(12) STANDARD PATENT (11) Application No. **AU 2014238478 B2**
(19) AUSTRALIAN PATENT OFFICE

(54) Title
Halogenopyrazoles as inhibitors of thrombin

(51) International Patent Classification(s)
C07D 233/54 (2006.01) ***A61P 7/00*** (2006.01)
A61K 31/415 (2006.01) ***C07D 213/16*** (2006.01)

(21) Application No: **2014238478** (22) Date of Filing: **2014.03.17**

(87) WIPO No: **WO14/149139**

(30) Priority Data

(31) Number	(32) Date	(33) Country
61/789,358	**2013.03.15**	**US**
61/899,588	**2013.11.04**	**US**

(43) Publication Date: **2014.09.25**
(44) Accepted Journal Date: **2018.07.19**

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 September 2014 (25.09.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/149139 A3

(51) International Patent Classification:
C07D 233/54 (2006.01) *A61K 31/415* (2006.01)
C07D 213/16 (2006.01) *A61P 7/00* (2006.01)

(21) International Application Number:
PCT/US2014/000058

(22) International Filing Date:
17 March 2014 (17.03.2014)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/789,358 15 March 2013 (15.03.2013) US
61/899,588 4 November 2013 (04.11.2013) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(88) Date of publication of the international search report:
27 November 2014

(54) Title: HALOGENOPYRAZOLES AS INHIBITORS OF THROMBIN

(57) Abstract: There are provided inter alia multisubstituted aromatic compounds useful for the inhibition of thrombin, which compounds include substituted pyrazolyi. There are additionally provided pharmaceutical compositions. There are additionally provided methods of treating and preventing a disease or disorder, which disease or disorder is amenable to treatment or prevention by the inhibition of thrombin.

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HALOGENOPYRAZOLES AS INHIBITORS OF THROMBIN

BACKGROUND OF THE INVENTION

[0001] The present disclosure relates to compounds, e.g., multisubstituted aromatic compounds, which exhibit biological activity, e.g., inhibitory action, against thrombin (activated blood-coagulation factor II; EC 3.4.21.5).

[0002] In mammalian systems, blood vessel injuries result in bleeding events, which are dealt with by the blood coagulation cascade. The cascade includes the Extrinsic and Intrinsic pathways, involving the activation of at least 13 interconnected factors and a variety of co-factors and other regulatory proteins. Upon vascular injury, plasma factor VII interacts with exposed Tissue Factor (TF), and the resultant TF-fVIIa complex initiates a complex series of events. Factor fXa is produced directly 'downstream' from the TF-fVIIa complex, and amplified manifold via the Intrinsic Pathway. FXa then serves as the catalyst for formation of thrombin (fIIa), which in turn is the direct precursor to fibrinolysis. The outcome is a fibrinolytic clot, which stops the bleeding. Fibrinolysis of the polymeric clot into fibrin monomers leads to dissolution and a return of the system to the pre-clot state. The cascade is a complex balance of factors and co-factors and is tightly regulated.

[0003] In disease states, undesired up- or down-regulation of any factor leads to conditions such as bleeding or thrombosis. Historically, anticoagulants have been used in patients at risk of suffering from thrombotic complications, such as angina, stroke and heart attack.

[0004] Warfarin has enjoyed dominance as a first-in-line anticoagulant therapeutic. Developed in the 1940s, it is a Vitamin K antagonist and inhibits factors II, VII, IX and X, amongst others. It is administered orally, but its ease of use is tempered by other effects: it has a very long half life (>2 days) and has serious drug-drug interactions. Importantly, since Vitamin K is a ubiquitous cofactor within the coagulation cascade, antagonism results in the simultaneous inhibition of many clotting factors and thus can lead to significant bleeding complications.

[0005] Much attention has been focused on heparin, the naturally-occurring polysaccharide that activates AT III, the endogenous inhibitor of many of the factors in the coagulation cascade. The need for parenteral administration for the heparin-derived therapeutics, and the inconvenient requirements for close supervision for the orally available warfarin, has resulted

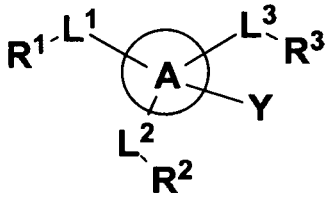
in a drive to discover and develop orally available drugs with wide therapeutic windows for safety and efficacy.

[0006] Indeed, the position of thrombin in the coagulation cascade has made it a popular target for drug discovery. Without wishing to be bound by any theory, it is believed that the ultimate development of direct thrombin inhibitors (DTIs) is usefully based upon the classical D-Phe-Pro-Arg motif, a sequence that mimics fibrinogen, which is a natural substrate of thrombin. Without further wishing to be bound by any theory, it is believed that the use of DTIs is very well precedented, such as with the hirudin-based anticoagulants, and thus there is strong interest in the discovery and development of novel DTIs.

[0007] A thorough discussion of thrombin and its roles in the coagulation process can be found in a variety of references, including the following which are incorporated herein by reference in their entireties and for all purposes: Wieland, H. A., *et al.*, 2003, *Curr Opin Investig Drugs*, 4:264-71; Gross, P. L. & Weitz, J. I., 2008, *Arterioscler Thromb Vasc Biol*, 28:380-6; Hirsh, J., *et al.*, 2005, *Blood*, 105:453-63; Prezelj, A., *et al.*, 2007, *Curr Pharm Des*, 13:287-312.

BRIEF SUMMARY OF THE INVENTION

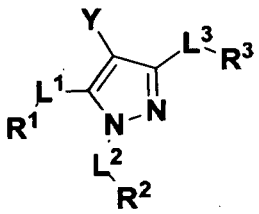
[0008] Embodiments of the invention encompass compounds with structure of Formula (Ia):



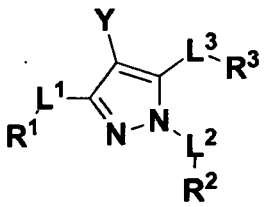
(Ia)

or pharmaceutically acceptable salt, ester, solvate, or prodrug thereof; wherein Ring A can be substituted or unsubstituted pyrazolyl; L^1 and L^3 can be independently a bond, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, -S-, -SO-, $-SO_2-$, -O-, $-NHSO_2-$, or $-NR^4-$; L^2 can be absent, a bond, substituted or unsubstituted alkylene, substituted or unsubstituted eteroalkylene, -S-, -SO-, $-SO_2-$, -O-, $-NHSO_2-$, or $-NR^4-$; R^1 and R^3 can be independently hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted fused ring aryl, or substituted or unsubstituted heteroaryl; R^2 can be absent,

hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted fused ring aryl, or substituted or unsubstituted heteroaryl, provided that when L^2 can be absent, R^2 can be absent; R^4 can be hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heterocycloalkenyl, and substituted or unsubstituted fused ring aryl or substituted or unsubstituted heteroaryl; and Y can be a halogen. In some embodiments of the methods, L^2 and R^2 can be absent. In some embodiments, the compound can have the structure of Formula (IIa) or Formula (IIb):



(IIa)



(IIb)

[0009] In some embodiments where the compound can have the structure of Formula (IIa), L^3 can be a bond, or substituted or unsubstituted alkylene, and R^3 can be substituted or unsubstituted aryl, substituted or unsubstituted fused ring aryl, substituted or unsubstituted heterocycloalkyl, or substituted or unsubstituted heteroaryl, and Y can be fluorine. In some embodiments where the compound can have the structure of Formula (IIa), L^3 can be -C(O)O-, R^3 can be substituted or unsubstituted alkyl, and Y can be fluorine. In some embodiments where the compound can have the structure of Formula (IIa), L^3 can be -C(O)NR^5-, R^5 can be hydrogen or alkyl, R^3 can be substituted or unsubstituted alkyl, or substituted or unsubstituted aryl, and Y can be fluorine. In some embodiments, R^3 can be substituted or unsubstituted phenyl. In some embodiments, the heteroaryl can be pyridyl, pyridazinyl, pyrimidinyl, thienyl, or furyl. In some embodiments, R^3 can be chloro-substituted thienyl. In some embodiments, the heterocycloalkyl can be morpholinyl, oxanyl, or oxetanyl. In some embodiments, the fused ring aryl can be benzodioxinyl or naphthyl. In some embodiments, L^1 can be a bond, -S-, -NR^4-, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene, and R^1 can be hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted fused ring

aryl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl. In some embodiments, the heteroaryl can be pyridyl, pyridazinyl, pyrimidinyl, thienyl, or furyl. In some embodiments, R^1 can be chloro-substituted thienyl. In some embodiments, the heterocycloalkyl can be morpholinyl, oxanyl, or oxetanyl. In some embodiments, the fused ring aryl can be benzodioxinyl or naphthyl. In some embodiments, R^1 can be substituted or unsubstituted phenyl. In some embodiments, L^2 can be a bond, and R^2 can be hydrogen. In some embodiments, L^2 can be substituted or unsubstituted alkylene or -C(O)-, and R^2 can be hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted fused ring aryl, or substituted or unsubstituted heteroaryl. In some embodiments, the heteroaryl can be pyridyl, pyridazinyl, pyrimidinyl, thienyl, or furyl. In some embodiments, R^2 can be substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocycloalkyl. In some embodiments, the heterocycloalkyl can be morpholinyl, oxanyl, or oxetanyl. In some embodiments, the fused ring aryl can be benzodioxinyl or naphthyl. In some embodiments, R^2 can be substituted or unsubstituted phenyl.

[0010] In some embodiments where the compound can have the structure of Formula (IIb), L^3 can be a bond, or substituted or unsubstituted alkylene, R^3 can be substituted or unsubstituted aryl, substituted or unsubstituted fused ring aryl, substituted or unsubstituted heterocycloalkyl, or substituted or unsubstituted heteroaryl, and Y can be fluorine. In some embodiments where the compound can have the structure of Formula (IIa), L^3 can be -C(O)O-, R^3 can be substituted or unsubstituted alkyl, and Y can be fluorine. In some embodiments where the compound can have the structure of Formula (IIa), L^3 can be $-C(O)NR^5-$, R^5 can be hydrogen or alkyl, R^3 can be substituted or unsubstituted alkyl, or substituted or unsubstituted aryl, and Y can be fluorine. In some embodiments, R^3 can be substituted or unsubstituted phenyl. In some embodiments, the heteroaryl can be pyridyl, pyridazinyl, pyrimidinyl, thienyl, or furyl. In some embodiments, R^3 can be chloro-substituted thienyl. In some embodiments, the heterocycloalkyl can be morpholinyl, oxanyl, or oxetanyl. In some embodiments, the fused ring aryl can be benzodioxinyl or naphthyl. In some embodiments, L^1 can be a bond, -S-, $-NR^4-$, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene, and R^1 can be hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted fused ring aryl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl.

In some embodiments, the heteroaryl can be pyridyl, pyridazinyl, pyrimidinyl, thienyl, or furyl. In some embodiments, R^1 can be chloro-substituted thienyl. In some embodiments, the heterocycloalkyl can be morpholinyl, oxanyl, or oxetanyl. In some embodiments, the fused ring aryl can be benzodioxinyl or naphthyl. In some embodiments, R^1 can be substituted or unsubstituted phenyl. In some embodiments, L^2 can be a bond, and R^2 can be hydrogen. In some embodiments, L^2 can be substituted or unsubstituted alkylene or -C(O)-, and R^2 can be hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted fused ring aryl, or substituted or unsubstituted heteroaryl. In some embodiments, the heteroaryl can be pyridyl, pyridazinyl, pyrimidinyl, thienyl, or furyl. In some embodiments, R^2 can be substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocycloalkyl. In some embodiments, the heterocycloalkyl can be morpholinyl, oxanyl, or oxetanyl. In some embodiments, the fused ring aryl can be benzodioxinyl or naphthyl. In some embodiments, R^2 can be substituted or unsubstituted phenyl. In some embodiments, the compound can be selected from those set forth in Table A.

[0011] Embodiments of the invention also encompass pharmaceutical compositions including such compounds, or a compound as set forth in Table A, and a pharmaceutically acceptable excipient. Embodiments of the invention also encompass methods for treating a disease or disorder in a subject, including administering such compounds or pharmaceutical compositions to a subject in need thereof in an amount effective to treat said disease or disorder. In some embodiments, the disease or disorder is a thrombotic disorder. In some embodiments, the thrombotic disorder is acute coronary syndrome, venous thromboembolism, arterial thromboembolism or cardiogenic thromboembolism. In some embodiments, the disease or disorder is fibrosis. In some embodiments, the disease or disorder is Alzheimer's Disease. In some embodiments, the disease or disorder is multiple sclerosis. In some embodiments, the disease or disorder is pain. In some embodiments, the disease or disorder is cancer. Embodiments of the invention also encompass methods for preventing a disease or disorder in a subject, including administering such compounds or pharmaceutical compositions to a subject in need thereof in an amount effective to prevent said disease or disorder. In some embodiments, the disease or disorder can be a thrombotic disorder. In some embodiments, the thrombotic disorder can be acute coronary syndrome, venous thromboembolism, arterial thromboembolism or cardiogenic thromboembolism. In

some embodiments, the thrombotic disorder can be disseminated intravascular coagulation. In some embodiments, the thrombotic disorder involves the presence or the potential formation of a blood clot thrombus.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] Not applicable.

DETAILED DESCRIPTION OF THE INVENTION

I. Definitions

[0013] The abbreviations used herein have their conventional meaning within the chemical and biological arts. The chemical structures and formulae set forth herein are constructed according to the standard rules of chemical valency known in the chemical arts.

[0014] Where substituent groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, e.g., $-CH_2O-$ is equivalent to $-OCH_2-$.

[0015] As used herein, the term "attached" signifies a stable covalent bond, certain preferred points of attachment being apparent to those of ordinary skill in the art.

[0016] The terms "halogen" or "halo" include fluorine, chlorine, bromine, and iodine. Additionally, terms such as "haloalkyl" are meant to include monohaloalkyl and polyhaloalkyl. For example, the term "halo(C_1-C_4)alkyl" includes, but is not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

[0017] The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight (i.e., unbranched) or branched chain, or combination thereof, which can be fully saturated, mono- or polyunsaturated and can include di- and multivalent radicals, having the number of carbon atoms designated (i.e., C_1-C_{10} means one to ten carbons). Examples of saturated hydrocarbon radicals include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, (cyclohexyl)methyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include, but are not limited to, vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butynyl, and

the higher homologs and isomers. Accordingly, the term "alkyl" can refer to C_1-C_{16} straight chain saturated, C_1-C_{16} branched saturated, C_3-C_8 cyclic saturated and C_1-C_{16} straight chain or branched saturated aliphatic hydrocarbon groups substituted with C_3-C_8 cyclic saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, this definition shall include but is not limited to methyl (Me), ethyl (Et), propyl (Pr), butyl (Bu), pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, isopropyl (i-Pr), isobutyl (i-Bu), tert-butyl (t-Bu), sec-butyl (s-Bu), isopentyl, neopentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopropylmethyl, and the like.

[0018] The term "alkylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkyl, as exemplified, but not limited by, $-CH_2CH_2CH_2CH_2-$. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred in the compounds disclosed herein. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms.

[0019] The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or combinations thereof, consisting of at least one carbon atom and at least one heteroatom selected from the group consisting of O, N, P, Si, and S, and wherein the nitrogen and sulfur atoms can optionally be oxidized, and the nitrogen heteroatom can optionally be quaternized. The heteroatom(s) O, N, P, S, and Si can be placed at any interior position of the heteroalkyl group or at the position at which the alkyl group is attached to the remainder of the molecule. Examples include, but are not limited to: $-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-CH_2-N(CH_3)-CH_3$, $-CH_2-S-CH_2-CH_3$, $-CH_2-CH_2$, $-S(O)-CH_3$, $-CH_2-CH_2-S(O)_2-CH_3$, $-CH=CH-O-CH_3$, $-Si(CH_3)_3$, $-CH_2-CH=N-OCH_3$, $-CH=CH-N(CH_3)-CH_3$, $-O-CH_3$, $-O-CH_2-CH_3$, and -CN. Up to two heteroatoms can be consecutive, such as, for example, $-CH_2-NH-OCH_3$.

[0020] Similarly, the term "heteroalkylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from heteroalkyl, as exemplified, but not limited by, $-CH_2-CH_2-S-CH_2-CH_2-$ and $-CH_2-S-CH_2-CH_2-NH-CH_2-$. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula $-C(O)_2R'-$ represents both $-C(O)_2R'-$ and $-R'C(O)_2-$. As described above, heteroalkyl groups, as used

herein, include those groups that are attached to the remainder of the molecule through a heteroatom, such as -C(O)R', -C(O)NR', -NR'R", -OR', -SR', and/or -SO_2R'. Where "heteroalkyl" is recited, followed by recitations of specific heteroalkyl groups, such as -NR'R" or the like, it will be understood that the terms heteroalkyl and -NR'R" are not redundant or mutually exclusive. Rather, the specific heteroalkyl groups are recited to add clarity. Thus, the term "heteroalkyl" should not be interpreted herein as excluding specific heteroalkyl groups, such as -NR'R" or the like.

[0021] The terms "cycloalkyl" and "heterocycloalkyl," by themselves or in combination with other terms, mean, unless otherwise stated, cyclic versions of "alkyl" and "heteroalkyl," respectively. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include, but are not limited to, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like. A "cycloalkylene" and a "heterocycloalkylene," alone or as part of another substituent, means a divalent radical derived from a cycloalkyl and heterocycloalkyl, respectively.

[0022] The term "alkenyl" includes C_2-C_{16} straight chain unsaturated, C_2-C_{11} branched unsaturated, C_5-C_8 unsaturated cyclic, and C_2-C_{16} straight chain or branched unsaturated aliphatic hydrocarbon groups substituted with C_3-C_8 cyclic saturated and unsaturated aliphatic hydrocarbon groups having the specified number of carbon atoms. Double bonds can occur in any stable point along the chain and the carbon-carbon double bonds can have either the *cis* or *trans* configuration. For example, this definition shall include but is not limited to ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl, undecenyl, 1,5-octadienyl, 1,4,7-nonatrienyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, ethylcyclohexenyl, butenylcyclopentyl, l-pentenyl-3-cyclohexenyl, and the like. Similarly, "heteroalkenyl" refers to heteroalkyl having one or more double bonds.

[0023] The term "alkynyl" refers in the customary sense to alkyl additionally having one or more triple bonds. The term "cycloalkenyl" refers to cycloalkyl additionally having one or more double bonds. The term "heterocycloalkenyl" refers to heterocycloalkyl additionally having one or more double bonds.

[0024] The term "acyl" means, unless otherwise stated, -C(O)R where R is a substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0025] Each of the above terms (e.g., "alkyl," "heteroalkyl," "aryl," and "heteroaryl") includes both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided herein.

[0026] Substituents for the alkyl and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be one or more of a variety of groups selected from, but not limited to, -OR', =O, =NR', =N-OR', -NR'R", -SR', -halogen, -SiR'R"R"', -OC(O)R', -C(O)R', -CO_2R', -CONR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R"', -NR"$C(O)_2$R', -NR-C(NR'R")=NR"', -S(O)R', -$S(O)_2$R', -$S(O)_2$NR'R", -$NRSO_2$R', -CN, and -NO_2 in a number ranging from zero to (2m'+1), where m' is the total number of carbon atoms in such radical. R', R", and R"' each preferably independently refer to hydrogen, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl (e.g., aryl substituted with 1-3 halogens), substituted or unsubstituted alkyl, alkoxy, or thioalkoxy groups, or arylalkyl groups. When a compound disclosed herein includes more than one R group, for example, each of the R groups is independently selected as are each R', R", and R"' group when more than one of these groups is present. When R' and R" are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 4-, 5-, 6-, or 7-membered ring. For example, -NR'R" includes, but is not limited to, 1-pyrrolidinyl and 4-morpholinyl. From the above discussion of substituents, one of skill in the art will understand that the term "alkyl" is meant to include groups including carbon atoms bound to groups other than hydrogen groups, such as haloalkyl (e.g., -CF_3 and -CH_2CF_3) and acyl (e.g., -$C(O)CH_3$, -$C(O)CF_3$, -$C(O)CH_2OCH_3$, and the like).

[0027] Similar to the substituents described for the alkyl radical, substituents for the aryl and heteroaryl groups are varied and are selected from, for example: -OR', -NR'R", -SR', -halogen, -SiR'R"R"', -OC(O)R', -C(O)R', -CO_2R', -CONR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R"', -NR"$C(O)_2$R', -NR-C(NR'R")=NR"', -S(O)R', -$S(O)_2$R', -$S(O)_2$NR'R", -$NRSO_2$R', -CN, -NO_2, -R', -N_3, -$CH(Ph)_2$, fluoro(C_1-C_4)alkoxy, and fluoro(C_1-C_4)alkyl, in a number ranging from zero to the total number of open valences on the aromatic ring system;

and where R', R", and R'" are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. When a compound disclosed herein includes more than one R group, for example, each of the R groups is independently selected as are each R', R", and R'" groups when more than one of these groups is present.

[0028] Two or more substituents can optionally be joined to form aryl, heteroaryl, cycloalkyl, or heterocycloalkyl groups. Such so-called ring-forming substituents are typically, though not necessarily, found attached to a cyclic base structure. In one embodiment, the ring-forming substituents are attached to adjacent members of the base structure. For example, two ring-forming substituents attached to adjacent members of a cyclic base structure create a fused ring structure. In another embodiment, the ring-forming substituents are attached to a single member of the base structure. For example, two ring-forming substituents attached to a single member of a cyclic base structure create a spirocyclic structure. In yet another embodiment, the ring-forming substituents are attached to non-adjacent members of the base structure.

[0029] Two of the substituents on adjacent atoms of the aryl or heteroaryl ring can optionally form a ring of the formula -T-C(O)-$(CRR')_q$-U-, wherein T and U are independently -NR-, -O-, -CRR'-, or a single bond, and q is an integer of from 0 to 3. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring can optionally be replaced with a substituent of the formula -A-$(CH_2)_r$-B-, wherein A and B are independently -CRR'-, -O-, -NR-, -S-, -S(O) -, -$S(O)_2$-, -$S(O)_2$NR'-, or a single bond, and r is an integer of from 1 to 4. One of the single bonds of the new ring so formed can optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring can optionally be replaced with a substituent of the formula -$(CRR')_s$-X'- $(C"R'")_d$-, where s and d are independently integers of from 0 to 3, and X' is -O-, -NR'-, -S-, -S(O)-, -$S(O)_2$-, or -$S(O)_2$NR'-. The substituents R, R', R", and R'" are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

[0030] As used herein, the terms "heteroatom" or "ring heteroatom" are meant to include oxygen (O), nitrogen (N), sulfur (S), phosphorus (P), and silicon (Si).

[0031] The term "alkyloxy" (e.g. methoxy, ethoxy, propyloxy, allyloxy, cyclohexyloxy) represents an alkyl group as defined above having the indicated number of carbon atoms attached through an oxygen bridge (-O-).

[0032] The term "alkylthio" (e.g. methylthio, ethylthio, propylthio, cyclohexylthio and the like) represents an alkyl group as defined above having the indicated number of carbon atoms attached through a sulfur bridge (-S-).

[0033] The term "alkylamino" represents one or two alkyl groups as defined above having the indicated number of carbon atoms attached through an amine bridge. The two alkyl groups canbe taken together with the nitrogen to which they are attached forming a cyclic system containing 3 to 8 carbon atoms with or without one C_1-C_{16}alkyl, arylC_0-C_{16}alkyl, or C_0-C_{16}alkylaryl substituent.

[0034] The term "alkylaminoalkyl" represents an alkylamino group attached through an alkyl group as defined above having the indicated number of carbon atoms.

[0035] The term "alkyloxy(alkyl)amino" (e.g. methoxy(methyl)amine, ethoxy(propyl)amine) represents an alkyloxy group as defined above attached through an amino group, the amino group itself having an alkyl substituent.

[0036] The term "alkylcarbonyl" (e.g. cyclooctylcarbonyl, pentylcarbonyl, 3-hexylcarbonyl) represents an alkyl group as defined above having the indicated number of carbon atoms attached through a carbonyl group.

[0037] The term "alkylcarboxy" (e.g. heptylcarboxy, cyclopropylcarboxy, 3-pentenylcarboxy) represents an alkylcarbonyl group as defined above wherein the carbonyl is in turn attached through an oxygen.

[0038] The term "alkylcarboxyalkyl" represents an alkylcarboxy group attached through an alkyl group as defined above having the indicated number of carbon atoms.

[0039] The term "alkylcarbonylamino" (e.g. hexylcarbonylamino, cyclopentylcarbonylaminomethyl, methylcarbonylaminophenyl) represents an alkylcarbonyl group as defined above wherein the carbonyl is in turn attached through the nitrogen atom of an amino group.

[0040] The nitrogen group can itself be substituted with an alkyl or aryl group.

[0041] The term “aryl” means, unless otherwise stated, a polyunsaturated, aromatic, hydrocarbon substituent, which can be a single ring or multiple rings (preferably from 1 to 3 rings) that are fused together (i.e., a fused ring aryl) or linked covalently. A fused ring aryl

refers to multiple rings fused together wherein at least one of the fused rings is an aryl ring. The term "heteroaryl" refers to aryl groups (or rings) that contain from one to four heteroatoms selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. Thus, the term "heteroaryl" includes fused ring heteroaryl groups (i.e., multiple rings fused together wherein at least one of the fused rings is a heteroaromatic ring). A 5,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 5 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. Likewise, a 6,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. And a 6,5-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and the other ring has 5 members, and wherein at least one ring is a heteroaryl ring. A heteroaryl group can be attached to the remainder of the molecule through a carbon or heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 3-quinolyl, and 6-quinolyl. Substituents for each of the above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below. An "arylene" and a "heteroarylene," alone or as part of another substituent, mean a divalent radical derived from an aryl and heteroaryl, respectively. Accordingly, the term "aryl" can represent an unsubstituted, mono-, di- or trisubstituted monocyclic, polycyclic, biaryl and heterocyclic aromatic groups covalently attached at any ring position capable of forming a stable covalent bond, certain preferred points of attachment being apparent to those skilled in the art (e. g. 3-indolyl, 4-imidazolyl). The aryl substituents are independently selected from the group consisting of halo, nitro, cyano, trihalomethyl, $C_{1\text{-}16}$alkyl, aryl$C_{1\text{-}16}$alkyl, $C_{0\text{-}16}$alkyloxy$C_{0\text{-}16}$alkyl, aryl$C_{0\text{-}16}$alkyloxy$C_{0\text{-}16}$alkyl, $C_{0\text{-}16}$alkylthio$C_{0\text{-}16}$alkyl, aryl$C_{0\text{-}16}$alkylthio$C_{0\text{-}16}$alkyl, $C_{0\text{-}16}$alkylamino$C_{0\text{-}16}$alkyl, aryl$C_{0\text{-}16}$alkylamino$C_{0\text{-}16}$alkyl, di(aryl$C_{1\text{-}16}$alkyl)amino$C_{0\text{-}16}$alkyl, $C_{1\text{-}16}$alkylcarbonyl$C_{0\text{-}16}$alkyl, aryl$C_{1\text{-}16}$alkylcarbonyl$C_{0\text{-}16}$alkyl, $C_{1\text{-}16}$alkylcarboxy$C_{0\text{-}16}$alkyl, aryl$C_{1\text{-}16}$alkylcarboxy$C_{0\text{-}16}$alkyl, $C_{1\text{-}16}$alkylcarbonylamino$C_{0\text{-}16}$alkyl, aryl$C_{1\text{-}16}$alkylcarbonylamino$C_{0\text{-}16}$alkyl,-$C_{0\text{-}16}$alkylCOOR$_4$, -$C_{0\text{-}16}$alkylCONR$_5$R$_6$ wherein R$_4$, R$_5$ and R$_6$ are independently selected from hydrogen, $C_{1\text{-}}$

C_{11}alkyl, arylC_0-C_{11}alkyl, or R_5 and R_6 are taken together with the nitrogen to which they are attached forming a cyclic system containing 3 to 8 carbon atoms with or without one C_{1-16}alkyl, arylC_0-C_{16}alkyl, or C_0-Cl_{16}alkylaryl substituent. Aryl includes but is not limited to pyrazolyl and triazolyl.

[0042] For brevity, the term "aryl" when used in combination with other terms (e.g., aryloxy, arylthioxy, arylalkyl) includes both aryl and heteroaryl rings as defined above. Thus, the terms "arylalkyl," "aralkyl" and the like are meant to include those radicals in which an aryl group is attached to an alkyl group (e.g., benzyl, phenethyl, pyridylmethyl, and the like) including those alkyl groups in which a carbon atom (e.g., a methylene group) has been replaced by, for example, an oxygen atom (e.g., phenoxymethyl, 2-pyridyloxymethyl, 3-(1-naphthyloxy)propyl, and the like), or a sulfur atom. Accordingly, the terms "arylalkyl" and the like (e.g. (4-hydroxyphenyl)ethyl, (2-aminonaphthyl)hexyl, pyridylcyclopentyl) represents an aryl group as defined above attached through an alkyl group as defined above having the indicated number of carbon atoms.

[0043] The term "oxo," as used herein, means an oxygen that is double bonded to a carbon atom.

[0044] The term "alkylsulfonyl," as used herein, means a moiety having the formula -S(O_2)-R', where R' is an alkyl group as defined above. R' can have a specified number of carbons (e.g., "C_1-C_4 alkylsulfonyl").

[0045] The term "carbonyloxy" represents a carbonyl group attached through an oxygen bridge.

[0046] In the above definitions, the terms "alkyl" and "alkenyl" can be used interchangeably in so far as a stable chemical entity is formed, as would be apparent to those skilled in the art.

[0047] The term "linker" refers to attachment groups interposed between substituents, e.g., R^1, R^2 or R^3 described herein, e.g., Formula (Ia) and generically referred to as R^n, and the group which is substituted, e.g., "ring A" group of e.g., Formula (Ia). In some embodiments, the linker includes amido (-CONH-R^n or -NHCO-R^n), thioamido (-CSNH-R^n or -NHCS-R^n), carboxyl (-CO_2-R^n or -OCOR^n), carbonyl (-CO-R^n), urea (-NHCONH-R^n), thiourea (-NHCSNH-R^n), sulfonamido (-$NHSO_2$-R^n or -SO_2NH-R^n), ether (-O-R^n), sulfonyl (-SO_2-R^n), sulfoxyl (-SO-R^n), carbamoyl (-$NHCO_2$-R^n or -OCONH-R^n), or amino (-NHR^n) linking moieties.

[0048] A "substituent group," as used herein, means a group selected from the following moieties:

(A) -OH, -NH_2, -SH, -CN, -CF_3, -NO_2, oxo, halogen, -COOH, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(B) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, substituted with at least one substituent selected from:

(i) oxo, -OH, -NH_2, -SH, -CN, -CF_3, -NO_2, halogen, -COOH, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(ii) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, substituted with at least one substituent selected from:

(a) oxo, -OH, -NH_2, -SH, -CN, -CF_3, -NO_2, halogen, -COOH, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(b) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, substituted with at least one substituent selected from: oxo, -OH, -NH_2, -SH, -CN, -CF_3, -NO_2, halogen, -COOH, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, and unsubstituted heteroaryl.

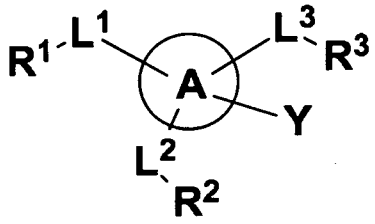
[0049] A "size-limited substituent" or " size-limited substituent group," as used herein, means a group selected from all of the substituents described above for a "substituent group," wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1-C_{20} alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_4-C_8 cycloalkyl, and each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 4 to 8 membered heterocycloalkyl.

[0050] A "lower substituent" or " lower substituent group," as used herein, means a group selected from all of the substituents described above for a "substituent group," wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1-C_8 alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_5-C_7 cycloalkyl, and each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 5 to 7 membered heterocycloalkyl.

[0051] The term "about" used in the context of a numeric value indicates a range of +/- 10% of the numeric value, unless expressly indicated otherwise.

II. Compounds

[0052] In one aspect, there is provided a compound with structure of Formula (Ia):



(Ia)

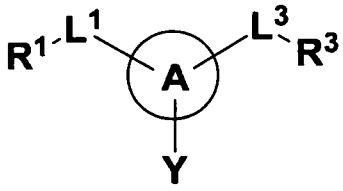
or pharmaceutically acceptable salt, ester, solvate, or prodrug thereof. Ring A is substituted or unsubsituted pyrazolyl. L^1 and L^3 are independently a bond, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, -S-, -SO-, $-SO_2-$, -O-, $-NHSO_2-$, or $-NR^4-$. L^2 is absent, a bond, a hydrogen, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, -S-, -SO-, $-SO_2-$, -O-, $-NHSO_2-$, or $-NR^4-$. R^1 and R^3 are independently hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted fused ring aryl,or substituted or unsubstituted heteroaryl. R^2 is absent, hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted fused ring aryl, or substituted or unsubstituted heteroaryl. R^4 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heterocycloalkenyl, substituted or unsubstituted fused ring aryl, or substituted or unsubstituted heteroaryl. Y is a halogen. . In some embodiments, R^2 can be absent provided L^2 is also absent.

[0053] In some embodiments, the compound is a pharmaceutically acceptable salt, ester, solvate, or prodrug of a compound of Formula (Ia). In some embodiments, the compound is not an ester, not a solvate, and not a prodrug.

[0054] Further to any embodiment above, in some embodiments L^1 is -S-, -NR^4-, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene, where R^4 is as described above in regards to formula Ia, and R^1 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted fused ring aryl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl. In some embodiments, R^3 is substituted or unsubstituted aryl. In some embodiments, R^3 is unsubstituted aryl. In some embodiments, R^3 is unsubstituted phenyl. In some embodiments, L^2 is a bond. In some embodiments, L^2 is a bond and R^2 is hydrogen. Y is fluorine.

[0055] Further to any embodiment above, in some embodiments L^2 is -C(O)-, and R^2 is substituted or unsubstituted alkyl, hydrogen, substituted or unsubstituted heteroalkyl, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heterocycloalkenyl, substituted or unsubstituted fused ring aryl, or substituted or unsubstituted heteroaryl. In some embodiments, R^2 is unsubstituted aryl. In some embodiments, R^2 is unsubstituted phenyl.

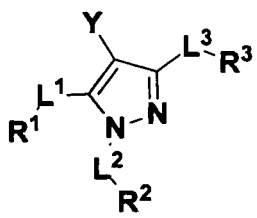
[0056] In some embodiments, L^2 and R^2 are absent, providing a compound with structure of Formula (Ib) following.



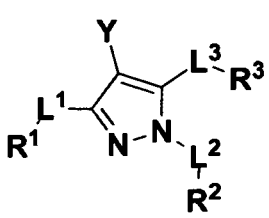
(Ib)

[0057] In some embodiments, the compound is a pharmaceutically acceptable salt, ester, solvate, or prodrug of a compound of Formula (Ib). In some embodiments, the compound is not an ester, not a solvate, and not a prodrug.

[0058] In some embodiments, there is provided a compound according to Formula (Ia) with structure of either of Formulae (IIa) or (IIb) following.



(IIa)



(IIb)

[0059] In some embodiments, the compound has the structure of Formula (IIa). In some embodiments, L^3 is a bond, or substituted or unsubstituted alkylene, and R^3 is substituted or unsubstituted aryl, substituted or unsubstituted fused ring aryl, substituted or unsubstituted heterocycloalkyl, or substituted or unsubstituted heteroaryl. In some embodiments, R^3 is substituted or unsubstituted phenyl, or substituted or unsubstituted thienyl. In some embodiments, R^3 is unsubstituted phenyl. In some embodiments, R^3 is unsubstituted thienyl. In some embodiments, R^3 is a chloro-substituted thienyl. In some embodiments, R^3 is substituted or unsubstituted pyridyl, or substituted or unsubstituted pyridazinyl. In some embodiments, R^3 is unsubstituted pyridyl. In some embodiments, R^3 is unsubstituted pyridazinyl. In some embodiments, R^3 is substituted or unsubstituted pyrimidinyl, or substituted or unsubstituted furyl. In some embodiments, R^3 is unsubstituted pyrimidinyl. In some embodiments, R^3 is unsubstituted furyl. In some embodiments, R^3 is substituted or unsubstituted morpholinyl, or substituted or unsubstituted oxanyl, or substituted or unsubstituted oxetanyl. In some embodiments, R^3 is unsubstituted morpholinyl. In some embodiments, R^3 is unsubstituted oxanyl. In some embodiments, R^3 is unsubstituted oxetanyl. In some embodiments, R^3 is substituted or unsubstituted benzodioxinyl, or substituted or unsubstituted naphthyl. In some embodiments, R^3 is unsubstituted benzodioxinyl. In some embodiments, R^3 is unsubstituted naphthyl. In some embodiments, R^3 is substituted or unsubstituted phenyl. In some embodiments, Y is fluorine.

[0060] In some embodiments, the compound has the structure of Formula (IIa) wherein L^3 is –C(O)O-, and R^3 is substituted or unsubstituted alkyl, and Y is fluorine.

[0061] In some embodiments, the compound has the structure of Formula (IIa) wherein L^3 is –C(O)NR^5-, R^5 is hydrogen or alkyl, and R^3 is substituted or unsubstituted alkyl and Y is fluorine.

[0062] Further to any embodiment above wherein the compound has the structure of Formula (IIa), in some embodiments, L^1 is -S-, a bond, -NR^4-, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene, where R^4 is as described in formula Ia and R^1 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted fused ring aryl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl. In some embodiments, R^1 is a substituted or unsubsituted pyridyl. In some embodiments, R^1 is a substituted or unsubsituted pyridazinyl. In some embodiments, R^1 is a substituted or unsubsituted pyrimidinyl. In some embodiments, R^1 is a substituted or unsubsituted thienyl. In some embodiments, R^1 is a substituted or

unsubsituted furyl. In some embodiments, R^1 is an unsubsituted pyridyl. In some embodiments, R^1 is an unsubsituted pyridazinyl. In some embodiments, R^1 is an unsubsituted pyrimidinyl. In some embodiments, R^1 is an unsubsituted thienyl. In some embodiments, R^1 is a chloro-substituted thienyl. In some embodiments, R^1 is an unsubsituted furyl. In some embodiments, R^1 is a substituted or unsubsituted morpholinyl. In some embodiments, R^1 is a substituted or unsubsituted oxanyl. In some embodiments, R^1 is a substituted or unsubsituted oxetanyl. In some embodiments, R^1 is an unsubsituted morpholinyl. In some embodiments, R^1 is an unsubsituted oxanyl. In some embodiments, R^1 is an unsubsituted oxetanyl. In some embodiments, R^1 is substituted or unsubstituted benzodioxinyl. In some embodiments, R^1 is substituted or unsubstituted naphthyl. In some embodiments, R^1 is unsubstituted benzodioxinyl. In some embodiments, R^1 is unsubstituted naphthyl. In some embodiments, R^1 is substituted or unsubstituted phenyl. In some embodiments, Y is fluorine.

[0063] Further to any embodiment above wherein the compound has the structure of Formula (IIa), in some embodiments, L^2 is a bond. In some embodiments, R^2 is hydrogen. In some embodiments, L^2 is substituted or unsubstituted alkylene or -C(O)-, and R^2 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted fused ring aryl, or substituted or unsubstituted heteroaryl. In some embodiments, R^2 is a substituted or unsubsituted pyridyl. In some embodiments, R^2 is a substituted or unsubsituted pyridazinyl. In some embodiments, R^2 is a substituted or unsubsituted pyrimidinyl. In some embodiments, R^2 is a substituted or unsubsituted thienyl. In some embodiments, R^2 is a substituted or unsubsituted furyl. In some embodiments, R^2 is an unsubsituted pyridyl. In some embodiments, R^2 is an unsubsituted pyridazinyl. In some embodiments, R^2 is an unsubsituted pyrimidinyl. In some embodiments, R^2 is an unsubsituted thienyl. In some embodiments, R^2 is a chloro-substituted thienyl. In some embodiments, R^2 is an unsubsituted furyl. In some embodiments, R^2 is a substituted or unsubsituted morpholinyl. In some embodiments, R^2 is a substituted or unsubsituted oxanyl. In some embodiments, R^2 is a substituted or unsubsituted oxetanyl. In some embodiments, R^2 is an unsubsituted morpholinyl. In some embodiments, R^2 is an unsubsituted oxanyl. In some embodiments, R^2 is an unsubsituted oxetanyl. In some embodiments, R^2 is substituted or unsubstituted benzodioxinyl. In some embodiments, R^2 is substituted or unsubstituted naphthyl. In some embodiments, R^2 is unsubstituted benzodioxinyl. In some embodiments,

R^2 is unsubstituted naphthyl. In some embodiments, R^2 is substituted or unsubstituted phenyl. In some embodiments, Y is fluorine.

[0064] In some embodiments, the compound has the structure of Formula (IIb). In some embodiments, L^3 is a bond, or substituted or unsubstituted alkylene, and R^3 is substituted or unsubstituted aryl, substituted or unsubstituted fused ring aryl, substituted or unsubstituted heterocycloalkyl, or substituted or unsubstituted heteroaryl. In some embodiments, R^3 is substituted or unsubstituted phenyl, or substituted or unsubstituted thienyl. In some embodiments, R^3 is unsubstituted phenyl. In some embodiments, R^3 is unsubstituted thienyl. In some embodiments, R^3 is a chloro-substituted thienyl. In some embodiments, R^3 is substituted or unsubstituted pyridyl, or substituted or unsubstituted pyridazinyl. In some embodiments, R^3 is unsubstituted pyridyl. In some embodiments, R^3 is unsubstituted pyridazinyl. In some embodiments, R^3 is substituted or unsubstituted pyrimidinyl, or substituted or unsubstituted furyl. In some embodiments, R^3 is unsubstituted pyrimidinyl. In some embodiments, R^3 is unsubstituted furyl. In some embodiments, R^3 is substituted or unsubstituted morpholinyl, or substituted or unsubstituted oxanyl, or substituted or unsubstituted oxetanyl. In some embodiments, R^3 is unsubstituted morpholinyl. In some embodiments, R^3 is unsubstituted oxanyl. In some embodiments, R^3 is unsubstituted oxetanyl. In some embodiments, R^3 is substituted or unsubstituted benzodioxinyl, or substituted or unsubstituted naphthyl. In some embodiments, R^3 is unsubstituted benzodioxinyl. In some embodiments, R^3 is unsubstituted naphthyl. In some embodiments, R^3 is substituted or unsubstituted phenyl. In some embodiments, Y is fluorine.

[0065] In some embodiments, the compound has the structure of Formula (IIb) wherein L^3 is –C(O)O-, and R^3 is substituted or unsubstituted alkyl, and Y is fluorine.

[0066] In some embodiments, the compound has the structure of Formula (IIb) wherein L^3 is $-C(O)NR^5-$, R^5 is hydrogen or alkyl, and R^3 is substituted or unsubstituted alkyl and Y is fluorine.

[0067] Further to any embodiment above wherein the compound has the structure of Formula (IIb), in some embodiments, L^1 is a bond, -S-, $-NR^4-$, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene, where R^4 is as described in formula Ia and R^1 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted fused ring aryl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl. In some embodiments, R^1 is a substituted or unsubsituted pyridyl. In some embodiments, R^1 is a substituted or unsubsituted pyridazinyl.

In some embodiments, R^1 is a substituted or unsubsituted pyrimidinyl. In some embodiments, R^1 is a substituted or unsubsituted thienyl. In some embodiments, R^1 is a substituted or unsubsituted furyl. In some embodiments, R^1 is an unsubsituted pyridyl. In some embodiments, R^1 is an unsubsituted pyridazinyl. In some embodiments, R^1 is an unsubsituted pyrimidinyl. In some embodiments, R^1 is an unsubsituted thienyl. In some embodiments, R^1 is a chloro-substituted thienyl. In some embodiments, R^1 is an unsubsituted furyl. In some embodiments, R^1 is a substituted or unsubsituted morpholinyl. In some embodiments, R^1 is a substituted or unsubsituted oxanyl. In some embodiments, R^1 is a substituted or unsubsituted oxetanyl. In some embodiments, R^1 is an unsubsituted morpholinyl. In some embodiments, R^1 is an unsubsituted oxanyl. In some embodiments, R^1 is an unsubsituted oxetanyl. In some embodiments, R^1 is substituted or unsubstituted benzodioxinyl. In some embodiments, R^1 is substituted or unsubstituted naphthyl. In some embodiments, R^1 is unsubstituted benzodioxinyl. In some embodiments, R^1 is unsubstituted naphthyl. In some embodiments, R^1 is substituted or unsubstituted phenyl. In some embodiments, Y is fluorine.

[0068] Further to any embodiment above wherein the compound has the structure of Formula (IIb), in some embodiments, L^2 is a bond or substituted or unsubstituted alkylene. In some embodiments, L^2 is a bond. In some embodiments, L^2 is unsubstituted alkylene. In some embodiments, L^2 is substituted alkylene. In some embodiments, R^2 is hydrogen. In some embodiments, R^2 is substituted or unsubstituted alkyl, or substituted or unsubstituted aryl. Further to any particular L^2, in some embodiments R^2 is substituted or unsubstituted alkyl, or substituted or unsubstituted aryl. In some embodiments, R^2 is unsubstituted alkyl. In some embodiments, R^2 is unsubstituted aryl. In some embodiments, R^3 is unsubstituted phenyl. In some embodiments, R^2 is substituted alkyl. In some embodiments, R^2 is substituted aryl. In some embodiments, Y is fluorine.

[0069] Further to any embodiment above wherein the compound has the structure of Formula (IIb), in some embodiments, L^2 is substituted or unsubstituted alkylene or -C(O)-, and R^2 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted fused ring aryl, or substituted or unsubstituted heteroaryl. In some embodiments, R^2 is a substituted or unsubsituted pyridyl. In some embodiments, R^2 is a substituted or unsubsituted pyridazinyl. In some embodiments, R^2 is a substituted or unsubsituted pyrimidinyl. In some embodiments, R^2 is a substituted or unsubsituted thienyl. In some embodiments, R^2 is a substituted or unsubsituted furyl. In some

embodiments, R^2 is an unsubsituted pyridyl. In some embodiments, R^2 is an unsubsituted pyridazinyl. In some embodiments, R^2 is an unsubsituted pyrimidinyl. In some embodiments, R^2 is an unsubsituted thienyl. In some embodiments, R^2 is a chloro-substituted thienyl. In some embodiments, R^2 is an unsubsituted furyl. In some embodiments, R^2 is a substituted or unsubsituted morpholinyl. In some embodiments, R^2 is a substituted or unsubsituted oxanyl. In some embodiments, R^2 is a substituted or unsubsituted oxetanyl. In some embodiments, R^2 is an unsubsituted morpholinyl. In some embodiments, R^2 is an unsubsituted oxanyl. In some embodiments, R^2 is an unsubsituted oxetanyl. In some embodiments, R^2 is substituted or unsubstituted benzodioxinyl. In some embodiments, R^2 is substituted or unsubstituted naphthyl. In some embodiments, R^2 is unsubstituted benzodioxinyl. In some embodiments, R^2 is unsubstituted naphthyl. In some embodiments, R^2 is substituted or unsubstituted phenyl. In some embodiments, Y is fluorine.

[0070] Exemplary compounds, e.g., multisubstituted aromatic compounds, in accordance with the present disclosure are provided herein. In Table A following, compound (Cmpd) number, chemical name (i.e., International Union of Pure and Applied Chemistry [IUPAC] name), molecular weight (MW_{calc} calculated mass) and biological activity (i.e., inhibition activity in a thrombin assay) are disclosed.

[0071] For Table A following, the disclosed compounds were assayed for inhibition of the protease activity of thrombin as described herein. In Table A, the level of inhibition in the thrombin assay is indicated as follows: a: $IC_{50} \leq 0.1$ μM; b: 0.1 μM < IC_{50} < 1 μM; c: $IC_{50} \geq$ 1 μM. Accordingly, in some embodiments, there is provided a compound as expressly set forth in Table A following.

Table A.

Cmpd No.	IUPAC Name	MW	Thrombin Activity
1	1-(5-[(5-chlorothiophen-2-yl)methyl]amino-3-(1-[5-(dimethylamino)naphthalen-1-yl]sulfonylpiperidin-4-yl)-4-fluoro-1H-pyrazol-1-yl)-3-hydroxy-2,2-dimethylpropan-1-one	648	a
2	1-(5-[(5-chlorothiophen-2-yl)methyl]amino-4-fluoro-3-(5-hydroxy-5,6,7,8-tetrahydronaphthalen-2-yl)-1H-pyrazol-1-yl)-2,2-dimethylpropan-1-one	462	c
3	1-(5-[(5-chlorothiophen-2-yl)methyl]amino-4-fluoro-3-(oxan-4-yl)-1H-pyrazol-1-yl)-2,2-dimethylpropan-1-one	400	a

4	1-(5-[(5-chlorothiophen-2-yl)methyl]amino-4-fluoro-3-(oxan-4-yl)-1H-pyrazol-1-yl)-3-hydroxy-2,2-dimethylpropan-1-one	416	a
5	1-(5-[(5-chlorothiophen-2-yl)methyl]amino-4-fluoro-3-(oxan-4-yl)-1H-pyrazol-1-yl)-3-methoxy-2,2-dimethylpropan-1-one	430	a
6	1-(5-[(5-chlorothiophen-2-yl)methyl]amino-4-fluoro-3-(piperidin-4-yl)-1H-pyrazol-1-yl)-2,2-dimethylpropan-1-one	399	a
7	1-(5-[(5-chlorothiophen-2-yl)methyl]amino-4-fluoro-3-(piperidin-4-yl)-1H-pyrazol-1-yl)-2-methoxy-2-methylpropan-1-one	415	a
8	1-(5-[(5-chlorothiophen-2-yl)methyl]amino-4-fluoro-3-(piperidin-4-yl)-1H-pyrazol-1-yl)-3-hydroxy-2,2-dimethylpropan-1-one	415	a
9	1-(5-[(5-chlorothiophen-2-yl)methyl]amino-4-fluoro-3-(piperidin-4-yl)-1H-pyrazol-1-yl)-3-methoxy-2,2-dimethylpropan-1-one	429	a
10	1-(5-[(5-chlorothiophen-2-yl)methyl]amino-4-fluoro-3-phenyl-1H-pyrazol-1-yl)-2,2-dimethylpropan-1-one	392	a
11	1-(5-[(5-chlorothiophen-2-yl)methyl]amino-4-fluoro-3-phenyl-1H-pyrazol-1-yl)-2-hydroxy-2-methylpropan-1-one	394	a
12	1-(5-[(5-chlorothiophen-2-yl)methyl]amino-4-fluoro-3-phenyl-1H-pyrazol-1-yl)-2-methoxy-2-methylpropan-1-one	408	a
13	1-(5-[(5-chlorothiophen-2-yl)methyl]amino-4-fluoro-3-phenyl-1H-pyrazol-1-yl)-3-(2-methoxyethoxy)-2,2-dimethylpropan-1-one	466	a
14	1-(5-[(5-chlorothiophen-2-yl)methyl]amino-4-fluoro-3-phenyl-1H-pyrazol-1-yl)-3-hydroxy-2,2-dimethylpropan-1-one	408	a
15	1-(5-[(5-chlorothiophen-2-yl)methyl]amino-4-fluoro-3-phenyl-1H-pyrazol-1-yl)-3-methoxy-2,2-dimethylpropan-1-one	422	a
16	1-[4-(5-[(5-chlorothiophen-2-yl)methyl]amino-1-(2,2-dimethylpropanoyl)-4-fluoro-1H-pyrazol-3-yl)phenyl]pyrrolidin-2-one	475	a
17	1-[4-(5-[(5-chlorothiophen-2-yl)methyl]amino-1-(2,3-dihydro-1,4-benzodioxine-5-carbonyl)-4-fluoro-1H-pyrazol-3-yl)phenyl]pyrrolidin-2-one	553	a
18	1-[4-(5-[(5-chlorothiophen-2-yl)methyl]amino-4-fluoro-1-(2-methoxybenzoyl)-1H-pyrazol-3-yl)phenyl]-2,2,2-trifluoroethan-1-ol	540	c
19	1-[4-(5-[(5-chlorothiophen-2-yl)methyl]amino-4-fluoro-1-(2-methoxybenzoyl)-1H-pyrazol-3-yl)phenyl]pyrrolidin-2-one	525	a
20	1-[4-(5-[(5-chlorothiophen-2-yl)methyl]amino-4-fluoro-1-(furan-3-carbonyl)-1H-pyrazol-3-yl)phenyl]pyrrolidin-2-one	485	c
21	1-[4-(5-[(5-chlorothiophen-2-yl)methyl]amino-4-fluoro-1H-pyrazol-3-yl)piperidine-1-carbonyl]cyclopropan-1-ol	399	b

22	1-[5-(benzylamino)-4-fluoro-3-(pyridin-2-yl)-1H-pyrazol-1-yl]-2,2-dimethylpropan-1-one	352	a
23	1-[5-(benzylamino)-4-fluoro-3-phenyl-1H-pyrazol-1-yl]-2,2-dimethylpropan-1-one	351	a
24	1-benzoyl-N-[(5-chlorothiophen-2-yl)methyl]-4-fluoro-3-(oxan-4-yl)-1H-pyrazol-5-amine	420	a
25	1-benzoyl-N-[(5-chlorothiophen-2-yl)methyl]-4-fluoro-5-(oxan-4-yl)-1H-pyrazol-3-amine	420	c
26	2-(5-[(5-chlorothiophen-2-yl)methyl]amino-4-fluoro-3-phenyl-1H-pyrazole-1-carbonyl)phenyl 5-(dimethylamino)naphthalene-1-sulfonate	661	b
27	4-(5-[(5-chlorothiophen-2-yl)methyl]amino-4-fluoro-3-phenyl-1H-pyrazole-1-carbonyl)phenyl 5-(dimethylamino)naphthalene-1-sulfonate	661	c
28	4-[4-(5-[(5-chlorothiophen-2-yl)methyl]amino-1-(2,2-dimethylpropanoyl)-4-fluoro-1H-pyrazol-3-yl)phenyl]morpholin-3-one	491	a
29	6-(5-[(5-chlorothiophen-2-yl)methyl]amino-1-(2,2-dimethylpropanoyl)-4-fluoro-1H-pyrazol-3-yl)-1,2,3,4-tetrahydronaphthalen-1-one	460	a
30	6-(5-[(5-chlorothiophen-2-yl)methyl]amino-4-fluoro-1-(2-methoxybenzoyl)-1H-pyrazol-3-yl)-1,2,3,4-tetrahydronaphthalen-1-ol	512	c
31	6-(5-[(5-chlorothiophen-2-yl)methyl]amino-4-fluoro-1-(2-methoxybenzoyl)-1H-pyrazol-3-yl)-1,2,3,4-tetrahydronaphthalen-1-one	510	a
32	N-[(5-chlorothiophen-2-yl)methyl]-1-(2,3-dihydro-1,4-benzodioxine-5-carbonyl)-4-fluoro-3-(oxan-4-yl)-1H-pyrazol-5-amine	478	a
33	N-[(5-chlorothiophen-2-yl)methyl]-1-(2,3-dihydro-1,4-benzodioxine-5-carbonyl)-4-fluoro-3-(piperidin-4-yl)-1H-pyrazol-5-amine	477	a
34	N-[(5-chlorothiophen-2-yl)methyl]-1-(2,3-dihydro-1,4-benzodioxine-5-carbonyl)-4-fluoro-3-phenyl-1H-pyrazol-5-amine	470	a
35	N-[(5-chlorothiophen-2-yl)methyl]-1-(2,3-dihydro-1,4-benzodioxine-5-carbonyl)-4-fluoro-5-(oxan-4-yl)-1H-pyrazol-3-amine	478	c
36	N-[(5-chlorothiophen-2-yl)methyl]-1-(2,4-dimethoxybenzoyl)-4-fluoro-3-(oxan-4-yl)-1H-pyrazol-5-amine	480	a
37	N-[(5-chlorothiophen-2-yl)methyl]-1-(2,4-dimethoxybenzoyl)-4-fluoro-3-(piperidin-4-yl)-1H-pyrazol-5-amine	479	a
38	N-[(5-chlorothiophen-2-yl)methyl]-1-(2,4-dimethoxybenzoyl)-4-fluoro-3-phenyl-1H-pyrazol-5-amine	472	a

39	N-[(5-chlorothiophen-2-yl)methyl]-1-(2,4-dimethoxybenzoyl)-4-fluoro-5-(oxan-4-yl)-1H-pyrazol-3-amine	480	c
40	N-[(5-chlorothiophen-2-yl)methyl]-3-(1-[5-(dimethylamino)naphthalen-1-yl]sulfonylpiperidin-4-yl)-4-fluoro-1-(2-methoxybenzoyl)-1H-pyrazol-5-amine	682	c
41	N-[(5-chlorothiophen-2-yl)methyl]-4-fluoro-1-(2-methoxybenzoyl)-3-(oxan-4-yl)-1H-pyrazol-5-amine	450	a
42	N-[(5-chlorothiophen-2-yl)methyl]-4-fluoro-1-(2-methoxybenzoyl)-3-(piperidin-4-yl)-1H-pyrazol-5-amine	449	a
43	N-[(5-chlorothiophen-2-yl)methyl]-4-fluoro-1-(2-methoxybenzoyl)-3-(pyridin-2-yl)-1H-pyrazol-5-amine	443	a
44	N-[(5-chlorothiophen-2-yl)methyl]-4-fluoro-1-(2-methoxybenzoyl)-3-phenyl-1H-pyrazol-5-amine	442	a
45	N-[(5-chlorothiophen-2-yl)methyl]-4-fluoro-1-(2-methoxybenzoyl)-5-(oxan-4-yl)-1H-pyrazol-3-amine	450	c
46	N-[(5-chlorothiophen-2-yl)methyl]-4-fluoro-1-(3-methyloxetane-3-carbonyl)-3-phenyl-1H-pyrazol-5-amine	406	c
47	N-[(5-chlorothiophen-2-yl)methyl]-4-fluoro-1-(4-methyloxane-4-carbonyl)-3-(oxan-4-yl)-1H-pyrazol-5-amine	442	a
48	N-[(5-chlorothiophen-2-yl)methyl]-4-fluoro-1-(4-methyloxane-4-carbonyl)-3-phenyl-1H-pyrazol-5-amine	434	a
49	N-[(5-chlorothiophen-2-yl)methyl]-4-fluoro-1-(furan-3-carbonyl)-3-(oxan-4-yl)-1H-pyrazol-5-amine	410	a
50	N-[(5-chlorothiophen-2-yl)methyl]-4-fluoro-1-(furan-3-carbonyl)-3-(piperidin-4-yl)-1H-pyrazol-5-amine	409	a
51	N-[(5-chlorothiophen-2-yl)methyl]-4-fluoro-1-(furan-3-carbonyl)-3-phenyl-1H-pyrazol-5-amine	402	a
52	N-[(5-chlorothiophen-2-yl)methyl]-4-fluoro-1-[4-(2-methoxyethoxy)benzoyl]-3-(oxan-4-yl)-1H-pyrazol-5-amine	494	a
53	N-[(5-chlorothiophen-2-yl)methyl]-4-fluoro-1-[4-(morpholin-4-yl)benzoyl]-3-(oxan-4-yl)-1H-pyrazol-5-amine	505	a
54	N-[(5-chlorothiophen-2-yl)methyl]-4-fluoro-3-(oxan-4-yl)-1-(thiophene-3-carbonyl)-1H-pyrazol-5-amine	426	a
55	N-[(5-chlorothiophen-2-yl)methyl]-5-(1-[5-(dimethylamino)naphthalen-1-yl]sulfonylpiperidin-4-yl)-4-fluoro-1-(2-methoxybenzoyl)-1H-pyrazol-3-amine	682	c
56	N-[(5-chlorothiophen-2-yl)methyl]-N-[4-fluoro-3-(5-oxo-5,6,7,8-tetrahydronaphthalen-2-yl)-1H-pyrazol-5-yl]-2-methoxybenzamide	510	c
57	N-[4-(5-[(5-chlorothiophen-2-yl)methyl]amino-4-fluoro-3-(piperidin-4-yl)-1H-pyrazole-1-carbonyl)phenyl]-5-(dimethylamino)naphthalene-1-sulfonamide	667	a

58	N-[4-(5-[(5-chlorothiophen-2-yl)methyl]amino-4-fluoro-3-phenyl-1H-pyrazole-1-carbonyl)phenyl]-5-(dimethylamino)naphthalene-1-sulfonamide	660	a
59	N-benzyl-4-fluoro-1-(2-methoxybenzoyl)-3-(pyridin-2-yl)-1H-pyrazol-5-amine	402	a
60	N-benzyl-4-fluoro-1-(2-methoxybenzoyl)-3-phenyl-1H-pyrazol-5-amine	401	a
61	[1-(5-[(5-chlorothiophen-2-yl)methyl]amino-4-fluoro-3-(oxan-4-yl)-1H-pyrazole-1-carbonyl)cyclopropyl]methanol	414	a
62	[1-(5-[(5-chlorothiophen-2-yl)methyl]amino-4-fluoro-3-phenyl-1H-pyrazole-1-carbonyl)cyclopropyl]methanol	406	a

[0072] Compounds disclosed herein also include racemic mixtures, stereoisomers and mixtures of the compounds, including isotopically-labeled and radio-labeled compounds. See e.g., Goding, 1986, MONOCLONAL ANTIBODIES PRINCIPLES AND PRACTICE; Academic Press, p. 104. Such isomers can be isolated by standard resolution techniques, including e.g., fractional crystallization, chiral chromatography, and the like. See e.g., Eliel, E. L. & Wilen S. H., 1993, STEREOCHEMISTRY IN ORGANIC COMPOUNDS ; John Wiley & Sons, New York.

[0073] In some embodiments, compounds disclosed herein have asymmetric centers and can occur as racemates, racemic mixtures, and as individual enantiomers or diastereoisomers, with all isomeric forms as well as mixtures thereof being contemplated for use in the compounds and methods described herein. The compounds contemplated for use in the compounds and methods described herein do not include those that are known in the art to be too unstable to synthesize and/or isolate.

[0074] The compounds disclosed herein can also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds can be radiolabeled with radioactive isotopes, such as for example tritium (^{3}H), iodine-125 (^{125}I), or carbon-14 (^{14}C). All isotopic variations of the compounds disclosed herein, whether radioactive or not, are encompassed within the contemplated scope.

[0075] In some embodiments, metabolites of the compounds disclosed herein are useful for the methods disclosed herein.

[0076] In some embodiments, compounds contemplated herein are provided in the form of a prodrug. The term "prodrug" refers to a compound that can be converted into a compound (e.g., a biologically active compound) described herein *in vivo*. Prodrugs can be useful for a

variety of reason known in the art, including e.g., ease of administration due e.g., to enhanced bioavailable in oral administration, and the like. The prodrug can also have improved solubility in pharmaceutical compositions over the biologically active compounds. An example, without limitation, of a prodrug is a compound which is administered as an ester (i.e., the "prodrug") to facilitate transmittal across a cell membrane where water solubility is detrimental to mobility but which then is metabolically hydrolyzed to the carboxylic acid, the active entity, once inside the cell where water-solubility is beneficial. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in DESIGN OF PRODRUGS, (ed. H. Bundgaard, Elsevier, 1985), which is hereby incorporated herein by reference for the limited purpose describing procedures and preparation of suitable prodrug derivatives.

[0077] Accordingly, in some embodiments, compounds contemplated herein are provided in the form of a prodrug ester. The term "prodrug ester" refers to derivatives of the compounds disclosed herein formed by the addition of any of a variety of ester-forming groups, e.g., groups known in the art, that are hydrolyzed under physiological conditions. Examples of prodrug ester groups include pivaloyloxymethyl, acetoxymethyl, phthalidyl, indanyl and methoxymethyl, as well as other such groups known in the art, including a (5-R-2-oxo-1,3-dioxolen-4-yl)methyl group. Other examples of prodrug ester groups can be found in, for example, T. Higuchi and V. Stella, in "Pro-drugs as Novel Delivery Systems", Vol. 14, A.C.S. Symposium Series, American Chemical Society (1975); and BIOREVERSIBLE CARRIERS IN DRUG DESIGN: THEORY AND APPLICATION, edited by E. B. Roche, Pergamon Press: New York, 14-21 (1987) (providing examples of esters useful as prodrugs for compounds containing carboxyl groups). Each of the above-mentioned references is herein incorporated by reference for the limited purpose of disclosing ester-forming groups that can form prodrug esters.

[0078] In some embodiments, prodrugs can be slowly converted to the compounds described herein useful for the methods described herein when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent.

[0079] Certain compounds disclosed herein can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of contemplated compounds. Certain compounds of the present invention can exist in multiple crystalline or amorphous forms. In

general, all physical forms are equivalent for the compounds and methods contemplated herein and are intended to be within the scope disclosed herein.

III. Biological Activities

[0080] In some embodiments, compounds described herein exhibit inhibitory activity against thrombin with activities ≥ 1 μM, e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100 μM, or even greater. In some embodiments, the compounds exhibit inhibitory activity against thrombin with activities between 0.1 μM and 1 μM, e.g., about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9 or 1.0 μM. In some embodiments, compounds described herein exhibit inhibitory activity against thrombin with activities ≤ 0.1 μM, e.g., about 1, 2, 5, 10, 15, 20, 30, 40, 50, 60, 70, 80, 90, or 100 nM. Ranges of values using a combination of any of the values recited herein as upper and/or lower limits are also contemplated, for example, but not limited to, 1-10 nM, 10-100 nM, 0.1–1 μM, 1–10 μM, 10-100 μM, 100-200 μM, 200-500 μM, or even 500-1000 μM. In some embodiments, the inhibitory activity is in the range of about 1-10 nM, 10-100 nM, 0.1–1 μM, 1–10 μM, 10-100 μM, 100-200 μM, 200-500 μM, or even 500-1000 μM. It is understood that for purposes of quantification, the terms "activity," "inhibitory activity," "biological activity," "thrombin activity" and the like in the context of an inhibitory compound disclosed herein can be quantified in a variety of ways known in the art. Unless indicated otherwise, as used herein such terms refer to IC_{50} in the customary sense (i.e., concentration to achieve half-maximal inhibition).

[0081] Inhibitory activity against thrombin in turn inhibits the blood coagulation process. Accordingly, compounds disclosed herein are indicated in the treatment or management of thrombotic disorders. In some embodiments, a dose or a therapeutically effective dose of a compound disclosed herein will be that which is sufficient to achieve a plasma concentration of the compound or its active metabolite(s) within a range set forth herein, e.g., about 1-10 nM, 10-100 nM, 0.1–1 μM, 1–10 μM, 10-100 μM, 100-200 μM, 200-500 μM, or even 500-1000 μM, preferably about 1-10 nM, 10-100 nM, or 0.1–1 μM. Without wishing to be bound by any theory, it is believe that such compounds are indicated in the treatment or management of thrombotic disorders.

IV. Methods of Treating and Preventing Disease

[0082] Thrombosis. Thrombotic diseases are the primary indications for thrombin inhibition, because of thrombin's location in the coagulation cascade and, in turn, the importance of the coagulation cascade in the progression of blood clotting processes. However, without wishing to be bound by any theory, it is believed the coagulation cascade in general, and thrombin in particular, is important in a variety other disease states.

[0083] It has been discovered that compounds described herein, e.g., multisubstituted aromatic compounds, exhibit inhibitory action against thrombin (activated blood-coagulation factor II; EC 3.4.21.5). This, in turn inhibits the blood coagulation process.

[0084] This inhibitory action is useful in the treatment of a variety of thrombotic disorders, such as, but not limited to, acute vascular diseases such as acute coronary syndromes; venous-, arterial- and cardiogenic thromboembolisms; the prevention of other states such as disseminated intravascular coagulation, or other conditions that involve the presence or the potential formation of a blood clot thrombus. Other indications for methods described herein include the following.

[0085] Cancer. It has long been recognized that cancer progression is accompanied by venous thrombosis, but it has not been understood how each disease is related. From several clinical trials studying the treatment of VTE, metaanalyses have shown that low molecular weight heparins (LMWHs) improve overall survival in subgroups of cancer patients. *See* e.g., Zacharski, L. R. & Lee, A. Y., 2008, *Expert Opin Investig Drugs*, 17:1029-1037; Falanga, A. & Piccioli, A., 2005, *Current Opinion in Pulmonary Medicine*, 11:403-407; Smorenburg, S. M., *et al.*, 1999, *Thromb Haemost*, 82:1600-1604; Hettiarachchi, R. J., *et al.*, 1999, *Thromb Haemost*, 82:947-952. This finding was substantiated in later clinical trials that measured specifically the survival of cancer patients. See e.g., Lee, A. Y.*et al.*, 2005, *J Clin Oncol*, 23:2123-2129; Klerk, C. P.*et al.*, *J Clin Oncol* 2005, 23:2130-2135; Kakkar, A. K., *et al.*, 2004, *J Clin Oncol*, 22:1944-1948; Altinbas, M., *et al.*, 2004, *J Thromb Haemost*, **2**:1266-1271.

[0086] More recently, researchers have focused on the specific anticancer effect of DTIs. For example, it was shown that heparin significantly prolonged the survival of patients with limited small cell lung cancer. See e.g., Akl, E. A., *et al.*, 2008, *J Exp Clin Cancer Res*, 27:4. Other investigators found that systemic use of argatroban reduced tumor mass and prolonged survival time in rat glioma models leading to the conclusion that argatroban should be considered as a novel therapeutic for glioma, a notoriously difficult to treat cancer type. See

e.g., Hua, Y., *et al.*, 2005, *Acta Neurochir*, Suppl 2005, 95:403-406; Hua, Y., *et al.*, 2005, *J Thromb Haemost,* 3:1917-1923. Very recently, it was demonstrated that dabigatran etexilate, a DTI recently FDA-approved (see e.g., Hughes, B., 2010, *Nat Rev Drug Discov*, 9:903-906) for DVT indications, inhibited both the invasion and metastasis of malignant breast tumors. See e.g., DeFeo, K.*et al.*, 2010, *Thrombosis Research*, 125 (Supplement 2): S188-S188; Defeo, K., *et al.*, 2010, *Cancer Biol Ther*, 10:1001-1008. Thus, dabigatran etexilate treatment led to a 50% reduction in tumor volume at 4 weeks with no weight loss in treated mice. Dabigatran etexilate also reduced tumor cells in the blood and liver micrometastases by 50-60%. These investigators concluded that dabigatran etexilate can be beneficial in not only preventing thrombotic events in cancer patients, but also as adjunct therapy to treat malignant tumors.

[0087] Further, hirudin and the LMWH nadroparin dramatically reduced the number of lung metastases when administered prior to cancer cell inoculation. *See* e.g., Hu, L., *et al.*, 2004, *Blood*, 104:2746-51.

[0088] The de novo thrombin inhibitor d-Arg-Oic-Pro-d-Ala-Phe(p-Me) has been found to block thrombin-stimulated invasion of prostate cancer cell line PC-3 in a concentration dependent manner. See e.g., Nieman, M. T., *et al.*, 2008, *J Thromb Haemost*, 6:837-845. A reduced rate of tumor growth was observed in mice dosed with the pentapeptide through their drinking water. The mice also showed reduced fold rate in tumor size and reduced overall tumor weight compared to untreated mice. Microscopic examination of treated tumors showed reduced number of large blood vessels thus concluding that the pentapeptide interfered with tumor angiogenesis. Nieman, M. T., *et al.*, *Thromb Haemost*, 104:1044-8.

[0089] In view of these and related studies, it is suggested that anticoagulants affect tumor metastasis; that is, angiogenesis, cancer cell adhesion, migration and invasion processes. *See* e.g., Van Noorden, C. J., *et al.*, 2010, *Thromb Res*, 125 Suppl 2:S77-79.

[0090] **Fibrosis.** Several studies have shown the utility of anticoagulant therapy in fibrotic disorders. For example, in a rat model of CCl_4-induced chronic liver injury, the DTI SSR182289 decreased liver fibrogenesis significantly after 7 weeks of administration. Similar observations were made in other studies using the LMWHs nadroparin, tinzaparin, enoxaparin, and dalteparin sodium. See e.g., Duplantier, J. G., *et al.*, 2004, *Gut*, 53:1682-1687; Abdel-Salam, O. M., *et al.*, 2005, *Pharmacol Res*, 51:59-67; Assy, N., *et al.*, 2007, *Dig Dis Sci*, 52:1187-1193; Abe, W., *et al.*, 2007, *J Hepatol*, 46:286-294.

[0091] In another example, the DTI melagatran greatly reduced ischemia reperfusion injury in a kidney transplant model in the large white pig. This led to a drastically improved kidney graft survival at 3 months. See e.g., Favreau, F., *et al.*, 2010, *Am J Transplant*, 10:30-39.

[0092] Recent studies have shown that in a bleomycin-induced mouse model of pulmonary fibrosis, dabigatran etexilate treatment reduced important profibrotic events in lung fibroblasts, including the production of collagen and connective tissue growth factor. *See* e.g., Silver, R. M., *et al.*, 2010, *Am. J. Respir. Crit. Care Med.*, 181:A6780; Bogatkevich, G. S., *et al.*, 2009, *Arthritis Rheum*, 60:3455-3464.

[0093] The above experimental evidence points to a close relationship between thrombin and fibrosis and suggests novel therapeutic opportunities for fibrosis using thrombin inhibitors. See e.g., Calvaruso, V., *et al.*, 2008, *Gut*, **57**:1722-1727; Chambers, R. C., 2008, *Br J Pharmacol*, 153 Suppl 1:S367-378; Chambers, R. C. & Laurent, G. J., 2002, *Biochem Soc Trans*, 30:194-200; Howell, D. C., *et al.*, 2001, *Am J Pathol*, 159:1383-1395.

[0094] **Alzheimer's Disease.** Very recent experiments confirm higher thrombin levels in brain endothelial cells of patients with Alzheimer's disease. While 'normal' thrombin levels are connected to regulatory CNS functions, thrombin accumulation in the brain is toxic. It has also been found that the neural thrombin inhibitor Protease Nexin 1 (PN-1) is significantly reduced in the Alzheimer's disease brain, despite the fact that PN-1 mRNA levels are unchanged. These observations have led some investigators to suggest that reduction of CNS-resident thrombin will prove useful in Alzheimer's Disease (AD) treatment. See e.g., Vaughan, P. J., *et al.*, 1994, *Brain Res*, 668:160-170; Yin, X., *et al.*, 2010, *Am J Pathol*, 176:1600-1606; Akiyama, H., *et al.*, 1992, *Neurosci Lett*, 146:152-154.

[0095] **Multiple Sclerosis.** Investigators found that hirudin treatment in an animal model of Multiple Sclerosis (MS) showed a dramatic improvement in disease severity. See e.g., Han, M. H., *et al.*, 2008, *Nature*, 451:1076-1081. Similar results were obtained following treatment with heparin (a DTI) and dermatan sulfate another coagulation inhibitor. See e.g., Chelmicka-Szorc, E. & Arnason, B. G., 1972, *Arch Neurol*, 27:153-158; Inaba, Y., *et al.*, 1999, *Cell Immunol*, 198:96-102. Other evidence shows that naturally occurring antithrombin III has anti-inflammatory effects in diseases such as endotoxemia and other sepsis-related conditions. See e.g., Wiedermann, C. J. & Romisch, J., 2002, *Acta Med Austriaca*, 29:89-92. Naturally occurring thrombin inhibitors are presumably synthesized *in situ* and have protective roles in CNS inflammation. Therefore, therapeutic thrombin inhibition has been proposed as a potential MS treatment. *See* e.g., Luo, W., *et al.*, 2009, In:

THROMBIN, Maragoudakis, M. E.; Tsopanoglou, N. E., Eds. Springer New York: 2009; pp 133-159.

[0096] Pain. In a rat pain model with partial lesion of the sciatic nerve, intrathecal hirudin prevented the development of neuropathic pain and curbed pain responses for 7 days. The investigators found that following injury, neuropathic pain was mediated by thrombin generation, which in turn activated PAR-1 receptor in the spinal cord. Hirudin inhibited thrombin generation and ultimately led to pain relief. See e.g., Garcia, P. S., *et al.*, 2010, *Thromb Haemost*, 103:1145-1151; Narita, M., *et al.*, 2005, *J Neurosci*, 25:10000-10009. Researchers hypothesize that thrombin and the PARs are involved not just as part of the coagulation cascade, but in inflammation, nociception and neurodevelopment. Development of a DTI to intersect an unexploited pharmacology will lead to pain therapeutics distinct from opioids and NSAIDs, whose shortcomings are well documented. See e.g., Garcia 2010, *Id.*

[0097] Accordingly, in a further aspect, there is provided a method for treating a disease or disorder in a subject in need thereof. The method includes administering a compound of any of Formulae (Ia), (Ib), (IIa) or (IIb) as disclosed herein, a compound as set forth in Table A, pharmaceutically acceptable salt, ester, solvate, or prodrug thereof, or pharmaceutical composition thereof, to a subject in need thereof in an amount effective to treat the disease or disorder. The terms "therapeutically effective amount," "amount effective to treat," "amount effective to prevent" and the like refer to that amount of drug or pharmaceutical agent (e.g., compound or pharmaceutical composition disclosed herein) that will elicit the biological or medical response of a tissue, system, animal, or human that is being sought by a researcher, veterinarian, medical doctor or other clinician.

[0098] In some embodiments, the disease or disorder is a thrombotic disease or disorder. In some embodiments, the thrombotic disease or disorder is acute coronary syndrome, venous thromboembolism, arterial thromboembolism or cardiogenic thromboembolism. In some embodiments, the thrombotic disease or disorder is acute coronary syndrome. In some embodiments, the thrombotic disease or disorder is venous thromboembolism. In some embodiments, the thrombotic disease or disorder is arterial thromboembolism. In some embodiments, the thrombotic disease or disorder is cardiogenic thromboembolism.

[0099] In some embodiments, the disease or disorder is fibrosis, Alzheimer's Disease, multiple sclerosis, pain, or cancer. In some embodiments, the disease or disorder is Alzheimer's Disease. In some embodiments, the disease or disorder is multiple sclerosis.

878 **[0100]** In some embodiments, the disease or disorder is fibrosis. In some embodiments
879 contemplating fibrosis, the method is directed to treating chronic liver injury. In some
880 embodiments, the disease or disorder is ischemia reperfusion injury. In some embodiments,
881 the disease or disorder is pulmonary fibrosis.

882 **[0101]** In some embodiments, the disease or disorder is pain. In some embodiments, the
883 pain is neuropathic pain.

884 **[0102]** In some embodiments, the disease or disorder is cancer. In some embodiments, the
885 cancer is limited small cell lung cancer. In some embodiments, the cancer is a glioma. In
886 some embodiments, the cancer is malignant breast cancer. In some embodiments, the cancer
887 is a micrometastasis. In some embodiments, the micrometastasis is of the blood or liver. In
888 some embodiments, the cancer is a lung metastasis. In some embodiments, the cancer is
889 prostatic cancer.

890 **[0103]** In another aspect, there is provided a method for preventing a disease or disorder in
891 a subject. The method includes administering a compound of any of Formulae (Ia), (Ib), (IIa)
892 or (IIb) as disclosed herein, compound as set forth in Table A herein, pharmaceutically
893 acceptable salt, ester, solvate, or prodrug thereof, or pharmaceutical composition thereof, to a
894 subject in need thereof in an amount effective to prevent the disease or disorder.

895 **[0104]** In some embodiments, the disease or disorder is a thrombotic disorder. In some
896 embodiments, the thrombotic disorder is acute coronary syndrome, venous
897 thromboembolism, arterial thromboembolism or cardiogenic thromboembolism. In some
898 embodiments, the thrombotic disease or disorder is disseminated intravascular coagulation.
899 In some embodiments, the thrombotic disorder involves the presence or the potential
900 formation of a blood clot thrombus.

901 **[0105]** Yet further to this aspect, in some embodiments, the disease or disorder is fibrosis,
902 Alzheimer's Disease, multiple sclerosis, pain, or cancer. In some embodiments, the disease
903 or disorder is fibrosis. In some embodiments, the disease or disorder is Alzheimer's Disease.
904 In some embodiments, the disease or disorder is multiple sclerosis. In some embodiments,
905 the disease or disorder is pain. In some embodiments, the disease or disorder is cancer.

906 **V. Assays**

907 **[0106]** Compounds described herein can be assayed, by a variety of methods known in the
908 art and described herein, for inhibition of biological activity, e.g., protease activity, of a
909 variety of proteins, e.g., thrombin. For example, the protease activity of such proteins, e.g.,

thrombin, can be monitored using a chromophoric substrate, e.g., a p-nitroanilide peptide substrate, which upon hydrolysis releases p-nitroanilide, which in turn gives rise to a color change which can be determined spectrophotometrically. *See* e.g., Lottenberg, R, *et al.*, 1983, *Biochemica et Biophysica Acta*, 752:539-557. Accordingly, the change in color can be monitored with a spectrophotometer at e.g., 405 nm to provide a signal which is directly proportional to the proteolytic activity of the enzyme.

[0107] The thrombin activity reported herein (e.g., Table A) was obtained as follows. Human thrombin was obtained from Haematologic Technologies Inc. The chromogenic substrate S-2238 was obtained from DiaPharma. Thrombin was assayed in buffer containing 0.05 M Tris (pH 7.4), 0.015 M NaCl and 0.01% PEG-8000. The final concentration of enzyme used was 3 nM thrombin. The final concentration of substrate used was 125 μM S-2238 for thrombin. All assays were performed in 96-well microtiter plates at room temperature (RT). The enzyme and inhibitor were pre-incubated for 10 minutes then substrate was added and read at 405 nm in a SpectraMax Plus Spectrophotometer (Molecular Devices). Inhibitor IC_{50} values were determined by adding test compound as ten point, three-fold serial dilutions in buffer solution, as known in the art. The plate was read at 10 minutes after substrate addition. The IC_{50} was calculated by plotting the percent (%) inhibition against compound concentration and fitting the data to a constrained four parameter sigmoidal curve, as known in the art.

VI. Pharmaceutical Compositions

[0108] In another aspect, there is provided a pharmaceutical composition comprising a compound disclosed herein and a pharmaceutically acceptable excipient. The compound is a compound of any of Formulae (Ia), (Ib), (IIa) or (IIb) as disclosed herein, a compound as set forth in Table A herein, or pharmaceutically acceptable salt, ester, solvate, or prodrug thereof. In some embodiments, the compound is set forth in Table A herein.

[0109] The term "pharmaceutically acceptable salts" is meant to include salts of the active compounds that are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds disclosed herein contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds disclosed herein contain relatively basic

functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, oxalic, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (*see*, for example, Berge *et al.*, "Pharmaceutical Salts", *Journal of Pharmaceutical Science*, 1977, *66*, 1-19). Certain specific compounds disclosed herein contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0110] Compounds disclosed herein can exist as salts, such as with pharmaceutically acceptable acids. Accordingly, the compounds contemplated herein include such salts. Examples of such salts include hydrochlorides, hydrobromides, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, tartrates (e.g., (+)-tartrates, (-)-tartrates, or mixtures thereof including racemic mixtures), succinates, benzoates, and salts with amino acids such as glutamic acid. These salts can be prepared by methods known to those skilled in the art.

[0111] The neutral forms of the compounds are preferably regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents.

[0112] Pharmaceutically acceptable salts of the compounds above, where a basic or acidic group is present in the structure, are also included within the scope of compounds contemplated herein. When an acidic substituent is present, such as $-NHSO_3H$, -COOH and $-P(O)(OH)_2$, there can be formed the ammonium, sodium, potassium, calcium salt, and the like, for use as the dosage form. Basic groups, such as amino or basic heteroaryl radicals, or pyridyl and acidic salts, such as hydrochloride, hydrobromide, acetate, maleate, palmoate, methanesulfonate, p-toluenesulfonate, and the like, can be used as the dosage form.

[0113] Also, in the embodiments in which R-COOH is present, pharmaceutically acceptable esters can be employed, e. g. , methyl, ethyl, tert-butyl, pivaloyloxymethyl, and the like, and those esters known in the art for modifying solubility or hydrolysis characteristics for use as sustained release or prodrug formulations.

A. Formulations

[0114] The compounds disclosed herein can be prepared and administered in a wide variety of oral, parenteral, and topical dosage forms. Thus, the compounds can be administered by injection (e.g. intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally). Also, the compounds described herein can be administered by inhalation, for example, intranasally. Additionally, the compounds disclosed herein can be administered transdermally. It is also envisioned that multiple routes of administration (e.g., intramuscular, oral, transdermal) can be used to administer the compounds disclosed herein. In some embodiments, the compounds disclosed herein can be administered orally as tablets, aqueous or oily suspensions, lozenges, troches, powders, granules, emulsions, capsules, syrups or elixirs. The composition for oral use can contain one or more agents selected from the group of sweetening agents, flavoring agents, coloring agents and preserving agents in order to produce pharmaceutically elegant and palatable preparations. Accordingly, there are also provided pharmaceutical compositions comprising a pharmaceutically acceptable carrier or excipient and one or more compounds disclosed herein.

[0115] In some embodiments, tablets contain the acting ingredient in admixture with non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets. These excipients can be, for example, (1) inert diluents, such as calcium carbonate, lactose, calcium phosphate, carboxymethylcellulose, or sodium phosphate; (2) granulating and disintegrating agents, such as corn starch or alginic acid; (3) binding agents, such as starch, gelatin or acacia; and (4) lubricating agents, such as magnesium stearate, stearic acid or talc. These tablets can be uncoated or coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate can be employed.

[0116] For preparing pharmaceutical compositions from the compounds disclosed herein, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A

solid carrier can be one or more substance that can also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

[0117] A compound disclosed herein, in the form of a free compound or a pharmaceutically-acceptable pro-drug, metabolite, analogue, derivative, solvate or salt, can be administered, for in vivo application, parenterally by injection or by gradual perfusion over time. Administration can be intravenously, intraperitoneally, intramuscularly, subcutaneously, intracavity, or transdermally. For *in vitro* studies the compounds can be added or dissolved in an appropriate biologically acceptable buffer and added to a cell or tissue.

[0118] In powders, the carrier is a finely divided solid in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

[0119] The powders and tablets preferably contain from 5% to 70% of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

[0120] For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

[0121] Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water/propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

[0122] When parenteral application is needed or desired, particularly suitable admixtures for the compounds disclosed herein are injectable, sterile solutions, preferably oily or aqueous solutions, as well as suspensions, emulsions, or implants, including suppositories. In

particular, carriers for parenteral administration include aqueous solutions of dextrose, saline, pure water, ethanol, glycerol, propylene glycol, peanut oil, sesame oil, polyoxyethylene-block polymers, and the like. Ampoules are convenient unit dosages. The compounds disclosed herein can also be incorporated into liposomes or administered via transdermal pumps or patches. Pharmaceutical admixtures suitable for use in the pharmaceuticals compositions and methods disclosed herein include those described, for example, in PHARMACEUTICAL SCIENCES (17th Ed., Mack Pub. Co., Easton, PA) and WO 96/05309, the teachings of both of which are hereby incorporated by reference.

[0123] In some embodiments, preparations for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Parenteral vehicles include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers (such as those based on Ringer's dextrose), and the like. Preservatives and other additives can also be present such as, for example, antimicrobials, anti-oxidants, chelating agents, growth factors and inert gases and the like.

[0124] Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizers, and thickening agents as desired. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

[0125] Also included are solid form preparations that are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations can contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

[0126] The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or

ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

[0127] The quantity of active component in a unit dose preparation can be varied or adjusted from 0.1 mg to 10000 mg, more typically 1.0 mg to 1000 mg, most typically 10 mg to 500 mg, according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

[0128] Some compounds can have limited solubility in water and therefore can require a surfactant or other appropriate co-solvent in the composition. Such co-solvents include: Polysorbate 20, 60, and 80; Pluronic F-68, F-84, and P-103; cyclodextrin; and polyoxyl 35 castor oil. Such co-solvents are typically employed at a level between about 0.01 % and about 2% by weight.

[0129] Viscosity greater than that of simple aqueous solutions can be desirable to decrease variability in dispensing the formulations, to decrease physical separation of components of a suspension or emulsion of formulation, and/or otherwise to improve the formulation. Such viscosity building agents include, for example, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxy propyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxy propyl cellulose, chondroitin sulfate and salts thereof, hyaluronic acid and salts thereof, and combinations of the foregoing. Such agents are typically employed at a level between about 0.01% and about 2% by weight.

[0130] The compositions disclosed herein can additionally include components to provide sustained release and/or comfort. Such components include high molecular weight, anionic mucomimetic polymers, gelling polysaccharides, and finely-divided drug carrier substrates. These components are discussed in greater detail in U.S. Pat. Nos. 4,911,920; 5,403,841; 5,212,162; and 4,861,760. The entire contents of these patents are incorporated herein by reference in their entirety for all purposes.

[0131] By the present, there are provided methods for ameliorating wound healing and for mediating tissue repair (including but not limited to treatment of peripheral and coronary vascular disease). According to these methods, a subject having a wound or in need of tissue repair, is treated at the site of the wound or damaged tissue or treated systemically, with a compound disclosed herein in the form of a free compound or a pharmaceutically-acceptable prodrug, metabolite, analogue, derivative, solvate or salt.

[0132] Generally, the terms "treating", "treatment" and the like are used herein to mean affecting a subject, tissue or cell to obtain a desired pharmacologic and/or physiologic effect. The effect can be prophylactic in terms of completely or partially preventing a disease or disorder or sign or symptom thereof, and/or can be therapeutic in terms of a partial or complete cure for a disorder and/or adverse effect attributable to it. "Treating" as used herein covers any treatment of, or prevention of a disease or disorder in a vertebrate, a mammal, particularly a human, and includes: (a) preventing the disease or disorder from occurring in a subject that can be predisposed to the disease or disorder, but has not yet been diagnosed as having it; (b) inhibiting the disease or disorder, i. e. , arresting its development; or (c) relieving or ameliorating the disease or disorder, i. e. , cause regression of the disease or disorder.

[0133] There are provided various pharmaceutical compositions useful for ameliorating diseases and disorders, including thrombosis. In some embodiments, the disease or disorder is a thrombotic disorder. In some embodiments, the disease or disorder is acute coronary syndrome, venous thromboembolism, arterial thromboembolism or cardiogenic thromboembolism. In some embodiments, the disease or disorder is fibrosis. In some embodiments, the disease or disorder is Alzheimer's Disease. In some embodiments, the disease or disorder is multiple sclerosis. In some embodiments, the disease or disorder is pain. In some embodiments, the disease or disorder is cancer. The pharmaceutical compositions according to one embodiment are prepared by formulating a compound disclosed herein in the form of a free compound or a pharmaceutically-acceptable pro-drug, metabolite, analogue, derivative, solvate or salt, either alone or together with other pharmaceutical agents, suitable for administration to a subject using carriers, excipients and additives or auxiliaries. Frequently used carriers or auxiliaries include magnesium carbonate, titanium dioxide, lactose, mannitol and other sugars, talc, milk protein, gelatin, starch, vitamins, cellulose and its derivatives, animal and vegetable oils, polyethylene glycols and solvents, such as sterile water, alcohols, glycerol and polyhydric alcohols. Intravenous vehicles include fluid and nutrient replenishers.

[0134] Preservatives include antimicrobial, anti-oxidants, chelating agents and inert gases. Other pharmaceutically acceptable carriers include aqueous solutions, non-toxic excipients, including salts, preservatives, buffers and the like, as described, for instance, in Remington's Pharmaceutical Sciences, 15th ed. Easton: Mack Publishing Co. , 1405-1412, 1461-1487 (1975) and The National Formulary XIV., 14th ed. Washington: American Pharmaceutical Association (1975), the contents of which are hereby incorporated by reference. The pH and

exact concentration of the various components of the pharmaceutical composition are adjusted according to routine skills in the art. *See* e.g., Goodman and Gilman (eds.), 1990, THE PHARMACOLOGICAL BASIS FOR THERAPEUTICS (7th ed.).

[0135] The pharmaceutical compositions are preferably prepared and administered in dose units. Solid dose units are tablets, capsules and suppositories. For treatment of a subject, depending on activity of the compound, manner of administration, nature and severity of the disease or disorder, age and body weight of the subject, different daily doses can be used.

[0136] Under certain circumstances, however, higher or lower daily doses can be appropriate. The administration of the daily dose can be carried out both by single administration in the form of an individual dose unit or else several smaller dose units and also by multiple administrations of subdivided doses at specific intervals.

[0137] The pharmaceutical compositions contemplated herein can be administered locally or systemically in a therapeutically effective dose. Amounts effective for this use will, of course, depend on the severity of the disease or disorder and the weight and general state of the subject. Typically, dosages used *in vitro* can provide useful guidance in the amounts useful for in situ administration of the pharmaceutical composition, and animal models can be used to determine effective dosages for treatment of particular disorders.

[0138] Various considerations are described, e. g. , in Langer, 1990, *Science*, **249**: 1527; Goodman and Gilman's (eds.), 1990, *Id.*, each of which is herein incorporated by reference and for all purposes. Dosages for parenteral administration of active pharmaceutical agents can be converted into corresponding dosages for oral administration by multiplying parenteral dosages by appropriate conversion factors. As to general applications, the parenteral dosage in mg/m2 times 1.8 = the corresponding oral dosage in milligrams ("mg"). As to oncology applications, the parenteral dosage in mg/m2 times 1.6 = the corresponding oral dosage in mg. An average adult weighs about 70 kg. *See* e.g., Miller-Keane, 1992, ENCYCLOPEDIA & DICTIONARY OF MEDICINE, NURSING & ALLIED HEALTH, 5th Ed., (W. B. Saunders Co.), pp. 1708 and 1651.

[0139] The method by which the compound disclosed herein can be administered for oral use would be, for example, in a hard gelatin capsule wherein the active ingredient is mixed with an inert solid diluent, or soft gelatin capsule, wherein the active ingredient is mixed with a co-solvent mixture, such as PEG 400 containing Tween-20. A compound disclosed herein can also be administered in the form of a sterile injectable aqueous or oleaginous solution or

suspension. The compound can generally be administered intravenously or as an oral dose of 0.1 ug to 20 mg/kg given, for example, every 3 - 12 hours.

[0140] Formulations for oral use can be in the form of hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin. They can also be in the form of soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin or olive oil.

[0141] Aqueous suspensions normally contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspension. Such excipients can be (1) suspending agent such as sodium carboxymethyl cellulose, methyl cellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; (2) dispersing or wetting agents which can be (a) naturally occurring phosphatide such as lecithin; (b) a condensation product of an alkylene oxide with a fatty acid, for example, polyoxyethylene stearate ; (c) a condensation product of ethylene oxide with a long chain aliphatic alcohol, for example, heptadecaethylenoxycetanol; (d) a condensation product of ethylene oxide with a partial ester derived from a fatty acid and hexitol such as polyoxyethylene sorbitol monooleate, or (e) a condensation product of ethylene oxide with a partial ester derived from fatty acids and hexitol anhydrides, for example polyoxyethylene sorbitan monooleate.

[0142] The pharmaceutical compositions can be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension can be formulated according to known methods using those suitable dispersing or wetting agents and suspending agents that have been mentioned above. The sterile injectable preparation can also a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil can be employed including synthetic mono-or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[0143] A compound disclosed herein can also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperature but liquid at the

rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter and polyethylene glycols.

[0144] The compounds disclosed herein as used in the methods disclosed herein can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

[0145] For topical use, creams, ointments, jellies, solutions or suspensions, etc. , containing the compounds disclosed herein, are employed.

[0146] In addition, some of the compounds disclosed herein can form solvates with water or common organic solvents. Such solvates are encompassed within the scope of the methods contemplated herein.

B. Effective Dosages

[0147] Pharmaceutical compositions provided herein include compositions wherein the active ingredient is contained in a therapeutically effective amount, i.e., in an amount effective to achieve its intended purpose. The actual amount effective for a particular application will depend, *inter alia,* on the condition being treated. For example, when administered in methods to treat thrombosis, such compositions will contain an amount of active ingredient effective to achieve the desired result (e.g. decreasing the extent of the thrombosis).

[0148] The dosage and frequency (single or multiple doses) of compound administered can vary depending upon a variety of factors, including route of administration; size, age, sex, health, body weight, body mass index, and diet of the recipient; nature and extent of symptoms of the disease being treated (e.g., the disease responsive to inhibition of thrombin); presence of other diseases or other health-related problems; kind of concurrent treatment; and complications from any disease or treatment regimen. Other therapeutic regimens or agents can be used in conjunction with the methods and compounds disclosed herein.

[0149] For any compound described herein, the therapeutically effective amount can be initially determined from a variety of techniques known in the art, e.g., biochemical characterization of inhibition of thrombin, cell culture assays, and the like. Target concentrations will be those concentrations of active compound(s) that are capable of decreasing thrombin enzymatic activity as measured, for example, using the methods described.

[0150] Therapeutically effective amounts for use in humans can be determined from animal models. For example, a dose for humans can be formulated to achieve a concentration that has been found to be effective in animals. The dosage in humans can be adjusted by monitoring thrombin inhibition and adjusting the dosage upwards or downwards, as described above.

[0151] Dosages can be varied depending upon the requirements of the patient and the compound being employed. The dose administered to a patient, in the context of the methods disclosed herein, should be sufficient to affect a beneficial therapeutic response in the patient over time. The size of the dose also will be determined by the existence, nature, and extent of any adverse side effects. Generally, treatment is initiated with smaller dosages, which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under circumstances is reached. In some embodiments of a method disclosed herein, the dosage range is 0.001% to 10% w/v. In some embodiments, the dosage range is 0.1% to 5% w/v.

[0152] Dosage amounts and intervals can be adjusted individually to provide levels of the administered compound effective for the particular clinical indication being treated. This will provide a therapeutic regimen that is commensurate with the severity of the individual's disease state.

[0153] Utilizing the teachings provided herein, an effective prophylactic or therapeutic treatment regimen can be planned that does not cause substantial toxicity and yet is entirely effective to treat the clinical symptoms demonstrated by the particular patient. This planning should involve the careful choice of active compound by considering factors such as compound potency, relative bioavailability, patient body weight, presence and severity of adverse side effects, preferred mode of administration, and the toxicity profile of the selected agent.

[0154] Accordingly, in some embodiments, dosage levels of the compounds disclosed herein as used in the present methods are of the order of e.g., about 0.1 mg to about 1 mg, about 1 mg to about 10 mg; about 0.5 mg to about 20 mg per kilogram body weight, an average adult weighing 70 kilograms, with a preferred dosage range between about 0.1 mg to about 20 mg per kilogram body weight per day (from about 0.7 mg to about 1.4 gm per patient per day). The amount of the compound disclosed herein that can be combined with the carrier materials to produce a single dosage will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for oral

administration to humans can contain about 5 ug to 1 g of a compound disclosed herein with an appropriate and convenient amount of carrier material that can vary from about 5 to 95 percent of the total composition. Dosage unit forms will generally contain between from about 0.1 mg to 500 mg of a compound disclosed herein.

[0155] It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

C. Toxicity

[0156] The ratio between toxicity and therapeutic effect for a particular compound is its therapeutic index and can be expressed as the ratio between LD_{50} (the amount of compound lethal in 50% of the population) and ED_{50} (the amount of compound effective in 50% of the population). Compounds that exhibit high therapeutic indices are preferred. Therapeutic index data obtained from *in vitro* assays, cell culture assays and/or animal studies can be used in formulating a range of dosages for use in humans. The dosage of such compounds preferably lies within a range of plasma concentrations that include the ED_{50} with little or no toxicity. The dosage can vary within this range depending upon the dosage form employed and the route of administration utilized. See, *e.g.* Fingl *et al., In:* THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, Ch.1, p.l, 1975. The exact formulation, route of administration, and dosage can be chosen by the individual practitioner in view of the patient's condition and the particular method in which the compound is used. For *in vitro* formulations, the exact formulation and dosage can be chosen by the individual practitioner in view of the patient's condition and the particular method in which the compound is used.

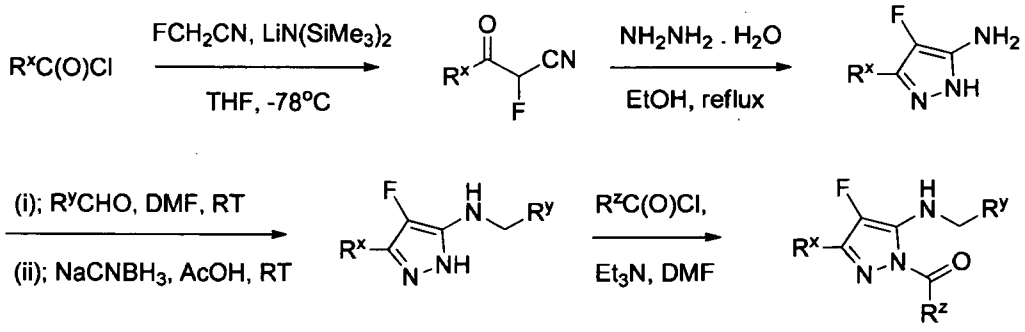
VII. Examples

[0157] The examples below are meant to illustrate certain embodiments of the invention and not to limit the scope of the invention. Abbreviations used herein have their conventional meaning in the art, unless indicated otherwise. Specific abbreviations include the following: Å = Ångström; Ac_2O = acetic anhydride; AcOH = acetic acid; aq = aqueous; Bt = benzotriazole; BOC = *N-tert*-butoxycarbonyl; br = broad; *t*-BuOH = *tert*-butanol; °C = degree Celsius; d = doublet; DABCO = 1,4-diazabicyclo[2.2.2]octane; DCE = 1,2-dichloroethane; DCM = dichloromethane; dd = doublet of doublets; DIEA = diethylisopropylamine; DMAP =

4-dimethylaminopyridine; DMF = *N*,*N*-dimethylformamide; DMSO = dimethylsulfoxide; δ = chemical shift (given in ppm, unless otherwise indicated); EDCI = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; eq = equivalent; Et_2O = diethyl ether; Et_3N = triethylamine; EtOAc = ethyl acetate; EtOH = ethanol; g = gram; h (or hr) = hour; HOBt = hydroxybenzotriazole; HPLC = high performance liquid chromatography; Hz = Hertz; IC_{50} = inhibitory concentration at 50% inhibition; *J* = coupling constant (given in Hz, unless otherwise indicated); LC = liquid chromatography; LHMDS = lithium hexamethyldisilazide; m = multiplet; M = molar; $[M+H]^+$ = parent mass spectrum peak plus H^+; MS = mass spectrum; ms = molecular sieves; MP = melting point; Me_2NH = dimethylamine; MeOH = methanol; mg = milligram; mL = milliliter; mM = millimolar; mmol = millimole; min = minute; μL = microliter; μM = micromolar; ng = nanogram; nM = nanomolar; NMR = nuclear magnetic resonance; ppm = parts per million; q = quartet; R_f = retention factor; RT = room temperature; s = singlet; t = triplet; TFA = trifluoroacetic acid; THF = tetrahydrofuran; TLC = thin layer chromatography.

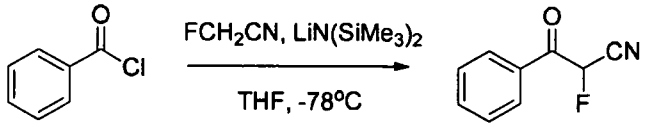
Example 1 - Preparation of Intermediate 1

[0158] General Scheme I. A synthetic scheme useful for synthesis of compounds described herein is disclosed in General Scheme I following, wherein the terms "R^x","R^y", and "R^z" are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloalkenyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or other groups obvious to those skilled in the art.



[0159] The synthesis of Intermediate 1 followed General Procedure 1 following.

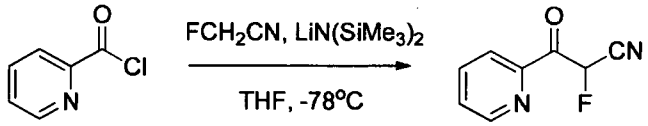
General Procedure 1



Intermediate 1

To a cold (−78 °C) solution of benzoyl chloride (5.0 mmol, 1.0 eq) and fluoroacetonitrile (278 µL, 5.0 mmol, 1.0 eq) in dry THF (15 mL) was added a solution of LHMDS in THF (1 M, 10 mL, 10.0 mmol, 2.0 eq). The mixture was allowed to reach room temperature, and 1N HCl was added dropwise achieving pH 2. The mixture was concentrated under reduced pressure to afford intermediate 1 in a form pure enough for the next step.

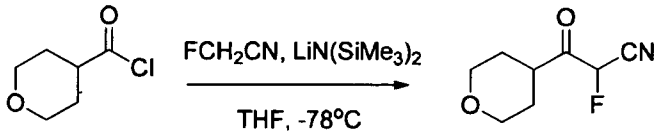
Example 2 - Preparation of Intermediate 2



Intermediate 2

[0160] General Procedure 1 was followed to obtain Intermediate 2. Thus, to a cold (−78 °C) solution of picolinoyl chloride (5.0 mmol, 1.0 eq) and fluoroacetonitrile (278 µL, 5.0 mmol, 1.0 eq) in dry THF (15 mL) was added a solution of LHMDS in THF (1 M, 10 mL, 10.0 mmol, 2.0 eq). The mixture was allowed to reach room temperature, and 1N HCl was added dropwise achieving pH 2. The mixture was concentrated under reduced pressure to afford intermediate 2 in a form pure enough for the next step.

Example 3 - Preparation of Intermediate 3



Intermediate 3

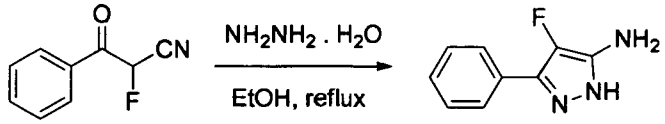
[0161] General Procedure 1 was followed to obtain Intermediate 3. Thus, to a cold (−78 °C) solution of pyran-4-carbonyl chloride (5.0 mmol, 1.0 eq) and fluoroacetonitrile (278 µL, 5.0 mmol, 1.0 eq) in dry THF (15 mL) was added a solution of LHMDS in THF (1 M, 10 mL, 10.0 mmol, 2.0 eq). The mixture was allowed to reach room temperature, and 1N HCl

was added dropwise achieving pH 2. The mixture was concentrated under reduced pressure to afford intermediate 3 in a form pure enough for the next step.

Example 4 - Preparation of Intermediate 4

[0162] The synthesis of Intermediate 4 followed the procedure of General Procedure 2 following.

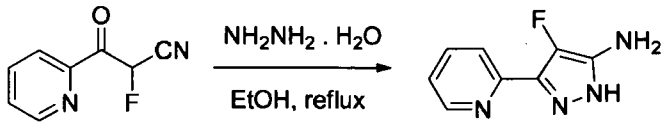
General Procedure 2



Intermediate 1 **Intermediate 4**

[0163] To a solution of intermediate 1 (5.0 mmol) in ethanol (15 mL) was added hydrazine monohydrate (582 μL, 12.0 mmol, 2.4 eq). The reaction was heated at reflux for 18 h. The reaction mixture was allowed to cool to room temperature, and the solvent was evaporated under reduced pressure. The residue was dissolved in dichloromethane (DCM) and washed with water. The organic phase was concentrated to give a crude product that was purified by silica column, yielding intermediate 4 as a light brown solid (0.56 g, 55%). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 4.80 (s, 2H), 7.28–7.32 (m, 1H), 7.41–7.45 (m, 2H), 7.62–7.64 (m, 2H), 11.88 (s, 1H).

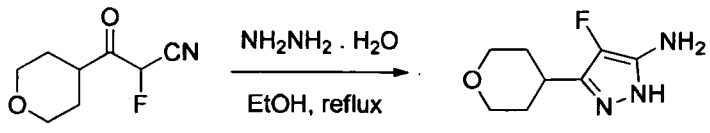
Example 5 - Preparation of Intermediate 5



Intermediate 2 **Intermediate 5**

[0164] General Procedure 2 was followed to convert Intermediate 2 to Intermediate 5

Example 6 - Preparation of Intermediate 6



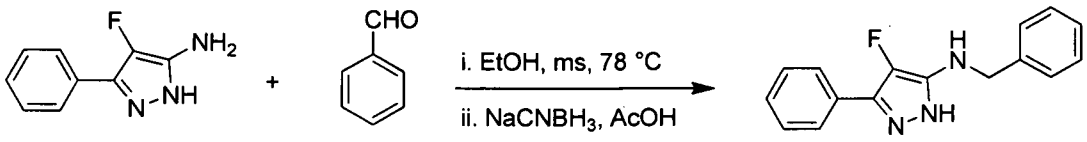
Intermediate 3 **Intermediate 6**

[0165] General Procedure 2 was followed to convert Intermediate 3 to Intermediate 6

Example 7 - Preparation of Intermediate 7

[0166] The synthesis of Intermediate 7 followed the procedure of General Procedure 3 following.

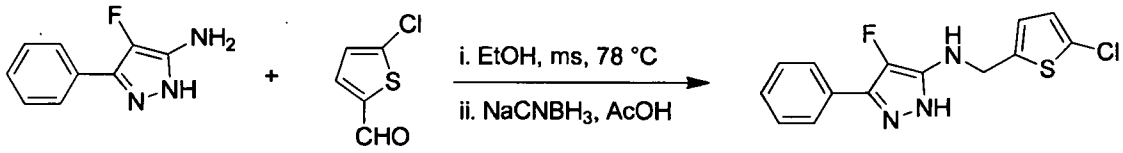
General Procedure 3



Intermediate 4 **Intermediate 7**

[0167] A solution of intermediate 4 (12.4 mmol) and benzaldehyde (24.8 mmol, 2 eq) in EtOH (20 mL) with molecular sieves (4Å powder) was refluxed for 8 h. Then was added a catalytic quantity of AcOH, $NaCNBH_3$ (1.6 g, 24.8 mmol, 2 eq) at 0 °C with stirring for 15 h at RT. The solvent was distilled off, and the residue was dissolved in EtOAc (200 mL) and filtered through a Celite® pad to remove inorganic materials. The filtrate was washed with saturated aqueous $NaHCO_3$ (2 × 20 mL), water (20 mL), brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resultant compound was purified by column chromatography over silica gel (100-200 mesh) by using a solvent gradient of 0-10% MeOH-$CHCl_3$ as the eluent to afford Intermediate 7.

Example 8 - Preparation of Intermediate 8



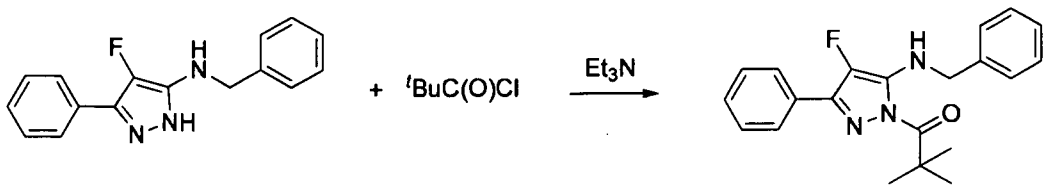
Intermediate 4 **Intermediate 8**

[0168] General Procedure 3 was followed to convert Intermediate 4 to Intermediate 8

Example 9 - Preparation of Compound 23

[0169] The synthesis of Compound 23 followed the procedure of General Procedure 4 following.

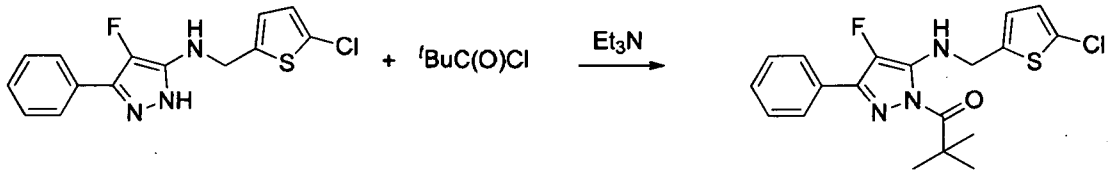
General Procedure 4



Intermediate 7 **Compound 23**

[0170] Pivaloyl chloride was added to a solution of Intermediate 7 in triethylamine (3 mL) at RT and stirred for 5 h. The reaction mixture was diluted with water (5 mL) and extracted with EtOAc (20 mL). The organic layer washed with water (2 × 5 mL), saturated aqueous $NaHCO_3$ (5 mL), brine (5 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude compound was purified by column chromatography over silica gel (100-200 mesh) by using a gradient mixture of 0-30% EtOAc-hexane as the eluent to afford Compound 23 (33%). MP 105-106°C; ^{1}H NMR: (DMSO-d_6) δ 7.77 (d, J = 7.4 Hz, 2H), 7.56-7.60 (m, 1H), 7.41-7.52 (m, 3H), 7.33-7.38 (m, 4H), 7.25 (br s, 1H), 4.53 (d, J = 6.2 Hz, 2H), 1.48 (s, 9H); MS: 352 $[M + H]^+$.

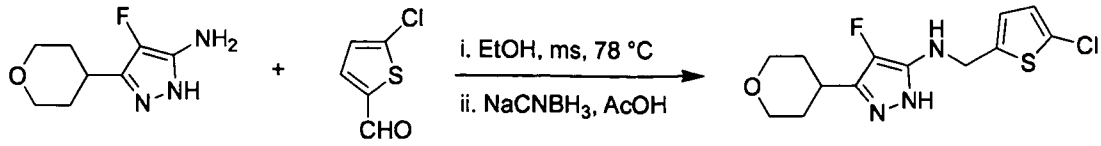
Example 10 - Preparation of Compound 10



Intermediate 8 **Compound 10**

[0171] General Procedure 4 was followed to convert Intermediate 8 to Compound 10. Thus, pivaloyl chloride was added to a solution of Intermediate 8 in triethylamine (3 mL) at RT and stirred for 5 h. The reaction mixture was diluted with water (5 mL) and extracted with EtOAc (20 mL). The organic layer washed with water (2 × 5 mL), saturated aqueous $NaHCO_3$ (5 mL), brine (5 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude compound was purified by column chromatography over silica gel (100-200 mesh) by using a gradient mixture of 0-30% EtOAc-hexane as the eluent to afford Compound 10 (35%). ^{1}H NMR: ($CDCl_3$) δ 7.8-7.9 (m, 2H), 7.40-7.48 (m, 3H), 7.10-7.18 (m, 1H), 6.74-6.81 (m, 2H), 4.63 (d, J = 6.2 Hz, 2H), 1.53 (s, 9H); MS: 392 $[M + H]^+$.

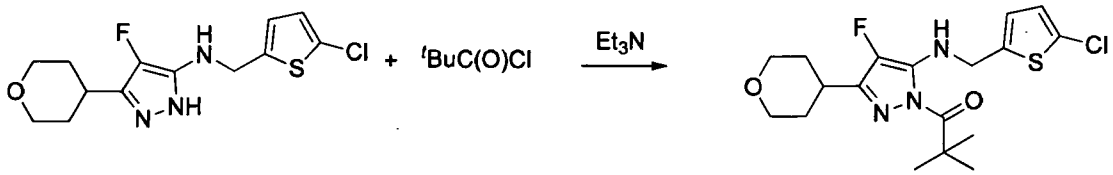
Example 11 - Preparation of Intermediate 9



Intermediate 6 **Intermediate 9**

[0172] General Procedure 3 was followed to convert Intermediate 6 to Intermediate 9

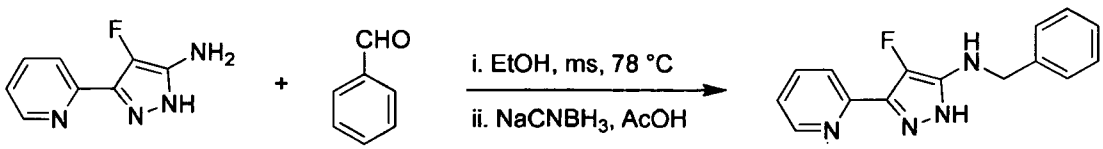
Example 12 - Preparation of Compound 3



Intermediate 9 **Compound 3**

[0173] General Procedure 4 was followed to convert Intermediate 9 to Compound 3. Thus, pivaloyl chloride was added to a solution of Intermediate 9 in triethylamine (3 mL) at RT and stirred for 5 h. The reaction mixture was diluted with water (5 mL) and extracted with EtOAc (20 mL). The organic layer washed with water (2 × 5 mL), saturated aqueous $NaHCO_3$ (5 mL), brine (5 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude compound was purified by column chromatography over silica gel (100-200 mesh) by using a gradient mixture of 0-30% EtOAc-hexane as the eluent to afford Compound 3 (46%). ^1H NMR: ($CDCl_3$) δ 7.03 (t, J = 7.0 Hz, 1H), 6.75 (br s, 2H), 4.54 (d, J = 6.2 Hz, 2H), 4.01 – 4.06 (m, 2H), 3.50 – 3.57 (m, 2H), 2.89 – 2.93 (m, 1H), 1.87 – 1.91 (m, 4H), 1.44 (s, 9H); MS: 400 $[M + H]^+$.

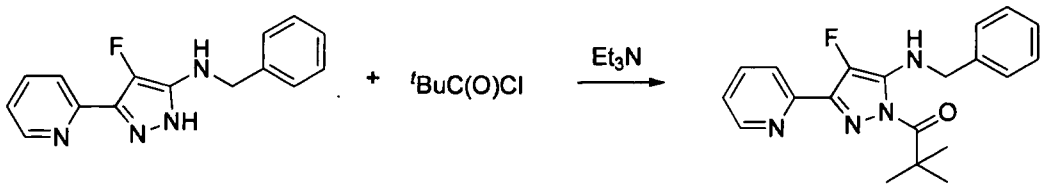
Example 13 - Preparation of Intermediate 10



Intermediate 5 **Intermediate 10**

[0174] General Procedure 3 was followed to convert Intermediate 5 to Intermediate 10

Example 14 - Preparation of Compound 22



Intermediate 10 **Compound 22**

[0175] General Procedure 4 was followed to convert Intermediate 10 to Compound 22. Thus, pivaloyl chloride was added to a solution of Intermediate 10 in triethylamine (3 mL) at RT and stirred for 5 h. The reaction mixture was diluted with water (5 mL) and extracted with EtOAc (20 mL). The organic layer washed with water (2 × 5 mL), saturated aqueous $NaHCO_3$ (5 mL), brine (5 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude compound was purified by column chromatography over silica gel (100-200 mesh) by using a gradient mixture of 0-30% EtOAc-hexane as the eluent to afford Compound 22 (40%). ^1H NMR: (DMSO-d_6) δ 8.6 (m, 1H), 7.83 – 7.91 (m, 2H), 7.55 (m, 1H), 7.25 – 7.45 (m, 6H), 4.52 - 4.54 (m, 2H), 1.48 (s, 9H); MS: 353.03 $[M + H]^+$.

[0176] The contents of all references, patents, and published applications cited herein are hereby incorporated by reference in their entirety and for all purposes.

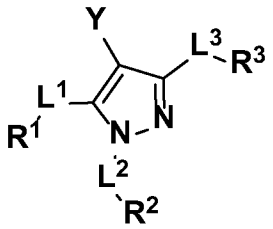
[0177] While the invention has been described in detail with reference to certain preferred embodiments thereof, it will be understood that modifications and variations are within the spirit and scope of that which is described and claimed.

2014238478 22 May 2018

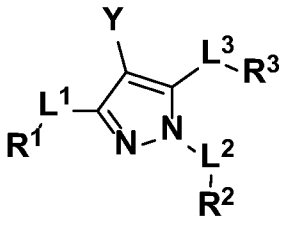
CLAIMS

The claims defining the invention are:

1. A compound with structure of Formula (Ia):



(IIa)



(IIb)

or pharmaceutically acceptable salt, ester, solvate, or prodrug thereof;

wherein

L^1 is $–NR^4$-;

L^2 is -C(=O)-;

L^3 is a bond, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, -S-, -SO-, $-SO_2$-, -O-, $-NHSO_2$-, or $–NR^4$-;

R^1 is substituted alkyl having one or more substituent groups, wherein any substituent group for said R^1 substituted alkyl is selected from the group consisting of -OH, $-NH_2$, -SH, -CN, $-CF_3$, $-NO_2$, halogen, -COOH, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

R^2 is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted fused ring aryl, or substituted or unsubstituted heteroaryl;

R^3 is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted fused ring aryl, or substituted or unsubstituted heteroaryl;

R^4 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene,

substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heterocycloalkenyl, and substituted or unsubstituted fused ring aryl or substituted or unsubstituted heteroaryl; and

Y is halogen,

wherein any substituted group may be substituted with one or more substituent group selected from the following moieties:

(A) -OH, $-NH_2$, -SH, -CN, $-CF_3$, $-NO_2$, oxo, halogen, -COOH, unsubstituted C_1-C_{24} alkyl, unsubstituted 2- to 20-membered heteroalkyl, unsubstituted C_3-C_8 cycloalkyl, unsubstituted 4- to 8-membered heterocycloalkyl, unsubstituted aryl, unsubstituted fused ring aryl, and unsubstituted heteroaryl, and

(B) C_1-C_{24} alkyl, 2- to 20-membered heteroalkyl, C_3-C_8 cycloalkyl, 4- to 8-membered heterocycloalkyl, aryl, fused ring aryl, and heteroaryl, substituted with at least one substituent selected from:

(i) oxo, -OH, $-NH_2$, -SH, -CN, $-CF_3$, $-NO_2$, halogen, -COOH, unsubstituted C_1-C_{24} alkyl, unsubstituted 2- to 20-membered heteroalkyl, unsubstituted C_3-C_8 cycloalkyl, unsubstituted 4- to 8-membered heterocycloalkyl, unsubstituted aryl, unsubstituted fused ring aryl, and unsubstituted heteroaryl, and

(ii) C_1-C_{24} alkyl, 2- to 20-membered heteroalkyl, C_3-C_8 cycloalkyl, 4- to 8-membered heterocycloalkyl, aryl, fused ring aryl, and heteroaryl, substituted with at least one substituent selected from:

(a) oxo, -OH, $-NH_2$, -SH, -CN, -CF3, $-NO_2$, halogen, -COOH, unsubstituted C_1-C_{24} alkyl, unsubstituted 2- to 20-membered heteroalkyl, unsubstituted C_3-C_8 cycloalkyl, unsubstituted 4- to 8-membered heterocycloalkyl, unsubstituted aryl, unsubstituted fused ring aryl, and unsubstituted heteroaryl, and

(b) C_1-C_{24} alkyl, 2- to 20-membered heteroalkyl, cycloalkyl, 4- to 8-membered heterocycloalkyl, aryl, fused ring aryl, or heteroaryl, substituted with at least one substituent selected from: oxo, -OH, $-NH_2$, -SH, -CN, $-CF_3$, $-NO_2$, halogen, -COOH, unsubstituted C_1-C_{24} alkyl, unsubstituted 2- to 20-membered heteroalkyl, unsubstituted C_3-C_8 cycloalkyl, unsubstituted 4- to 8-membered heterocycloalkyl, unsubstituted aryl, and unsubstituted heteroaryl; and

wherein any R^1, R^2, R^3, or R^4 substituted group may have a linker interposed between the substituted group and the substituent group, wherein the linker is selected from: amido

(-CONH-R^n or -NHCO-R^n), thioamido (-CSNH-R^n or -NHCS-R^n), carboxyl (-CO_2-R^n or -OCOR^n), carbonyl (-CO-R^n), urea (-NHCONH-R^n), thiourea (-NHCSNH-R^n), sulfonamido (-$NHSO_2$-R^n or -SO_2NH-R^n), ether (-O-R^n), sulfonyl (-SO_2-R^n), sulfoxyl (-SO-R^n), carbamoyl (-$NHCO_2$-R^n or -OCONH-R^n), or amino (-NHR^n).

2. The compound according to claim 1, with structure of Formula (IIa), wherein L^3 is a bond, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene, and R^3 is substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted fused ring aryl, substituted or unsubstituted heterocycloalkyl, or substituted or unsubstituted heteroaryl.

3. The compound according to claim 1, with structure of Formula (IIa), wherein Y is fluorine.

4. The compound according to claim 2, wherein Y is fluorine.

5. The compound according to claim 2, wherein R^3 is substituted or unsubstituted phenyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, or substituted or unsubstituted fused ring aryl.

6. The compound according to claim 5, wherein R^3 is substituted or unsubstituted heteroaryl selected from the group consisting of substituted or unsubstituted pyridyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted thienyl, and substituted or unsubstituted furyl; or wherein R^3 is substituted or unsubstituted heterocycloalkyl selected from the group consisting of substituted or unsubstituted morpholinyl, substituted or unsubstituted oxanyl, and substituted or unsubstituted oxetanyl; or wherein R^3 is substituted or unsubstituted fused ring aryl selected from the group consisting of substituted or unsubstituted benzodioxinyl and substituted or unsubstituted naphthyl, .

7 The compound according to claim 6, wherein R^3 is chloro-substituted thienyl.

8. The compound according to claim 2, wherein R^1 is substituted alkyl having at least one substituted or unsubstituted heteroaryl substituent selected from the group consisting of substituted or unsubstituted pyridyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted thienyl, and substituted or unsubstituted furyl; or wherein R^1 is substituted alkyl having at least one substituted or unsubstituted heterocycloalkyl substituent selected from the group consisting of substituted or unsubstituted morpholinyl, substituted or unsubstituted oxanyl, and substituted or unsubstituted oxetanyl; or wherein R^1 is substituted alkyl having at least one substituted or

unsubstituted fused ring aryl substituent selected from the group consisting of substituted or unsubstituted benzodioxinyl and substituted or unsubstituted naphthyl; or wherein R^1 is substituted alkyl having at least one substituted or unsubstituted phenyl substituent.

9. The compound according to claim 8, wherein R^1 is substituted alkyl having at least one chloro-substituted thienyl substituent.

10. The compound according to claim 2, wherein R^2 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted fused ring aryl, or substituted or unsubstituted heteroaryl.

11. The compound according to claim 10, wherein R^2 is substituted or unsubstituted heteroaryl selected from the group consisting of substituted or unsubstituted pyridyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted thienyl, and substituted or unsubstituted furyl; or wherein R^2 is substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocycloalkyl; or wherein R^2 is substituted or unsubstituted heterocycloalkyl selected from the group consisting of substituted or unsubstituted morpholinyl, substituted or unsubstituted oxanyl, and substituted or unsubstituted oxetanyl; or wherein R^2 is substituted or unsubstituted fused ring aryl selected from the group consisting of substituted or unsubstituted benzodioxinyl and substituted or unsubstituted naphthyl; or wherein R^2 is substituted or unsubstituted phenyl.

12. The compound according to any of claims 1 to 11, selected from the group consisting of:

1-(5-{[(5-chlorothiophen-2-yl)methyl]amino}-3-(1-{[5-(dimethylamino)naphthalen-1-yl]sulfonyl}piperidin-4-yl)-4-fluoro-1H-pyrazol-1-yl)-3-hydroxy-2,2-dimethylpropan-1-one;

1-(5-{[(5-chlorothiophen-2-yl)methyl]amino}-4-fluoro-3-(5-hydroxy-5,6,7,8-tetrahydronaphthalen-2-yl)-1H-pyrazol-1-yl)-2,2-dimethylpropan-1-one;

1-(5-{[(5-chlorothiophen-2-yl)methyl]amino}-4-fluoro-3-(oxan-4-yl)-1H-pyrazol-1-yl)-2,2-dimethylpropan-1-one;

1-(5-{[(5-chlorothiophen-2-yl)methyl]amino}-4-fluoro-3-(oxan-4-yl)-1H-pyrazol-1-yl)-3-hydroxy-2,2-dimethylpropan-1-one;

1-(5-{[(5-chlorothiophen-2-yl)methyl]amino}-4-fluoro-3-(oxan-4-yl)-1H-pyrazol-1-yl)-3-methoxy-2,2-dimethylpropan-1-one;

1-(5-{[(5-chlorothiophen-2-yl)methyl]amino}-4-fluoro-3-(piperidin-4-yl)-1H-pyrazol-1-yl)-2,2-dimethylpropan-1-one;
1-(5-{[(5-chlorothiophen-2-yl)methyl]amino}-4-fluoro-3-(piperidin-4-yl)-1H-pyrazol-1-yl)-2-methoxy-2-methylpropan-1-one;
1-(5-{[(5-chlorothiophen-2-yl)methyl]amino}-4-fluoro-3-(piperidin-4-yl)-1H-pyrazol-1-yl)-3-hydroxy-2,2-dimethylpropan-1-one;
1-(5-{[(5-chlorothiophen-2-yl)methyl]amino}-4-fluoro-3-(piperidin-4-yl)-1H-pyrazol-1-yl)-3-methoxy-2,2-dimethylpropan-1-one;
1-(5-{[(5-chlorothiophen-2-yl)methyl]amino}-4-fluoro-3-phenyl-1H-pyrazol-1-yl)-2,2-dimethylpropan-1-one;
1-(5-{[(5-chlorothiophen-2-yl)methyl]amino}-4-fluoro-3-phenyl-1H-pyrazol-1-yl)-2-hydroxy-2-methylpropan-1-one;
1-(5-{[(5-chlorothiophen-2-yl)methyl]amino}-4-fluoro-3-phenyl-1H-pyrazol-1-yl)-2-methoxy-2-methylpropan-1-one;
1-(5-{[(5-chlorothiophen-2-yl)methyl]amino}-4-fluoro-3-phenyl-1H-pyrazol-1-yl)-3-(2-methoxyethoxy)-2,2-dimethylpropan-1-one;
1-(5-{[(5-chlorothiophen-2-yl)methyl]amino}-4-fluoro-3-phenyl-1H-pyrazol-1-yl)-3-hydroxy-2,2-dimethylpropan-1-one;
1-(5-{[(5-chlorothiophen-2-yl)methyl]amino}-4-fluoro-3-phenyl-1H-pyrazol-1-yl)-3-methoxy-2,2-dimethylpropan-1-one;
1-[4-(5-{[(5-chlorothiophen-2-yl)methyl]amino}-1-(2,2-dimethylpropanoyl)-4-fluoro-1H-pyrazol-3-yl)phenyl]pyrrolidin-2-one;
1-[4-(5-{[(5-chlorothiophen-2-yl)methyl]amino}-1-(2,3-dihydro-1,4-benzodioxine-5-carbonyl)-4-fluoro-1H-pyrazol-3-yl)phenyl]pyrrolidin-2-one;
1-[4-(5-{[(5-chlorothiophen-2-yl)methyl]amino}-4-fluoro-1-(2-methoxybenzoyl)-1H-pyrazol-3-yl)phenyl]-2,2,2-trifluoroethan-1-ol;
1-[4-(5-{[(5-chlorothiophen-2-yl)methyl]amino}-4-fluoro-1-(2-methoxybenzoyl)-1H-pyrazol-3-yl)phenyl]pyrrolidin-2-one;
1-[4-(5-{[(5-chlorothiophen-2-yl)methyl]amino}-4-fluoro-1-(furan-3-carbonyl)-1H-pyrazol-3-yl)phenyl]pyrrolidin-2-one;
1-[5-(benzylamino)-4-fluoro-3-(pyridin-2-yl)-1H-pyrazol-1-yl]-2,2-dimethylpropan-1-one;
1-[5-(benzylamino)-4-fluoro-3-phenyl-1H-pyrazol-1-yl]-2,2-dimethylpropan-1-one;
1-benzoyl-N-[(5-chlorothiophen-2-yl)methyl]-4-fluoro-3-(oxan-4-yl)-1H-pyrazol-5-amine;

1-benzoyl-N-[(5-chlorothiophen-2-yl)methyl]-4-fluoro-5-(oxan-4-yl)-1H-pyrazol-3-amine;
2-(5-{[(5-chlorothiophen-2-yl)methyl]amino}-4-fluoro-3-phenyl-1H-pyrazole-1-carbonyl)phenyl 5-(dimethylamino)naphthalene-1-sulfonate;
4-(5-{[(5-chlorothiophen-2-yl)methyl]amino}-4-fluoro-3-phenyl-1H-pyrazole-1-carbonyl)phenyl 5-(dimethylamino)naphthalene-1-sulfonate;
4-[4-(5-{[(5-chlorothiophen-2-yl)methyl]amino}-1-(2,2-dimethylpropanoyl)-4-fluoro-1H-pyrazol-3-yl)phenyl]morpholin-3-one;
6-(5-{[(5-chlorothiophen-2-yl)methyl]amino}-1-(2,2-dimethylpropanoyl)-4-fluoro-1H-pyrazol-3-yl)-1,2,3,4-tetrahydronaphthalen-1-one;
6-(5-{[(5-chlorothiophen-2-yl)methyl]amino}-4-fluoro-1-(2-methoxybenzoyl)-1H-pyrazol-3-yl)-1,2,3,4-tetrahydronaphthalen-1-ol;
6-(5-{[(5-chlorothiophen-2-yl)methyl]amino}-4-fluoro-1-(2-methoxybenzoyl)-1H-pyrazol-3-yl)-1,2,3,4-tetrahydronaphthalen-1-one;
N-[(5-chlorothiophen-2-yl)methyl]-1-(2,3-dihydro-1,4-benzodioxine-5-carbonyl)-4-fluoro-3-(oxan-4-yl)-1H-pyrazol-5-amine;
N-[(5-chlorothiophen-2-yl)methyl]-1-(2,3-dihydro-1,4-benzodioxine-5-carbonyl)-4-fluoro-3-(piperidin-4-yl)-1H-pyrazol-5-amine;
N-[(5-chlorothiophen-2-yl)methyl]-1-(2,3-dihydro-1,4-benzodioxine-5-carbonyl)-4-fluoro-3-phenyl-1H-pyrazol-5-amine;
N-[(5-chlorothiophen-2-yl)methyl]-1-(2,3-dihydro-1,4-benzodioxine-5-carbonyl)-4-fluoro-5-(oxan-4-yl)-1H-pyrazol-3-amine;
N-[(5-chlorothiophen-2-yl)methyl]-1-(2,4-dimethoxybenzoyl)-4-fluoro-3-(oxan-4-yl)-1H-pyrazol-5-amine;
N-[(5-chlorothiophen-2-yl)methyl]-1-(2,4-dimethoxybenzoyl)-4-fluoro-3-(piperidin-4-yl)-1H-pyrazol-5-amine;
N-[(5-chlorothiophen-2-yl)methyl]-1-(2,4-dimethoxybenzoyl)-4-fluoro-3-phenyl-1H-pyrazol-5-amine;
N-[(5-chlorothiophen-2-yl)methyl]-1-(2,4-dimethoxybenzoyl)-4-fluoro-5-(oxan-4-yl)-1H-pyrazol-3-amine;
N-[(5-chlorothiophen-2-yl)methyl]-3-(1-{[5-(dimethylamino)naphthalen-1-yl]sulfonyl}piperidin-4-yl)-4-fluoro-1-(2-methoxybenzoyl)-1H-pyrazol-5-amine;
N-[(5-chlorothiophen-2-yl)methyl]-4-fluoro-1-(2-methoxybenzoyl)-3-(oxan-4-yl)-1H-pyrazol-5-amine;

N-[(5-chlorothiophen-2-yl)methyl]-4-fluoro-1-(2-methoxybenzoyl)-3-(piperidin-4-yl)-1H-pyrazol-5-amine;
N-[(5-chlorothiophen-2-yl)methyl]-4-fluoro-1-(2-methoxybenzoyl)-3-(pyridin-2-yl)-1H-pyrazol-5-amine;
N-[(5-chlorothiophen-2-yl)methyl]-4-fluoro-1-(2-methoxybenzoyl)-3-phenyl-1H-pyrazol-5-amine;
N-[(5-chlorothiophen-2-yl)methyl]-4-fluoro-1-(2-methoxybenzoyl)-5-(oxan-4-yl)-1H-pyrazol-3-amine;
N-[(5-chlorothiophen-2-yl)methyl]-4-fluoro-1-(3-methyloxetane-3-carbonyl)-3-phenyl-1H-pyrazol-5-amine;
N-[(5-chlorothiophen-2-yl)methyl]-4-fluoro-1-(4-methyloxane-4-carbonyl)-3-(oxan-4-yl)-1H-pyrazol-5-amine;
N-[(5-chlorothiophen-2-yl)methyl]-4-fluoro-1-(4-methyloxane-4-carbonyl)-3-phenyl-1H-pyrazol-5-amine;
N-[(5-chlorothiophen-2-yl)methyl]-4-fluoro-1-(furan-3-carbonyl)-3-(oxan-4-yl)-1H-pyrazol-5-amine;
N-[(5-chlorothiophen-2-yl)methyl]-4-fluoro-1-(furan-3-carbonyl)-3-(piperidin-4-yl)-1H-pyrazol-5-amine;
N-[(5-chlorothiophen-2-yl)methyl]-4-fluoro-1-(furan-3-carbonyl)-3-phenyl-1H-pyrazol-5-amine;
N-[(5-chlorothiophen-2-yl)methyl]-4-fluoro-1-[4-(2-methoxyethoxy)benzoyl]-3-(oxan-4-yl)-1H-pyrazol-5-amine;
N-[(5-chlorothiophen-2-yl)methyl]-4-fluoro-1-[4-(morpholin-4-yl)benzoyl]-3-(oxan-4-yl)-1H-pyrazol-5-amine;
N-[(5-chlorothiophen-2-yl)methyl]-4-fluoro-3-(oxan-4-yl)-1-(thiophene-3-carbonyl)-1H-pyrazol-5-amine;
N-[(5-chlorothiophen-2-yl)methyl]-5-(1-{[5-(dimethylamino)naphthalen-1-yl]sulfonyl}piperidin-4-yl)-4-fluoro-1-(2-methoxybenzoyl)-1H-pyrazol-3-amine;
N-[4-(5-{[(5-chlorothiophen-2-yl)methyl]amino}-4-fluoro-3-(piperidin-4-yl)-1H-pyrazole-1-carbonyl)phenyl]-5-(dimethylamino)naphthalene-1-sulfonamide;
N-[4-(5-{[(5-chlorothiophen-2-yl)methyl]amino}-4-fluoro-3-phenyl-1H-pyrazole-1-carbonyl)phenyl]-5-(dimethylamino)naphthalene-1-sulfonamide;
N-benzyl-4-fluoro-1-(2-methoxybenzoyl)-3-(pyridin-2-yl)-1H-pyrazol-5-amine;

N-benzyl-4-fluoro-1-(2-methoxybenzoyl)-3-phenyl-1H-pyrazol-5-amine;
[1-(5-{[(5-chlorothiophen-2-yl)methyl]amino}-4-fluoro-3-(oxan-4-yl)-1H-pyrazole-1-carbonyl)cyclopropyl]methanol; and
[1-(5-{[(5-chlorothiophen-2-yl)methyl]amino}-4-fluoro-3-phenyl-1H-pyrazole-1-carbonyl)cyclopropyl]methanol.

13. A pharmaceutical composition comprising a compound according to any of claims 1 to 12, and a pharmaceutically acceptable excipient.

14. A method for treating a disease or disorder responsive to inhibition of thrombin in a subject, comprising administering a compound according to any of claims 1 to 12 or a pharmaceutical composition according to claim 13, to a subject in need thereof in an amount effective to treat said disease or disorder.

15. The method according to claim 14, wherein said disease or disorder is a thrombotic disorder, or a disease or disorder involving a blood clot thrombus.

16. The method according to claim 15, wherein said thrombotic disorder comprises at least one of acute coronary syndrome, thromboembolism, and thrombosis.

17. The method according to claim 14, wherein said disease or disorder is one or more selected from the group consisting of fibrosis, Alzheimer's Disease, multiple sclerosis, pain, inflammation, and a type of cancer selected from the group consisting of small cell lung cancer, glioma, prostate cancer, and breast cancer.

18. The method according to claim 14, wherein said compound acts by inhibiting thrombin.

19. The pharmaceutical composition of claim 13, for use in a method of treating a disease or disorder responsive to inhibition of thrombin in a subject, comprising administering to a subject in need thereof an amount of the composition effective to treat said disease or disorder.

20. The method according to claim 16, wherein the thromboembolism comprises at least one of venous thromboembolism, arterial thromboembolism, and cardiogenic thromboembolism.

21. The method according to claim 20, wherein the venous thromboembolism comprises at least one of deep vein thrombosis and pulmonary embolism.

22. The method according to claim 21, wherein the at least one of deep vein thrombosis and pulmonary embolism occurs following a medical procedure.

23. The method according to claim 15, wherein said thrombotic disorder involves dysfunctional coagulation or disseminated intravascular coagulation, or wherein said thrombotic disorder involves a blood clot thrombus and further involves at least one of stroke and one or more transient ischemic attacks (TIA), or wherein said thrombotic disorder involves a blood clot thrombus and further involves pulmonary hypertension.

24. The method according to claim 23, wherein the subject is undergoing percutaneous coronary intervention (PCI), or wherein said thrombotic disease or disorder involving a blood clot thrombus further involves stroke and wherein the subject has non-valvular atrial fibrillation; or wherein the pulmonary hypertension is caused by at least one of one or more left heart disorder and chronic thromboembolic disease; or wherein the pulmonary hypertension is associated with at least one of one or more lung disease, including pulmonary fibrosis (idiopathic or otherwise), and hypoxia.

25. The method according to claim 14, wherein the subject has had at least one previous myocardial infarction.

26. The method according to claim 20, wherein the venous thromboembolism is associated with at least one of formation of a thrombus within a vein associated with one or more acquired or inherited risk factors and embolism of peripheral veins caused by a detached thrombus.

27. The method according to claim 26, wherein the one or more risk factors comprise a previous venous thromboembolism.

28. The method according to claim 20, wherein the cardiogenic thromboembolism is due to formation of a thrombus in the heart associated with at least one of cardiac arrhythmia, a heart valve defect, prosthetic heart valves or heart disease, and embolism of peripheral arteries caused by a detached thrombus, or wherein the cardiogenic thromboembolism is due to non-valvular atrial fibrillation.

29. The method according to claim 28, wherein the detached thrombus is in the brain (ischemic stroke), or wherein the detached thrombus causes a transient ischemic attack (TIA).

30. The method according to claim 16, wherein the thrombosis is arterial thrombosis.

31. The method according to claim 30, wherein the arterial thrombosis is due to one or more underlying atherosclerotic processes in the arteries.

32. The method according to claim 31, wherein the one or more underlying atherosclerotic processes in the arteries cause at least one of obstruction or occlusion of an artery, myocardial ischemia (angina pectoris, acute coronary syndrome), myocardial infarction, obstruction or occlusion of a peripheral artery (ischemic peripheral artery disease), and obstruction or occlusion of the artery after a procedure on a blood vessel (reocclusion or restenosis after transluminal coronary angioplasty, reocclusion or restenosis after percutaneous transluminal angioplasty of peripheral arteries).

33. The method according to claim 14, wherein the treatment further comprises an adjunct therapy.

34. The method according to claim 33, wherein the subject has myocardial infarction, and the adjunct therapy is in conjunction with thrombolytic therapy; or wherein the subject has at least one of unstable angina pectoris, thrombosis, and heparin-induced thrombocytopenia, and the adjunct therapy is in combination with antiplatelet therapy; or wherein the subject has non-valvular atrial fibrillation, and the adjunct therapy is in conjunction with other therapies.