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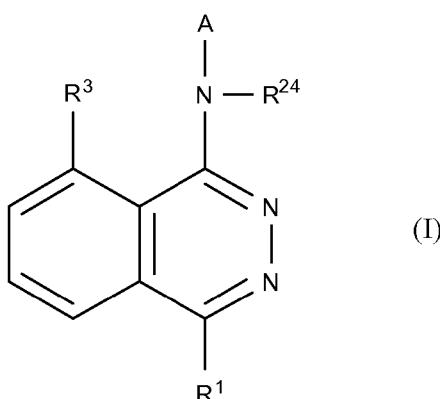
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(54) Title: PHTHALAZINES AS POTASSIUM ION CHANNEL INHIBITORS



(57) Abstract: A compound of formula (I), wherein A, R¹, R³, and R²⁴ are described herein. The compounds are useful as inhibitors of potassium channel function and in the treatment and prevention of arrhythmia, I_{Kur}-associated disorders, and other disorders mediated by ion channel function.



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PHTHALAZINES AS POTASSIUM ION CHANNEL INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Non-Provisional Application No.

5 14/200,063 filed March 7, 2014 and U.S. Provisional Application No. 61/775,748 filed
March 11, 2013, whose contents are hereby incorporated by reference.

FIELD OF THE INVENTION

The present invention provides for phthalazines useful as inhibitors of potassium
10 channel function (especially inhibitors of the K_v1 subfamily of voltage gated K^+ channels,
more especially inhibitors of $K_v1.5$ (which have been linked to the ultra-rapidly
activating delayed rectifier K^+ current I_{Kur}), and/or $K_v1.3$ channels, and/or $K_v1.1$
channels) and to pharmaceutical compositions containing such compounds. The present
invention further provides for methods of using such compounds in the treatment and
15 prevention of arrhythmia, I_{Kur} -associated disorders, and other disorders mediated by ion
channel function.

BACKGROUND OF THE INVENTION

The ultra-rapidly activating delayed rectifier K^+ current (I_{Kur}) is believed to
20 represent the native counterpart to a cloned potassium channel designated $K_v1.5$ and,
while present in human atrium, it appears to be absent in human ventricle. Furthermore,
because of its rapidity of activation and limited slow inactivation, I_{Kur} is believed to
contribute significantly to repolarization in human atrium. Consequently, a specific
blocker of I_{Kur} , that is a compound which blocks $K_v1.5$, would overcome the short
25 coming of other compounds by prolonging refractoriness by retarding repolarization in
the human atrium without causing the delays in ventricular repolarization that underlie
arrhythmogenic after depolarizations and acquired long QT syndrome observed during
treatment with current Class III antiarrhythmic agents. (Antiarrhythmic agents of Class
III are drugs that cause a selective prolongation of the duration of the action potential
30 without significant cardiac depression.)

Immunoregulatory abnormalities have been shown to exist in a wide variety of
autoimmune and chronic inflammatory diseases, including systemic lupus erythematosus,

chronic rheumatoid arthritis, type I and II diabetes mellitus, inflammatory bowel disease, biliary cirrhosis, uveitis, multiple sclerosis and other disorders such as Crohn's disease, ulcerative colitis, bullous pemphigoid, sarcoidosis, psoriasis, ichthyosis, Graves' ophthalmopathy and asthma. Although the underlying pathogenesis of each of these 5 conditions may vary, they have in common the appearance of a variety of auto-antibodies and self-reactive lymphocytes. Such self-reactivity may be due, in part, to a loss of the homeostatic controls under which the normal immune system operates. Similarly, following a bone-marrow or an organ transplantation, lymphocytes recognize the foreign tissue antigens and begin to produce immune mediators which lead to graft rejection or 10 graft-vs-host rejection.

One end result of an autoimmune or a rejection process is tissue destruction caused by inflammatory cells and the mediators they release. Anti-inflammatory agents such as NSAIDs act principally by blocking the effect or secretion of these mediators but do nothing to modify the immunologic basis of the disease. On the other hand, cytotoxic 15 agents, such as cyclophosphamide, act in such a nonspecific fashion in which both the normal and autoimmune responses are shut off. Indeed, patients treated with such nonspecific immunosuppressive agents are as likely to succumb to infection as they are to their autoimmune disease.

Cyclosporin A, which was approved by the US FDA in 1983 is currently the 20 leading drug used to prevent rejection of transplanted organs. In 1993, FK-506 (PROGRAF®) was approved by the US FDA for the prevention of rejection in liver transplantation. Cyclosporin A and FK-506 act by inhibiting the body's immune system from mobilizing its vast arsenal of natural protecting agents to reject the transplant's foreign protein. In 1994, Cyclosporin A was approved by the US FDA for the treatment 25 of severe psoriasis and has been approved by European regulatory agencies for the treatment of atopic dermatitis. Though these agents are effective in fighting transplant rejection, Cyclosporin A and FK-506 are known to cause several undesirable side effects including nephrotoxicity, neurotoxicity, and gastrointestinal discomfort. Therefore, a selective immunosuppressant without these side effects still remains to be developed.

30 Potassium channel inhibitors as described here promise to be the solution to this problem, since inhibitors of K_v1.3, for example, are immunosuppressive. See Wulff et al., "Potassium channels as therapeutic targets for autoimmune disorders", *Curr. Opin. Drug*

Discov. Devel., 6(5):640-647 (Sep. 2003); Shah et al., "Immunosuppressive effects of a K_v1.3 inhibitor", *Cell Immunol.*, 221(2):100-106 (Feb. 2003); Hanson et al., "UK-78,282, a novel piperidine compound that potently blocks the K_v1.3 voltage-gated potassium channel and inhibits human T cell activation", *Br. J. Pharmacol.*, 126(8):1707-1716 (Apr. 5 1999).

Inhibitors of K_v1.5 and other K_v1.x channels stimulate gastrointestinal motility. Thus, the compounds of the invention are believed to be useful in treating motility disorders such as reflux esophagitis. See Frey et al., "Blocking of cloned and native delayed rectifier K channels from visceral smooth muscles by phencyclidine", 10 *Neurogastroenterol. Motil.*, 12(6):509-516 (Dec. 2000); Hatton et al., "Functional and molecular expression of a voltage-dependent K(+) channel (K_v1.1) in interstitial cells of Cajal", *J. Physiol.*, 533(Pt 2):315-327 (Jun. 1, 2001); Vianna-Jorge et al., "Shaker-type K_v1 channel blockers increase the peristaltic activity of guinea-pig ileum by stimulating acetylcholine and tachykinins release by the enteric nervous system", *Br. J. Pharmacol.*, 15 138(1):57-62 (Jan. 2003); Koh et al., "Contribution of delayed rectifier potassium currents to the electrical activity of murine colonic smooth muscle", *J. Physiol.*, 515(Pt. 2):475-487 (Mar. 1, 1999).

Inhibitors of K_v1.5 relax pulmonary artery smooth muscle. Thus, the compounds of the invention are believed to be useful in treating hypertension and otherwise 20 improving vascular health. See Davies et al., "K_v channel subunit expression in rat pulmonary arteries", *Lung*, 179(3):147-161 (2001), Epub. Feb. 4, 2002; Pozeg et al., "In vivo gene transfer of the O₂-sensitive potassium channel K_v1.5 reduces pulmonary hypertension and restores hypoxic pulmonary vasoconstriction in chronically hypoxic rats", *Circulation*, 107(15):2037-2044 (Apr. 22, 2003), Epub. Apr. 14, 2003.

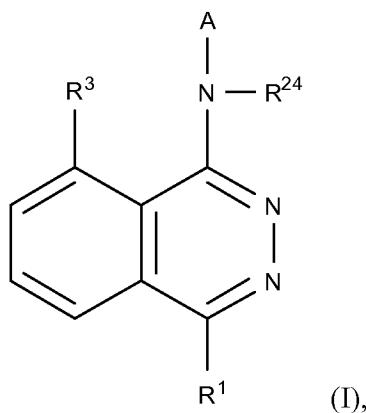
25 Inhibitors of K_v1.3 increase insulin sensitivity. Hence, the compounds of the invention are believed to be useful in treating diabetes. See Xu et al., "The voltage-gated potassium channel K_v1.3 regulates peripheral insulin sensitivity", *Proc. Natl. Acad. Sci. USA*, 101(9):3112-3117 (Mar. 2, 2004), Epub. Feb. 23, 2004; MacDonald et al., "Members of the K_v1 and K_v2 voltage-dependent K(+) channel families regulate insulin 30 secretion", *Mol. Endocrinol.*, 15(8):1423-1435 (Aug. 2001); MacDonald et al., "Voltage-dependent K(+) channels in pancreatic beta cells: role, regulation and potential as therapeutic targets", *Diabetologia*, 46(8):1046-1062 (Aug. 2003), Epub. Jun. 27, 2003.

Stimulation of $K_v1.1$ is believed to reduce seizure activity by hyperpolarizing neurons. Thus, the compounds of the invention are believed to be useful in treating seizures, including seizures associated with epilepsy and other neurological diseases. See Rho et al., "Developmental seizure susceptibility of $Kv1.1$ potassium channel knockout mice", *Dev. Neurosci.*, 21(3-5):320-327 (Nov. 1999); Coleman et al., "Subunit composition of K_v1 channels in human CNS", *J. Neurochem.*, 73(2):849-858 (Aug. 1999); Lopantsev et al., "Hyperexcitability of CA3 pyramidal cells in mice lacking the potassium channel subunit $K_v1.1$ ", *Epilepsia*, 44(12):1506-1512 (Dec. 2003); Wickenden, "Potassium channels as anti-epileptic drug targets", *Neuropharmacology*, 43(7):1055-1060 (Dec. 2002).

Inhibition of $K_v1.x$ channels improves cognition in animal models. Thus, the compounds of the invention are believed to be useful in improving cognition and/or treating cognitive disorders. See Cochran et al., "Regionally selective alterations in local cerebral glucose utilization evoked by charybdotoxin, a blocker of central voltage-activated K^+ -channels", *Eur. J. Neurosci.*, 14(9):1455-1463 (Nov. 2001); Kourrich et al., "Kaliotoxin, a $K_v1.1$ and $K_v1.3$ channel blocker, improves associative learning in rats", *Behav. Brain Res.*, 120(1):35-46 (Apr. 8, 2001).

SUMMARY OF THE INVENTION

20 In accordance with the present invention, acyclic compounds and related compounds are provided that have the general structure of formula (I):



wherein A, R^1 , R^3 , and R^{24} are defined below.

25 By use of a respective effective amount of at least one compound described herein, provided are methods of treating (including ameliorating), reducing the risk of or

preventing arrhythmias, atrial fibrillation, atrial flutter, supraventricular arrhythmias, gastrointestinal disorders (such as reflux esophagitis or a motility disorder), inflammatory or immunological disease (such as chronic obstructive pulmonary disease), diabetes, cognitive disorders, migraine, epilepsy, hypertension, or treating I_{Kur} -associated

5 conditions, or controlling heart rate.

Also provided are pharmaceutical compositions comprising a therapeutically effective amount of at least one compound described herein and a pharmaceutically acceptable vehicle or carrier thereof. Such compositions can further comprise one or more other agent(s). For example, at least one other anti-arrhythmic agent (such as 10 sotalol, dofetilide, diltiazem or Verapamil), or at least one calcium channel blocker, or at least one anti-platelet agent (such as clopidogrel, cangrelor, ticlopidine, CS-747, ifetroban and aspirin), or at least one anti-hypertensive agent (such as a beta adrenergic blocker, ACE inhibitor (e.g., captopril, zofenopril, fosinopril, enalapril, ceranopril, cilazopril, delapril, pentopril, quinapril, ramipril, or lisinopril), A II antagonist, ET 15 antagonist, Dual ET/A II antagonist, or vasopepsidase inhibitor (e.g., omapatrilat or gemopatrilat)), or at least one anti thrombotic/anti thrombolytic agent (such as tPA, recombinant tPA, TNK, nPA, factor VIIa inhibitors, factor Xa inhibitors (such as apixaban), factor XIa inhibitors or thrombin inhibitors), or at least one anti coagulant (such as warfarin or a heparin), or at least one HMG-CoA reductase inhibitor 20 (pravastatin, lovastatin, atorvastatin, simvastatin, NK-104 or ZD-4522), or at least one anti diabetic agent (such as a biguanide or a biguanide/glyburide combination), or at least one thyroid mimetic, or at least one mineralocorticoid receptor antagonist (such as spironolactone or eplerinone), or at least one cardiac glycoside (such as digitalis or ouabain).

25 Another aspect of this invention is directed to methods of treating, inhibiting, or ameliorating the symptoms of a disease or disorder that is modulated or otherwise affected by inhibitors of potassium channel function (especially inhibitors of the K_v1 subfamily of voltage gated K^+ channels, more especially inhibitors of $K_v1.5$ (which have been linked to the ultra-rapidly activating delayed rectifier K^+ current I_{Kur}), and/or $K_v1.3$ 30 channels, and/or $K_v1.1$ channels), comprising administering to a subject in need thereof a therapeutically effective amount of a compound of the present invention or an individual isomer or mixture of isomers or a pharmaceutically acceptable salt thereof.

Another aspect of this invention is directed to methods of treating, inhibiting, or ameliorating arrhythmia, or maintaining normal sinus rhythm, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of the present invention or an individual isomer or mixture of isomers or a pharmaceutically acceptable salt thereof.

5 Another aspect of this invention is directed to methods of controlling heart rate, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of the present invention or an individual isomer or mixture of isomers or a pharmaceutically acceptable salt thereof.

10

DEFINITIONS

The terms "alk" or "alkyl" refer to straight or branched chain hydrocarbon groups having 1 to 12 carbon atoms, or 1 to 8 carbon atoms, 1 to 6 carbon atoms, 1 to 4 carbon atoms, or 1 to 3 carbon atoms, such as methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, 15 t-butyl, pentyl, hexyl, heptyl, octyl, or any subset of the foregoing. The term "substituted alkyl" refers to alkyl groups substituted with one or more groups (such as by groups described above in the definition of R¹⁰), such as selected from aryl, substituted aryl, heterocyclo, substituted heterocyclo, carbocyclo, substituted carbocyclo, halo, hydroxy, alkoxy (optionally substituted), aryloxy (optionally substituted), alkylester (optionally substituted), arylester (optionally substituted), alkanoyl (optionally substituted), aryol (optionally substituted), cyano, nitro, amino, substituted amino, amido, lactam, urea, 20 urethane and sulfonyl, or any subset of the foregoing.

The term "alkenyl" refers to straight or branched chain hydrocarbon groups having 2 to 12 carbon atoms, or 2 to 4 carbon atoms, and at least one double carbon to 25 carbon bond (either cis or trans), such as ethenyl. The term "substituted alkenyl" refers to alkenyl groups substituted with one or more groups (such as by groups described above in the definition of R¹⁰), such as selected from aryl, substituted aryl, heterocyclo, substituted heterocyclo, carbocyclo, substituted carbocyclo, halo, hydroxy, alkoxy (optionally substituted), aryloxy (optionally substituted), alkylester (optionally substituted), arylester (optionally substituted), alkanoyl (optionally substituted), aryol (optionally substituted), cyano, nitro, amino, substituted amino, amido, lactam, urea, urethane and sulfonyl, or any subset of the foregoing.

The term "alkynyl" refers to straight or branched chain hydrocarbon groups having 2 to 12 carbon atoms, or 2 to 4 carbon atoms, and at least one triple carbon to carbon bond, such as ethynyl. The term "substituted alkynyl" refers to alkynyl groups substituted with one or more groups (such as by groups described above in the definition of R¹⁰), such as selected from aryl, substituted aryl, heterocyclo, substituted heterocyclo, carbocyclo, substituted carbocyclo, halo, hydroxy, alkoxy (optionally substituted), aryloxy (optionally substituted), alkylester (optionally substituted), arylester (optionally substituted), alkanoyl (optionally substituted), aryol (optionally substituted), cyano, nitro, amino, substituted amino, amido, lactam, urea, urethane and sulfonyl, or any subset of the foregoing.

The term "aryl" refers to aromatic homocyclic (*i.e.*, hydrocarbon) mono-, bi- or tricyclic ring-containing groups such as having 6 to 12 members such as phenyl, naphthyl and biphenyl. Phenyl is an example of an aryl group. The term "substituted aryl" refers to aryl groups substituted with one or more groups (such as by groups described above in the definition of R¹⁰), such as selected from alkyl, substituted alkyl, alkenyl (optionally substituted), aryl (optionally substituted), heterocyclo (optionally substituted), halo, hydroxy, alkoxy (optionally substituted), aryloxy (optionally substituted), alkanoyl (optionally substituted), aroyl, (optionally substituted), alkylester (optionally substituted), arylester (optionally substituted), cyano, nitro, amino, substituted amino, amido, lactam, urea, urethane and sulfonyl, or any subset of the foregoing, where optionally one or more pair of substituents together with the atoms to which they are bonded form a 3 to 7 member ring.

The term "cycloalkyl" refers to mono-, bi- or tri homocyclic ring groups of 3 to 15 carbon atoms which are, respectively, fully saturated and partially unsaturated. The rings of multi-ring cycloalkyl groups may be fused, bridged and/or joined through one or more spiro unions. The term "substituted cycloalkyl" refers to a cycloalkyl group substituted with one or more groups (such as by groups described above in the definition of R¹⁰), such as selected from aryl, substituted aryl, heterocyclo, substituted heterocyclo, carbocyclo, substituted carbocyclo, halo, hydroxy, alkoxy (optionally substituted), aryloxy (optionally substituted), alkylester (optionally substituted), arylester (optionally substituted), alkanoyl (optionally substituted), aryol (optionally substituted), cyano, nitro,

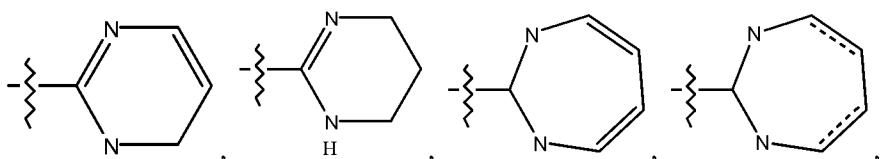
amino, substituted amino, amido, lactam, urea, urethane and sulfonyl, or any subset of the foregoing.

The terms "halogen" and "halo" refer to fluorine, chlorine, bromine and iodine.

The term "haloalkyl" is intended to include both branched and straight-chain 5 saturated aliphatic hydrocarbon groups, for example CF_3 , having the specified number of carbon atoms, substituted with 1 or more halogen, up to and including perhalo alkyls (where all hydrogen atoms are replaced with a halogen).

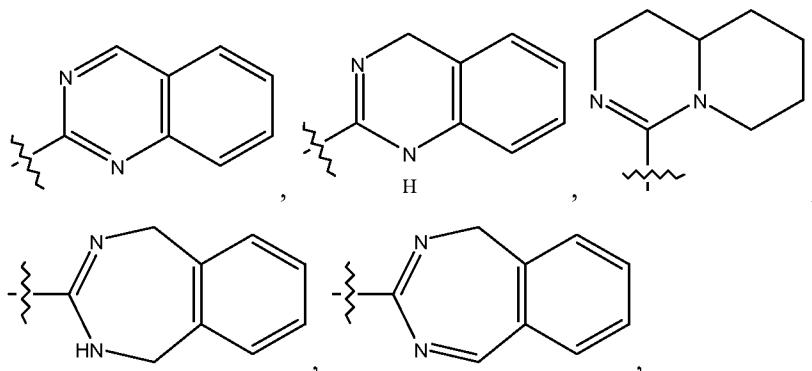
The terms "heterocycle", "heterocyclic", "heterocyclic group" or "heterocyclo" refer to fully saturated or partially or completely unsaturated, including aromatic 10 ("heteroaryl") or nonaromatic cyclic groups (for example, 3 to 13 ring member monocyclic, 7 to 17 ring member bicyclic, or 10 to 20 ring member tricyclic ring systems, such as, in certain embodiments, a monocyclic or bicyclic ring containing a total of 3 to 10 ring atoms) which have at least one heteroatom in at least one carbon atom-containing ring. Each ring of the heterocyclic group containing a heteroatom may have 1, 15 2, 3 or 4 heteroatoms selected from nitrogen atoms, oxygen atoms and/or sulfur atoms, where the nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatoms may optionally be quaternized. The heterocyclic group may be attached at any heteroatom or carbon atom of the ring or ring system. The rings of multi-ring heterocycles may be fused, bridged and/or joined through one or more spiro unions.

20 Exemplary monocyclic heterocyclic groups include azetidinyl, pyrrolidinyl, pyrrolyl, pyrazolyl, oxetanyl, pyrazolinyl, imidazolyl, imidazolinyl, imidazolidinyl, oxazolyl, oxazolidinyl, isoxazolinyl, isoxazolyl, thiazolyl, thiadiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, furyl, tetrahydrofuryl, thienyl, oxadiazolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, 25 azepinyl, 4-piperidonyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, tetrahydropyranyl, tetrazoyl, triazolyl, morpholinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, 1,3-dioxolane and tetrahydro-1,1-dioxothienyl,



and the like.

Exemplary bicyclic heterocyclic groups include indolyl, benzothiazolyl, benzoxazolyl, benzothienyl, quinuclidinyl, quinolinyl, tetra-hydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuryl, benzofuranyl, dihydrobenzofuranyl, chromonyl, coumarinyl, benzodioxolyl, dihydrobenzodioxolyl, 5 benzodioxinyl, cinnolinyl, quinoxaliny, indazolyl, pyrrolopyridyl, furopyridinyl (such as furo[2,3-c]pyridinyl, furo[3,2-b]pyridinyl or furo[2,3-b]pyridinyl), dihydroisoindolyl, dihydroquinazolinyl (such as 3,4-dihydro-4-oxo-quinazolinyl), tetrahydroquinolinyl, azabicycloalkyls (such as 6-azabicyclo[3.2.1]octane), azaspiroalkyls (such as 1,4 dioxa-8-azaspiro[4.5]decane), imidazopyridinyl (such as imidazo[1,5-a]pyridin-3-yl), 10 triazolopyridinyl (such as 1,2,4-triazolo[4,3-a]pyridin-3-yl), and hexahydroimidazopyridinyl (such as 1,5,6,7,8,8a-hexahydroimidazo[1,5-a]pyridin-3-yl),



and the like.

15 Exemplary tricyclic heterocyclic groups include carbazolyl, benzidolyl, phenanthrolinyl, acridinyl, phenanthridinyl, xanthenyl and the like.

The terms "substituted heterocycle", "substituted heterocyclic", "substituted heterocyclic group" and "substituted heterocyclo" refer to heterocycle, heterocyclic and heterocyclo groups substituted with one or more groups (such as by groups described above in the definition of R¹⁰), such as selected from alkyl, substituted alkyl, alkenyl, 20 oxo, aryl, substituted aryl, heterocyclo, substituted heterocyclo, carbocyclo (optionally substituted), halo, hydroxy, alkoxy (optionally substituted), aryloxy (optionally substituted), alkanoyl (optionally substituted), aroyl (optionally substituted), alkylester (optionally substituted), arylester (optionally substituted), cyano, nitro, amido, amino, 25 substituted amino, lactam, urea, urethane, sulfonyl, or any subset of the foregoing, where optionally one or more pair of substituents together with the atoms to which they are bonded form a 3 to 7 member ring.

The term "alkanoyl" refers to alkyl group (which may be optionally substituted as described above) linked to a carbonyl group (*i.e.*, -C(O)-alkyl). Similarly, the term "aryloyl" refers to an aryl group (which may be optionally substituted as described above) linked to a carbonyl group (*i.e.*, -C(O)-aryl).

5 Throughout the specification, groups and substituents thereof may be chosen to provide stable moieties and compounds.

Compounds described herein may form salts or solvates which are also within the scope of this invention. Reference to a compound described herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as 10 employed herein, denotes acidic and/or basic salts formed with inorganic and/or organic acids and bases. In addition, when a compound described herein contains both a basic moiety and an acidic moiety, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. In one embodiment, the salts are pharmaceutically acceptable (*i.e.*, non-toxic, physiologically acceptable), although other 15 salts are also useful, *e.g.*, in isolation or purification steps which may be employed during preparation. Salts of the compounds described herein may be formed, for example, by reacting a compound with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

20 The present invention is intended to cover the compounds in their neutral state, salts of those compounds, or mixtures of the compounds in their neutral state with one or more salt forms, or mixtures of salt forms.

The compounds described herein which contain a basic moiety may form salts with a variety of organic and inorganic acids. Exemplary acid addition salts include 25 acetates (such as those formed with acetic acid or trihaloacetic acid, for example, trifluoroacetic acid), adipates, alginates, ascorbates, aspartates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, cyclopentanepropionates, digluconates, dodecylsulfates, ethanesulfonates, fumarates, glucoheptanoates, glycerophosphates, hemisulfates, 30 heptanoates, hexanoates, hydrochlorides (formed with hydrochloric acid), hydrobromides (formed with hydrogen bromide), hydroiodides, 2-hydroxyethanesulfonates, lactates, maleates (formed with maleic acid), methanesulfonates (formed with methanesulfonic

acid), 2-naphthalenesulfonates, nicotinates, nitrates, oxalates, pectinates, persulfates, 3-phenylpropionates, phosphates, picrates, pivalates, propionates, salicylates, succinates, sulfates (such as those formed with sulfuric acid), sulfonates (such as those mentioned herein), tartrates, thiocyanates, toluenesulfonates such as tosylates, undecanoates, and the like.

5 The compounds described herein which contain an acidic moiety may form salts with a variety of organic and inorganic bases. Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic 10 amines) such as benzathines, dicyclohexylamines, hydrabamines (formed with N,N-bis(dehydroabietyl)ethylenediamine), N-methyl-D-glucamines, N-methyl-D-glucamides, *t*-butyl amines, and salts with amino acids such as arginine, lysine and the like.

15 Basic nitrogen-containing groups may be quaternized with agents such as lower alkyl halides (e.g., methyl, ethyl, propyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g., dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (e.g., decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides), aralkyl halides (e.g., benzyl and phenethyl bromides), and others.

20 Any compound that can be converted *in vivo* to provide the bioactive agent (*i.e.*, the compound of formula (I)) is a prodrug within the scope and spirit of the invention.

25 The term "prodrugs" as employed herein includes esters and carbonates formed by reacting one or more hydroxyls of compounds of formula (I) with alkyl, alkoxy, or aryl substituted acylating agents employing procedures known to those skilled in the art to generate acetates, pivalates, methylcarbonates, benzoates, and the like.

30 Various forms of prodrugs are well known in the art and are described in:

- a) Wermuth, C.G. et al., *The Practice of Medicinal Chemistry*, Chapter 31, Academic Press (1996);
- b) *Design of Prodrugs*, H. Bundgaard, ed., Elsevier (1985);
- c) Bundgaard, H., Chapter 5, "Design and Application of Prodrugs", Krosgaard-Larsen, P. et al., eds., *A Textbook of Drug Design and Development*, pp. 113-191, Harwood Academic Publishers (1991); and
- d) Testa, B. et al., *Hydrolysis in Drug and Prodrug Metabolism*, Wiley-VCH (2003).

[0100] "Pharmaceutically acceptable" refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for contact with the tissues of human beings and animals without 5 excessive toxicity, irritation, allergic response, or other problems or complications commensurate with a reasonable benefit/risk ratio or which have otherwise been approved by the United States Food and Drug Administration as being acceptable for use in humans or domestic animals.

The various compounds described herein, or their pharmaceutically acceptable 10 salts, may contain one or more asymmetric centers and may thus give rise to isomers, such as enantiomers, diastereomers, and other stereoisomeric forms. Such forms may be defined, in terms of absolute stereochemistry, as (R)- or (S)-, or as (D)- or (L)- for amino acids. The present invention is meant to include all such possible individual stereoisomers and mixtures thereof, including their racemic and optically pure 15 enantiomeric or diastereomeric forms. The compounds may be prepared as racemates and can conveniently be used as such, or optically active (+) and (-), (R)- and (S)-, or (D)- and (L)- isomers or corresponding diastereomers may be prepared using chiral synthons or chiral reagents, or they may be resolved from racemic mixtures using conventional 20 techniques, such as chiral chromatography or reverse phase HPLC. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both *E* and *Z* 25 geometric isomers.

The invention also includes isotopically-labeled compounds of the invention, wherein one or more atoms is replaced by an atom having the same atomic number, but 25 an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as ²H or D and ³H or T, carbon such as ¹¹C, ¹³C, and ¹⁴C, chlorine, such as ³⁶Cl, fluorine such as ¹⁸F, iodine, such as ¹²³I and ¹²⁵I, nitrogen, such as ¹³N and ¹⁵N, oxygen, such as ¹⁵O, ¹⁷O, and ¹⁸O, phosphorus, such as ³²P, 30 and sulfur, such as ³⁵S. Certain isotopically-labeled compounds of the invention, for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, ³H, and carbon-14, ¹⁴C, are

particularly useful for this purpose in view of their ease of incorporation and ready means of detection. Substitution with heavier isotopes such as deuterium, ²H or D, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increase *in vivo* half-life or reduced dosage requirements, and hence may be preferred in 5 some circumstances. Substitution with positron emitting isotopes, such as ¹¹C, ¹⁸F, ¹⁵O, and ¹³N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

To the extent that compounds described herein, and salts thereof, may exist in their tautomeric form, all such tautomeric forms are contemplated herein as part of the 10 present invention.

All stereoisomers of the present compounds, such as those which may exist due to asymmetric carbons on the various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons) and diastereomeric forms are contemplated within the scope of this invention. Individual stereoisomers of the 15 compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction 20 mixture, and formulation into an efficacious therapeutic agent. The present invention is intended to cover stable compounds.

"Therapeutically effective amount" refers to that amount of a compound which, when administered to a subject, is sufficient to effect treatment for a disease or disorder described herein. The amount of a compound which constitutes a "therapeutically effective amount" will vary depending on the compound, the disorder and its severity, and the age of the subject to be treated, but can be determined routinely by one of 25 ordinary skill in the art.

When any variable (e.g., R¹³) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition 30 at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R¹³, then said group may optionally be substituted with up to two R¹³ groups and R¹³ at each occurrence is selected independently from the definition of R¹³. Also,

combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

"Treating" or "treatment" as used herein covers the treatment, prophylaxis, and/or reducing the risk, of a disease or disorder described herein, or treatment, prophylaxis, or

5 reducing the risk of a symptom of a disease or disorder, in a subject, such as a human, and includes:

- i. inhibiting a disease or disorder, *i.e.*, arresting its development; or
- ii. relieving a disease or disorder, *i.e.*, causing regression of the disorder.

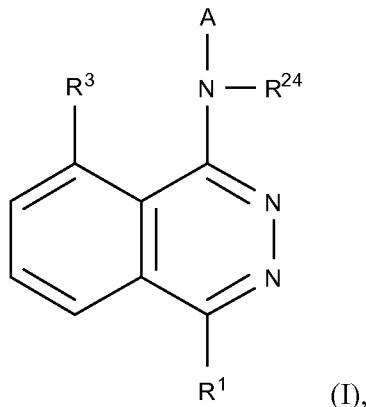
10 "Subject" refers to a warm blooded animal such as a mammal, such as a human, or a human child, which is afflicted with, or has the potential to be afflicted with one or more diseases and disorders described herein.

The terms "including", "such as", "for example" and the like are intended to refer to exemplary embodiments and not to limit the scope of the present invention.

15

DETAILED DESCRIPTION OF THE INVENTION

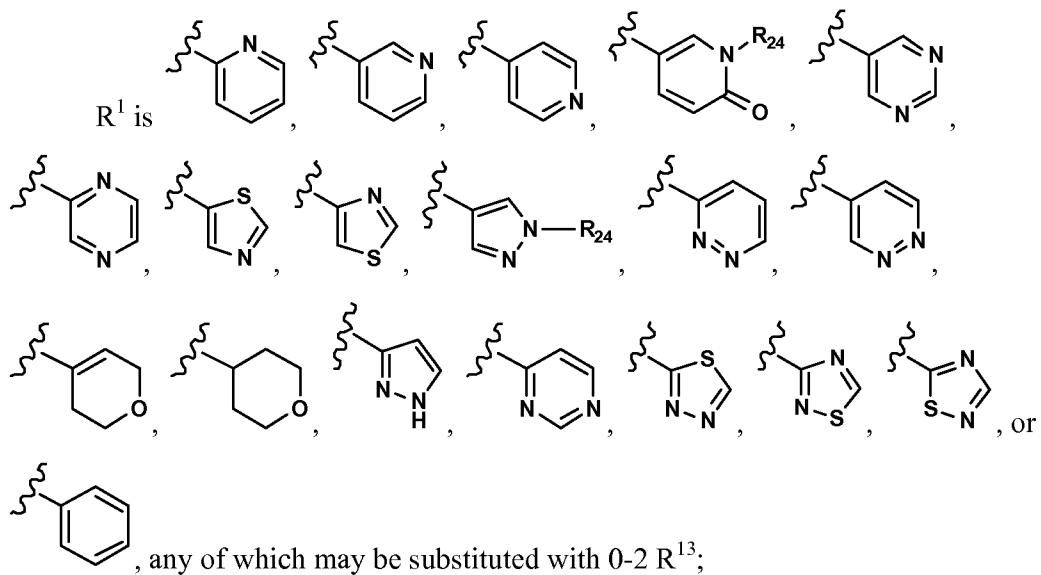
In accordance with the present invention, compounds of formula (I) are provided



or enantiomers, diastereomers, tautomers, prodrugs or salts thereof, wherein:

20 A is $-(CH_2)_m-R^2$, $-CH(R^{26})-R^2$, $-(CH_2)_{n-1}-O-R^2$, $-(CH_2)_{n-1}-NR^{25}-R^2$, $-CH(R^{26})-CO_2-R^2$, or $-(CH_2)_{n-1}-NR^{25}-CO_2-R^2$;

R¹ is C₁₋₁₀ alkyl substituted with 1-2 -OH, haloC₁₋₁₀ alkyl, C₂₋₁₂ alkenyl, or C₃₋₁₀ cycloalkyl, wherein the cycloalkyl may be substituted with 0-2 R¹³; or



5 R² is phenyl, cyclopentyl, cyclohexyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, piperidinyl, pyridinone, pyrrolidinyl, tetrahydropyran, or thiazolyl, any of which are substituted with 0-2 R^{2a};

10 R^{2a}, at each occurrence, is independently H, -OH, F, Cl, Br, I, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, haloC₁₋₁₀ alkyl, C₃₋₁₀ cycloalkyl, C₂₋₁₂ alkenyl, C₂₋₁₂ alkynyl, C₆₋₁₀aryl, a 4- to 12-membered heteroaryl, a 4- to 12-membered heterocyclyl, a 4- to 12-membered heteroaryl-C₁₋₁₀ alkyl, -CN, -NO₂, -(CH₂)_m-SO₂R¹⁴, -NR¹⁴SO₂R¹⁴, =O, -CONR¹⁴R¹⁴, -(CH₂)_m-SO₂NR¹⁴R¹⁴, -(CH₂)_m-NR¹⁴SO₂R¹⁴, -(CH₂)_n-NR¹⁴SO₂NR¹⁴R¹⁴, -NR¹⁴SO₂NR¹⁴R¹⁴, -CO₂NR¹⁴R¹⁴, -NR¹⁴CO₂NR¹⁴R¹⁴, -NR¹⁴COR¹⁴, -SO₂NR¹⁴COR¹⁴, -SO₂NR¹⁴CONR¹⁴R¹⁴, -NR¹⁴CO₂R¹⁴, -CO₂R¹⁴, -NR¹⁴R¹⁴, -NR¹⁴CONR¹⁴R¹⁴, 15 -C(=NOR¹⁴)NR¹⁴R¹⁴, -CONR¹⁴OR¹⁴ or -NCOR¹⁴, wherein the alkyl, cycloalkyl, alkenyl, alkoxy, aryl, heteroaryl and heterocyclyl may be substituted with 0-2 R^{14a}, and the heteroaryl and heterocyclyl consist of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, S, or O;

20 R³ is phenyl, pyridinyl, pyrimidinyl, dihydropyran, or tetrahydropyran any of which may be substituted with 0-1 R^{3a};

R^{3a} is halo, CN, NH₂, -O-C₁₋₃alkyl, or morpholinyl;

25 R¹³, at each occurrence, is independently H, -OH, F, Cl, Br, I, CN, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, haloC₁₋₁₀ alkyl, C₃₋₁₀ cycloalkyl, C₂₋₁₂ alkenyl, C₂₋₁₂ alkynyl, C₆₋₁₀aryl, a 4- to 12-membered heteroaryl, a 4- to 12-membered heterocyclyl, a 4- to 12-membered heteroaryl-C₁₋₁₀ alkyl, -CN, -NO₂, -(CH₂)_m-SO₂R¹⁴, -NR¹⁴SO₂R¹⁴, =O, -CONR¹⁴R¹⁴,

$-(CH_2)_m-SO_2NR^{14}R^{14}$, $-(CH_2)_m-NR^{14}SO_2R^{14}$, $-(CH_2)_n-NR^{14}SO_2NR^{14}R^{14}$,
 $-NR^{14}SO_2NR^{14}R^{14}$, $-CO_2NR^{14}R^{14}$, $-NR^{14}CO_2NR^{14}R^{14}$, $-NR^{14}COR^{14}$, $-SO_2NR^{14}COR^{14}$,
 $-SO_2NR^{14}CONR^{14}R^{14}$, $-NR^{14}CO_2R^{14}$, $-CO_2R^{14}$, $-NR^{14}R^{14}$, $-NR^{14}CONR^{14}R^{14}$,

$-C(=NOR^{14})NR^{14}R^{14}$, $-CONR^{14}OR^{14}$ or $-NCOR^{14}$, OR^{14} , wherein the alkyl, cycloalkyl,

5 alkenyl, alkoxy, aryl, heteroaryl and heterocyclyl may be substituted with 0-2 R^{14a} , and the heteroaryl and heterocyclyl consist of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, S, or O;

R^{14} , at each occurrence, is independently selected from hydrogen, C_{1-10} alkyl, C_{3-10} cycloalkyl, C_{6-10} aryl, a 4- to 12-membered heteroaryl or a 4- to 12-membered

10 heterocyclyl, wherein the alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl may be substituted with 0-3 R^{14a} and the heteroaryl and heterocyclyl consist of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, S, or O; or

15 alternatively, two R^{14} 's are taken together with the atoms to which they are attached to form a cyclic ring, wherein the cyclic ring may be substituted with 0-1 R^{14a} and optionally contain 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, S, or O;

R^{14a} , at each occurrence, is independently selected from F, Cl, Br, I, C_{1-10} alkyl, halo C_{1-10} alkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, a 4- to 12-membered heteroaryl, a 4- to

20 12-membered heterocyclyl, F, Cl, Br, I, -CN, $-NO_2$, $-CO_2R^{26}$, $-CO_2NR^{24}R^{24}$, $-OCF_3$, $-OR^{25}$, $=O$, $-CONR^{24}R^{24}$, $-COR^{24}$, $-SO_2R^{24}$, $-NR^{24}R^{24}$, $-NR^{24}CO_2R^{24}$, $-SO_2NR^{24}R^{24}$, or C_{6-10} aryl C_{1-10} alkyl, wherein the heteroaryl and heterocyclyl consist of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, S, or O;

R^{24} , at each occurrence, is independently selected from hydrogen, C_{1-10} alkyl,

25 C_{3-6} cycloalkyl, or phenyl;

R^{25} , at each occurrence, is independently selected from hydrogen, C_{1-10} alkyl, C_{3-6} cycloalkyl, or phenyl;

R^{26} , at each occurrence, is independently selected from hydrogen, C_{1-10} alkyl, C_{3-6} cycloalkyl, or phenyl;

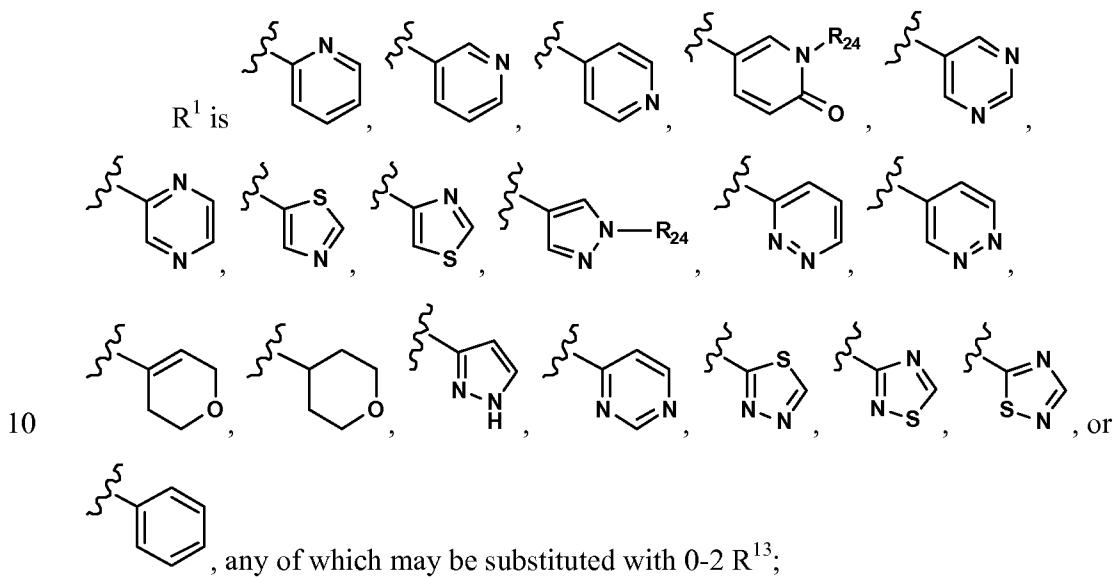
30 m is 0 to 4;

n is 0 to 4; and

n-1 is 2 to 4.

In another aspect, the present invention provides compound of formula (I), or enantiomers, diastereomers, tautomers, prodrugs or salts thereof, wherein:

A is $-(\text{CH}_2)_m\text{R}^2$, $-\text{CH}(\text{R}^{26})\text{R}^2$, $-(\text{CH}_2)_{n-1}\text{O-R}^2$, $-(\text{CH}_2)_{n-1}\text{NR}^{25}\text{R}^2$,
5 $-\text{CH}(\text{R}^{26})\text{CO}_2\text{R}^2$, or $-(\text{CH}_2)_{n-1}\text{NR}^{25}\text{CO}_2\text{R}^2$;
R¹ is C₁₋₁₀ alkyl substituted with 1-2 -OH, haloC₁₋₁₀ alkyl, C₂₋₁₂ alkenyl, or C₃₋₁₀ cycloalkyl, wherein the cycloalkyl may be substituted with 0-2 R¹³; or



R^2 is phenyl, cyclopentyl, cyclohexyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, piperidinyl, pyridinone, pyrrolidinyl, tetrahydropyran, or thiazolyl, any of which are substituted with 0-2 R^{2a} ;

15 R^{2a} , at each occurrence, is independently H, -OH, F, Cl, Br, I, C_{1-10} alkyl, C_{1-10} alkoxy, halo C_{1-10} alkyl, C_{3-10} cycloalkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{6-10} aryl, a 4- to 12-membered heteroaryl, a 4- to 12-membered heterocyclyl, a 4- to 12-membered heteroaryl- C_{1-10} alkyl, -CN, -NO₂, -(CH₂)_m-SO₂R¹⁴, -NR¹⁴SO₂R¹⁴, =O, -CONR¹⁴R¹⁴, -(CH₂)_m-SO₂NR¹⁴R¹⁴, -(CH₂)_m-NR¹⁴SO₂R¹⁴, -(CH₂)_n-NR¹⁴SO₂NR¹⁴R¹⁴,

20 -NR¹⁴SO₂NR¹⁴R¹⁴, -CO₂NR¹⁴R¹⁴, -NR¹⁴CO₂NR¹⁴R¹⁴, -NR¹⁴COR¹⁴, -SO₂NR¹⁴COR¹⁴, -SO₂NR¹⁴CONR¹⁴R¹⁴, -NR¹⁴CO₂R¹⁴, -CO₂R¹⁴, -NR¹⁴R¹⁴, -NR¹⁴CONR¹⁴R¹⁴, -C(=NOR¹⁴)NR¹⁴R¹⁴, -CONR¹⁴OR¹⁴ or -NR¹⁴COR¹⁴, wherein the alkyl, cycloalkyl, alkenyl, alkoxy, aryl, heteroaryl and heterocyclyl may be substituted with 0-2 R^{14a} , and the heteroaryl and heterocyclyl consist of carbon atoms and 1, 2, 3, or 4 heteroatoms

25 independently selected from the group consisting of N, S, or O;

R^3 is phenyl, pyridinyl, pyrimidinyl, dihydropyran, or tetrahydropyran any of which may be substituted with 0-1 R^{3a} ;

R^{3a} is halo, CN, NH₂, -O-C₁₋₃alkyl, or morpholinyl;

R^{13} , at each occurrence, is independently H, -OH, F, Cl, Br, I, CN, C₁₋₁₀ alkyl,

5 C₁₋₁₀ alkoxy, haloC₁₋₁₀ alkyl, C₃₋₁₀ cycloalkyl, C₂₋₁₂ alkenyl, C₂₋₁₂ alkynyl, C₆₋₁₀aryl, a 4- to 12-membered heteroaryl, a 4- to 12-membered heterocyclyl, a 4- to 12-membered heteroaryl-C₁₋₁₀ alkyl, -CN, -NO₂, -(CH₂)_m-SO₂R¹⁴, -NR¹⁴SO₂R¹⁴, =O, -CONR¹⁴R¹⁴, -(CH₂)_m-SO₂NR¹⁴R¹⁴, -(CH₂)_m-NR¹⁴SO₂R¹⁴, -(CH₂)_n-NR¹⁴SO₂NR¹⁴R¹⁴, -NR¹⁴SO₂NR¹⁴R¹⁴, -CO₂NR¹⁴R¹⁴, -NR¹⁴CO₂NR¹⁴R¹⁴, -NR¹⁴COR¹⁴, -SO₂NR¹⁴COR¹⁴, 10 -SO₂NR¹⁴CONR¹⁴R¹⁴, -NR¹⁴CO₂R¹⁴, -CO₂R¹⁴, -NR¹⁴R¹⁴, -NR¹⁴CONR¹⁴R¹⁴, -C(=NOR¹⁴)NR¹⁴R¹⁴, -CONR¹⁴OR¹⁴ or -NR¹⁴COR¹⁴, OR¹⁴, wherein the alkyl, cycloalkyl, alkenyl, alkoxy, aryl, heteroaryl and heterocyclyl may be substituted with 0-2 R^{14a}, and the heteroaryl and heterocyclyl consist of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, S, or O;

15 R^{14} , at each occurrence, is independently selected from hydrogen, C₁₋₁₀ alkyl, C₃₋₁₀ cycloalkyl, C₆₋₁₀ aryl, a 4- to 12-membered heteroaryl or a 4- to 12-membered heterocyclyl, wherein the alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl may be substituted with 0-3 R^{14a} and the heteroaryl and heterocyclyl consist of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, S, or O;

20 or

alternatively, two R^{14} 's are taken together with the atoms to which they are attached to form a cyclic ring, wherein the cyclic ring may be substituted with 0-1 R^{14a} and optionally contain 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, S, or O;

25 R^{14a} , at each occurrence, is independently selected from F, Cl, Br, I, C₁₋₁₀ alkyl, haloC₁₋₁₀alkyl, C₆₋₁₀aryl, C₃₋₁₀cycloalkyl, a 4- to 12-membered heteroaryl, a 4- to 12-membered heterocyclyl, F, Cl, Br, I, -CN, -NO₂, -CO₂R²⁶, -CO₂NR²⁴R²⁴, -OCF₃, -OR²⁵, =O, -CONR²⁴R²⁴, -COR²⁴, -SO₂R²⁴, -NR²⁴R²⁴, -NR²⁴CO₂R²⁴, -SO₂NR²⁴R²⁴, or C₆₋₁₀arylC₁₋₁₀alkyl, wherein the heteroaryl and heterocyclyl consist of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, S, or O;

30 R^{24} , at each occurrence, is independently selected from hydrogen, C₁₋₁₀alkyl, C₃₋₆cycloalkyl, or phenyl;

R^{25} , at each occurrence, is independently selected from hydrogen, C₁₋₁₀alkyl, C₃₋₆cycloalkyl, or phenyl;

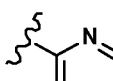
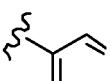
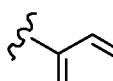
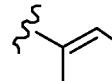
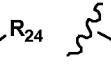
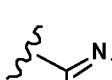
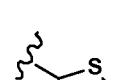
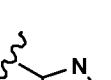
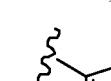
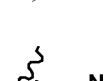
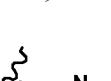
R^{26} , at each occurrence, is independently selected from hydrogen, C₁₋₁₀alkyl, C₃₋₆cycloalkyl, or phenyl;

5 m is 0 to 4;
 n is 0 to 4; and
 n-1 is 2 to 4.

In another aspect, the present invention provides compound of formula (I), or
10 enantiomers, diastereomers, tautomers, prodrugs or salts thereof, wherein:

A is $-(CH_2)_m-R^2$, $-CH(R^{26})-R^2$, $-C(R^{26})_2-R^2$, $-(CH_2)_{n-1}-O-R^2$, $-(CH_2)_{n-1}-NR^{25}-R^2$, $-CH(R^{26})-CO_2-R^2$, or $-(CH_2)_{n-1}-NR^{25}-CO_2-R^2$;

R^1 is C_{1-10} alkyl substituted with 1-2 -OH, halo C_{1-10} alkyl, C_{2-12} alkenyl, or C_{3-10} cycloalkyl, wherein the cycloalkyl may be substituted with 0-2 R^{13} ; or

15 R^1 is  ,  ,  ,  ,  ,
 ,  ,  ,  ,  ,  ,
 ,  ,  ,  ,  ,  ,  , or
 , any of which may be substituted with 0-2 R^{13} ;

20 R² is phenyl, cyclopentyl, cyclohexyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, piperidinyl, pyridinone, pyrrolidinyl, tetrahydropyran, or thiazolyl, any of which are substituted with 0-2 R^{2a};

²⁵ R^{2a}, at each occurrence, is independently H, -OH, F, Cl, Br, I, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, haloC₁₋₁₀ alkyl, C₃₋₁₀ cycloalkyl, C₂₋₁₂ alkenyl, C₂₋₁₂ alkynyl, C₆₋₁₀aryl, a 4- to 12-membered heteroaryl, a 4- to 12-membered heterocycl, a 4- to 12-membered heteroaryl-C₁₋₁₀ alkyl, -CN, -NO₂, -(CH₂)_m-SO₂R¹⁴, -NR¹⁴SO₂R¹⁴, =O, -CONR¹⁴R¹⁴,

$-(CH_2)_m-SO_2NR^{14}R^{14}$, $-(CH_2)_m-NR^{14}SO_2R^{14}$, $-(CH_2)_n-NR^{14}SO_2NR^{14}R^{14}$,
 $-NR^{14}SO_2NR^{14}R^{14}$, $-CO_2NR^{14}R^{14}$, $-NR^{14}CO_2NR^{14}R^{14}$, $-NR^{14}COR^{14}$, $-SO_2NR^{14}COR^{14}$,
 $-SO_2NR^{14}CONR^{14}R^{14}$, $-NR^{14}CO_2R^{14}$, $-CO_2R^{14}$, $-NR^{14}R^{14}$, $-NR^{14}CONR^{14}R^{14}$,

$-C(=NOR^{14})NR^{14}R^{14}$, $-CONR^{14}OR^{14}$ or $-NR^{14}COR^{14}$, wherein the alkyl, cycloalkyl,

5 alkenyl, alkoxy, aryl, heteroaryl and heterocyclyl may be substituted with 0-2 R^{14a} , and the heteroaryl and heterocyclyl consist of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, S, or O;

R^3 is phenyl, pyridinyl, pyrimidinyl, dihydropyran, or tetrahydropyran any of which may be substituted with 0-1 R^{3a} ;

10 R^{3a} is halo, CN, NH₂, -O-C₁₋₃alkyl, or morpholinyl;

R^{13} , at each occurrence, is independently H, -OH, F, Cl, Br, I, CN, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, haloC₁₋₁₀ alkyl, C₃₋₁₀ cycloalkyl, C₂₋₁₂ alkenyl, C₂₋₁₂ alkynyl, C₆₋₁₀ aryl, a 4- to 12-membered heteroaryl, a 4- to 12-membered heterocyclyl, a 4- to 12-membered heteroaryl-C₁₋₁₀ alkyl, -CN, -NO₂, $-(CH_2)_m-SO_2R^{14}$, $-NR^{14}SO_2R^{14}$, =O, -CONR¹⁴R¹⁴,
15 $-(CH_2)_m-SO_2NR^{14}R^{14}$, $-(CH_2)_m-NR^{14}SO_2R^{14}$, $-(CH_2)_n-NR^{14}SO_2NR^{14}R^{14}$,
 $-NR^{14}SO_2NR^{14}R^{14}$, $-CO_2NR^{14}R^{14}$, $-NR^{14}CO_2NR^{14}R^{14}$, $-NR^{14}COR^{14}$, $-SO_2NR^{14}COR^{14}$,
 $-SO_2NR^{14}CONR^{14}R^{14}$, $-NR^{14}CO_2R^{14}$, $-CO_2R^{14}$, $-NR^{14}R^{14}$, $-NR^{14}CONR^{14}R^{14}$,
 $-C(=NOR^{14})NR^{14}R^{14}$, $-CONR^{14}OR^{14}$, $-NR^{14}COR^{14}$, or OR¹⁴, wherein the alkyl, cycloalkyl, alkenyl, alkoxy, aryl, heteroaryl and heterocyclyl may be substituted with 0-2

20 R^{14a}, and the heteroaryl and heterocyclyl consist of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, S, or O; or

R^{13} is SO₂NHP(O)(OH)₂;

25 R^{14} , at each occurrence, is independently selected from hydrogen, C₁₋₁₀ alkyl, C₃₋₁₀ cycloalkyl, C₆₋₁₀ aryl, a 4- to 12-membered heteroaryl or a 4- to 12-membered heterocyclyl, wherein the alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl may be substituted with 0-3 R^{14a} and the heteroaryl and heterocyclyl consist of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, S, or O; or

30 alternatively, two R^{14} 's are taken together with the atoms to which they are attached to form a cyclic ring, wherein the cyclic ring may be substituted with 0-1 R^{14a} and optionally contain 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, S, or O;

R^{14a} , at each occurrence, is independently selected from F, Cl, Br, I, C₁₋₁₀ alkyl, haloC₁₋₁₀alkyl, C₆₋₁₀aryl, C₃₋₁₀cycloalkyl, a 4- to 12-membered heteroaryl, a 4- to 12-membered heterocyclyl, F, Cl, Br, I, -CN, -NO₂, -CO₂R²⁶, -CO₂NR²⁴R²⁴, -OCF₃, -OR²⁵, =O, -CONR²⁴R²⁴, -COR²⁴, -SO₂R²⁴, -NR²⁴SO₂R²⁴, -NR²⁴R²⁴, -NR²⁴CO₂R²⁴, -SO₂NR²⁴R²⁴, or C₆₋₁₀arylC₁₋₁₀alkyl, wherein the heteroaryl and heterocyclyl consist of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, S, or O, and wherein the aryl and heteroaryl is optionally substituted with 0-1 of: halo, C₁₋₃alkyl, C₁₋₃haloalkyl, -O-C₁₋₃alkyl, or -O- C₁₋₃haloalkyl;

5 R²⁴, at each occurrence, is independently selected from hydrogen, C₁₋₁₀alkyl, C₃₋₆cycloalkyl, or phenyl;

10 R²⁵, at each occurrence, is independently selected from hydrogen, C₁₋₁₀alkyl, C₁₋₆haloalkyl, C₃₋₆cycloalkyl, -(CH₂)-phenyl, or phenyl;

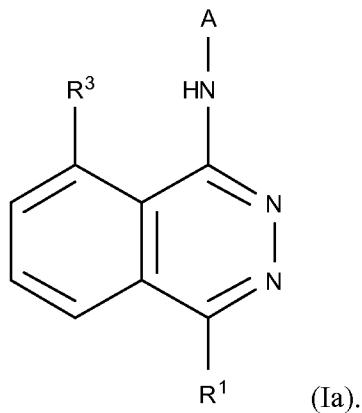
15 R²⁶, at each occurrence, is independently selected from hydrogen, -OH, C₁₋₁₀alkyl, C₃₋₆cycloalkyl, or phenyl;

m is 0 to 4;

n is 0 to 4; and

n-1 is 2 to 4.

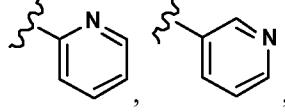
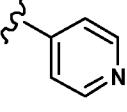
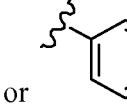
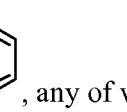
20 In another aspect, the present invention provides compound of formula (Ia), or enantiomers, diastereomers, tautomers, prodrugs or salts thereof, wherein:



25 In another aspect, the present invention provides compound of formula (I) or (Ia), or enantiomers, diastereomers, tautomers, prodrugs or salts thereof, wherein:

A is -(CH₂)_m-R²;

R^1 is C_{1-6} alkyl substituted with 1-2 -OH, C_{2-6} alkenyl, or C_{3-6} cycloalkyl, wherein the cycloalkyl may be substituted with 0-2 R^{13} ; or

R^1 is , , , or , any of which may be substituted with 0-2 R^{13} ;

5 R^2 is phenyl or pyridinyl;

R^3 is phenyl;

R^{13} , at each occurrence, is independently H, C_{1-6} alkyl, $-NR^{14}SO_2R^{14}$, $-CONR^{14}R^{14}$, $-SO_2NR^{14}R^{14}$, $-NR^{14}CO_2NR^{14}R^{14}$, $-NR^{14}COR^{14}$, or $-NR^{14}R^{14}$, wherein the alkyl may be substituted with 0-2 R^{14a} ;

10 R^{14} , at each occurrence, is independently selected from hydrogen, C_{1-6} alkyl, or phenyl, wherein the alkyl and phenyl may be substituted with 0-3 R^{14a} , and the heterocyclyl is pyrrolidinyl, or dioxanyl;

R^{14a} , at each occurrence, is independently selected from F, Cl, Br, I, C_{1-6} alkyl, phenyl, C_{3-6} cycloalkyl, $-OR^{25}$ or dioxanyl;

15 R^{24} , at each occurrence, is independently selected from hydrogen, C_{1-10} alkyl, C_{3-6} cycloalkyl, or phenyl;

R^{25} , at each occurrence, is independently selected from hydrogen, C_{1-10} alkyl, C_{3-6} cycloalkyl, or phenyl;

20 R^{26} , at each occurrence, is independently selected from hydrogen, C_{1-10} alkyl, C_{3-6} cycloalkyl, or phenyl;

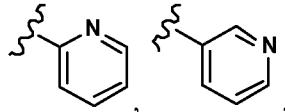
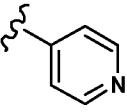
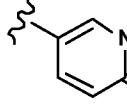
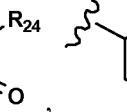
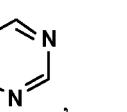
m is 0 to 4;

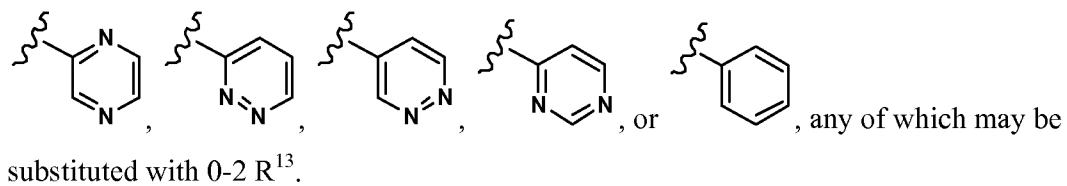
n is 0 to 2; and

$n-1$ is 2 to 4.

25 In another aspect, the present invention provides compound of formula (I) or (Ia), or enantiomers, diastereomers, tautomers, prodrugs or salts thereof, wherein:

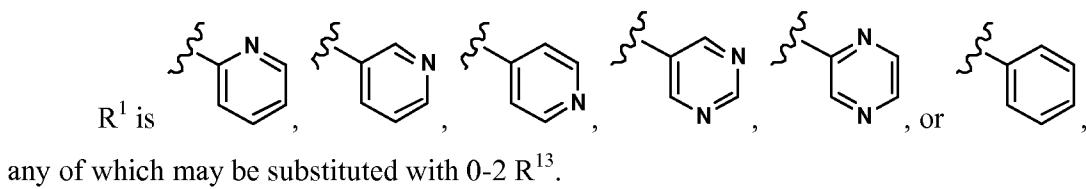
R^1 is C_{1-10} alkyl substituted with 1-2 -OH, halo C_{1-10} alkyl, or C_{3-10} cycloalkyl, wherein the cycloalkyl may be substituted with 0-2 R^{13} ; or

R^1 is , , , , or ,



5 In another aspect, the present invention provides compound of formula (I) or (Ia), or enantiomers, diastereomers, tautomers, prodrugs or salts thereof, wherein:

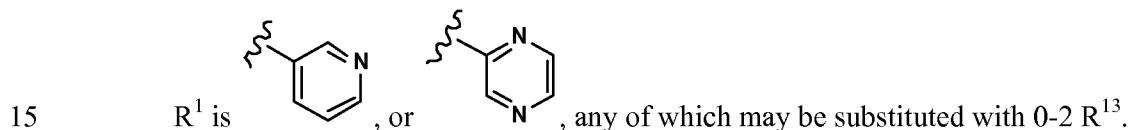
R¹ is C₁₋₁₀ alkyl substituted with 1-2 -OH, haloC₁₋₁₀ alkyl, or C₃₋₁₀ cycloalkyl, wherein the cycloalkyl may be substituted with 0-1 R¹³; or



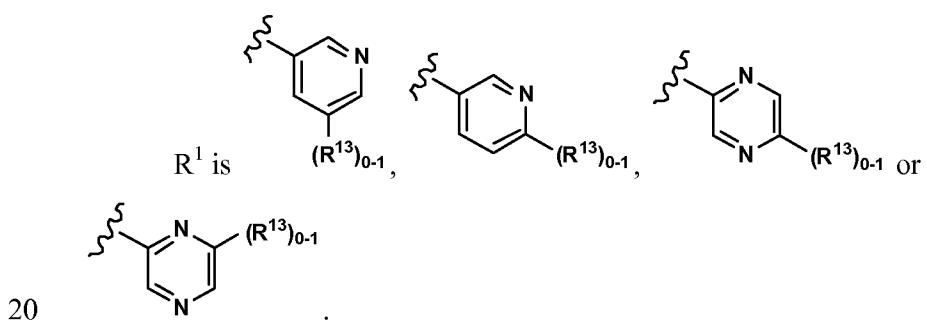
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In another aspect, the present invention provides compound of formula (I) or (Ia), or enantiomers, diastereomers, tautomers, prodrugs or salts thereof, wherein:

R¹ is C₁₋₁₀ alkyl substituted with 1-2 -OH, haloC₁₋₁₀ alkyl, C₃₋₁₀ cycloalkyl, wherein the cycloalkyl may be substituted with 0-1 R¹³; or



In another aspect, the present invention provides compound of formula (I) or (Ia), or enantiomers, diastereomers, tautomers, prodrugs or salts thereof, wherein:



20

In another aspect, the present invention provides compound of formula (I) or (Ia), or enantiomers, diastereomers, tautomers, prodrugs or salts thereof, wherein:

R¹³, at each occurrence, is independently H, -OH, F, Cl, Br, I, C₁₋₆ alkyl, C₁₋₆ alkoxy, haloC₁₋₆ alkyl, C₃₋₆ cycloalkyl, phenyl, a 4- to 12-membered heteroaryl, wherein
5 the heteroaryl is selected from tetrazolyl, -CN, -NO₂, -(CH₂)_m-SO₂R¹⁴, -NR¹⁴SO₂R¹⁴, -CONR¹⁴R¹⁴, -(CH₂)_m-SO₂NR¹⁴R¹⁴, -NR¹⁴CO₂NR¹⁴R¹⁴, -NR¹⁴CO₂NR^{14b}R^{14b}, -NR¹⁴COR¹⁴, -NR¹⁴CO₂R¹⁴, -CO₂R¹⁴, or -NR¹⁴R¹⁴, wherein the alkyl, cycloalkyl, phenyl, and heteroaryl may be substituted with 0-2 R^{14a}, and the heteroaryl and heterocyclyl consist of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the
10 group consisting of N, S, or O;

R¹⁴, at each occurrence, is independently selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, phenyl, wherein the alkyl, cycloalkyl, and phenyl, may be substituted with 0-3 R^{14a}, or

15 alternatively, two R^{14b}'s are taken together with the atoms to which they are attached to form a cyclic ring, wherein the cyclic ring is morpholinyl, piperidinyl, or piperazinyl, and may be substituted with 0-1 C₁₋₆alkyl; and

R^{14a}, at each occurrence, is independently selected from F, Cl, Br, I, C₁₋₆ alkyl, haloC₁₋₆alkyl, phenyl, or C₃₋₆cycloalkyl.

20 In another aspect, the present invention provides compound of formula (I) or (Ia), or enantiomers, diastereomers, tautomers, prodrugs or salts thereof, wherein:

R¹³, at each occurrence, is independently H, C₁₋₆ alkyl, a 4- to 12-membered heteroaryl, wherein the heteroaryl is selected from tetrazolyl, -CN, -NR¹⁴SO₂R¹⁴, -CONR¹⁴R¹⁴, -SO₂NR¹⁴R¹⁴, -NR¹⁴CO₂NR¹⁴R¹⁴, -NR¹⁴CO₂NR^{14b}R^{14b}, -NR¹⁴COR¹⁴,
25 -CO₂R¹⁴, or -NR¹⁴R¹⁴, wherein the alkyl, and heteroaryl may be substituted with 0-2 R^{14a};

R¹⁴, at each occurrence, is independently selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, or phenyl, wherein the alkyl, cycloalkyl, and phenyl, may be substituted with 0-3 R^{14a}, or

30 two R^{14b}'s are taken together with the atoms to which they are attached to form a cyclic ring, wherein the cyclic ring is morpholinyl, and may be substituted with 0-1 C₁₋₆alkyl; and

R^{14a} , at each occurrence, is independently selected from F, Cl, Br, I, C₁₋₆ alkyl, haloC₁₋₆alkyl, phenyl, or C₃₋₆cycloalkyl.

In another aspect, the present invention provides compound of formula (I) or (Ia),
5 wherein:

R^{13} , at each occurrence, is independently H, -OH, F, Cl, Br, I, C₁₋₆ alkyl, C₁₋₆ alkoxy, haloC₁₋₆ alkyl, C₃₋₆ cycloalkyl, phenyl, a 4- to 12-membered heteroaryl, wherein the heteroaryl is selected from tetrazolyl, -CN, -NO₂, -(CH₂)_m-SO₂R¹⁴, -NR¹⁴SO₂R¹⁴, -CONR¹⁴R¹⁴, -(CH₂)_m-SO₂NR¹⁴R¹⁴, -NR¹⁴CO₂NR¹⁴R¹⁴, -NR¹⁴CO₂NR¹⁴R^{1b}, -NR¹⁴COR¹⁴,
10 -NR¹⁴CO₂R¹⁴, -CO₂R¹⁴, or -NR¹⁴R¹⁴, wherein the alkyl, cycloalkyl, phenyl, and heteroaryl may be substituted with 0-2 R^{14a}, and the heteroaryl and heterocyclyl consist of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, S, or O;

R^{14} , at each occurrence, is independently selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, phenyl, wherein the alkyl, cycloalkyl, and phenyl, may be substituted with 0-3 R^{14a}; or

alternatively, two R¹⁴'s are taken together with the atoms to which they are attached to form a cyclic ring, wherein the cyclic ring is morpholinyl, piperidinyl, or piperazinyl, and may be substituted with 0-1 C₁₋₆alkyl;

20 R^{14a} , at each occurrence, is independently selected from F, Cl, Br, I, C₁₋₆ alkyl, haloC₁₋₆alkyl, phenyl, C₃₋₆cycloalkyl.

In another aspect, the present invention provides compound of formula (I) or (Ia), or enantiomers, diastereomers, tautomers, prodrugs or salts thereof, wherein:

25 R^{13} , at each occurrence, is independently H, -CN, -NHSO₂R¹⁴, -CONH₂, -SO₂NR¹⁴R¹⁴, -NHCO₂NR^{14b}R^{14b}, -NHCOR¹⁴, or -NH₂; and

R^{14} , at each occurrence, is independently selected from hydrogen, or methyl.

In another aspect, the present invention provides compound of formula (I) or (Ia),
30 or enantiomers, diastereomers, tautomers, prodrugs or salts thereof, wherein:

R^{13} , at each occurrence, is -SO₂NH₂.

In another aspect, the present invention provides compound of formula (I) or (Ia), or enantiomers, diastereomers, tautomers, prodrugs or salts thereof, wherein:

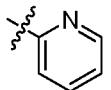
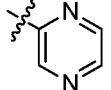
A is $-(CH_2)_m-R^2$, $-CH(R^{26})-R^2$, $-(CH_2)_{n-1}-O-R^2$, $-(CH_2)_{n-1}-NR^{25}-R^2$, $-CH(R^{26})-CO_2-R^2$, or $-(CH_2)_{n-1}-NR^{25}-CO_2-R^2$;

5 R^2 is phenyl, pyridinyl, pyrazinyl, pyrimidinyl, piperidinyl, or pyridinone, any of which are substituted with 0-2 R^{2a} ; and

R^{2a} , at each occurrence, is independently H, -OH, F, C_{1-6} alkyl, C_{1-6} alkoxy, or $6-SO_2NR^{14}R^{14}$.

10 In another aspect, the present invention provides compound of formula (I) or (Ia), or enantiomers, diastereomers, tautomers, prodrugs or salts thereof, wherein:

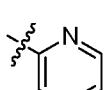
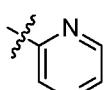
A is $-(CH_2)-R^2$;

R^2 is phenyl,  or , any of which are substituted with 0-1 R^{2a} ; and

15 R^{2a} , at each occurrence, is independently H, -OH, F, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or $SO_2NR^{14}R^{14}$.

In another aspect, the present invention provides compound of formula (I) or (Ia), or enantiomers, diastereomers, tautomers, prodrugs or salts thereof, wherein:

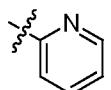
A is $-(CH_2)-R^2$;

20 R^2 is phenyl,  or , any of which are substituted with 0-1 R^{2a} ; or

R^{2a} , at each occurrence, is independently H, -OH, F, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or $SO_2NR^{14}R^{14}$.

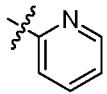
25 In another aspect, the present invention provides compound of formula (I) or (Ia), or enantiomers, diastereomers, tautomers, prodrugs or salts thereof, wherein:

A is $-(CH_2)-R^2$; and

R^2 is phenyl or .

In another aspect, the present invention provides compound of formula (I) or (Ia), or enantiomers, diastereomers, tautomers, prodrugs or salts thereof, wherein:

A is-(CH₂)-R²;



R² is phenyl, , or C₁₋₆alkyl, any of which are substituted with 0-1 R^{2a}; and
5 R^{2a}, at each occurrence, is independently H or F.

In another aspect, the present invention provides compound of formula (I) or (Ia), or enantiomers, diastereomers, tautomers, prodrugs or salts thereof, wherein:

R³ is phenyl.

10

In another aspect, the present invention provides compound of formula (I) or (Ia), or enantiomers, diastereomers, tautomers, prodrugs or salts thereof, wherein:

R²⁴, at each occurrence, is independently selected from hydrogen, C₁₋₆alkyl, C₃₋₆cycloalkyl, or phenyl;

15

R²⁵, at each occurrence, is independently selected from hydrogen, C₁₋₆alkyl, C₃₋₆cycloalkyl, or phenyl; and

R²⁶, at each occurrence, is independently selected from hydrogen, C₁₋₆alkyl, C₃₋₆cycloalkyl, or phenyl.

20

In another aspect, the present invention provides compound of formula (I) or (Ia), or enantiomers, diastereomers, tautomers, prodrugs or salts thereof, wherein:

R²⁴, at each occurrence, is independently selected from hydrogen, methyl or ethyl;

R²⁵, at each occurrence, is independently selected from hydrogen methyl or ethyl; and

25

R²⁶, at each occurrence, is independently selected from hydrogen, methyl or ethyl.

In another aspect, the present invention provides compound of formula (I) or (Ia), or enantiomers, diastereomers, tautomers, prodrugs or salts thereof, wherein:

m is 0-2; and

30

n-1 is 1-2.

In another aspect, the present invention provides compound of formula (I) or (Ia), or enantiomers, diastereomers, tautomers, prodrugs or salts thereof, wherein:

m is 1 or 2;

n-1 is 2; and

5 n is 1.

In another aspect, the present invention provides compound of formula (I) or (Ia), or salts thereof, wherein:

R¹³ is SO₂NHP(O)(OH)₂.

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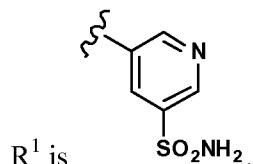
In another aspect, the present invention provides compound of formula (I) or (Ia), or salts thereof, wherein:

R¹ pyridinyl substituted with 1 R¹³; and

R¹³ is SO₂NHP(O)(OH)₂.

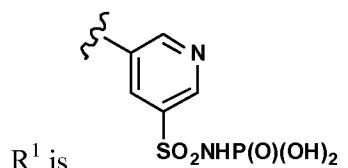
15

In another aspect, the present invention provides compound of formula (I) or (Ia), or salts thereof, wherein:



20

In another aspect, the present invention provides compound of formula (I) or (Ia), or salts thereof, wherein:



25

In another embodiment, compounds, enantiomers, diastereomers, tautomers, or salt thereof, of the present invention are selected from the compounds exemplified in the examples.

In one embodiment, pharmaceutical compositions comprising a therapeutically effective amount of at least one compound of formula (I), (Ia), and/or compounds exemplified in the examples.

In another embodiment, pharmaceutical compositions comprising a 5 therapeutically effective amount of at least one compound of formula (I), (Ia), and/or compounds exemplified in the examples, and at least one other therapeutic agent, for example, anti-arrhythmic agents, calcium channel blockers, anti-platelet agents, anti-hypertensive agents, anti thrombotic/anti thrombolytic agents, anti coagulants, HMG-CoA reductase inhibitors, anti diabetic agents, thyroid mimetics, mineralocorticoid 10 receptor antagonists, and cardiac glycosides, are provided.

In yet another embodiment, pharmaceutical compositions comprising a therapeutically effective amount of at least one compound of formula (I), (Ia), or compounds exemplified in the examples, and at least one other therapeutic agent, for example, sotalol, dofetilide, diltiazem, verapamil, clopidogrel, cangrelor, ticlopidine, 15 CS-747, ifetroban, aspirin, a beta adrenergic blocker, an ACE inhibitor, an A II antagonist, an ET antagonist, a dual ET/A II antagonist, a vasopepsidase inhibitor, tPA, recombinant tPA, TNK, nPA, a factor VIIa inhibitor, a factor Xa inhibitor, a factor XIa inhibitor, a thrombin inhibitor, warfarin, a heparin, pravastatin, lovastatin, atorvastatin, simvastatin, NK-104, ZD-4522, a biguanide, a biguanide/glyburide combination, 20 spironolactone, eplerinone, digitalis and ouabain, are provided.

In still yet another embodiment, pharmaceutical compositions comprising a therapeutically effective amount of at least one compound of formula (I), (Ia), or compounds exemplified in the examples, and at least one other therapeutic agent, for example, captopril, zofenopril, fosinopril, enalapril, ceranopril, cilazopril, delapril, 25 pentopril, quinapril, ramipril, lisinopril, omapatrilat, gemopatrilat, and apixaban, are provided.

In one embodiment, methods of treating or preventing arrhythmia comprising administering to a patient in need thereof an effective amount of at least one compound of formula (I), (Ia), or compounds exemplified in the examples, are provided.

30 In another embodiment, methods of treating or preventing supraventricular arrhythmia, for example, atrial fibrillation and atrial flutter, comprising administering to a

patient in need thereof an effective amount of at least one compound of formula (I), (Ia), or compounds exemplified in the examples, are provided.

In one embodiment, a method of controlling heart rate comprising administering to a patient in need thereof an effective amount of at least one compound of formula (I), (Ia), or compounds exemplified in the examples, is provided.

10 In another embodiment, methods of treating an I_{Kur} -associated conditions, for example, gastrointestinal disorders, such as reflux esophagitis and a motility disorder; inflammatory and/or immunological diseases, such as chronic obstructive pulmonary disease; diabetes; cognitive disorders; migraines; epilepsy; and hypertension, comprising administering to a patient in need thereof an effective amount of at least one compound of formula (I), (Ia), or compounds exemplified in the examples, are provided.

15 Another aspect of this invention is directed to a composition comprising a compound of the invention together with a pharmaceutically acceptable carrier, diluent, or excipient. When water is a carrier or diluent, the composition optionally further comprises another pharmaceutically acceptable carrier or diluent and/or a pharmaceutically acceptable excipient. Within this aspect are such compositions for pharmaceutical use.

20 Another aspect of this invention is directed to treatment of diseases or disorders associated with inhibition of potassium channel function, wherein the disease or disorder is atrial fibrillation, controlling heart rate, and/or prophylactically treating arrhythmia, comprising administering a therapeutically effective amount of a compound of the present invention or an individual isomer or mixture of isomers or a pharmaceutically acceptable salt thereof.

25 The compounds of the invention may be useful in therapy. The compounds of the invention may be used for the manufacture of a medicament for the treatment and/or prophylaxis of diseases or disorders associated with inhibition of potassium channel function, of the K_v1 subfamily of voltage gated K^+ channels, of $K_v1.5$ (which have been linked to the ultra-rapidly activating delayed rectifier K^+ current I_{Kur} , and/or $K_v1.3$ channels, and/or $K_v1.1$ channels.

30 The compounds of the invention can be used alone, in combination with other compounds of the present invention, or in combination with one or more, preferably one to two other agent(s).

The invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof. This invention also encompasses all combinations of alternative aspects of the invention noted herein. It is understood that any and all embodiments of the present invention may be taken in conjunction with any 5 other embodiment to describe additional embodiments of the present invention. Furthermore, any elements of an embodiment may be combined with any and all other elements from any of the embodiments to describe additional embodiments.

SYNTHESIS

10 The compounds of the present invention can be prepared in a number of ways known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or by variations thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to, 15 those described below. The reactions are performed in a solvent or solvent mixture appropriate to the reagents and materials employed and suitable for the transformations being effected. It will be understood by those skilled in the art of organic synthesis that the functionality present on the molecule should be consistent with the transformations proposed. This will sometimes require a judgment to modify the order of the synthetic 20 steps or to select one particular process scheme over another in order to obtain a desired compound of the invention.

The novel compounds of this invention may be prepared using the reactions and techniques described in this section. Also, in the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including 25 choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, are chosen to be the conditions standard for that reaction, which should be readily recognized by one skilled in the art. Restrictions to the substituents that are compatible with the reaction conditions will be readily apparent to one skilled in the art and alternate methods must then be used.

30 The compounds of the present invention may be prepared by the exemplary processes described in the following schemes and working examples, as well as relevant published literature procedures that are used by one skilled in the art. Exemplary

reagents and procedures for these reactions appear hereinafter and in the working examples. Protection and de-protection of functional groups in the processes below may be carried out by procedures generally known in the art (see, for example, Greene, T.W. et al., *Protecting Groups in Organic Synthesis*, Third Edition, Wiley (1999). General 5 methods of organic synthesis and functional group transformations are found in: Trost, B.M. et al., eds., *Comprehensive Organic Synthesis: Selectivity, Strategy & Efficiency in Modern Organic Chemistry*, Pergamon Press, New York, NY (1991); March, J., *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, Fourth Edition, Wiley & Sons, New York, NY (1992); Katritzky, A.R. et al., eds., *Comprehensive 10 Organic Functional Groups Transformations*, First Edition, Elsevier Science Inc., Tarrytown, NY (1995); Larock, R.C., *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, NY (1989); and references therein.

ABBREVIATIONS

15 Abbreviations as used herein, are defined as follows: "1 x" for once, "2 x" for twice, "3 x" for thrice, "°C" for degrees Celsius, "eq" for equivalent or equivalents, "g" for gram or grams, "mg" for milligram or milligrams, "L" for liter or liters, "mL" for milliliter or milliliters, "µL" for microliter or microliters, "N" for normal, "M" for molar, "nM" for nanomolar, "mol" for mole or moles, "mmol" for millimole or millimoles, 20 "min" for minute or minutes, "h" for hour or hours, "rt" for room temperature, "Rt" for retention time, "atm" for atmosphere, "psi" for pounds per square inch, "conc." for concentrate, "sat" or "sat'd" for saturated, "MW" for molecular weight, "mp" for melting point, "MS" or "Mass Spec" for mass spectrometry, "ESI" for electrospray ionization mass spectroscopy, "HR" for high resolution, "HRMS" for high resolution mass 25 spectrometry, "LCMS" for liquid chromatography mass spectrometry, "HPLC" for high pressure liquid chromatography, "RP HPLC" for reverse phase HPLC, "TLC" or "tlc" for thin layer chromatography, "NMR" for nuclear magnetic resonance spectroscopy, "nOe" for nuclear Overhauser effect spectroscopy, "¹H" for proton, "δ" for delta, "s" for singlet, "d" for doublet, "t" for triplet, "q" for quartet, "m" for multiplet, "br" for broad, "Hz" for 30 hertz, and "α", "β", "R", "S", "E", and "Z" are stereochemical designations familiar to one skilled in the art.

Solvents, temperatures, pressures, and other reaction conditions may readily be selected by one of ordinary skill in the art. Starting materials are commercially available or can be readily prepared by one of ordinary skill in the art using known methods. For all of the schemes and compounds described below X¹, X², A and R¹ are as described for 5 a compound of Formula (I). The following are the definitions of symbols used in the Examples:

Al ₂ O ₃	Aluminum oxide
Ar	Aryl
BF ₃ .OEt ₂	Boron trifluoride etherate
CH ₂ Cl ₂	Dichloromethane
CHCl ₃	Chloroform
CDCl ₃	Deuterated chloroform
CD ₃ OD	Deuterated methanol
DCM	Dichloromethane
DIPEA	N,N-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	N,N-dimethyl formamide
DMSO	Dimethyl sulfoxide
DMSO-d ₆	Deuterated dimethyl sulfoxide
Et	Ethyl
EtOAc	Ethyl acetate
EtOH	Ethanol
HATU	(O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate)
HCl	Hydrochloric acid
HCOOH	Formic acid
HCOONH ₄	Ammonium formate
KI	Potassium iodide

K ₂ CO ₃	Potassium carbonate
KOAc	Potassium acetate
K ₃ PO ₄	Potassium phosphate
LiOH	Lithium hydroxide
Me	Methyl
MeOH	Methanol
NaH	Sodium hydride
NaHCO ₃	Sodium bicarbonate
NaNO ₂	Sodium nitrite
Na ₂ SO ₄	Sodium sulfate
Na ₂ S ₂ O ₃	Sodium thiosulfate
NH ₃	Ammonia
NH ₄ OAc	Ammonium acetate
Pd/C	Palladium on carbon
Pd ₂ (dba) ₃	Tris(dibenzylideneacetone)dipalladium (0)
Pd(dppf) ₂ Cl ₂ :CH ₂ Cl ₂	[1,1'Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane
POCl ₃	Phosphorus oxychloride
THF	Tetrahydrofuran
TFA	Trifluoroacetic acid

SYNTHESIS

A particularly useful compendium of synthetic methods which may be applicable to the preparation of compounds of the present invention may be found in Larock, R.C., 5 *Comprehensive Organic Transformations*, VCH, New York (1989). Preferred methods include, but are not limited to, those described below. All references cited herein are hereby incorporated in their entirety herein by reference.

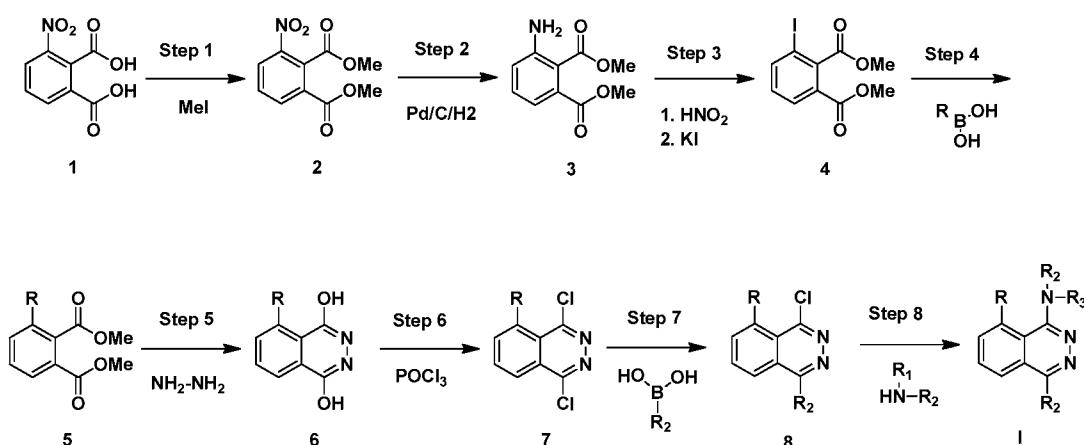
The novel compounds of this invention may be prepared using the reactions and techniques described in this section. Also, in the description of the synthetic methods 10 described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, are chosen to be the conditions standard for that reaction, which

should be readily recognized by one skilled in the art. Restrictions to the substituents that are compatible with the reaction conditions will be readily apparent to one skilled in the art and alternate methods must then be used.

It will also be recognized that another major consideration in the planning of any synthetic route in this field is the judicious choice of the protecting group used for protection of the reactive functional groups present in the compounds described in this invention. An authoritative account describing the many alternatives to the trained practitioner is Greene et al. (*Protective Groups in Organic Synthesis*, Wiley and Sons (1991)).

10

Scheme 1



Compounds of general formula (I) may be synthesized according to Scheme 1. Commercially available nitrophthalic acid can be converted to the corresponding diester 2, using for example methyl iodide. Dimethyl 3-nitrophthalate 2, was reduced to get 3-aminodimethylphthalate 3 (for example, Thottumkara et al *Tetrahedron Letters*, 43:569-572 (2002)). Dimethyl 3-aminophthalate 3 was subjected to diazotization conditions followed by treatment with KI to afford dimethyl 3-iodophthalate 4. Suzuki mediated cross-coupling with boronic acids or esters using palladium catalysts yielded compounds shown by structure 5 where R = alkyl, optionally substituted aryl, optionally substituted heteroaryl. Treatment of compound 5 with hydrazine hydrate (for example in solvents like water, ethanol, toluene, etc.) undergoes cyclization to furnish phthalazinedioines 6. Compound 6 was converted to the corresponding dichloro phthalazine 7 using chlorinating agents for example, phosphorous oxychloride. Dichloro-5-phthalazine 7 was

converted to compounds **8** under palladium mediated Suzuki cross-coupling with boronic esters or acids. Displacement of the second chloride with various amines generated compounds of the general formula (I).

5

EXAMPLES

The following Examples are offered to better illustrate, but not limit some of the preferred embodiments of the application and are not meant to be limiting of the scope of the invention. Abbreviations and chemical symbols have their usual and customary meanings unless otherwise indicated. Unless otherwise indicated, the compounds 10 described herein have been prepared, isolated and characterized using the schemes and other methods disclosed herein or may be prepared using the same.

General Methods

The following methods were used in the working Examples, except where noted 15 otherwise.

Analytical HPLC and HPLC/MS Methods Employed in Characterization of Examples

Preparative HPLC was carried on AGILENT® 1200 series, Shimadzu prominence or Waters systems. Preparative SFC was performed on Thar instrument. Reverse phase 20 analytical HPLC/MS was performed on AGILENT® 1200 systems coupled with Mass Spectrometers. LCMS was performed on AGILENT® 1200 or Waters AQUITY® system coupled with Mass Spectrometer. Chiral analytical LC was performed on a Thar Analytical SFC instrument.

25 *Condition 1:*

Column = Ascentis Express C18, 2.1 x 50 mm, 2.7 μ m

Solvent A = CH₃CN (2%) + 10 mM NH₄COOH in H₂O (98%)

Solvent B = CH₃CN (98%) + 10 mM NH₄COOH in H₂O (2%)

Start %B = 0; Final %B = 100

30 Gradient time = 1.4 min; Stop time = 4 min

Isocratic time = 1.6 min

Flow Rate = 1 mL/min; Wavelength = 220 nm

Condition 2:

Column = Ascentis Express C8, 2.1 x 50 mm, 2.7 μ m

Solvent A = CH₃CN (2%) + 10 mM NH₄COOH in H₂O (98%)

5 Solvent B = CH₃CN (98%) + 10 mM NH₄COOH in H₂O (2%)

Start %B = 0; Final %B = 100

Gradient time = 1.5 min; Stop time = 4 min

Isocratic time = 1.7 min

Flow Rate = 1 mL/min; Wavelength = 220 nm

10

Condition 3:

Column = Ascentis Express C8, 2.1 x 50 mm, 2.7 μ m

Solvent A = CH₃CN (10%) + 10 mM NH₄COOH in H₂O (90%)

Solvent B = CH₃CN (90%) + 10 mM NH₄COOH in H₂O (10%)

15 Start %B = 0; Final %B = 100

Gradient time = 1.6 min; Stop time = 4 min

Isocratic time = 1.6 min

Flow Rate = 1 mL/min; Wavelength = 220 nm

20 *Condition 4:*

Column = Ascentis Express C18 2.1 x 50 mm, 2.7 μ m

Solvent A = CH₃CN (2%) + 10 mM NH₄COOH in H₂O (98%)

Solvent B = CH₃CN (98%) + 10 mM NH₄COOH in H₂O (2%)

Start %B = 0; Final %B = 100

25 Gradient time = 1.5 min; Stop time = 4 min

Isocratic time = 1.7 min

Flow Rate = 1 mL/min; Wavelength = 220 nm

Condition 5:

30 Column = XBridge C18, 2.1 x 50 mm, 2.5 μ m

Solvent A = CH₃CN (5%) + 10 mM NH₄HCO₃ in H₂O (95%)

Solvent B = CH₃CN (95%) + 10 mM NH₄HCO₃ in H₂O (5%)

Start %B = 0; Final %B = 100

Gradient time = 1.7 min; Stop time = 4 min

Isocratic time = 1.5 min

Flow Rate = 1 mL/min; Wavelength = 220 nm

5

Condition 6:

Column = ZORBAX® SB-Aq, 4.6 x 50 mm, 3.5 μ m

Solvent A = CH₃CN (5%) + 10 mM NH₄COOH in H₂O (95%)

Solvent B = CH₃CN (95%) + 10 mM NH₄COOH in H₂O (5%)

10 Start %B = 5; Final %B = 95

Gradient time = 1.7 min; Stop time = 4 min

Isocratic time = 1.5 min

Flow Rate = 1 mL/min; Wavelength = 220 nm

15 *Condition 7:*

Column = Ascentis Express C8, 2.1 x 50 mm, 2.7 μ m

Solvent A = CH₃CN (2%) + 10 mM NH₄COOH in H₂O (98%)

Solvent B = CH₃CN (98%) + 10 mM NH₄COOH in H₂O (2%)

Start %B = 0; Final %B = 100

20 Gradient time = 1.5 min; Stop time = 4 min

Isocratic time = 1.7 min

Flow Rate = 1 mL/min; Wavelength = 220 nm

Condition 8:

25 Column = XBridge BEH C18, 2.1 x 50 mm, 2.5 μ m

Solvent A = 0.1% HCOOH in H₂O

Solvent B = 0.07% HCOOH in CH₃CN

Start %B = 10; Final %B = 100

Gradient time = 2.0 min; Stop time = 4.0 min

30 Isocratic time = 1. min

Flow Rate = 1.2 mL/min; Wavelength = 220 nm

Condition 9:

Column = ZORBAX® SB C18, 2.1 x 30 mm, 3.5 μ m

Solvent A = CH₃CN (2%) + 10 mM NH₄COOH in H₂O (98%)

Solvent B = CH₃CN (98%) + 10 mM NH₄COOH in H₂O (2%)

5 Start %B = 6; Final %B = 100

Gradient time = 1.5 min; Stop time = 3 min

Isocratic time = 0.7 min

Flow Rate = 1.5 mL/min; Wavelength = 220 nm

10 *Condition 10:*

Column = Kinetex C-18, 2.1 x 50 mm, 2.6 μ m

Solvent A = CH₃CN (2%) + 0.1% NH₄COOH in H₂O (98%)

Solvent B = CH₃CN (98%) + 0.1% NH₄COOH in H₂O (2%)

Start %B = 0; Final %B = 100

15 Gradient time = 1.7 min; Stop time = 4 min

Isocratic time = 1.5 min

Flow Rate = 1 mL/min; Wavelength = 220 nm

Condition 11:

20 Column = Acquity BEH C18, 2.1 x 50 mm, 1.7 μ m

Solvent A = Buffer: CH₃CN (95:5)

Solvent B = Buffer: CH₃CN (5:95)

Buffer = 10 mM NH₄OAc in H₂O (pH 5, adjusted with HCOOH)

Start %B = 5; Final %B = 95

25 Gradient time = 1.1 min; Stop time = 2.4 min

Isocratic time = 0.6 min

Flow Rate = 0.8 mL/min; Wave length = 220 nm

Condition 12:

30 Column : Acquity BEH C18, 2.1 x 50 mm, 1.7 μ m

Solvent A = 0.1% TFA in H₂O

Solvent B = 0.1% TFA in CH₃CN

Start %B = 2; Final %B = 98

Gradient time = 1 min; Stop time = 2.2 min

Isocratic time = 0.6 min

Flow Rate = 0.8 mL/min; Wave length = 220 nm

5

Condition 13:

Column = SYMMETRY® C18, 250 x 19 mm, 7 μ m

Solvent A = 10 mM NH₄OAc in H₂O (pH 4.5, adjusted with AcOH)

Solvent B = CH₃CN

10 Start %B = 50; Final %B = 90

Gradient time = 10 min; Stop time = 19 min

Isocratic time = 5 min

Flow = 17 mL/min; Wave length = 220 nm

15 *Condition 14:*

Column = SunFire C18, 19 x 150 mm, 5 μ m

Solvent A = 10 mM NH₄OAc in H₂O (pH 4.5, adjusted with AcOH)

Solvent B = CH₃CN

Isocratic = A: B (20:80)

20 Flow = 16 mL/min; Wave length = 220 nm

Condition 15:

Column = XSelect C18, 19 x 150 mm, 5 μ m

Solvent A = 10 mM NH₄OAc in H₂O

25 Solvent B = CH₃CN

Start %B = 30; Final %B = 70

Gradient time-1 = 12 min;

Start %B = 70; Final %B = 100

Gradient time = 3 min; Stop time = 19 min

30 Flow = 16 mL/min; Wave length = 220 nm

Condition 16:

Column = Inertsil ods, 19 x 250 mm, 5.0 μ m

Solvent A = 10 mM NH₄OAc in H₂O

Solvent B = CH₃CN

Start %B = 30; Final %B = 70

5 Gradient time-1 = 5 min;

Final %B = 100

Gradient time-2 = 8 min; Stop time = 15 min

Flow = 16 mL/min; Wave length = 220 nm

10 *Condition 17:*

Column = Inertsil ods, 19 x 250 mm, 5.0 μ m

Solvent A = 10 mM NH₄OAc in H₂O

Solvent B = CH₃CN

Start %B = 30; Final %B = 70

15 Gradient time-1 = 12 min;

Final %B = 100

Gradient time-2 = 3 min; Stop time = 20 min

Flow = 16 mL/min; Wave length = 220 nm

20 *Condition 18:*

Column = XBridge C18, 19 x 150 mm, 5 μ m

Solvent A = 10 mM NH₄OAc in H₂O (pH 4.5, adjusted with AcOH)

Solvent B = CH₃CN

Start %B = 10; Final %B = 40

25 Gradient time-1 = 10 min;

Final %B = 100

Gradient time-2 = 5 min; Stop time = 20 min

Flow = 17 mL/min; Wave length = 220 nm

30 *Condition 19:*

Column = XBridge C18, 19 x 150 mm, 5 μ m

Solvent A = 10 mM NH₄OAc in H₂O (pH 4.5, adjusted with AcOH)

Solvent B = CH₃CN

Start %B = 30; Final %B = 70

Gradient time-1 = 10 min;

Final %B = 100

5 Gradient time-2 = 5 min; Stop time = 20 min

Flow = 16 mL/min; Wave length = 220 nm

Condition 20:

Column = Kinetex C18, 19 x 150 mm, 5 μ m

10 Solvent A = 10 mM NH₄OAc in H₂O

Solvent B = CH₃CN

Start %B = 20; Final %B = 50

Gradient time-1 = 10 min;

Final %B = 100

15 Gradient time-2 = 2 min; Stop time = 20 min

Flow = 15 mL/min; Wave length = 220 nm

Condition 21:

Column = Atlantis C18, 19 x 250 mm, 7 μ m

20 Solvent A = 10 mM NH₄OAc in H₂O (pH 4.5, adjusted with AcOH)

Solvent B = CH₃CN

Start %B = 30; Final %B = 70

Gradient time-1 = 11 min;

Final %B = 100

25 Gradient time-2 = 4 min; Stop time = 20 min

Flow = 16 mL/min; Wave length = 220 nm

Condition 22:

Column = SunFire C18, 19 x 150 mm, 5 μ m

30 Solvent A = 10 mM NH₄OAc in H₂O (pH 4.5, adjusted with AcOH)

Solvent B = CH₃CN

Start %B = 20; Final %B = 70

Gradient time-1 = 10 min;

Final %B = 100

Gradient time-2 = 5 min; Stop time = 20 min

Flow = 16 mL/min; Wave length = 220 nm

5

Condition 23:

Column = SYMMETRY® C18, 19 x 250 mm, 5 μ m

Solvent A = 10 mM NH₄OAc in H₂O (pH 4.5, adjusted with AcOH)

Solvent B = CH₃CN

10 Start %B = 20; Final %B = 90

Gradient time = 10 min; Stop time = 20 min

Flow = 16 mL/min; Wave length = 220 nm

Condition 24:

15 Column = XBridge Phenyl, 4.6 x 150 mm, 3.5 μ m

Solvent A = Buffer: CH₃CN (95:5)

Solvent B = Buffer: CH₃CN (5:95)

Buffer = 0.05% TFA in H₂O (pH 2.5, adjusted with dilute ammonia)

Start %B = 10; Final %B = 100

20 Gradient time = 12 min; Stop time = 23 min

Isocratic time = 3 min

Flow Rate = 1 mL/min; Wavelength = 220 and 254 nm

Condition 25:

25 Column = SunFire C18, 4.6 x 150 mm, 3.5 μ m

Solvent A = Buffer: CH₃CN (95:5)

Solvent B = Buffer: CH₃CN (5:95)

Buffer = 0.05% TFA in H₂O (pH 2.5, adjusted with dilute ammonia)

Start %B = 10; Final %B = 100

30 Gradient time = 12 min; Stop time = 23 min

Isocratic time = 3 min

Flow Rate = 1 mL/min; Wavelength = 220 and 254 nm

Condition 26:

Column = SunFire C18, 4.6 x 150 mm, 3.5 μ m

Solvent A = Buffer: CH₃CN (95:5)

5 Solvent B = Buffer: CH₃CN (5:95)

Buffer = 0.05% TFA in H₂O (pH 2.5, adjusted with dilute ammonia)

Start %B = 0; Final %B = 50

Gradient time-1 = 15 min

Final %B = 100

10 Gradient time-2 = 3 min

Isocratic time = 5 min

Stop time = 28 min

Flow Rate = 1 mL/min; Wavelength = 220 and 254 nm

15 *Condition 27:*

Column = SunFire C18, 4.6 x 150 mm, 3.5 μ m

Solvent A = Buffer: CH₃CN (95:5)

Solvent B = Buffer: CH₃CN (5:95)

Buffer = 0.05% TFA in H₂O (pH 2.5, adjusted with dilute ammonia)

20 Start %B = 10; Final %B = 100

Gradient time = 25 min; Stop time = 30 min

Isocratic time = 5 min

Flow Rate = 1 mL/min; Wavelength = 220 and 254 nm

25 *Condition 28:*

Column = SunFire C18, 4.6 x 150 mm, 3.5 μ m

Solvent A = Buffer: CH₃CN (95:5)

Solvent B = Buffer: CH₃CN (5:95)

Buffer = 0.05% TFA in H₂O (pH 2.5, adjusted with dilute ammonia)

30 Start % B = 10; Final %B = 100

Gradient time = 12 min; Stop time = 15 min

Isocratic time = 3 min

Flow Rate = 1 mL/min; Wavelength = 220 and 254 nm

Condition 29:

Column = CHIRALCEL® OJH, 250 x 4.6 mm, 5 μ m

5 Solvent A = CO₂

Solvent B = 0.3% DEA in MeOH

Isocratic = A: B (85:15)

Flow = 3 mL/min; Wave length = 220 nm

10 *Condition 30:*

Column = SunFire C-18, 19 x 150 mm, 5 μ

Solvent A = 10 mM NH₄OAc in H₂O (pH 4.5, adjusted with AcOH)

Solvent B = CH₃CN

Start %B = 10; Final %B = 45

15 Gradient time = 10 min;

Flow = 16 mL/min; Wave length = 220 nm

Condition 31:

Column = KROMASIL® Packed C-18, 19 x 250 mm, 5 μ

20 Solvent A = 10 mM NH₄OAc in H₂O (pH 4.5, adjusted with AcOH)

Solvent B = CH₃CN

Start %B = 40; Final %B = 80

Gradient time-1 = 10 min;

Start %B = 80; Final %B = 100

25 Gradient time-2 = 5 min;

Flow = 16 mL/min; Wave length = 220 nm

Condition 32:

Column = XSelect C-18, 19 x 150 mm, 5 μ

30 Solvent A = 10 mM NH₄OAc in H₂O (pH 4.5, adjusted with AcOH)

Solvent B = CH₃CN

Start %B = 30; Final %B = 70

Gradient time-1 = 10 min;

Start %B = 70; Final %B = 100

Gradient time-2 = 5 min;

Flow = 16 mL/min; Wave length = 220 nm

5

Condition 33:

Column = SYMMETRY® C8, 19 x 300 mm, 7 μ

Solvent A = 10 mM NH₄OAc in H₂O (pH 4.5, adjusted with AcOH)

Solvent B = CH₃CN

10 Start %B = 50; Final %B = 90

Gradient time = 10 min;

Flow = 15 mL/min; Wave length = 220 nm

Condition 34:

15 Column = Ascentis Express C18, 2.1 x 50 mm, 2.7 μ

Solvent A = CH₃CN (2%) + 10 mM NH₄COOH in H₂O (98%)

Solvent B = CH₃CN (98%) + 10 mM NH₄COOH in H₂O (2%)

Start %B = 0; Final %B = 100

Gradient time = 1.7 min; Stop time = 4 min

20 Isocratic time = 1.5 min

Flow Rate = 1 mL/min; Wavelength = 220 nm

Condition 35:

Column = XBridge Phenyl, 4.6 x 150 mm, 5 μ

25 Solvent A = Buffer: CH₃CN (95:5)

Solvent B = Buffer: CH₃CN (5:95)

Buffer = 10 mM NH₄OAc in H₂O

Start %B = 10; Final %B = 100

Gradient time = 25 min; Stop time = 32 min

30 Isocratic time = 5 min

Flow Rate = 1 mL/min; Wavelength = 220 and 254 nm

Condition 36:

Column = XBridge Prep OBD C18, 19 x 150 mm, 5 μ

Solvent A = 10 mM NH₄OAc in H₂O (pH 4.5, adjusted with AcOH)

Solvent B = CH₃CN

5 Start %B = 10; Final %B = 45

Gradient time-1 = 8 min;

Isocratic time = 8 min;

Start %B = 45; Final %B = 100

Gradient time-2 = 2 min;

10 Isocratic time = 3 min;

Flow = 15 mL/min; Wave length = 220 nm

Condition 37:

Column = Ascentis Express C18, 2.1 x 50 mm, 2.7 μ

15 Solvent A = CH₃CN (5%) + 10 mM NH₄OAc in H₂O (95%)

Solvent B = CH₃CN (95%) + 10 mM NH₄OAc in H₂O (5%)

Start %B = 0; Final %B = 100

Gradient time = 3.0 min; Stop time = 4 min

Flow Rate = 1.1 mL/min; Wavelength = 220 nm

20

Condition 38:

Column = Ascentis Express C18, 2.1 x 50 mm, 2.7 μ

Solvent A = CH₃CN (2%) + 10 mM NH₄COOH in H₂O (98%)

Solvent B = CH₃CN (98%) + 10 mM NH₄COOH in H₂O (2%)

25 Start %B = 0; Final %B = 100

Gradient time = 1.7 min; Stop time = 4 min

Isocratic time = 1.7 min

Flow Rate = 1 mL/min; Wavelength = 220 nm

30 *Condition 39:*

Column = Kinetex C-18, 2.1 x 50 mm, 2.6 μ

Solvent A = CH₃CN (2%) + 10 mM NH₄COOH in H₂O (98%)

Solvent B = CH₃CN (98%) + 10 mM NH₄COOH in H₂O (2%)

Start %B = 0; Final %B = 100

Gradient time = 1.7 min; Stop time = 4 min

Isocratic time = 1.5 min

5 Flow Rate = 1 mL/min; Wavelength = 220 nm

Condition 40:

Column = Ascentis Express C18, 2.1 x 50 mm, 2.7 μ

Solvent A = CH₃CN (2%) + 10 mM NH₄COOH in H₂O (98%)

10 Solvent B = CH₃CN (98%) + 10 mM NH₄COOH in H₂O (2%)

Start %B = 0; Final %B = 100

Gradient time = 1.7 min; Stop time = 4 min

Isocratic time = 1.3 min

Flow Rate = 1 mL/min; Wavelength = 220 nm

15

Condition 41:

Column = WHELK-O® 1 (R,R), 250 x 4.6 mm, 5 μ

Solvent A = CO₂

Solvent B = 30 mM Ammonia in MeOH

20 Isocratic = A: B (3:2)

Flow = 4 mL/min; Wave length = 210 nm

Condition 42:

Column = Gemini C18, 21.1 x 250 mm, 5 μ

25 Solvent A = H₂O

Solvent B = CH₃CN

Start %B = 10; Final %B = 55

Gradient time = 16 min;

Flow = 17 mL/min; Wave length = 220 nm

30

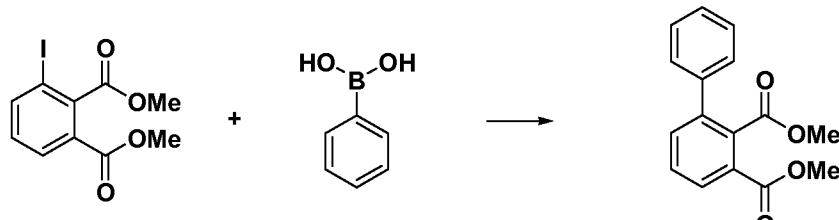
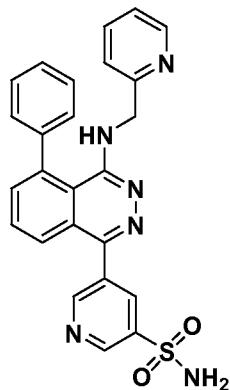
NMR Employed in Characterization of Examples

¹H NMR spectra were obtained with Bruker or JEOL® Fourier transform spectrometers operating at frequencies as follows: ¹H NMR: 400 MHz or 300 MHz (Bruker). ¹³C NMR: 100 MHz or 75 MHz (Bruker). Spectra data are reported in the format: chemical shift (multiplicity, coupling constants, number of hydrogens). Chemical shifts are specified in ppm downfield of a tetramethylsilane internal standard (δ units, tetramethylsilane = 0 ppm) and/or referenced to solvent peaks, which in ¹H NMR spectra appear at 2.49 ppm for CD₂HSOCD₃, 3.30 ppm for CD₂HOD, and 7.24 ppm for CHCl₃, and which in ¹³C NMR spectra appear at 39.7 ppm for CD₃SOCD₃, 49.0 ppm for CD₃OD, and 77.0 ppm for CDCl₃. All ¹³C NMR spectra were proton decoupled.

10

Example 1

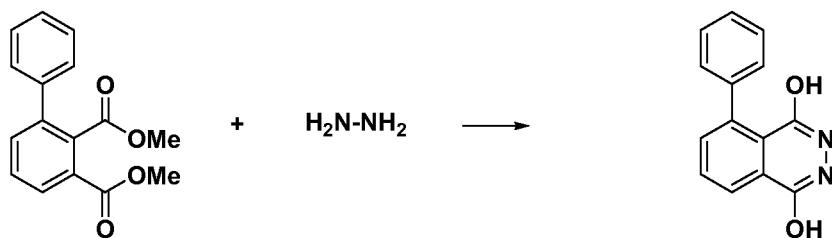
5-(5-Phenyl-4-(pyridin-2-ylmethylamino)phthalazin-1-yl)pyridine-3-sulfonamide



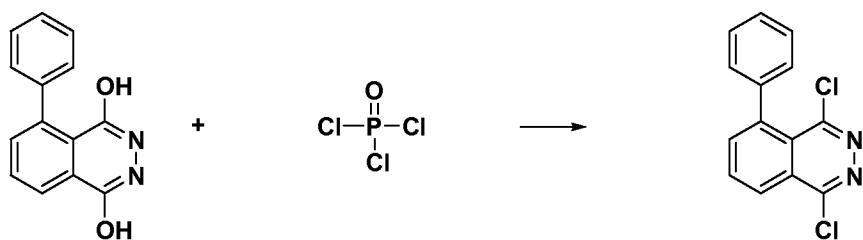
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A solution of dimethyl 3-iodophthalate (WO 2008/115516) (1.00 g, 3.12 mmol), phenylboronic acid (0.571 g, 4.69 mmol), K₂CO₃ (0.880 g, 9.30 mmol) in 1,4-dioxane (15 mL) and water (4 mL) was purged with nitrogen for 30 min. Pd(dppf)Cl₂:DCM (0.219 g, 0.312 mmol) was added and the reaction mixture was heated at 100 °C for 12 h. The reaction mixture was filtered through a pad of CELITE® and the pad was washed with water (50 mL). The filtrate was extracted with EtOAc (2 x 100 mL). The combined

organic extracts were dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The resulting residue was purified by combiflash (REDISEP®, silica gel, 12 g, 20% EtOAc/hexanes) to obtain dimethyl [1,1'-biphenyl]-2,3-dicarboxylate (0.65 g, 77.0%) as an off-white solid. LCMS (*Condition 11*): retention time 0.96 min, 5 $[\text{M}-\text{MeOH}+1] = 239.3$. ^1H NMR (400 MHz, DMSO-d_6) δ 3.59 (s, 3 H), 3.85 (s, 3 H), 7.33-7.49 (m, 5 H), 7.68-7.70 (m, 2 H), 7.95-8.00 (m, 1 H).

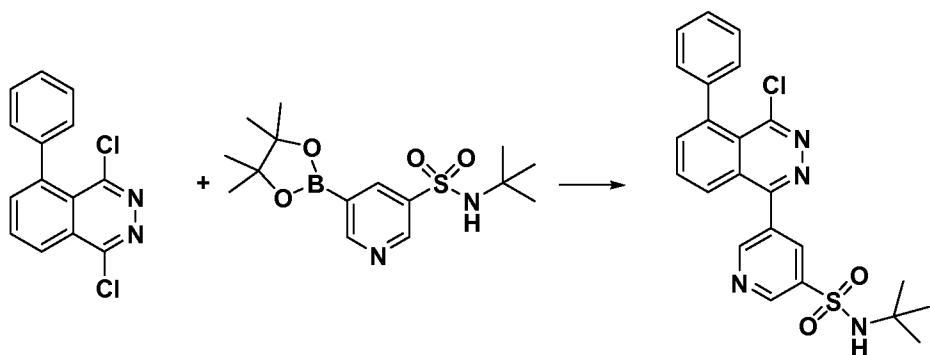


A solution of dimethyl [1,1'-biphenyl]-2,3-dicarboxylate (0.600 g, 2.22 mmol) in 10 hydrazine hydrate (5.00 mL, 159 mmol) was heated in a sealed tube at 100 °C for 16 h. The reaction mixture was acidified to pH~3 with 1.5N HCl. The resulting precipitate was filtered, washed with water (3 x 50 mL) and hexanes (2 x 50 mL). The precipitate was dried under vacuum to yield 5-phenylphthalazine-1,4-diol (0.450 g, 85.0%) as an off-white solid. LCMS (*Condition 11*): retention time 0.76 min, $[\text{M}+1] = 239.4$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.29-7.34 (m, 5 H), 7.60 (d, $J = 7.6$ Hz, 1 H), 7.89 (t, $J = 7.6$ Hz, 1 H), 8.13 (br s, 1 H), 11.40 (br s, 2 H).

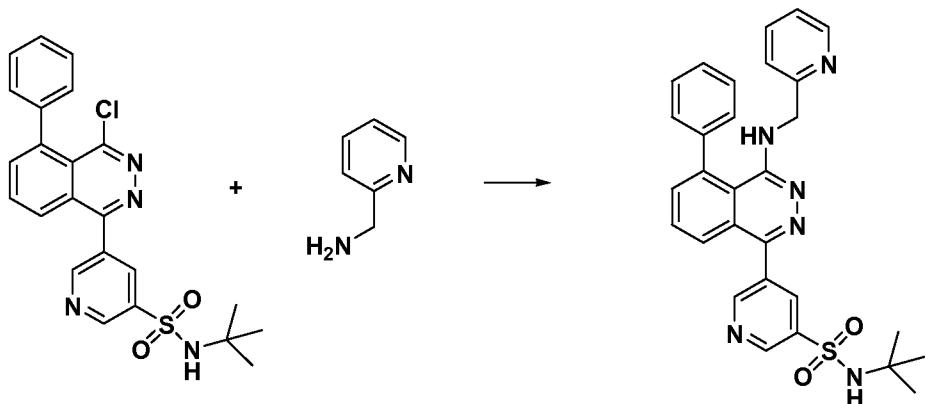


A solution of 5-phenylphthalazine-1,4-diol (0.200 g, 0.839 mmol) in POCl_3 (2.00 20 mL, 21.5 mmol) was added N,N-dimethylbenzylamine (0.106 mL, 0.839 mmol) and the contents were heated in a sealed tube at 100 °C for 16 h. The reaction mixture was allowed to cool to room temperature and concentrated under reduced pressure. The residue was dissolved in DCM (50 mL) and washed with ice cold solution of saturated NaHCO_3 (2 x 5 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 ,

filtered and concentrated under reduced pressure. The resulting residue was purified by combiflash (REDISEP®, silica gel, 12 g, 20% EtOAc/hexanes) to obtain 1,4-dichloro-5-phenylphthalazine (0.120 g, 52.0%) as a yellow solid. LCMS (*Condition 11*): retention time 1.12 min, [M+1] = 275.3. ^1H NMR (300 MHz, DMSO-d₆) δ 7.39-7.52 (m, 5 H), 8.05 (dd, *J* = 1.2 Hz, *J* = 7.6 Hz, 1 H), 8.26 (dd, *J* = 7.2 Hz, *J* = 7.6 Hz, 1 H), 8.41 (dd, *J* = 1.2 Hz, *J* = 7.2 Hz, 1 H).



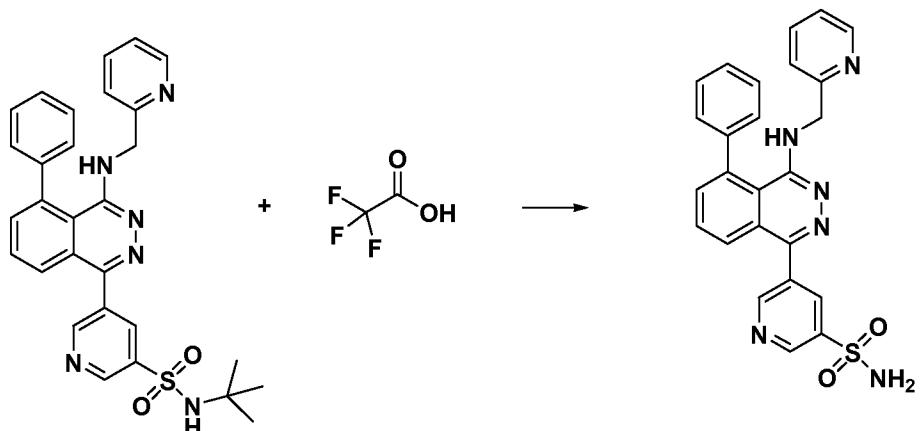
To a solution of 1,4-dichloro-5-phenylphthalazine (0.400 g, 1.45 mmol) and N-(*tert*-butyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide (0.742 g, 2.18 mmol) (Johnson et al., WO 2011/28741) in 1,4-dioxane (15 mL) and water (3 mL) was added K₃PO₄ (0.617 g, 2.91 mmol) and the contents purged with nitrogen for 10 min. Tricyclohexylphosphine (10.2 mg, 0.0360 mmol) was added followed by Pd₂(dba)₃ (0.0130 g, 0.0150 mmol) and heated at 95 °C for 12 h. The reaction mixture was allowed to cool to ambient temperature. The reaction mixture was diluted with HCOONH₄ buffer (pH~5) solution and extracted with EtOAc (3 x 75 mL). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by combiflash (REDISEP®, silica gel, 12 g, 30% EtOAc/hexanes) to obtain N-(*tert*-butyl)-5-(4-chloro-5-phenylphthalazin-1-yl)pyridine-3-sulfonamide (0.500 g, 76.0%) as a pale yellow solid. LCMS (*Condition 11*): retention time 1.04 min, [M+1] = 453.2. ^1H NMR (400 MHz, DMSO-d₆) δ 1.20 (s, 9 H), 7.43-7.46 (m, 2 H), 7.50-7.54 (m, 3 H), 7.98 (s, 1 H), 7.99 (dd, *J* = 1.2 Hz, *J* = 8.0 Hz, 1 H), 8.03 (dd, *J* = 1.2 Hz, *J* = 7.2 Hz, 1 H), 8.15 (dd, *J* = 7.2 Hz, *J* = 8.0 Hz, 1 H), 8.58 (t, *J* = 2.0 Hz, 1 H), 9.17 (d, *J* = 2.0 Hz, 1 H), 9.23 (d, *J* = 2.0 Hz, 1 H).



To a solution of N-(*tert*-butyl)-5-(4-chloro-5-phenylphthalazin-1-yl)pyridine-3-sulfonamide (0.400 g, 0.883 mmol) in toluene (5 mL) was added pyridin-2-ylmethanamine (0.0950 g, 0.883 mmol) and the contents were heated at 100 °C for 12 h.

5 The volatile components were removed under reduced pressure and the resulting residue was purified by preparative HPLC (*Condition 16* as described in general methods) to yield N-(*tert*-butyl)-5-(5-phenyl-4-((pyridin-2-ylmethyl)amino)phthalazin-1-yl)pyridine-3-sulfonamide (35.0 mg, 7.55%) as a white solid. LCMS (*Condition 4*): retention time 2.47 min, [M+1] = 525.2. HPLC (*Condition 28*): retention time = 6.97 min, purity 10 96.32%. ¹H NMR (400 MHz, CD₃OD) δ 1.30 (s, 9 H), 4.68 (s, 2 H), 7.24 (dd, *J* = 4.8 Hz, *J* = 7.2 Hz, 1 H), 7.27 (d, *J* = 7.6 Hz, 1 H), 7.52 (br s, 5 H), 7.72 (dd, *J* = 1.6 Hz, *J* = 7.6 Hz, 1 H), 7.77 (dd, *J* = 1.2 Hz, *J* = 7.2 Hz, 1 H), 7.84 (dd, *J* = 1.2 Hz, *J* = 8.4 Hz, 1 H), 7.91-7.96 (m, 1 H), 8.31 (d, *J* = 4.4 Hz, 1 H), 8.55 (t, *J* = 2.0 Hz, 1 H), 9.07 (d, *J* = 2.0 Hz, 1 H), 9.18 (d, *J* = 2.0 Hz, 1 H).

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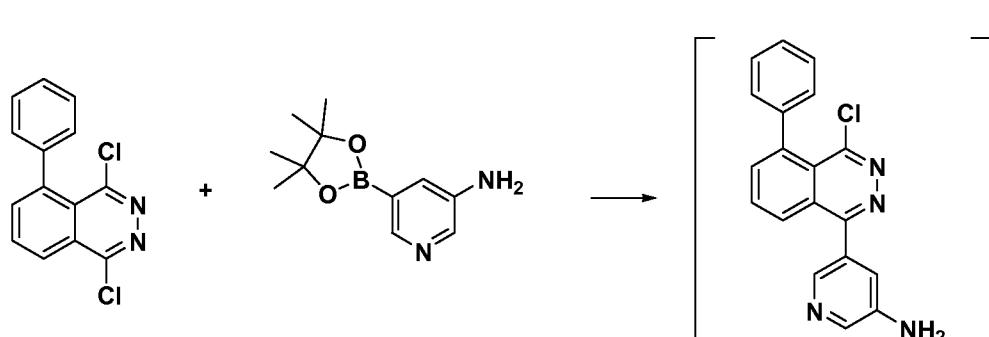
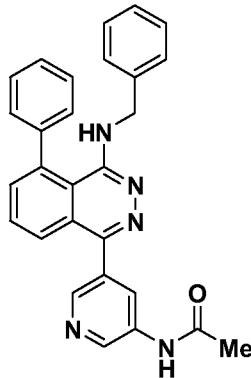


N-(*tert*-Butyl)-5-(5-phenyl-4-((pyridin-2-ylmethyl)amino)phthalazin-1-yl)pyridine-3-sulfonamide (0.0300 g, 0.0570 mmol) was dissolved in TFA (5.00 mL, 64.9 mmol) and stirred at room temperature for 12 h. TFA was removed under reduced pressure and reaction mixture was diluted with saturated NaHCO₃ (50 mL). The reaction mixture was extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by preparative HPLC (*Condition 16* as described in general methods) to afford 5-(5-phenyl-4-((pyridin-2-ylmethyl)amino)phthalazin-1-yl)pyridine-3-sulfonamide (10.0 mg, 37.3%) as a white solid. LCMS (*Condition 4*): retention time 2.25 min, [M+1] = 469.2. HPLC (*Condition 28*): retention time = 5.73 min, purity 99.07%.
¹H NMR (400 MHz, CD₃OD) δ 4.68 (s, 2 H), 7.24 (dd, *J* = 4.8 Hz, *J* = 7.6 Hz, 1 H), 7.27 (d, *J* = 7.6 Hz, 1 H), 7.52 (br s, 5 H), 7.71-7.77 (m, 2 H), 7.88 (dd, *J* = 1.6 Hz, *J* = 8.4 Hz, 1 H), 7.95 (dd, *J* = 7.2 Hz, *J* = 8.4 Hz, 1 H), 8.30-8.31 (m, 1 H), 8.57 (dd, *J* = 2.0 Hz, *J* = 2.4 Hz, 1 H), 9.07 (d, *J* = 2.0 Hz, 1 H), 9.21 (d, *J* = 2.4 Hz, 1 H).

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Example 2

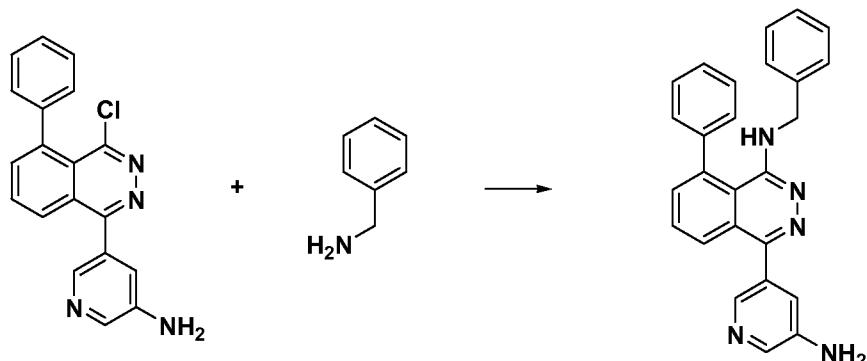
N-(5-(4-(Benzylamino)-5-phenylphthalazin-1-yl)pyridin-3-yl)acetamide



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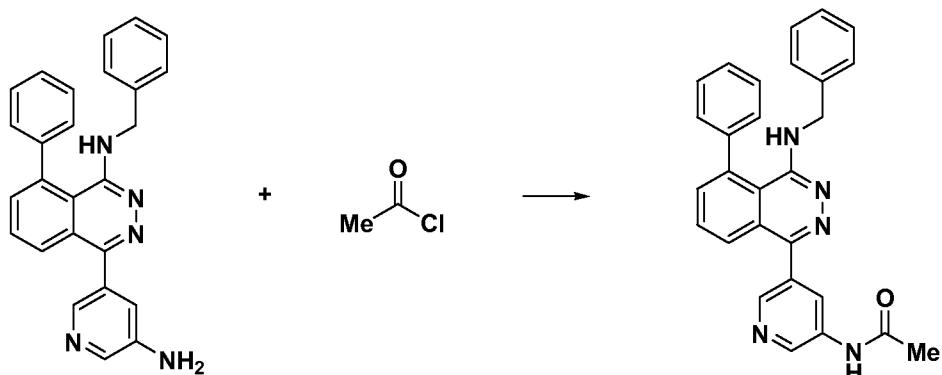
5-(4-Chloro-5-phenylphthalazin-1-yl)pyridin-3-amine (0.800 g, 66.1% yield) was prepared from 1,4-dichloro-5-phenylphthalazine (1.00 g, 3.63 mmol), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-amine (0.960 g, 4.36 mmol, commercial), K₃PO₄ (0.772 g, 3.63 mmol), Pd₂(dba)₃ (0.0330 g, 0.0360 mmol) and 5 tricyclohexylphosphine (0.0200 g, 0.0730 mmol) by the methods described for the preparation of N-(*tert*-butyl)-5-(4-chloro-5-phenylphthalazin-1-yl)pyridine-3-sulfonamide in Example 1. The crude residue was taken to the next step without further purification. LCMS (*Condition 11*): retention time 0.86 min, [M+1] = 333.1.

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4-(5-Aminopyridin-3-yl)-N-benzyl-8-phenylphthalazin-1-amine (0.300 g, 30.9% yield, white solid) was prepared from 5-(4-chloro-5-phenylphthalazin-1-yl)pyridin-3-amine (0.800 g, 2.40 mmol) and benzylamine (10.0 mL, 92.0 mmol) by the methods described for the preparation of N-(*tert*-butyl)-5-(5-phenyl-4-((pyridin-2-ylmethyl)amino)phthalazin-1-yl)pyridine-3-sulfonamide in Example 1. The residue was purified by combiflash (REDISEP®, silica gel, 12 g, 8% MeOH/CHCl₃). The resulting residue was further purified by preparative HPLC (*Condition 21* as described in general methods). LCMS (*Condition 5*): retention time 2.03 min, [M+1] = 404.6. HPLC (*Condition 28*): retention time = 5.47 min, purity 97.63%. ¹H NMR (400 MHz, DMSO-d₆) δ 4.49 (d, *J* = 5.2 Hz, 2 H), 4.99 (t, *J* = 5.2 Hz, 1 H), 5.52 (s, 2 H), 7.01-7.03 (m, 2 H), 7.15-7.28 (m, 4 H), 7.43-7.50 (m, 5 H), 7.66 (dd, *J* = 2.0 Hz, *J* = 6.4 Hz, 1 H), 7.85-7.90 (m, 2 H), 7.94 (d, *J* = 2.0 Hz, 1 H), 8.09 (d, *J* = 2.0 Hz, 1 H).

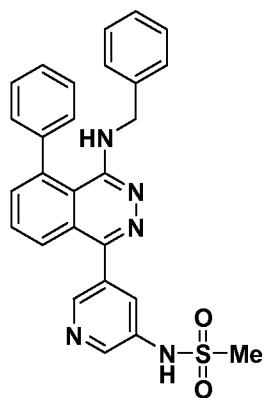


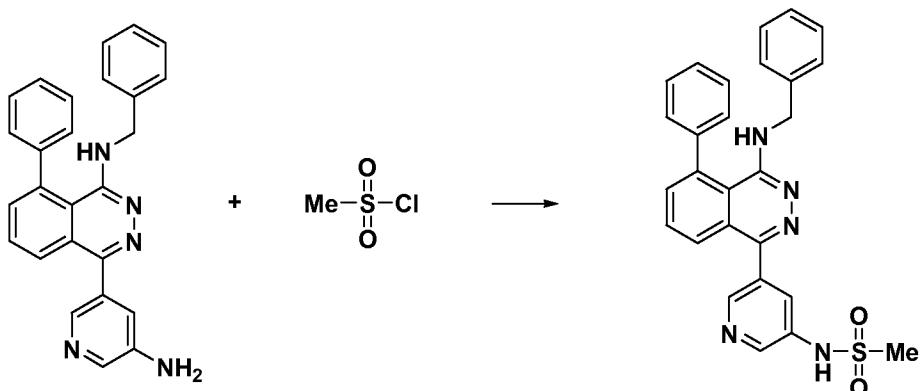
To a solution of 4-(5-aminopyridin-3-yl)-N-benzyl-8-phenylphthalazin-1-amine (60.0 mg, 0.149 mmol) in DCM (20 mL) was added pyridine (0.0241 mL, 0.297 mmol) at room temperature followed by acetyl chloride (0.0106 mL, 0.149 mmol) and stirred at the 5 same temperature for 5 h. The volatile components were removed under reduced pressure and the resulting residue was purified by preparative HPLC (*Condition 19* as described in general methods) to yield N-(5-(4-(benzylamino)-5-phenylphthalazin-1-yl)pyridin-3-yl)acetamide (45.0 mg, 67.9%) as a white solid. LCMS (*Condition 4*): retention time 2.44 min, [M+1] = 446.2. HPLC (*Condition 28*): retention time = 6.44 min, purity 10 97.94%. ^1H NMR (400 MHz, DMSO- d_6) δ 2.13 (s, 3 H), 4.51 (d, J = 4.8 Hz, 2 H), 5.06 (dd, J = 4.8 Hz, J = 5.2 Hz, 1 H), 7.02-7.04 (m, 2 H), 7.23-7.29 (m, 3 H), 7.42-7.52 (m, 5 H), 7.68 (dd, J = 1.6 Hz, J = 7.2 Hz, 1 H), 7.85-7.93 (m, 2 H), 8.36 (dd, J = 2.0 Hz, J = 2.4 Hz, 1 H), 8.52 (d, J = 2.0 Hz, 1 H), 8.84 (d, J = 2.0 Hz, 1 H), 10.37 (s, 1 H).

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Example 3

N-(5-(4-(Benzylamino)-5-phenylphthalazin-1-yl)pyridin-3-yl)methanesulfonamide



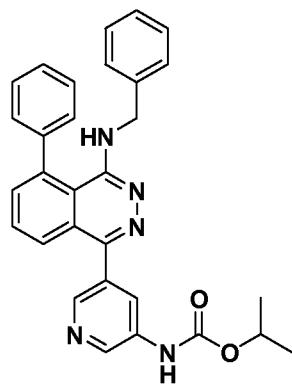


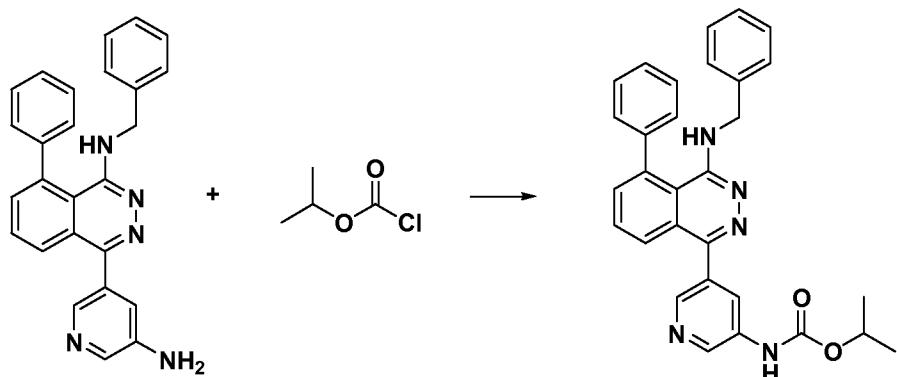
To a solution of 4-(5-aminopyridin-3-yl)-N-benzyl-8-phenylphthalazin-1-amine (60.0 mg, 0.149 mmol) in DCM (20 mL) was added pyridine (0.0241 mL, 0.297 mmol) at room temperature followed by methanesulfonyl chloride (0.0120 mL, 0.149 mmol) and 5 the reaction mixture stirred for 5 h. The volatile components were removed under reduced pressure and the resulting residue was purified by preparative HPLC (*Condition 22* as described in general methods) to obtain N-(5-(4-(benzylamino)-5-phenylphthalazin-1-yl)pyridin-3-yl)methanesulfonamide (50.0 mg, 69.8%) as a white solid. LCMS (*Condition 4*): retention time 2.45 min, [M+1] = 482.2. HPLC (*Condition 28*): retention 10 time = 6.83 min, purity 97.53%. ¹H NMR (400 MHz, DMSO-d₆) δ 2.97 (s, 3 H), 4.51 (d, *J* = 4.8 Hz, 2 H), 5.06 (t, *J* = 4.8 Hz, 1 H), 7.02-7.03 (m, 2 H), 7.22-7.28 (m, 3 H), 7.43-7.52 (m, 5 H), 7.68 (dd, *J* = 2.4 Hz, *J* = 5.6 Hz, 1 H), 7.72 (br s, 1 H), 7.87-7.90 (m, 2 H), 8.35 (br s, 1 H), 8.40 (d, *J* = 1.6 Hz, 1 H), 10.25 (br s, 1 H).

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Example 4

Isopropyl 5-(4-(benzylamino)-5-phenylphthalazin-1-yl)pyridin-3-yl)carbamate



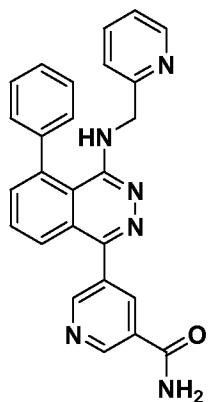


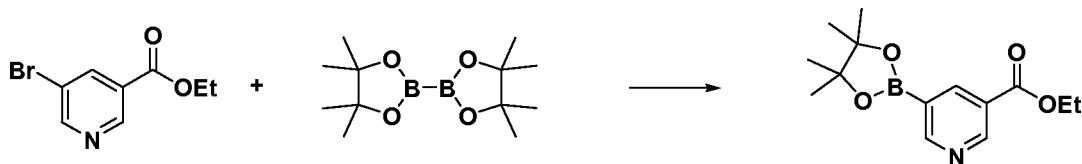
To a solution of 4-(5-aminopyridin-3-yl)-N-benzyl-8-phenylphthalazin-1-amine (60.0 mg, 0.149 mmol) in DCM (20 mL) was added pyridine (0.241 mL, 0.297 mmol) at room temperature followed by isopropyl carbonochloride (18.2 mg, 0.149 mmol) and the reaction mixture stirred for 5 h. The volatile components were removed under reduced pressure and the resulting residue was purified by preparative HPLC (*Condition 23* as described in general methods) to afford isopropyl (5-(4-(benzylamino)-5-phenylphthalazin-1-yl)pyridin-3-yl)carbamate (50.0 mg, 68.7%) as a white solid. LCMS (*Condition 4*): retention time 2.60 min, [M+1] = 490.2. HPLC (*Condition 28*): retention time = 7.65 min, purity 99.27%. ¹H NMR (400 MHz, DMSO-d₆) δ 1.29 (d, *J* = 6.4 Hz, 6 H), 4.51 (d, *J* = 4.8 Hz, 2 H), 4.93 (sept, *J* = 6.4 Hz, 1 H), 5.06 (dd, *J* = 4.8 Hz, *J* = 5.2 Hz, 1 H), 7.01-7.03 (m, 2 H), 7.21-7.28 (m, 3 H), 7.42-7.52 (m, 5 H), 7.69 (dd, *J* = 1.2 Hz, *J* = 6.8 Hz, 1 H), 7.85-7.93 (m, 2 H), 8.16 (br s, 1 H), 8.47 (d, *J* = 1.6 Hz, 1 H), 8.80 (d, *J* = 2.4 Hz, 1 H), 10.00 (s, 1 H).

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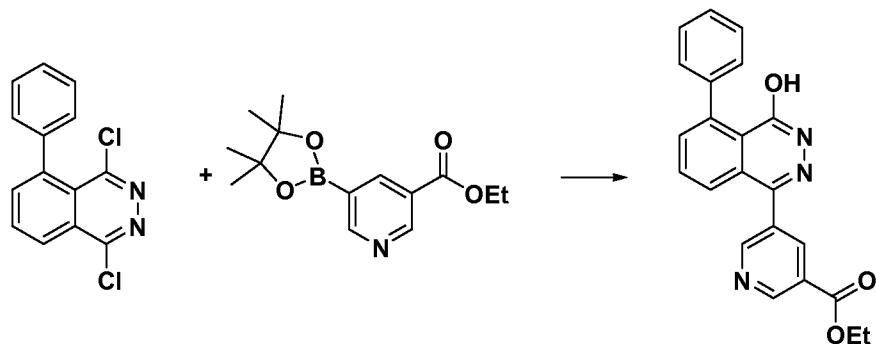
Example 5

5-(5-Phenyl-4-(pyridin-2-ylmethylamino)phthalazin-1-yl)nicotinamide



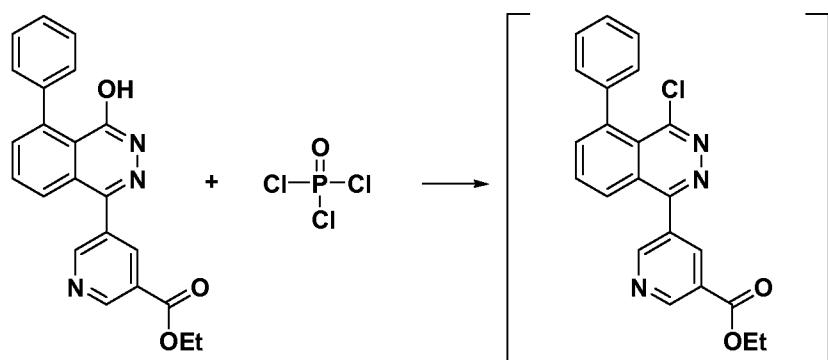


To a solution of 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl (1,3,2-dioxaborolan-2-yl))-1,3,2-dioxaborolane (1.54 g, 6.09 mmol) and tricyclohexylphosphonium tetrafluoroborate (0.112 g, 0.304) in 1,4-dioxane (20 mL) at ambient temperature was added KOAc (1.71 g, 17.4 mmol) and the reaction mixture was purged with nitrogen gas for 10 min. The reaction mixture was heated to 80 °C. Pd₂(dba)₃ (0.199 g, 0.217 mmol) was added to the reaction mixture and the resulting reaction mixture purged with nitrogen for 10 min at 80 °C. The reaction mixture was heated to 90 °C and a solution of ethyl 5-bromonicotinate (1.00 g, 4.35 mmol) in 1,4-dioxane (5 mL) was added. The resulting mixture was stirred at 100 °C for 16 h. The reaction mixture was allowed to cool to ambient temperature, filtered through CELITE® and the filtrate was concentrated under reduced pressure to obtain ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate (1.50 g). The residue was taken to the next step without further purification. LCMS (Condition 11): retention time 0.52 min, [M+1] = 196.1. ¹H NMR (400 MHz, DMSO-d₆) δ 1.16 (s, 12 H), 1.35 (t, *J* = 7.2 Hz, 3 H), 4.36 (q, *J* = 7.2 Hz, 2 H), 8.43 (dd, *J* = 1.6 Hz, *J* = 2.0 Hz, 1 H), 8.95 (d, *J* = 1.6 Hz, 1 H), 9.16 (br s, 1 H).

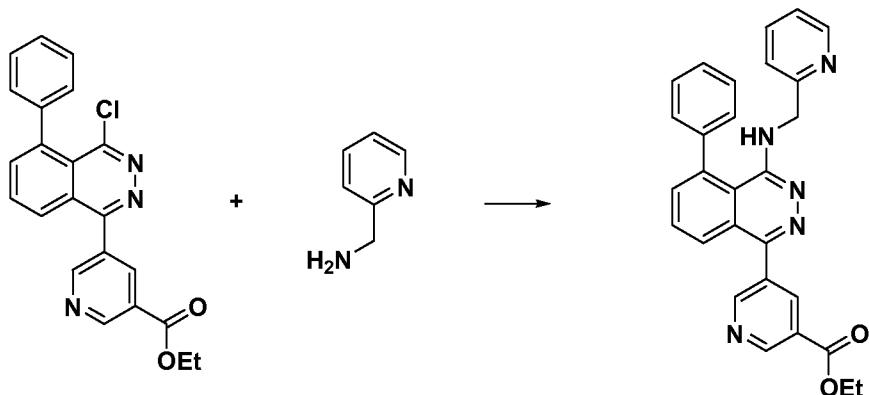


To a solution of 1,4-dichloro-5-phenylphthalazine (5.00 g, 18.2 mmol) in 1,4-dioxane (50 mL) and water (9 mL) was added ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate (5.32 g, 27.3 mmol), and K₃PO₄ (7.72 g, 36.3 mmol). The contents were purged with nitrogen for 10 min. Tricyclohexylphosphonium tetrafluoroborate (0.402 g, 1.09 mmol) was added followed by Pd₂(dba)₃ (0.416 g, 0.454

mmol) and the reaction mixture was heated at 95 °C for 12 h. The reaction mixture was allowed to cool to ambient temperature and diluted with HCOONH₄ buffer (pH~5) solution. The reaction mixture was extracted with EtOAc (3 x 75 mL). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was triturated with EtOAc to afford ethyl 5-(4-hydroxy-5-phenylphthalazin-1-yl)nicotinate (3.50 g, 44.1%) as an off-white solid which is 85% pure by LC-MS. LCMS (*Condition 1*): retention time 2.52 min, [M+1] = 372.0. ¹H NMR (400 MHz, DMSO-d₆) δ 1.37 (t, *J* = 7.2 Hz, 3 H), 4.41 (q, *J* = 7.2 Hz, 2 H), 7.33-7.42 (m, 5 H), 7.62-7.65 (m, 2 H), 7.92 (dd, *J* = 7.6 Hz, *J* = 8.0 Hz, 1 H), 8.49 (t, *J* = 2.0 Hz, 1 H), 9.07 (d, *J* = 2.0 Hz, 1 H), 9.25 (d, *J* = 2.0 Hz, 1 H), 12.74 (br s, 1 H).

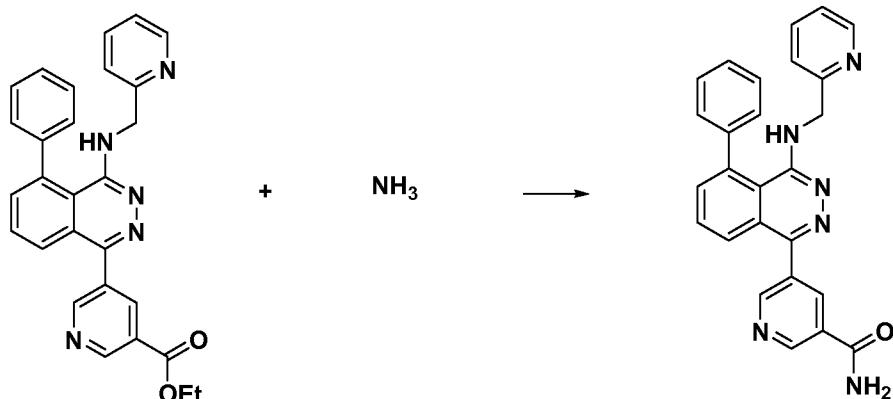


To a solution of ethyl 5-(4-hydroxy-5-phenylphthalazin-1-yl)nicotinate (3.50 g, 9.42 mmol) in toluene (35 mL) was added POCl₃ (26.4 mL, 283 mmol) followed by N,N-dimethylbenzylamine (1.5 mL, 9.42 mmol). The resulting mixture was heated in a sealed tube at 100 °C for 12 h. The reaction mixture was allowed to cool to room temperature and concentrated under reduced pressure. The residue was dissolved in EtOAc (200 mL) and washed with saturated NaHCO₃ (2 x 50 mL) solution. The combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to yield ethyl 5-(4-chloro-5-phenylphthalazin-1-yl)nicotinate (3.50 g) as a yellow solid with LC-MS purity of 47% which was taken for the next step without further purification. LCMS (*Condition 12*): retention time 0.97 min, [M+1] = 390.0.



Ethyl 5-(5-phenyl-4-((pyridin-2-ylmethyl)amino)phthalazin-1-yl)nicotinate (3.10 g, 88.0%, brown solid) was prepared from 5-(4-chloro-5-phenylphthalazin-1-yl)nicotinate (3.00 g, 7.70 mmol) and 2-(aminomethyl)pyridine (10.0 mL, 97.0 mmol) by the methods described for the preparation of N-(*tert*-butyl)-5-(5-phenyl-4-((pyridin-2-ylmethyl)amino)phthalazin-1-yl)pyridine-3-sulfonamide in Example 1. The residue was purified by preparative HPLC (*Condition 15* as described in general methods). LCMS (*Condition 2*): retention time 1.90 min, [M+1] = 462.2. HPLC (*Condition 25*): retention time = 7.06 min, purity 96.07%. ¹H NMR (400 MHz, DMSO-d₆) δ 1.38 (t, *J* = 7.2 Hz, 3 H), 4.42 (q, *J* = 7.2 Hz, 2 H), 4.67 (d, *J* = 4.4 Hz, 2 H), 6.35 (dd, *J* = 4.0 Hz, *J* = 4.4 Hz, 1 H), 7.21-7.25 (m, 1 H), 7.28 (d, *J* = 8.0 Hz, 1 H), 7.50-7.61 (m, 5 H), 7.69-7.73 (m, 2 H), 7.84 (dd, *J* = 1.6 Hz, *J* = 8.4 Hz, 1 H), 7.93 (dd, *J* = 7.2 Hz, *J* = 8.4 Hz, 1 H), 8.23 (dt, *J* = 0.8 Hz, *J* = 4.8 Hz, 1 H), 8.53 (t, *J* = 2.0 Hz, 1 H), 9.11 (d, *J* = 2.0 Hz, 1 H), 9.24 (d, *J* = 2.0 Hz, 1 H).

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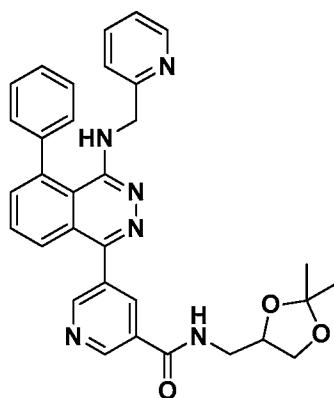


A solution of ethyl 5-(5-phenyl-4-((pyridin-2-ylmethyl)amino)phthalazin-1-yl)nicotinate (230 mg, 0.288 mmol) in MeOH (5 mL) was purged with ammonia gas for 5

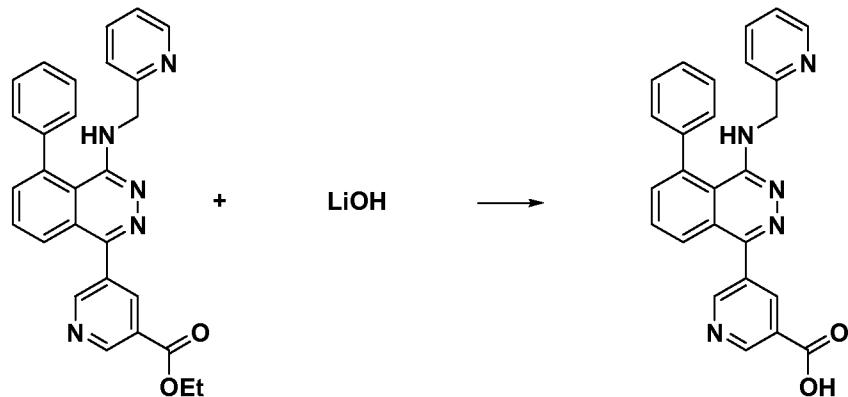
minutes at -10 °C. The reaction mixture was heated in a sealed tube at 70 °C for 12 h. The volatile components were removed under reduced pressure and the resulting residue was purified by HPLC (*Condition 20* as described in general methods) to afford 5-(5-phenyl-4-((pyridin-2-ylmethyl)amino)phthalazin-1-yl)nicotinamide (50.0 mg, 39.8%) as a yellow solid. LCMS (*Condition 2*): retention time 1.90 min, [M+1] = 433.0. HPLC (*Condition 25*): retention time = 5.20 min, purity 98.63%. ¹H NMR (400 MHz, DMSO-d₆) δ 4.66 (d, *J* = 4.0 Hz, 2 H), 6.32 (dd, *J* = 4.0 Hz, *J* = 4.4 Hz, 1 H), 7.22-7.24 (m, 1 H), 7.28 (d, *J* = 7.6 Hz, 1 H), 7.51-7.60 (m, 5 H), 7.68-7.73 (m, 3 H), 7.84 (dd, *J* = 1.2 Hz, *J* = 8.4 Hz, 1 H), 7.93 (dd, *J* = 7.2 Hz, *J* = 8.4 Hz, 1 H), 8.22-8.24 (m, 1 H), 8.28 (br s, 1 H), 8.51 (t, *J* = 2.0 Hz, 1 H), 8.99 (d, *J* = 2.0 Hz, 1 H), 9.18 (d, *J* = 2.0 Hz, 1 H).

Example 6

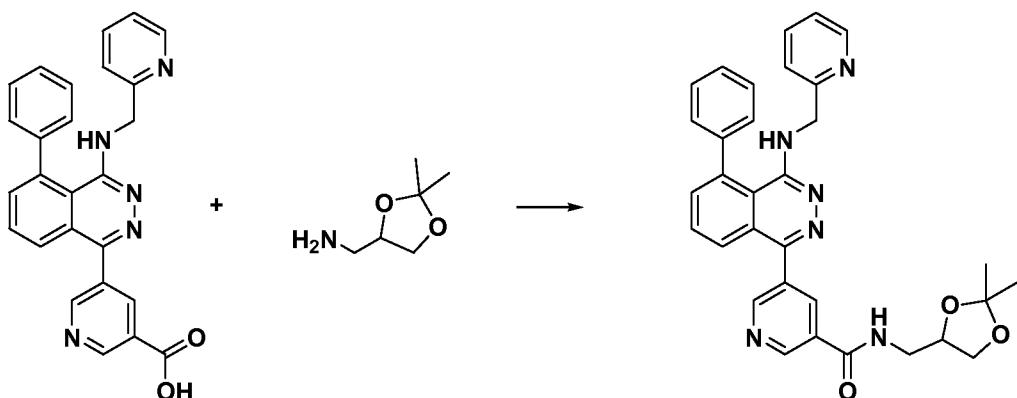
N-(2,3-Dihydroxypropyl)-5-(5-phenyl-4-(pyridin-2-ylmethylamino)phthalazin-1-yl)nicotinamide



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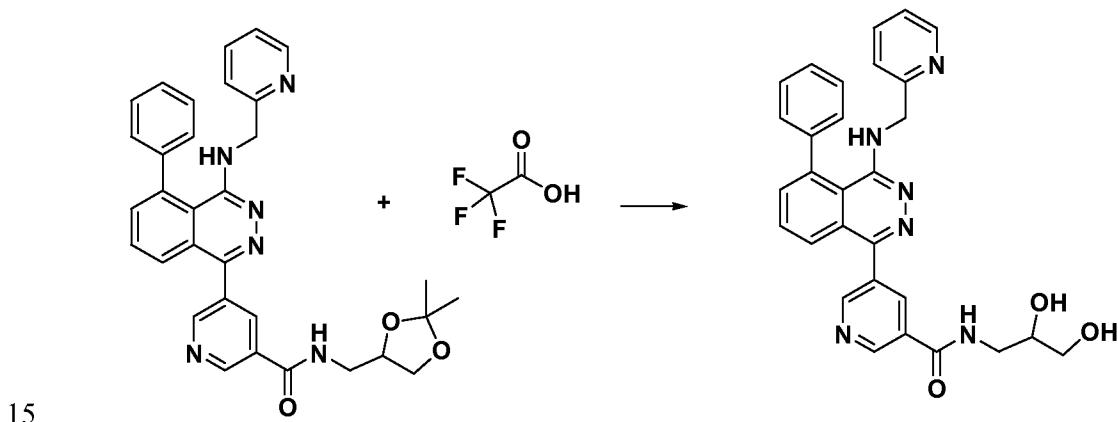


To a solution of ethyl 5-(5-phenyl-4-((pyridin-2-ylmethyl)amino)phthalazin-1-yl)nicotinate (0.120 g, 0.260 mmol) in EtOH (6 mL) and THF (6 mL) was added LiOH (0.0620 g, 2.60 mmol) in water (3 mL) at room temperature. The reaction mixture was stirred at the same temperature for 16 h. Then the reaction mixture was concentrated under reduced pressure and the resulting residue was diluted with water (5 mL). The reaction mixture was extracted with EtOAc and the aqueous layer was separated. The aqueous layer was acidified to pH 5 with citric acid and extracted with EtOAc. The organic extract was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by HPLC (*Condition 13* as described in general methods) to afford 5-(5-phenyl-4-((pyridin-2-ylmethyl)amino)phthalazin-1-yl)nicotinic acid (0.0150 g, 13.3%). LCMS (*Condition 2*): retention time 1.54 min, [M-1] = 432.0. HPLC (*Condition 25*): retention time = 5.86 min, purity 95.51%. ¹H NMR (400 MHz, DMSO-d₆) δ 4.66 (d, *J* = 4.4 Hz, 2 H), 6.25 (dd, *J* = 4.0 Hz, *J* = 4.4 Hz, 1 H), 7.20-7.24 (m, 1 H), 7.28 (d, *J* = 7.6 Hz, 1 H), 7.52-7.59 (m, 5 H), 7.68-7.73 (m, 2 H), 7.82 (dd, *J* = 1.2 Hz, *J* = 8.4 Hz, 1 H), 7.91 (dd, *J* = 7.2 Hz, *J* = 8.4 Hz, 1 H), 8.22-8.25 (m, 1 H), 8.35 (dd, *J* = 1.6 Hz, *J* = 2.0 Hz, 1 H), 8.74 (d, *J* = 2.0 Hz, 1 H), 9.09 (d, *J* = 1.6 Hz, 1 H).



To a solution of 5-(5-phenyl-4-((pyridin-2-ylmethyl)amino)phthalazin-1-yl)nicotinic acid (0.200 g, 0.461 mmol) in DMF (5 mL) was added HATU (0.526 g, 1.38 mmol) at ambient temperature. DMAP (0.169 g, 1.38 mmol) was added followed by (2,2-dimethyl-1,3-dioxolan-4-yl)methanamine (0.0610 g, 0.461 mmol, commercial) and the contents were stirred at ambient temperature for 16 h. The reaction mixture was concentrated under reduced pressure and the residue was diluted with water. The reaction

mixture was extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The resulting residue was purified by combiflash (REDISEP®, silica gel, 12 g, 50% EtOAc/hexanes) to obtain N-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-5-(5-phenyl-4-((pyridin-2-ylmethyl)amino)phthalazin-1-yl)nicotinamide (0.0300 g, 11.9%) as an off-white solid. LCMS (*Condition 7*): retention time 1.76 min, $[\text{M}+1] = 547.2$. HPLC (*Condition 24*): retention time 7.68 min, Purity 96.10%. ^1H NMR (400 MHz, DMSO- d_6) δ 1.27 (s, 3H), 1.36 (s, 3H), 3.31-3.51 (m, 2H), 3.74 (dd, $J = 5.6$ Hz, $J = 8.4$ Hz, 1H), 4.03 (dd, $J = 6.0$ Hz, $J = 8.4$ Hz, 1H), 4.26 (m, 1H), 4.66 (d, $J = 4.0$ Hz, 2H), 6.33 (dd, $J = 4.0$ Hz, $J = 4.4$ Hz, 1H), 7.22 (dd, $J = 5.2$ Hz, $J = 6.4$ Hz, 1H), 7.29 (d, $J = 6.8$ Hz, 1H), 7.50-7.59 (m, 5H), 7.69-7.73 (m, 2H), 7.84 (dd, $J = 1.6$ Hz, $J = 8.0$ Hz, 1H), 7.93 (dd, $J = 7.2$ Hz, $J = 8.0$ Hz, 1H), 8.23 (d, $J = 4.8$ Hz, 1H), 8.51 (t, $J = 2.0$ Hz, 1H), 8.94 (dd, $J = 5.6$ Hz, $J = 6.0$ Hz, 1H), 9.0 (d, $J = 2.0$ Hz, 1H), 9.16 (d, $J = 2.0$ Hz, 1H).



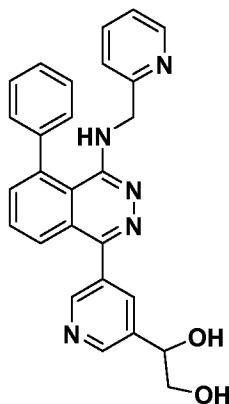
To N-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-5-(5-phenyl-4-((pyridin-2-ylmethyl)amino)phthalazin-1-yl)nicotinamide (0.0200 g, 0.0370 mmol) was added TFA (0.00282 mL, 0.0370 mmol) at room temperature and was heated at 50 °C for 4 h. TFA was removed under reduced pressure and reaction mixture was diluted with saturated NaHCO_3 (50 mL). The reaction mixture was extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The resulting residue was purified by preparative HPLC (*Condition 14* as described in general methods) to afford N-(2,3-dihydroxypropyl)-5-(5-phenyl-4-((pyridin-2-ylmethyl)amino)phthalazin-1-yl)nicotinamide (0.0120 g, 65%).

25 LCMS (*Condition 7*): retention time 1.59 min, $[\text{M}+1] = 507.2$. HPLC (*Condition 25*):

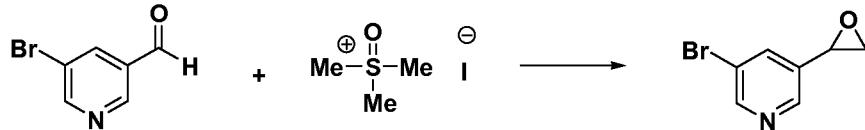
retention time 5.23 min, Purity 97.90%. ^1H NMR (400 MHz, DMSO-d₆) δ 3.21-3.49 (m, 4 H), 3.63-3.72 (m, 1 H), 4.55-4.60 (m, 1 H), 4.66 (d, J = 4.0 Hz, 2 H), 4.84 (br s, 1 H), 6.32 (dd, J = 4.0 Hz, J = 4.4 Hz, 1 H), 7.22 (dd, J = 4.8 Hz, J = 6.8 Hz, 1 H), 7.28 (d, J = 8.0 Hz, 1 H), 7.50-7.58 (m, 5 H), 7.68-7.73 (m, 2 H), 7.80 (dd, J = 1.6 Hz, J = 8.4 Hz, 1 H), 7.93 (dd, J = 7.2 Hz, J = 8.4 Hz, 1 H), 8.23 (d, J = 4.8 Hz, 1 H), 8.51 (t, J = 2.0 Hz, 1 H), 8.75 (t, J = 5.6 Hz, 1 H), 8.98 (d, J = 2.0 Hz, 1 H), 9.16 (d, J = 2.0 Hz, 1 H).

Example 7

1-(5-(5-Phenyl-4-(pyridin-2-ylmethylamino)phthalazin-1-yl)pyridin-3-yl)ethane-1,2-diol

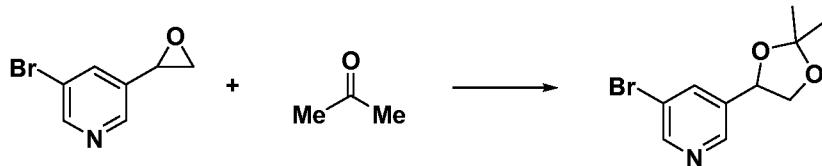


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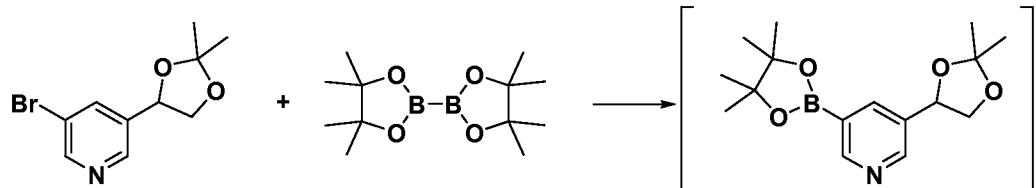


To a solution of trimethylsulfoxonium iodide (7.10 g, 32.3 mmol) in DMSO (25 mL) was added NaH (95%, 0.774 g, 32.3 mmol) portionwise at ambient temperature 15 followed by dropwise addition of 5-bromonicotinaldehyde (3.00 g, 16.1 mmol) in DMSO (15 mL) over 15 min. The reaction mixture was quenched by the addition of ice cold water (200 mL) and the resulting mixture extracted with EtOAc (2 x 150 mL). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by combiflash (REDISEP®, 20 silica gel, 40 g, 25% EtOAc/hexanes) to obtain 3-bromo-5-(oxiran-2-yl)pyridine (1.00 g, 31.0%) as a pale yellow liquid. LCMS (Condition 8): retention time 1.83 min, [M+2] = 202.2. ^1H NMR (400 MHz, CDCl₃) δ 2.79 (dd, J = 2.4 Hz, J = 5.2 Hz, 1 H), 3.20 (dd, J =

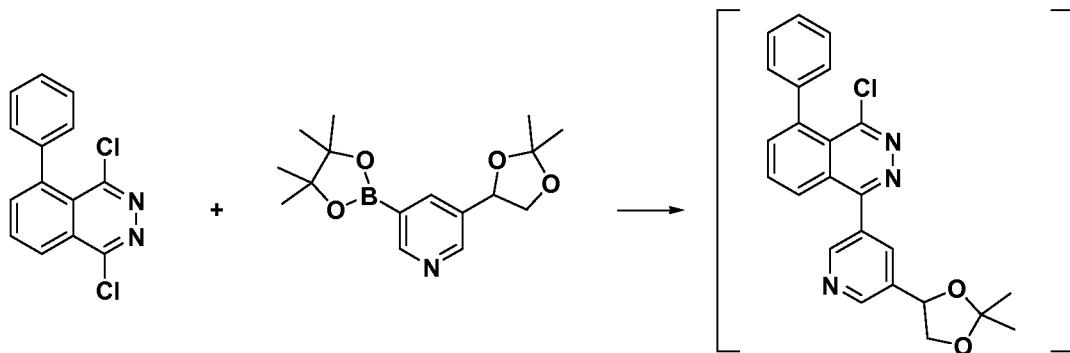
4.0 Hz, J = 5.2 Hz, 1 H), 3.87 (dd, J = 2.4 Hz, J = 4.0 Hz, 1 H), 7.69 (dd, J = 1.6 Hz, J = 2.0 Hz, 1 H), 8.50 (d, J = 1.6 Hz, 1 H), 8.62 (d, J = 2.0 Hz, 1 H).



5 To a solution of 3-bromo-5-(oxiran-2-yl)pyridine (1.00 g, 5.00 mmol) in acetone (25 mL) was added $\text{BF}_3\cdot\text{OEt}_2$ (0.950 mL, 7.50 mmol) dropwise at ambient temperature and the reaction mixture was stirred for 14 h. The reaction mixture was diluted with water (15 mL) and extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 , filtered and evaporated under reduced pressure. The 10 resulting residue was purified by combiflash (REDISEP®, silica gel, 40 g, 25% $\text{EtOAc}/\text{hexanes}$) to obtain 3-bromo-5-(2,2-dimethyl-1,3-dioxolan-4-yl)pyridine (0.700 g, 54.2%) as a pale yellow liquid. LCMS (*Condition 8*): retention time 2.17 min, $[\text{M}+2] = 260.0$. ^1H NMR (400 MHz, CDCl_3) δ 1.48 (s, 3 H), 1.55 (s, 3 H), 3.72 (dd, J = 7.6 Hz, J = 8.4 Hz, 1 H), 4.36 (dd, J = 6.4 Hz, J = 8.4 Hz, 1 H), 5.08 (dd, J = 6.4 Hz, J = 7.6 Hz, 1 H), 7.85-7.86 (m, 1 H), 8.49 (d, J = 1.6 Hz, 1 H), 8.62 (d, J = 2.0 Hz, 1 H).

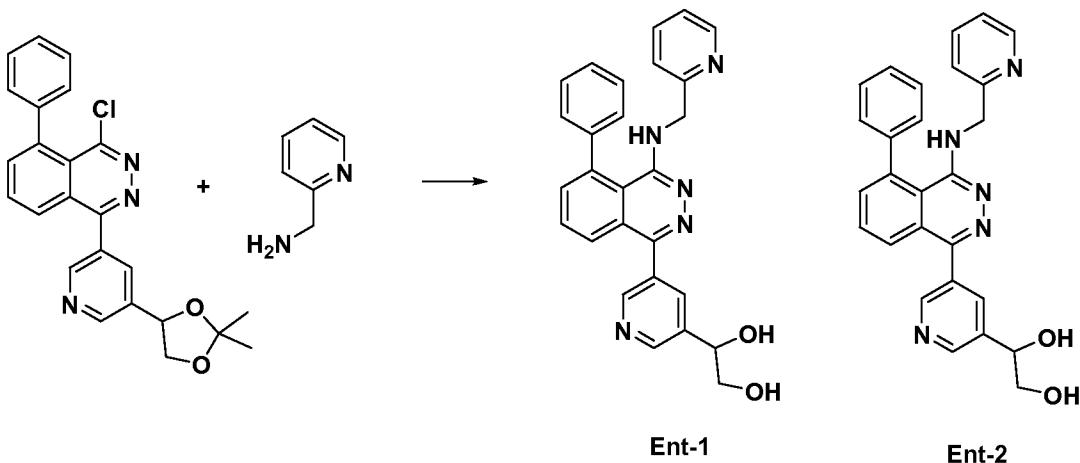


20 A solution of 3-bromo-5-(2,2-dimethyl-1,3-dioxolan-4-yl)pyridine (100 mg, 0.387 mmol), bis(pinacolato)diboron (148 mg, 0.581 mmol) and KOAc (114 mg, 1.16 mmol) in 1,4-dioxane (10 mL) was purged with nitrogen for 30 min. Then $\text{Pd}(\text{dppf})\text{Cl}_2\text{-CH}_2\text{Cl}_2$ (32.0 mg, 0.0390 mmol) was added and the reaction mixture was heated in a sealed tube at 100 °C for 14 h. The reaction mixture was allowed to cool to ambient temperature and filtered through CELITE®. The filtrate was concentrated under reduced pressure to yield 3-(2,2-dimethyl-1,3-dioxolan-4-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (90.0 mg, 76.0%) as a viscous oil which was used in the next step without further purification. LCMS (*Condition 11*): retention time 0.95 min, $[\text{M}+1] = 306.1$.



4-Chloro-1-(5-(2,2-dimethyl-1,3-dioxolan-4-yl)pyridin-3-yl)-5-phenylphthalazine (1.00 g, 82.0% yield) was prepared from 1,4-dichloro-5-phenylphthalazine (0.800 g, 2.91 mmol), 3-(2,2-dimethyl-1,3-dioxolan-4-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (0.887 g, 2.91 mmol), K_3PO_4 (0.617 g, 2.91 mmol), tricyclohexylphosphine (0.0160 g, 0.0580 mmol) and $Pd_2(dba)_3$ (0.0270 g, 0.0290 mmol) by the methods described for N-(*tert*-butyl)-5-(4-chloro-5-phenylphthalazin-1-yl)pyridine-3-sulfonamide in Example 1. The crude product was taken to next step without purification. LCMS

10 (Condition 11): retention time 1.05 min, $[M+1] = 418.1$.



To a solution of 4-chloro-1-(5-(2,2-dimethyl-1,3-dioxolan-4-yl)pyridin-3-yl)-5-phenylphthalazine (1.00 g, 2.39 mmol) in toluene (5 mL) was added pyridin-2-ylmethanamine (5.00 mL, 48.5 mmol) the contents were heated at 100 °C for 12 h. The reaction mixture was diluted with DCM (200 mL) and washed with 1.5N HCl (2 x 20 mL). The organic extract was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The resulting crude was purified by preparative HPLC

(*Condition 18* as described in general methods) to obtain 1-(5-(5-phenyl-4-((pyridin-2-ylmethyl) amino)phthalazin-1-yl)pyridin-3-yl)ethane-1,2-diol (55.0 mg, 5.11%) as a white solid. The racemic product (50 mg) was resolved into individual enantiomers by chiral SFC (*Condition 29* as described in general methods).

5

Ent-1:

1-(5-(5-Phenyl-4-((pyridin-2-ylmethyl)amino)phthalazin-1-yl)pyridin-3-yl)ethane-1,2-diol (18.0 mg). Chiral HPLC (*Condition 29*): retention time 7.38 min, Purity 100%. LCMS (*Condition 4*): retention time 2.15 min, [M+1] = 450.2.

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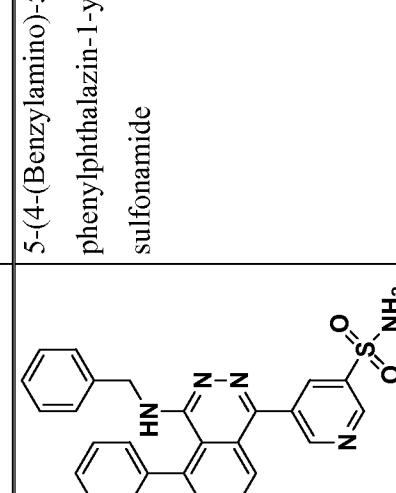
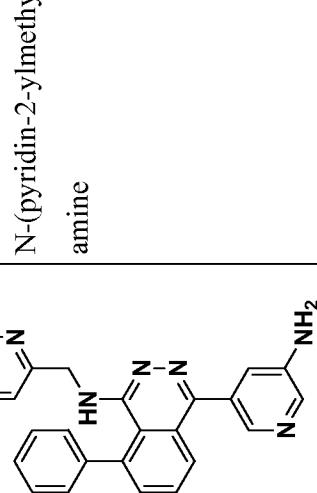
Ent-2:

1-(5-(5-Phenyl-4-((pyridin-2-ylmethyl)amino)phthalazin-1-yl)pyridin-3-yl)ethane-1,2-diol (15.0 mg). Chiral HPLC (*Condition 29*): retention time 8.83 min, Purity 98.16%. LCMS (*Condition 2*): retention time 1.65 min, [M+1] = 450.2.

15

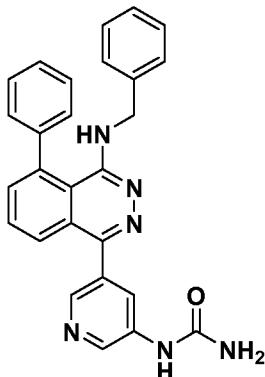
¹H NMR (400 MHz, DMSO-d₆) δ 3.53-3.66 (m, 2 H), 4.65 (d, *J* = 4.4 Hz, 2 H), 4.68-4.75 (m, 1 H), 4.87 (dd, *J* = 5.6 Hz, *J* = 6.0 Hz, 1 H), 5.54 (d, *J* = 4.4 Hz, 1 H), 6.26 (t, *J* = 4.4 Hz, 1 H), 7.18-7.24 (m, 1 H), 7.27 (d, *J* = 8.0 Hz, 1 H), 7.51-7.58 (m, 5 H), 7.68-7.73 (m, 2 H), 7.84-7.93 (m, 2 H), 8.01 (t, *J* = 2.0 Hz, 1 H), 8.23 (dd, *J* = 3.2 Hz, *J* = 4.4 Hz, 1 H), 8.69 (d, *J* = 2.0 Hz, 1 H), 8.73 (d, *J* = 2.0 Hz, 1 H).

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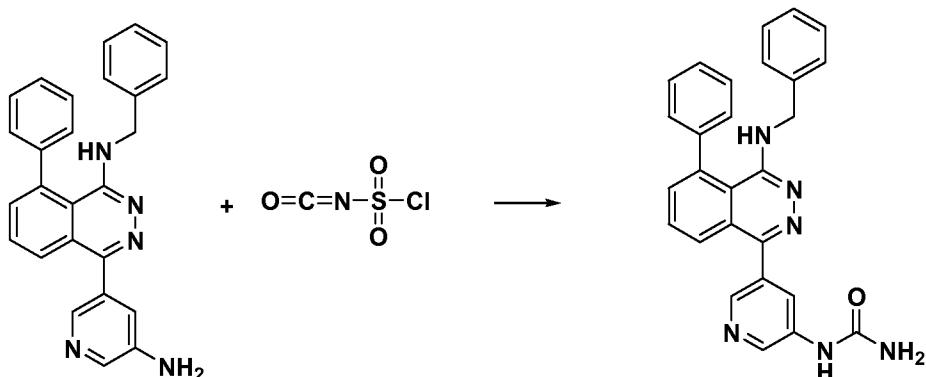
Ex. No.	Structure	Name	¹ H NMR	LC/MS Rt (min) Method M+H
8		5-(4-(Benzylamino)-5-phenylphthalazin-1-yl)pyridine-3-sulfonamide	¹ H NMR (400 MHz, DMSO-d ₆) δ 4.53 (d, <i>J</i> = 4.8 Hz, 2 H), 5.15 (t, <i>J</i> = 4.8 Hz, 1 H), 7.02-7.05 (m, 2 H), 7.23-7.29 (m, 3 H), 7.45-7.52 (m, 5 H), 7.72-7.74 (m, 3 H), 7.86 (dd, <i>J</i> = 1.2 Hz, <i>J</i> = 8.4 Hz, 1 H), 7.95 (dd, <i>J</i> = 7.2 Hz, <i>J</i> = 8.4 Hz, 1 H), 8.47 (t, <i>J</i> = 2.0 Hz, 1 H), 9.09 (d, <i>J</i> = 2.0 Hz, 1 H), 9.12 (d, <i>J</i> = 2.0 Hz, 1 H).	2.27 <i>Condition 10</i> 466.0 (M-H)
9		4-(5-Aminopyridin-3-yl)-8-phenyl-N-(pyridin-2-ylmethyl)phthalazin-1-amine	¹ H NMR (400 MHz, DMSO-d ₆) δ 4.63 (d, <i>J</i> = 4.4 Hz, 2 H), 5.52 (s, 2 H), 6.20 (dd, <i>J</i> = 4.0 Hz, <i>J</i> = 4.4 Hz, 1 H), 7.16 (dd, <i>J</i> = 2.0 Hz, <i>J</i> = 2.4 Hz, 1 H), 7.20-7.23 (m, 1 H), 7.26 (d, <i>J</i> = 7.6 Hz, 1 H), 7.49-7.57 (m, 5 H), 7.65-7.72 (m, 2 H), 7.85-7.92 (m, 2 H), 7.96 (d, <i>J</i> = 2.0 Hz, 1 H), 8.08 (d, <i>J</i> = 2.8 Hz, 1 H), 8.23 (dt, <i>J</i> = 0.8 Hz, <i>J</i> = 4.0 Hz, 1 H).	2.26 <i>Condition 4</i> 405.2

Example 10

1-(5-(4-(Benzylamino)-5-phenylphthalazin-1-yl)pyridin-3-yl)urea



5



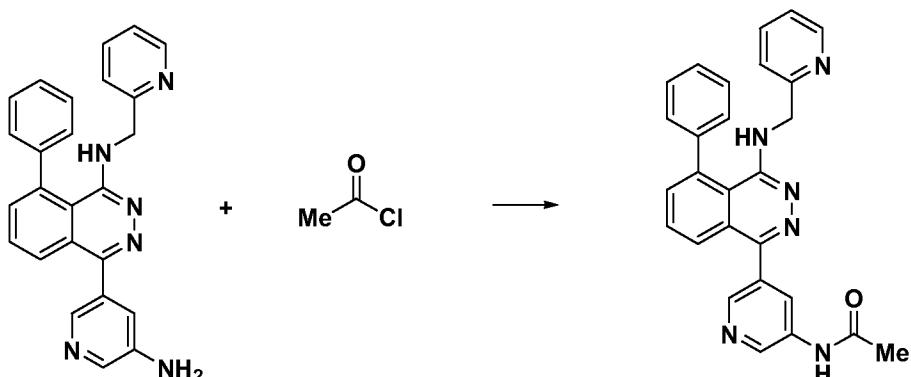
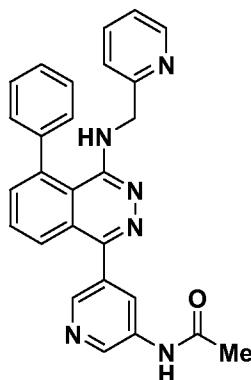
To a solution of 4-(5-aminopyridin-3-yl)-N-benzyl-8-phenylphthalazin-1-amine (60.0 mg, 0.149 mmol) in dichloromethane (10 mL) was added chlorosulfonyl isocyanate (0.0191 mL, 0.223 mmol) dropwise at 0 °C and the reaction mixture allowed to stir for 2 h while warming to ambient temperature. The volatile components were evaporated under reduced pressure and the resulting residue was cooled to 0 °C. 1.5N HCl was added and the reaction mixture stirred for an additional 2 h. The reaction mixture was adjusted to pH~8 by the addition of aqueous sodium bicarbonate. The resulting solution was extracted with ethyl acetate (3 x 5 mL). The combined organic layers were dried over 10 Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by preparative HPLC (*Condition 30* as described in general methods) to afford 1-(5-(4-(benzylamino)-5-phenylphthalazin-1-yl)pyridin-3-yl)urea (2.00 mg, 3.01%) as a white solid. LCMS (*Condition 4*): retention time 2.32 min, [M+1] = 447.2. HPLC (*Condition 28*): retention time = 6.13 min, purity 98.80%. ¹H NMR (400 MHz, DMSO-
15 Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by preparative HPLC (*Condition 30* as described in general methods) to afford 1-(5-(4-(benzylamino)-5-phenylphthalazin-1-yl)pyridin-3-yl)urea (2.00 mg, 3.01%) as a white solid. LCMS (*Condition 4*): retention time 2.32 min, [M+1] = 447.2. HPLC (*Condition 28*): retention time = 6.13 min, purity 98.80%. ¹H NMR (400 MHz, DMSO-

d₆) δ 4.51 (d, *J* = 4.8 Hz, 2 H), 5.04 (t, *J* = 4.8 Hz, 1 H), 6.10 (s, 2 H), 7.02 (dd, *J* = 1.2 Hz, *J* = 6.8 Hz, 2 H), 7.22-7.28 (m, 3 H), 7.43-7.51 (m, 5 H), 7.68 (dd, *J* = 1.2 Hz, *J* = 7.6 Hz, 1 H), 7.85-7.92 (m, 2 H), 8.24 (dd, *J* = 2.0 Hz, *J* = 2.4 Hz, 1 H), 8.37 (d, *J* = 2.0 Hz, 1 H), 8.64 (d, *J* = 2.4 Hz, 1 H), 8.94 (s, 1 H).

5

Example 11

N-(5-(5-Phenyl-4-(pyridin-2-ylmethylamino)phthalazin-1-yl)pyridin-3-yl)acetamide



10

To a solution of 4-(5-aminopyridin-3-yl)-8-phenyl-N-(pyridin-2-ylmethyl)phthalazin-1-amine (50.0 mg, 0.124 mmol) in dichloromethane (5 mL) at ambient temperature was added pyridine (0.0200 mL, 0.247 mmol) followed by acetyl chloride (0.0132 mL, 0.185 mmol). After stirring for 5 h at room temperature, the reaction mixture was diluted with dichloromethane (50 mL) and the organic portion washed with water (10 mL) followed by brine (10 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by preparative HPLC (*Condition 31* as described in general methods) to obtain N-(5-(5-phenyl-4-((pyridin-2-ylmethyl)amino)phthalazin-1-yl)pyridin-3-yl)acetamide (25.0 mg, 45.3%) as

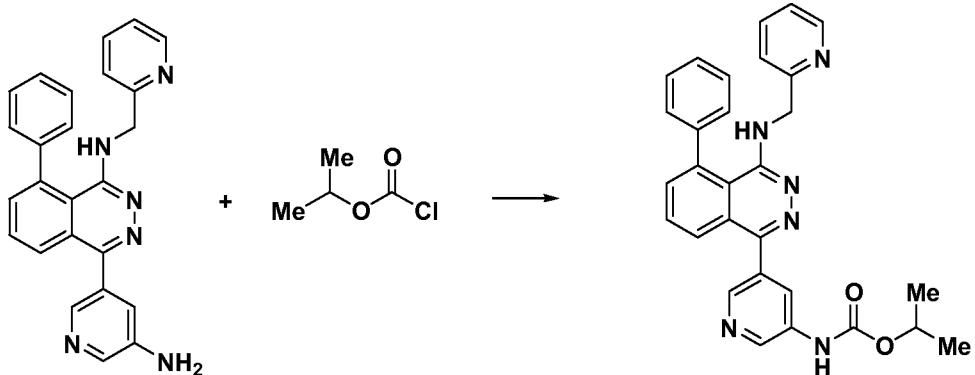
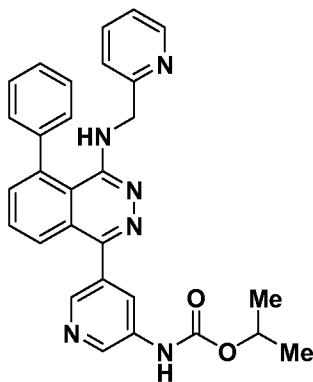
a white solid. LCMS (*Condition 4*): retention time 2.08 min, [M+1] = 447.2. HPLC (*Condition 28*): retention time = 5.63 min, purity 94.65%. ^1H NMR (400 MHz, CD_3OD) δ 2.21 (s, 3 H), 4.65 (s, 2 H), 7.21-7.26 (m, 2 H), 7.49 (br s, 5 H), 7.69-7.73 (m, 2 H), 7.88-7.94 (m, 2 H), 8.28-8.30 (m, 1 H), 8.42 (dd, J = 2.0 Hz, J = 2.4 Hz, 1 H), 8.55 (d, J = 2.0 Hz, 1 H), 8.90 (d, J = 2.4 Hz, 1 H).

5

Example 12

Isopropyl 5-(5-phenyl-4-(pyridin-2-ylmethylamino)phthalazin-1-yl)pyridin-3-ylcarbamate

10



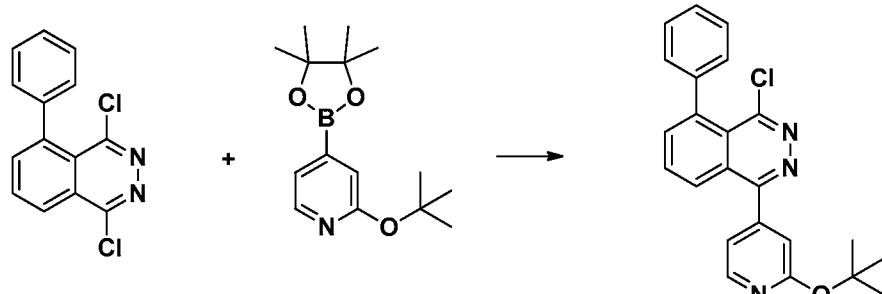
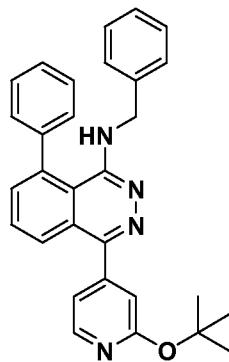
To a solution of 4-(5-aminopyridin-3-yl)-8-phenyl-N-(pyridin-2-ylmethyl)phthalazin-1-amine (50.0 mg, 0.124 mmol) in dichloromethane (5 mL) at room temperature was added pyridine (0.0200 mL, 0.247 mmol) followed by isopropyl carbonochloridate (18.2 mg, 0.148 mmol). The reaction mixture was stirred at ambient temperature for 12 h then diluted with dichloromethane (50 mL) and the organic portion washed with water (10 mL) followed by brine (10 mL). The organic layer was dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The resulting residue was

purified by preparative HPLC (*Condition 32* as described in general methods) to afford isopropyl (5-(5-phenyl-4-((pyridin-2-ylmethyl)amino)phthalazin-1-yl)pyridin-3-yl)carbamate (35.0 mg, 57.7%). LCMS (*Condition 4*): retention time 2.16 min, [M+1] = 491.0. HPLC (*Condition 28*): retention time = 6.66 min, purity 95.13%. ¹H NMR (400 MHz, DMSO-d₆) δ 1.29 (d, *J* = 6.0 Hz, 6 H), 4.65 (d, *J* = 4.0 Hz, 2 H), 4.93 (sept, *J* = 6.0 Hz, 1 H), 6.28 (t, *J* = 4.0 Hz, 1 H), 7.22 (dd, *J* = 6.0 Hz, *J* = 7.6 Hz, 1 H), 7.28 (d, *J* = 8.0 Hz, 1 H), 7.45-7.60 (m, 5 H), 7.68-7.73 (m, 2 H), 7.84-7.93 (m, 2 H), 8.17 (t, *J* = 2.0 Hz, 1 H), 8.22-8.24 (m, 1 H), 8.48 (d, *J* = 2.0 Hz, 1 H), 8.81 (d, *J* = 2.0 Hz, 1 H), 10.00 (s, 1 H).

10

Example 13

N-Benzyl-4-(2-*tert*-butoxypyridin-4-yl)-8-phenylphthalazin-1-amine



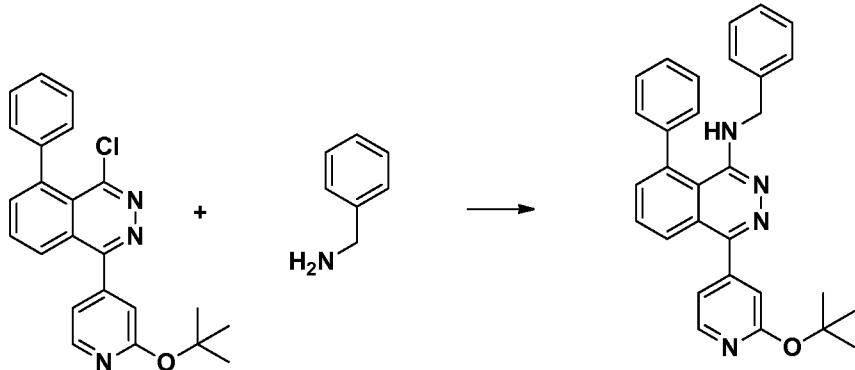
15

To a solution of 1,4-dichloro-5-phenylphthalazine (0.400 g, 1.45 mmol), 2-(*tert*-butoxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (0.484 g, 1.75 mmol) in dioxane (20 mL) and water (2 mL) was added phosphoric acid, potassium salt (0.617 g, 2.91 mmol). The reaction mixture was purged with nitrogen gas for 30 min and then Pd₂(dba)₃ (0.013 g, 0.015 mmol) was added followed by tricyclohexylphosphonium tetrafluoroborate (11 mg, 0.029 mmol). The purging was continued for a further 15 min

and the reaction mixture heated to 95 °C for 12 h. The reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography using CombiFlash

5 Isco (REDISEP®, SiO₂, 12 g, 0-30% ethyl acetate/petroleum ether) to get 1-(2-(*tert*-butoxy)pyridin-4-yl)-4-chloro-5-phenylphthalazine (0.400 g, 33.2%) as a brown solid. LCMS (*Condition 11*): retention time 1.22 min, [M+1] = 390.2. ¹H NMR (400 MHz, DMSO-d₆) δ 1.70 (s, 9 H), 6.84 (br s, 1 H), 7.05 (dd, *J* = 1.2 Hz, *J* = 5.2 Hz, 1 H), 7.36-7.44 (m, 2 H), 7.47-7.51 (m, 3 H), 8.06 (dd, *J* = 1.2 Hz, *J* = 7.6 Hz, 1 H), 8.15 (dd, *J* = 0.8 Hz, *J* = 4.8 Hz, 1 H), 8.26 (dd, *J* = 7.2 Hz, *J* = 8.0 Hz, 1 H), 8.47 (d, *J* = 1.2 Hz, *J* = 8.4 Hz, 1 H).

10



15 Benzylamine (5.00 mL, 45.8 mmol) was added to 1-(2-(*tert*-butoxy)pyridin-4-yl)-4-chloro-5-phenylphthalazine (0.200 g, 0.513 mmol) and heated in a sealed tube at 100 °C for 12 h. The reaction mixture was diluted with dichloromethane (100 mL) and washed with water (50 mL) followed by brine (25 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography using CombiFlash Isco (REDISEP®, basic Al₂O₃, 80 g, 0-70% ethyl acetate/petroleum ether) to remove excess benzyl amine. The resulting residue was then purified by preparative HPLC (*Condition 33* as described in general methods) to afford N-benzyl-4-(2-(*tert*-butoxy)pyridin-4-yl)-8-phenylphthalazin-1-amine (0.120 g, 50.8%) as a white solid. LCMS (*Condition 34*): retention time 2.67 min, [M+1] = 461.2. HPLC (*Condition 35*): retention time = 21.80 min, purity 99.30%. ¹H NMR (400 MHz, DMSO-d₆) δ 1.63 (s, 9 H), 4.50 (d, *J* = 5.2 Hz, 2 H), 5.07 (t, *J* = 5.2 Hz, 1 H), 6.90 (dd, *J* = 0.4 Hz, *J* = 0.8 Hz, 1 H), 7.00-7.03 (m, 2 H), 7.17 (dd, *J* = 1.6 Hz, *J* = 5.2 Hz, 1 H), 7.36-7.44 (m, 2 H), 7.47-7.51 (m, 3 H), 8.06 (dd, *J* = 1.2 Hz, *J* = 7.6 Hz, 1 H), 8.15 (dd, *J* = 0.8 Hz, *J* = 4.8 Hz, 1 H), 8.26 (dd, *J* = 7.2 Hz, *J* = 8.0 Hz, 1 H), 8.47 (d, *J* = 1.2 Hz, *J* = 8.4 Hz, 1 H).

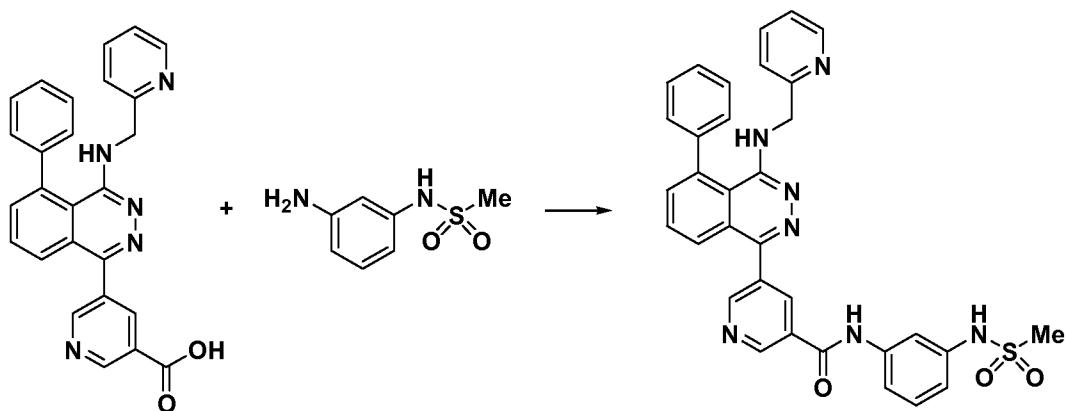
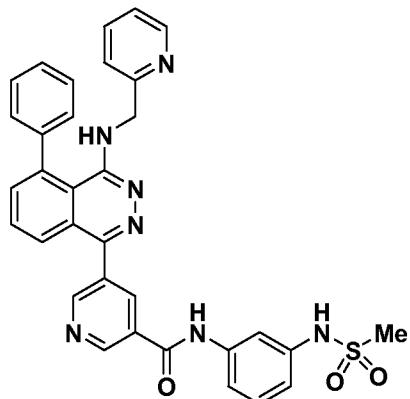
20

25

Hz, 1 H), 7.22-7.28 (m, 3 H), 7.42-7.50 (m, 5 H), 7.67 (dd, J = 1.2 Hz, J = 6.8 Hz, 1 H), 7.85-7.93 (m, 2 H), 8.31 (dd, J = 0.4 Hz, J = 5.2 Hz, 1 H).

Example 14

5 N-(3-(Methylsulfonamido)phenyl)-5-(5-phenyl-4-(pyridin-2-ylmethylamino)phthalazin-1-yl)nicotinamide



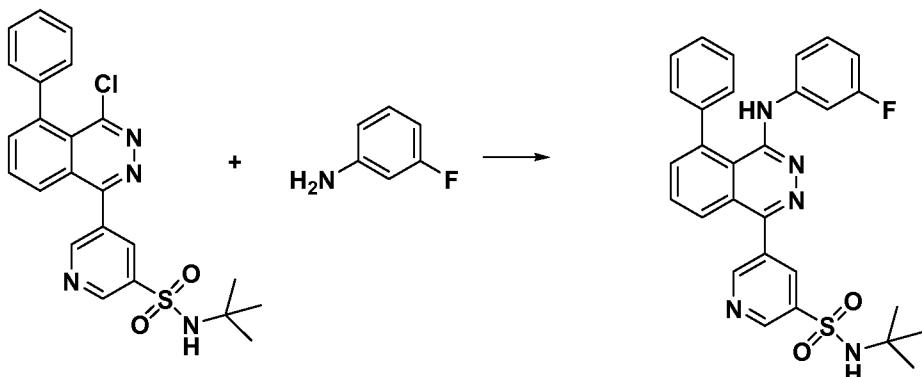
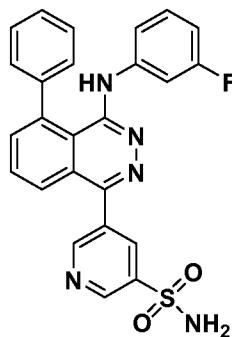
10 5-(5-Phenyl-4-((pyridin-2-ylmethyl)amino)phthalazin-1-yl)nicotinic acid (15.0 mg, 0.0350 mmol) was added to *N*-(3-aminophenyl)methanesulfonamide (7.73 mg, 0.0420 mmol) and a solution of HATU (19.7 mg, 0.0520 mmol) and DIPEA (0.0180 mL, 0.104 mmol) in DMF (0.5 mL) was added. The reaction mixture was stirred for 5 hours at room temperature. The volatile components were removed under high vacuum and the 15 residue was purified by reverse phase preparative HPLC (*Condition 36* as described in general methods) to afford N-(3-(methylsulfonamido)phenyl)-5-(5-phenyl-4-((pyridin-2-ylmethyl)amino)phthalazin-1-yl)nicotinamide (5.79 mg, 26.4%) as a white solid. LCMS (*Condition 37*): retention time 1.63 min, [M+1] = 602.1, purity 95.02%. ^1H NMR (400

MHz, DMSO-d₆) δ 3.01 (s, 3 H), 4.67 (d, *J* = 4.4 Hz, 2 H), 6.34 (t, *J* = 4.4 Hz, 1 H), 6.95-6.99 (m, 1 H), 7.21-7.24 (m, 1 H), 7.28 (d, *J* = 8.0 Hz, 1 H), 7.30 (t, *J* = 8.0 Hz, 1 H), 7.50-7.58 (m, 6 H), 7.68-7.77 (m, 3 H), 7.90-7.94 (m, 2 H), 8.22-8.24 (m, 1 H), 8.61 (t, *J* = 2.0 Hz, 1 H), 9.05 (d, *J* = 2.0 Hz, 1 H), 9.26 (d, *J* = 2.0 Hz, 1 H), 10.60 (s, 1 H).

5

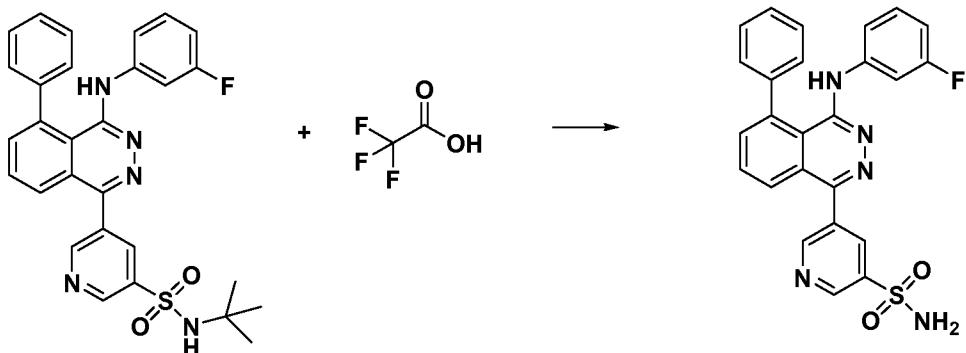
Example 15

5-(4-(3-Fluorophenylamino)-5-phenylphthalazin-1-yl)pyridine-3-sulfonamide



10

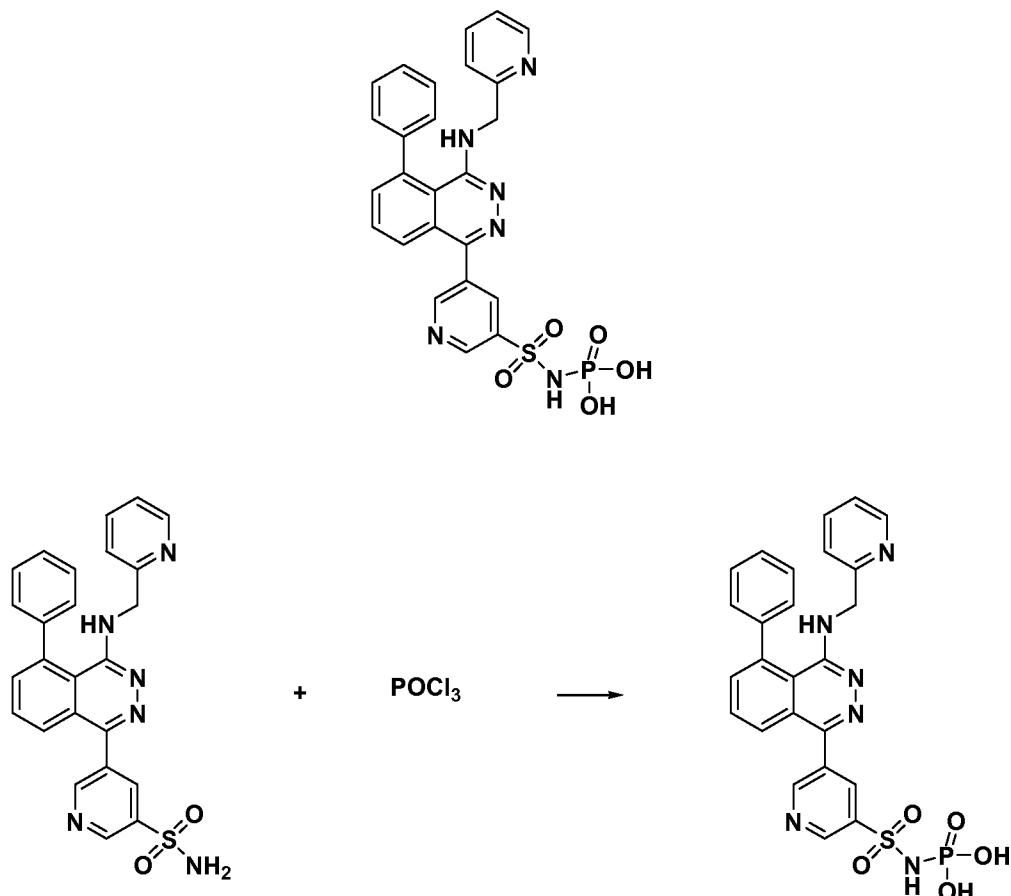
N-(*tert*-Butyl)-5-(4-chloro-5-phenylphthalazin-1-yl)pyridine-3-sulfonamide (1.00 g, 2.21 mmol) in 3-fluoroaniline (2.94 g, 26.5 mmol) was heated in a sealed tube at 100 °C for 12 h. On cooling, the volatile components were removed under reduced pressure and the resulting residue was purified by combiflash (REDISEP®, silica gel, 24 g, 60% EtOAc/hexanes) to obtain N-(*tert*-butyl)-5-(4-(3-fluorophenylamino)-5-phenylphthalazin-1-yl)pyridine-3-sulfonamide (0.70 g, 60%) as a brown solid. LCMS (Condition 11): retention time 1.20 min, [M+1] = 528.4. ¹H NMR (400 MHz, DMSO-d₆) δ 1.94 (s, 9 H), 6.50 (dd, *J* = 1.2 Hz, *J* = 8.4 Hz, 1 H), 6.76 (td, *J* = 2.5 Hz, *J* = 8.4 Hz, 1 H), 7.19-7.25 (m, 2 H), 7.53-7.66 (m, 6 H), 7.88-7.93 (m, 3 H), 8.05 (dd, *J* = 6.8 Hz, *J* = 8.4 Hz, 1 H), 8.54 (t, *J* = 2.0 Hz, 1 H), 9.15 (d, *J* = 2.0 Hz, 1 H), 9.16 (d, *J* = 2.0 Hz, 1 H).



N-(*tert*-Butyl)-5-(4-((3-fluorophenyl)amino)-5-phenylphthalazin-1-yl)pyridine-3-sulfonamide (0.600 g, 1.14 mmol) was dissolved in TFA (10.0 mL, 130 mmol) and 5 heated to 65 °C for 4 h. TFA was removed under reduced pressure and the resulting residue was diluted with saturated NaHCO₃ (100 mL). The reaction mixture was extracted with EtOAc (3 x 100 mL). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by combiflash (REDISEP®, silica gel, 40 g, 0-6% MeOH/DCM) to 10 afford 5-(4-((3-fluorophenyl)amino)-5-phenylphthalazin-1-yl)pyridine-3-sulfonamide (0.15 g, 27%) as an off-white solid. LCMS (*Condition 38*): retention time 2.12 min, [M+1] = 472.2. HPLC (*Condition 25*): retention time = 9.61 min, purity 99.78%. ¹H NMR (400 MHz, DMSO-d₆) δ 6.50 (dd, *J* = 1.6 Hz, *J* = 8.0 Hz, 1 H), 6.76 (td, *J* = 2.0 Hz, *J* = 8.4 Hz, 1 H), 7.19-7.25 (m, 2 H), 7.53-7.66 (m, 6 H), 7.76 (br s, 2 H), 7.90 (dd, *J* = 1.2 Hz, *J* = 7.2 Hz, 1 H), 7.95 (dd, *J* = 1.2 Hz, *J* = 8.0 Hz, 1 H), 8.05 (dd, *J* = 7.2 Hz, *J* = 8.0 Hz, 1 H), 8.54 (dd, *J* = 2.0 Hz, *J* = 2.4 Hz, 1 H), 9.15 (d, *J* = 2.0 Hz, 1 H), 9.16 (d, *J* = 2.4 Hz, 1 H).

Example 16

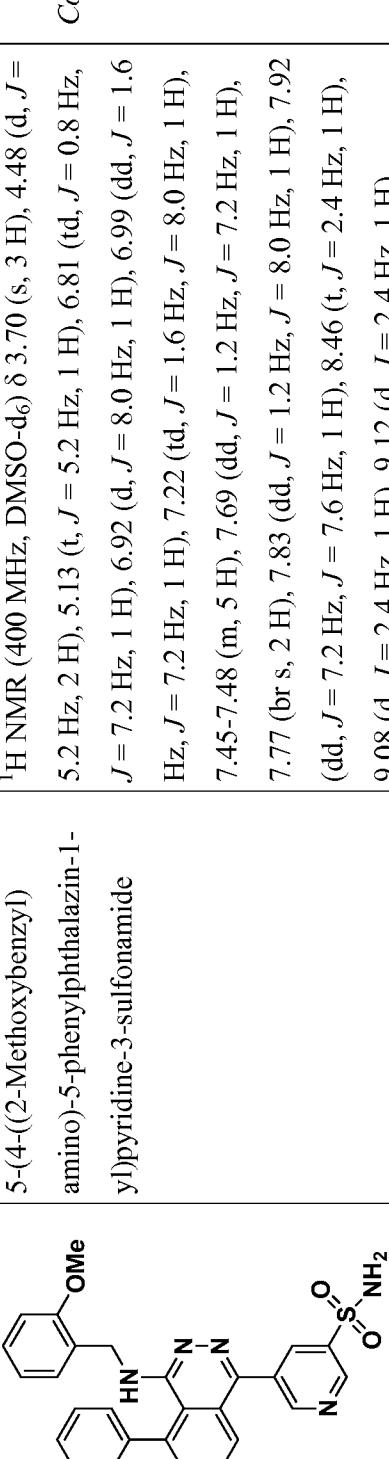
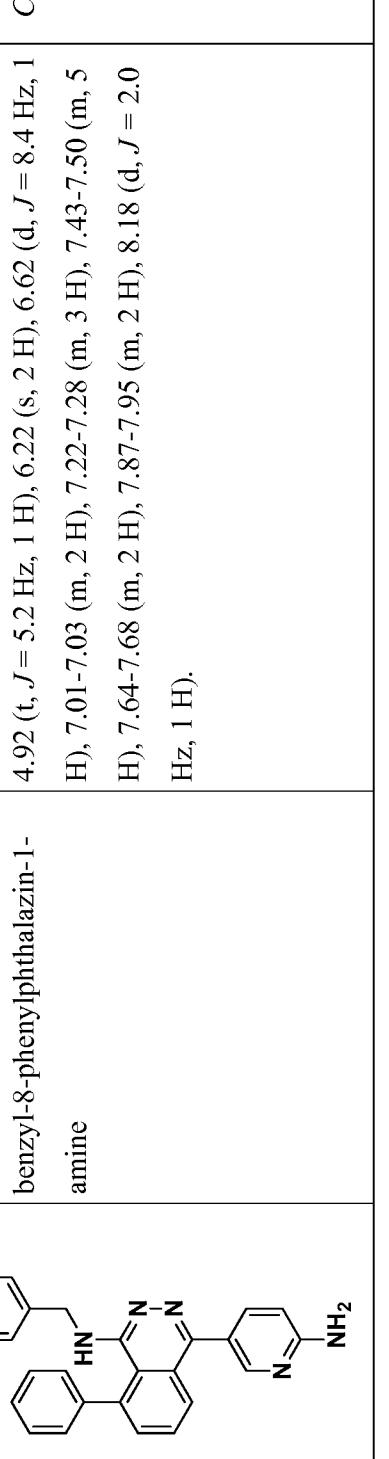
20 5-(5-Phenyl-4-(pyridin-2-ylmethylamino)phthalazin-1-yl)pyridin-3-ylsulfonylphosphoramicidic acid

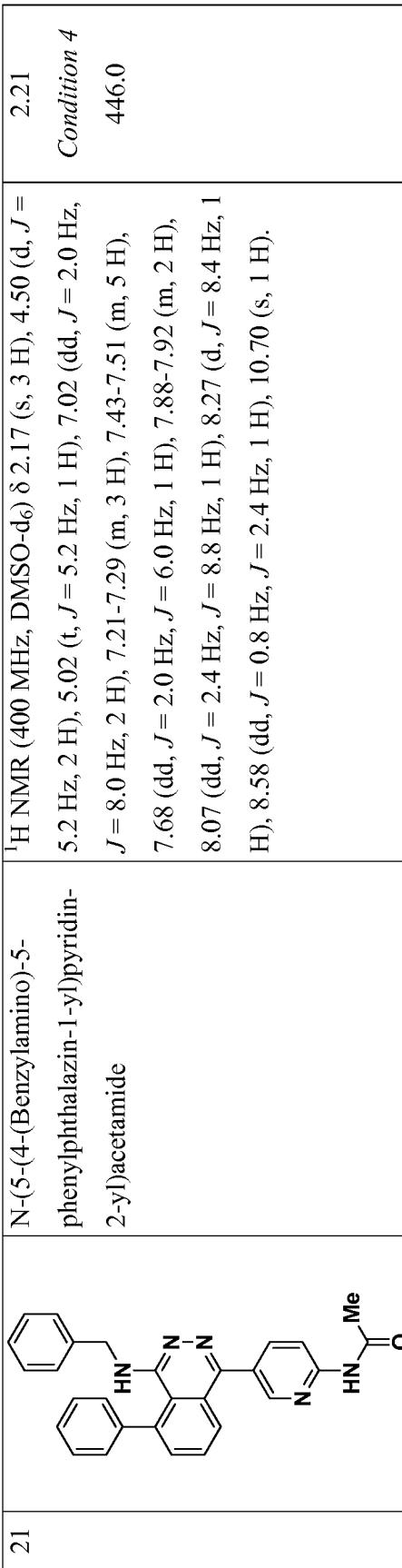
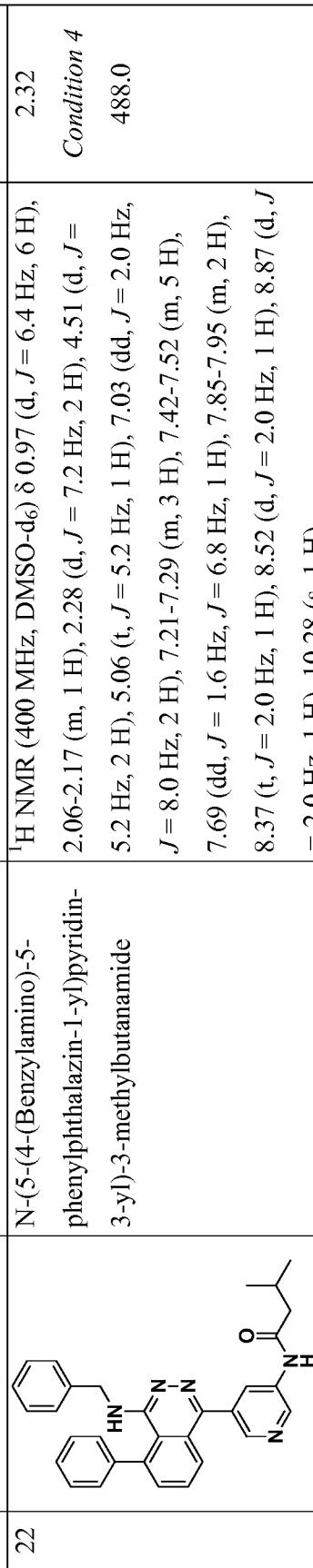


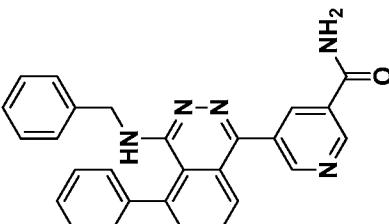
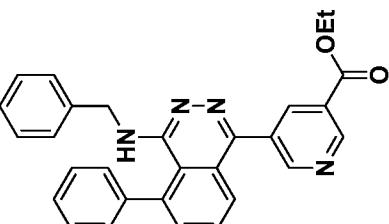
To a solution of 5-(5-phenyl-4-((pyridin-2-ylmethyl)amino)phthalazin-1-yl)pyridine-3-sulfonamide (1.00 g, 2.13 mmol) in dichloromethane (25 mL) was added DIPEA (1.49 mL, 8.54 mmol) at 0 °C and the reaction mixture was stirred for 10 min. POCl_3 (0.597 mL, 6.40 mmol) was added at 0 °C and the reaction mixture was allowed to stir for 3 h while warming to ambient temperature. DCM and excess POCl_3 was evaporated under reduced pressure. To the resulting residue was added ice-cold water (5 mL) and the resulting mixture stirred for 30 minutes at ambient temperature. The resulting precipitate was filtered and the solid washed successively with acetonitrile (10 mL) and acetone (10 mL). The solid was dissolved in 1.5N HCl (10 mL) and allowed to stir at ambient temperature for 3 h and the residue was purified by preparative HPLC (*Condition 42* as described in general methods). Fractions containing the product were collected, combined and evaporated under reduced pressure at low temperature (30 °C). The residue was lyophilized with water to obtain 5-(5-phenyl-4-(pyridin-2-ylmethylamino)phthalazin-1-yl)pyridin-3-ylsulfonylphosphoramicidic acid (600 mg, 51.3%) as a white solid. LCMS (*Condition 2*): retention time 1.60 min, $[\text{M}+1] = 549.2$.

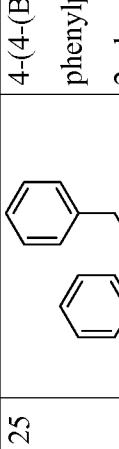
HPLC (*Condition 26*): retention time = 11.16 min, purity 99.05%. ^1H NMR (400 MHz, DMSO- d_6) δ 4.67 (d, J = 3.6 Hz, 2 H), 6.48 (br s, 1 H), 7.21-7.25 (m, 1 H), 7.28 (d, J = 8.0 Hz, 1 H), 7.51-7.59 (m, 5 H), 7.69-7.74 (m, 2 H), 7.91-7.94 (m, 2 H), 8.21-8.23 (m, 1 H), 8.51 (t, J = 2.0 Hz, 1 H), 9.10 (t, J = 2.0 Hz, 1 H), 9.13 (t, J = 2.0 Hz, 1 H).

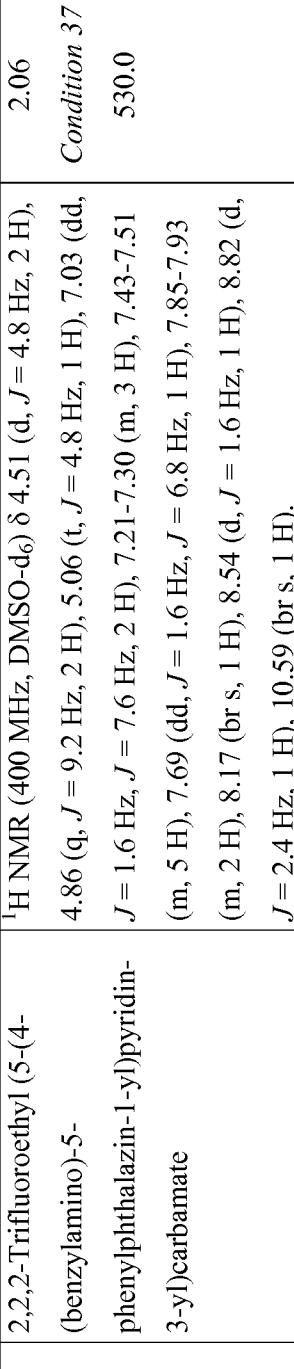
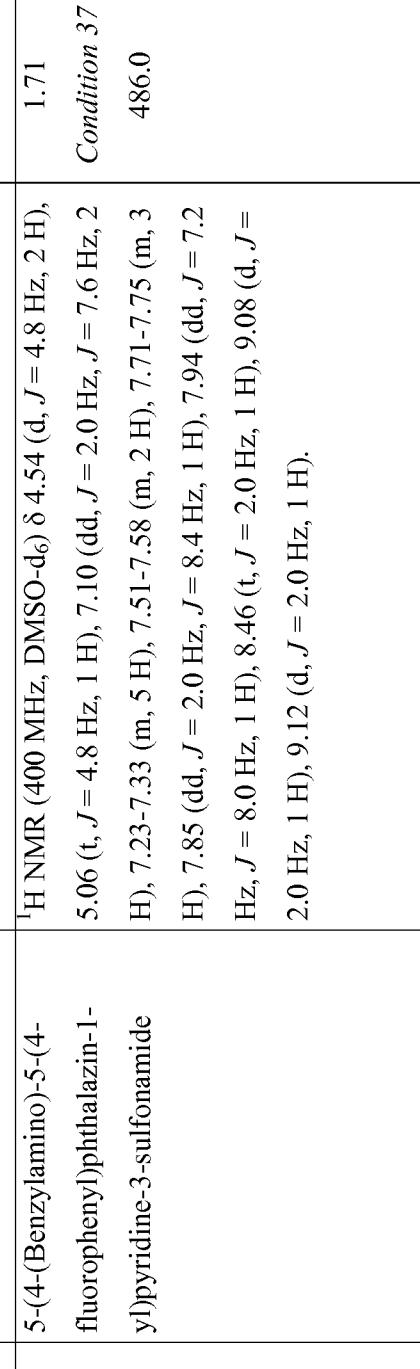
Ex. No.	Structure	Name	¹ H NMR	LC/MS Rt (min) Method M+H
17		5-(4-(Benzylamino)-5-phenylphthalazin-1-yl)pyridine-3-sulfonamide	¹ H NMR (400 MHz, DMSO-d ₆) δ 4.53 (d, <i>J</i> = 4.8 Hz, 2 H), 5.15 (t, <i>J</i> = 4.8 Hz, 1 H), 7.02-7.05 (m, 2 H), 7.23-7.29 (m, 3 H), 7.45-7.52 (m, 5 H), 7.72-7.74 (m, 3 H), 7.86 (dd, <i>J</i> = 1.2 Hz, <i>J</i> = 8.4 Hz, 1 H), 7.95 (dd, <i>J</i> = 7.2 Hz, <i>J</i> = 8.4 Hz, 1 H), 8.47 (t, <i>J</i> = 2.0 Hz, 1 H), 9.09 (d, <i>J</i> = 2.0 Hz, 1 H), 9.12 (d, <i>J</i> = 2.0 Hz, 1 H).	2.27 <i>Condition 10</i> 466.0 (M-H)
18		4-(5-Aminopyridin-3-yl)-8-phenyl-N-(pyridin-2-ylmethyl)phthalazin-1-amine	¹ H NMR (400 MHz, DMSO-d ₆) δ 4.63 (d, <i>J</i> = 4.4 Hz, 2 H), 5.52 (s, 2 H), 6.20 (dd, <i>J</i> = 4.0 Hz, <i>J</i> = 4.4 Hz, 1 H), 7.16 (dd, <i>J</i> = 2.0 Hz, <i>J</i> = 2.4 Hz, 1 H), 7.20-7.23 (m, 1 H), 7.26 (d, <i>J</i> = 7.6 Hz, 1 H), 7.49-7.57 (m, 5 H), 7.65-7.72 (m, 2 H), 7.85-7.92 (m, 2 H), 7.96 (d, <i>J</i> = 2.0 Hz, 1 H), 8.08 (d, <i>J</i> = 2.8 Hz, 1 H), 8.23 (dt, <i>J</i> = 0.8 Hz, <i>J</i> = 4.0 Hz, 1 H).	2.26 <i>Condition 4</i> 405.2

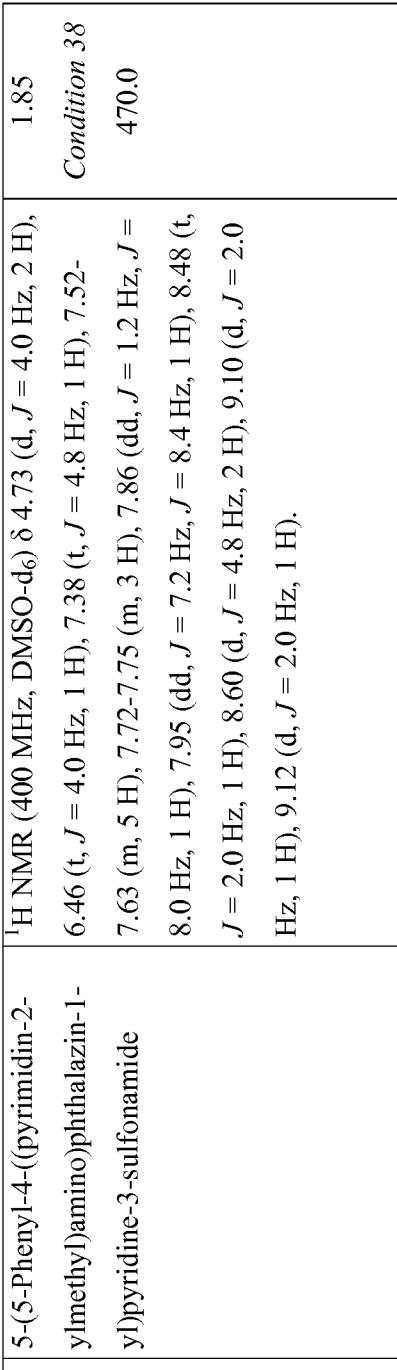
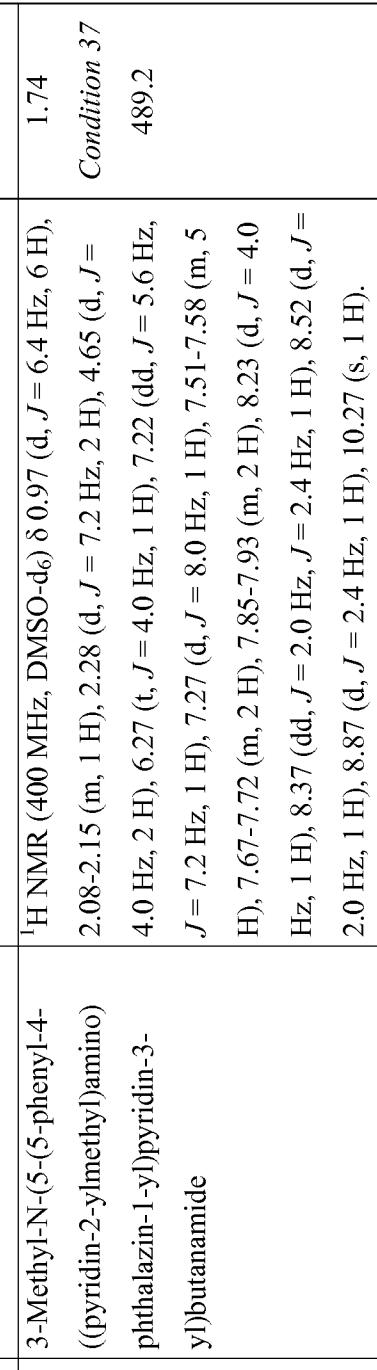
19	 <p>5-((2-Methoxybenzyl)amino)-5-phenylphthalazin-1-yl)pyridine-3-sulfonamide</p>	¹ H NMR (400 MHz, DMSO-d ₆) δ 3.70 (s, 3 H), 4.48 (d, <i>J</i> = 5.2 Hz, 2 H), 5.13 (t, <i>J</i> = 5.2 Hz, 1 H), 6.81 (td, <i>J</i> = 0.8 Hz, <i>J</i> = 7.2 Hz, 1 H), 6.92 (d, <i>J</i> = 8.0 Hz, 1 H), 6.99 (dd, <i>J</i> = 1.6 Hz, <i>J</i> = 7.2 Hz, 1 H), 7.22 (td, <i>J</i> = 1.6 Hz, 1 H), 7.45-7.48 (m, 5 H), 7.69 (dd, <i>J</i> = 1.2 Hz, <i>J</i> = 7.2 Hz, 1 H), 7.77 (br s, 2 H), 7.83 (dd, <i>J</i> = 1.2 Hz, <i>J</i> = 8.0 Hz, 1 H), 7.92 (dd, <i>J</i> = 7.2 Hz, <i>J</i> = 7.6 Hz, 1 H), 8.46 (t, <i>J</i> = 2.4 Hz, 1 H), 9.08 (d, <i>J</i> = 2.4 Hz, 1 H), 9.12 (d, <i>J</i> = 2.4 Hz, 1 H).	¹ H NMR (400 MHz, DMSO-d ₆) δ 3.70 (s, 3 H), 4.48 (d, <i>J</i> = 5.2 Hz, 2 H), 5.13 (t, <i>J</i> = 5.2 Hz, 1 H), 6.81 (td, <i>J</i> = 0.8 Hz, <i>J</i> = 7.2 Hz, 1 H), 6.92 (d, <i>J</i> = 8.0 Hz, 1 H), 6.99 (dd, <i>J</i> = 1.6 Hz, <i>J</i> = 7.2 Hz, 1 H), 7.22 (td, <i>J</i> = 1.6 Hz, 1 H), 7.45-7.48 (m, 5 H), 7.69 (dd, <i>J</i> = 1.2 Hz, <i>J</i> = 7.2 Hz, 1 H), 7.77 (br s, 2 H), 7.83 (dd, <i>J</i> = 1.2 Hz, <i>J</i> = 8.0 Hz, 1 H), 7.92 (dd, <i>J</i> = 7.2 Hz, <i>J</i> = 7.6 Hz, 1 H), 8.46 (t, <i>J</i> = 2.4 Hz, 1 H), 9.08 (d, <i>J</i> = 2.4 Hz, 1 H), 9.12 (d, <i>J</i> = 2.4 Hz, 1 H).	Condition 39 498.0
20	 <p>4-(6-Aminopyridin-3-yl)-N-(benzyl-8-phenylphthalazin-1-yl)amine</p>	¹ H NMR (400 MHz, DMSO-d ₆) δ 4.48 (d, <i>J</i> = 5.2 Hz, 2 H), 4.92 (t, <i>J</i> = 5.2 Hz, 1 H), 6.22 (s, 2 H), 6.62 (d, <i>J</i> = 8.4 Hz, 1 H), 7.01-7.03 (m, 2 H), 7.22-7.28 (m, 3 H), 7.43-7.50 (m, 5 H), 7.64-7.68 (m, 2 H), 7.87-7.95 (m, 2 H), 8.18 (d, <i>J</i> = 2.0 Hz, 1 H).	¹ H NMR (400 MHz, DMSO-d ₆) δ 4.48 (d, <i>J</i> = 5.2 Hz, 2 H), 4.92 (t, <i>J</i> = 5.2 Hz, 1 H), 6.22 (s, 2 H), 6.62 (d, <i>J</i> = 8.4 Hz, 1 H), 7.01-7.03 (m, 2 H), 7.22-7.28 (m, 3 H), 7.43-7.50 (m, 5 H), 7.64-7.68 (m, 2 H), 7.87-7.95 (m, 2 H), 8.18 (d, <i>J</i> = 2.0 Hz, 1 H).	Condition 4 404.0

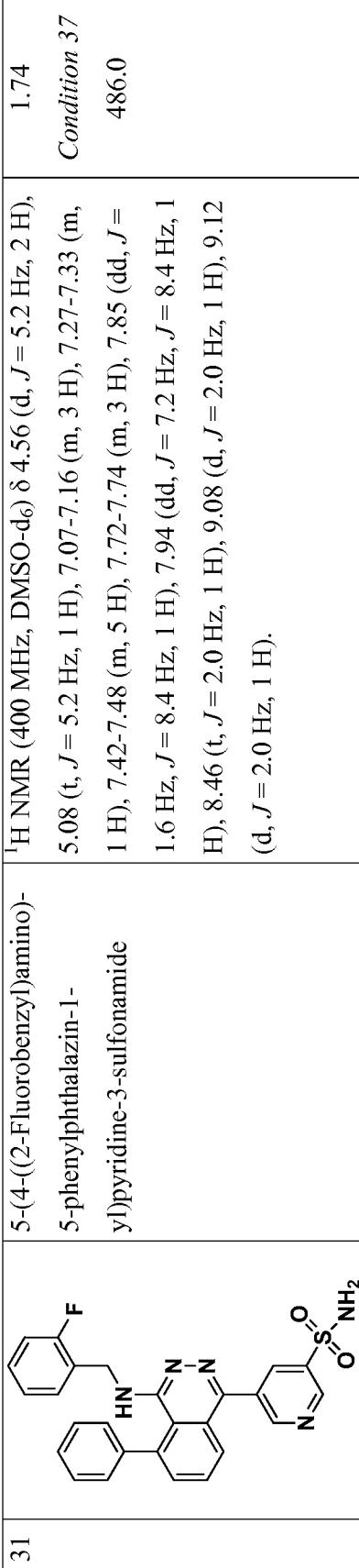
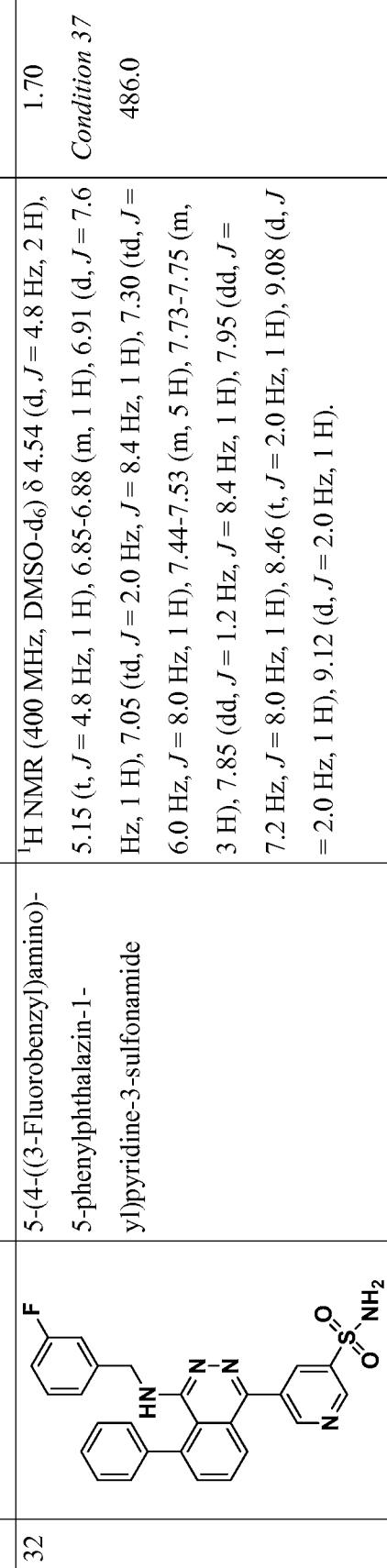
21	 <p>N-(5-(4-(Benzylamino)-5-phenylphthalazin-1-yl)pyridin-2-yl)acetamide</p>	¹ H NMR (400 MHz, DMSO-d ₆) δ 2.17 (s, 3 H), 4.50 (d, <i>J</i> = 5.2 Hz, 2 H), 5.02 (t, <i>J</i> = 5.2 Hz, 1 H), 7.02 (dd, <i>J</i> = 2.0 Hz, <i>J</i> = 8.0 Hz, 2 H), 7.21-7.29 (m, 3 H), 7.43-7.51 (m, 5 H), 7.68 (dd, <i>J</i> = 2.0 Hz, <i>J</i> = 6.0 Hz, 1 H), 7.88-7.92 (m, 2 H), 8.07 (dd, <i>J</i> = 2.4 Hz, <i>J</i> = 8.8 Hz, 1 H), 8.27 (d, <i>J</i> = 8.4 Hz, 1 H), 8.58 (dd, <i>J</i> = 0.8 Hz, <i>J</i> = 2.4 Hz, 1 H), 10.70 (s, 1 H).	2.21 446.0 <i>Condition 4</i>
22	 <p>N-(5-(4-(Benzylamino)-5-phenylphthalazin-1-yl)pyridin-3-yl)-3-methylbutanamide</p>	¹ H NMR (400 MHz, DMSO-d ₆) δ 0.97 (d, <i>J</i> = 6.4 Hz, 6 H), 2.06-2.17 (m, 1 H), 2.28 (d, <i>J</i> = 7.2 Hz, 2 H), 4.51 (d, <i>J</i> = 5.2 Hz, 2 H), 5.06 (t, <i>J</i> = 5.2 Hz, 1 H), 7.03 (dd, <i>J</i> = 2.0 Hz, <i>J</i> = 8.0 Hz, 2 H), 7.21-7.29 (m, 3 H), 7.42-7.52 (m, 5 H), 7.69 (dd, <i>J</i> = 1.6 Hz, <i>J</i> = 6.8 Hz, 1 H), 7.85-7.95 (m, 2 H), 8.37 (t, <i>J</i> = 2.0 Hz, 1 H), 8.52 (d, <i>J</i> = 2.0 Hz, 1 H), 8.87 (d, <i>J</i> = 2.0 Hz, 1 H), 10.28 (s, 1 H).	2.32 488.0 <i>Condition 4</i>

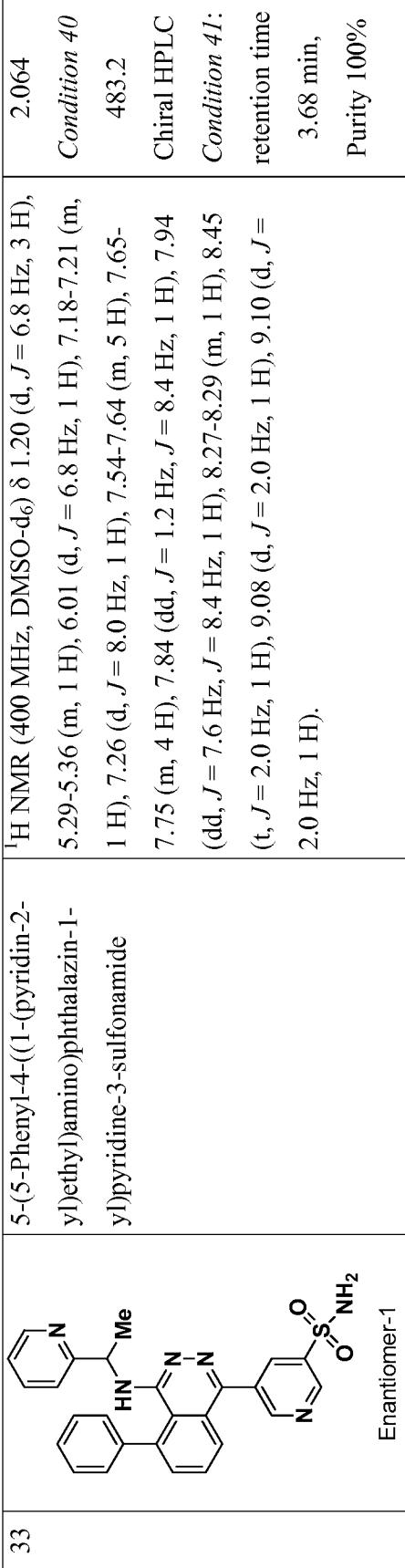
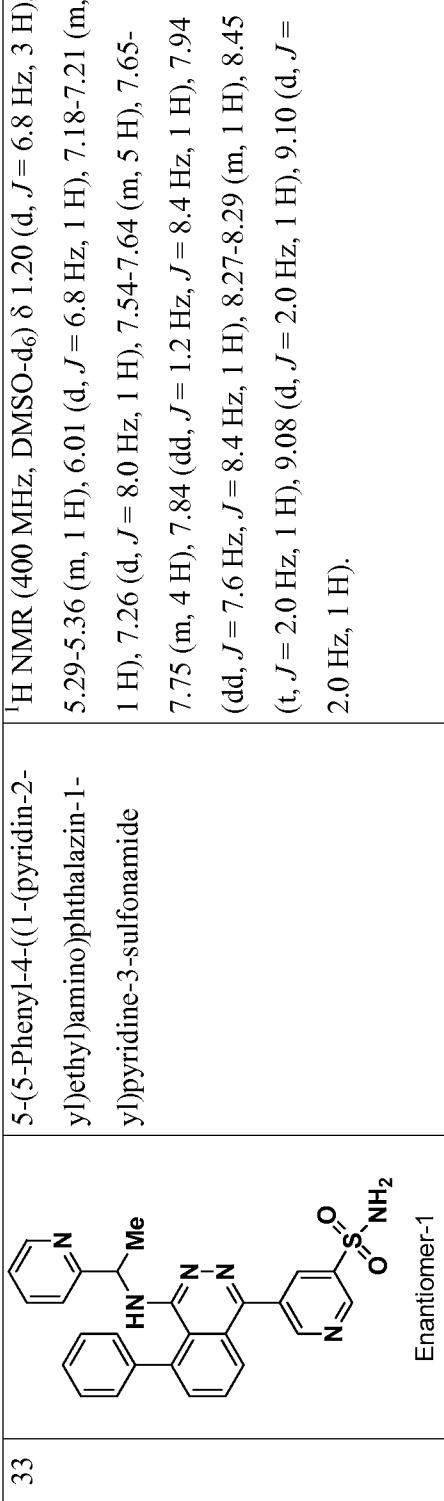
23	 <p>5-(4-(Benzylamino)-5-phenylphthalazin-1-yl)nicotinamide</p>	^1H NMR (400 MHz, DMSO-d ₆) δ 4.51 (d, <i>J</i> = 4.8 Hz, 2 H), 5.09 (t, <i>J</i> = 4.8 Hz, 1 H), 7.02 (dd, <i>J</i> = 2.0 Hz, <i>J</i> = 8.0 Hz, 2 H), 7.22-7.28 (m, 3 H), 7.43-7.51 (m, 5 H), 7.70-7.72 (m, 2 H), 7.85 (dd, <i>J</i> = 1.6 Hz, <i>J</i> = 8.4 Hz, 1 H), 7.92 (dd, <i>J</i> = 7.2 Hz, <i>J</i> = 8.4 Hz, 1 H), 8.29 (br s, 1 H), 8.49 (t, <i>J</i> = 2.0 Hz, 1 H), 8.98 (d, <i>J</i> = 2.0 Hz, 1 H), 9.18 (d, <i>J</i> = 2.0 Hz, 1 H).	<i>Condition 34</i> 2.05 432.0
24	 <p>Ethyl 5-(4-(benzylamino)-5-phenylphthalazin-1-yl)nicotinate</p>	^1H NMR (400 MHz, DMSO-d ₆) δ 1.37 (t, <i>J</i> = 7.2 Hz, 3 H), 4.40 (q, <i>J</i> = 7.2 Hz, 2 H), 4.51 (d, <i>J</i> = 5.2 Hz, 2 H), 5.11 (t, <i>J</i> = 5.2 Hz, 1 H), 7.03 (dd, <i>J</i> = 2.0 Hz, <i>J</i> = 8.0 Hz, 2 H), 7.22-7.29 (m, 3 H), 7.43-7.50 (m, 5 H), 7.71 (dd, <i>J</i> = 1.6 Hz, <i>J</i> = 7.2 Hz, 1 H), 7.85 (dd, <i>J</i> = 1.2 Hz, <i>J</i> = 8.4 Hz, 1 H), 7.92 (dd, <i>J</i> = 7.6 Hz, <i>J</i> = 8.0 Hz, 1 H), 8.51 (t, <i>J</i> = 2.0 Hz, 1 H), 9.10 (d, <i>J</i> = 2.0 Hz, 1 H), 9.24 (d, <i>J</i> = 2.0 Hz, 1 H).	<i>Condition 34</i> 2.36 461.0

 <p>25</p>	<p>4-(4-(Benzylamino)-5-phenylphthalazin-1-yl)pyridin-2-ol</p> <p>¹H NMR (400 MHz, DMSO-d₆) δ 4.49 (d, <i>J</i> = 4.8 Hz, 2 H), 5.07 (t, <i>J</i> = 4.8 Hz, 1 H), 6.42 (dd, <i>J</i> = 1.2 Hz, 1 H), 6.52 (d, <i>J</i> = 1.2 Hz, 1 H), 6.99-7.09 (m, 2 H), 7.20-7.28 (m, 3 H), 7.40-7.48 (m, 5 H), 7.54 (d, <i>J</i> = 6.8 Hz, 1 H), 7.68 (dd, <i>J</i> = 2.0 Hz, <i>J</i> = 6.8 Hz, 1 H), 7.88-7.97 (m, 2 H), 11.80 (br s, 1 H).</p>	<p>¹H NMR (400 MHz, DMSO-d₆) δ 4.49 (d, <i>J</i> = 4.8 Hz, 2 H), 5.07 (t, <i>J</i> = 4.8 Hz, 1 H), 6.42 (dd, <i>J</i> = 1.2 Hz, 1 H), 6.52 (d, <i>J</i> = 1.2 Hz, 1 H), 6.99-7.09 (m, 2 H), 7.20-7.28 (m, 3 H), 7.40-7.48 (m, 5 H), 7.54 (d, <i>J</i> = 6.8 Hz, 1 H), 7.68 (dd, <i>J</i> = 2.0 Hz, <i>J</i> = 6.8 Hz, 1 H), 7.88-7.97 (m, 2 H), 11.80 (br s, 1 H).</p> <p>Condition 34</p> <p>405.0</p>
 <p>26</p>	<p>N-Benzyl-4-(2-methoxy-5-phenylpyrimidin-4-yl)-8-phenylphthalazin-1-amine</p>	<p>¹H NMR (400 MHz, DMSO-d₆) δ 4.05 (s, 3 H), 4.51 (d, <i>J</i> = 4.8 Hz, 2 H), 5.07 (t, <i>J</i> = 4.8 Hz, 1 H), 7.03 (dd, <i>J</i> = 2.0 Hz, <i>J</i> = 8.0 Hz, 2 H), 7.21-7.28 (m, 3 H), 7.44-7.51 (m, 5 H), 7.71 (dd, <i>J</i> = 2.8 Hz, <i>J</i> = 6.0 Hz, 1 H), 7.90-7.93 (m, 2 H), 8.92 (s, 2 H).</p> <p>Condition 4</p> <p>420.0</p>

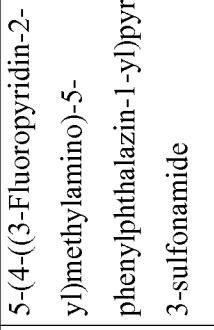
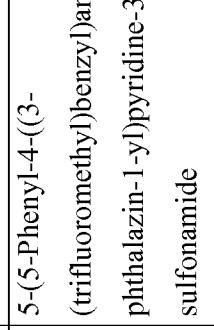
27		¹ H NMR (400 MHz, DMSO-d ₆) δ 4.51 (d, <i>J</i> = 4.8 Hz, 2 H), 4.86 (q, <i>J</i> = 9.2 Hz, 2 H), 5.06 (t, <i>J</i> = 4.8 Hz, 1 H), 7.03 (dd, <i>J</i> = 1.6 Hz, <i>J</i> = 7.6 Hz, 2 H), 7.21-7.30 (m, 3 H), 7.43-7.51 (m, 5 H), 7.69 (dd, <i>J</i> = 1.6 Hz, <i>J</i> = 6.8 Hz, 1 H), 7.85-7.93 (m, 2 H), 8.17 (br s, 1 H), 8.54 (d, <i>J</i> = 1.6 Hz, 1 H), 8.82 (d, <i>J</i> = 2.4 Hz, 1 H), 10.59 (br s, 1 H).	¹ H NMR (400 MHz, DMSO-d ₆) δ 4.54 (d, <i>J</i> = 4.8 Hz, 2 H), 5.06 (t, <i>J</i> = 4.8 Hz, 1 H), 7.10 (dd, <i>J</i> = 2.0 Hz, <i>J</i> = 7.6 Hz, 2 H), 7.23-7.33 (m, 5 H), 7.51-7.58 (m, 2 H), 7.71-7.75 (m, 3 H), 7.85 (dd, <i>J</i> = 2.0 Hz, <i>J</i> = 8.4 Hz, 1 H), 7.94 (dd, <i>J</i> = 7.2 Hz, <i>J</i> = 8.0 Hz, 1 H), 8.46 (t, <i>J</i> = 2.0 Hz, 1 H), 9.08 (d, <i>J</i> = 2.0 Hz, 1 H), 9.12 (d, <i>J</i> = 2.0 Hz, 1 H).	<i>Condition 37</i> 530.0
28				<i>Condition 37</i> 486.0

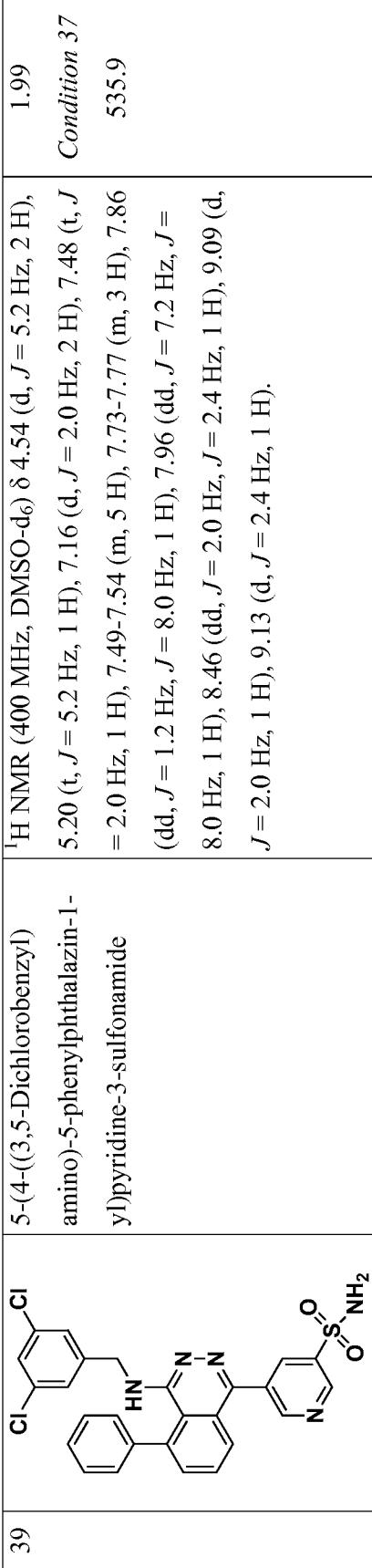
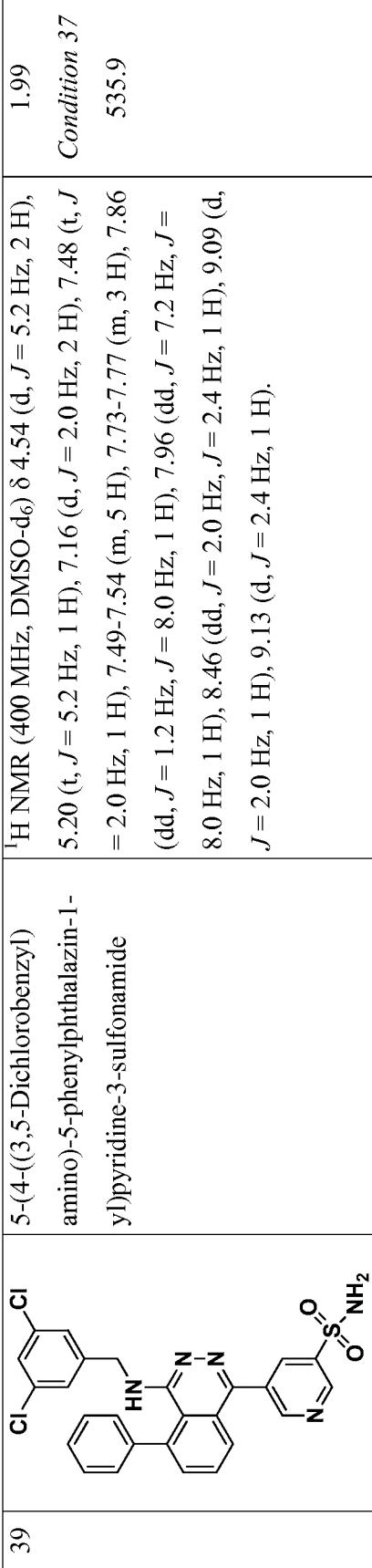
29	 <p>5-(5-Phenyl-4-((pyrimidin-2-ylmethyl)amino)phthalazin-1-yl)pyridine-3-sulfonamide</p>	<p>¹H NMR (400 MHz, DMSO-d₆) δ 4.73 (d, <i>J</i> = 4.0 Hz, 2 H), 6.46 (t, <i>J</i> = 4.0 Hz, 1 H), 7.38 (t, <i>J</i> = 4.8 Hz, 1 H), 7.52-7.63 (m, 5 H), 7.72-7.75 (m, 3 H), 7.86 (dd, <i>J</i> = 1.2 Hz, <i>J</i> = 8.0 Hz, 1 H), 7.95 (dd, <i>J</i> = 7.2 Hz, <i>J</i> = 8.4 Hz, 1 H), 8.48 (t, <i>J</i> = 2.0 Hz, 1 H), 8.60 (d, <i>J</i> = 4.8 Hz, 2 H), 9.10 (d, <i>J</i> = 2.0 Hz, 1 H), 9.12 (d, <i>J</i> = 2.0 Hz, 1 H).</p>	<p>Condition 38 470.0</p>
30	 <p>3-Methyl-N-(5-(5-phenyl-4-((pyrimidin-2-ylmethyl)amino)phthalazin-1-yl)pyridin-3-yl)butanamide</p>	<p>¹H NMR (400 MHz, DMSO-d₆) δ 0.97 (d, <i>J</i> = 6.4 Hz, 6 H), 2.08-2.15 (m, 1 H), 2.28 (d, <i>J</i> = 7.2 Hz, 2 H), 4.65 (d, <i>J</i> = 4.0 Hz, 2 H), 6.27 (t, <i>J</i> = 4.0 Hz, 1 H), 7.22 (dd, <i>J</i> = 5.6 Hz, <i>J</i> = 7.2 Hz, 1 H), 7.27 (d, <i>J</i> = 8.0 Hz, 1 H), 7.51-7.58 (m, 5 H), 7.67-7.72 (m, 2 H), 7.85-7.93 (m, 2 H), 8.23 (d, <i>J</i> = 4.0 Hz, 1 H), 8.37 (dd, <i>J</i> = 2.0 Hz, <i>J</i> = 2.4 Hz, 1 H), 8.52 (d, <i>J</i> = 2.0 Hz, 1 H), 8.87 (d, <i>J</i> = 2.4 Hz, 1 H), 10.27 (s, 1 H).</p>	<p>Condition 37 489.2</p>

31	 <p>5-((2-Fluorobenzyl)amino)-5-phenylphthalazin-1-ylpyridine-3-sulfonamide</p>	^1H NMR (400 MHz, DMSO-d ₆) δ 4.56 (d, <i>J</i> = 5.2 Hz, 2 H), 5.08 (t, <i>J</i> = 5.2 Hz, 1 H), 7.07-7.16 (m, 3 H), 7.27-7.33 (m, 1 H), 7.42-7.48 (m, 5 H), 7.72-7.74 (m, 3 H), 7.85 (dd, <i>J</i> = 1.6 Hz, <i>J</i> = 8.4 Hz, 1 H), 7.94 (dd, <i>J</i> = 7.2 Hz, <i>J</i> = 8.4 Hz, 1 H), 8.46 (t, <i>J</i> = 2.0 Hz, 1 H), 9.08 (d, <i>J</i> = 2.0 Hz, 1 H), 9.12 (d, <i>J</i> = 2.0 Hz, 1 H).	<i>Condition 37</i> 486.0	1.74
32	 <p>5-((3-Fluorobenzyl)amino)-5-phenylphthalazin-1-ylpyridine-3-sulfonamide</p>	^1H NMR (400 MHz, DMSO-d ₆) δ 4.54 (d, <i>J</i> = 4.8 Hz, 2 H), 5.15 (t, <i>J</i> = 4.8 Hz, 1 H), 6.85-6.88 (m, 1 H), 6.91 (d, <i>J</i> = 7.6 Hz, 1 H), 7.05 (td, <i>J</i> = 2.0 Hz, <i>J</i> = 8.4 Hz, 1 H), 7.30 (td, <i>J</i> = 6.0 Hz, <i>J</i> = 8.0 Hz, 1 H), 7.44-7.53 (m, 5 H), 7.73-7.75 (m, 3 H), 7.85 (dd, <i>J</i> = 1.2 Hz, <i>J</i> = 8.4 Hz, 1 H), 7.95 (dd, <i>J</i> = 7.2 Hz, <i>J</i> = 8.0 Hz, 1 H), 8.46 (t, <i>J</i> = 2.0 Hz, 1 H), 9.08 (d, <i>J</i> = 2.0 Hz, 1 H), 9.12 (d, <i>J</i> = 2.0 Hz, 1 H).	<i>Condition 37</i> 486.0	1.70

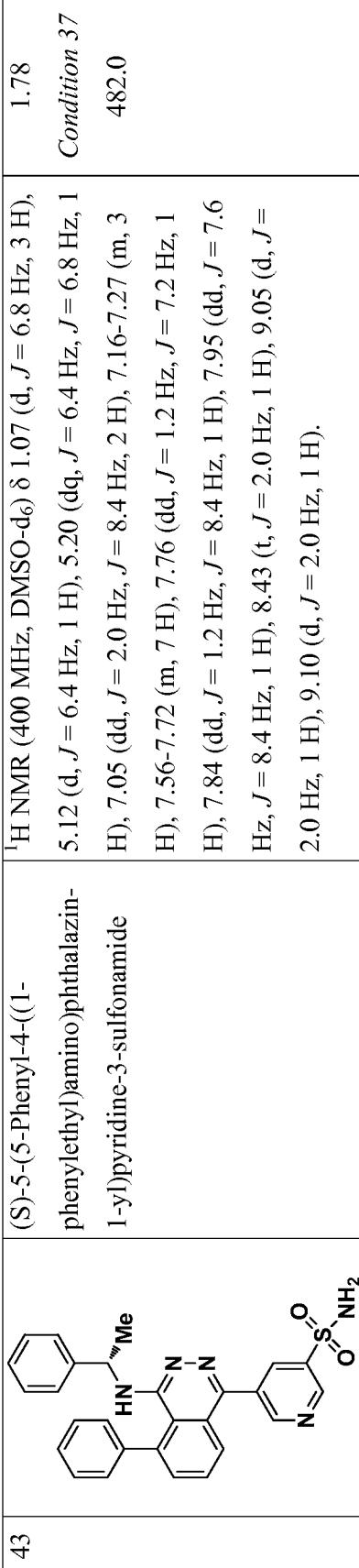
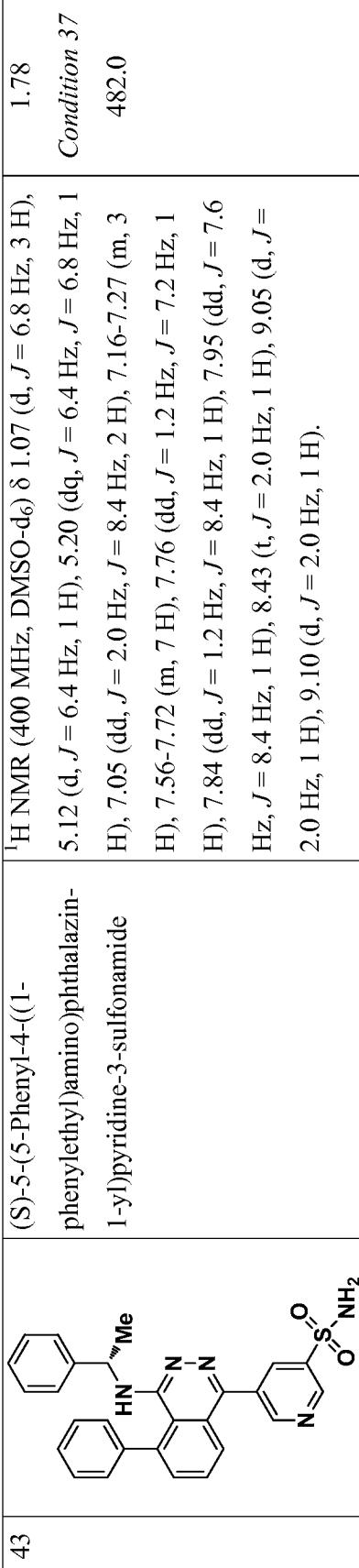
<p>33</p>  <p>Enantiomer-1</p> <p>¹H NMR (400 MHz, DMSO-d₆) δ 1.20 (d, <i>J</i> = 6.8 Hz, 3 H), 5.29-5.36 (m, 1 H), 6.01 (d, <i>J</i> = 6.8 Hz, 1 H), 7.18-7.21 (m, 1 H), 7.26 (d, <i>J</i> = 8.0 Hz, 1 H), 7.54-7.64 (m, 5 H), 7.65-7.75 (m, 4 H), 7.84 (dd, <i>J</i> = 1.2 Hz, <i>J</i> = 8.4 Hz, 1 H), 7.94 (dd, <i>J</i> = 7.6 Hz, <i>J</i> = 8.4 Hz, 1 H), 8.27-8.29 (m, 1 H), 8.45 (t, <i>J</i> = 2.0 Hz, 1 H), 9.08 (d, <i>J</i> = 2.0 Hz, 1 H), 9.10 (d, <i>J</i> = 2.0 Hz, 1 H).</p>	<p>Condition 40 Chiral HPLC Condition 41: retention time 3.68 min, Purity 100%</p>
<p>34</p>  <p>Enantiomer-2</p> <p>¹H NMR (400 MHz, DMSO-d₆) δ 1.20 (d, <i>J</i> = 6.8 Hz, 3 H), 5.29-5.36 (m, 1 H), 6.01 (d, <i>J</i> = 6.8 Hz, 1 H), 7.18-7.21 (m, 1 H), 7.26 (d, <i>J</i> = 8.0 Hz, 1 H), 7.54-7.64 (m, 5 H), 7.65-7.75 (m, 4 H), 7.84 (dd, <i>J</i> = 1.2 Hz, <i>J</i> = 8.4 Hz, 1 H), 7.94 (dd, <i>J</i> = 7.6 Hz, <i>J</i> = 8.4 Hz, 1 H), 8.27-8.29 (m, 1 H), 8.45 (t, <i>J</i> = 2.0 Hz, 1 H), 9.08 (d, <i>J</i> = 2.0 Hz, 1 H), 9.10 (d, <i>J</i> = 2.0 Hz, 1 H).</p>	<p>Condition 40 Chiral HPLC Condition 41: retention time 4.43 min, Purity 99.38%</p>

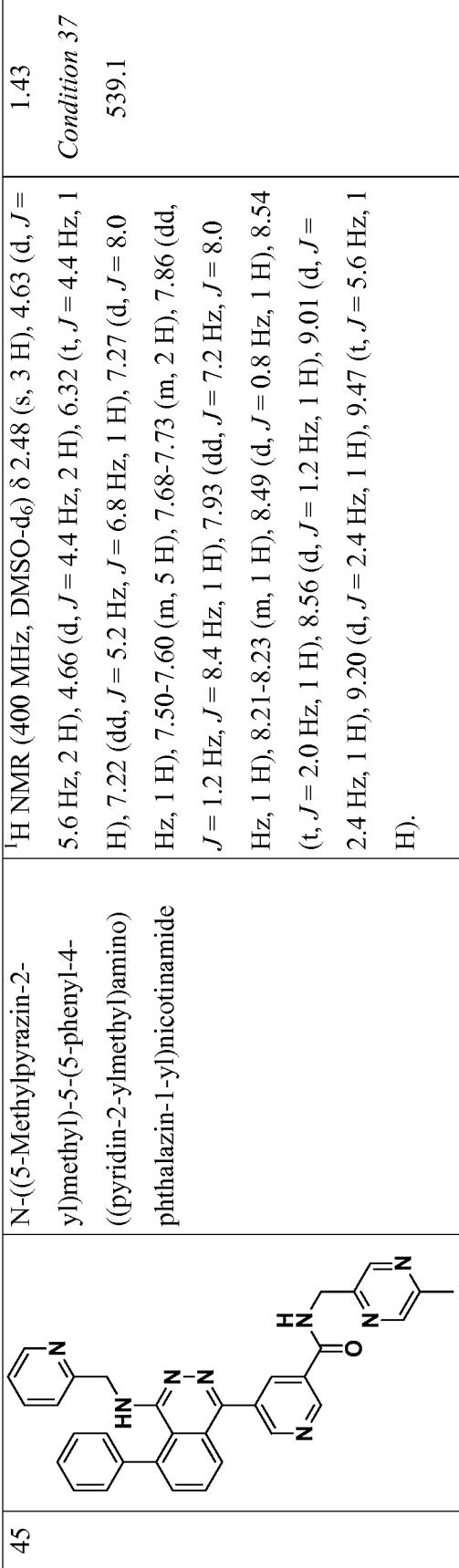
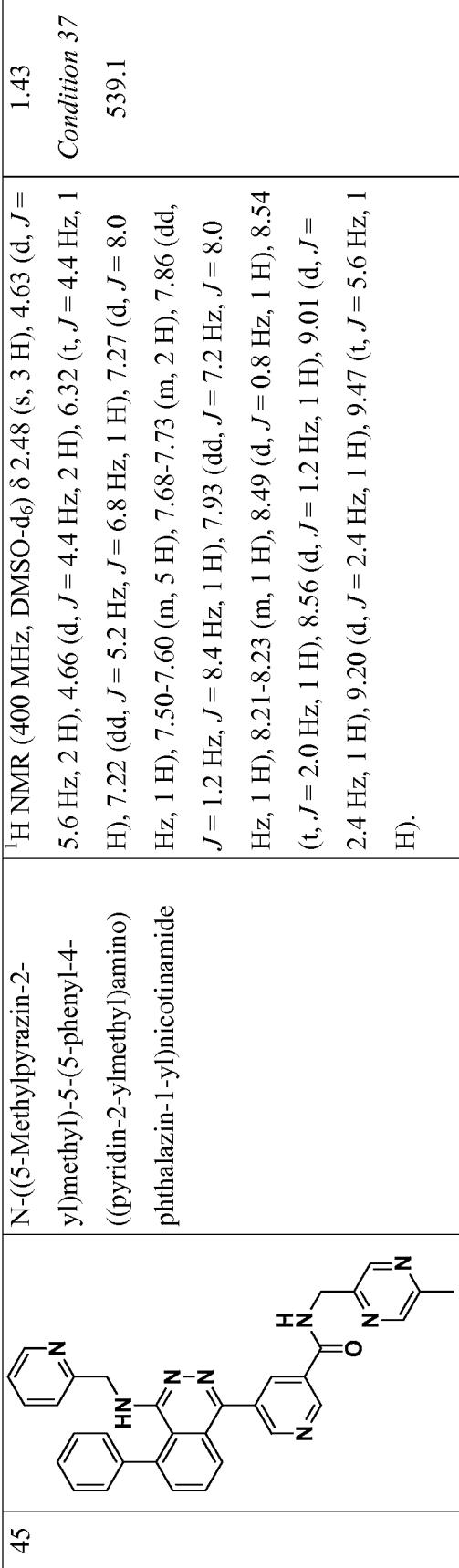
35	<p>5-(5-Phenyl-4-((2-(pyridin-2-yl)propan-2-yl)amino)phthalazin-1-yl)pyridine-3-sulfonamide</p>	<p>¹H NMR (400 MHz, DMSO-d₆) δ 1.45 (s, 6 H), 5.78 (s, 1 H), 7.14 (ddd, <i>J</i> = 0.8 Hz, <i>J</i> = 4.8 Hz, <i>J</i> = 6.0 Hz, 1 H), 7.34 (d, <i>J</i> = 8.0 Hz, 1 H), 7.56-7.65 (m, 8 H), 7.77 (dd, <i>J</i> = 1.2 Hz, <i>J</i> = 7.2 Hz, 1 H), 7.84 (dd, <i>J</i> = 1.2 Hz, <i>J</i> = 8.4 Hz, 1 H), 7.94 (dd, <i>J</i> = 7.2 Hz, <i>J</i> = 8.4 Hz, 1 H), 8.34-8.36 (m, 1 H), 8.41 (t, <i>J</i> = 2.0 Hz, 1 H), 9.04 (d, <i>J</i> = 2.0 Hz, 1 H), 9.07 (d, <i>J</i> = 2.0 Hz, 1 H).</p>	<p>Condition 37</p> <p>497.0</p> <p>1.64</p>
36	<p>5-(4-((2,6-Difluorobenzyl)amino)-5-phenylphthalazin-1-yl)pyridine-3-sulfonamide</p>	<p>¹H NMR (400 MHz, DMSO-d₆) δ 4.58 (d, <i>J</i> = 4.8 Hz, 2 H), 4.84 (t, <i>J</i> = 4.8 Hz, 1 H), 7.04 (t, <i>J</i> = 8.0 Hz, 2 H), 7.35-7.41 (m, 6 H), 7.70-7.73 (m, 3 H), 7.84 (dd, <i>J</i> = 1.2 Hz, <i>J</i> = 8.4 Hz, 1 H), 7.94 (dd, <i>J</i> = 7.2 Hz, <i>J</i> = 8.4 Hz, 1 H), 8.47 (t, <i>J</i> = 2.0 Hz, 1 H), 9.09 (d, <i>J</i> = 2.0 Hz, 1 H), 9.13 (d, <i>J</i> = 2.0 Hz, 1 H).</p>	<p>Condition 37</p> <p>504.0</p> <p>1.68</p>

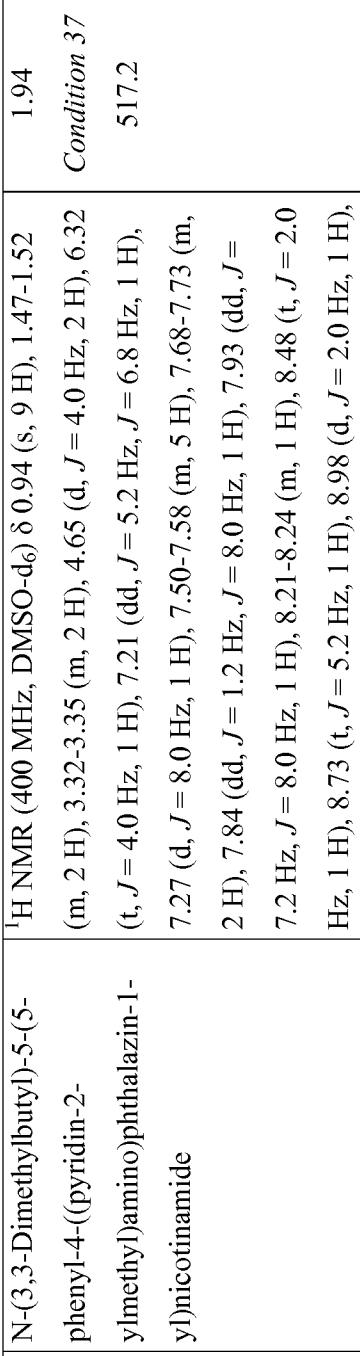
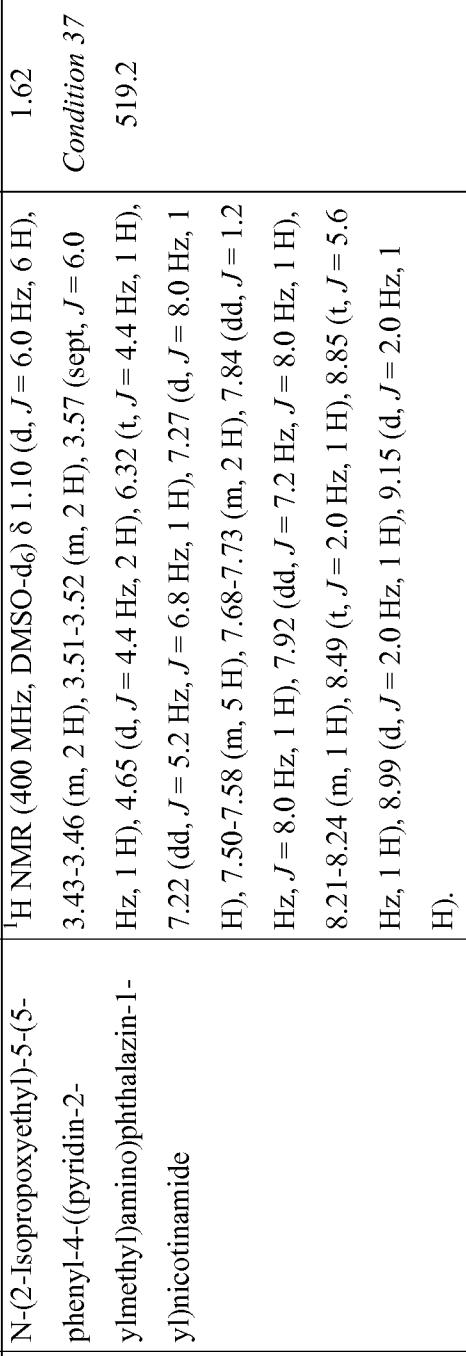
37	 <p>5-((3-Fluoropyridin-2-yl)methylamino)-5-phenylphthalazin-1-yl)pyridine-3-sulfonamide</p>	<p>¹H NMR (400 MHz, DMSO-d₆) δ 4.72 (br d, <i>J</i> = 2.4 Hz, 2 H), 6.49 (t, <i>J</i> = 4.8 Hz, 1 H), 7.36-7.39 (m, 1 H), 7.50-7.74 (m, 9 H), 7.86 (dd, <i>J</i> = 1.2 Hz, 1 H), 7.95 (dd, <i>J</i> = 7.2 Hz, <i>J</i> = 8.4 Hz, 1 H), 8.05-8.06 (m, 1 H), 8.48 (t, <i>J</i> = 2.0 Hz, 1 H), 9.10 (d, <i>J</i> = 2.0 Hz, 1 H), 9.13 (d, <i>J</i> = 2.0 Hz, 1 H).</p>	<p>Condition 37 487.0</p>
38	 <p>5-(5-Phenyl-4-((3-(trifluoromethyl)benzyl)amino)phthalazin-1-yl)pyridine-3-sulfonamide</p>	<p>¹H NMR (400 MHz, DMSO-d₆) δ 4.62 (d, <i>J</i> = 5.2 Hz, 2 H), 5.20 (t, <i>J</i> = 5.2 Hz, 1 H), 7.40-7.54 (m, 8 H), 7.62 (d, <i>J</i> = 8.0 Hz, 1 H), 7.73-7.76 (m, 3 H), 7.86 (dd, <i>J</i> = 1.2 Hz, <i>J</i> = 8.4 Hz, 1 H), 7.96 (dd, <i>J</i> = 7.2 Hz, <i>J</i> = 8.0 Hz, 1 H), 8.46 (t, <i>J</i> = 2.0 Hz, 1 H), 9.09 (d, <i>J</i> = 2.0 Hz, 1 H), 9.12 (d, <i>J</i> = 2.0 Hz, 1 H).</p>	<p>Condition 37 536.0</p>

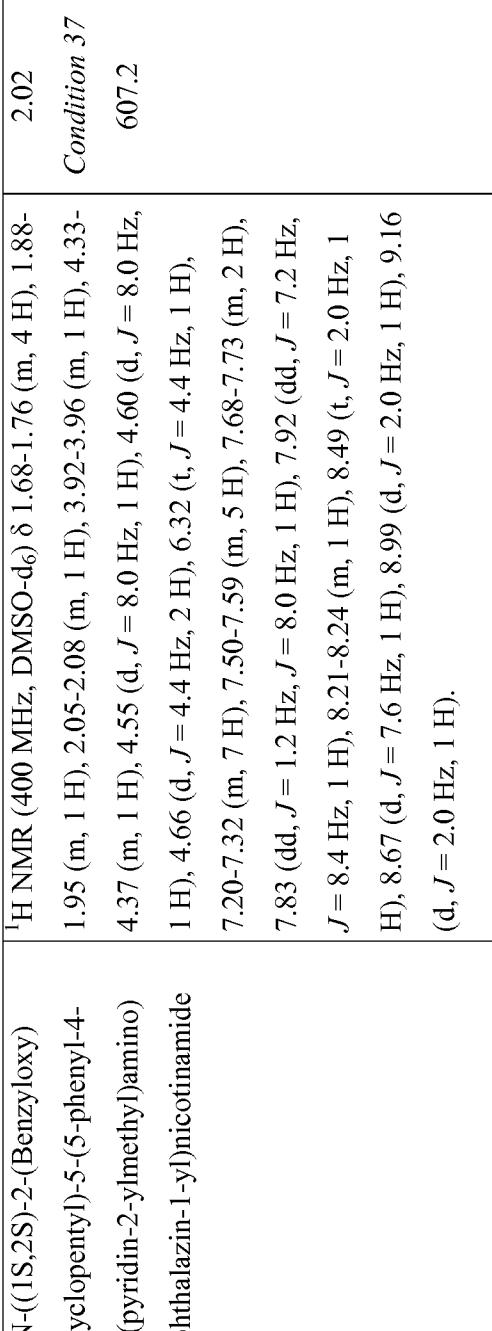
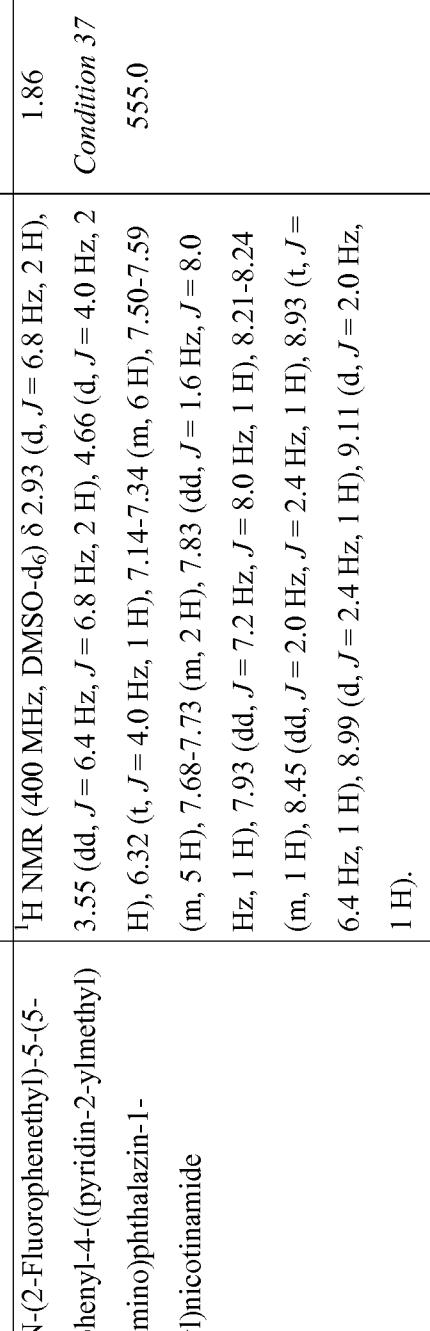
39	 <p>5-((3,5-Dichlorobenzyl)amino)-5-phenylphthalazin-1-yl)pyridine-3-sulfonamide</p> <p>¹H NMR (400 MHz, DMSO-d₆) δ 4.54 (d, <i>J</i> = 5.2 Hz, 2 H), 5.20 (t, <i>J</i> = 5.2 Hz, 1 H), 7.16 (d, <i>J</i> = 2.0 Hz, 2 H), 7.48 (t, <i>J</i> = 2.0 Hz, 1 H), 7.49-7.54 (m, 5 H), 7.73-7.77 (m, 3 H), 7.86 (dd, <i>J</i> = 1.2 Hz, <i>J</i> = 8.0 Hz, 1 H), 7.96 (dd, <i>J</i> = 7.2 Hz, <i>J</i> = 8.0 Hz, 1 H), 8.46 (dd, <i>J</i> = 2.0 Hz, <i>J</i> = 2.4 Hz, 1 H), 9.09 (d, <i>J</i> = 2.0 Hz, 1 H), 9.13 (d, <i>J</i> = 2.4 Hz, 1 H).</p>	¹ H NMR (400 MHz, DMSO-d ₆) δ 4.58 (d, <i>J</i> = 5.2 Hz, 2 H), 5.19 (t, <i>J</i> = 5.2 Hz, 1 H), 7.06 (br s, 1 H), 7.13 (d, <i>J</i> = 7.6 Hz, 1 H), 7.20-7.25 (m, 1 H), 7.39-7.53 (m, 6 H), 7.73-7.76 (m, 3 H), 7.86 (dd, <i>J</i> = 1.2 Hz, <i>J</i> = 8.4 Hz, 1 H), 7.96 (dd, <i>J</i> = 7.2 Hz, <i>J</i> = 8.4 Hz, 1 H), 8.46 (dd, <i>J</i> = 2.0 Hz, <i>J</i> = 2.4 Hz, 1 H), 9.09 (d, <i>J</i> = 2.0 Hz, 1 H), 9.13 (d, <i>J</i> = 2.4 Hz, 1 H).
40	 <p>5-(5-Phenyl-4-((3-(trifluoromethoxy)benzyl)amino)phthalazin-1-yl)pyridine-3-sulfonamide</p>	¹ H NMR (400 MHz, DMSO-d ₆) δ 4.58 (d, <i>J</i> = 5.2 Hz, 2 H), 5.19 (t, <i>J</i> = 5.2 Hz, 1 H), 7.06 (br s, 1 H), 7.13 (d, <i>J</i> = 7.6 Hz, 1 H), 7.20-7.25 (m, 1 H), 7.39-7.53 (m, 6 H), 7.73-7.76 (m, 3 H), 7.86 (dd, <i>J</i> = 1.2 Hz, <i>J</i> = 8.4 Hz, 1 H), 7.96 (dd, <i>J</i> = 7.2 Hz, <i>J</i> = 8.4 Hz, 1 H), 8.46 (dd, <i>J</i> = 2.0 Hz, <i>J</i> = 2.4 Hz, 1 H), 9.09 (d, <i>J</i> = 2.0 Hz, 1 H), 9.13 (d, <i>J</i> = 2.4 Hz, 1 H).

41	<p>¹H NMR (400 MHz, DMSO-d₆) δ 3.30-3.41 (m, 1 H), 3.66-3.71 (m, 1 H), 4.55-4.59 (m, 1 H), 5.26 (t, <i>J</i> = 5.2 Hz, 1 H), 5.32 (d, <i>J</i> = 4.4 Hz, 1 H), 7.17-7.25 (m, 5 H), 7.28-7.55 (m, 5 H), 7.68 (dd, <i>J</i> = 1.2 Hz, <i>J</i> = 7.2 Hz, 1 H), 7.73 (br s, 2 H), 7.83 (dd, <i>J</i> = 1.2 Hz, <i>J</i> = 8.4 Hz, 1 H), 7.92 (dd, <i>J</i> = 7.2 Hz, <i>J</i> = 8.0 Hz, 1 H), 8.46 (t, <i>J</i> = 2.0 Hz, 1 H), 9.08 (d, <i>J</i> = 2.0 Hz, 1 H), 9.12 (d, <i>J</i> = 2.0 Hz, 1 H).</p>	¹ H NMR (400 MHz, DMSO-d ₆) δ 3.30-3.41 (m, 1 H), 3.66-3.71 (m, 1 H), 4.55-4.59 (m, 1 H), 5.26 (t, <i>J</i> = 5.2 Hz, 1 H), 5.32 (d, <i>J</i> = 4.4 Hz, 1 H), 7.17-7.25 (m, 5 H), 7.28-7.55 (m, 5 H), 7.68 (dd, <i>J</i> = 1.2 Hz, <i>J</i> = 7.2 Hz, 1 H), 7.73 (br s, 2 H), 7.83 (dd, <i>J</i> = 1.2 Hz, <i>J</i> = 8.4 Hz, 1 H), 7.92 (dd, <i>J</i> = 7.2 Hz, <i>J</i> = 8.0 Hz, 1 H), 8.46 (t, <i>J</i> = 2.0 Hz, 1 H), 9.08 (d, <i>J</i> = 2.0 Hz, 1 H), 9.12 (d, <i>J</i> = 2.0 Hz, 1 H).	Condition 37 498.0
42	<p>¹H NMR (400 MHz, DMSO-d₆) δ 1.07 (d, <i>J</i> = 6.8 Hz, 3 H), 5.12 (d, <i>J</i> = 6.4 Hz, 1 H), 5.20 (dq, <i>J</i> = 6.4 Hz, <i>J</i> = 6.8 Hz, 1 H), 7.05 (dd, <i>J</i> = 2.0 Hz, 2 H), 7.16-7.27 (m, 3 H), 7.56-7.72 (m, 7 H), 7.76 (dd, <i>J</i> = 1.2 Hz, <i>J</i> = 7.2 Hz, 1 H), 7.84 (dd, <i>J</i> = 1.2 Hz, <i>J</i> = 8.4 Hz, 1 H), 7.95 (dd, <i>J</i> = 7.6 Hz, <i>J</i> = 8.4 Hz, 1 H), 8.43 (t, <i>J</i> = 2.0 Hz, 1 H), 9.05 (d, <i>J</i> = 2.0 Hz, 1 H), 9.10 (d, <i>J</i> = 2.0 Hz, 1 H).</p>	¹ H NMR (400 MHz, DMSO-d ₆) δ 1.07 (d, <i>J</i> = 6.8 Hz, 3 H), 5.12 (d, <i>J</i> = 6.4 Hz, 1 H), 5.20 (dq, <i>J</i> = 6.4 Hz, <i>J</i> = 6.8 Hz, 1 H), 7.05 (dd, <i>J</i> = 2.0 Hz, 2 H), 7.16-7.27 (m, 3 H), 7.56-7.72 (m, 7 H), 7.76 (dd, <i>J</i> = 1.2 Hz, <i>J</i> = 7.2 Hz, 1 H), 7.84 (dd, <i>J</i> = 1.2 Hz, <i>J</i> = 8.4 Hz, 1 H), 7.95 (dd, <i>J</i> = 7.6 Hz, <i>J</i> = 8.4 Hz, 1 H), 8.43 (t, <i>J</i> = 2.0 Hz, 1 H), 9.05 (d, <i>J</i> = 2.0 Hz, 1 H), 9.10 (d, <i>J</i> = 2.0 Hz, 1 H).	Condition 37 482.0

43	 <p>(S)-5-(5-Phenyl-4-((1-phenylethyl)amino)phthalazin-1-yl)pyridine-3-sulfonamide</p> <p>¹H NMR (400 MHz, DMSO-d₆) δ 1.07 (d, <i>J</i> = 6.8 Hz, 3 H), 5.12 (d, <i>J</i> = 6.4 Hz, 1 H), 5.20 (dq, <i>J</i> = 6.4 Hz, <i>J</i> = 6.8 Hz, 1 H), 7.05 (dd, <i>J</i> = 2.0 Hz, <i>J</i> = 8.4 Hz, 2 H), 7.16-7.27 (m, 3 H), 7.56-7.72 (m, 7 H), 7.76 (dd, <i>J</i> = 1.2 Hz, <i>J</i> = 7.2 Hz, 1 H), 7.84 (dd, <i>J</i> = 1.2 Hz, <i>J</i> = 8.4 Hz, 1 H), 7.95 (dd, <i>J</i> = 7.6 Hz, <i>J</i> = 8.4 Hz, 1 H), 8.43 (t, <i>J</i> = 2.0 Hz, 1 H), 9.05 (d, <i>J</i> = 2.0 Hz, 1 H), 9.10 (d, <i>J</i> = 2.0 Hz, 1 H).</p>	¹ H NMR (400 MHz, DMSO-d ₆) δ 1.07 (d, <i>J</i> = 6.8 Hz, 3 H), 5.12 (d, <i>J</i> = 6.4 Hz, 1 H), 5.20 (dq, <i>J</i> = 6.4 Hz, <i>J</i> = 6.8 Hz, 1 H), 7.05 (dd, <i>J</i> = 2.0 Hz, <i>J</i> = 8.4 Hz, 2 H), 7.16-7.27 (m, 3 H), 7.56-7.72 (m, 7 H), 7.76 (dd, <i>J</i> = 1.2 Hz, <i>J</i> = 7.2 Hz, 1 H), 7.84 (dd, <i>J</i> = 1.2 Hz, <i>J</i> = 8.4 Hz, 1 H), 7.95 (dd, <i>J</i> = 7.6 Hz, <i>J</i> = 8.4 Hz, 1 H), 8.43 (t, <i>J</i> = 2.0 Hz, 1 H), 9.05 (d, <i>J</i> = 2.0 Hz, 1 H), 9.10 (d, <i>J</i> = 2.0 Hz, 1 H).
44	 <p>5-(5-Phenyl-4-((2-((4-(trifluoromethoxy)benzyl)amino)benzyl)amino)phthalazin-1-yl)-N-(4-(trifluoromethoxy)benzyl)nicotinamide</p>	¹ H NMR (400 MHz, DMSO-d ₆) δ 4.57 (d, <i>J</i> = 6.0 Hz, 2 H), 4.66 (d, <i>J</i> = 4.4 Hz, 2 H), 6.32 (t, <i>J</i> = 4.4 Hz, 1 H), 7.22 (dd, <i>J</i> = 5.2 Hz, <i>J</i> = 6.8 Hz, 1 H), 7.27 (d, <i>J</i> = 7.6 Hz, 1 H), 7.34 (d, <i>J</i> = 7.6 Hz, 2 H), 7.48-7.60 (m, 7 H), 7.68-7.73 (m, 2 H), 7.85 (dd, <i>J</i> = 1.6 Hz, <i>J</i> = 8.4 Hz, 1 H), 7.92 (dd, <i>J</i> = 7.2 Hz, <i>J</i> = 8.4 Hz, 1 H), 8.20-8.23 (m, 1 H), 8.54 (t, <i>J</i> = 2.0 Hz, 1 H), 9.01 (d, <i>J</i> = 2.0 Hz, 1 H), 9.21 (d, <i>J</i> = 2.0 Hz, 1 H), 9.41 (t, <i>J</i> = 6.0 Hz, 1 H).

45	<p>N-((5-Methylpyrazin-2-yl)methyl)-5-(5-phenyl-4-((pyridin-2-ylmethyl)amino)phthalazin-1-yl)nicotinamide</p>  <p>¹H NMR (400 MHz, DMSO-d₆) δ 2.48 (s, 3 H), 4.63 (d, <i>J</i> = 5.6 Hz, 2 H), 4.66 (d, <i>J</i> = 4.4 Hz, 2 H), 6.32 (t, <i>J</i> = 4.4 Hz, 1 H), 7.22 (dd, <i>J</i> = 5.2 Hz, <i>J</i> = 6.8 Hz, 1 H), 7.27 (d, <i>J</i> = 8.0 Hz, 1 H), 7.50-7.60 (m, 5 H), 7.68-7.73 (m, 2 H), 7.86 (dd, <i>J</i> = 1.2 Hz, <i>J</i> = 8.4 Hz, 1 H), 7.93 (dd, <i>J</i> = 7.2 Hz, <i>J</i> = 8.0 Hz, 1 H), 8.21-8.23 (m, 1 H), 8.49 (d, <i>J</i> = 0.8 Hz, 1 H), 8.54 (t, <i>J</i> = 2.0 Hz, 1 H), 8.56 (d, <i>J</i> = 1.2 Hz, 1 H), 9.01 (d, <i>J</i> = 2.4 Hz, 1 H), 9.20 (d, <i>J</i> = 2.4 Hz, 1 H), 9.47 (t, <i>J</i> = 5.6 Hz, 1 H).</p>	<p>¹H NMR (400 MHz, DMSO-d₆) δ 3.28 (s, 3 H), 3.47-3.50 (m, 4 H), 4.65 (d, <i>J</i> = 4.4 Hz, 2 H), 6.32 (t, <i>J</i> = 4.4 Hz, 1 H), 7.21 (dd, <i>J</i> = 5.2 Hz, <i>J</i> = 6.8 Hz, 1 H), 7.27 (d, <i>J</i> = 7.6 Hz, 1 H), 7.50-7.60 (m, 5 H), 7.68-7.73 (m, 2 H), 7.84 (dd, <i>J</i> = 1.2 Hz, <i>J</i> = 8.4 Hz, 1 H), 7.93 (dd, <i>J</i> = 7.2 Hz, <i>J</i> = 8.0 Hz, 1 H), 8.21-8.23 (m, 1 H), 8.50 (t, <i>J</i> = 2.0 Hz, 1 H), 8.87 (t, <i>J</i> = 4.8 Hz, 1 H), 8.99 (d, <i>J</i> = 2.0 Hz, 1 H), 9.16 (d, <i>J</i> = 2.0 Hz, 1 H).</p>
46	<p>N-(2-Methoxyethyl)-5-(5-phenyl-4-((pyridin-2-ylmethyl)amino)phthalazin-1-yl)nicotinamide</p> 	<p>¹H NMR (400 MHz, DMSO-d₆) δ 3.28 (s, 3 H), 3.47-3.50 (m, 4 H), 4.65 (d, <i>J</i> = 4.4 Hz, 2 H), 6.32 (t, <i>J</i> = 4.4 Hz, 1 H), 7.21 (dd, <i>J</i> = 5.2 Hz, <i>J</i> = 6.8 Hz, 1 H), 7.27 (d, <i>J</i> = 7.6 Hz, 1 H), 7.50-7.60 (m, 5 H), 7.68-7.73 (m, 2 H), 7.84 (dd, <i>J</i> = 1.2 Hz, <i>J</i> = 8.4 Hz, 1 H), 7.93 (dd, <i>J</i> = 7.2 Hz, <i>J</i> = 8.0 Hz, 1 H), 8.21-8.23 (m, 1 H), 8.50 (t, <i>J</i> = 2.0 Hz, 1 H), 8.87 (t, <i>J</i> = 4.8 Hz, 1 H), 8.99 (d, <i>J</i> = 2.0 Hz, 1 H), 9.16 (d, <i>J</i> = 2.0 Hz, 1 H).</p>

47		¹ H NMR (400 MHz, DMSO-d ₆) δ 0.94 (s, 9 H), 1.47-1.52 (m, 2 H), 3.32-3.35 (m, 2 H), 4.65 (d, <i>J</i> = 4.0 Hz, 2 H), 6.32 (t, <i>J</i> = 4.0 Hz, 1 H), 7.21 (dd, <i>J</i> = 5.2 Hz, <i>J</i> = 6.8 Hz, 1 H), 7.27 (d, <i>J</i> = 8.0 Hz, 1 H), 7.50-7.58 (m, 5 H), 7.68-7.73 (m, 2 H), 7.84 (dd, <i>J</i> = 1.2 Hz, <i>J</i> = 8.0 Hz, 1 H), 7.93 (dd, <i>J</i> = 7.2 Hz, <i>J</i> = 8.0 Hz, 1 H), 8.21-8.24 (m, 1 H), 8.48 (t, <i>J</i> = 2.0 Hz, 1 H), 8.73 (t, <i>J</i> = 5.2 Hz, 1 H), 8.98 (d, <i>J</i> = 2.0 Hz, 1 H), 9.14 (d, <i>J</i> = 2.0 Hz, 1 H).	¹ H NMR (400 MHz, DMSO-d ₆) δ 0.94 (s, 9 H), 1.47-1.52 (m, 2 H), 3.32 (t, <i>J</i> = 4.0 Hz, 2 H), 6.32 (t, <i>J</i> = 4.0 Hz, 1 H), 7.21 (dd, <i>J</i> = 5.2 Hz, <i>J</i> = 6.8 Hz, 1 H), 7.27 (d, <i>J</i> = 8.0 Hz, 1 H), 7.50-7.58 (m, 5 H), 7.68-7.73 (m, 2 H), 7.84 (dd, <i>J</i> = 1.2 Hz, <i>J</i> = 8.0 Hz, 1 H), 7.93 (dd, <i>J</i> = 7.2 Hz, <i>J</i> = 8.0 Hz, 1 H), 8.21-8.24 (m, 1 H), 8.48 (t, <i>J</i> = 2.0 Hz, 1 H), 8.73 (t, <i>J</i> = 5.2 Hz, 1 H), 8.98 (d, <i>J</i> = 2.0 Hz, 1 H), 9.14 (d, <i>J</i> = 2.0 Hz, 1 H).
48		¹ H NMR (400 MHz, DMSO-d ₆) δ 1.10 (d, <i>J</i> = 6.0 Hz, 6 H), 3.43-3.46 (m, 2 H), 3.51-3.52 (m, 2 H), 3.57 (sept, <i>J</i> = 6.0 Hz, 1 H), 4.65 (d, <i>J</i> = 4.4 Hz, 2 H), 6.32 (t, <i>J</i> = 4.4 Hz, 1 H), 7.22 (dd, <i>J</i> = 5.2 Hz, <i>J</i> = 6.8 Hz, 1 H), 7.27 (d, <i>J</i> = 8.0 Hz, 1 H), 7.50-7.58 (m, 5 H), 7.68-7.73 (m, 2 H), 7.84 (dd, <i>J</i> = 1.2 Hz, <i>J</i> = 8.0 Hz, 1 H), 7.92 (dd, <i>J</i> = 7.2 Hz, <i>J</i> = 8.0 Hz, 1 H), 8.21-8.24 (m, 1 H), 8.49 (t, <i>J</i> = 2.0 Hz, 1 H), 8.85 (t, <i>J</i> = 5.6 Hz, 1 H), 8.99 (d, <i>J</i> = 2.0 Hz, 1 H), 9.15 (d, <i>J</i> = 2.0 Hz, 1 H).	¹ H NMR (400 MHz, DMSO-d ₆) δ 1.10 (d, <i>J</i> = 6.0 Hz, 6 H), 3.43-3.46 (m, 2 H), 3.51-3.52 (m, 2 H), 3.57 (sept, <i>J</i> = 6.0 Hz, 1 H), 4.65 (d, <i>J</i> = 4.4 Hz, 2 H), 6.32 (t, <i>J</i> = 4.4 Hz, 1 H), 7.22 (dd, <i>J</i> = 5.2 Hz, <i>J</i> = 6.8 Hz, 1 H), 7.27 (d, <i>J</i> = 8.0 Hz, 1 H), 7.50-7.58 (m, 5 H), 7.68-7.73 (m, 2 H), 7.84 (dd, <i>J</i> = 1.2 Hz, <i>J</i> = 8.0 Hz, 1 H), 7.92 (dd, <i>J</i> = 7.2 Hz, <i>J</i> = 8.0 Hz, 1 H), 8.21-8.24 (m, 1 H), 8.49 (t, <i>J</i> = 2.0 Hz, 1 H), 8.85 (t, <i>J</i> = 5.6 Hz, 1 H), 8.99 (d, <i>J</i> = 2.0 Hz, 1 H), 9.15 (d, <i>J</i> = 2.0 Hz, 1 H).

49		¹ H NMR (400 MHz, DMSO-d ₆) δ 1.68-1.76 (m, 4 H), 1.88-1.95 (m, 1 H), 2.05-2.08 (m, 1 H), 3.92-3.96 (m, 1 H), 4.33-4.37 (m, 1 H), 4.55 (d, <i>J</i> = 8.0 Hz, 1 H), 4.60 (d, <i>J</i> = 8.0 Hz, 1 H), 4.66 (d, <i>J</i> = 4.4 Hz, 2 H), 6.32 (t, <i>J</i> = 4.4 Hz, 1 H), 7.20-7.32 (m, 7 H), 7.50-7.59 (m, 5 H), 7.68-7.73 (m, 2 H), 7.83 (dd, <i>J</i> = 1.2 Hz, <i>J</i> = 8.0 Hz, 1 H), 7.92 (dd, <i>J</i> = 7.2 Hz, <i>J</i> = 8.4 Hz, 1 H), 8.21-8.24 (m, 1 H), 8.49 (t, <i>J</i> = 2.0 Hz, 1 H), 8.67 (d, <i>J</i> = 7.6 Hz, 1 H), 8.99 (d, <i>J</i> = 2.0 Hz, 1 H), 9.16 (d, <i>J</i> = 2.0 Hz, 1 H).	¹ H NMR (400 MHz, DMSO-d ₆) δ 1.68-1.76 (m, 4 H), 1.88-1.95 (m, 1 H), 2.05-2.08 (m, 1 H), 3.92-3.96 (m, 1 H), 4.33-4.37 (m, 1 H), 4.55 (d, <i>J</i> = 8.0 Hz, 1 H), 4.60 (d, <i>J</i> = 8.0 Hz, 1 H), 4.66 (d, <i>J</i> = 4.4 Hz, 2 H), 6.32 (t, <i>J</i> = 4.4 Hz, 1 H), 7.20-7.32 (m, 7 H), 7.50-7.59 (m, 5 H), 7.68-7.73 (m, 2 H), 7.83 (dd, <i>J</i> = 1.2 Hz, <i>J</i> = 8.0 Hz, 1 H), 7.92 (dd, <i>J</i> = 7.2 Hz, <i>J</i> = 8.4 Hz, 1 H), 8.21-8.24 (m, 1 H), 8.49 (t, <i>J</i> = 2.0 Hz, 1 H), 8.67 (d, <i>J</i> = 7.6 Hz, 1 H), 8.99 (d, <i>J</i> = 2.0 Hz, 1 H), 9.16 (d, <i>J</i> = 2.0 Hz, 1 H).
50		¹ H NMR (400 MHz, DMSO-d ₆) δ 2.93 (d, <i>J</i> = 6.8 Hz, 2 H), 3.55 (dd, <i>J</i> = 6.4 Hz, <i>J</i> = 6.8 Hz, 2 H), 4.66 (d, <i>J</i> = 4.0 Hz, 2 H), 6.32 (t, <i>J</i> = 4.0 Hz, 1 H), 7.14-7.34 (m, 6 H), 7.50-7.59 (m, 5 H), 7.68-7.73 (m, 2 H), 7.83 (dd, <i>J</i> = 1.6 Hz, <i>J</i> = 8.0 Hz, 1 H), 7.93 (dd, <i>J</i> = 7.2 Hz, <i>J</i> = 8.0 Hz, 1 H), 8.21-8.24 (m, 1 H), 8.45 (dd, <i>J</i> = 2.0 Hz, <i>J</i> = 2.4 Hz, 1 H), 8.93 (t, <i>J</i> = 6.4 Hz, 1 H), 8.99 (d, <i>J</i> = 2.4 Hz, 1 H), 9.11 (d, <i>J</i> = 2.0 Hz, 1 H).	¹ H NMR (400 MHz, DMSO-d ₆) δ 2.93 (d, <i>J</i> = 6.8 Hz, 2 H), 3.55 (dd, <i>J</i> = 6.4 Hz, <i>J</i> = 6.8 Hz, 2 H), 4.66 (d, <i>J</i> = 4.0 Hz, 2 H), 6.32 (t, <i>J</i> = 4.0 Hz, 1 H), 7.14-7.34 (m, 6 H), 7.50-7.59 (m, 5 H), 7.68-7.73 (m, 2 H), 7.83 (dd, <i>J</i> = 1.6 Hz, <i>J</i> = 8.0 Hz, 1 H), 7.93 (dd, <i>J</i> = 7.2 Hz, <i>J</i> = 8.0 Hz, 1 H), 8.21-8.24 (m, 1 H), 8.45 (dd, <i>J</i> = 2.0 Hz, <i>J</i> = 2.4 Hz, 1 H), 8.93 (t, <i>J</i> = 6.4 Hz, 1 H), 8.99 (d, <i>J</i> = 2.4 Hz, 1 H), 9.11 (d, <i>J</i> = 2.0 Hz, 1 H).

UTILITY

In general, compounds of the present invention, such as particular compounds disclosed in the preceding examples, have been shown to inhibit the K_v1 subfamily of voltage-gated K^+ channels (for example, by displaying % inhibition values $\geq 14\%$,

5 preferably $\geq 30\%$, more preferably $\geq 40\%$, even more preferably $\geq 50\%$, at 0.3 micromolar concentration in an assay such as those set forth below). By displaying activity as inhibitors of the K_v1 subfamily of voltage-gated K^+ channels, compounds of the present invention are expected to be useful in the treatment of human diseases associated with the K_v1 subfamily of voltage-gated K^+ channels.

10 Assays to determine the degree of activity of a compound as an I_{Kur} inhibitor are well known in the art and are described in references such as *J. Gen. Physiol.*, 101(4):513-543 (Apr. 1993), and *Br. J. Pharmacol.*, 115(2):267-274 (May 1995).

Assays to determine the degree of activity of a compound as an inhibitor of other members of the K_v1 subfamily are also well known in the art. For example, inhibition of

15 $K_v1.1$, $K_v1.2$ and $K_v1.3$ can be measured using procedures described by Grissmer, S. et al., *Mol. Pharmacol.*, 45(6):1227-1234 (Jun. 1994); inhibition of $K_v1.4$ can be measured using procedures described by Petersen, K.R. et al., *Pflugers Arch.*, 437(3):381-392 (Feb. 1999); inhibition of $K_v1.6$ can be measured using procedures described by Bowlby, M.R. et al., *J. Neurophysiol.* 73(6):2221-2229 (Jun. 1995); and inhibition of $K_v1.7$ can be

20 measured using procedures described by Kalman, K. et al., *J. Biol. Chem.*, 273(10):5851-5857 (Mar. 6, 1998).

Examples 1-50, as shown in Table 2, were assayed for block of I_{Kur} current in patch clamped mammalian L-929 cells which were injected with human K_v 1.5 mRNA and stably expressed I_{Kur} protein (as described in the references described below).

25 Inhibition data at 0.3 mM concentration for the Examples are shown in Table 2.

1. Synders, D.J.; et al., "A rapidly activating and slowly inactivating potassium channel cloned from human heart: functional analysis after stable mammalian cell culture expression", *J. Gen. Physiol.*, 101:513-543 (1993).
2. Zhou, Z. et al., "Block of HERG potassium channels by the antihistamine astemizole and its metabolites desmethylastemizole and norastemizole", *J. Cardiovasc. Electrophysiol.*, 10(6):836-843 (1999).

Table 2

Example	KV1_5% Inh L929 @0.3 µM
1	79.54
2	83.91
3	77.31
4	95.43
5	76.05
6	38.28
7	15.97
8	90.47
9	87.07
10	51.09
11	78.75
12	91.58
13	43.04
14	70.96
19	72.53
20	92.79
21	97.87
22	91.54
23	83.5
24	96.52
25	80.15
26	93.11
27	77.97
28	41.49
29	68.07
30	92.48
31	87.44
32	53.19

Example	KV1_5% Inh L929 @0.3 μ M
33	71.14
34	84
35	86.26
36	91.1
37	78.56
38	94.93
39	78.37
40	90.25
41	93.55
42	91.25
43	86.78
44	96.45
45	75.61
46	51.14
47	96.4
48	71.12
49	93.86
50	98.56

Example 16 is a prodrug of Example 1. Pro-drug cleavage to the respective parent compound was demonstrated in *in vivo* rat PK evaluation and at all doses administered PO. Additionally, pro-drugs evaluated in rat to determine the effect of pH modulators on PO PK utilizing Pentagastrin or Famotidine pre-treatment demonstrated that the pro-drug mitigated the pH dependent absorption in this model. Therefore, Example 16 is useful in the inhibition of potassium channel function and is useful in the treatment and prevention of arrhythmia, I_{Kur} -associated disorders, and other disorders mediated by ion channel function, by providing Example 1 which has been shown to be an inhibitor of potassium channel function.

Compounds within the scope of the present invention inhibit the K_v1 subfamily of voltage-gated K^+ channels, and as such are believed to be useful in the treatment and/or

prevention of various disorders: cardiac arrhythmias, including supraventricular arrhythmias, atrial arrhythmias, atrial flutter, atrial fibrillation, complications of cardiac ischemia, and use as heart rate control agents, including maintaining normal sinus rhythm; angina pectoris including relief of Prinzmetal's symptoms, vasospastic symptoms and variant symptoms; gastrointestinal disorders including reflux esophagitis, functional dyspepsia, motility disorders (including constipation and diarrhea), and irritable bowel syndrome; disorders of vascular and visceral smooth muscle including asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome, peripheral vascular disease (including intermittent claudication), venous insufficiency, impotence, cerebral and coronary spasm and Raynaud's disease; inflammatory and immunological disease including inflammatory bowel disease, rheumatoid arthritis, graft rejection, asthma. chronic obstructive pulmonary disease, cystic fibrosis and atherosclerosis; cell proliferative disorders including restenosis and cancer (including leukemia); disorders of the auditory system; disorders of the visual system including macular degeneration and cataracts; diabetes including diabetic retinopathy, diabetic nephropathy and diabetic neuropathy; muscle disease including myotonia and wasting; peripheral neuropathy; cognitive disorders; migraine; memory loss including Alzheimer's and dementia; CNS mediated motor dysfunction including Parkinson's disease, and ataxia; epilepsy; and other ion channel mediated disorders.

20 As inhibitors of the K_v1 subfamily of voltage-gated K^+ channels compounds of the present invention are believed to be useful to treat a variety of further disorders including resistance by transplantation of organs or tissue, graft-versus-host diseases brought about by medulla ossium transplantation, rheumatoid arthritis, systemic lupus erythematosus, Hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis, type I diabetes uveitis, juvenile-onset or recent-onset diabetes mellitus, posterior uveitis, allergic encephalomyelitis, glomerulonephritis, infectious diseases caused by pathogenic microorganisms, inflammatory and hyperproliferative skin diseases, psoriasis, atopical dermatitis, contact dermatitis, eczematous dermatitises, seborrhoeis dermatitis, Lichen planus, Pemphigus, bullous pemphigoid, Epidermolysis bullosa, urticaria, angioedemas, 25 vasculitides, erythemas, cutaneous eosinophilias, Lupus erythematosus, acne, Alopecia areata, keratoconjunctivitis, vernal conjunctivitis, uveitis associated with Behcet's disease, keratitis, herpetic keratitis, conical cornea, dystrophia epithelialis corneae,

corneal leukoma, ocular pemphigus, Mooren's ulcer Scleritis, Graves' ophthalmopathy, Vogt-Koyanagi-Harada syndrome, sarcoidosis, pollen allergies, reversible obstructive airway disease, bronchial asthma, allergic asthma, intrinsic asthma, extrinsic asthma, dust asthma, chronic or inveterate asthma, late asthma and airway hyper-responsiveness,

5 bronchitis, gastric ulcers, vascular damage caused by ischemic diseases and thrombosis, ischemic bowel diseases, inflammatory bowel diseases, necrotizing enterocolitis, intestinal lesions associated with thermal burns and leukotriene B4-mediated diseases, Coeliac diseases, proctitis, eosinophilic gastroenteritis, mastocytosis, Crohn's disease, ulcerative colitis, migraine, rhinitis, eczema, interstitial nephritis, Good-pasture's

10 syndrome, hemolytic-uremic syndrome, diabetic nephropathy, multiple myositis, Guillain-Barre syndrome, Meniere's disease, polyneuritis, multiple neuritis, mononeuritis, radiculopathy, hyperthyroidism, Basedow's disease, pure red cell aplasia, aplastic anemia, hypoplastic anemia, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, agranulocytosis, pernicious anemia, megaloblastic anemia, anerythroplasia,

15 osteoporosis, sarcoidosis, fibroid lung, idiopathic interstitial pneumonia, dermatomyositis, leukoderma vulgaris, ichthyosis vulgaris, photoallergic sensitivity, cutaneous T cell lymphoma, arteriosclerosis, atherosclerosis, aortitis syndrome, polyarteritis nodosa, myocarditis, scleroderma, Wegener's granuloma, Sjögren's syndrome, adiposis, eosinophilic fascitis, lesions of gingiva, periodontium, alveolar bone,

20 substantia osses dentis, glomerulonephritis, male pattern alopecia or alopecia senilis by preventing epilation or providing hair germination and/or promoting hair generation and hair growth, muscular dystrophy; Pyoderma and Sezary's syndrome, Addison's disease, ischemia-reperfusion injury of organs which occurs upon preservation, transplantation or ischemic disease, endotoxin-shock, pseudomembranous colitis, colitis caused by drug or

25 radiation, ischemic acute renal insufficiency, chronic renal insufficiency, toxinosis caused by lung-oxygen or drugs, lung cancer, pulmonary emphysema, cataracta, siderosis, retinitis, pigmentosa, senile macular degeneration, vitreal scarring, corneal alkali burn, dermatitis erythema multiforme, linear IgA bullous dermatitis and cement dermatitis, gingivitis, periodontitis, sepsis, pancreatitis, diseases caused by environmental pollution,

30 aging, carcinogenis, metastasis of carcinoma and hypobaropathy, disease caused by histamine or leukotriene-C4 release, Behcet's disease, autoimmune hepatitis, primary biliary cirrhosis sclerosing cholangitis, partial liver resection, acute liver necrosis,

necrosis caused by toxin, viral hepatitis, shock, or anoxia, B-virus hepatitis, non-A/non-B hepatitis, cirrhosis, alcoholic cirrhosis, hepatic failure, fulminant hepatic failure, late-onset hepatic failure, "acute-on-chronic" liver failure, augmentation of chemotherapeutic effect, cytomegalovirus infection, HCMV infection, AIDS, cancer, senile dementia, 5 trauma, and chronic bacterial infection.

The compounds of the present invention are suspected antiarrhythmic agents which are useful in the prevention and treatment (including partial alleviation or cure) of arrhythmias. As inhibitors of $K_v1.5$, compounds within the scope of the present invention are particularly useful in the selective prevention and treatment of supraventricular 10 arrhythmias such as atrial fibrillation, and atrial flutter. By "selective prevention and treatment of supraventricular arrhythmias" is meant the prevention or treatment of supraventricular arrhythmias wherein the ratio of the prolongation of the atrial effective refractory period to the prolongation of the ventricular effective refractory period is greater than 1:1. This ratio can also be greater than 4:1, even greater than 10:1. In 15 addition, the ratio may be such that prolongation of the atrial effective refractory response period is achieved without significantly detectable prolongation of the ventricular effective refractory period.

In addition, the compounds within the scope of the present invention block I_{Kur} , and thus may be useful in the prevention and treatment of all I_{Kur} -associated conditions. 20 An " I_{Kur} -associated condition" is a disorder which may be prevented, partially alleviated or cured by the administration of an I_{Kur} blocker. The $K_v1.5$ gene is known to be expressed in stomach tissue, intestinal/colon tissue, the pulmonary artery, and pancreatic beta cells. Thus, administration of an I_{Kur} blocker can provide useful treatment for disorders such as: reflux esophagitis, functional dyspepsia, constipation, asthma, and 25 diabetes. Additionally, $K_v1.5$ is known to be expressed in the anterior pituitary. Thus, administration of an I_{Kur} blocker can stimulate growth hormone secretion. I_{Kur} inhibitors can additionally be useful in cell proliferative disorders such as leukemia, and autoimmune diseases such as rheumatoid arthritis and transplant rejection.

The present invention thus provides methods for the prevention or treatment of 30 one or more of the aforementioned disorders, comprising the step of administering to a subject in need thereof an effective amount of at least one compound of the formula (I), (Ia), or compounds exemplified in the examples,. Other therapeutic agents such as those

described below may be employed with the inventive compounds in the present methods. In the methods of the present invention, such other therapeutic agent(s) may be administered prior to, simultaneously with or following the administration of the compound(s) of the present invention.

5

DOSAGE AND FORMULATION

The present invention also provides pharmaceutical compositions comprising at least one of the compounds of the formula (I), (Ia), or compounds exemplified in the examples, or salts thereof capable of preventing or treating one or more of the 10 aforementioned disorders in an amount effective therefor, and a pharmaceutically acceptable vehicle or diluent. The compositions of the present invention may contain other therapeutic agents as described below, and may be formulated, for example, by employing conventional solid or liquid vehicles or diluents, as well as pharmaceutical additives of a type appropriate to the mode of desired administration (for example, 15 excipients, binders, preservatives, stabilizers, flavors, etc.) according to techniques such as those well known in the art of pharmaceutical formulation.

The compounds of the formula (I), (Ia), or compounds exemplified in the examples, may be administered by any suitable means, for example, orally, such as in the form of tablets, capsules, granules or powders; sublingually; buccally; parenterally, such 20 as by subcutaneous, intravenous, intramuscular, or intrasternal injection or infusion techniques (e.g., as sterile injectable aqueous or non aqueous solutions or suspensions); nasally such as by inhalation spray; topically, such as in the form of a cream or ointment; or rectally such as in the form of suppositories; in dosage unit formulations containing non toxic, pharmaceutically acceptable vehicles or diluents. The present compounds 25 may, for example, be administered in a form suitable for immediate release or extended release. Immediate release or extended release may be achieved by the use of suitable pharmaceutical compositions comprising the present compounds, or, particularly in the case of extended release, by the use of devices such as subcutaneous implants or osmotic pumps. In the case where the compounds of formula (I), (Ia), or compounds exemplified 30 in the examples, are being administered to prevent or treat arrhythmias, the compounds may be administered to achieve chemical conversion to normal sinus rhythm, or may optionally be used in conjunction with electrical cardioconversion.

Exemplary compositions for oral administration include suspensions which may contain, for example, microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners or flavoring agents such as those known in the art; and immediate release tablets which may contain, for example, microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and/or lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants such as those known in the art. The compounds of formula (I), (Ia), or compounds exemplified in the examples, may also be delivered through the oral cavity by sublingual and/or buccal administration. Molded tablets, compressed tablets or freeze-dried tablets are exemplary forms which may be used. Exemplary compositions include those formulating the present compound(s) with fast dissolving diluents such as mannitol, lactose, sucrose and/or cyclodextrins. Also included in such formulations may be high molecular weight excipients such as celluloses (AVICEL®) or polyethylene glycols (PEG). Such formulations may also include an excipient to aid mucosal adhesion such as hydroxy propyl cellulose (HPC), hydroxy propyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (SCMC), maleic anhydride copolymer (e.g., Gantrez), and agents to control release such as polyacrylic copolymer (e.g., Carbopol 934). Lubricants, glidants, flavors, coloring agents and stabilizers may also be added for ease of fabrication and use.

Exemplary compositions for nasal aerosol or inhalation administration include solutions in saline which may contain, for example, benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, and/or other solubilizing or dispersing agents such as those known in the art.

Exemplary compositions for parenteral administration include injectable solutions or suspensions which may contain, for example, suitable non toxic, parenterally acceptable diluents or solvents, such as mannitol, 1,3 butanediol, water, Ringer's solution, an isotonic sodium chloride solution, or other suitable dispersing or wetting and suspending agents, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

Exemplary compositions for rectal administration include suppositories which may contain, for example, a suitable non irritating excipient, such as cocoa butter,

synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures, but liquefy and/or dissolve in the rectal cavity to release the drug.

Exemplary compositions for topical administration include a topical carrier such as Plastibase (mineral oil gelled with polyethylene).

5 The effective amount of a compound of the present invention may be determined by one of ordinary skill in the art, and includes exemplary dosage amounts for an adult human of from about 0.001 to 100 mg/kg of body weight of active compound per day, which may be administered in a single dose or in the form of individual divided doses, such as from 1 to 4 times per day. It will be understood that the specific dose level and
10 frequency of dosage for any particular subject may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the species, age, body weight, general health, sex and diet of the subject, the mode and time of administration, rate of excretion, drug combination, and severity of the particular condition. Preferred subjects
15 for treatment include animals, most preferably mammalian species such as humans, and domestic animals such as dogs, cats and the like, subject to the aforementioned disorders.

The compounds of the present invention may be employed alone or in combination with each other and/or other suitable therapeutic agents useful in the treatment of the aforementioned disorders or other disorders, including: other
20 antiarrhythmic agents such as Class I agents (e.g., propafenone), Class II agents (e.g., carvadiol and propranolol), Class III agents (e.g., sotalol, dofetilide, amiodarone, azimilide and ibutilide), Class IV agents (e.g., diltiazem and verapamil), 5HT antagonists (e.g., sulamserod, serraline and tropisetron), and dronedarone; calcium channel blockers (both L-type and T-type) such as diltiazem, verapamil, nifedipine, amlodipine and
25 mybepridil; Cyclooxygenase inhibitors (*i.e.*, COX-1 and/or COX-2 inhibitors) such as aspirin, indomethacin, ibuprofen, piroxicam, naproxen, CELEBREX®, VIOXX® and NSAIDs; anti-platelet agents such as GPIIb/IIIa blockers (e.g., abciximab, eptifibatide and tirofiban), P2Y12 antagonists (e.g., clopidogrel, cangrelor, ticlopidine and CS-747), P2Y1 antagonists, thromboxane receptor antagonists (e.g., ifetroban), aspirin, and PDE-
30 III inhibitors (e.g., dipyridamole) with or without aspirin; diuretics such as chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorothiazide, trichloromethiazide, polythiazide,

benzthiazide, ethacrynic acid tricrynafen, chlorthalidone, furosemide, musolimine, bumetanide, triam trenene, amiloride, and spironolactone; anti-hypertensive agents such as alpha adrenergic blockers, beta adrenergic blockers, calcium channel blockers, diuretics, renin inhibitors, ACE inhibitors, (e.g., captopril, zofenopril, fosinopril, 5 enalapril, ceranopril, cilazopril, delapril, pentopril, quinapril, ramipril, lisinopril), A II antagonists (e.g., losartan, irbesartan, valsartan), ET antagonists (e.g., sitaxsentan, atrsentan and compounds disclosed in U.S. Patent Nos. 5,612,359 and 6,043,265), Dual ET/AII antagonist (e.g., compounds disclosed in WO 00/01389), neutral endopeptidase (NEP) inhibitors, vasopepsidase inhibitors (dual NEP-ACE inhibitors) (e.g., omapatrilat 10 and gemopatrilat), nitrates, and combinations of such anti-hypertensive agents; antithrombotic/thrombolytic agents such as tissue plasminogen activator (tPA), recombinant tPA, tenecteplase (TNK), lanoteplase (nPA), factor VIIa inhibitors, factor Xa inhibitors (such as razaxaban), XIa inhibitors, thrombin inhibitors (e.g., hirudin and argatroban), PAI-1 inhibitors (*i.e.*, inactivators of tissue plasminogen activator 15 inhibitors), α 2-antiplasmin inhibitors, streptokinase, urokinase, prourokinase, anisoylated plasminogen streptokinase activator complex, and animal or salivary gland plasminogen activators; anticoagulants such as warfarin and heparins (including unfractionated and low molecular weight heparins such as enoxaparin and dalteparin); HMG-CoA reductase inhibitors such as pravastatin lovastatin, atorvastatin, simvastatin, NK-104 (a.k.a. 20 itavastatin, or nisvastatin or nisbastatin) and ZD-4522 (a.k.a. rosuvastatin, or atavastatin or visastatin); other cholesterol/lipid lowering agents such as squalene synthetase inhibitors, fibrates, and bile acid sequestrants (e.g., QUESTRAN®); antiproliferative agents such as cyclosporin A, TAXOL®, FK 506, and adriamycin; antitumor agents such as TAXOL®, adriamycin, epothilones, cisplatin and carboplatin; anti-diabetic agents 25 such as biguanides (e.g., metformin), glucosidase inhibitors (e.g., acarbose), insulins, meglitinides (e.g., repaglinide), sulfonylureas (e.g., glimepiride, glyburide and glipizide), biguanide/glyburide combinations (*i.e.*, GLUCOVANCE®), thiazolidinediones (e.g., troglitazone, rosiglitazone and pioglitazone), PPAR-gamma agonists, aP2 inhibitors, and DP4 inhibitors; thyroid mimetics (including thyroid receptor antagonists) (e.g., 30 thyrotropin, polythyroid, KB-130015, and dronedarone); Mineralocorticoid receptor antagonists such as spironolactone and eplerinone; growth hormone secretagogues; anti-osteoporosis agents (e.g., alendronate and raloxifene); hormone replacement therapy

agents such as estrogen (including conjugated estrogens in premarin), and estradiol; antidepressants such as nefazodone and sertraline; antianxiety agents such as diazepam, lorazepam, buspirone, and hydroxyzine pamoate; oral contraceptives; anti-ulcer and gastroesophageal reflux disease agents such as famotidine, ranitidine, and omeprazole;

5 anti-obesity agents such as orlistat; cardiac glycosides including digitalis and ouabain; phosphodiesterase inhibitors including PDE III inhibitors (e.g., cilostazol), and PDE V inhibitors (e.g., sildenafil); protein tyrosine kinase inhibitors; steroidal anti-inflammatory agents such as prednisone, and dexamethasone; and other anti-inflammatory agents such as ENBREL®. The combinations can be co-formulated or in the form of kits packaged to

10 provide appropriate dosages for co-administration.

The above other therapeutic agents, when employed in combination with the compounds of the present invention, may be used, for example, in those amounts indicated in the *Physicians' Desk Reference* (PDR) or as otherwise determined by one of ordinary skill in the art.

15 Publications and references, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference in their entirety in the entire portion cited as if each individual publication or reference were specifically and individually indicated to be incorporated by reference herein as being fully set forth. Any patent application to which this application claims priority is also

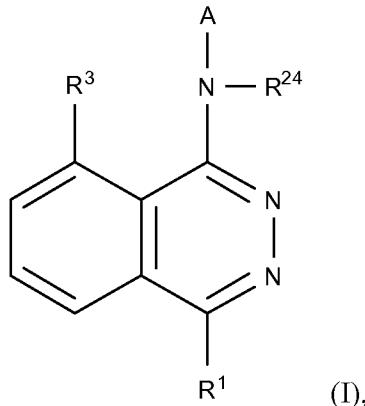
20 incorporated by reference herein in the manner described above for publications and references.

While this invention has been described with an emphasis upon particular embodiments, it will be obvious to those of ordinary skill in the art that variations in the particular compounds and methods may be used and that it is intended that the invention

25 may be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications encompassed within the spirit and scope of the invention as defined by the claims that follow.

WHAT IS CLAIMED IS:

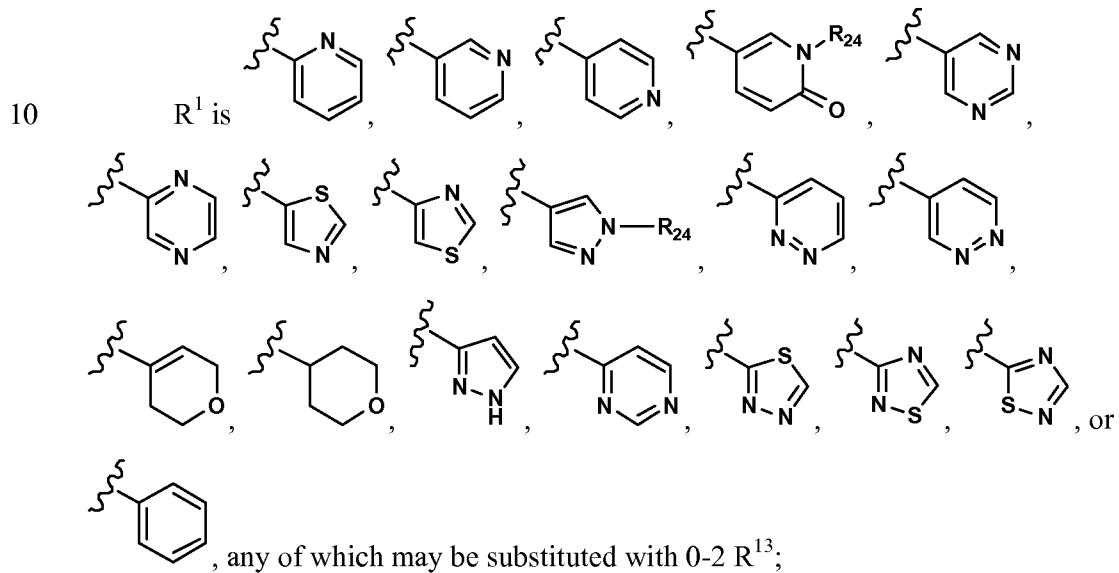
1. A compound of formula (I):



5 or an enantiomer, diastereomer, tautomer, or salt thereof, wherein:

A is $-(CH_2)_m-R^2$, $-CH(R^{26})-R^2$, $-C(R^{26})_2-R^2$, $-(CH_2)_{n-1}-O-R^2$, $-(CH_2)_{n-1}-NR^{25}-R^2$, $-CH(R^{26})-CO_2-R^2$, or $-(CH_2)_{n-1}-NR^{25}-CO_2-R^2$;

R¹ is C₁₋₁₀ alkyl substituted with 1-2 -OH, haloC₁₋₁₀ alkyl, C₂₋₁₂ alkenyl, or C₃₋₁₀ cycloalkyl, wherein the cycloalkyl may be substituted with 0-2 R¹³; or



15 R² is phenyl, cyclopentyl, cyclohexyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, piperidinyl, pyridinone, pyrrolidinyl, tetrahydropyran, or thiazolyl, any of which are substituted with 0-2 R^{2a};

R^{2a}, at each occurrence, is independently H, -OH, F, Cl, Br, I, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, haloC₁₋₁₀ alkyl, C₃₋₁₀ cycloalkyl, C₂₋₁₂ alkenyl, C₂₋₁₂ alkynyl, C₆₋₁₀aryl, a 4- to

12-membered heteroaryl, a 4- to 12-membered heterocyclyl, a 4- to 12-membered heteroaryl-C₁₋₁₀ alkyl, -CN, -NO₂, -(CH₂)_m-SO₂R¹⁴, -NR¹⁴SO₂R¹⁴, =O, -CONR¹⁴R¹⁴, -(CH₂)_m-SO₂NR¹⁴R¹⁴, -(CH₂)_m-NR¹⁴SO₂R¹⁴, -(CH₂)_n-NR¹⁴SO₂NR¹⁴R¹⁴, -NR¹⁴SO₂NR¹⁴R¹⁴, -CO₂NR¹⁴R¹⁴, -NR¹⁴CO₂NR¹⁴R¹⁴, -NR¹⁴COR¹⁴, -SO₂NR¹⁴COR¹⁴, -SO₂NR¹⁴CONR¹⁴R¹⁴, -NR¹⁴CO₂R¹⁴, -CO₂R¹⁴, -NR¹⁴R¹⁴, -NR¹⁴CONR¹⁴R¹⁴, -C(=NOR¹⁴)NR¹⁴R¹⁴, -CONR¹⁴OR¹⁴ or -NR¹⁴COR¹⁴, wherein the alkyl, cycloalkyl, alkenyl, alkoxy, aryl, heteroaryl and heterocyclyl may be substituted with 0-2 R^{14a}, and the heteroaryl and heterocyclyl consist of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, S, or O;

10 R³ is phenyl, pyridinyl, pyrimidinyl, dihydropyran, or tetrahydropyran any of which may be substituted with 0-1 R^{3a};

R^{3a} is halo, CN, NH₂, -O-C₁₋₃alkyl, or morpholinyl;

R¹³, at each occurrence, is independently H, -OH, F, Cl, Br, I, CN, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, haloC₁₋₁₀ alkyl, C₃₋₁₀ cycloalkyl, C₂₋₁₂ alkenyl, C₂₋₁₂ alkynyl, C₆₋₁₀aryl, a 4- to 12-membered heteroaryl, a 4- to 12-membered heterocyclyl, a 4- to 12-membered heteroaryl-C₁₋₁₀ alkyl, -CN, -NO₂, -(CH₂)_m-SO₂R¹⁴, -NR¹⁴SO₂R¹⁴, =O, -CONR¹⁴R¹⁴, -(CH₂)_m-SO₂NR¹⁴R¹⁴, -(CH₂)_m-NR¹⁴SO₂R¹⁴, -(CH₂)_n-NR¹⁴SO₂NR¹⁴R¹⁴, -NR¹⁴SO₂NR¹⁴R¹⁴, -CO₂NR¹⁴R¹⁴, -NR¹⁴CO₂NR¹⁴R¹⁴, -NR¹⁴COR¹⁴, -SO₂NR¹⁴COR¹⁴, -SO₂NR¹⁴CONR¹⁴R¹⁴, -NR¹⁴CO₂R¹⁴, -CO₂R¹⁴, -NR¹⁴R¹⁴, -NR¹⁴CONR¹⁴R¹⁴, -C(=NOR¹⁴)NR¹⁴R¹⁴, -CONR¹⁴OR¹⁴, -NR¹⁴COR¹⁴, or OR¹⁴, wherein the alkyl, cycloalkyl, alkenyl, alkoxy, aryl, heteroaryl and heterocyclyl may be substituted with 0-2 R^{14a}, and the heteroaryl and heterocyclyl consist of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, S, or O; or

20 R¹³ is SO₂NHP(O)(OH)₂;

25 R¹⁴, at each occurrence, is independently selected from hydrogen, C₁₋₁₀ alkyl, C₃₋₁₀ cycloalkyl, C₆₋₁₀aryl, a 4- to 12-membered heteroaryl or a 4- to 12-membered heterocyclyl, wherein the alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl may be substituted with 0-3 R^{14a} and the heteroaryl and heterocyclyl consist of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, S, or O; or

30 alternatively, two R¹⁴'s are taken together with the atoms to which they are attached to form a cyclic ring, wherein the cyclic ring may be substituted with 0-1 R^{14a}

and optionally contain 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, S, or O;

R^{14a}, at each occurrence, is independently selected from F, Cl, Br, I, C₁₋₁₀ alkyl, haloC₁₋₁₀alkyl, C₆₋₁₀aryl, C₃₋₁₀cycloalkyl, a 4- to 12-membered heteroaryl, a 4- to 12-membered heterocyclyl, F, Cl, Br, I, -CN, -NO₂, -CO₂R²⁶, -CO₂NR²⁴R²⁴, -OCF₃, -OR²⁵, =O, -CONR²⁴R²⁴, -COR²⁴, -SO₂R²⁴, -NR²⁴SO₂R²⁴, -NR²⁴R²⁴, -NR²⁴CO₂R²⁴, -SO₂NR²⁴R²⁴, or C₆₋₁₀arylC₁₋₁₀alkyl, wherein the heteroaryl and heterocyclyl consist of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, S, or O, and wherein the aryl and heteroaryl is optionally substituted with 0-1 halo or C₁₋₃alkyl;

R²⁴, at each occurrence, is independently selected from hydrogen, C₁₋₁₀alkyl, C₃₋₆cycloalkyl, or phenyl;

R²⁵, at each occurrence, is independently selected from hydrogen, C₁₋₁₀alkyl, C₁₋₆haloalkyl, C₃₋₆cycloalkyl, -(CH₂)-phenyl or phenyl;

R²⁶, at each occurrence, is independently selected from hydrogen, C₁₋₁₀alkyl, C₃₋₆cycloalkyl, or phenyl;

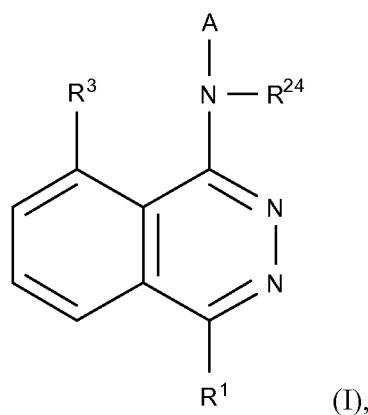
m is 0 to 4;

n is 0 to 4; and

n-1 is 2 to 4.

20

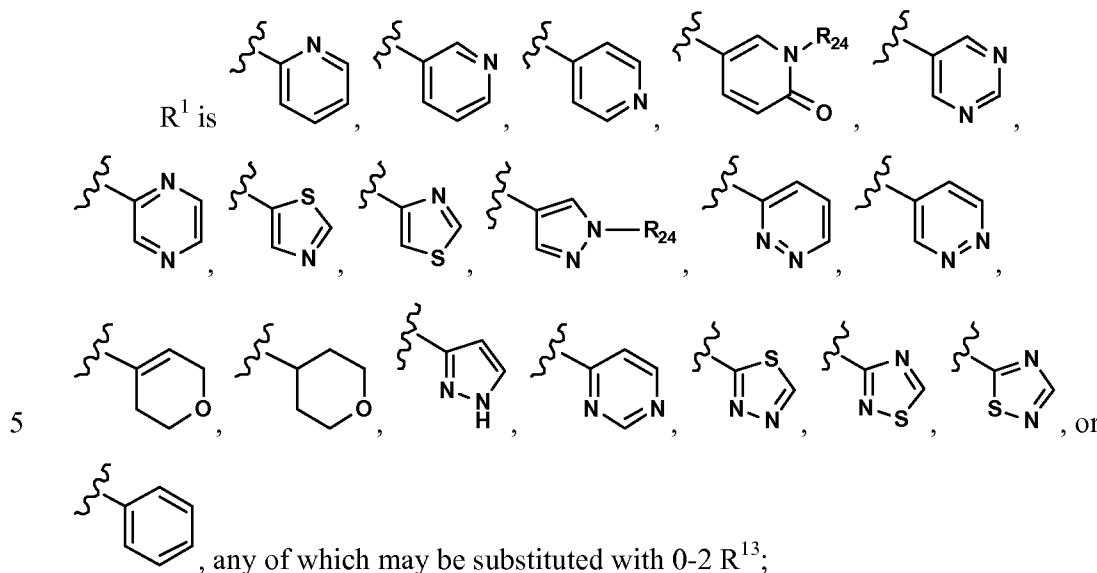
2. A compound of formula (I):



or an enantiomer, diastereomer, tautomer, or salt thereof, wherein:

A is -(CH₂)_m-R², -CH(R²⁶)-R², -(CH₂)_{n-1}-O-R², -(CH₂)_{n-1}-NR²⁵-R², -CH(R²⁶)-CO₂-R², or -(CH₂)_{n-1}-NR²⁵-CO₂-R²;

R¹ is C₁₋₁₀ alkyl substituted with 1-2 -OH, haloC₁₋₁₀ alkyl, C₂₋₁₂ alkenyl, C₃₋₁₀ cycloalkyl, wherein the cycloalkyl may be substituted with 0-2 R¹³; or



R^2 is phenyl, cyclopentyl, cyclohexyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, piperidinyl, pyridinone, pyrrolidinyl, tetrahydropyran, or thiazolyl, any of which are substituted with 0-2 R^{2a} ;

10 R^{2a}, at each occurrence, is independently H, -OH, F, Cl, Br, I, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, haloC₁₋₁₀ alkyl, C₃₋₁₀ cycloalkyl, C₂₋₁₂ alkenyl, C₂₋₁₂ alkynyl, C₆₋₁₀aryl, a 4- to 12-membered heteroaryl, a 4- to 12-membered heterocyclyl, a 4- to 12-membered heteroaryl-C₁₋₁₀ alkyl, -CN, -NO₂, -(CH₂)_m-SO₂R¹⁴, -NR¹⁴SO₂R¹⁴, =O, -CONR¹⁴R¹⁴, -(CH₂)_m-SO₂NR¹⁴R¹⁴, -(CH₂)_m-NR¹⁴SO₂R¹⁴, -(CH₂)_n-NR¹⁴SO₂NR¹⁴R¹⁴,
15 -NR¹⁴SO₂NR¹⁴R¹⁴, -CO₂NR¹⁴R¹⁴, -NR¹⁴CO₂NR¹⁴R¹⁴, -NR¹⁴COR¹⁴, -SO₂NR¹⁴COR¹⁴,
 -SO₂NR¹⁴CONR¹⁴R¹⁴, -NR¹⁴CO₂R¹⁴, -CO₂R¹⁴, -NR¹⁴R¹⁴, -NR¹⁴CONR¹⁴R¹⁴,
 -C(=NOR¹⁴)NR¹⁴R¹⁴, -CONR¹⁴OR¹⁴ or -NCOR¹⁴, wherein the alkyl, cycloalkyl, alkenyl, alkoxy, aryl, heteroaryl and heterocyclyl may be substituted with 0-2 R^{14a}, and the heteroaryl and heterocyclyl consist of carbon atoms and 1, 2, 3, or 4 heteroatoms
20 independently selected from the group consisting of N, S, or O;

R^3 is phenyl, pyridinyl, pyrimidinyl, dihydropyran, or tetrahydropyran, any of which may be substituted with 0-1 R^{3a} ;

R^{3a} is halo, CN, NH_2 , $-O-C_{1-3}alkyl$, or morpholinyl;

25 R¹³, at each occurrence, is independently H, -OH, F, Cl, Br, I, CN, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, haloC₁₋₁₀ alkyl, C₃₋₁₀ cycloalkyl, C₂₋₁₂ alkenyl, C₂₋₁₂ alkynyl, C₆₋₁₀aryl, a 4-

to 12-membered heteroaryl, a 4- to 12-membered heterocyclyl, a 4- to 12-membered heteroaryl-C₁₋₁₀ alkyl, -CN, -NO₂, -(CH₂)_m-SO₂R¹⁴, -NR¹⁴SO₂R¹⁴, =O, -CONR¹⁴R¹⁴, -(CH₂)_m-SO₂NR¹⁴R¹⁴, -(CH₂)_m-NR¹⁴SO₂R¹⁴, -(CH₂)_n-NR¹⁴SO₂NR¹⁴R¹⁴, -NR¹⁴SO₂NR¹⁴R¹⁴, -CO₂NR¹⁴R¹⁴, -NR¹⁴CO₂NR¹⁴R¹⁴, -NR¹⁴COR¹⁴, -SO₂NR¹⁴COR¹⁴, 5 -SO₂NR¹⁴CONR¹⁴R¹⁴, -NR¹⁴CO₂R¹⁴, -CO₂R¹⁴, -NR¹⁴R¹⁴, -NR¹⁴CONR¹⁴R¹⁴, -C(=NOR¹⁴)NR¹⁴R¹⁴, -CONR¹⁴OR¹⁴ or -NCOR¹⁴, OR¹⁴, wherein the alkyl, cycloalkyl, alkenyl, alkoxy, aryl, heteroaryl and heterocyclyl may be substituted with 0-2 R^{14a}, and the heteroaryl and heterocyclyl consist of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, S, or O;

10 R¹⁴, at each occurrence, is independently selected from hydrogen, C₁₋₁₀ alkyl, C₃₋₁₀ cycloalkyl, C₆₋₁₀ aryl, a 4- to 12-membered heteroaryl or a 4- to 12-membered heterocyclyl, wherein the alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl may be substituted with 0-3 R^{14a} and the heteroaryl and heterocyclyl consist of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, S, or O;

15 or alternatively, two R¹⁴'s are taken together with the atoms to which they are attached to form a cyclic ring, wherein the cyclic ring may be substituted with 0-1 R^{14a} and optionally contain 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, S, or O;

20 R^{14a}, at each occurrence, is independently selected from F, Cl, Br, I, C₁₋₁₀ alkyl, haloC₁₋₁₀alkyl, C₆₋₁₀aryl, C₃₋₁₀cycloalkyl, a 4- to 12-membered heteroaryl, a 4- to 12-membered heterocyclyl, F, Cl, Br, I, -CN, -NO₂, -CO₂R₂₆, -CO₂NR₂₄R₂₄, -OCF₃, -OR₂₅, =O, -CONR²⁴R²⁴, -COR²⁴, -SO₂R²⁴, -NR²⁴R²⁴, -NR²⁴CO₂R²⁴, -SO₂NR²⁴R²⁴, or C₆₋₁₀arylC₁₋₁₀alkyl, wherein the heteroaryl and heterocyclyl consist of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, S, or O;

25 R²⁴, at each occurrence, is independently selected from hydrogen, C₁₋₁₀alkyl, C₃₋₆cycloalkyl, or phenyl;

R²⁵, at each occurrence, is independently selected from hydrogen, C₁₋₁₀alkyl, C₃₋₆cycloalkyl, or phenyl;

30 R₂₆, at each occurrence, is independently selected from hydrogen, C₁₋₁₀alkyl, C₃₋₆cycloalkyl, or phenyl;

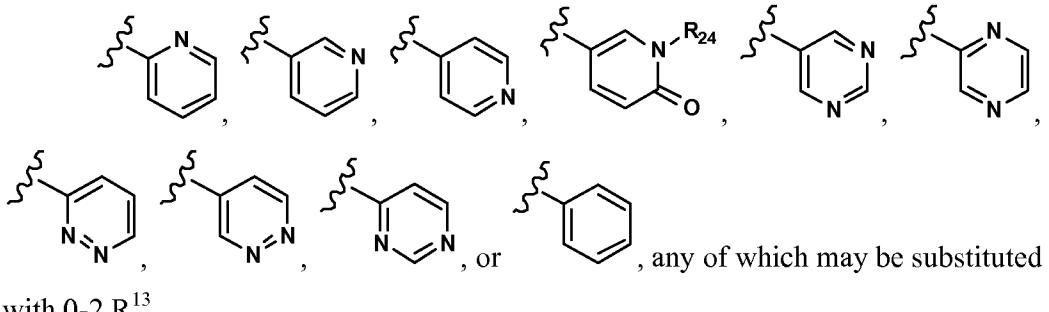
m is 0 to 4;

n is 0 to 4; and

n-1 is 2 to 4.

3. The compound of claims 1-2, or salt thereof, wherein:

5 one of R¹ is C₁₋₁₀ alkyl substituted with 1-2 -OH, haloC₁₋₁₀ alkyl, or C₃₋₁₀ cycloalkyl, wherein the cycloalkyl may be substituted with 0-2 R¹³; or



10

4. The compound of claims 1-3, or salt thereof, wherein:

R¹³, at each occurrence, is independently H, -OH, F, Cl, Br, I, C₁₋₆ alkyl, C₁₋₆ alkoxy, haloC₁₋₆ alkyl, C₃₋₆ cycloalkyl, phenyl, or a 4- to 12-membered heteroaryl, wherein the heteroaryl is selected from tetrazolyl, -CN, -NO₂, -(CH₂)_m-SO₂R¹⁴, -NR¹⁴SO₂R¹⁴, -CONR¹⁴R¹⁴, -(CH₂)_m-SO₂NR¹⁴R¹⁴, -NR¹⁴CO₂NR¹⁴R¹⁴, -NR¹⁴CO₂NR^{14b}R^{14b}, -NR¹⁴COR¹⁴, -NR¹⁴CO₂R¹⁴, -CO₂R¹⁴, or -NR¹⁴R¹⁴, wherein the alkyl, cycloalkyl, phenyl, and heteroaryl may be substituted with 0-2 R^{14a}, and the heteroaryl and heterocyclyl consist of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, S, or O;

20 R¹⁴, at each occurrence, is independently selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, or phenyl, wherein the alkyl, cycloalkyl, and phenyl, may be substituted with 0-3 R^{14a}; or

25 alternatively, two R^{14b}'s are taken together with the atoms to which they are attached to form a cyclic ring, wherein the cyclic ring is morpholinyl, piperidinyl, or piperazinyl, and may be substituted with 0-1 C₁₋₆alkyl; and

25 R^{14a}, at each occurrence, is independently selected from F, Cl, Br, I, C₁₋₆ alkyl, haloC₁₋₆alkyl, phenyl, or C₃₋₆cycloalkyl.

5. The compound of claims 1-4, or salt thereof, wherein:

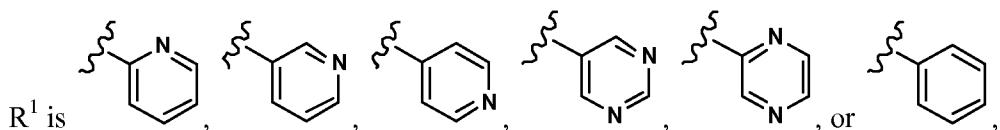
A is $-(CH_2)_m-R^2$, $-CH(R^{26})-R^2$, $-(CH_2)_{n-1}-O-R^2$, $-(CH_2)_{n-1}-NR^{25}-R^2$,
 $-CH(R^{26})-CO_2-R^2$, or $-(CH_2)_{n-1}-NR^{25}-CO_2-R^2$;

R² is phenyl, pyridinyl, pyrazinyl, pyrimidinyl, piperidinyl, or pyridinone, any of
5 which are substituted with 0-2 R^{2a}; and

R^{2a}, at each occurrence, is independently H, -OH, F, C₁₋₆ alkyl, C₁₋₆ alkoxy, or
6-SO₂NR¹⁴R¹⁴.

6. The compound of claims 1-5, or salt thereof, wherein:

10 R¹ is C₁₋₁₀ alkyl substituted with 1-2 -OH, haloC₁₋₁₀ alkyl, or C₃₋₁₀ cycloalkyl,
wherein the cycloalkyl may be substituted with 0-1 R¹³; or



any of which may be substituted with 0-2 R¹³.

15 7. The compound of claims 1-6, or salt thereof, wherein:

R¹³, at each occurrence, is independently H, C₁₋₆ alkyl, or a 4- to 12-membered heteroaryl, wherein the heteroaryl is selected from tetrazolyl, -CN, -NR¹⁴SO₂R¹⁴, -CONR¹⁴R¹⁴, -SO₂NR¹⁴R¹⁴, -NR¹⁴CO₂NR¹⁴R¹⁴, -NR¹⁴CO₂NR^{14b}R^{14b}, -NR¹⁴COR¹⁴, -CO₂R¹⁴, or -NR¹⁴R¹⁴, wherein the alkyl, and heteroaryl may be substituted with 0-2 R^{14a};

20 R¹⁴, at each occurrence, is independently selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, or phenyl, wherein the alkyl, cycloalkyl, and phenyl, may be substituted with 0-3 R^{14a};

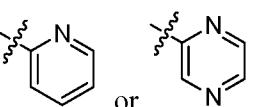
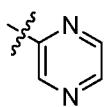
two R^{14b}'s are taken together with the atoms to which they are attached to form a cyclic ring, wherein the cyclic ring is morpholinyl, and may be substituted with 0-1

25 C₁₋₆alkyl; and

R^{14a}, at each occurrence, is independently selected from F, Cl, Br, I, C₁₋₆ alkyl, haloC₁₋₆alkyl, phenyl, or C₃₋₆cycloalkyl.

8. The compound of claims 1-7, or salt thereof, wherein:

30 A is-(CH₂)-R²;


R² is phenyl, or  any of which are substituted with 0-1 R^{2a}; and
R^{2a}, at each occurrence, is independently H, -OH, F, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, or SO₂NR¹⁴R¹⁴.

5 9. The compound of claims 1-8, or salt thereof, wherein:
R³ is phenyl.

10 10. The compound of claims 1-9, or salt thereof, wherein:
R¹³ is SO₂NHP(O)(OH)₂.

10 11. The compound of claims 1-10, wherein:
R¹³, at each occurrence, is independently H, -CN, -NHSO₂R¹⁴, -CONH₂,
-SO₂NR¹⁴R¹⁴, -NHCO₂NR^{14b}R^{14b}, -NHCOR¹⁴, or -NH₂; and
R¹⁴, at each occurrence, is independently selected from hydrogen or methyl.

15 12. A compound, enantiomer, diastereomer, or salt thereof, selected from the
compounds set forth in the examples.

20 13. A pharmaceutical composition comprising a therapeutically effective
amount of at least one compound of any one of claims 1 to 12.

14. The pharmaceutical composition of claim 13, further comprising at least
one other therapeutic agent.

25 15. A method of treating arrhythmia comprising administering to a patient in
need thereof an effective amount of at least one compound of any one of claims 1 to 12.

16. A method of controlling heart rate comprising administering to a patient in
need thereof an effective amount of at least one compound of any one of claims 1 to 12.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/022252

A. CLASSIFICATION OF SUBJECT MATTER
 INV. C07D401/04 C07D401/12 C07D401/14 A61K31/502 A61P9/06
 C07D403/04

ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Further documents are listed in the continuation of Box C.



See patent family annex.

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 April 2014	08/05/2014

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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