser | Pro | Asp | Leu | Ser | Lys | Val | Arg | Ser | Asn | Cys | Pro | Lys | Ala |
|    |       |              |     |     | 245 |     |     |     |     | 250 |     |     |     |     | 255 |     |
| 60 | Met   | Lys          | Arg | Leu | Met | Ala | Glu | Cys | Leu | Lys | Lys | Lys | Arg | Asp | Glu | Arg |
|    |       |              |     | 260 |     |     |     |     | 265 |     |     |     |     | 270 |     |     |
| 65 | Pro   | Leu          | Phe | Pro | Gln | Ile | Leu | Ala | Ser | Ile | Glu | Leu | Leu | Ala | Arg | Ser |
|    |       |              | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |
| 70 | Leu   | Pro          | Lys | Ile | His | Arg |     |     |     |     |     |     |     |     |     |     |
|    | 290   |              |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 75 | <210> | 5            |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 80 | <211> | 333          |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 85 | <212> | PRT          |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 90 | <213> | Homo sapiens |     |     |     |     |     |     |     |     |     |     |     |     |     |     |

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<400> 5

|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| 5  | Met | Glu | Leu | Lys | Asp | Asp | Asp | Phe | Glu | Lys | Ile | Ser | Glu | Leu | Gly | Ala | 1   | 5   | 10  | 15  |
| 10 | Gly | Asn | Gly | Gly | Val | Val | Phe | Lys | Val | Ser | His | Lys | Pro | Ser | Gly | Leu | 20  | 25  | 30  |     |
| 15 | Val | Met | Ala | Arg | Lys | Leu | Ile | His | Leu | Glu | Ile | Lys | Pro | Ala | Ile | Arg | 35  | 40  | 45  |     |
| 20 | Asn | Gln | Ile | Ile | Arg | Glu | Leu | Gln | Val | Leu | His | Glu | Cys | Asn | Ser | Pro | 50  | 55  | 60  |     |
| 25 | Tyr | Ile | Val | Gly | Phe | Tyr | Gly | Ala | Phe | Tyr | Ser | Asp | Gly | Glu | Ile | Ser | 65  | 70  | 75  | 80  |
| 30 | Ile | Cys | Met | Glu | His | Met | Asp | Gly | Gly | Ser | Leu | Asp | Gln | Val | Leu | Lys | 85  | 90  | 95  |     |
| 35 | Lys | Ala | Gly | Arg | Ile | Pro | Glu | Gln | Ile | Leu | Gly | Lys | Val | Ser | Ile | Ala | 100 | 105 | 110 |     |
| 40 | Val | Ile | Lys | Gly | Leu | Thr | Tyr | Leu | Arg | Glu | Lys | His | Lys | Ile | Met | His | 115 | 120 | 125 |     |
| 45 | Arg | Asp | Val | Lys | Pro | Ser | Asn | Ile | Leu | Val | Asn | Ser | Arg | Gly | Glu | Ile | 130 | 135 | 140 |     |
| 50 | Lys | Leu | Cys | Asp | Phe | Gly | Val | Ser | Gly | Gln | Leu | Ile | Asp | Ser | Met | Ala | 145 | 150 | 155 | 160 |
| 55 | Asn | Ser | Phe | Val | Gly | Thr | Arg | Ser | Tyr | Met | Ser | Pro | Glu | Arg | Leu | Gln | 165 | 170 | 175 |     |
| 60 | Gly | Thr | His | Tyr | Ser | Val | Gln | Ser | Asp | Ile | Trp | Ser | Met | Gly | Leu | Ser | 180 | 185 | 190 |     |
| 65 | Leu | Val | Glu | Met | Ala | Val | Gly | Arg | Tyr | Pro | Ile | Pro | Pro | Pro | Asp | Ala | 195 | 200 | 205 |     |
| 70 | Lys | Glu | Leu | Glu | Leu | Met | Phe | Gly | Cys | Gln | Val | Glu | Gly | Asp | Ala | Ala | 210 | 215 | 220 |     |
| 75 | Glu | Thr | Pro | Pro | Arg | Pro | Arg | Thr | Pro | Gly | Arg | Pro | Leu | Ser | Ser | Tyr | 225 | 230 | 235 | 240 |

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Gly Met Asp Ser Arg Pro Pro Met Ala Ile Phe Glu Leu Leu Asp Tyr  
245 250 255

5 Ile Val Asn Glu Pro Pro Pro Lys Leu Pro Ser Gly Val Phe Ser Leu  
260 265 270

10 Glu Phe Gln Asp Phe Val Asn Lys Cys Leu Ile Lys Asn Pro Ala Glu  
275 280 285

Arg Ala Asp Leu Lys Gln Leu Met Val His Ala Phe Ile Lys Arg Ser  
290 295 300

15 Asp Ala Glu Glu Val Asp Phe Ala Gly Trp Leu Cys Ser Thr Ile Gly  
305 310 315 320

20 Leu Asn Gln Pro Ser Thr Pro Thr His Ala Ala Gly Val  
325 330

<210> 6  
<211> 360  
25 <212> PRT  
<213> Homo sapiens

<400> 6

30 Met Ser Gln Glu Arg Pro Thr Phe Tyr Arg Gln Glu Leu Asn Lys Thr  
1 5 10 15

Ile Trp Glu Val Pro Glu Arg Tyr Gln Asn Leu Ser Pro Val Gly Ser  
35 20 25 30

Gly Ala Tyr Gly Ser Val Cys Ala Ala Phe Asp Thr Lys Thr Gly Leu  
35 40 45

40 Arg Val Ala Val Lys Lys Leu Ser Arg Pro Phe Gln Ser Ile Ile His  
50 55 60

45 Ala Lys Arg Thr Tyr Arg Glu Leu Arg Leu Leu Lys His Met Lys His  
65 70 75 80

Glu Asn Val Ile Gly Leu Leu Asp Val Phe Thr Pro Ala Arg Ser Leu  
50 85 90 95

Glu Glu Phe Asn Asp Val Tyr Leu Val Thr His Leu Met Gly Ala Asp  
100 105 110

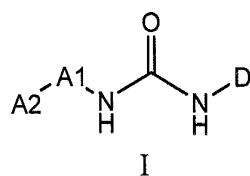
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115 120 125

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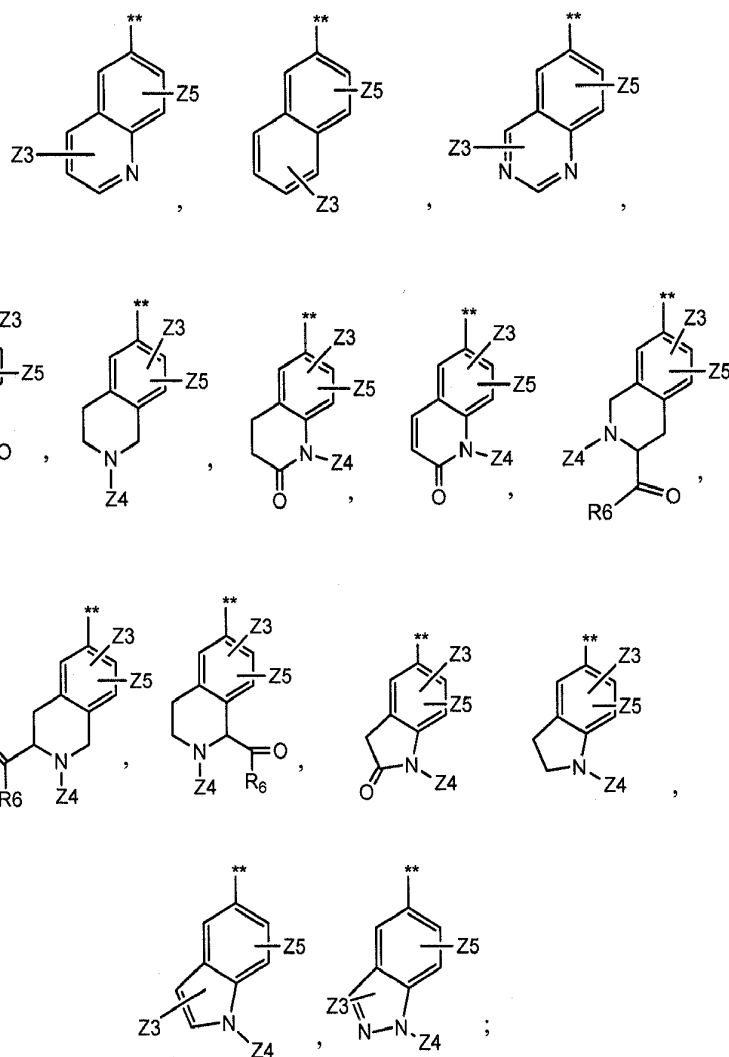
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|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
|    | Phe | Leu | Ile | Tyr | Gln | Ile | Leu | Arg | Gly | Leu | Lys | Tyr | Ile | His | Ser | Ala |  |
|    | 130 |     |     |     |     |     | 135 |     |     |     |     | 140 |     |     |     |     |  |
| 5  | Asp | Ile | Ile | His | Arg | Asp | Leu | Lys | Pro | Ser | Asn | Leu | Ala | Val | Asn | Glu |  |
|    | 145 |     |     |     |     | 150 |     |     |     |     | 155 |     |     |     |     | 160 |  |
| 10 | Asp | Cys | Glu | Leu | Lys | Ile | Leu | Asp | Phe | Gly | Leu | Ala | Arg | His | Thr | Asp |  |
|    |     |     |     |     | 165 |     |     |     |     | 170 |     |     |     |     | 175 |     |  |
| 15 | Asp | Glu | Met | Thr | Gly | Tyr | Val | Ala | Thr | Arg | Trp | Tyr | Arg | Ala | Pro | Glu |  |
|    |     |     |     | 180 |     |     |     |     | 185 |     |     |     |     | 190 |     |     |  |
| 20 | Ile | Met | Leu | Asn | Trp | Met | His | Tyr | Asn | Gln | Thr | Val | Asp | Ile | Trp | Ser |  |
|    |     | 195 |     |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |  |
| 25 | Val | Gly | Cys | Ile | Met | Ala | Glu | Leu | Leu | Thr | Gly | Arg | Thr | Leu | Phe | Pro |  |
|    | 210 |     |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |  |
| 30 | Gly | Thr | Asp | His | Ile | Asn | Gln | Leu | Gln | Gln | Ile | Met | Arg | Leu | Thr | Gly |  |
|    | 225 |     |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |  |
| 35 | Thr | Pro | Pro | Ala | Tyr | Leu | Ile | Asn | Arg | Met | Pro | Ser | His | Glu | Ala | Arg |  |
|    |     |     |     | 245 |     |     |     |     | 250 |     |     |     |     | 255 |     |     |  |
| 40 | Asn | Tyr | Ile | Gln | Ser | Leu | Thr | Gln | Met | Pro | Lys | Met | Asn | Phe | Ala | Asn |  |
|    |     |     |     | 260 |     |     |     |     | 265 |     |     |     |     | 270 |     |     |  |
| 45 | Val | Phe | Ile | Gly | Ala | Asn | Pro | Leu | Ala | Val | Asp | Leu | Leu | Glu | Lys | Met |  |
|    |     | 275 |     |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |  |
| 50 | Leu | Val | Leu | Asp | Ser | Asp | Lys | Arg | Ile | Thr | Ala | Ala | Gln | Ala | Leu | Ala |  |
|    | 290 |     |     |     |     |     | 295 |     |     |     | 300 |     |     |     |     |     |  |
| 55 | His | Ala | Tyr | Phe | Ala | Gln | Tyr | His | Asp | Pro | Asp | Asp | Glu | Pro | Val | Ala |  |
|    | 305 |     |     |     |     | 310 |     |     |     |     | 315 |     |     |     |     | 320 |  |
| 60 | Asp | Pro | Tyr | Asp | Gln | Ser | Phe | Glu | Ser | Arg | Asp | Leu | Leu | Ile | Asp | Glu |  |
|    |     |     |     | 325 |     |     |     |     |     | 330 |     |     |     |     | 335 |     |  |
| 65 | Trp | Lys | Ser | Leu | Thr | Tyr | Asp | Glu | Val | Ile | Ser | Phe | Val | Pro | Pro | Pro |  |
|    |     |     |     | 340 |     |     |     |     | 345 |     |     |     |     | 350 |     |     |  |
| 70 | Leu | Asp | Gln | Glu | Glu | Met | Glu | Ser |     |     |     |     |     |     |     |     |  |
|    |     |     | 355 |     |     |     |     | 360 |     |     |     |     |     |     |     |     |  |

## Claims

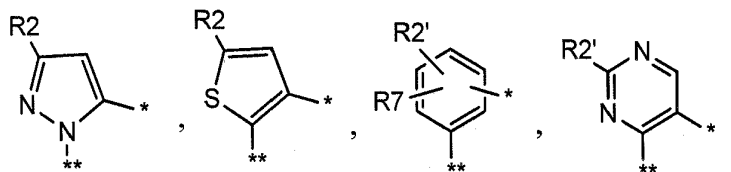
1. A compound of the formula



wherein A2 is selected from the group consisting of

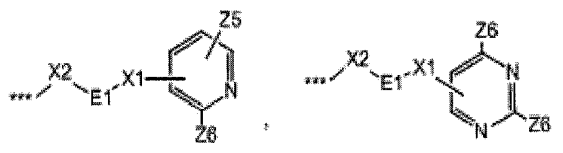


wherein each Z3 and Z5 is independently attached to either aryl or heteroaryl ring of the A2 bicyclic ring;  
 wherein the symbol (\*\*) denotes the attachment to the A1 moiety of formula I;  
 A1 is selected from the group consisting of



wherein the symbol (\*) denotes the attachment to the W moiety of formula I and the symbol (\*\*) denotes the attachment to the A2 moiety of formula I;

D is selected from the group consisting of



wherein E1 is selected from the group consisting phenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyrrolidiny, piperidiny, thienyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, pyrrolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, furyl, imidazolyl, pyridyl, pyrimidinyl and naphthyl;

X1 is selected from the group consisting of O, S, NR3, -C(=O)-, -O-(CH<sub>2</sub>)<sub>n</sub>-, -S-(CH<sub>2</sub>)<sub>n</sub>-, -NR3-(CH<sub>2</sub>)<sub>n</sub>-, -O-(CH<sub>2</sub>)<sub>q</sub>-O-, -O-(CH<sub>2</sub>)<sub>q</sub>-NR3-, -N(R3)-(CH<sub>2</sub>)<sub>q</sub>-N(R3)-, -(CH<sub>2</sub>)<sub>n</sub>-N(R4)-C(=O)-, -(CH<sub>2</sub>)<sub>n</sub>-N(R4)-C(=O)(CH<sub>2</sub>)<sub>n</sub>-, -(CH<sub>2</sub>)<sub>n</sub>-CO-N(R4)-, -(CH<sub>2</sub>)<sub>p</sub>-, C2-C5alkenyl, C2-C5alkynyl, C3-C6cycloalkyl, and a direct bond wherein the E1 ring and the E2 ring are directly linked by a covalent bond;

and wherein the carbon atoms of -(CH<sub>2</sub>)<sub>n</sub>-, -(CH<sub>2</sub>)<sub>q</sub>-, (CH<sub>2</sub>)<sub>p</sub>-, C2-C5alkenyl, and C2-C5alkynyl moieties of X1 may be further substituted by one or more C1-C6alkyl;

X2 is selected from the group consisting of C1-C6 alkyl, C3-C6 branched alkyl, or a direct bond wherein E1 is directly linked to the Y group of formula I;

and wherein the carbon atoms of -(CH<sub>2</sub>)<sub>n</sub>-, -(CH<sub>2</sub>)<sub>q</sub>-, -(CH<sub>2</sub>)<sub>p</sub>-, C2-C5alkenyl, and C2-C5alkynyl of X2 can be further substituted by one or more C1-C6alkyl;

each R2 is selected from the group consisting of, alkyl, branched alkyl, fluoroalkyl wherein the alkyl group is partially or fully fluorinated, and R19 substituted C3-C8carbocyclyl wherein R19 is H, and C1-C6alkyl;

each R2' is selected from the group consisting of halogen and R2;

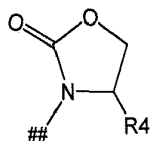
each R3 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, C3-C7carbocyclyl, or phenyl;

wherein two R3 moieties independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C7alkyl are attached to the same nitrogen heteroatom, the two R3 moieties may cyclize to form a C3-C7 heterocyclyl ring;

each R4 is selected from the group consisting of H, C1-C6alkyl, hydroxyC1-C6 alkyl, dihydroxyC1-C6alkyl, C1-C6alkoxyC1-C6alkyl, branched C3-C7alkyl, branched hydroxyC1-C6 alkyl, branched C1-C6alkoxyC1-C6alkyl, branched dihydroxyC1-C6alkyl, carbocyclyl, hydroxyl substituted carbocyclyl, alkoxy substituted carbocyclyl, dihydroxy substituted carbocyclyl, phenyl, heteroaryl, heterocyclyl, phenylC1-C6alkyl, heteroarylC1-C6alkyl, and heterocyclylC1-C6alkyl;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom may cyclize to form a C3-C7 heterocyclyl ring;

each R5 is independently and individually selected from the group consisting of



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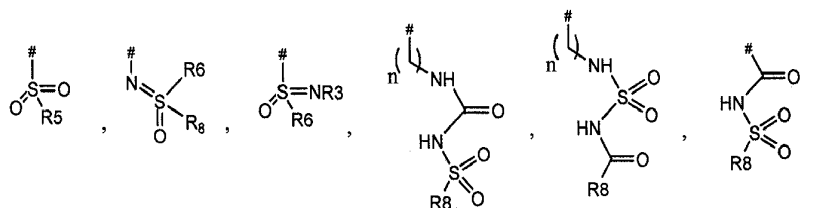
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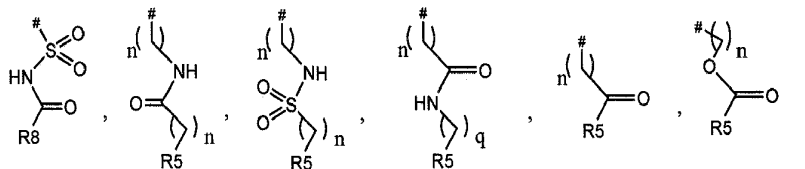
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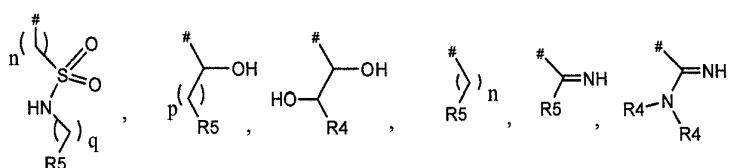


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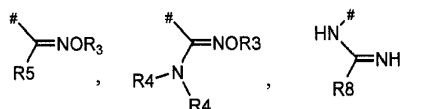


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wherein the symbol (#) indicates the point of attachment of the Z3 moiety to the A2 ring of formula I;  
in the event that Z3 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

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wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z3 may cyclize to form a C3-C7 heterocyclyl ring;

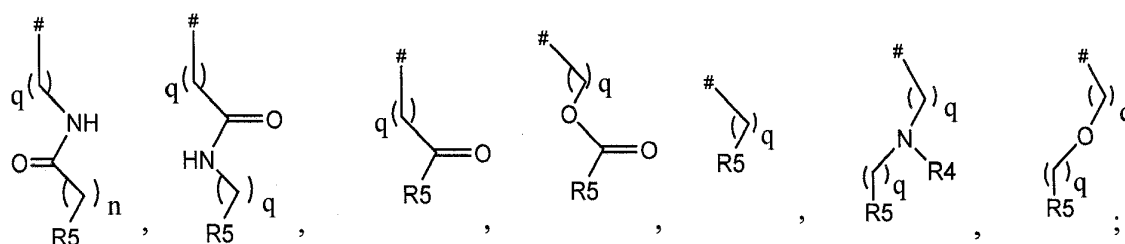
wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z3 may cyclize to form a C3-C7 heterocyclyl ring;

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each Z4 is a substituent attached to a ring nitrogen and is independently and individually selected from the group consisting of H, C1-C6alkyl, hydroxyC2-C6alkyl, C1-C6alkoxyC2-C6alkyl, (R4)<sub>2</sub>N-C2-C6alkyl, (R4)<sub>2</sub>N-C2-C6alkylN(R4)-C2-C6alkyl, (R4)<sub>2</sub>N-C2-C6alkyl-O-C2-C6alkyl, (R4)<sub>2</sub>N-CO-C2-C6alkyl, carboxyC2-C6alkyl, C1-C6alkoxycarbonylC2-C6alkyl, -C2-C6alkylN(R4)C(O)R8, R8-C(=NR3)-, SO<sub>2</sub>R8, -COR8, heteroaryl, heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, heteroarylC2-C6alkyl, heterocyclylC2-C6alkyl, arylaminoC2-C6alkyl, heteroarylC2-C6alkyl, heterocyclylC2-C6alkyl, and moieties of the formulae

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wherein the symbol (#) indicates the point of attachment of the Z4 moiety to the A2 ring for formula I;  
in the event that Z4 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or

more C1-C6alkyls;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z4 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z4 may cyclize to form a C3-C7 heterocyclyl ring;

Z5 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, halogen, fluoroalkyl, cyano, hydroxyl, alkoxy, oxo, aminocarbonyl, carbonylamino, aminosulfonyl, sulfonylamino, -N(R3)<sub>2</sub>, -O-(CH<sub>2</sub>)<sub>q</sub>-N(R4)<sub>2</sub>, -N(R3)-(CH<sub>2</sub>)<sub>q</sub>-N(R4)<sub>2</sub>, -R5, -O-(CH<sub>2</sub>)<sub>q</sub>-O-Alkyl, -O-(CH<sub>2</sub>)<sub>q</sub>-N(R4)<sub>2</sub>, -N(R3)-(CH<sub>2</sub>)<sub>q</sub>-O-Alkyl, -N(R3)-(CH<sub>2</sub>)<sub>q</sub>-N(R4)<sub>2</sub>, -O-(CH<sub>2</sub>)<sub>q</sub>-R5, and -N(R3)-(CH<sub>2</sub>)<sub>q</sub>-R5;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z5 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z5 may cyclize to form a C3-C7 heterocyclyl ring;

Each Z6 is independently and individually selected from the group consisting of -CON(R3)<sub>2</sub>, -CON(R4)<sub>2</sub>, heteroaryl, -N(R4)COR8, (R3)<sub>2</sub>N-, -N(R3)COR8, (R4)<sub>2</sub>N-, H, C1-C6alkyl, branched C3-C7alkyl, hydroxyl, C1-C6alkoxy, -R5, -N(R3)SO<sub>2</sub>R6-, -COR5, -SO<sub>2</sub>NHR4, heterocyclyl, heteroaryloxy, heterocycloxy, arylamino, heteroarylamino, and heterocyclylamino;

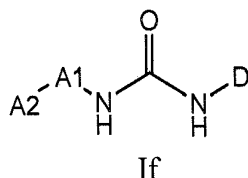
wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z6 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z6 may cyclize to form a C3-C7 heterocyclyl ring;

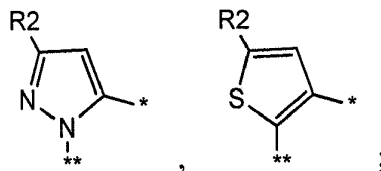
and n is 0-4; p is 1-4; q is 2-6; r is 0 or 1; v is 1 or 2;

and tautomers, diastereomers, geometric isomers, enantiomers, hydrates, prodrugs and salts of any of the foregoing.

## 2. A compounds of claim 1 having the formula If

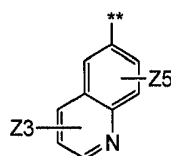


wherein A1 is selected from the group consisting of

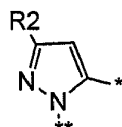


wherein the symbol (\*) denotes the attachment to the NH moiety of formula If and the symbol (\*\*) denotes the attachment to the A2 moiety of formula If.

## 3. A compound of claim 1 or claim 2 wherein A2 is

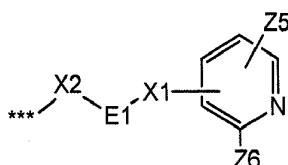


4. A compound of any one of claims 1 to 3 wherein A1 is



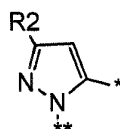
wherein R2 is selected from the group consisting of branched alkyl, alkyl, fluoroalkyl wherein the alkyl group is partially or fully fluorinated; wherein the symbol (\*) denotes the attachment to the NH moiety of formula I and the symbol (\*\*) denotes the attachment to the A2 moiety of formula I.

5. A compound of any one of claims 1 to 4 wherein D is

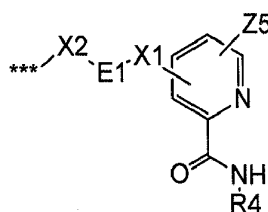


6. A compound of any one of claims 1 to 3, wherein

A1 is selected from the group consisting of



wherein R2 is selected from the group consisting of branched alkyl, alkyl, fluoroalkyl wherein the alkyl group is partially or fully fluorinated;  
wherein the symbol (\*) denotes the attachment to the NH moiety of formula I and the symbol (\*\*) denotes the attachment to the A2 moiety of formula I;  
D is selected from the group consisting of



X1 is O.

7. A compound selected from

1-(3-tert-butyl-1-(quinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea,

- 1-(3-tert-butyl-1-(4-(hydroxymethyl)naphthalen-2-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea,  
 1-(1-(4-(aminomethyl)naphthalen-2-yl)-3-tert-butyl-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea,  
 1-(3-tert-butyl-1-(1H-indol-5-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea,  
 1-(3-tert-butyl-1-(indolin-5-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea,  
 5 1-(3-tert-butyl-1-(1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea,  
 1-(3-tert-butyl-1-(1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea,  
 1-(3-tert-butyl-1-(1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(5-chloropyridin-3-yloxy)phenyl)urea,  
 10 1-(3-tert-butyl-1-(2-oxo-1,2-dihydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea,  
 1-(3-tert-butyl-1-(2-oxo-1,2-dihydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea,  
 1-(3-tert-butyl-1-(2-oxo-1,2-dihydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea,  
 15 1-(3-cyclopentyl-1-(2-oxo-1,2-dihydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea,  
 1-(3-cyclopentyl-1-(2-oxo-1,2-dihydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea,  
 1-(3-tert-butyl-1-(2-(piperazin-1-yl)quinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea,  
 20 1-(1-(2-(2-aminoethylamino)quinolin-6-yl)-3-tert-butyl-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea,  
 1-(3-tert-butyl-1-(2-((R)-3-(dimethylamino)pyrrolidin-1-yl)quinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea,  
 1-(3-tert-butyl-1-(2-(methylamino)quinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea,  
 25 1-(3-tert-butyl-1-(2-(dimethylamino)quinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea,  
 1-(1-(2-aminoquinolin-6-yl)-3-tert-butyl-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea,  
 30 1-(3-tert-butyl-1-(3-carbamoyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea,  
 1-(3-tert-butyl-1-(1-(methylcarbamoyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea,  
 1-(1-(3-((2,3-dihydroxypropyl)carbamoyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)-3-tert-butyl-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea,  
 35 6-(3-tert-butyl-5-(3-(3-(pyridin-3-yloxy)phenyl)ureido)-1H-pyrazol-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid,  
 1-(3-tert-butyl-1-(3-(methylcarbamoyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea,  
 40 1-(1-(1-((2,3-dihydroxypropyl)carbamoyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)-3-tert-butyl-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea,  
 1-(1-(4-(2-amino-2-oxoethyl)naphthalen-2-yl)-3-tert-butyl-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea,  
 1-(3-tert-butyl-1-(4-(2-(2,3-dihydroxypropylamino)-2-oxoethyl)naphthalen-2-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea.  
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8. A pharmaceutical composition comprising a compound of claims 1 to 7 together with a pharmaceutically acceptable carrier, said carrier including an additive selected from the group including adjuvants, excipients, diluents, and stabilizers.
- 50 9. A compound of any one of claims 1 to 7 for use in treating an individual suffering from a condition selected from the group consisting of cancer and hyperproliferative diseases, secondary cancer growth arising from metastasis, diseases **characterized by** hyper-vascularization, diseases characterized angiogenesis, inflammation, osteoarthritis, respiratory diseases, stroke, systemic shock, immunological diseases, cardiovascular disease, chronic myelogenous leukemia, acute lymphocytic leukemia, gastrointestinal stromal tumors, hypereosinophilic syndrome, glioblastomas,  
 55 ovarian cancer, pancreatic cancer, prostate cancer, lung cancers, breast cancers, kidney cancers, cervical carcinomas, metastasis of primary solid tumor secondary sites, ocular diseases **characterized by** hyperproliferation leading to blindness including various retinopathies including diabetic retinopathy and age-related macular degeneration, rheumatoid arthritis, melanomas, human inflammation, rheumatoid spondylitis, osteoarthritis, asthma,

gouty arthritis, sepsis, septic shock, endotoxic shock, Gram-negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, stroke, reperfusion injury, neural trauma, neural ischemia, psoriasis, restenosis, chronic pulmonary inflammatory disease, bone resorptive diseases, graft-versus-host reaction, Chron's disease, ulcerative colitis, inflammatory bowel disease, pyresis, and combinations thereof.

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10. The compound for the use of claim 9, wherein said compound is to be administered orally, parenterally, by inhalation, or subcutaneously.

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## EUROPEAN SEARCH REPORT

Application Number  
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| DOCUMENTS CONSIDERED TO BE RELEVANT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                             |                                                       |                                                                                                     |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|-----------------------------------------------------------------------------------------------------|
| Category                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Citation of document with indication, where appropriate, of relevant passages                                                                                                                                                                                                                                                               | Relevant to claim                                     | CLASSIFICATION OF THE APPLICATION (IPC)                                                             |
| A                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | WO 2004/060306 A2 (DECIPHERA PHARMACEUTICALS INC [US]; FLYNN DANIEL L [US]; PETRILLO PETE)<br>22 July 2004 (2004-07-22)<br>* the whole document *                                                                                                                                                                                           | 1-10                                                  | INV.<br>C07D401/04<br>C07D401/14<br>A61K31/17<br>A61K31/47<br>A61K31/4155<br>A61P35/00<br>A61P29/00 |
| A                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | TOMINAGA Y ET AL: "GENERAL MODEL FOR ESTIMATION OF THE INHIBITION OF KINASES USING MONTE CARLO SIMULATIONS", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US LNKD-DOI:10.1021/JM0304358,<br>vol. 47, no. 10, 2 April 2004 (2004-04-02), pages 2534-2549, XP003003665, ISSN: 0022-2623<br>* Table 6, compound M9 * | 1-10                                                  |                                                                                                     |
| A                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | WO 99/32455 A1 (BAYER AG [US])<br>1 July 1999 (1999-07-01)<br>* claim 1; examples *                                                                                                                                                                                                                                                         | 1-10                                                  |                                                                                                     |
| A                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | WO 99/32110 A1 (BAYER AG [US])<br>1 July 1999 (1999-07-01)<br>* claim 1; examples *                                                                                                                                                                                                                                                         | 1-10                                                  | TECHNICAL FIELDS SEARCHED (IPC)<br>C07D<br>A61K<br>A61P                                             |
| A                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | REGAN J ET AL: "Pyrazole urea-based inhibitors of p38 MAP kinase: from lead compound to clinical candidate", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US LNKD-DOI:10.1021/JM020057R,<br>vol. 45, no. 14, 25 May 2002 (2002-05-25), pages 2994-3008, XP002243050, ISSN: 0022-2623<br>* examples *              | 1-10                                                  |                                                                                                     |
| The present search report has been drawn up for all claims                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                             |                                                       |                                                                                                     |
| Place of search<br>The Hague                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                             | Date of completion of the search<br>11 September 2015 | Examiner<br>Bosma, Peter                                                                            |
| CATEGORY OF CITED DOCUMENTS<br>X : particularly relevant if taken alone<br>Y : particularly relevant if combined with another document of the same category<br>A : technological background<br>O : non-written disclosure<br>P : intermediate document<br>T : theory or principle underlying the invention<br>E : earlier patent document, but published on, or after the filing date<br>D : document cited in the application<br>L : document cited for other reasons<br>& : member of the same patent family, corresponding document |                                                                                                                                                                                                                                                                                                                                             |                                                       |                                                                                                     |



## EUROPEAN SEARCH REPORT

Application Number  
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| DOCUMENTS CONSIDERED TO BE RELEVANT                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                   |                                         |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|
| Category                                                                                                                                                                                                                               | Citation of document with indication, where appropriate, of relevant passages                                                                                                                                                                                                                                                                       | Relevant to claim                                                                                                                                                                                                                                                                                 | CLASSIFICATION OF THE APPLICATION (IPC) |
| A                                                                                                                                                                                                                                      | <p>DUMAS J ET AL: "1-Phenyl-5-pyrazolyl ureas: potent and selective p38 kinase inhibitors", BIOORGANIC &amp; MEDICINAL CHEMISTRY LETTERS, PERGAMON, ELSEVIER SCIENCE, GB LNKD-DOI:10.1016/S0960-894X(00)00272-9, vol. 10, no. 18, 1 September 2000 (2000-09-01), pages 2051-2054, XP004208309, ISSN: 0960-894X</p> <p>* examples *</p> <p>-----</p> | 1-10                                                                                                                                                                                                                                                                                              |                                         |
|                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                   | TECHNICAL FIELDS SEARCHED (IPC)         |
|                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                   |                                         |
| The present search report has been drawn up for all claims                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                   |                                         |
| Place of search<br><b>The Hague</b>                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                     | Date of completion of the search<br><b>11 September 2015</b>                                                                                                                                                                                                                                      | Examiner<br><b>Bosma, Peter</b>         |
| CATEGORY OF CITED DOCUMENTS                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                     | <p>T : theory or principle underlying the invention<br/> E : earlier patent document, but published on, or after the filing date<br/> D : document cited in the application<br/> L : document cited for other reasons</p> <p>&amp; : member of the same patent family, corresponding document</p> |                                         |
| <p>X : particularly relevant if taken alone<br/> Y : particularly relevant if combined with another document of the same category<br/> A : technological background<br/> O : non-written disclosure<br/> P : intermediate document</p> |                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                   |                                         |

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## 摘要

本發明提供了新型化合物和利用上述化合物來治療炎症性疾病、增殖性疾病、癌症、和血管過度形成為特徵的疾病。在首選的實施例中，調節p38激酶蛋白、ab1激酶蛋白、bcr-ab1激酶蛋白、braf激酶蛋白、VEGFR激酶蛋白、或PDGFR激酶蛋白的激活狀態包括上述激酶蛋白與新型化合物接觸的步驟。