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(71) Applicant: **MERCK SHARP & DOHME LLC** [US/US];
126 East Lincoln Avenue, Rahway, New Jersey 07065 (US).

(72) Inventors; and

(71) Applicants (for US only): **CERNAKA, Natalija** [LV/US];
213 E. Grand Avenue, South San Francisco, California
94080 (US). **OGAWA, Anthony, K.** [US/US]; 213 E.
Grand Avenue, South San Francisco, California 94080
(US). **CHENG, Alan, C.** [US/US]; 213 E. Grand Avenue,
South San Francisco, California 94080 (US). **BAO, Jian-
ming** [US/US]; 16 Andrews Lane, Princeton, New Jersey
08540 (US). **SHARP, Phillip Patrick** [US/US]; 1 Clarence
Place, Unit 2, San Francisco, California 94107 (US).
LOPEZ, Jovan Alexander [US/US]; 111 Park Street, Apt.
15R, New Haven, Connecticut 06511 (US). **XIAO, Dong**
[US/US]; 33 Avenue Louis Pasteur, Boston, Massachusetts
02115-5727 (US). **TANG, Haiqun** [US/US]; 2000 Gallop-
ing Hill Road, Kenilworth, New Jersey 07033 (US).

(74) Common Representative: **MERCK SHARP & DOHME
LLC**; 126 East Lincoln Avenue, Rahway, New Jersey
07065 (US).

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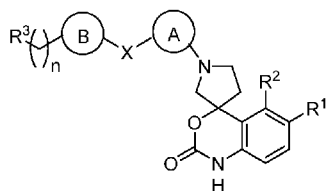
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(54) Title: PLASMA KALLIKREIN INHIBITORS



I

(57) Abstract: The present invention provides a compound of Formula I and pharmaceutical compositions comprising one or more said compounds, and methods for using said compounds for treating or preventing one or more disease states that could benefit from inhibition of plasma kallikrein, including hereditary angioedema, uveitis, posterior uveitis, wet age-related macular degeneration, diabetic macular edema, diabetic retinopathy and retinal vein occlusion. The compounds are selective inhibitors of plasma kallikrein.



TITLE OF THE INVENTION

PLASMA KALLIKREIN INHIBITORS

BACKGROUND OF THE INVENTION

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Patients presenting genetic deficiency on C1-inhibitor suffer from hereditary angioedema (HAE), a lifelong disease that results in intermittent swelling throughout the body, including the hands, feet, face, throat, genitals and gastrointestinal tract. Analysis of blisters arising from acute episodes have been shown to contain high levels of plasma kallikrein, and treatment with a protein-based reversible plasma kallikrein inhibitor, Ecallantide (Kalbitor), has been approved by the FDA for the treatment of acute attacks of HAE (Schneider, L, *et al.*, J. Allergy Clin. Immunol., 120: p.416 (2007)). Recently, an oral plasma kallikrein inhibitor, Berotralstat, gained FDA approval for the prevention of HAE attacks (Zuraw, B., *et al.*, J. Allergy Clin. Immunol. (2020).

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Additionally, the plasma kallikrein-kinin system is abnormally abundant in patients diagnosed with advanced diabetic macular edema (DME). Recent publications have shown that plasma kallikrein contributes to observed retinal vascular leakage and dysfunction in diabetic rodent models (A. Clermont, *et al.*, Diabetes, 60:1590 (2011)), and that treatment with a small molecule plasma kallikrein inhibitor ameliorated the observed retinal vascular permeability and other abnormalities related to retinal blood flow.

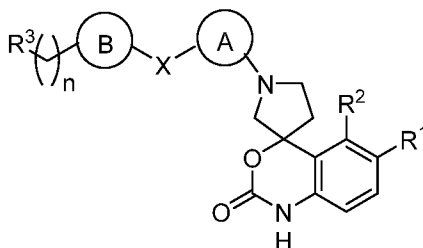
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It would be desirable in the art to develop plasma kallikrein inhibitors having utility to treat a wide range of disorders, including hereditary angioedema, diabetic macular edema and diabetic retinopathy.

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SUMMARY OF THE INVENTION

The present invention relates to compounds of Formula I:



I

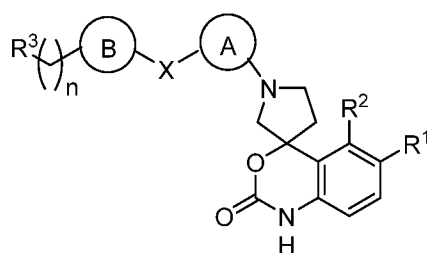
and pharmaceutically acceptable salts thereof. The compounds of Formula I are inhibitors of plasma kallikrein, and as such may be useful in the treatment, inhibition or amelioration of one

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or more disease states that could benefit from inhibition of plasma kallikrein, including hereditary angioedema, uveitis, posterior uveitis, wet age-related macular degeneration, diabetic macular edema, diabetic retinopathy and retinal vein occlusion. The compounds of this invention could further be used in combination with other therapeutically effective agents, including but not limited to, other drugs useful for the treatment of hereditary angioedema, uveitis, posterior uveitis, wet age-related macular degeneration, diabetic macular edema, diabetic retinopathy and retinal vein occlusion. The invention furthermore relates to processes for preparing compounds of Formula I, and pharmaceutical compositions which comprise compounds of Formula I and pharmaceutically acceptable salts thereof.

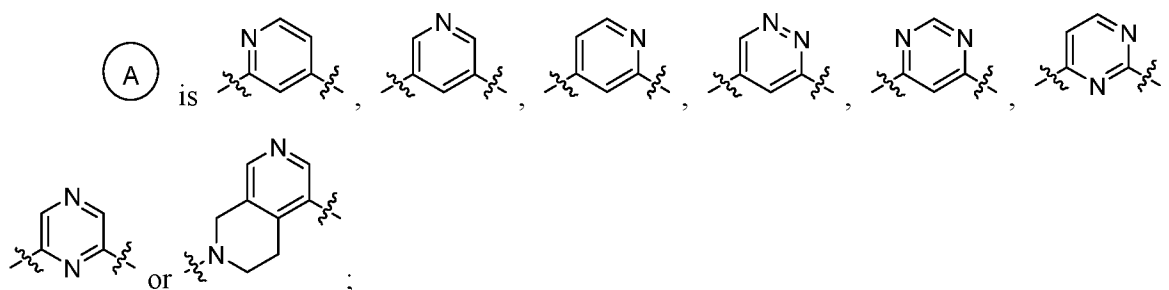
DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to compounds of Formula I:



I

wherein X is $-\text{CH}_2-$, $-\text{NH}(\text{C}=\text{O})\text{CH}_2-$ or $-(\text{C}=\text{O})\text{NHCH}_2-$;



wherein group B is phenyl or heteroaryl, which can be monocyclic or bicyclic, wherein said phenyl is optionally substituted with halo and said heteroaryl is optionally substituted with halo, hydroxy, C_{1-6} alkyl or oxo;

R^1 is selected from the group consisting of hydrogen, halo, hydroxy and C_{1-6} alkyl;

R^2 is selected from the group consisting of hydrogen, halo, hydroxy and C_{1-6} alkyl;

R^3 is selected from the group consisting of hydrogen, heterocyclyl, which can be monocyclic or bicyclic, heteroaryl and NR^4R^5 , wherein said heteroaryl is optionally substituted with one or two substituents independently selected from the group consisting of oxo and C_{1-6}

alkyl and said heterocyclyl is optionally substituted with one to three substituents independently selected from the group consisting of halo, hydroxy, cyano and R^x ;

R^4 is selected from the group consisting of hydrogen, cyclopropyl and C_{1-6} alkyl;

R^5 is selected from the group consisting of hydrogen and C_{1-6} alkyl, which is optionally substituted with one to three substituents selected from the group consisting of halo, hydroxy and cyano;

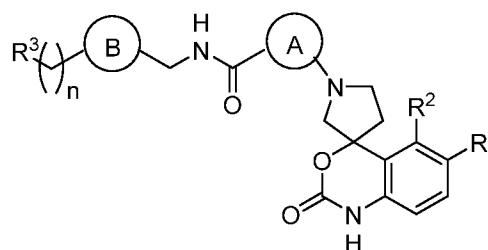
R^x is hydrogen or C_{1-6} alkyl, which is optionally substituted with one to three substituents selected from the group consisting of halo, hydroxy and methoxy;

n is an integer from zero to two;

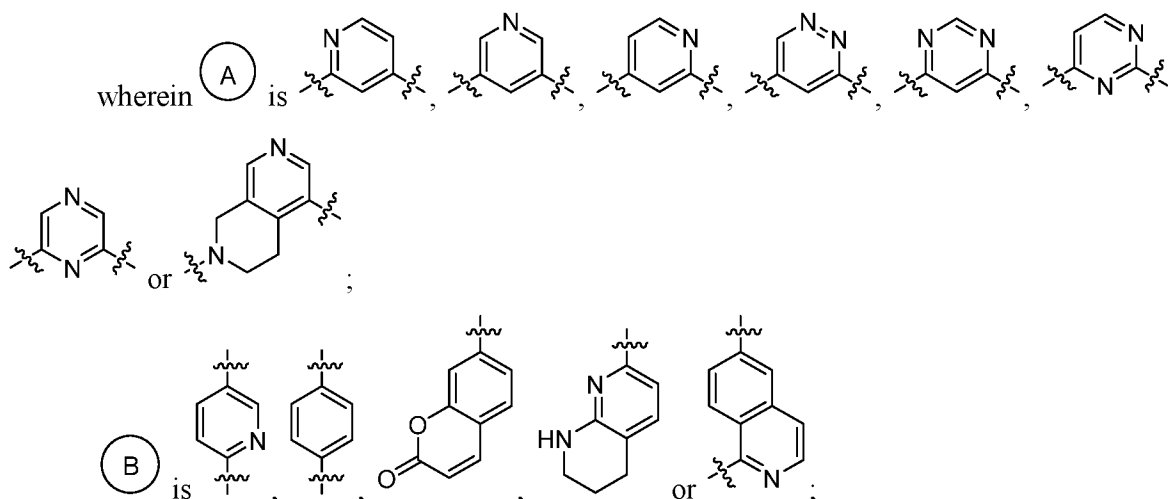
or a pharmaceutically acceptable salt thereof.

In an embodiment of the invention, X is $-CH_2-$. In another embodiment of the invention, X is $-NH(C=O)CH_2-$. In another embodiment of the invention, X is $-(C=O)NHCH_2-$.

The present invention also relates to compounds of Formula Ia:



Ia



R^1 is selected from the group consisting of hydrogen, halo, hydroxy and C_{1-6} alkyl;

R^2 is selected from the group consisting of hydrogen, halo, hydroxy and C_{1-6} alkyl;

R^3 is selected from the group consisting of hydrogen, heterocyclyl, which can be

monocyclic or bicyclic, heteroaryl and NR^4R^5 , wherein said heteroaryl is optionally substituted with one or two substituents independently selected from the group consisting of oxo and C_{1-6} alkyl and said heterocyclyl is optionally substituted with one to three substituents independently selected from the group consisting of halo, hydroxy, cyano and R^x ;

5 R^4 is selected from the group consisting of hydrogen, cyclopropyl and C_{1-6} alkyl;

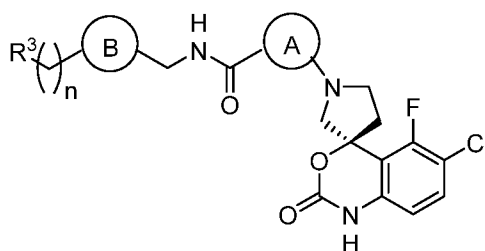
R^5 is selected from the group consisting of hydrogen and C_{1-6} alkyl, which is optionally substituted with one to three substituents selected from the group consisting of halo, hydroxy and cyano;

10 R^x is hydrogen or C_{1-6} alkyl, which is optionally substituted with one to three substituents selected from the group consisting of halo, hydroxy and methoxy;

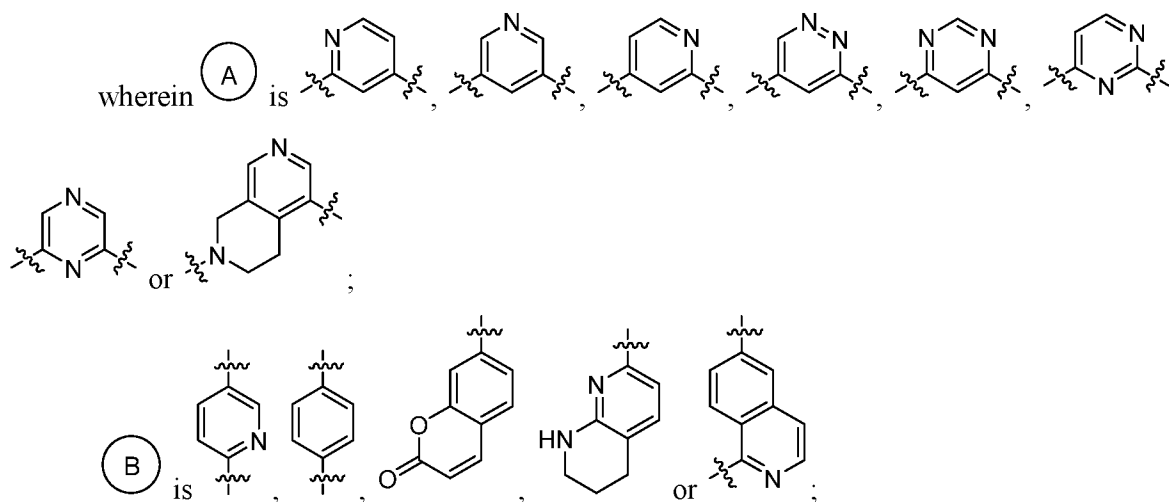
n is an integer from zero to two;

or a pharmaceutically acceptable salt thereof.

The present invention also relates to compounds of Formula 1b:



Ib



20 R^3 is selected from the group consisting of hydrogen, heterocyclyl, which can be monocyclic or bicyclic, heteroaryl and NR^4R^5 , wherein said heteroaryl is optionally substituted with one or two substituents independently selected from the group consisting of oxo and C_{1-6} alkyl and said heterocyclyl is optionally substituted with one to three substituents independently

selected from the group consisting of halo, hydroxy, cyano and R^x ;

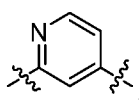
R^4 is selected from the group consisting of hydrogen, cyclopropyl and C_{1-6} alkyl;

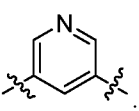
R^5 is selected from the group consisting of hydrogen and C_{1-6} alkyl, which is optionally substituted with one to three substituents selected from the group consisting of halo, hydroxy and cyano;

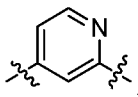
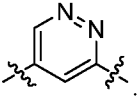
R^x is hydrogen or C_{1-6} alkyl, which is optionally substituted with one to three substituents selected from the group consisting of halo, hydroxy and methoxy;

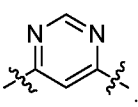
n is an integer from zero to two;

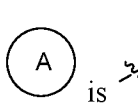
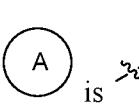
or a pharmaceutically acceptable salt thereof

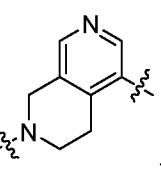
10 In an embodiment of the invention, (A) is . In another embodiment

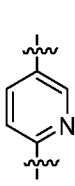
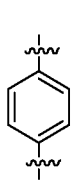
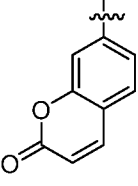
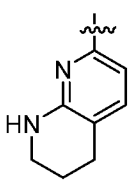
of the invention, (A) is . In another embodiment of the invention, (A) is

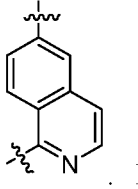
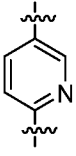
. In another embodiment of the invention, (A) is . In another

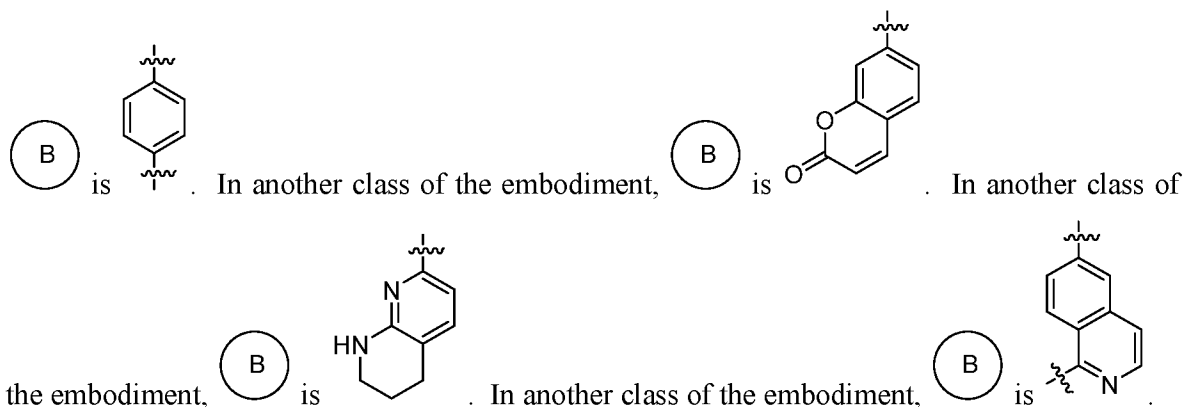
embodiment of the invention, (A) is . In another embodiment of the invention,

(A) is . In another embodiment of the invention, (A) is . In another

15 embodiment of the invention, (A) is .

In an embodiment of the invention, (B) is , , , or 

. In a class of the embodiment, (B) is . In another class of the embodiment,



In an embodiment of the invention, R^1 is halo. In a class of the embodiment, R^1 is chloro. In another class of the embodiment, R^1 is fluoro.

5 In an embodiment of the invention, R^2 is halo. In a class of the embodiment, R^2 is chloro. In another class of the embodiment, R^2 is fluoro.

In an embodiment of the invention, R^3 is heterocyclyl, which is optionally substituted with one to three halo, or R^x . In another embodiment of the invention, R^3 is heteroaryl, which is optionally substituted with methyl or oxo.

10 In an embodiment of the invention, R^4 is hydrogen, cyclopropyl or methyl.

In an embodiment of the invention, R^5 is C_{1-6} alkyl, which is optionally substituted with one to three halo, or cyano.

In an embodiment of the invention, n is zero. In another embodiment of the invention, n is one. In another embodiment of the invention, n is two.

15 In an embodiment of the invention, n is one, and R^3 is heteroaryl, which is optionally substituted with methyl or oxo.

In an embodiment of the invention, R^4 is hydrogen, cyclopropyl or methyl, and R^5 is C_{1-6} alkyl, which is optionally substituted with one to three halo, or cyano.

20 Reference to the preferred classes and subclasses set forth above is meant to include all combinations of particular and preferred groups unless stated otherwise.

Specific embodiments of the present invention include, but are not limited to the compounds identified herein as Examples 1 to 52 or pharmaceutically acceptable salts thereof.

Also included within the scope of the present invention is a pharmaceutical composition which is comprised of a compound of Formula I, Ia or Ib as described above and a pharmaceutically acceptable carrier. The invention is also contemplated to encompass a pharmaceutical composition which is comprised of a pharmaceutically acceptable carrier and any of the compounds specifically disclosed in the present application. These and other aspects of the invention will be apparent from the teachings contained herein.

The invention includes compositions for treating diseases or condition in which plasma kallikrein activity is implicated. Accordingly the invention includes compositions for treating impaired visual activity, diabetic retinopathy, wet age-related macular degeneration, diabetic macular edema, retinal vein occlusion, hereditary angioedema, diabetes, pancreatitis, cerebral hemorrhage, nephropathy, cardiomyopathy, neuropathy, inflammatory bowel disease, arthritis, inflammation, septic shock, hypotension, cancer, adult respiratory distress syndrome, disseminated intravascular coagulation, blood coagulation during cardiopulmonary bypass surgery, and bleeding from postoperative surgery in a mammal, comprising a compound of the invention in a pharmaceutically acceptable carrier. A class of the invention includes compositions for treating hereditary angioedema, uveitis, posterior uveitis, wet age-related macular degeneration, diabetic macular edema, diabetic retinopathy and retinal vein occlusion. These compositions may optionally include anti-inflammatory agents, anti-VEGF agents, immunosuppressive agents, anticoagulants, antiplatelet agents, and thrombolytic agents. The compositions can be added to blood, blood products, or mammalian organs in order to effect the desired inhibitions.

The invention also includes compositions for preventing or treating retinal vascular permeability associated with diabetic retinopathy and diabetic macular edema in a mammal, comprising a compound of the invention in a pharmaceutically acceptable carrier. These compositions may optionally include anti-inflammatory agents, anti-VEGF agents, immunosuppressive agents, anticoagulants, antiplatelet agents, and thrombolytic agents.

The invention also includes compositions for treating inflammatory conditions of the eye, which includes, but is not limited to, uveitis, posterior uveitis, macular edema, acute macular degeneration, wet age-related macular degeneration, retinal detachments, retinal vein occlusion, ocular tumors, fungal infections, viral infections, multifocal choroiditis, diabetic uveitis, diabetic macular edema, diabetic retinopathy, proliferative vitreoretinopathy, sympathetic ophthalmia, Vogt Koyanagi-Harada syndrome, histoplasmosis and uveal diffusion. These compositions may optionally include anti-inflammatory agents, anti-VEGF agents, immunosuppressive agents, anticoagulants, antiplatelet agents, and thrombolytic agents.

The invention also includes compositions treating posterior eye disease, which includes, but is not limited to, uveitis, posterior uveitis, wet age-related macular degeneration, diabetic macular edema, diabetic retinopathy and retinal vein occlusion. These compositions may optionally include anti-inflammatory agents, anti-VEGF agents, immunosuppressive agents, anticoagulants, antiplatelet agents, and thrombolytic agents.

It will be understood that the invention is directed to the compounds of structural

Formula I, Ia and Ib described herein, as well as the pharmaceutically acceptable salts of the compounds of structural Formula I, Ia and Ib and also salts that are not pharmaceutically acceptable when they are used as precursors to the free compounds or their pharmaceutically acceptable salts or in other synthetic manipulations.

5 The compounds of the present invention may be administered in the form of a pharmaceutically acceptable salt. The term "pharmaceutically acceptable salt" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. Salts of basic compounds encompassed within the term "pharmaceutically acceptable salt" refer to non-toxic salts of the compounds of this
10 invention which are generally prepared by reacting the free base with a suitable organic or inorganic acid. Representative salts of basic compounds of the present invention include, but are not limited to, the following: acetate, ascorbate, adipate, alginate, aspirate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, butyrate, camphorate, camphorsulfonate, camsylate, carbonate, chloride, clavulanate, citrate, cyclopentane propionate,
15 diethylacetic, digluconate, dihydrochloride, dodecylsulfanate, edetate, edisylate, estolate, esylate, ethanesulfonate, formic, fumarate, gluceptate, glucoheptanoate, gluconate, glutamate, glycerophosphate, glycolylarsanilate, hemisulfate, heptanoate, hexanoate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, 2-hydroxyethanesulfonate, hydroxynaphthoate, iodide, isonicotinic, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate,
20 mesylate, methylbromide, methylnitrate, methylsulfate, methanesulfonate, mucate, 2-naphthalenesulfonate, napsylate, nicotinate, nitrate, N-methylglucamine ammonium salt, oleate, oxalate, pamoate (embonate), palmitate, pantothenate, pectinate, persulfate, phosphate/diphosphate, pimelic, phenylpropionic, polygalacturonate, propionate, salicylate, stearate, sulfate, subacetate, succinate, tannate, tartrate, teoclate, thiocyanate, tosylate,
25 triethiodide, trifluoroacetate, undeconate, valerate and the like. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof include, but are not limited to, salts derived from inorganic bases including aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, mangamous, potassium, sodium, zinc, and the like. Salts derived from pharmaceutically acceptable organic
30 non-toxic bases include salts of primary, secondary, and *tertiary* amines, cyclic amines, dicyclohexyl amines and basic ion-exchange resins, such as arginine, betaine, caffeine, choline, N,N-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine,

piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like. Also, included are the basic nitrogen-containing groups may be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates like dimethyl, 5 diethyl, dibutyl; and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides and others.

These salts can be obtained by known methods, for example, by mixing a compound of the present invention with an equivalent amount and a solution containing a 10 desired acid, base, or the like, and then collecting the desired salt by filtering the salt or distilling off the solvent. The compounds of the present invention and salts thereof may form solvates with a solvent such as water, ethanol, or glycerol. The compounds of the present invention may form an acid addition salt and a salt with a base at the same time according to the type of substituent of the side chain.

15 If the compounds of Formula I, Ia or Ib simultaneously contain acidic and basic groups in the molecule the invention also includes, in addition to the salt forms mentioned, inner salts or betaines (zwitterions).

The present invention encompasses all stereoisomeric forms of the compounds of Formula I, Ia and Ib. Unless a specific stereochemistry is indicated, the present invention is 20 meant to comprehend all such isomeric forms of these compounds. Centers of asymmetry that are present in the compounds of Formula I, Ia and Ib can all independently of one another have (R) configuration or (S) configuration. When bonds to the chiral carbon are depicted as straight lines in the structural Formulas of the invention, it is understood that both the (R) and (S) configurations of the chiral carbon, and hence both each individual enantiomer and mixtures 25 thereof, are embraced within the Formula. When a particular configuration is depicted, that enantiomer (either (R) or (S), at that center) is intended. Similarly, when a compound name is recited without a chiral designation for a chiral carbon, it is understood that both the (R) and (S) configurations of the chiral carbon, and hence individual enantiomers and mixtures thereof, are embraced by the name. The production of specific stereoisomers or mixtures thereof may be 30 identified in the Examples where such stereoisomers or mixtures were obtained, but this in no way limits the inclusion of all stereoisomers and mixtures thereof from being within the scope of this invention.

Unless a specific enantiomer or diastereomer is indicated, the invention includes all possible enantiomers and diastereomers and mixtures of two or more stereoisomers, for

example mixtures of enantiomers and/or diastereomers, in all ratios. Thus, enantiomers are a subject of the invention in enantiomerically pure form, both as levorotatory and as dextrorotatory antipodes, in the form of racemates and in the form of mixtures of the two enantiomers in all ratios. In the case of a cis/trans isomerism the invention includes both the cis form and the trans form as well as mixtures of these forms in all ratios. The preparation of individual stereoisomers can be carried out, if desired, by separation of a mixture by customary methods, for example by chromatography or crystallization, by the use of stereochemically uniform starting materials for the synthesis or by stereoselective synthesis. Optionally a derivatization can be carried out before a separation of stereoisomers. The separation of a mixture of stereoisomers can be carried out at an intermediate step during the synthesis of a compound of Formula I, Ia or Ib, or it can be done on a final racemic product. Absolute stereochemistry may be determined by X-ray crystallography of crystalline products or crystalline intermediates which are derivatized, if necessary, with a reagent containing a stereogenic center of known configuration. Where compounds of this invention are capable of tautomerization, all individual tautomers as well as mixtures thereof are included in the scope of this invention. The present invention includes all such isomers, as well as salts, solvates (including hydrates) and solvated salts of such racemates, enantiomers, diastereomers and tautomers and mixtures thereof.

In the compounds of the invention, the atoms may exhibit their natural isotopic abundances, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature. The present invention is meant to include all suitable isotopic variations of the specifically and generically described compounds. For example, different isotopic forms of hydrogen (H) include protium (1H) and deuterium (2H). Protium is the predominant hydrogen isotope found in nature. Enriching for deuterium may afford certain therapeutic advantages, such as increasing *in vivo* half-life or reducing dosage requirements, or may provide a compound useful as a standard for characterization of biological samples. Isotopically-enriched compounds can be prepared without undue experimentation by conventional techniques well known to those skilled in the art or by processes analogous to those described in the general process schemes and examples herein using appropriate isotopically-enriched reagents and/or intermediates.

When any variable (e.g. R^x , etc.) occurs more than one time in any constituent, its definition on each occurrence is independent at every other occurrence. Also, combinations of substituents and variables are permissible only if such combinations result in stable compounds. Lines drawn into the ring systems from substituents represent that the indicated bond may be

attached to any of the substitutable ring atoms. If the ring system is bicyclic, it is intended that the bond be attached to any of the suitable atoms on either ring of the bicyclic moiety.

It is understood that one or more silicon (Si) atoms can be incorporated into the compounds of the instant invention in place of one or more carbon atoms by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art from readily available starting materials. Carbon and silicon differ in their covalent radius leading to differences in bond distance and the steric arrangement when comparing analogous C-element and Si-element bonds. These differences lead to subtle changes in the size and shape of silicon-containing compounds when compared to carbon. One of ordinary skill in the art would understand that size and shape differences can lead to subtle or dramatic changes in potency, solubility, lack of off-target activity, packaging properties, and so on. (Diass, J. O. *et al.* Organometallics (2006) 5:1188-1198; Showell, G.A. *et al.* Bioorganic & Medicinal Chemistry Letters (2006) 16:2555-2558).

It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials. If a substituent is itself substituted with more than one group, it is understood that these multiple groups may be on the same carbon or on different carbons, so long as a stable structure results. The phrase “optionally substituted” (with one or more substituents) should be understood as meaning that the group in question is either unsubstituted or may be substituted with one or more substituents.

Furthermore, compounds of the present invention may exist in amorphous form and/or one or more crystalline forms, and as such all amorphous and crystalline forms and mixtures thereof of the compounds of Formula I, Ia and Ib are intended to be included within the scope of the present invention. In addition, some of the compounds of the instant invention may form solvates with water (i.e., a hydrate) or common organic solvents. Such solvates and hydrates, particularly the pharmaceutically acceptable solvates and hydrates, of the instant compounds are likewise encompassed within the scope of this invention, along with un-solvated and anhydrous forms.

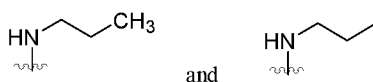
Also, in the case of a carboxylic acid (-COOH) or alcohol group being present in the compounds of the present invention, pharmaceutically acceptable esters of carboxylic acid derivatives, such as methyl, ethyl, or pivaloyloxymethyl, or acyl derivatives of alcohols, such as *O*-acetyl, *O*-pivaloyl, *O*-benzoyl, and *O*-aminoacyl, can be employed. Included are those esters

and acyl groups known in the art for modifying the solubility or hydrolysis characteristics for use as sustained-release or prodrug formulations.

Any pharmaceutically acceptable pro-drug modification of a compound of this invention which results in conversion in vivo to a compound within the scope of this invention is also within the scope of this invention. For example, esters can optionally be made by esterification of an available carboxylic acid group or by formation of an ester on an available hydroxy group in a compound. Similarly, labile amides can be made. Pharmaceutically acceptable esters or amides of the compounds of this invention may be prepared to act as pro-drugs which can be hydrolyzed back to an acid (or -COO^- depending on the pH of the fluid or tissue where conversion takes place) or hydroxy form particularly in vivo and as such are encompassed within the scope of this invention. Examples of pharmaceutically acceptable pro-drug modifications include, but are not limited to, -C_{1-6} alkyl esters and -C_{1-6} alkyl substituted with phenyl esters.

Accordingly, the compounds within the generic structural formulas, embodiments and specific compounds described and claimed herein encompass salts, all possible stereoisomers and tautomers, physical forms (e.g., amorphous and crystalline forms), solvate and hydrate forms thereof and any combination of these forms, as well as the salts thereof, pro-drug forms thereof, and salts of pro-drug forms thereof, where such forms are possible unless specified otherwise.

Except where noted herein, the terms "alkyl" and "alkylene" are intended to include both branched- and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. Commonly used abbreviations for alkyl groups are used throughout the specification, e.g. methyl, may be represented by conventional abbreviations including "Me" or CH_3 or a symbol that is an extended bond as the terminal group, e.g. " $\text{---}\text{X}$ ", ethyl may be represented by "Et" or CH_2CH_3 , propyl may be represented by "Pr" or $\text{CH}_2\text{CH}_2\text{CH}_3$, butyl may be represented by "Bu" or $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, etc. " C_{1-4} alkyl" (or " C_{1-4} alkyl") for example, means linear or branched chain alkyl groups, including all isomers, having the specified number of carbon atoms. For example, the structures



have equivalent meanings. C_{1-4} alkyl includes n-, iso-, sec- and t-butyl, n- and isopropyl, ethyl and methyl. If no number is specified, 1-4 carbon atoms are intended for linear or branched alkyl groups.

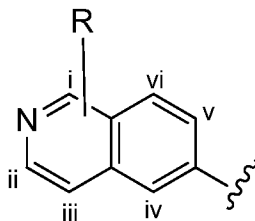
Except where noted, the term “heteroaryl”, as used herein, represents a stable monocyclic or bicyclic ring system of up to 10 atoms in each ring, wherein at least one ring is aromatic, and at least one ring contains from 1 to 4 heteroatoms selected from the group consisting of O, N and S. Bicyclic heteroaryl ring systems include fused ring systems, where two rings share two atoms, and spiro ring systems, where two rings share one atom. Heteroaryl groups within the scope of this definition include but are not limited to: azaindolyl, benzoimidazolyl, benzisoxazolyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, dihydroindenyl, furanyl, indolinyl, indolyl, indolaziny, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthalenyl, naphthpyridinyl, oxadiazolyl, oxazolyl, oxazoline, isoxazoline, pyranyl, pyrazinyl, pyrazolyl, pyrazolopyrimidinyl, pyridazinyl, pyridopyridinyl, pyridinyl, pyridyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalyl, tetrahydronaphthyridinyl, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, dihydrobenzoimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydroindolyl, dihydroquinolinyl, dihydrobenzodioxinyl, dihydropyrazoloxazinyl, dihydropyrazolythiazinedioxidyl, methylenedioxybenzene, benzothiazolyl, benzothienyl, quinolinyl, isoquinolinyl, oxazolyl, tetra-hydroquinoline, sulfolanyl, 1,3-benzodioxolyl, 3-oxo-3,4-dihydro-2N-benzo[b][1,4]thiazine, imidazopyridinyl, 2-oxo-2,3-dihydroimidazolyl, 3,4-dihydrobenzoxazinyl, 2-oxo-2,3-dihydrooxazolyl, dihydroisobenzofuranyl, 1-oxoisoindolinyl, dioxido-2,3-dihydrobenzothiazolyl, 2-oxopyridyl, tetrahydroisoquinolyl, tetrahydrothiazolo[5,4-c]pyridyl, 4-oxo-dihydroquinazolinyl, dihydro-1'H-spirocyclopropane-1,4'-isoquinolyl. If the heteroaryl contains nitrogen atoms, it is understood that the corresponding N-oxides thereof are also encompassed by this definition.

The term "heterocycle" or “heterocyclyl” as used herein is intended to mean a stable nonaromatic monocyclic or bicyclic ring system of up to 10 atoms in each ring, unless otherwise specified, containing from 1 to 4 heteroatoms selected from the group consisting of O, N, S, SO, or SO₂. Bicyclic heterocyclic ring systems include fused ring systems, where two rings share two atoms, and spiro ring systems, where two rings share one atom. “Heterocyclyl” therefore includes, but is not limited to the following: azabicyclohexanyl, azaspirohexanyl, azaspirononanyl, azaspirooctanyl, azetidiny, dioxanyl, isochromanyl, oxadiazaspirodecenyl, oxaspirooctanyl, oxazolidinonyl, 2-oxo-azabicyclo[3.1.0]hexanyl, piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, tetrahydrofurnayl, tetrahydropyranyl, dihydropiperidinyl, tetrahydrothiophenyl and the like. If the heterocycle contains a nitrogen, it is understood that the corresponding N-oxides thereof are also encompassed by this definition.

Except where noted, the term "halogen" or "halo" means fluorine, chlorine, bromine or iodine.

"Celite®" (Fluka) diatomite is diatomaceous earth, and can be referred to as "celite".

5 Except where noted herein, structures containing substituent variables such as variable "R" below:



which are depicted as not being attached to any one particular bicyclic ring carbon, represent structures in which the variable can be optionally attached to any bicyclic ring carbon atom. For example, variable R shown in the above structure can be attached to any one of 6 bicyclic ring carbon atoms i, ii, iii, iv, v or vi.

Except where noted herein, bicyclic ring systems include fused ring systems, where two rings share two atoms, and spiro ring systems, where two rings share one atom.

The invention also relates to medicaments containing at least one compound of the Formula I, Ia and Ib and/or of a pharmaceutically acceptable salt of the compound of the Formula I, Ia and Ib and/or an optionally stereoisomeric form of the compound of the Formula I, Ia and Ib or a pharmaceutically acceptable salt of the stereoisomeric form of the compound of Formula I, Ia and Ib, together with a pharmaceutically suitable and pharmaceutically acceptable vehicle, additive and/or other active substances and auxiliaries.

20 The term "patient" used herein is taken to mean mammals such as primates, humans, sheep, horses, cattle, pigs, dogs, cats, rats, and mice.

The medicaments according to the invention can be administered by oral, inhalative, rectal or transdermal administration or by subcutaneous, intraarticular, intraperitoneal or intravenous injection. Oral administration is preferred. Coating of stents with compounds of the Formulas I and other surfaces which come into contact with blood in the body is possible.

The invention also relates to a process for the production of a medicament, which comprises bringing at least one compound of the Formula I or Ia into a suitable administration form using a pharmaceutically suitable and pharmaceutically acceptable carrier and optionally further suitable active substances, additives or auxiliaries.

30 Suitable solid or galenical preparation forms are, for example, granules, powders,

coated tablets, tablets, (micro)capsules, suppositories, syrups, juices, suspensions, emulsions, drops or injectable solutions and preparations having prolonged release of active substance, in whose preparation customary excipients such as vehicles, disintegrants, binders, coating agents, swelling agents, glidants or lubricants, flavorings, sweeteners and solubilizers are used.

5 Frequently used auxiliaries which may be mentioned are magnesium carbonate, titanium dioxide, lactose, mannitol and other sugars, talc, lactose, gelatin, starch, cellulose and its derivatives, animal and plant oils such as cod liver oil, sunflower, peanut or sesame oil, polyethylene glycol and solvents such as, for example, sterile water and mono- or polyhydric alcohols such as glycerol.

10 The dosage regimen utilizing the plasma kallikrein inhibitors is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the
15 effective amount of the drug required to prevent, counter, or arrest the progress of the condition.

Oral dosages of the plasma kallikrein inhibitors, when used for the indicated effects, will range between about 0.01 mg per kg of body weight per day (mg/kg/day) to about 30 mg/kg/day, preferably 0.025-7.5 mg/kg/day, more preferably 0.1-2.5 mg/kg/day, and most preferably 0.1-0.5 mg/kg/day (unless specified otherwise, amounts of active ingredients are on
20 free base basis). For example, an 80 kg patient would receive between about 0.8 mg/day and 2.4 g/day, preferably 2-600 mg/day, more preferably 8-200 mg/day, and most preferably 8-40 mg/day. A suitably prepared medicament for once a day administration would thus contain between 0.8 mg and 2.4 g, preferably between 2 mg and 600 mg, more preferably between 8 mg and 200 mg, and most preferably 8 mg and 40 mg, e.g., 8 mg, 10 mg, 20 mg and 40 mg. Advantageously,
25 the plasma kallikrein inhibitors may be administered in divided doses of two, three, or four times daily. For administration twice a day, a suitably prepared medicament would contain between 0.4 mg and 4 g, preferably between 1 mg and 300 mg, more preferably between 4 mg and 100 mg, and most preferably 4 mg and 20 mg, e.g., 4 mg, 5 mg, 10 mg and 20 mg.

Intravenously, the patient would receive the active ingredient in quantities
30 sufficient to deliver between 0.025-7.5 mg/kg/day, preferably 0.1-2.5 mg/kg/day, and more preferably 0.1-0.5 mg/kg/day. Such quantities may be administered in a number of suitable ways, e.g. large volumes of low concentrations of active ingredient during one extended period of time or several times a day, low volumes of high concentrations of active ingredient during a short period of time, e.g. once a day. Typically, a conventional intravenous formulation may be

prepared which contains a concentration of active ingredient of between about 0.01-1.0 mg/mL, e.g. 0.1 mg/mL, 0.3 mg/mL, and 0.6 mg/mL, and administered in amounts per day of between 0.01 mL/kg patient weight and 10.0 mL/kg patient weight, e.g. 0.1 mL/kg, 0.2 mL/kg, 0.5 mL/kg. In one example, an 80 kg patient, receiving 8 mL twice a day of an intravenous formulation having a concentration of active ingredient of 0.5 mg/mL, receives 8 mg of active ingredient per day. Glucuronic acid, L-lactic acid, acetic acid, citric acid or any pharmaceutically acceptable acid/conjugate base with reasonable buffering capacity in the pH range acceptable for intravenous administration may be used as buffers. The choice of appropriate buffer and pH of a formulation, depending on solubility of the drug to be administered, is readily made by a person having ordinary skill in the art.

Compounds of Formula I, Ia and Ib can be administered both as a monotherapy and in combination with other therapeutic agents, including but not limited to anti-inflammatory agents, anti-VEGF agents, immunosuppressive agents, anticoagulants, antiplatelet agents, and thrombolytic agents.

An "anti-inflammatory agent" is any agent which is directly or indirectly effective in the reduction of inflammation when administered at a therapeutically effective level. "Anti-inflammatory agent" includes, but is not limited to steroidal anti-inflammatory agents and glucocorticoids. Suitable anti-inflammatory agents include, but are not limited to, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone and triamcinolone.

An "anti-VEGF agent" is any agent which is directly or indirectly effective in inhibiting the activity of VEGF (Vascular Endothelial Growth Factor). Suitable anti-VEGF agents include, but are not limited to, bevacizumab, ranibizumab, brolucizumab and aflibercept.

An "immunosuppressant agent" is any agent which is directly or indirectly effective in suppressing, or reducing, the strength of the body's immune system. Suitable immunosuppressant agents include, but are not limited to, corticosteroids (for example, prednisone, budesonide, prednisolone), janus kinase inhibitors (for example, tofacitinib), calcineurin inhibitors (for example, cyclosporin, tacrolimus), mTOR inhibitors (for example, sirolimus, everolimus), IMDH inhibitors (for example, azathioprine, leflunomide, mycophenolate), biologics (for example, abatacept, adalimumab, anakinra, certolizumab, etanercept, golimumab, infliximab, ixekizumab, natalizumab, rituximab, secukinumab, tocilizumab, ustekinumab, vedolizumab), and monoclonal antibodies (for example, basiliximab, daclizumab).

Suitable anticoagulants include, but are not limited to, factor XIa inhibitors, thrombin inhibitors, thrombin receptor antagonists, factor VIIa inhibitors, factor Xa inhibitors, factor IXa inhibitors, factor XIIa inhibitors, adenosine diphosphate antiplatelet agents (e.g., P2Y₁₂ antagonists), fibrinogen receptor antagonists (e.g. to treat or prevent unstable angina or to prevent reocclusion after angioplasty and restenosis), other anticoagulants such as aspirin, and thrombolytic agents such as plasminogen activators or streptokinase to achieve synergistic effects in the treatment of various vascular pathologies. Such anticoagulants include, for example, apixaban, dabigatran, cangrelor, ticagrelor, vorapaxar, clopidogrel, edoxaban, mipomersen, prasugrel, rivaroxaban, and semuloparin. For example, patients suffering from coronary artery disease, and patients subjected to angioplasty procedures, would benefit from coadministration of fibrinogen receptor antagonists and thrombin inhibitors.

In certain embodiments the anti-inflammatory agents, anti-VEGF agents, immunosuppressant agents, anticoagulants, antiplatelet agents, and thrombolytic agents described herein are employed in their conventional dosage ranges and regimens as reported in the art, including, for example, the dosages described in editions of the Physicians' Desk Reference, such as the 70th edition (2016) and earlier editions. In other embodiments, the anti-inflammatory agents, anti-VEGF agents, immunosuppressant agents, anticoagulants, antiplatelet agents, and thrombolytic agents described herein are employed in lower than their conventional dosage ranges.

Alternatively or additionally, one or more additional pharmacologically active agents may be administered in combination with a compound of the invention. The additional active agent (or agents) is intended to mean a pharmaceutically active agent (or agents) that is active in the body, including pro-drugs that convert to pharmaceutically active form after administration, which is different from the compound of the invention, and also includes free-acid, free-base and pharmaceutically acceptable salts of said additional active agents when such forms are sold commercially or are otherwise chemically possible. Generally, any suitable additional active agent or agents, including but not limited to anti-hypertensive agents, additional diuretics, anti-atherosclerotic agents such as a lipid modifying compound, anti-diabetic agents and/or anti-obesity agents may be used in any combination with the compound of the invention in a single dosage formulation (a fixed dose drug combination), or may be administered to the patient in one or more separate dosage formulations which allows for concurrent or sequential administration of the active agents (co-administration of the separate active agents). Examples of additional active agents which may be employed include but are not limited to angiotensin converting enzyme inhibitors (e.g. alacepril, benazepril, captopril, ceronapril, cilazapril, delapril,

enalapril, enalaprilat, fosinopril, imidapril, lisinopril, moveltipril, perindopril, quinapril, ramipril, spirapril, temocapril, or trandolapril); angiotensin II receptor antagonists also known as angiotensin receptor blockers or ARBs, which may be in free-base, free-acid, salt or pro-drug form, such as azilsartan, e.g., azilsartan medoxomil potassium (EDARBI®), candesartan, e.g.,
5 candesartan cilexetil (ATACAND®), eprosartan, e.g., eprosartan mesylate (TEVETAN®), irbesartan (AVAPRO®), losartan, e.g., losartan potassium (COZAAR®), olmesartan, e.g., olmesartan medoximil (BENICAR®), telmisartan (MICARDIS®), valsartan (DIOVAN®), and any of these drugs used in combination with a thiazide-like diuretic such as hydrochlorothiazide (e.g., HYZAAR®, DIOVAN HCT®, ATACAND HCT®), etc.); potassium sparing diuretics such
10 as amiloride HCl, spironolactone, epleranone, triamterene, each with or without HCTZ; neutral endopeptidase inhibitors (e.g., thiorphan and phosphoramidon); aldosterone antagonists; aldosterone synthase inhibitors; renin inhibitors; enalkrein; RO 42-5892; A 65317; CP 80794; ES 1005; ES 8891; SQ 34017; aliskiren (2(S),4(S),5(S),7(S)-N-(2-carbamoyl-2-methylpropyl)-5-amino-4-hydroxy-2,7-diisopropyl-8-[4-methoxy-3-(3-methoxypropoxy)-phenyl]-octanamid
15 hemifumarate) SPP600, SPP630 and SPP635); endothelin receptor antagonists; vasodilators (e.g. nitroprusside); calcium channel blockers (e.g., amlodipine, nifedipine, verapamil, diltiazem, felodipine, gallopamil, niludipine, nimodipine, nicardipine); potassium channel activators (e.g., nicorandil, pinacidil, cromakalim, minoxidil, aprilkalim, loprazolam); sympatholitics; beta-adrenergic blocking drugs (e.g., acebutolol, atenolol, betaxolol, bisoprolol, carvedilol,
20 metoprolol, metoprolol tartate, nadolol, propranolol, sotalol, timolol); alpha adrenergic blocking drugs (e.g., doxazosin, prazosin or alpha methyl dopa); central alpha adrenergic agonists; peripheral vasodilators (e.g. hydralazine); lipid lowering agents, e.g., HMG-CoA reductase inhibitors such as simvastatin and lovastatin which are marketed as ZOCOR® and MEVACOR® in lactone pro-drug form and function as inhibitors after administration, and pharmaceutically
25 acceptable salts of dihydroxy open ring acid HMG-CoA reductase inhibitors such as atorvastatin (particularly the calcium salt sold in LIPITOR®), rosuvastatin (particularly the calcium salt sold in CRESTOR®), pravastatin (particularly the sodium salt sold in PRAVACHOL®), and fluvastatin (particularly the sodium salt sold in LESCOL®); a cholesterol absorption inhibitor such as ezetimibe (ZETIA®), and ezetimibe in combination with any other lipid lowering agents
30 such as the HMG-CoA reductase inhibitors noted above and particularly with simvastatin (VYTORIN®) or with atorvastatin calcium; niacin in immediate-release or controlled release forms, and particularly niacin in combination with a DP antagonist such as laropiprant and/or with an HMG-CoA reductase inhibitor; niacin receptor agonists such as acipimox and acifran, as

well as niacin receptor partial agonists; metabolic altering agents including insulin sensitizing agents and related compounds for the treatment of diabetes such as biguanides (e.g., metformin), meglitinides (e.g., repaglinide, nateglinide), sulfonylureas (e.g., chlorpropamide, glimepiride, glipizide, glyburide, tolazamide, tolbutamide), thiazolidinediones also referred to as glitazones (e.g., pioglitazone, rosiglitazone), alpha glucosidase inhibitors (e.g., acarbose, miglitol), dipeptidyl peptidase inhibitors, (e.g., sitagliptin (JANUVIA®), alogliptin, vildagliptin, saxagliptin, linagliptin, dutogliptin, gemigliptin), ergot alkaloids (e.g., bromocriptine), combination medications such as JANUMET® (sitagliptin with metformin), and injectable diabetes medications such as exenatide and pramlintide acetate; inhibitors of glucose uptake, such as sodium-glucose transporter (SGLT) inhibitors and its various isoforms, such as SGLT-1, SGLT-2 (e.g., ASP-1941, TS-071, BI-10773, tofogliflozin, LX-4211, canagliflozin, dapagliflozin, ertugliflozin, ipragliflozin, remogliflozin and sotagliflozin), and SGLT-3; or with other drugs beneficial for the prevention or the treatment of the above-mentioned diseases including but not limited to diazoxide; and including the free-acid, free-base, and pharmaceutically acceptable salt forms, pro-drug forms, e.g., esters, and salts of pro-drugs of the above medicinal agents, where chemically possible. Trademark names of pharmaceutical drugs noted above are provided for exemplification of the marketed form of the active agent(s); such pharmaceutical drugs could be used in a separate dosage form for concurrent or sequential administration with a compound of the invention, or the active agent(s) therein could be used in a fixed dose drug combination including a compound of the invention.

Typical doses of the plasma kallikrein inhibitors of the invention in combination with other suitable agents may be the same as those doses of plasma kallikrein inhibitors administered without coadministration of additional agents, or may be substantially less than those doses of plasma kallikrein inhibitors administered without coadministration of additional agents, depending on a patient's therapeutic needs.

The compounds are administered to a mammal in a therapeutically effective amount. By "therapeutically effective amount" it is meant an amount of a compound of the present invention that, when administered alone or in combination with an additional therapeutic agent to a mammal, is effective to treat (i.e., prevent, inhibit or ameliorate) the disease condition or treat the progression of the disease in a host.

The compounds of the invention are preferably administered alone to a mammal in a therapeutically effective amount. However, the compounds of the invention can also be administered in combination with an additional therapeutic agent, as defined below, to a mammal in a therapeutically effective amount. When administered in a combination, the combination of

compounds is preferably, but not necessarily, a synergistic combination. Synergy, as described for example by Chou and Talalay, *Adv. Enzyme Regul.* 1984, 22, 27-55, occurs when the effect (in this case, inhibition of the desired target) of the compounds when administered in combination is greater than the additive effect of each of the compounds when administered individually as a single agent. In general, a synergistic effect is most clearly demonstrated at suboptimal concentrations of the compounds. Synergy can be in terms of lower cytotoxicity, increased anticoagulant effect, or some other beneficial effect of the combination compared with the individual components.

By “administered in combination” or “combination therapy” it is meant that the compound of the present invention and one or more additional therapeutic agents are administered concurrently to the mammal being treated. When administered in combination each component may be administered at the same time or sequentially in any order at different points in time. Thus, each component may be administered separately but sufficiently closely in time so as to provide the desired therapeutic effect. The administration of each component does not need to be via the same route of administration; for example, one component can be administered orally, and another can be delivered into the vitreous of the eye.

The present invention is not limited in scope by the specific embodiments disclosed in the examples which are intended as illustrations of a few aspects of the invention and any embodiments that are functionally equivalent are within the scope of this invention. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the relevant art and are intended to fall within the scope of the appended claims.

GENERAL METHODS

Compounds of the present invention may be prepared using conventional techniques or according to the methodology outlined in the following general synthetic schemes. One skilled in the art can vary the procedures and reagents shown to arrive at similar intermediates and/or final compounds.

NMR spectra were measured on VARIAN or Bruker NMR Systems (400, 500 or 600 MHz). Chemical shifts are reported in ppm downfield and up field from tetramethylsilane (TMS) and referenced to either internal TMS or solvent resonances (^1H NMR: δ 7.27 for CDCl_3 , δ 2.50 for $(\text{CD}_3)(\text{CHD}_2)\text{SO}$, and ^{13}C NMR: δ 77.02 for CDCl_3 , δ 39.51 for $(\text{CD}_3)_2\text{SO}$. Coupling constants (J) are expressed in hertz (Hz), and spin multiplicities are given as s (singlet), d (doublet), dd (double doublet), t (triplet), m (multiplet), and br (broad). Chiral resolutions can be performed on either Waters Thar 80 SFC or Berger MG II preparative SFC systems. LC-MS data

can be recorded on SHIMADAZU LC-MS-2020, SHIMADAZU LC-MS-2010, or Agilent 1100 series LC-MS, Agilent Prime-1260, or Waters Acquity LC-MS instruments using C18 columns employing a MeCN gradient in water containing 0.02 to 0.1% TFA. UV detections were at 220 and/or 254 nm and ESI ionization was used for MS detection.

When chiral resolution was achieved by chromatography using chiral columns, the chiral columns used for SFC chiral resolutions are listed in tables. Some of the chiral columns used were CHIRALPAK AD, CHIRALCEL OJ, CHIRALPAK AS, CHIRALPAK AY, CHIRALPAK IA, CHIRALPAK AD-H, and CHIRALPAK AS-H. Henceforth, they will be referred by their two or three letter abbreviations. As a convention, the fast-eluting isomer from a chiral resolution is always listed first in this table followed immediately by the slower-eluting isomer from the same resolution. If more than two isomers were separated, they will be always listed in the tables in order they were eluted, such as Peak 1 followed by Peak 2, Peak 3 and so on. A * symbol near a chiral center in a structure denotes that this chiral center was resolved by chiral resolution without its stereochemical configuration unambiguously determined.

Several catalysts and ligands are used in the following procedures. "RuPhos" is 2-Dicyclohexylphosphino-2',6'-diisopropoxybiphenyl. "RuPhos Pd G3" is (2-Dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate. "Xphos" is 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl. "Xphos Pd G3" is (2-Dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate. "Ni(II) pre-catalyst ([Ni(dtbbpy)(H₂O)₄]Cl₂)" is [4,4'-bis(1,1-dimethylethyl)-2,2'-bipyridine]nickel(II) dichloride. "[Ir{dFCF₃ppy}₂(dtbbpy)]PF₆" is [4,4'-Bis(1,1-dimethylethyl)-2,2'-bipyridine-*N*¹,*N*^{1'}]bis[3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl-*N*]phenyl-C]Iridium(III) hexafluorophosphate. These catalysts and ligands are available from Millipore Sigma.

Also, TLC is thin layer chromatography; UV is ultraviolet; W is watts; wt. % is percentage by weight; x g is times gravity; α_D is the specific rotation of polarized light at 589 nm; °C is degrees Celsius; % w/v is percentage in weight of the former agent relative to the volume of the latter agent; cpm is counts per minute; δ_H is chemical shift; Rochelle's salt is potassium sodium tartrate; MS is mass spectrum, and a mass spectrum obtained by ES-MS may be denoted herein by "LC-MS"; *m/z* is mass to charge ratio.

For purposes of this specification, the following abbreviations have the indicated meanings:

Ac	Acetyl
ACN	Acetonitrile
AcOH	acetic acid
aq.	aqueous
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Boc or BOC	<i>tert</i> -butoxycarbonyl
br	broad
Bu or ⁿ Bu	Butyl (normal)
calcd.	calculated
δ	chemical shift
d	doublet
dba	dibenzylideneacetone
DCM	dichloromethane
dd	doublet of doublets
DIEA	or <i>N,N</i> -diisopropylethylamine
Hünig's base	
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DTT	dithiothreitol
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDTA	ethylenediamine tetraacetic acid
equiv.	equivalent
ESI	electrospray ionization
Et	ethyl
Et ₂ O	diethyl ether
EtOH	ethanol
EtOAc	ethyl acetate
g	grams
GST	glutathione S-transferase
h	hour
HATU	<i>N,N,N',N'</i> -tetramethyl- <i>O</i> -(7-azabenzotriazol-1-yl)uronium hexafluorophosphate

HPLC	high-performance liquid chromatography
Hz	Hertz
IPA	isopropanol
ⁱ Pr	isopropyl
<i>J</i>	coupling constant
LC	liquid chromatography
LCMS	liquid chromatography mass spectrometry
LED	light emitting diode
m	multiplet
M	molar
Me	methyl
MeOH	methanol
mg	milligrams
MHz	megahertz
min	minute
μL	microliters
mL	milliliters
mM	millimolar
mmol	millimoles
MS	mass spectrometry
<i>N</i>	nitrogen substituted
nm	nanometer
NMR	nuclear magnetic resonance spectroscopy
OAc	acetate
Ph	phenyl
Pr	propyl
q	quartet
<i>rac</i>	racemic mixture
RT or rt	room temperature (ambient, about 25 °C)
s	singlet
satd.	saturated

SFC	supercritical fluid chromatography
t	triplet
T3P	propanephosphonic acid anhydride
^t Bu	<i>tert</i> -butyl
^t BuOH	<i>tert</i> -butyl alcohol
TEA	triethylamine (Et ₃ N)
<i>tert</i>	tertiary
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
Tris	tris(hydroxymethyl)aminomethane

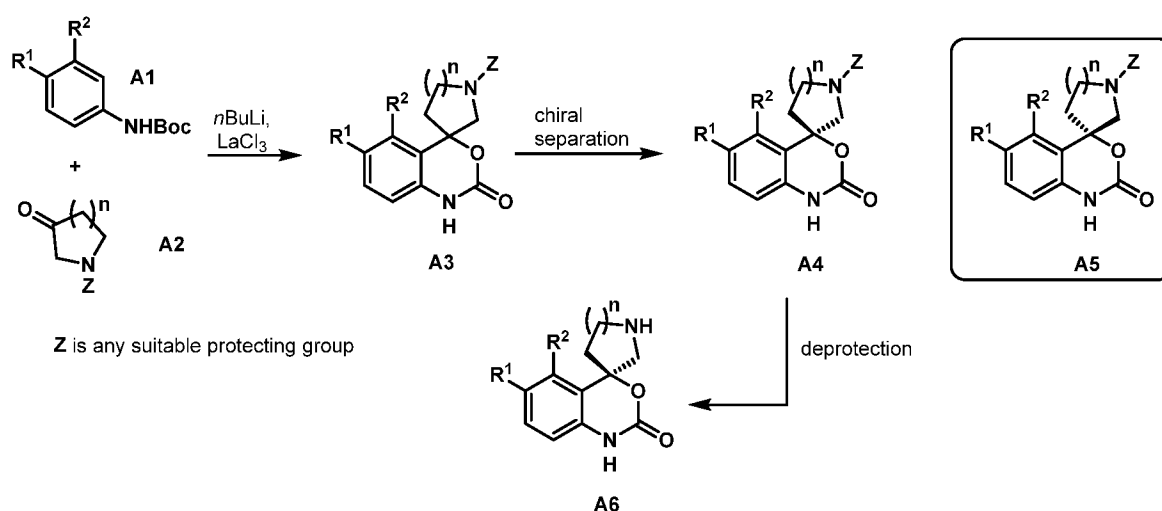
General

Starting materials used were obtained from commercial sources or prepared in other examples, unless otherwise noted.

- 5 The methods used for the preparation of the compounds of this invention are illustrated by the following schemes. Unless specified otherwise, all starting materials used are commercially available.

General Schemes

Scheme A.

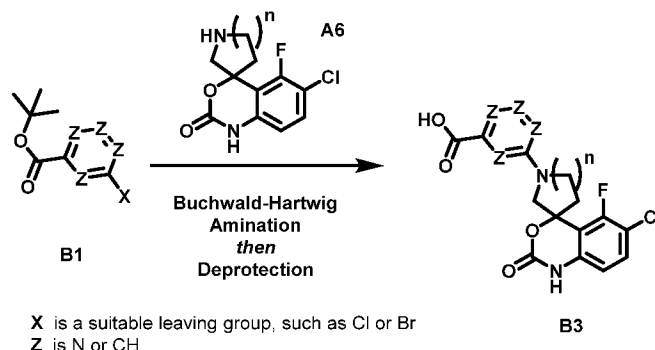


Scheme A illustrates the synthetic sequence for preparation of substituted spirocarbamates **A6** from a Boc-protected aniline **A1** and ketone **A2**. Directed lithiation of aniline **A1** and addition into the heterocyclic ketone **A2** occurs in the presence of Lewis acid (eg. LaCl₃). The tertiary

alcohol undergoes *in situ* cyclization onto the carbamate to give spirocarbamate derivative **A3**, which can be subjected to chiral separation, preferably using supercritical flow chromatography (SFC) to afford enantiomers **A4** and **A5**. Deprotection of either enantiomer (**A4**, e.g.) gives the secondary amine **A6**.

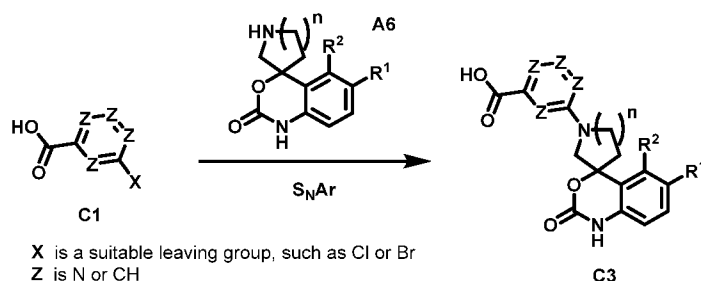
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Scheme B.



Scheme **B** illustrates the synthetic sequence for preparation of *N*-heteroarylated carboxylic acids of spirocarbamate **B3** from halogen-bearing heteroaromatic *tert*-butyl ester **B1** and spirocarbamate **B2**. A Buchwald-Hartwig amination between **B1** and **B2** can be affected using a suitable palladium pre-catalyst containing a monodentate phosphine ligand, such as RuPhos Pd G3, and suitable alkoxide base, such as NaO^tBu, followed by deprotection with TFA to give spirocarbamate derivative **B3**.

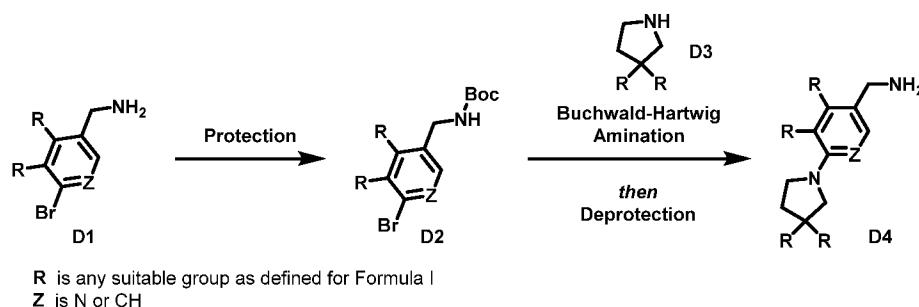
15 Scheme C.



Scheme **C** illustrates the synthetic sequence for preparation of *N*-heteroarylated carboxylic acids of spirocarbamate **C3** from halogen-bearing heteroaromatic carboxylic acid **C1** and spirocarbamate **C2**. S_NAr between **C1** and **C2** can be affected using a suitable amine base, such as TEA or DIEA, or a solid base, such as Cs₂CO₃ or NaO^tBu, or the like, to give spirocarbamate derivative **C3**.

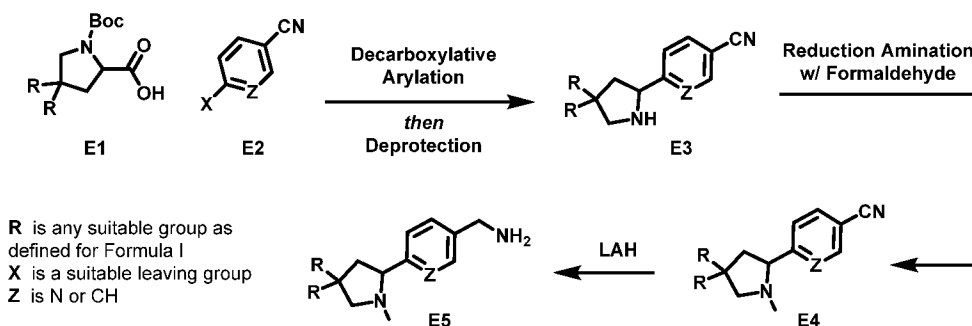
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Scheme D.



- Scheme **D** illustrates the synthetic sequence for preparation of substituted *N*-linked pyrrolidyl benzylamine **D4** from Boc-protected benzylamine **D2** and substituted pyrrolidine **D3**. Boc-protection of benzylamine **D1** afford Boc-protected intermediate **D2**, which can be reacted with substituted pyrrolidine **D3** in a Buchwald-Hartwig amination using a suitable palladium pre-catalyst, such as RuPhos Pd 3G or XPhos Pd 3G. Alternatively, a suitable palladium (0) source can be used, such as Pd₂(dba)₃, in the presence of a suitable phosphine ligand, such as RuPhos, XPhos, or BINAP, to affect the transformation. In either case, the amination reaction is conducted in the presence of an appropriate base, such as NaO^tBu or Cs₂CO₃. Deprotection using TFA affords substituted pyrrolidyl benzylamine **D4**.

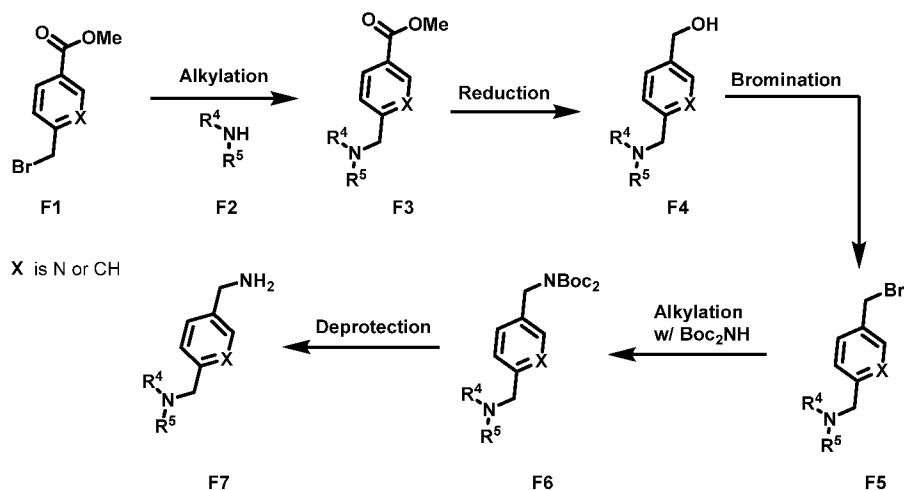
Scheme E.



- Scheme **E** illustrates the synthetic sequence for preparation of substituted C-2-linked pyrrolidyl benzylamine **E5** from Boc-protected 2-carboxypyrrolidine **E1** and cyanoaryl halide **E2**. Decarboxylative arylation using dual Ir/Ni catalysis with **E1** and **E2** is conducted using a combination of suitable Ir-photocatalyst, such as [Ir{dF(CF₃)ppy}₂(bpy)]PF₆, Ni(II) pre-catalyst ([Ni(dtbppy)(H₂O)₄]Cl₂), in the presence of a suitable base, such as Cs₂CO₃. Reactions can be performed in a photoreactor equipped with a blue LED. The resulting Boc-protected intermediates are deprotected with TFA to afford C-2-linked pyrrolidyl nitrile aromatic **E3**. *N*-methylation can be achieved by way of reductive amination with formaldehyde using a mild reducing agent [NaHB(OAc)₃, e.g.] to afford intermediate **E4**. Reduction of the nitrile with a

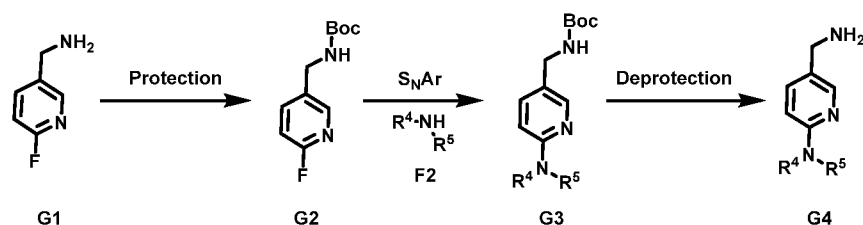
suitable reducing agent, such as LAH, yields substituted C-2-linked pyrrolidyl benzylamine **E5**.

Scheme F.



- 5 Scheme **F** illustrates the synthetic sequence for preparation of benzylamine **F7** from benzyl bromide **F1** and nitrogen heterocycle **F2**. Alkylation between benzyl bromide **F1** and nitrogen heterocycle **F2** can be carried out in the presence of a suitable base, such as K₂CO₃ or NaH, to give alkylated intermediate **F3**. The subsequent reduction of the methyl ester to the alcohol is affected with a mild reducing agent, such as NaBH₄, to give benzylic alcohol intermediate **F4**.
- 10 Conversion to the benzylic bromide occurred with a suitable brominating reagent (PBr₃ or HBr, e.g.) affords intermediate **F5**, which can be subjected to alkylation with *bis*-Boc amine to give Boc-protected intermediate **F6**. Deprotection with TFA yields benzyl amine intermediate **F7**.

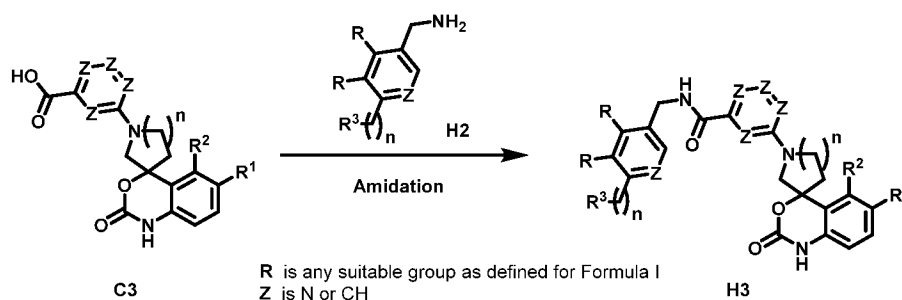
Scheme G.



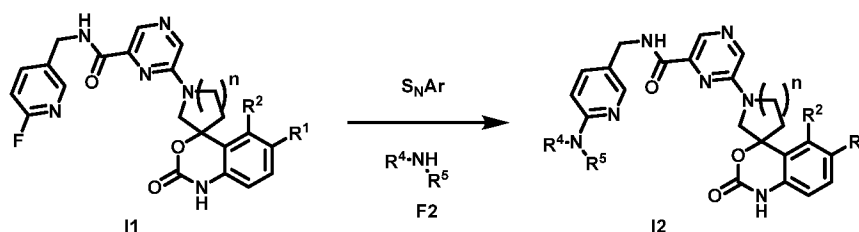
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Scheme **G** illustrates the synthetic sequence for preparation of benzylamine **G5** from fluoropyridine **G1**. Fluoropyridine **G1** is first Boc-protected to give intermediate **G2**, followed by S_NAr reaction with disubstituted amines such as **G3** using a suitable base, as indicated previously in **Scheme C**, to give Boc-protected intermediate **G4**, which can subsequently be

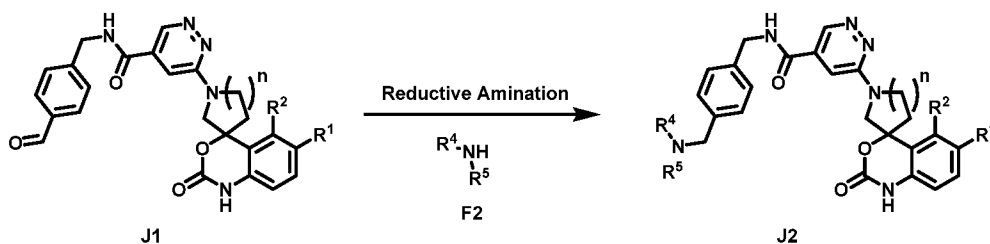
20 deprotected with TFA to afford benzyl amine intermediate **G5**.

Scheme H.

Scheme **H** illustrates the synthetic sequence for preparation of amide **H3** from carboxylic acid **H1** and amine **H2**. Amide coupling between **H1** and **H2** is performed with a suitable amide coupling reagent, such as HATU or T3P, in the presence of an appropriate amine base (TEA or DIEA) to afford amide **H3**.

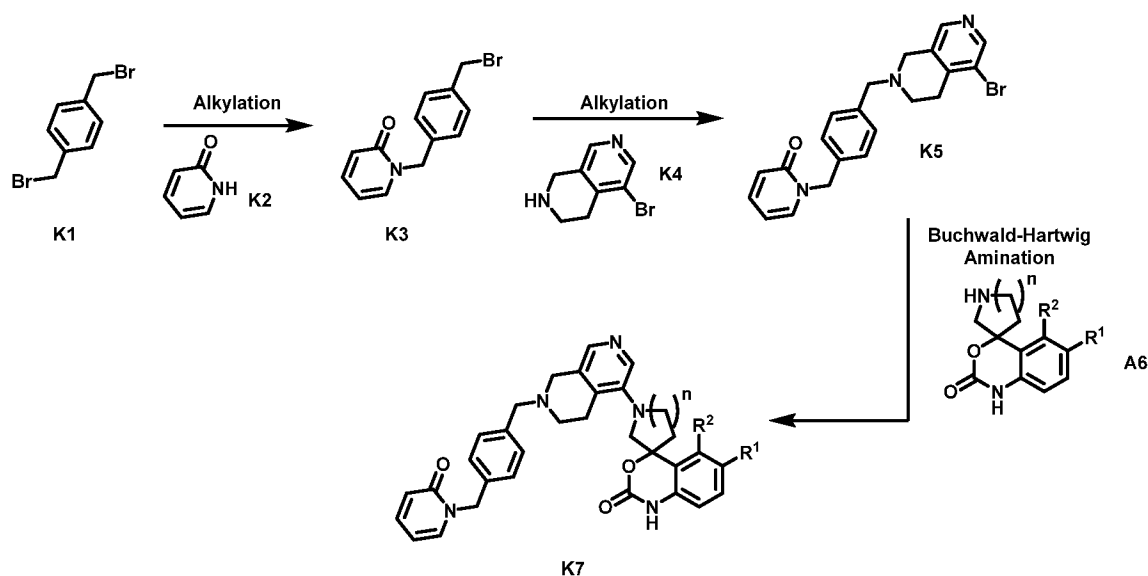
Scheme I.

Scheme **I** illustrates the synthetic sequence for preparation of S_NAr adduct **I2** from fluoropyridine intermediate **I1** and disubstituted amine **F2**. S_NAr between fluoropyridine **I1** and disubstituted amine **F2** is performed using a suitable base, as indicated previously in **Scheme C**, to afford S_NAr adduct **I2**.

Scheme J.

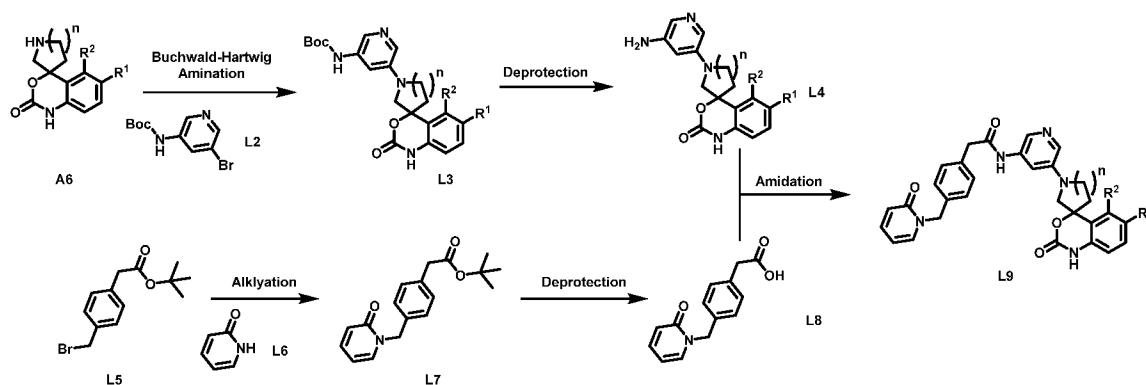
Scheme **J** illustrates the synthetic sequence for preparation of reductive amination product **J2** from benzaldehyde precursor **J1** and substituted amine **F2**. The reductive amination between **J1** and **F2** proceeds following similar conditions as those described above in **Scheme E** to afford the desired target (**J2**).

Scheme K.



Scheme **K** illustrates the synthetic sequence for the construction of naphthyhydrin intermediate **K7**. Alkylation of dibromo xylene **K1** with pyridone **K2** is performed in the presence of a suitable base, such as K_2CO_3 , to afford benzyl bromide intermediate **K3**, which undergoes alkylation with naphthyhydrin **K4** to afford naphthyhydrin bromide **K5**. Naphthyhydrin bromide **K5** is coupled to spirocarbamate **A6** using Buchwald-Hartwig amination conditions using conditions similar to those described above in **Scheme D** to afford naphthyhydrin **K7**.

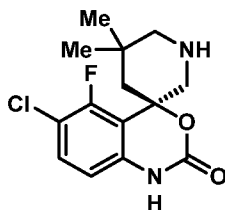
10 Scheme L.



Scheme **L** illustrates the synthetic sequence for the construction of acetamide **L9**. To arrive at amine **L4**, spirocarbamate **L1** and aryl bromide **L2** are coupled by way of Buchwald-Hartwig amination conditions as described above in **Scheme D** to afford Boc-protected intermediate **L3**, which can be deprotected using TFA to give amine **L4**. To arrive at carboxylic acid **L8**, pyridone **L6** is alkylated with ester **L5** using a suitable base, such as NaH , to afford an ester intermediate

L7 that is then deprotected with TFA to give carboxylic acid **L8**. Amine **L4** and carboxylic acid **L8** are reacted under similar conditions to those described above in **Scheme H** to afford acetamide **L9**.

Intermediate i-1



(R)-6-Chloro-5-fluoro-5',5'-dimethylspiro[benzo[d][1,3]oxazine-4,3'-piperidin]-2(1H)-one

Step 1: tert-Butyl 6-chloro-5-fluoro-5',5'-dimethyl-2-oxo-1,2-

dihydrospiro[benzo[d][1,3]oxazine-4,3'-piperidine]-1'-carboxylate: THF (55 mL) was added to

tert-butyl (4-chloro-3-fluorophenyl)carbamate (2.21 g, 9.0 mmol) under a N₂ atmosphere. The solution was cooled down to -78 °C. To the stirring solution, *n*BuLi (11 mL of a 2.5 M hexanes solution, 27.9 mmol) was added over 40 min. The reaction mixture was allowed to stir at -78 °C for an additional 45 min. Then, a solution of LaCl₃•2LiCl (22.5 mL of a 0.6 M THF solution, 13.5 mmol) and *tert*-butyl 3,3-dimethyl-5-oxopiperidine-1-carboxylate (3.1 g, 13.5 mmol) was added at -78 °C over a period of 40 min to the reaction mixture. The reaction mixture was

allowed to warm to rt and stirred for 16 h. KO^tBu (5.3 mL of a 1.7 M THF solution, 9.0 mmol) was added to the reaction mixture, the solution was heated to 60 °C and stirred for an additional 3 h. Then, the flask was cooled to rt, quenched with 1 M HCl and diluted with EtOAc. The layers were separated and the aq. phase extracted with EtOAc. The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, hexanes : EtOAc) to afford mixture of enantiomers of the title compound. The enantiomeric title compounds were separated by chiral chromatography (SFC, DAICEL CHIRALPAK IC; 0.1%NH₃H₂O-IPA Begin B 25% End B 25%) to furnish the individual isomer compounds in pure form. The faster eluting *S*-enantiomer of the title compound was obtained: [M+Na]⁺ = 421.2 (calcd. 421.1). The slower eluting desired isomer of the title compound was obtained (*R*-enantiomer): LCMS [M+Na]⁺ = 421.2 (calcd. 421.1).

Step 2: (R)-6-Chloro-5-fluoro-5',5'-dimethylspiro[benzo[d][1,3]oxazine-4,3'-piperidin]-2(1H)-

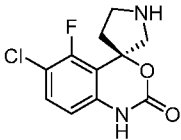
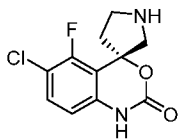
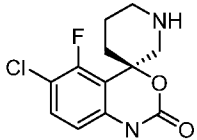
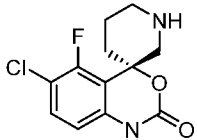
one: HCl (25 mL of a 4 M dioxane solution, 100 mmol) was added to a suspension of (*R*)-*tert*-butyl 6-chloro-5-fluoro-5',5'-dimethyl-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-

piperidine]-1'-carboxylate (7.98 g, 20 mmol) in 1,4-dioxane (30 mL). The reaction mixture was

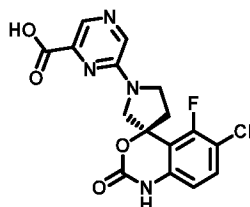
heated to 90 °C and stirred vigorously for 12 h. Then, the flask was cooled to rt and the solvents

were removed under reduced pressure to give the crude title compound. The crude product was carried forward to the next step without further purification. LCMS $[M+H]^+ = 299.1$ (calcd. 299.1).

Intermediate Table 1. The following compounds were prepared using procedures similar to those described for **Intermediate i-1** using the appropriate starting materials.

Intermediate	Structure	Name	LCMS $[M+H]^+$
i-2		(<i>R</i>)-6-Chloro-5-fluorospiro[benzo[<i>d</i>][1,3]oxazine-4,3'-pyrrolidin]-2(1 <i>H</i>)-one	Calcd. 257.1, found 257.0
i-3		(<i>S</i>)-6-Chloro-5-fluorospiro[benzo[<i>d</i>][1,3]oxazine-4,3'-pyrrolidin]-2(1 <i>H</i>)-one	Calcd. 257.1, found 257.0
i-4		(<i>R</i>)-6-Chloro-5-fluorospiro[benzo[<i>d</i>][1,3]oxazine-4,3'-piperidin]-2(1 <i>H</i>)-one	Calcd. 271.1, found 271.0
i-5		(<i>S</i>)-6-Chloro-5-fluorospiro[benzo[<i>d</i>][1,3]oxazine-4,3'-piperidin]-2(1 <i>H</i>)-one	Calcd. 271.1, found 271.0

Intermediate i-6



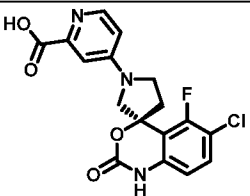
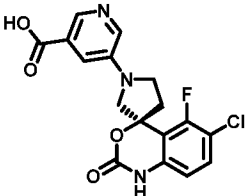
(*S*)-6-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[*d*][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)pyrazine-2-carboxylic acid

A mixture of *tert*-butyl 6-chloropyrazine-2-carboxylate (254 mg, 1.18 mmol), (*S*)-6-chloro-5-fluorospiro[benzo[*d*][1,3]oxazine-4,3'-pyrrolidin]-2(1*H*)-one 2,2,2-trifluoroacetate (483 mg, 1.30 mmol), sodium *tert*-butoxide (341 mg, 3.55 mmol), and methanesulfonato(2-dicyclohexylphosphino-2',6'-di-*i*-propoxy-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl)palladium (99 mg, 0.12 mmol) was diluted in 1,4-dioxane (3.5 mL) and sonicated for approximately 1 min.

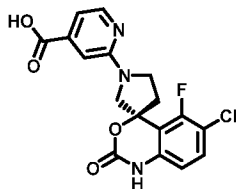
The reaction was then heated to 100 °C and allowed to stir at 100 °C overnight. The reaction was cooled to rt, TFA (2 mL) was added, and the resulting mixture was allowed to stir at rt for 1 h. The mixture was concentrated, and the crude residue was purified by reversed-phase preparatory-HPLC (C18 stationary phase, ACN/water + 0.1% TFA) to afford the title compound.

5 LCMS $[M+H]^+ = 379.1$ (calcd. 379.1).

Intermediate Table 2. The following compounds were prepared using procedures similar to those described for **Intermediate i-6** using the appropriate starting materials.

Intermediate	Structure	Name	LCMS $[M+H]^+$
i-7		(S)-4-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)picolinic acid	Calcd. 378.1, found 378.0
i-8		(S)-5-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)nicotinic acid	Calcd. 378.1, found 378.0

Intermediate i-9



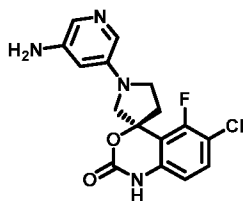
(S)-2-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)isonicotinic acid

1,4-Dioxane (0.3 mL) was added to a mixture of ethyl 6-chloropyrimidine-4-carboxylate (25 mg, 0.14 mmol), (S)-6-chloro-5-fluorospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-2(1H)-one hydrochloride (44 mg, 0.15 mmol), and sodium *tert*-butoxide (39 mg, 0.41 mmol), and the resulting mixture was sonicated for approximately 1 min. The reaction was heated to 100 °C for 30 min, cooled to rt, and concentrated to afford a crude residue that was purified by reversed-phase preparatory-HPLC (C18 stationary phase, ACN/water + 0.1% TFA). LCMS $[M+H]^+ = 378.0$ (calcd. 378.1).

Intermediate Table 3. The following compounds were prepared using procedures similar to those described for **Intermediate i-9** using the appropriate starting materials.

Intermediate	Structure	Name	LCMS [M+H] ⁺
i-10		(S)-2-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)pyrimidine-4-carboxylic acid	Calcd. 379.1, found 378.9
i-11		(S)-6-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)pyrimidine-4-carboxylic acid	Calcd. 379.1, found 378.9
i-12		(S)-6-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)pyridazine-4-carboxylic acid	Calcd. 379.1, found 379.1

Intermediate i-13



(S)-1'-(5-Aminopyridin-3-yl)-6-chloro-5-fluorospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-2(1H)-one

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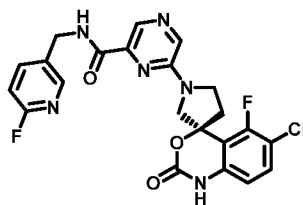
1,4-Dioxane (1.0 mL) was added to a mixture of methanesulfonato(2-dicyclohexylphosphino-2',6'-di-*i*-propoxy-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl)palladium(II) (11 mg, 0.013 mmol), sodium *tert*-butoxide (52 mg, 0.54 mmol), (S)-6-chloro-5-fluorospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-2(1H)-one 2,2,2-trifluoroacetate (75 mg, 0.20 mmol), and *tert*-butyl (5-bromopyridin-3-yl)(*tert*-butoxycarbonyl)carbamate (50 mg, 0.13 mmol), and the resulting mixture was stirred at 100 °C for 8 h. The reaction was cooled to rt and concentrated to afford a residue that was diluted with TFA (0.5 mL) and allowed to stir at rt for 2 h. Concentration afforded a crude residue that was purified by reversed-phase preparatory-HPLC (C18 stationary phase, ACN/water + 0.1% TFA) to yield the title compound. LCMS [M+H]⁺ = 349.0 (calcd.

10

15

349.1).

Intermediate i-14



(S)-6-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)-N-((6-fluoropyridin-3-yl)methyl)pyrazine-2-carboxamide

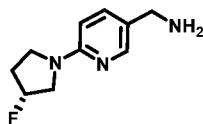
To a solution of (S)-6-(6-chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)pyrazine-2-carboxylic acid (200 mg, 0.406 mmol) in DMF (4 mL) was added (6-fluoropyridin-3-yl)methanamine (102 mg, 0.812 mmol) and DIEA (350 μ L, 2.03 mmol). The mixture was sonicated to dissolve the solids, HATU (30 mg, 0.079 mmol) was added, and the reaction was stirred at rt for 1 h. Satd. aq. NH_4Cl was added, and the resulting suspension was filtered. The solid filter cake was washed with water, and dried to afford the title compound as a crude product that was carried on without further purification. LCMS $[\text{M}+\text{H}]^+ = 487.1$ (calcd. 487.1).

Intermediate Table 4. The following compounds were prepared using procedures similar to those described for **Intermediate i-14** using the appropriate starting materials.

Intermediate	Structure	Name	LCMS $[\text{M}+\text{H}]^+$
i-15		(S)-6-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)-N-(4-formylbenzyl)pyridazine-4-carboxamide	Calcd. 496.1, found 496.0
i-16		(S)-6-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)-N-((6-fluoropyridin-3-yl)methyl)pyridazine-4-carboxamide	Calcd. 487.1, found 487.1

15

Intermediate i-17

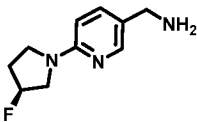
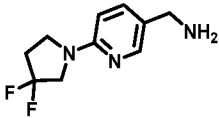
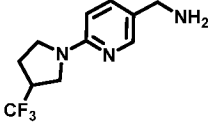


(R)-6-(3-Fluoropyrrolidin-1-yl)pyridin-3-ylmethanamine

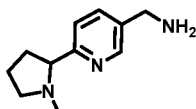
To a mixture containing *tert*-butyl ((6-bromopyridin-3-yl)methyl)carbamate (100 mg, 0.348

mmol), Cs₂CO₃ (113 mg, 0.348 mmol), Pd₂(dba)₃ (319 mg, 0.348 mmol), BINAP (217 mg, 0.348 mmol), and 3-(trifluoromethyl)pyrrolidine (73 mg, 0.52 mmol) was added 1,4-dioxane (1 mL). The reaction vial was sealed and then placed into 100 °C preheated aluminum block and heated for 12 h. The reaction mixture was then cooled to ambient temperature, concentrated to dryness, and the crude material was purified by column chromatography (silica, EtOAc/hexanes) to yield the title compound. LCMS [M+H]⁺ = 196.1 (calcd. 196.1).

Intermediate Table 5. The following compounds were prepared using procedures, similar to those described for **Intermediate i-17** using the appropriate starting materials.

Intermediate	Structure	Name	LCMS [M+H] ⁺
i-18		(S)-(6-(3-Fluoropyrrolidin-1-yl)pyridin-3-yl)methanamine	Calcd. 196.1, found 196.1
i-19		(6-(3,3-Difluoropyrrolidin-1-yl)pyridin-3-yl)methanamine	Calcd. 214.1, found 214.1
i-20		(6-(3-(Trifluoromethyl)pyrrolidin-1-yl)pyridin-3-yl)methanamine	Calcd. 246.1, found 246.1

Intermediate i-21



(6-(1-Methylpyrrolidin-2-yl)pyridin-3-yl)methanamine

Step 1: 6-(Pyrrolidin-2-yl)nicotinonitrile 2,2,2-trifluoroacetate. A mixture containing (*tert*-Butoxycarbonyl)proline (466 mg, 2.17 mmol), 6-chloronicotinonitrile (150 mg, 1.08 mmol), [4,4'-Bis(1,1-dimethylethyl)-2,2'-bipyridine-*N*¹,*N*^{1'}][bis[3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl-*N*]phenyl-C]]Iridium(III) hexafluorophosphate (12 mg, 11 μmol) was purged with N₂, and DMF (1 mL) was added. The reaction vessel was placed into a photoreactor and irradiated for 2 h. The resulting mixture was then poured into 1 M LiCl and extracted with EtOAc. The combined organic phases were washed with water and brine, dried over Na₂SO₄, and concentrated to afford a crude residue that was purified by column

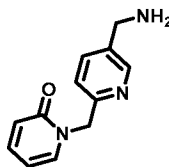
chromatography on silica gel (0-50% EtOAc/hexanes). The resulting intermediate product was treated with TFA (1.0 mL) at rt for 10 min and concentrated to afford the title compound. LCMS $[M+H]^+ = 174.1$ (calc'd 174.1)

Step 2: (4-(1-Methylpyrrolidin-2-yl)phenyl)nicotinonitrile. To a solution of 6-(pyrrolidin-2-yl)nicotinonitrile 2,2,2-trifluoroacetate (375 mg, 1.31 mmol), formaldehyde (110 μ l, 1.44 mmol), and DIEA (680 μ l, 3.92 mmol) in DMF (1 mL) was added sodium triacetoxyborohydride (553 mg, 2.61 mmol). The reaction mixture was stirred overnight at rt. The reaction mixture was poured into 1M LiCl and adjusted to pH 10 with 1 M NaOH. The mixture was extracted with DCM, and the combined organics were dried over Na_2SO_4 , and concentrated to afford a crude product that was carried on without further purification. LCMS $[M+H]^+ = 188.1$ (calc'd 188.1)

Step3: (6-(1-Methylpyrrolidin-2-yl)pyridin-3-yl)methanamine. To a cold solution of LAH (30 mg, 0.80 mmol) in THF (2.7 mL) was added 6-(1-methylpyrrolidin-2-yl)nicotinonitrile (50 mg, 0.267 mmol). The resulting mixture was stirred at 0 °C and allowed to warm to rt and then stirred overnight. Once starting material was consumed, the mixture was chilled to 0 °C and quenched with water. DCM and 40% aqueous Rochelle's salt was then added, and the mixture was extracted with DCM. The combined organics were dried over Na_2SO_4 , passed through Celite®, and concentrated to give a final product. LCMS $[M+H]^+ = 192.1$ (calcd. 192.1).

Intermediate Table 6. The following compounds were prepared using procedures similar to those described for **Intermediate i-21** using the appropriate starting materials.

Intermediate	Structure	Name	LCMS $[M+H]^+$
i-22		(4-(1-Methylpyrrolidin-2-yl)phenyl)methanamine	Calcd. 191.2, found 190.1
i-23		(4-(4,4-Difluoro-1-methylpyrrolidin-2-yl)phenyl)methanamine	Calcd. 227.1, found 226.1
i-24		(6-(4,4-Difluoro-1-methylpyrrolidin-2-yl)pyridin-3-yl)methanamine	Calcd. 228.1, found 228.1

Intermediate i-251-((5-(Aminomethyl)pyridin-2-yl)methyl)pyridin-2(1H)-one

Step1: *tert*-Butyl (*tert*-butoxycarbonyl)((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-

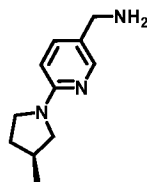
5 yl)methyl)carbamate: DMF (1 mL) was added to a mixture containing 1-((5-(chloromethyl)pyridin-2-yl)methyl)pyridin-2(1H)-one (0.023 g, 0.1 mmol) and di-*tert*-butyl iminodicarboxylate (24 mg, 0.11 mmol). Cesium carbonate (65 mg, 0.20 mmol) was then added in one portion. The resulting mixture was stirred at 40 °C for 1 h, evaporated, and the resulting residue was dissolved in water and extracted with EtOAc. The combined organics were washed
10 with brine, dried over Na₂SO₄, and concentrated to dryness to give the title compound. LCMS [M+H]⁺ = 416.1 (calc'd 416.2)

Step2: 1-((5-(Aminomethyl)pyridin-2-yl)methyl)pyridin-2(1H)-one. *tert*-Butyl (*tert*-

butoxycarbonyl)((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)carbamate (42 mg, 0.10 mmol) was dissolved in TFA (100 µl, 1.30 mmol). The reaction mixture was stirred at rt for
15 30 min. The reaction was concentrated to give the title compound that was carried on without further purification. LCMS [M+H]⁺ = 216.1 (calcd. 216.1).

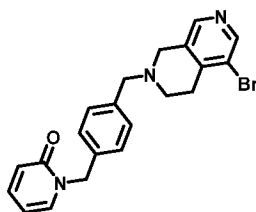
Intermediate Table 7. The following compounds were prepared using procedures similar to those described for **Intermediate i-25** using the appropriate starting materials.

Intermediate	Structure	Name	LCMS [M+H] ⁺
i-26		1-(4-(Aminomethyl)benzyl)pyridin-2(1H)-one	Calcd. 215.1, found 215.1
i-27		(4-((4-Methyl-1H-pyrazol-1-yl)methyl)phenyl)methanamine	Calcd. 202.1, found 202.1
i-28		(6-((4-Methyl-1H-pyrazol-1-yl)methyl)pyridin-3-yl)methanamine	Calcd. 203.1, found 203.1

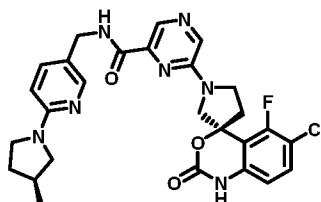
Intermediate i-29(S)-6-(3-methylpyrrolidin-1-yl)pyridin-3-ylmethanamine

Step1: *tert*-Butyl (S)-((6-(3-methylpyrrolidin-1-yl)pyridin-3-yl)methyl)carbamate: *tert*-Butyl ((6-fluoropyridin-3-yl)methyl)carbamate (527 mg, 2.33 mmol) and (S)-3-methylpyrrolidine hydrochloride (290 mg, 2.39 mmol) were mixed with DIEA (1.2 mL, 7.0 mmol), and the resulting mixture was then stirred overnight at 100 °C for 8 h. The reaction mixture was then cooled to rt, filtered, and purified by reversed-phase preparatory-HPLC (C18 stationary phase, ACN/water + 0.1% TFA) to afford the title compound. LCMS $[M+H]^+ = 292.2$ (calc'd 291.2)

Step2: (S)-6-(3-Methylpyrrolidin-1-yl)pyridin-3-ylmethanamine (S)-*tert*-Butyl ((6-(3-methylpyrrolidin-1-yl)pyridin-3-yl)methyl)carbamate (268 mg, 0.920 mmol) was mixed with TFA (710 μ l, 9.20 mmol) and the reaction was stirred at rt for 30 min. The reaction was concentrated to afford the title compound that was carried on without further purification. LCMS $[M+H]^+ = 192.1$ (calcd. 192.1).

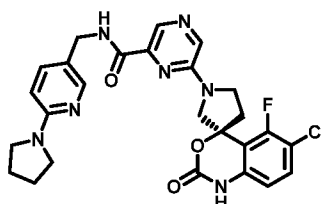
Intermediate i-30

1-(4-((5-Bromo-3,4-dihydro-2,7-naphthyridin-2(1H)-yl)methyl)benzyl)pyridin-2(1H)-one. DMF (3.5 mL) was added to a mixture of 5-bromo-1,2,3,4-tetrahydro-2,7-naphthyridine (70 mg, 0.33 mmol), 1-(4-(bromomethyl)benzyl)pyridin-2(1H)-one (83 mg, 0.30 mmol) and potassium carbonate (82 mg, 0.60 mmol), and the resulting mixture was stirred at 40 °C overnight. The reaction was cooled to rt, water was added, and the mixture was extracted with DCM. The combined organics were washed with brine, dried over Na₂SO₄, and concentrated to afford a crude residue that was purified by column chromatography on (silica; DCM/hexanes/MeOH). LCMS $[M+H]^+ = 410.0$ (Calcd. 410.1)

Example 1

(S)-6-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)-N-((6-((S)-3-methylpyrrolidin-1-yl)pyridin-3-yl)methyl)pyrazine-2-carboxamide

- 5 DIEA (41 μ L, 0.23 mmol) was added to a mixture of (S)-6-(6-chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)pyrazine-2-carboxylic acid (23 mg, 0.047 mmol) and (S)-6-(3-methylpyrrolidin-1-yl)pyridin-3-ylmethanamine 2,2,2-trifluoroacetate (17 mg, 0.056 mmol) in DMF (0.5 mL). HATU (30 mg, 0.079 mmol) was added in one portion, and the reaction was stirred at rt overnight. The crude reaction mixture was
- 10 diluted with DMSO, filtered and purified by reversed-phase preparatory-HPLC (C18 stationary phase, ACN/water + 0.1% TFA) to yield the title compound. ^1H NMR (600 MHz, CD_3OD) δ 8.46 (s, 1H), 8.27 (s, 1H), 8.02 (d, J = 9.4 Hz, 1H), 7.84 (s, 1H), 7.51 (t, J = 8.1 Hz, 1H), 7.08 (d, J = 9.4 Hz, 1H), 6.82 (d, J = 8.7 Hz, 1H), 4.51 (s, 2H), 4.34 (d, J = 12.7 Hz, 1H), 4.17 (d, J = 12.9 Hz, 1H), 4.03 (t, J = 9.3 Hz, 1H), 3.91 (q, J = 10.2 Hz, 1H), 3.73 (d, J = 30.2 Hz, 2H), 3.57
- 15 (d, J = 8.1 Hz, 1H), 3.13 (s, 1H), 2.92 (q, J = 9.9 Hz, 1H), 2.72 (dd, J = 13.4, 6.3 Hz, 1H), 2.55 (d, J = 6.7 Hz, 1H), 2.29 (s, 1H), 1.79 (p, J = 8.9 Hz, 1H), 1.20 (d, J = 6.6 Hz, 3H). LCMS $[\text{M}+\text{H}]^+ = 552.0$ (calcd. 552.2).

Example 2

- 20 (S)-6-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)-N-((6-(pyrrolidin-1-yl)pyridin-3-yl)methyl)pyrazine-2-carboxamide

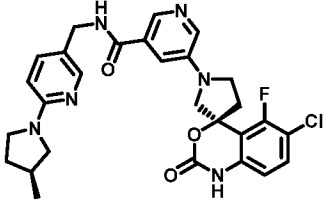
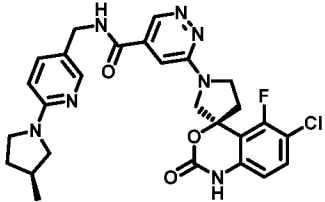
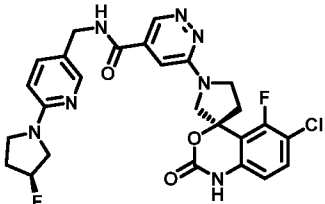
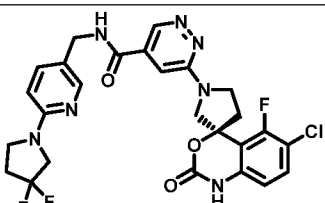
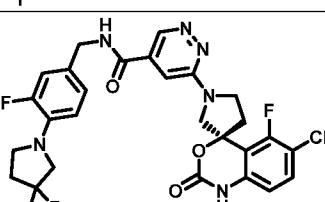
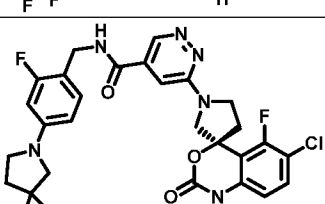
DIEA (180 μ L, 1.03 mmol) was added to a mixture of azetidine (29 mg, 0.51 mmol) and (S)-6-(6-chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)-N-((6-fluoropyridin-3-yl)methyl)pyrazine-2-carboxamide (50 mg, 0.10 mmol). The reaction was

25 stirred at 115 $^{\circ}\text{C}$ overnight. The reaction was cooled to rt and purified by reversed-phase preparatory-HPLC (C18 stationary phase, ACN/water + 0.1% TFA) to yield the title compound. ^1H NMR (600 MHz, CD_3OD) δ 8.55 (s, 1H), 8.48 (s, 1H), 8.15 (s, 1H), 8.05 (s, 1H), 7.60-7.50

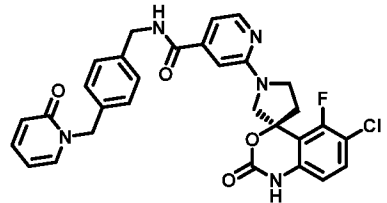
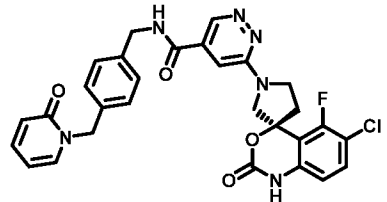
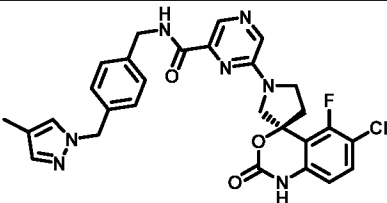
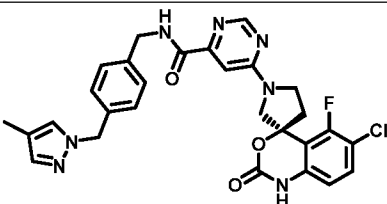
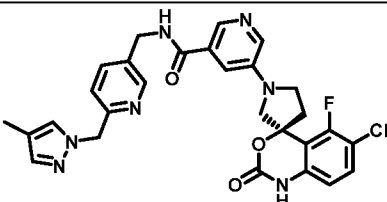
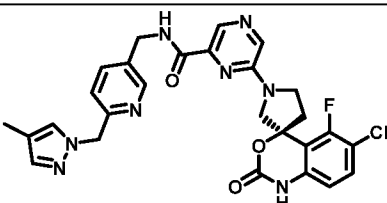
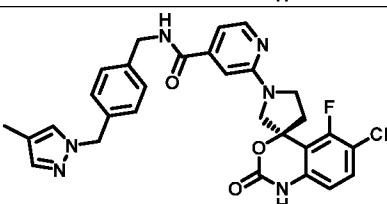
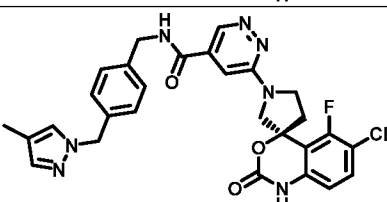
(m, 1H), 7.50-7.40 (m, 1H), 6.80-6.70 (m, 1H), 6.50-6.40 (m, 1H) 4.50-4.40 (m, 2H), 2.35-2.25 (m, 1H), 4.10-4.00 (m, 1H), 4.00-3.90 (m, 1H), 3.90-3.80 (m, 1H), 3.45-3.35 (m, 1H), 3.20 (s, 1H), 2.95-2.85 (m, 1H), 2.7-2.6 (m, 1H). LCMS $[M+H]^+ = 538.3$ (calcd. 538.2).

The compounds below were prepared following procedures similar to those described for

5 **Examples 1 and 2** using appropriate starting materials.

Example	Structure	Name	LCMS $[M+H]^+$
3		(S)-5-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)-N-((6-((S)-3-methylpyrrolidin-1-yl)pyridin-3-yl)methyl)nicotinamide	Calcd. 551.2, Found 551.4
4		(S)-6-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)-N-((6-((S)-3-methylpyrrolidin-1-yl)pyridin-3-yl)methyl)pyridazine-4-carboxamide	Calcd. 552.2, Found 552.1
5		(S)-6-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)-N-((6-((S)-3-fluoropyrrolidin-1-yl)pyridin-3-yl)methyl)pyridazine-4-carboxamide	Calcd. 556.2, Found 556.1
6		(S)-6-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)-N-((6-(3,3-difluoropyrrolidin-1-yl)pyridin-3-yl)methyl)pyridazine-4-carboxamide	Calcd. 574.2, Found 574.0
7		(S)-6-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)-N-(4-(3,3-difluoropyrrolidin-1-yl)-3-fluorobenzyl)pyridazine-4-carboxamide	Calcd. 591.1, Found 591.0
8		(S)-6-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)-N-(4-(3,3-difluoropyrrolidin-1-yl)-2-fluorobenzyl)pyridazine-4-carboxamide	Calcd. 591.1, Found 591.1

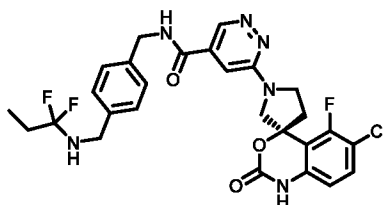
Example	Structure	Name	LCMS [M+H] ⁺
9		(S)-6-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)-N-((6-(3-(trifluoromethyl)pyrrolidin-1-yl)pyridin-3-yl)methyl)pyridazine-4-carboxamide	Calcd. 606.2, Found 606.1
10		(S)-6-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)-N-(4-(1-methylpyrrolidin-2-yl)benzyl)pyridazine-4-carboxamide	Calcd. 551.2, Found 551.2
11		(S)-6-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)-N-((6-(1-methylpyrrolidin-2-yl)pyridin-3-yl)methyl)pyridazine-4-carboxamide	Calcd. 552.2, Found 552.4
12		(S)-6-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)-N-(4-(4,4-difluoro-1-methylpyrrolidin-2-yl)benzyl)pyridazine-4-carboxamide	Calcd. 587.2, Found 587.1
13		(S)-6-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)-N-((6-(4,4-difluoro-1-methylpyrrolidin-2-yl)pyridin-3-yl)methyl)pyridazine-4-carboxamide	Calcd. 588.2, Found 588.1
14		(S)-6-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)-N-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)pyrazine-2-carboxamide	Calcd. 576.1, Found 576.1
15		(S)-5-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)-N-((6-((2-oxopyridin-1(2H)-yl)methyl)pyridin-3-yl)methyl)nicotinamide	Calcd. 575.2, Found 575.3

Example	Structure	Name	LCMS [M+H] ⁺
16		(S)-2-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)-N-((2-oxopyridin-1(2H)-yl)methyl)benzylisonicotinamide	Calcd. 574.2, Found 574.0
17		(S)-6-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)-N-((2-oxopyridin-1(2H)-yl)methyl)benzylpyridazine-4-carboxamide	Calcd. 575.2, Found 575.4
18		(S)-6-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)-N-((4-methyl-1H-pyrazol-1-yl)methyl)benzylpyrazine-2-carboxamide	Calcd. 562.2, Found 562.1
19		(S)-6-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)-N-((4-methyl-1H-pyrazol-1-yl)methyl)benzylpyrimidine-4-carboxamide	Calcd. 562.2, Found 562.5
20		(S)-5-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)-N-((6-((4-methyl-1H-pyrazol-1-yl)methyl)pyridin-3-yl)methyl)nicotinamide	Calcd. 562.2, Found 562.3
21		(S)-6-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)-N-((6-((4-methyl-1H-pyrazol-1-yl)methyl)pyridin-3-yl)methyl)pyrazine-2-carboxamide	Calcd. 563.2, Found 563.3
22		(S)-2-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)-N-((4-methyl-1H-pyrazol-1-yl)methyl)benzylisonicotinamide	Calcd. 561.2, Found 561.1
23		(S)-6-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)-N-((4-methyl-1H-pyrazol-1-yl)methyl)benzylpyridazine-4-carboxamide	Calcd. 562.2, Found 562.2

Example	Structure	Name	LCMS [M+H] ⁺
24		(S)-2-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)-N-(4-((4-methyl-1H-pyrazol-1-yl)methyl)benzyl)pyrimidine-4-carboxamide	Calcd. 562.2, Found 562.0
25		(S)-4-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)-N-(4-((4-methyl-1H-pyrazol-1-yl)methyl)benzyl)picolinamide	Calcd. 561.2, Found 561.0
26		(S)-5-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)-N-(4-((4-methyl-1H-pyrazol-1-yl)methyl)benzyl)nicotinamide	Calcd. 561.2, Found 561.0
27		(S)-6-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)-N-((6-(3-(methoxymethyl)azetidin-1-yl)pyridin-3-yl)methyl)pyridazine-4-carboxamide	Calcd. 568.2, Found 568.3
28		(S)-6-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)-N-((6-(4-methylpiperazin-1-yl)pyridin-3-yl)methyl)pyridazine-4-carboxamide	Calcd. 567.20, Found 567.3
29		(S)-6-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)-N-((6-(6-morpholinopyridin-3-yl)methyl)pyridazine-4-carboxamide	Calcd. 554.2, Found 554.3
30		(S)-6-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)-N-((2-oxo-2H-chromen-7-yl)methyl)pyrazine-2-carboxamide	Calcd. 536.1, Found 536.0

Example	Structure	Name	LCMS [M+H] ⁺
31		(S)-6-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)-N-((5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)methyl)pyrazine-2-carboxamide	Calcd. 524.2, Found 524.0
32		(S)-N-((1-Aminoisoquinolin-6-yl)methyl)-6-(6-chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)pyrazine-2-carboxamide	Calcd. 534.1, Found 534.0
33		(S)-6-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)-N-((6-(3-fluoroazetidin-1-yl)pyridin-3-yl)methyl)pyrazine-2-carboxamide	Calcd. 542.1, Found 542.3
34		(S)-6-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)-N-((6-(3-methoxymethyl)azetidin-1-yl)pyridin-3-yl)methyl)pyrazine-2-carboxamide	Calcd. 568.2, Found 568.3
35		(S)-6-(6-chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)-N-((6-(3-hydroxy-3-methylazetidin-1-yl)pyridin-3-yl)methyl)pyrazine-2-carboxamide	Calcd. 568.2, Found 568.3
36		(S)-6-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)-N-((6-(3-hydroxy-3-(trifluoromethyl)azetidin-1-yl)pyridin-3-yl)methyl)pyrazine-2-carboxamide	Calcd. 608.1, Found 608.2
37		(S)-N-((6-(Azetidin-1-yl)pyridin-3-yl)methyl)-6-(6-chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)pyrazine-2-carboxamide	Calcd. 524.2, Found 524.0

Example	Structure	Name	LCMS [M+H] ⁺
38		(S)-6-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)-N-((6-((S)-3-fluoropyrrolidin-1-yl)pyridin-3-yl)methyl)pyrazine-2-carboxamide	Calcd. 556.2, Found 557.1
39		(S)-6-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)-N-((6-((R)-3-fluoropyrrolidin-1-yl)pyridin-3-yl)methyl)pyrazine-2-carboxamide	Calcd. 556.2, Found 556.3
40		N-((6-(3-Azabicyclo[3.1.0]hexan-3-yl)pyridin-3-yl)methyl)-6-((S)-6-chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)pyrazine-2-carboxamide	Calcd. 550.2, Found 550.4
41		(S)-6-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)-N-((6-(piperidin-1-yl)pyridin-3-yl)methyl)pyrazine-2-carboxamide	Calcd. 552.2, Found 552.3
42		(S)-6-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)-N-((6-morpholinopyridin-3-yl)methyl)pyrazine-2-carboxamide	Calcd. 554.2, Found 554.3
43		(S)-6-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)-N-((6-(4-methylpiperazin-1-yl)pyridin-3-yl)methyl)pyrazine-2-carboxamide	Calcd. 567.2, Found 567.4

Example 44

(S)-6-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)-N-

(4-(((1,1-difluoropropyl)amino)methyl)benzyl)pyridazine-4-carboxamide

DCE (1 mL) was added to a mixture of (S)-6-(6-chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)-N-(4-formylbenzyl)pyridazine-4-carboxamide (30 mg, 0.060 mmol) and 1,1-difluoropropan-1-amine (12 mg, 0.12 mmol).

- 5 Sodium triacetoxymethylborohydride (51 mg, 0.24 mmol) was added in one portion, and the resulting mixture was stirred at rt for 3 h. The reaction mixture was diluted with MeOH and concentrated to afford a crude residue that was purified by reversed-phase preparatory-HPLC (C18 stationary phase, ACN/water + 0.1% TFA) to yield the title compound. ¹H NMR (400 MHz, CD₃OD) δ 10.98 (s, 1H), 9.47 (t, *J* = 5 Hz, 1H), 8.87 (s, 1H), 7.58-7.56 (m, 2H), 7.48-7.46 (m, 3H), 7.45-7.39 (m, 3H), 6.84-6.84 (m, 2H), 4.50 (d, *J* = 10 Hz, 2H), 4.34 (s, 1H), 4.1 (s, 3H), 4.03 (d, *J* = 15 Hz, 1H), 2.78-2.62 (m, 2H), 1.71 (t, *J* = 20 Hz, 3H). LCMS [M+H]⁺ = 575.1 (calcd. 575.2).

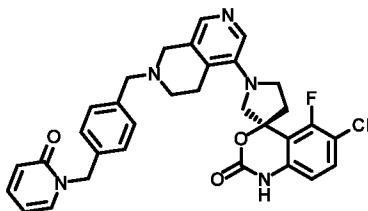
The compounds below were prepared following procedures similar to those described for

Example 44 using appropriate starting materials.

Example	Structure	Name	LCMS [M+H] ⁺
45		N-(4-((<i>sec</i> -Butylamino)methyl)benzyl)-6-(((S)-6-chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)pyridazine-4-carboxamide	Calcd. 553.2, Found 553.1
46		(S)-6-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)-N-(4-(((1,1,1-trifluorobutan-2-yl)amino)methyl)benzyl)pyridazine-4-carboxamide	Calcd. 607.2, Found 608.0
47		(S)-6-(6-chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)-N-(4-((3-fluoroazetidin-1-yl)methyl)benzyl)pyridazine-4-carboxamide	Calcd. 555.2, Found 555.0

Example	Structure	Name	LCMS [M+H] ⁺
48		(S)-6-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)-N-(4-((isopropyl(methyl)amino)methyl)benzyl)pyridazine-4-carboxamide	Calcd. 553.2, Found 553.0
49		(S)-6-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)-N-(4-(((2-cyanoethyl)(cyclopropyl)amino)methyl)benzyl)pyridazine-4-carboxamide	Calcd. 590.2, Found 590.1
50		(S)-6-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)-N-(4-(((3-cyano-3-fluoroazetidin-1-yl)methyl)benzyl)pyridazine-4-carboxamide	Calcd. 580.2, Found 580.1

Example 51



(S)-6-Chloro-5-fluoro-1'-(7-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-5,6,7,8-tetrahydro-2,7-naphthyridin-4-yl)spiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-2(1H)-one

5

DMA (0.7 mL) was added to a mixture of 1-(4-((5-bromo-3,4-dihydro-2,7-naphthyridin-2(1H)-yl)methyl)benzyl)pyridin-2(1H)-one (87 mg, 0.21 mmol), (S)-6-chloro-5-fluorospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-2(1H)-one 2,2,2-trifluoroacetate (79 mg, 0.21 mmol), (2-Dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl)[2-(2'-amino-1,1'-

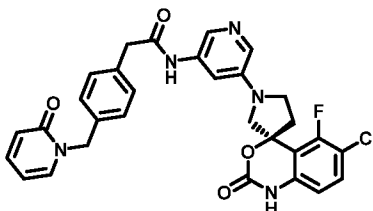
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biphenyl)]palladium(II) methanesulfonate (27 mg, 0.032 mmol), and sodium *tert*-butoxide (61 mg, 0.64 mmol). The resulting mixture was heated to 100 °C for 12 h. The reaction mixture was cooled to rt and purified by reversed-phase preparatory-HPLC (C18 stationary phase, ACN/water + 0.1% TFA) to yield the title compound. ¹H NMR (500 MHz, *d*₆-DMSO) δ 7.99 (s, 1H), 7.86 (s,

1H), 7.79 (d, $J = 6.6$ Hz, 1H), 7.54 (t, $J = 8.2$ Hz, 1H), 7.46 – 7.39 (m, 2H), 7.34 (d, $J = 7.9$ Hz, 3H), 7.26 (d, $J = 8.2$ Hz, 3H), 6.78 (d, $J = 8.5$ Hz, 1H), 6.55 (s, 3H), 6.42 (d, $J = 8.8$ Hz, 1H), 6.25 (t, $J = 6.3$ Hz, 1H), 3.84 (d, $J = 11.2$ Hz, 1H), 3.70 (d, $J = 14.4$ Hz, 2H), 3.66 – 3.59 (m, 2H), 2.79 (s, 2H), 2.64 (d, $J = 4.8$ Hz, 2H). LCMS $[M+H]^+ = 586.0$ (calcd. 586.2).

5

Example 52



(S)-N-(5-(6-Chloro-5-fluoro-2-oxo-1,2-dihydrospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-1'-yl)pyridin-3-yl)-2-(4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)acetamide

10 DMA (0.2 mL) was added to a mixture of (S)-1'-(5-aminopyridin-3-yl)-6-chloro-5-fluorospiro[benzo[d][1,3]oxazine-4,3'-pyrrolidin]-2(1H)-one (25 mg, 0.072 mmol) and 2-(4-((2-oxopyridin-1(2H)-yl)methyl)phenyl)acetic acid (17 mg, 0.072 mmol). DIEA (50 μ L, 0.29 mmol) was added, followed by the addition of HATU (27 mg, 0.072 mmol) in one portion. The resulting mixture was stirred at rt for 2 h, at which time, the reaction was diluted with DMSO

15 and purified by reversed-phase preparatory-HPLC (C18 stationary phase, ACN/water + 0.1% TFA) to yield the title compound. ^1H NMR (400 MHz, CD_3OD) δ 10.8 (s, 1H), 10.7 (s, 1H), 8.31 (s, 1H), 7.84 (s, 1H), 7.78-7.76 (m, 1H), 7.59-7.56 (m, 1H), 7.50 (s, 1H), 7.44-7.41 (m, 1H), 7.30-7.24 (m, 4H), 6.82 (d, $J = 10$ Hz, 1H), 6.41 (d, $J = 10$ Hz, 1H), 6.25 (dd, $J = 10.0$ Hz, $J = 5$ Hz, 1H), 5.06 (s, 2H), 3.89 (s, 2H), 3.67 (s, 1H), 2.76-2.69 (m, 1H), 2.64-2.49 (m, 1H). LCMS

20 $[M+H]^+ = 574.0$ (calcd. 574.2).

Plasma Kallikrein assay

The effectiveness of a compound of the present invention as an inhibitor of plasma kallikrein can be determined using a relevant purified serine protease, and an appropriate synthetic substrate. The rate of hydrolysis of the chromogenic or fluorogenic substrate by the relevant serine protease was measured both in the absence and presence of compounds of the present invention. Assays were conducted at rt or at 37 $^\circ\text{C}$. Hydrolysis of the substrate resulted in release of amino trifluoromethylcoumarin (AFC), which was monitored spectrofluorometrically by measuring the increase in emission at 510 nm with excitation at 405 nm. A decrease in the

25

30 rate of fluorescence change in the presence of inhibitor is indicative of enzyme inhibition. Such

methods are known to one skilled in the art. The results of this assay are expressed as the half-maximal inhibitory concentrations (IC_{50}), or the inhibitory constant, K_i .

Plasma kallikrein determinations were made in 50 mM HEPES buffer at pH 7.4 containing 150 mM NaCl, 5 mM $CaCl_2$, and 0.1% PEG 8000 (polyethylene glycol; Fisher Scientific). Determinations were made using purified Human plasma kallikrein at a final concentration of 0.5 nM (Enzyme Research Laboratories) and the synthetic substrate, Acetyl-K-P-R-AFC (Sigma # C6608) at a concentration of 100 mM.

Activity assays were performed by diluting a stock solution of substrate at least tenfold to a final concentration ≤ 0.2 Km into a solution containing enzyme or enzyme equilibrated with inhibitor. Times required to achieve equilibration between enzyme and inhibitor were determined in control experiments. The reactions were performed under linear progress curve conditions and fluorescence increase measured at 405 Ex/510 Em nm. Values were converted to percent inhibition of the control reaction (after subtracting 100% Inhibition value). IC_{50} was determined by inflection point from a four parameter logistic curve fit. K_i was calculated using the Cheng Prusoff equation, $K_i = IC_{50}/(1+([S]/K_m))$.

The activities shown by this assay indicate that the compounds of the invention may be therapeutically useful for treating or preventing various ophthalmic, cardiovascular and/or cerebrovascular thromboembolic conditions in patients suffering from unstable angina, acute coronary syndrome, refractory angina, myocardial infarction, transient ischemic attacks, atrial fibrillation, stroke such as thrombotic stroke or embolic stroke, venous thrombosis, coronary and cerebral arterial thrombosis, cerebral and pulmonary embolism, atherosclerosis, deep vein thrombosis, disseminated intravascular coagulation, reocclusion or restenosis of recanalized vessels, hereditary angioedema, uveitis, posterior uveitis, wet age-related macular degeneration, diabetic macular edema, diabetic retinopathy and retinal vein occlusion.

Factor XIa assay

The effectiveness of a compound of the present invention as an inhibitor of Coagulation factor XIa can be determined using a relevant purified serine protease, and an appropriate synthetic substrate. The rate of hydrolysis of the chromogenic or fluorogenic substrate by the relevant serine protease was measured both in the absence and presence of compounds of the present invention. Assays were conducted at rt or at 37 °C. Hydrolysis of the substrate resulted in release of amino trifluoromethylcoumarin (AFC), which was monitored spectrofluorometrically by measuring the increase in emission at 510 nm with excitation at 405 nm. A decrease in the rate of fluorescence change in the presence of inhibitor is indicative of

enzyme inhibition. Such methods are known to one skilled in the art. The results of this assay are expressed as the half-maximal inhibitory concentrations (IC_{50}), or the inhibitory constant, K_i .

Compounds were pre-incubated for 30 min at 25 °C with human (0.04 nM) factor XIa in 50 mM HEPES buffer with 150 mM sodium chloride, 5 mM calcium chloride, 0.1% PEG 8000, pH 7.4. factor XIa enzymatic activity was determined by addition of the substrate glycine-proline-arginine-7-amido-4-trifluoromethylcoumarin (GPR-AFC) and measurement of the fluorescence at 400/505 nm after a 60 min incubation at 25 °C. The % inhibition for each data point was calculated from the data and analyzed using the log (inhibitor) vs. response four parameters equation to determine the half-maximal inhibitory concentrations (IC_{50}). The IC_{50} were converted to equilibrium inhibitory constants (K_i) using the Cheng-Prusoff equation.

The activities shown by this assay indicate that the compounds of the invention may be therapeutically useful for treating or preventing various cardiovascular and/or cerebrovascular thromboembolic conditions in patients suffering from unstable angina, acute coronary syndrome, refractory angina, myocardial infarction, transient ischemic attacks, atrial fibrillation, stroke such as thrombotic stroke or embolic stroke, venous thrombosis, coronary and cerebral arterial thrombosis, cerebral and pulmonary embolism, atherosclerosis, deep vein thrombosis, disseminated intravascular coagulation, and reocclusion or restenosis of recanalized vessels.

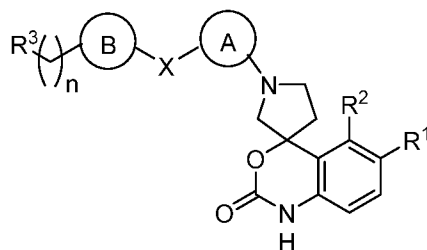
Plasma Kallikrein (PKal) IC_{50} (nM) and Factor XIa (FXIa) IC_{50} (nM) for selected compounds are as follows:

Example	PKal IC_{50} (nM)	FXIa IC_{50} (nM)
1	19.3	10000
2	6.8	10000
3	9.5	10000
4	1.2	7439
5	3.0	5654
6	4.0	10000
7	33.5	10000
8	30.4	10000
9	7.5	10000
10	2.5	10000
11	3.9	10000
12	39.6	10000
13	81.6	10000
14	1.6	10000
15	0.6	10000

Example	PKal IC ₅₀ (nM)	FXIa IC ₅₀ (nM)
16	50.0	10000
17	16.3	10000
18	12.8	10000
19	25.6	10000
20	1.3	10000
21	2.3	10000
22	4.7	10000
23	0.5	10000
24	13.6	10000
25	16.5	10000
26	3.1	10000
27	14.3	10000
28	1.9	10000
29	5.0	10000
30	20.9	10000
31	8.6	10000
32	19.0	10000
33	25.4	10000
34	5.4	10000
35	28.4	10000
36	43.7	10000
37	44.4	10000
38	35.8	10000
39	25.8	10000
40	18.6	10000
41	35.4	10000
42	11.8	10000
43	1.7	10000
44	58.3	7664
45	15.8	10000
46	38.0	10000
47	13.8	10000
48	5.9	10000
49	8.9	10000
50	26.6	10000
51	45.9	10000
52	19.0	10000

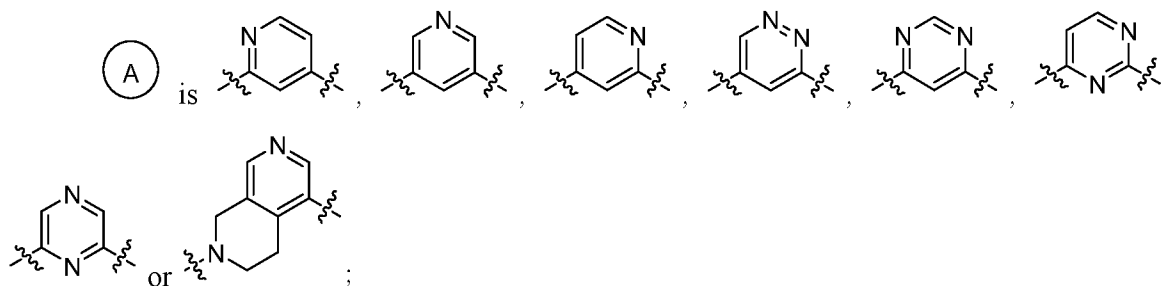
WHAT IS CLAIMED IS:

1. A compound of the Formula I:



I

wherein X is $-\text{CH}_2-$, $-\text{NH}(\text{C}=\text{O})\text{CH}_2-$ or $-(\text{C}=\text{O})\text{NHCH}_2-$;



is phenyl or heteroaryl, which can be monocyclic or bicyclic, wherein said phenyl is optionally substituted with halo and said heteroaryl is optionally substituted with halo, hydroxy, C_{1-6} alkyl or oxo;

R^1 is selected from the group consisting of hydrogen, halo, hydroxy and C_{1-6} alkyl;

R^2 is selected from the group consisting of hydrogen, halo, hydroxy and C_{1-6} alkyl;

R^3 is selected from the group consisting of hydrogen, heterocyclyl, which can be monocyclic or bicyclic, heteroaryl and NR^4R^5 , wherein said heteroaryl is optionally substituted with one or two substituents independently selected from the group consisting of oxo and C_{1-6} alkyl and said heterocyclyl is optionally substituted with one to three substituents independently selected from the group consisting of halo, hydroxy, cyano and R^x ;

R^4 is selected from the group consisting of hydrogen, cyclopropyl and C_{1-6} alkyl;

R^5 is selected from the group consisting of hydrogen and C_{1-6} alkyl, which is optionally substituted with one to three substituents selected from the group consisting of halo, hydroxy and cyano;

R^x is hydrogen or C_{1-6} alkyl, which is optionally substituted with one to three substituents selected from the group consisting of halo, hydroxy and methoxy;

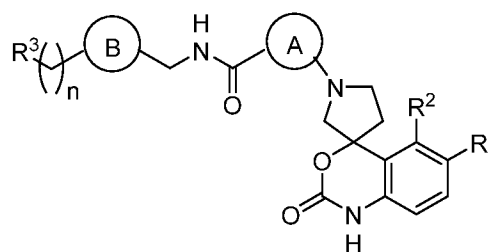
n is an integer from zero to two;

or a pharmaceutically acceptable salt thereof.

2. The compound of Claim 1 wherein X is $-(C=O)NHCH_2-$, or a pharmaceutically acceptable salt thereof.

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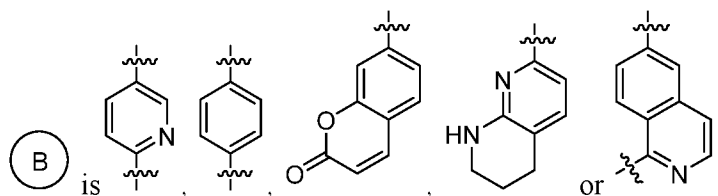
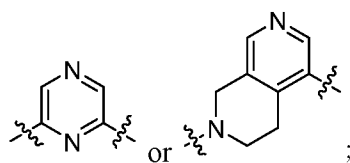
3. The compound of Claims 1 or 2 of the Formula Ia:



Ia

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wherein (A) is



R^1 is selected from the group consisting of hydrogen, halo, hydroxy and C_{1-6} alkyl;

R^2 is selected from the group consisting of hydrogen, halo, hydroxy and C_{1-6} alkyl;

15

R^3 is selected from the group consisting of hydrogen, heterocyclyl, which can be monocyclic or bicyclic, heteroaryl and NR^4R^5 , wherein said heteroaryl is optionally substituted with one or two substituents independently selected from the group consisting of oxo and C_{1-6} alkyl and said heterocyclyl is optionally substituted with one to three substituents independently selected from the group consisting of halo, hydroxy, cyano and R^x ;

20

R^4 is selected from the group consisting of hydrogen, cyclopropyl and C_{1-6} alkyl;

R^5 is selected from the group consisting of hydrogen and C_{1-6} alkyl, which is optionally substituted with one to three substituents selected from the group consisting of halo, hydroxy and cyano;

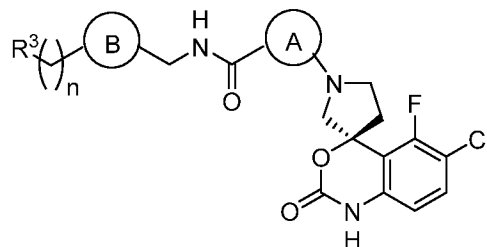
R^x is hydrogen or C_{1-6} alkyl, which is optionally substituted with one to three substituents selected from the group consisting of halo, hydroxy and methoxy;

n is an integer from zero to two;

or a pharmaceutically acceptable salt thereof.

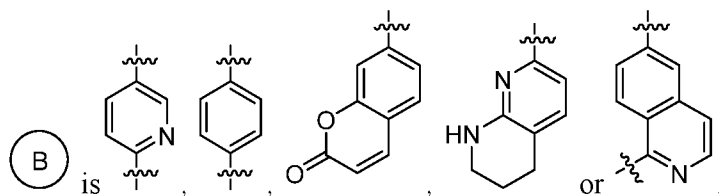
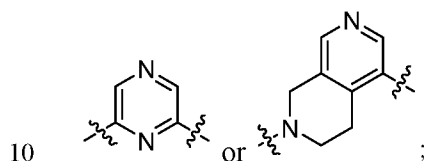
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4. The compound of Claim 1 of the Formula 1b:



Ib

wherein (A) is



R^3 is selected from the group consisting of hydrogen, heterocyclyl, which can be monocyclic or bicyclic, heteroaryl and NR^4R^5 , wherein said heteroaryl is optionally substituted with one or two substituents independently selected from the group consisting of oxo and C_{1-6} alkyl and said heterocyclyl is optionally substituted with one to three substituents independently selected from the group consisting of halo, hydroxy, cyano and R^x ;

R^4 is selected from the group consisting of hydrogen, cyclopropyl and C_{1-6} alkyl;

R^5 is selected from the group consisting of hydrogen and C_{1-6} alkyl, which is optionally substituted with one to three substituents selected from the group consisting of halo, hydroxy and cyano;

20

R^x is hydrogen or C_{1-6} alkyl, which is optionally substituted with one to three substituents selected from the group consisting of halo, hydroxy and methoxy;

n is an integer from zero to two;
or a pharmaceutically acceptable salt thereof.

5. The compound of any of Claims 1 to 4 wherein R¹ is halo and R² is halo, or a pharmaceutically acceptable salt thereof.

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6. The compound of any of Claims 1 to 5 wherein n is zero, and R³ is heterocyclyl, which is optionally substituted with one to three halo, or R^x, or a pharmaceutically acceptable salt thereof.

7. The compound of any of Claims 1 to 5 wherein n is one, and R³ is heteroaryl, which is optionally substituted with methyl or oxo, or a pharmaceutically acceptable salt thereof.

10

8. The compound of any of Claims 1 to 7 wherein R⁴ is hydrogen, cyclopropyl or methyl, and R⁵ is C₁₋₆ alkyl, which is optionally substituted with one to three halo, or cyano, or a pharmaceutically acceptable salt thereof.

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9. The compound of Claim 1 selected from any one of compounds 1-52, or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition comprising a compound of any one of Claims 1 to 9 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

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11. A method for treating impaired visual activity, diabetic retinopathy, diabetic macular edema, retinal vein occlusion, hereditary angioedema, diabetes, pancreatitis, cerebral hemorrhage, nephropathy, cardiomyopathy, neuropathy, inflammatory bowel disease, arthritis, inflammation, septic shock, hypotension, cancer, adult respiratory distress syndrome, disseminated intravascular coagulation, blood coagulation during cardiopulmonary bypass surgery, or bleeding from postoperative surgery in a mammal, comprising administering a composition of Claim 10 to a mammal in need of thereof.

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12. A method for treating uveitis, posterior uveitis, wet age-related macular degeneration, diabetic macular edema, diabetic retinopathy or retinal vein occlusion in a mammal comprising administering a composition of Claim 10 to a mammal in need thereof.

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13. A method of treating diabetic retinopathy or diabetic macular edema in a mammal

comprising administering a composition of Claim 10 to a mammal in need thereof.

14. A method of treating retinal vein occlusion in a mammal comprising administering a composition of Claim 10 to a mammal in need thereof.

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15. A compound according to any one of Claims 1 to 9, or a pharmaceutically acceptable salt thereof, for use in the manufacture of a medicament for treating uveitis, posterior uveitis, wet age-related macular degeneration, diabetic macular edema, diabetic retinopathy or retinal vein occlusion in a mammal in need thereof.

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16. The compound according to any one of Claims 1 to 9, or a pharmaceutically acceptable salt thereof, for use in therapy.

17. The composition of Claim 10 further comprising another agent selected from the group consisting of anti-inflammatory agents, anti-VEGF agents, immunosuppressive agents, anticoagulants, antiplatelet agents, and thrombolytic agents.

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18. The method of Claim 11 further comprising another agent selected from the group consisting of anti-inflammatory agents, anti-VEGF agents, immunosuppressive agents, anticoagulants, antiplatelet agents, and thrombolytic agents.

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 22/20487

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 31/537; C07D 498/10; A61P 7/02; A61P 7/04 (2022.01)

CPC - A61K 31/537; C07D 498/10; A61P 7/02; A61P 7/04

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)

See Search History document

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

See Search History document

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

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 9,957,229 B2 (INCYTE CORPORATION et al.) 1 May 2018 (01.05.2018) abstract; col 16, ln 38 to col 17, ln 8; col 110, ln 1-5	1-4, 9
A	KELEMEN et al. 'Spiro[pyrrolidine-3,3'-oxindoles] and Their Indoline Analogues as New 5-HT6 Receptor Chemotypes', Molecules 2017, Vol.22, No.2221; pages 1-25; doi:10.3390/molecules22122221. pg 4, Table 2	1-4, 9
A	WO 2015/164308 A1 (MERCK SHARP & DOHME CORP.) 29 October 2015 (29.10.2015) pg 3, ln 25 to pg 4, ln 1; pg 77, ln 1-4; pg 78, ln 16-20	1-4, 9
A	WO 2017/074833 A1 (MERCK SHARP & DOHME CORP.) 4 May 2017 (04.05.2017) pg 90, ln 1-5	1-4, 9

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"D" document cited by the applicant in the international application

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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

"&" document member of the same patent family

Date of the actual completion of the international search

04 May 2022

Date of mailing of the international search report

JUN 14 2022

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Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-8300

Authorized officer

Kari Rodriguez

Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 22/20487

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 5-8 and 10-18
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.