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(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.

1 **HALOGENOPYRAZOLES AS INHIBITORS OF THROMBIN**

2

3 **BACKGROUND OF THE INVENTION**4 **[0001]** The present disclosure relates to compounds, e.g., multisubstituted aromatic
5 compounds, which exhibit biological activity, e.g., inhibitory action, against thrombin
6 (activated blood-coagulation factor II; EC 3.4.21.5).7 **[0002]** In mammalian systems, blood vessel injuries result in bleeding events, which are
8 dealt with by the blood coagulation cascade. The cascade includes the Extrinsic and Intrinsic
9 pathways, involving the activation of at least 13 interconnected factors and a variety of co-
10 factors and other regulatory proteins. Upon vascular injury, plasma factor VII interacts with
11 exposed Tissue Factor (TF), and the resultant TF-fVIIa complex initiates a complex series of
12 events. Factor fXa is produced directly 'downstream' from the TF-fVIIa complex, and
13 amplified manifold via the Intrinsic Pathway. FXa then serves as the catalyst for formation
14 of thrombin (fIIa), which in turn is the direct precursor to fibrinolysis. The outcome is a
15 fibrinolytic clot, which stops the bleeding. Fibrinolysis of the polymeric clot into fibrin
16 monomers leads to dissolution and a return of the system to the pre-clot state. The cascade is
17 a complex balance of factors and co-factors and is tightly regulated.18 **[0003]** In disease states, undesired up- or down-regulation of any factor leads to conditions
19 such as bleeding or thrombosis. Historically, anticoagulants have been used in patients at
20 risk of suffering from thrombotic complications, such as angina, stroke and heart attack.21 **[0004]** Warfarin has enjoyed dominance as a first-in-line anticoagulant therapeutic.
22 Developed in the 1940s, it is a Vitamin K antagonist and inhibits factors II, VII, IX and X,
23 amongst others. It is administered orally, but its ease of use is tempered by other effects: it
24 has a very long half life (>2 days) and has serious drug-drug interactions. Importantly, since
25 Vitamin K is a ubiquitous cofactor within the coagulation cascade, antagonism results in the
26 simultaneous inhibition of many clotting factors and thus can lead to significant bleeding
27 complications.28 **[0005]** Much attention has been focused on heparin, the naturally-occurring polysaccharide
29 that activates AT III, the endogenous inhibitor of many of the factors in the coagulation
30 cascade. The need for parenteral administration for the heparin-derived therapeutics, and the
31 inconvenient requirements for close supervision for the orally available warfarin, has resulted

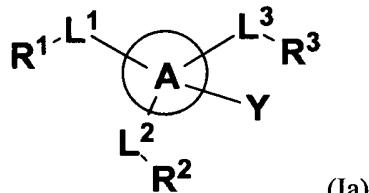
32 in a drive to discover and develop orally available drugs with wide therapeutic windows for
 33 safety and efficacy.

34 [0006] Indeed, the position of thrombin in the coagulation cascade has made it a popular
 35 target for drug discovery. Without wishing to be bound by any theory, it is believed that the
 36 ultimate development of direct thrombin inhibitors (DTIs) is usefully based upon the classical
 37 D-Phe-Pro-Arg motif, a sequence that mimics fibrinogen, which is a natural substrate of
 38 thrombin. Without further wishing to be bound by any theory, it is believed that the use of
 39 DTIs is very well precedented, such as with the hirudin-based anticoagulants, and thus there
 40 is strong interest in the discovery and development of novel DTIs.

41 [0007] A thorough discussion of thrombin and its roles in the coagulation process can be
 42 found in a variety of references, including the following which are incorporated herein by
 43 reference in their entireties and for all purposes: Wieland, H. A., *et al.*, 2003, *Curr Opin*
 44 *Investig Drugs*, 4:264-71; Gross, P. L. & Weitz, J. I., 2008, *Arterioscler Thromb Vasc Biol*,
 45 28:380-6; Hirsh, J., *et al.*, 2005, *Blood*, 105:453-63; Prezelj, A., *et al.*, 2007, *Curr Pharm*
 46 *Des*, 13:287-312.

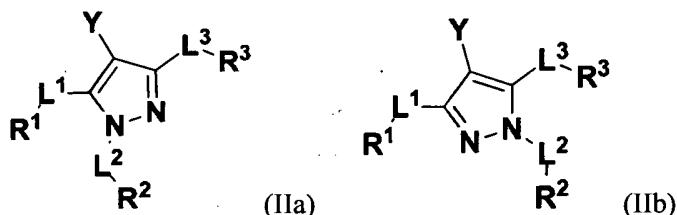
47 **BRIEF SUMMARY OF THE INVENTION**

48 [0008] Embodiments of the invention encompass compounds with structure of Formula
 49 (Ia):



51 or pharmaceutically acceptable salt, ester, solvate, or prodrug thereof; wherein Ring A can be
 52 substituted or unsubstituted pyrazolyl; L¹ and L³ can be independently a bond, substituted or
 53 unsubstituted alkylene, substituted or unsubstituted heteroalkylene, -S-, -SO-, -SO₂-, -O-,
 54 -NHSO₂-, or -NR⁴-; L² can be absent, a bond, substituted or unsubstituted alkylene,
 55 substituted or unsubstituted heteroalkylene, -S-, -SO-, -SO₂-, -O-, -NHSO₂-, or -NR⁴-; R¹
 56 and R³ can be independently hydrogen, halogen, substituted or unsubstituted alkyl,
 57 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
 58 unsubstituted cycloalkenyl, substituted or unsubstituted heterocycloalkyl, substituted or
 59 unsubstituted heterocycloalkenyl, substituted or unsubstituted aryl, substituted or
 60 unsubstituted fused ring aryl, or substituted or unsubstituted heteroaryl; R² can be absent,

61 hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted
62 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl,
63 substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloalkenyl,
64 substituted or unsubstituted aryl, substituted or unsubstituted fused ring aryl, or substituted or
65 unsubstituted heteroaryl, provided that when L^2 can be absent, R^2 can be absent; R^4 can be
66 hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl,
67 substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted
68 or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or
69 unsubstituted aryl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted
70 heterocycloalkenyl, and substituted or unsubstituted fused ring aryl or substituted or
71 unsubstituted heteroaryl; and Y can be a halogen. In some embodiments of the methods, L^2
72 and R^2 can be absent. In some embodiments, the compound can have the structure of Formula
73 (IIa) or Formula (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

91 aryl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl.
92 In some embodiments, the heteroaryl can be pyridyl, pyridazinyl, pyrimidinyl, thienyl, or
93 furyl. In some embodiments, R¹ can be chloro-substituted thienyl. In some embodiments, the
94 heterocycloalkyl can be morpholinyl, oxanyl, or oxetanyl. In some embodiments, the fused
95 ring aryl can be benzodioxinyl or naphthyl. In some embodiments, R¹ can be substituted or
96 unsubstituted phenyl. In some embodiments, L² can be a bond, and R² can be hydrogen. In
97 some embodiments, L² can be substituted or unsubstituted alkylene or -C(O)-, and R² can be
98 hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl,
99 substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted
100 or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloalkenyl, substituted
101 or unsubstituted aryl, substituted or unsubstituted fused ring aryl, or substituted or
102 unsubstituted heteroaryl. In some embodiments, the heteroaryl can be pyridyl, pyridazinyl,
103 pyrimidinyl, thienyl, or furyl. In some embodiments, R² can be substituted or unsubstituted
104 alkyl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted
105 heterocycloalkyl. In some embodiments, the heterocycloalkyl can be morpholinyl, oxanyl, or
106 oxetanyl. In some embodiments, the fused ring aryl can be benzodioxinyl or naphthyl. In
107 some embodiments, R² can be substituted or unsubstituted phenyl.

108 [0010] In some embodiments where the compound can have the structure of Formula (IIb),
109 L³ can be a bond, or substituted or unsubstituted alkylene, R³ can be substituted or
110 unsubstituted aryl, substituted or unsubstituted fused ring aryl, substituted or unsubstituted
111 heterocycloalkyl, or substituted or unsubstituted heteroaryl, and Y can be fluorine. In some
112 embodiments where the compound can have the structure of Formula (IIa), L³ can be
113 -C(O)O-, R³ can be substituted or unsubstituted alkyl, and Y can be fluorine. In some
114 embodiments where the compound can have the structure of Formula (IIa), L³ can be
115 -C(O)NR⁵-, R⁵ can be hydrogen or alkyl, R³ can be substituted or unsubstituted alkyl, or
116 substituted or unsubstituted aryl, and Y can be fluorine. In some embodiments, R³ can be
117 substituted or unsubstituted phenyl. In some embodiments, the heteroaryl can be pyridyl,
118 pyridazinyl, pyrimidinyl, thienyl, or furyl. In some embodiments, R³ can be chloro-
119 substituted thienyl. In some embodiments, the heterocycloalkyl can be morpholinyl, oxanyl,
120 or oxetanyl. In some embodiments, the fused ring aryl can be benzodioxinyl or naphthyl. In
121 some embodiments, L¹ can be a bond, -S-, -NR⁴-, substituted or unsubstituted alkylene, or
122 substituted or unsubstituted heteroalkylene, and R¹ can be hydrogen, substituted or
123 unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted fused ring
124 aryl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl.

125 In some embodiments, the heteroaryl can be pyridyl, pyridazinyl, pyrimidinyl, thienyl, or
126 furyl. In some embodiments, R¹ can be chloro-substituted thienyl. In some embodiments, the
127 heterocycloalkyl can be morpholinyl, oxanyl, or oxetanyl. In some embodiments, the fused
128 ring aryl can be benzodioxinyl or naphthyl. In some embodiments, R¹ can be substituted or
129 unsubstituted phenyl. In some embodiments, L² can be a bond, and R² can be hydrogen. In
130 some embodiments, L² can be substituted or unsubstituted alkylene or -C(O)-, and R² can be
131 hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl,
132 substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted
133 or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloalkenyl, substituted
134 or unsubstituted aryl, substituted or unsubstituted fused ring aryl, or substituted or
135 unsubstituted heteroaryl. In some embodiments, the heteroaryl can be pyridyl, pyridazinyl,
136 pyrimidinyl, thienyl, or furyl. In some embodiments, R² can be substituted or unsubstituted
137 alkyl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted
138 heterocycloalkyl. In some embodiments, the heterocycloalkyl can be morpholinyl, oxanyl, or
139 oxetanyl. In some embodiments, the fused ring aryl can be benzodioxinyl or naphthyl. In
140 some embodiments, R² can be substituted or unsubstituted phenyl. In some embodiments, the
141 compound can be selected from those set forth in Table A.

142 [0011] Embodiments of the invention also encompass pharmaceutical compositions
143 including such compounds, or a compound as set forth in Table A, and a pharmaceutically
144 acceptable excipient. Embodiments of the invention also encompass methods for treating a
145 disease or disorder in a subject, including administering such compounds or pharmaceutical
146 compositions to a subject in need thereof in an amount effective to treat said disease or
147 disorder. In some embodiments, the disease or disorder is a thrombotic disorder. In some
148 embodiments, the thrombotic disorder is acute coronary syndrome, venous
149 thromboembolism, arterial thromboembolism or cardiogenic thromboembolism. In some
150 embodiments, the disease or disorder is fibrosis. In some embodiments, the disease or
151 disorder is Alzheimer's Disease. In some embodiments, the disease or disorder is multiple
152 sclerosis. In some embodiments, the disease or disorder is pain. In some embodiments, the
153 disease or disorder is cancer. Embodiments of the invention also encompass methods for
154 preventing a disease or disorder in a subject, including administering such compounds or
155 pharmaceutical compositions to a subject in need thereof in an amount effective to prevent
156 said disease or disorder. In some embodiments, the disease or disorder can be a thrombotic
157 disorder. In some embodiments, the thrombotic disorder can be acute coronary syndrome,
158 venous thromboembolism, arterial thromboembolism or cardiogenic thromboembolism. In

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

162 **BRIEF DESCRIPTION OF THE DRAWINGS**

163 [0012] Not applicable.

164 **DETAILED DESCRIPTION OF THE INVENTION**

165 **I. Definitions**

166 [0013] The abbreviations used herein have their conventional meaning within the chemical
167 and biological arts. The chemical structures and formulae set forth herein are constructed
168 according to the standard rules of chemical valency known in the chemical arts.

169 [0014] Where substituent groups are specified by their conventional chemical formulae,
170 written from left to right, they equally encompass the chemically identical substituents that
171 would result from writing the structure from right to left, e.g., -CH₂O- is equivalent to
172 -OCH₂-.

173 [0015] As used herein, the term “attached” signifies a stable covalent bond, certain
174 preferred points of attachment being apparent to those of ordinary skill in the art.

175 [0016] The terms “halogen” or “halo” include fluorine, chlorine, bromine, and iodine.
176 Additionally, terms such as “haloalkyl” are meant to include monohaloalkyl and
177 polyhaloalkyl. For example, the term “halo(C₁-C₄)alkyl” includes, but is not limited to,
178 fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-
179 bromopropyl, and the like.

180 [0017] The term “alkyl,” by itself or as part of another substituent, means, unless otherwise
181 stated, a straight (i.e., unbranched) or branched chain, or combination thereof, which can be
182 fully saturated, mono- or polyunsaturated and can include di- and multivalent radicals, having
183 the number of carbon atoms designated (i.e., C₁-C₁₀ means one to ten carbons). Examples of
184 saturated hydrocarbon radicals include, but are not limited to, groups such as methyl, ethyl, n-
185 propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, (cyclohexyl)methyl, homologs and
186 isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated
187 alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated
188 alkyl groups include, but are not limited to, vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-
189 (butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butynyl, and

190 the higher homologs and isomers. Accordingly, the term "alkyl" can refer to C₁-C₁₆ straight
191 chain saturated, C₁-C₁₆ branched saturated, C₃-C₈ cyclic saturated and C₁-C₁₆ straight chain or
192 branched saturated aliphatic hydrocarbon groups substituted with C₃-C₈ cyclic saturated
193 aliphatic hydrocarbon groups having the specified number of carbon atoms. For example,
194 this definition shall include but is not limited to methyl (Me), ethyl (Et), propyl (Pr), butyl
195 (Bu), pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, isopropyl (i-Pr), isobutyl (i-Bu), tert-
196 butyl (t-Bu), sec-butyl (s-Bu), isopentyl, neopentyl, cyclopropyl, cyclobutyl, cyclopentyl,
197 cyclohexyl, cycloheptyl, cyclooctyl, cyclopropylmethyl, and the like.

198 [0018] The term "alkylene," by itself or as part of another substituent, means, unless
199 otherwise stated, a divalent radical derived from an alkyl, as exemplified, but not limited by,
200 -CH₂CH₂CH₂CH₂- . Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon
201 atoms, with those groups having 10 or fewer carbon atoms being preferred in the compounds
202 disclosed herein. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene
203 group, generally having eight or fewer carbon atoms.

204 [0019] The term "heteroalkyl," by itself or in combination with another term, means, unless
205 otherwise stated, a stable straight or branched chain, or combinations thereof, consisting of at
206 least one carbon atom and at least one heteroatom selected from the group consisting of O, N,
207 P, Si, and S, and wherein the nitrogen and sulfur atoms can optionally be oxidized, and the
208 nitrogen heteroatom can optionally be quaternized. The heteroatom(s) O, N, P, S, and Si can
209 be placed at any interior position of the heteroalkyl group or at the position at which the alkyl
210 group is attached to the remainder of the molecule. Examples include, but are not limited to:
211 -CH₂-CH₂-O-CH₃, -CH₂-CH₂-NH-CH₃, -CH₂-CH₂-N(CH₃)-CH₃, -CH₂-S-CH₂-CH₃,
212 -CH₂-CH₂, -S(O)-CH₃, -CH₂-CH₂-S(O)₂-CH₃, -CH=CH-O-CH₃, -Si(CH₃)₃,
213 -CH₂-CH=N-OCH₃, -CH=CH-N(CH₃)-CH₃, -O-CH₃, -O-CH₂-CH₃, and -CN. Up to two
214 heteroatoms can be consecutive, such as, for example, -CH₂-NH-OCH₃.

215 [0020] Similarly, the term "heteroalkylene," by itself or as part of another substituent, means,
216 unless otherwise stated, a divalent radical derived from heteroalkyl, as exemplified, but not
217 limited by, -CH₂-CH₂-S-CH₂-CH₂- and -CH₂-S-CH₂-CH₂-NH-CH₂- . For heteroalkylene
218 groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxy,
219 alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and
220 heteroalkylene linking groups, no orientation of the linking group is implied by the direction
221 in which the formula of the linking group is written. For example, the formula -C(O)₂R'-
222 represents both -C(O)₂R'- and -R'C(O)₂- . As described above, heteroalkyl groups, as used

223 herein, include those groups that are attached to the remainder of the molecule through a
224 heteroatom, such as -C(O)R', -C(O)NR', -NR'R", -OR', -SR', and/or -SO₂R'. Where
225 "heteroalkyl" is recited, followed by recitations of specific heteroalkyl groups, such as
226 -NR'R" or the like, it will be understood that the terms heteroalkyl and -NR'R" are not
227 redundant or mutually exclusive. Rather, the specific heteroalkyl groups are recited to add
228 clarity. Thus, the term "heteroalkyl" should not be interpreted herein as excluding specific
229 heteroalkyl groups, such as -NR'R" or the like.

230 [0021] The terms "cycloalkyl" and "heterocycloalkyl," by themselves or in combination with
231 other terms, mean, unless otherwise stated, cyclic versions of "alkyl" and "heteroalkyl,"
232 respectively. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at
233 which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl
234 include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-
235 cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl
236 include, but are not limited to, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-
237 piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl,
238 tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like. A
239 "cycloalkylene" and a "heterocycloalkylene," alone or as part of another substituent, means a
240 divalent radical derived from a cycloalkyl and heterocycloalkyl, respectively.

241 [0022] The term "alkenyl" includes C₂-C₁₆ straight chain unsaturated, C₂-C₁₁ branched
242 unsaturated, C₅-C₈ unsaturated cyclic, and C₂-C₁₆ straight chain or branched unsaturated
243 aliphatic hydrocarbon groups substituted with C₃-C₈ cyclic saturated and unsaturated
244 aliphatic hydrocarbon groups having the specified number of carbon atoms. Double bonds
245 can occur in any stable point along the chain and the carbon-carbon double bonds can have
246 either the *cis* or *trans* configuration. For example, this definition shall include but is not
247 limited to ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl,
248 undecenyl, 1,5-octadienyl, 1,4,7-nonatrienyl, cyclopentenyl, cyclohexenyl, cycloheptenyl,
249 cyclooctenyl, ethylcyclohexenyl, butenylcyclopentyl, 1-pentenyl-3-cyclohexenyl, and the like.
250 Similarly, "heteroalkenyl" refers to heteroalkyl having one or more double bonds.

251 [0023] The term "alkynyl" refers in the customary sense to alkyl additionally having one or
252 more triple bonds. The term "cycloalkenyl" refers to cycloalkyl additionally having one or
253 more double bonds. The term "heterocycloalkenyl" refers to heterocycloalkyl additionally
254 having one or more double bonds.

255 [0024] The term “acyl” means, unless otherwise stated, -C(O)R where R is a substituted or
256 unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted
257 heteroalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
258 substituted or unsubstituted heteroaryl.

259 [0025] Each of the above terms (e.g., “alkyl,” “heteroalkyl,” “aryl,” and “heteroaryl”)
260 includes both substituted and unsubstituted forms of the indicated radical. Preferred
261 substituents for each type of radical are provided herein.

262 [0026] Substituents for the alkyl and heteroalkyl radicals (including those groups often
263 referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl,
264 heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be one or more of a variety of
265 groups selected from, but not limited to, -OR', =O, =NR', =N-OR', -NR'R", -SR', -halogen,
266 -SiR'R"R"', -OC(O)R', -C(O)R', -CO₂R', -CONR'R", -OC(O)NR'R", -NR"C(O)R',
267 -NR'-C(O)NR"R"', -NR"C(O)R", -NR-C(NR'R")=NR"', -S(O)R', -S(O)₂R', -S(O)₂NR'R",
268 -NRSO₂R', -CN, and -NO₂ in a number ranging from zero to (2m'+1), where m' is the total
269 number of carbon atoms in such radical. R', R", and R''' each preferably independently refer
270 to hydrogen, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl,
271 substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl (e.g., aryl
272 substituted with 1-3 halogen(s), substituted or unsubstituted alkyl, alkoxy, or thioalkoxy
273 groups, or arylalkyl groups. When a compound disclosed herein includes more than one R
274 group, for example, each of the R groups is independently selected as are each R', R", and R'''
275 group when more than one of these groups is present. When R' and R" are attached to the
276 same nitrogen atom, they can be combined with the nitrogen atom to form a 4-, 5-, 6-, or 7-
277 membered ring. For example, -NR'R" includes, but is not limited to, 1-pyrrolidinyl and 4-
278 morpholinyl. From the above discussion of substituents, one of skill in the art will
279 understand that the term “alkyl” is meant to include groups including carbon atoms bound to
280 groups other than hydrogen groups, such as haloalkyl (e.g., -CF₃ and -CH₂CF₃) and acyl (e.g.,
281 -C(O)CH₃, -C(O)CF₃, -C(O)CH₂OCH₃, and the like).

282 [0027] Similar to the substituents described for the alkyl radical, substituents for the aryl
283 and heteroaryl groups are varied and are selected from, for example: -OR', -NR'R", -SR',
284 -halogen, -SiR'R"R"', -OC(O)R', -C(O)R', -CO₂R', -CONR'R", -OC(O)NR'R", -NR"C(O)R',
285 -NR'-C(O)NR"R"', -NR"C(O)R", -NR-C(NR'R")=NR"', -S(O)R', -S(O)₂R', -S(O)₂NR'R",
286 -NRSO₂R', -CN, -NO₂, -R', -N₃, -CH(Ph)₂, fluoro(C₁-C₄)alkoxy, and fluoro(C₁-C₄)alkyl, in a
287 number ranging from zero to the total number of open valences on the aromatic ring system;

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

294 [0028] Two or more substituents can optionally be joined to form aryl, heteroaryl, cycloalkyl,
295 or heterocycloalkyl groups. Such so-called ring-forming substituents are typically, though
296 not necessarily, found attached to a cyclic base structure. In one embodiment, the ring-
297 forming substituents are attached to adjacent members of the base structure. For example,
298 two ring-forming substituents attached to adjacent members of a cyclic base structure create a
299 fused ring structure. In another embodiment, the ring-forming substituents are attached to a
300 single member of the base structure. For example, two ring-forming substituents attached to
301 a single member of a cyclic base structure create a spirocyclic structure. In yet another
302 embodiment, the ring-forming substituents are attached to non-adjacent members of the base
303 structure.

304 [0029] Two of the substituents on adjacent atoms of the aryl or heteroaryl ring can optionally
305 form a ring of the formula -T-C(O)-(CRR')_q-U-, wherein T and U are independently -NR-,
306 -O-, -CRR'-, or a single bond, and q is an integer of from 0 to 3. Alternatively, two of the
307 substituents on adjacent atoms of the aryl or heteroaryl ring can optionally be replaced with a
308 substituent of the formula -A-(CH₂)_r-B-, wherein A and B are independently -CRR'-, -O-,
309 -NR-, -S-, -S(O)-, -S(O)₂-, -S(O)₂NR'-, or a single bond, and r is an integer of from 1 to 4.
310 One of the single bonds of the new ring so formed can optionally be replaced with a double
311 bond. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring
312 can optionally be replaced with a substituent of the formula -(CRR')_s-X'- (C"R"")_d-, where s
313 and d are independently integers of from 0 to 3, and X' is -O-, -NR'-, -S-, -S(O)-, -S(O)₂-, or
314 -S(O)₂NR'-. The substituents R, R', R", and R"" are preferably independently selected from
315 hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl,
316 substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and
317 substituted or unsubstituted heteroaryl.

318 [0030] As used herein, the terms "heteroatom" or "ring heteroatom" are meant to include
319 oxygen (O), nitrogen (N), sulfur (S), phosphorus (P), and silicon (Si).

320 [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-).

323 [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-).

326 [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 can be taken together with the nitrogen to which they are attached forming a cyclic system containing 3 to 8 carbon atoms with or without one C₁-C₁₆alkyl, arylC₀-C₁₆alkyl, or C₀-C₁₆alkylaryl substituent.

331 [0034] The term "alkylaminoalkyl" represents an alkylamino group attached through an alkyl group as defined above having the indicated number of carbon atoms.

333 [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.

336 [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.

339 [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.

342 [0038] The term "alkylcarboxyalkyl" represents an alkylcarboxy group attached through an alkyl group as defined above having the indicated number of carbon atoms.

344 [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.

348 [0040] The nitrogen group can itself be substituted with an alkyl or aryl group.

349 [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

352 refers to multiple rings fused together wherein at least one of the fused rings is an aryl ring.
353 The term "heteroaryl" refers to aryl groups (or rings) that contain from one to four
354 heteroatoms selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally
355 oxidized, and the nitrogen atom(s) are optionally quaternized. Thus, the term "heteroaryl"
356 includes fused ring heteroaryl groups (i.e., multiple rings fused together wherein at least one
357 of the fused rings is a heteroaromatic ring). A 5,6-fused ring heteroarylene refers to two rings
358 fused together, wherein one ring has 5 members and the other ring has 6 members, and
359 wherein at least one ring is a heteroaryl ring. Likewise, a 6,6-fused ring heteroarylene refers
360 to two rings fused together, wherein one ring has 6 members and the other ring has 6
361 members, and wherein at least one ring is a heteroaryl ring. And a 6,5-fused ring
362 heteroarylene refers to two rings fused together, wherein one ring has 6 members and the
363 other ring has 5 members, and wherein at least one ring is a heteroaryl ring. A heteroaryl
364 group can be attached to the remainder of the molecule through a carbon or heteroatom.
365 Non-limiting examples of aryl and heteroaryl groups include phenyl, 1-naphthyl, 2-naphthyl,
366 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl,
367 pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-
368 isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl,
369 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl,
370 purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxaliny, 5-
371 quinoxaliny, 3-quinolyl, and 6-quinolyl. Substituents for each of the above noted aryl and
372 heteroaryl ring systems are selected from the group of acceptable substituents described
373 below. An "arylene" and a "heteroarylene," alone or as part of another substituent, mean a
374 divalent radical derived from an aryl and heteroaryl, respectively. Accordingly, the term
375 "aryl" can represent an unsubstituted, mono-, di- or trisubstituted monocyclic, polycyclic,
376 biaryl and heterocyclic aromatic groups covalently attached at any ring position capable of
377 forming a stable covalent bond, certain preferred points of attachment being apparent to those
378 skilled in the art (e. g. 3-indolyl, 4-imidazolyl). The aryl substituents are independently
379 selected from the group consisting of halo, nitro, cyano, trihalomethyl, C₁₋₁₆alkyl, arylC₁₋
380 ₁₆alkyl, C₀₋₁₆alkyloxyC₀₋₁₆alkyl, arylC₀₋₁₆alkyloxyC₀₋₁₆alkyl, C₀₋₁₆alkylthioC₀₋₁₆alkyl,
381 arylC₀₋₁₆alkylthioC₀₋₁₆alkyl, C₀₋₁₆alkylaminoC₀₋₁₆alkyl, arylC₀₋₁₆alkylaminoC₀₋₁₆alkyl,
382 di(arylC₁₋₁₆alkyl)aminoC₀₋₁₆alkyl, C₁₋₁₆alkylcarbonylC₀₋₁₆alkyl, arylC₁₋₁₆alkylcarbonylC₀₋
383 ₁₆alkyl, C₁₋₁₆alkylcarboxyC₀₋₁₆alkyl, arylC₁₋₁₆alkylcarboxyC₀₋₁₆alkyl, C₁₋
384 ₁₆alkylcarbonylaminoC₀₋₁₆alkyl, arylC₁₋₁₆alkylcarbonylaminoC₀₋₁₆alkyl, -C₀₋₁₆alkylCOOR₄, -
385 C₀₋₁₆alkylCONR₅R₆ wherein R₄, R₅ and R₆ are independently selected from hydrogen, C₁₋

386 $C_{11}alkyl$, $arylC_0-C_{11}alkyl$, or R_5 and R_6 are taken together with the nitrogen to which they are
387 attached forming a cyclic system containing 3 to 8 carbon atoms with or without one C_1 .
388 $C_{16}alkyl$, $arylC_0-C_{16}alkyl$, or $C_0-Cl_{16}alkylaryl$ substituent. Aryl includes but is not limited to
389 pyrazolyl and triazolyl.

390 [0042] For brevity, the term "aryl" when used in combination with other terms (e.g., aryloxy,
391 arylthioxy, arylalkyl) includes both aryl and heteroaryl rings as defined above. Thus, the
392 terms "arylalkyl," "aralkyl" and the like are meant to include those radicals in which an aryl
393 group is attached to an alkyl group (e.g., benzyl, phenethyl, pyridylmethyl, and the like)
394 including those alkyl groups in which a carbon atom (e.g., a methylene group) has been
395 replaced by, for example, an oxygen atom (e.g., phenoxyethyl, 2-pyridyloxymethyl, 3-(1-
396 naphthoxy)propyl, and the like), or a sulfur atom. Accordingly, the terms "arylalkyl" and
397 the like (e.g. (4-hydroxyphenyl)ethyl, (2-aminonaphthyl)hexyl, pyridylcyclopentyl)
398 represents an aryl group as defined above attached through an alkyl group as defined above
399 having the indicated number of carbon atoms.

400 [0043] The term "oxo," as used herein, means an oxygen that is double bonded to a carbon
401 atom.

402 [0044] The term "alkylsulfonyl," as used herein, means a moiety having the formula
403 $-S(O_2)-R'$, where R' is an alkyl group as defined above. R' can have a specified number of
404 carbons (e.g., " C_1-C_4 alkylsulfonyl").

405 [0045] The term "carbonyloxy" represents a carbonyl group attached through an oxygen
406 bridge.

407 [0046] In the above definitions, the terms "alkyl" and "alkenyl" can be used
408 interchangeably in so far as a stable chemical entity is formed, as would be apparent to those
409 skilled in the art.

410 [0047] The term "linker" refers to attachment groups interposed between substituents, e.g.,
411 R^1 , R^2 or R^3 described herein, e.g., Formula (Ia) and generically referred to as R^n , and the
412 group which is substituted, e.g., "ring A" group of e.g., Formula (Ia). In some embodiments,
413 the linker includes amido (-CONH- R^n or -NHCO- R^n), thioamido (-CSNH- R^n or -NHCS- R^n),
414 carboxyl (-CO₂- R^n or -OCORⁿ), carbonyl (-CO- R^n), urea (-NHCONH- R^n), thiourea
415 (-NHCSNH- R^n), sulfonamido (-NHSO₂- R^n or -SO₂NH- R^n), ether (-O- R^n), sulfonyl
416 (-SO₂- R^n), sulfoxyl (-SO- R^n), carbamoyl (-NHCO₂- R^n or -OCONH- R^n), or amino (-NHRⁿ)
417 linking moieties.

418 [0048] A “substituent group,” as used herein, means a group selected from the following
419 moieties:

420 (A) -OH, -NH₂, -SH, -CN, -CF₃, -NO₂, oxo, halogen, -COOH, unsubstituted alkyl,
421 unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl,
422 unsubstituted aryl, unsubstituted heteroaryl, and
423 (B) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, substituted with
424 at least one substituent selected from:

425 (i) oxo, -OH, -NH₂, -SH, -CN, -CF₃, -NO₂, halogen, -COOH, unsubstituted alkyl,
426 unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl,
427 unsubstituted aryl, unsubstituted heteroaryl, and

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

430 (a) oxo, -OH, -NH₂, -SH, -CN, -CF₃, -NO₂, halogen, -COOH, unsubstituted alkyl,
431 unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted
432 heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

433 (b) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, substituted
434 with at least one substituent selected from: oxo, -OH, -NH₂, -SH, -CN, -CF₃,
435 -NO₂, halogen, -COOH, unsubstituted alkyl, unsubstituted heteroalkyl,
436 unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, and
437 unsubstituted heteroaryl.

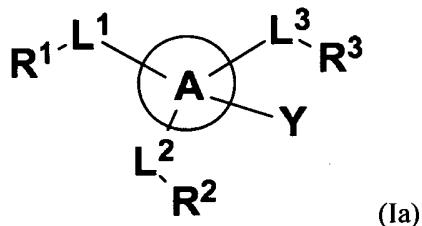
438 [0049] A “size-limited substituent” or “size-limited substituent group,” as used herein,
439 means a group selected from all of the substituents described above for a “substituent group,”
440 wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C₁-C₂₀ alkyl,
441 each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20
442 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or
443 unsubstituted C₄-C₈ cycloalkyl, and each substituted or unsubstituted heterocycloalkyl is a
444 substituted or unsubstituted 4 to 8 membered heterocycloalkyl.

445 [0050] A “lower substituent” or “lower substituent group,” as used herein, means a group
446 selected from all of the substituents described above for a “substituent group,” wherein each
447 substituted or unsubstituted alkyl is a substituted or unsubstituted C₁-C₈ alkyl, each
448 substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered
449 heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C₅-
450 C₇ cycloalkyl, and each substituted or unsubstituted heterocycloalkyl is a substituted or
451 unsubstituted 5 to 7 membered heterocycloalkyl.

452 [0051] The term “about” used in the context of a numeric value indicates a range of +/-
 453 10% of the numeric value, unless expressly indicated otherwise.

454 **II. Compounds**

455 [0052] In one aspect, there is provided a compound with structure of Formula (Ia):



456

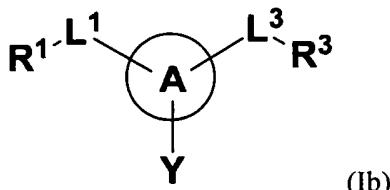
457 or pharmaceutically acceptable salt, ester, solvate, or prodrug thereof. Ring A is substituted
 458 or unsubstituted pyrazolyl. L¹ and L³ are independently a bond, substituted or unsubstituted
 459 alkylene, substituted or unsubstituted heteroalkylene, -S-, -SO-, -SO₂-, -O-, -NHSO₂-, or -
 460 NR⁴-. L² is absent, a bond, a hydrogen, substituted or unsubstituted alkylene, substituted or
 461 unsubstituted heteroalkylene, -S-, -SO-, -SO₂-, -O-, -NHSO₂-, or -NR⁴-. R¹ and R³ are
 462 independently hydrogen, halogen, substituted or unsubstituted alkyl, substituted or
 463 unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted
 464 cycloalkenyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted
 465 heterocycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted fused ring
 466 aryl, or substituted or unsubstituted heteroaryl. R² is absent, hydrogen, halogen, substituted or
 467 unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted
 468 cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted
 469 heterocycloalkyl, substituted or unsubstituted heterocycloalkenyl, substituted or unsubstituted
 470 aryl, substituted or unsubstituted fused ring aryl, or substituted or unsubstituted heteroaryl.
 471 R⁴ is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl,
 472 substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or
 473 unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or
 474 unsubstituted aryl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted
 475 heterocycloalkenyl, substituted or unsubstituted fused ring aryl, or substituted or
 476 unsubstituted heteroaryl. Y is a halogen. . In some embodiments, R² can be absent provided
 477 L² is also absent.

478 [0053] In some embodiments, the compound is a pharmaceutically acceptable salt, ester,
 479 solvate, or prodrug of a compound of Formula (Ia). In some embodiments, the compound is
 480 not an ester, not a solvate, and not a prodrug.

481 [0054] Further to any embodiment above, in some embodiments L^1 is -S-, -NR⁴-,
482 substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene, where R⁴
483 is as described above in regards to formula Ia, and R¹ is hydrogen, substituted or
484 unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted fused ring
485 aryl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl.
486 In some embodiments, R³ is substituted or unsubstituted aryl. In some embodiments, R³ is
487 unsubstituted aryl. In some embodiments, R³ is unsubstituted phenyl. In some embodiments,
488 L² is a bond. In some embodiments, L² is a bond and R² is hydrogen. Y is fluorine.

489 [0055] Further to any embodiment above, in some embodiments L^2 is $-C(O)-$, and R^2 is
490 substituted or unsubstituted alkyl, hydrogen, substituted or unsubstituted heteroalkyl,
491 substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted
492 or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or
493 unsubstituted aryl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted
494 heterocycloalkenyl, substituted or unsubstituted fused ring aryl, or substituted or
495 unsubstituted heteroaryl. In some embodiments, R^2 is unsubstituted aryl. In some
496 embodiments, R^2 is unsubstituted phenyl.

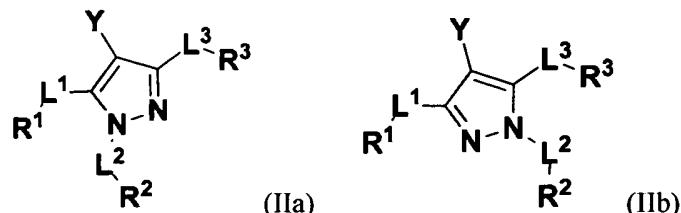
497 [0056] In some embodiments, L^2 and R^2 are absent, providing a compound with structure
498 of Formula (Ib) following.



499

500 [0057] In some embodiments, the compound is a pharmaceutically acceptable salt, ester,
501 solvate, or prodrug of a compound of Formula (Ib). In some embodiments, the compound is
502 not an ester, not a solvate, and not a prodrug.

503 [0058] In some embodiments, there is provided a compound according to Formula (Ia) with
504 structure of either of Formulae (IIa) or (IIb) following.



506 [0059] In some embodiments, the compound has the structure of Formula (IIa). In some
507 embodiments, L^3 is a bond, or substituted or unsubstituted alkylene, and R^3 is substituted or
508 unsubstituted aryl, substituted or unsubstituted fused ring aryl, substituted or unsubstituted
509 heterocycloalkyl, or substituted or unsubstituted heteroaryl. In some embodiments, R^3 is
510 substituted or unsubstituted phenyl, or substituted or unsubstituted thienyl. In some
511 embodiments, R^3 is unsubstituted phenyl. In some embodiments, R^3 is unsubstituted thienyl.
512 In some embodiments, R^3 is a chloro-substituted thienyl. In some embodiments, R^3 is
513 substituted or unsubstituted pyridyl, or substituted or unsubstituted pyridazinyl. In some
514 embodiments, R^3 is unsubstituted pyridyl. In some embodiments, R^3 is unsubstituted
515 pyridazinyl. In some embodiments, R^3 is substituted or unsubstituted pyrimidinyl, or
516 substituted or unsubstituted furyl. In some embodiments, R^3 is unsubstituted pyrimidinyl. In
517 some embodiments, R^3 is unsubstituted furyl. In some embodiments, R^3 is substituted or
518 unsubstituted morpholinyl, or substituted or unsubstituted oxanyl, or substituted or
519 unsubstituted oxetanyl. In some embodiments, R^3 is unsubstituted morpholinyl. In some
520 embodiments, R^3 is unsubstituted oxanyl. In some embodiments, R^3 is unsubstituted
521 oxetanyl. In some embodiments, R^3 is substituted or unsubstituted benzodioxinyl, or
522 substituted or unsubstituted naphthyl. In some embodiments, R^3 is unsubstituted
523 benzodioxinyl. In some embodiments, R^3 is unsubstituted naphthyl. In some embodiments,
524 R^3 is substituted or unsubstituted phenyl. In some embodiments, Y is fluorine.

525 [0060] In some embodiments, the compound has the structure of Formula (IIa) wherein L^3
526 is $-C(O)O-$, and R^3 is substituted or unsubstituted alkyl, and Y is fluorine.

527 [0061] In some embodiments, the compound has the structure of Formula (IIa) wherein L^3
528 is $-C(O)NR^5-$, R^5 is hydrogen or alkyl, and R^3 is substituted or unsubstituted alkyl and Y is
529 fluorine.

530 [0062] Further to any embodiment above wherein the compound has the structure of
531 Formula (IIa), in some embodiments, L^1 is $-S-$, a bond, $-NR^4-$, substituted or unsubstituted
532 alkylene, or substituted or unsubstituted heteroalkylene, where R^4 is as described in formula
533 Ia and R^1 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl,
534 substituted or unsubstituted fused ring aryl, substituted or unsubstituted heteroaryl, or
535 substituted or unsubstituted heterocycloalkyl. In some embodiments, R^1 is a substituted or
536 unsubstituted pyridyl. In some embodiments, R^1 is a substituted or unsubstituted pyridazinyl.
537 In some embodiments, R^1 is a substituted or unsubstituted pyrimidinyl. In some embodiments,
538 R^1 is a substituted or unsubstituted thienyl. In some embodiments, R^1 is a substituted or

539 unsubstituted furyl. In some embodiments, R¹ is an unsubstituted pyridyl. In some
540 embodiments, R¹ is an unsubstituted pyridazinyl. In some embodiments, R¹ is an unsubstituted
541 pyrimidinyl. In some embodiments, R¹ is an unsubstituted thienyl. In some embodiments, R¹
542 is a chloro-substituted thienyl. In some embodiments, R¹ is an unsubstituted furyl. In some
543 embodiments, R¹ is a substituted or unsubstituted morpholinyl. In some embodiments, R¹ is a
544 substituted or unsubstituted oxanyl. In some embodiments, R¹ is a substituted or unsubstituted
545 oxetanyl. In some embodiments, R¹ is an unsubstituted morpholinyl. In some embodiments,
546 R¹ is an unsubstituted oxanyl. In some embodiments, R¹ is an unsubstituted oxetanyl. In some
547 embodiments, R¹ is substituted or unsubstituted benzodioxinyl. In some embodiments, R¹ is
548 substituted or unsubstituted naphthyl. In some embodiments, R¹ is unsubstituted
549 benzodioxinyl. In some embodiments, R¹ is unsubstituted naphthyl. In some embodiments,
550 R¹ is substituted or unsubstituted phenyl. In some embodiments, Y is fluorine.

551 [0063] Further to any embodiment above wherein the compound has the structure of
552 Formula (IIa), in some embodiments, L² is a bond. In some embodiments, R² is hydrogen. In
553 some embodiments, L² is substituted or unsubstituted alkylene or -C(O)-, and R² is
554 hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl,
555 substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted
556 or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloalkenyl, substituted
557 or unsubstituted aryl, substituted or unsubstituted fused ring aryl, or substituted or
558 unsubstituted heteroaryl. In some embodiments, R² is a substituted or unsubstituted pyridyl. In
559 some embodiments, R² is a substituted or unsubstituted pyridazinyl. In some embodiments, R²
560 is a substituted or unsubstituted pyrimidinyl. In some embodiments, R² is a substituted or
561 unsubstituted thienyl. In some embodiments, R² is a substituted or unsubstituted furyl. In some
562 embodiments, R² is an unsubstituted pyridyl. In some embodiments, R² is an unsubstituted
563 pyridazinyl. In some embodiments, R² is an unsubstituted pyrimidinyl. In some embodiments,
564 R² is an unsubstituted thienyl. In some embodiments, R² is a chloro-substituted thienyl. In
565 some embodiments, R² is an unsubstituted furyl. In some embodiments, R² is a substituted or
566 unsubstituted morpholinyl. In some embodiments, R² is a substituted or unsubstituted oxanyl.
567 In some embodiments, R² is a substituted or unsubstituted oxetanyl. In some embodiments, R²
568 is an unsubstituted morpholinyl. In some embodiments, R² is an unsubstituted oxanyl. In some
569 embodiments, R² is an unsubstituted oxetanyl. In some embodiments, R² is substituted or
570 unsubstituted benzodioxinyl. In some embodiments, R² is substituted or unsubstituted
571 naphthyl. In some embodiments, R² is unsubstituted benzodioxinyl. In some embodiments,

572 R² is unsubstituted naphthyl. In some embodiments, R² is substituted or unsubstituted phenyl.
573 In some embodiments, Y is fluorine.

574 [0064] In some embodiments, the compound has the structure of Formula (IIb). In some
575 embodiments, L³ is a bond, or substituted or unsubstituted alkylene, and R³ is substituted or
576 unsubstituted aryl, substituted or unsubstituted fused ring aryl, substituted or unsubstituted
577 heterocycloalkyl, or substituted or unsubstituted heteroaryl. In some embodiments, R³ is
578 substituted or unsubstituted phenyl, or substituted or unsubstituted thienyl. In some
579 embodiments, R³ is unsubstituted phenyl. In some embodiments, R³ is unsubstituted thienyl.
580 In some embodiments, R³ is a chloro-substituted thienyl. In some embodiments, R³ is
581 substituted or unsubstituted pyridyl, or substituted or unsubstituted pyridazinyl. In some
582 embodiments, R³ is unsubstituted pyridyl. In some embodiments, R³ is unsubstituted
583 pyridazinyl. In some embodiments, R³ is substituted or unsubstituted pyrimidinyl, or
584 substituted or unsubstituted furyl. In some embodiments, R³ is unsubstituted pyrimidinyl. In
585 some embodiments, R³ is unsubstituted furyl. In some embodiments, R³ is substituted or
586 unsubstituted morpholinyl, or substituted or unsubstituted oxanyl, or substituted or
587 unsubstituted oxetanyl. In some embodiments, R³ is unsubstituted morpholinyl. In some
588 embodiments, R³ is unsubstituted oxanyl. In some embodiments, R³ is unsubstituted
589 oxetanyl. In some embodiments, R³ is substituted or unsubstituted benzodioxinyl, or
590 substituted or unsubstituted naphthyl. In some embodiments, R³ is unsubstituted
591 benzodioxinyl. In some embodiments, R³ is unsubstituted naphthyl. In some embodiments,
592 R³ is substituted or unsubstituted phenyl. In some embodiments, Y is fluorine.

593 [0065] In some embodiments, the compound has the structure of Formula (IIb) wherein L³
594 is -C(O)O-, and R³ is substituted or unsubstituted alkyl, and Y is fluorine.

595 [0066] In some embodiments, the compound has the structure of Formula (IIb) wherein L³
596 is -C(O)NR⁵-, R⁵ is hydrogen or alkyl, and R³ is substituted or unsubstituted alkyl and Y is
597 fluorine.

598 [0067] Further to any embodiment above wherein the compound has the structure of
599 Formula (IIb), in some embodiments, L¹ is a bond, -S-, -NR⁴-, substituted or unsubstituted
600 alkylene, or substituted or unsubstituted heteroalkylene, where R⁴ is as described in formula
601 Ia and R¹ is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl,
602 substituted or unsubstituted fused ring aryl, substituted or unsubstituted heteroaryl, or
603 substituted or unsubstituted heterocycloalkyl. In some embodiments, R¹ is a substituted or
604 unsubstituted pyridyl. In some embodiments, R¹ is a substituted or unsubstituted pyridazinyl.

605 In some embodiments, R¹ is a substituted or unsubstituted pyrimidinyl. In some embodiments,
606 R¹ is a substituted or unsubstituted thienyl. In some embodiments, R¹ is a substituted or
607 unsubstituted furyl. In some embodiments, R¹ is an unsubstituted pyridyl. In some
608 embodiments, R¹ is an unsubstituted pyridazinyl. In some embodiments, R¹ is an unsubstituted
609 pyrimidinyl. In some embodiments, R¹ is an unsubstituted thienyl. In some embodiments, R¹
610 is a chloro-substituted thienyl. In some embodiments, R¹ is an unsubstituted furyl. In some
611 embodiments, R¹ is a substituted or unsubstituted morpholinyl. In some embodiments, R¹ is a
612 substituted or unsubstituted oxanyl. In some embodiments, R¹ is a substituted or unsubstituted
613 oxetanyl. In some embodiments, R¹ is an unsubstituted morpholinyl. In some embodiments,
614 R¹ is an unsubstituted oxanyl. In some embodiments, R¹ is an unsubstituted oxetanyl. In some
615 embodiments, R¹ is substituted or unsubstituted benzodioxinyl. In some embodiments, R¹ is
616 substituted or unsubstituted naphthyl. In some embodiments, R¹ is unsubstituted
617 benzodioxinyl. In some embodiments, R¹ is unsubstituted naphthyl. In some embodiments,
618 R¹ is substituted or unsubstituted phenyl. In some embodiments, Y is fluorine.

619 [0068] Further to any embodiment above wherein the compound has the structure of
620 Formula (IIb), in some embodiments, L² is a bond or substituted or unsubstituted alkylene. In
621 some embodiments, L² is a bond. In some embodiments, L² is unsubstituted alkylene. In
622 some embodiments, L² is substituted alkylene. In some embodiments, R² is hydrogen. In
623 some embodiments, R² is substituted or unsubstituted alkyl, or substituted or unsubstituted
624 aryl. Further to any particular L², in some embodiments R² is substituted or unsubstituted
625 alkyl, or substituted or unsubstituted aryl. In some embodiments, R² is unsubstituted alkyl.
626 In some embodiments, R² is unsubstituted aryl. In some embodiments, R³ is unsubstituted
627 phenyl. In some embodiments, R² is substituted alkyl. In some embodiments, R² is
628 substituted aryl. In some embodiments, Y is fluorine.

629 [0069] Further to any embodiment above wherein the compound has the structure of
630 Formula (IIb), in some embodiments, L² is substituted or unsubstituted alkylene or -C(O)-,
631 and R² is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted
632 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl,
633 substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloalkenyl,
634 substituted or unsubstituted aryl, substituted or unsubstituted fused ring aryl, or substituted or
635 unsubstituted heteroaryl. In some embodiments, R² is a substituted or unsubstituted pyridyl. In
636 some embodiments, R² is a substituted or unsubstituted pyridazinyl. In some embodiments, R²
637 is a substituted or unsubstituted pyrimidinyl. In some embodiments, R² is a substituted or
638 unsubstituted thienyl. In some embodiments, R² is a substituted or unsubstituted furyl. In some

639 embodiments, R⁴ is an unsubstituted pyridyl. In some embodiments, R⁴ is an unsubstituted
 640 pyridazinyl. In some embodiments, R² is an unsubstituted pyrimidinyl. In some embodiments,
 641 R² is an unsubstituted thienyl. In some embodiments, R² is a chloro-substituted thienyl. In
 642 some embodiments, R² is an unsubstituted furyl. In some embodiments, R² is a substituted or
 643 unsubstituted morpholinyl. In some embodiments, R² is a substituted or unsubstituted oxanyl.
 644 In some embodiments, R² is a substituted or unsubstituted oxetanyl. In some embodiments, R²
 645 is an unsubstituted morpholinyl. In some embodiments, R² is an unsubstituted oxanyl. In some
 646 embodiments, R² is an unsubstituted oxetanyl. In some embodiments, R² is substituted or
 647 unsubstituted benzodioxinyl. In some embodiments, R² is substituted or unsubstituted
 648 naphthyl. In some embodiments, R² is unsubstituted benzodioxinyl. In some embodiments,
 649 R² is unsubstituted naphthyl. In some embodiments, R² is substituted or unsubstituted phenyl.
 650 In some embodiments, Y is fluorine.

651 [0070] Exemplary compounds, e.g., multisubstituted aromatic compounds, in accordance
 652 with the present disclosure are provided herein. In Table A following, compound (Cmpd)
 653 number, chemical name (i.e., International Union of Pure and Applied Chemistry [IUPAC]
 654 name), molecular weight (MW_{calc} calculated mass) and biological activity (i.e., inhibition
 655 activity in a thrombin assay) are disclosed.

656 [0071] For Table A following, the disclosed compounds were assayed for inhibition of the
 657 protease activity of thrombin as described herein. In Table A, the level of inhibition in the
 658 thrombin assay is indicated as follows: a: IC₅₀ ≤ 0.1 μM; b: 0.1 μM < IC₅₀ < 1 μM; c: IC₅₀ ≥
 659 1 μM. Accordingly, in some embodiments, there is provided a compound as expressly set
 660 forth in Table A following.

661 **Table A.**

662

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-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-chlorothiophen-2-yl)methyl]amino-4-fluoro-3-(oxan-4-yl)-1H-pyrazole-1-carbonyl]cyclopropyl]methanol	414	a
62	[1-[(5-chlorothiophen-2-yl)methyl]amino-4-fluoro-3-phenyl-1H-pyrazole-1-carbonyl]cyclopropyl]methanol	406	a

663

664

665 [0072] Compounds disclosed herein also include racemic mixtures, stereoisomers and
 666 mixtures of the compounds, including isotopically-labeled and radio-labeled compounds. See
 667 e.g., Goding, 1986, MONOCLONAL ANTIBODIES PRINCIPLES AND PRACTICE; Academic Press,
 668 p. 104. Such isomers can be isolated by standard resolution techniques, including e.g.,
 669 fractional crystallization, chiral chromatography, and the like. See e.g., Eliel, E. L. & Wilen
 670 S. H., 1993, STEREOCHEMISTRY IN ORGANIC COMPOUNDS ; John Wiley & Sons, New York.

671 [0073] In some embodiments, compounds disclosed herein have asymmetric centers and
 672 can occur as racemates, racemic mixtures, and as individual enantiomers or diastereoisomers,
 673 with all isomeric forms as well as mixtures thereof being contemplated for use in the
 674 compounds and methods described herein. The compounds contemplated for use in the
 675 compounds and methods described herein do not include those that are known in the art to be
 676 too unstable to synthesize and/or isolate.

677 [0074] The compounds disclosed herein can also contain unnatural proportions of atomic
 678 isotopes at one or more of the atoms that constitute such compounds. For example, the
 679 compounds can be radiolabeled with radioactive isotopes, such as for example tritium (³H),
 680 iodine-125 (¹²⁵I), or carbon-14 (¹⁴C). All isotopic variations of the compounds disclosed
 681 herein, whether radioactive or not, are encompassed within the contemplated scope.

682 [0075] In some embodiments, metabolites of the compounds disclosed herein are useful for
 683 the methods disclosed herein.

684 [0076] In some embodiments, compounds contemplated herein are provided in the form of
 685 a prodrug. The term "prodrug" refers to a compound that can be converted into a compound
 686 (e.g., a biologically active compound) described herein *in vivo*. Prodrugs can be useful for a

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

698 [0077] Accordingly, in some embodiments, compounds contemplated herein are provided
699 in the form of a prodrug ester. The term "prodrug ester" refers to derivatives of the
700 compounds disclosed herein formed by the addition of any of a variety of ester-forming
701 groups, e.g., groups known in the art, that are hydrolyzed under physiological conditions.
702 Examples of prodrug ester groups include pivaloyloxymethyl, acetoxyethyl, phthalidyl,
703 indanyl and methoxymethyl, as well as other such groups known in the art, including a (5-R-
704 2-oxo-1,3-dioxolen-4-yl)methyl group. Other examples of prodrug ester groups can be found
705 in, for example, T. Higuchi and V. Stella, in "Pro-drugs as Novel Delivery Systems", Vol. 14,
706 A.C.S. Symposium Series, American Chemical Society (1975); and BIOREVERSIBLE
707 CARRIERS IN DRUG DESIGN: THEORY AND APPLICATION, edited by E. B. Roche, Pergamon
708 Press: New York, 14-21 (1987) (providing examples of esters useful as prodrugs for
709 compounds containing carboxyl groups). Each of the above-mentioned references is herein
710 incorporated by reference for the limited purpose of disclosing ester-forming groups that can
711 form prodrug esters.

712 [0078] In some embodiments, prodrugs can be slowly converted to the compounds described
713 herein useful for the methods described herein when placed in a transdermal patch reservoir
714 with a suitable enzyme or chemical reagent.

715 [0079] Certain compounds disclosed herein can exist in unsolvated forms as well as solvated
716 forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated
717 forms and are encompassed within the scope of contemplated compounds. Certain
718 compounds of the present invention can exist in multiple crystalline or amorphous forms. In

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

721 **III. Biological Activities**

722 [0080] In some embodiments, compounds described herein exhibit inhibitory activity
723 against thrombin with activities $\geq 1 \mu\text{M}$, e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14,
724 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
725 μM , or even greater. In some embodiments, the compounds exhibit inhibitory activity
726 against thrombin with activities between $0.1 \mu\text{M}$ and $1 \mu\text{M}$, e.g., about 0.1, 0.2, 0.3, 0.4, 0.5,
727 0.6, 0.7, 0.8, 0.9 or $1.0 \mu\text{M}$. In some embodiments, compounds described herein exhibit
728 inhibitory activity against thrombin with activities $\leq 0.1 \mu\text{M}$, e.g., about 1, 2, 5, 10, 15, 20,
729 30, 40, 50, 60, 70, 80, 90, or 100 nM . Ranges of values using a combination of any of the
730 values recited herein as upper and/or lower limits are also contemplated, for example, but not
731 limited to, 1-10 nM , 10-100 nM , 0.1-1 μM , 1-10 μM , 10-100 μM , 100-200 μM , 200-500
732 μM , or even 500-1000 μM . In some embodiments, the inhibitory activity is in the range of
733 about 1-10 nM , 10-100 nM , 0.1-1 μM , 1-10 μM , 10-100 μM , 100-200 μM , 200-500 μM , or
734 even 500-1000 μM . It is understood that for purposes of quantification, the terms "activity,"
735 "inhibitory activity," "biological activity," "thrombin activity" and the like in the context of
736 an inhibitory compound disclosed herein can be quantified in a variety of ways known in the
737 art. Unless indicated otherwise, as used herein such terms refer to IC_{50} in the customary
738 sense (i.e., concentration to achieve half-maximal inhibition).

739 [0081] Inhibitory activity against thrombin in turn inhibits the blood coagulation process.
740 Accordingly, compounds disclosed herein are indicated in the treatment or management of
741 thrombotic disorders. In some embodiments, a dose or a therapeutically effective dose of a
742 compound disclosed herein will be that which is sufficient to achieve a plasma concentration
743 of the compound or its active metabolite(s) within a range set forth herein, e.g., about 1-10
744 nM , 10-100 nM , 0.1-1 μM , 1-10 μM , 10-100 μM , 100-200 μM , 200-500 μM , or even
745 500-1000 μM , preferably about 1-10 nM , 10-100 nM , or 0.1-1 μM . Without wishing to be
746 bound by any theory, it is believed that such compounds are indicated in the treatment or
747 management of thrombotic disorders.

748 **IV. Methods of Treating and Preventing Disease**

749 [0082] **Thrombosis.** Thrombotic diseases are the primary indications for thrombin
750 inhibition, because of thrombin's location in the coagulation cascade and, in turn, the
751 importance of the coagulation cascade in the progression of blood clotting processes.
752 However, without wishing to be bound by any theory, it is believed the coagulation cascade
753 in general, and thrombin in particular, is important in a variety other disease states.

754 [0083] It has been discovered that compounds described herein, e.g., multisubstituted
755 aromatic compounds, exhibit inhibitory action against thrombin (activated blood-coagulation
756 factor II; EC 3.4.21.5). This, in turn inhibits the blood coagulation process.

757 [0084] This inhibitory action is useful in the treatment of a variety of thrombotic disorders,
758 such as, but not limited to, acute vascular diseases such as acute coronary syndromes;
759 venous-, arterial- and cardiogenic thromboembolisms; the prevention of other states such as
760 disseminated intravascular coagulation, or other conditions that involve the presence or the
761 potential formation of a blood clot thrombus. Other indications for methods described herein
762 include the following.

763 [0085] **Cancer.** It has long been recognized that cancer progression is accompanied by
764 venous thrombosis, but it has not been understood how each disease is related. From several
765 clinical trials studying the treatment of VTE, metaanalyses have shown that low molecular
766 weight heparins (LMWHs) improve overall survival in subgroups of cancer patients. See
767 e.g., Zacharski, L. R. & Lee, A. Y., 2008, *Expert Opin Investig Drugs*, 17:1029-1037;
768 Falanga, A. & Piccioli, A., 2005, *Current Opinion in Pulmonary Medicine*, 11:403-407;
769 Smorenburg, S. M., et al., 1999, *Thromb Haemost*, 82:1600-1604; Hettiarachchi, R. J., et al.,
770 1999, *Thromb Haemost*, 82:947-952. This finding was substantiated in later clinical trials
771 that measured specifically the survival of cancer patients. See e.g., Lee, A. Y. et al., 2005, *J*
772 *Clin Oncol*, 23:2123-2129; Klerk, C. P. et al., *J Clin Oncol* 2005, 23:2130-2135; Kakkar, A.
773 K., et al., 2004, *J Clin Oncol*, 22:1944-1948; Altinbas, M., et al., 2004, *J Thromb Haemost*,
774 2:1266-1271.

775 [0086] More recently, researchers have focused on the specific anticancer effect of DTIs.
776 For example, it was shown that heparin significantly prolonged the survival of patients with
777 limited small cell lung cancer. See e.g., Akl, E. A., et al., 2008, *J Exp Clin Cancer Res*, 27:4.
778 Other investigators found that systemic use of argatroban reduced tumor mass and prolonged
779 survival time in rat glioma models leading to the conclusion that argatroban should be
780 considered as a novel therapeutic for glioma, a notoriously difficult to treat cancer type. See

781 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; Deleo, 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.

792 [0087] Further, hirudin and the LMWH nadroparin dramatically reduced the number of 793 lung metastases when administered prior to cancer cell inoculation. See e.g., Hu, L., *et al.*, 794 2004, *Blood*, 104:2746-51.

795 [0088] The de novo thrombin inhibitor d-Arg-Oic-Pro-d-Ala-Phe(p-Me) has been found to 796 block thrombin-stimulated invasion of prostate cancer cell line PC-3 in a concentration 797 dependent manner. See e.g., Nieman, M. T., *et al.*, 2008, *J Thromb Haemost*, 6:837-845. A 798 reduced rate of tumor growth was observed in mice dosed with the pentapeptide through their 799 drinking water. The mice also showed reduced fold rate in tumor size and reduced overall 800 tumor weight compared to untreated mice. Microscopic examination of treated tumors 801 showed reduced number of large blood vessels thus concluding that the pentapeptide 802 interfered with tumor angiogenesis. Nieman, M. T., *et al.*, *Thromb Haemost*, 104:1044-8.

803 [0089] In view of these and related studies, it is suggested that anticoagulants affect tumor 804 metastasis; that is, angiogenesis, cancer cell adhesion, migration and invasion processes. See 805 e.g., Van Noorden, C. J., *et al.*, 2010, *Thromb Res*, 125 Suppl 2:S77-79.

806 [0090] **Fibrosis.** Several studies have shown the utility of anticoagulant therapy in fibrotic 807 disorders. For example, in a rat model of CCl₄-induced chronic liver injury, the DTI 808 SSR182289 decreased liver fibrogenesis significantly after 7 weeks of administration. 809 Similar observations were made in other studies using the LMWHs nadroparin, tinzaparin, 810 enoxaparin, and dalteparin sodium. See e.g., Duplantier, J. G., *et al.*, 2004, *Gut*, 53:1682- 811 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.

813 [0091] In another example, the DTI melagatran greatly reduced ischemia reperfusion injury
814 in a kidney transplant model in the large white pig. This led to a drastically improved kidney
815 graft survival at 3 months. See e.g., Favreau, F., *et al.*, 2010, *Am J Transplant*, 10:30-39.

816 [0092] Recent studies have shown that in a bleomycin-induced mouse model of pulmonary
817 fibrosis, dabigatran etexilate treatment reduced important profibrotic events in lung
818 fibroblasts, including the production of collagen and connective tissue growth factor. See e.g.,
819 Silver, R. M., *et al.*, 2010, *Am. J. Respir. Crit. Care Med.*, 181:A6780; Bogatkevich, G. S., *et*
820 *al.*, 2009, *Arthritis Rheum*, 60:3455-3464.

821 [0093] The above experimental evidence points to a close relationship between thrombin
822 and fibrosis and suggests novel therapeutic opportunities for fibrosis using thrombin
823 inhibitors. See e.g., Calvaruso, V., *et al.*, 2008, *Gut*, 57:1722-1727; Chambers, R. C., 2008,
824 *Br J Pharmacol*, 153 Suppl 1:S367-378; Chambers, R. C. & Laurent, G. J., 2002, *Biochem
825 Soc Trans*, 30:194-200; Howell, D. C., *et al.*, 2001, *Am J Pathol*, 159:1383-1395.

826 [0094] **Alzheimer's Disease.** Very recent experiments confirm higher thrombin levels in
827 brain endothelial cells of patients with Alzheimer's disease. While 'normal' thrombin levels
828 are connected to regulatory CNS functions, thrombin accumulation in the brain is toxic. It
829 has also been found that the neural thrombin inhibitor Protease Nexin 1 (PN-1) is
830 significantly reduced in the Alzheimer's disease brain, despite the fact that PN-1 mRNA
831 levels are unchanged. These observations have led some investigators to suggest that
832 reduction of CNS-resident thrombin will prove useful in Alzheimer's Disease (AD) treatment.
833 See e.g., Vaughan, P. J., *et al.*, 1994, *Brain Res*, 668:160-170; Yin, X., *et al.*, 2010, *Am J
834 Pathol*, 176:1600-1606; Akiyama, H., *et al.*, 1992, *Neurosci Lett*, 146:152-154.

835 [0095] **Multiple Sclerosis.** Investigators found that hirudin treatment in an animal model
836 of Multiple Sclerosis (MS) showed a dramatic improvement in disease severity. See e.g.,
837 Han, M. H., *et al.*, 2008, *Nature*, 451:1076-1081. Similar results were obtained following
838 treatment with heparin (a DTI) and dermatan sulfate another coagulation inhibitor. See e.g.,
839 Chelmicka-Szorc, E. & Arnason, B. G., 1972, *Arch Neurol*, 27:153-158; Inaba, Y., *et al.*,
840 1999, *Cell Immunol*, 198:96-102. Other evidence shows that naturally occurring
841 antithrombin III has anti-inflammatory effects in diseases such as endotoxemia and other
842 sepsis-related conditions. See e.g., Wiedermann, C. J. & Romisch, J., 2002, *Acta Med
843 Austriaca*, 29:89-92. Naturally occurring thrombin inhibitors are presumably synthesized *in
844 situ* and have protective roles in CNS inflammation. Therefore, therapeutic thrombin
845 inhibition has been proposed as a potential MS treatment. See e.g., Luo, W., *et al.*, 2009, In:

846 THROMBIN, Maragoudakis, M. E.; Tsopanoglou, N. E., Eds. Springer New York: 2009; pp
847 133-159.

848 [0096] **Pain.** In a rat pain model with partial lesion of the sciatic nerve, intrathecal hirudin
849 prevented the development of neuropathic pain and curbed pain responses for 7 days. The
850 investigators found that following injury, neuropathic pain was mediated by thrombin
851 generation, which in turn activated PAR-1 receptor in the spinal cord. Hirudin inhibited
852 thrombin generation and ultimately led to pain relief. See e.g., Garcia, P. S., *et al.*, 2010,
853 *Thromb Haemost*, 103:1145-1151; Narita, M., *et al.*, 2005, *J Neurosci*, 25:10000-10009.
854 Researchers hypothesize that thrombin and the PARs are involved not just as part of the
855 coagulation cascade, but in inflammation, nociception and neurodevelopment. Development
856 of a DTI to intersect an unexploited pharmacology will lead to pain therapeutics distinct from
857 opioids and NSAIDs, whose shortcomings are well documented. See e.g., Garcia 2010, *Id.*

858 [0097] Accordingly, in a further aspect, there is provided a method for treating a disease or
859 disorder in a subject in need thereof. The method includes administering a compound of any
860 of Formulae (Ia), (Ib), (IIa) or (IIb) as disclosed herein, a compound as set forth in Table A,
861 pharmaceutically acceptable salt, ester, solvate, or prodrug thereof, or pharmaceutical
862 composition thereof, to a subject in need thereof in an amount effective to treat the disease or
863 disorder. The terms "therapeutically effective amount," "amount effective to treat," "amount
864 effective to prevent" and the like refer to that amount of drug or pharmaceutical agent (e.g.,
865 compound or pharmaceutical composition disclosed herein) that will elicit the biological or
866 medical response of a tissue, system, animal, or human that is being sought by a researcher,
867 veterinarian, medical doctor or other clinician.

868 [0098] In some embodiments, the disease or disorder is a thrombotic disease or disorder.
869 In some embodiments, the thrombotic disease or disorder is acute coronary syndrome, venous
870 thromboembolism, arterial thromboembolism or cardiogenic thromboembolism. In some
871 embodiments, the thrombotic disease or disorder is acute coronary syndrome. In some
872 embodiments, the thrombotic disease or disorder is venous thromboembolism. In some
873 embodiments, the thrombotic disease or disorder is arterial thromboembolism. In some
874 embodiments, the thrombotic disease or disorder is cardiogenic thromboembolism.

875 [0099] In some embodiments, the disease or disorder is fibrosis, Alzheimer's Disease,
876 multiple sclerosis, pain, or cancer. In some embodiments, the disease or disorder is
877 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.,

910 thrombin, can be monitored using a chromophoric substrate, e.g., a p-nitroanilide peptide
911 substrate, which upon hydrolysis releases p-nitroanilide, which in turn gives rise to a color
912 change which can be determined spectrophotometrically. *See* e.g., Lottenberg, R, *et al.*,
913 1983, *Biochimica et Biophysica Acta*, 752:539-557. Accordingly, the change in color can be
914 monitored with a spectrophotometer at e.g., 405 nm to provide a signal which is directly
915 proportional to the proteolytic activity of the enzyme.

916 [0107] The thrombin activity reported herein (e.g., Table A) was obtained as follows.
917 Human thrombin was obtained from Haematologic Technologies Inc. The chromogenic
918 substrate S-2238 was obtained from DiaPharmä. Thrombin was assayed in buffer containing
919 0.05 M Tris (pH 7.4), 0.015 M NaCl and 0.01% PEG-8000. The final concentration of
920 enzyme used was 3 nM thrombin. The final concentration of substrate used was 125 μ M S-
921 2238 for thrombin. All assays were performed in 96-well microtiter plates at room
922 temperature (RT). The enzyme and inhibitor were pre-incubated for 10 minutes then
923 substrate was added and read at 405 nm in a SpectraMax Plus Spectrophotometer (Molecular
924 Devices). Inhibitor IC₅₀ values were determined by adding test compound as ten point, three-
925 fold serial dilutions in buffer solution, as known in the art. The plate was read at 10 minutes
926 after substrate addition. The IC₅₀ was calculated by plotting the percent (%) inhibition
927 against compound concentration and fitting the data to a constrained four parameter
928 sigmoidal curve, as known in the art.

929 **VI. Pharmaceutical Compositions**

930 [0108] In another aspect, there is provided a pharmaceutical composition comprising a
931 compound disclosed herein and a pharmaceutically acceptable excipient. The compound is a
932 compound of any of Formulae (Ia), (Ib), (IIa) or (IIb) as disclosed herein, a compound as set
933 forth in Table A herein, or pharmaceutically acceptable salt, ester, solvate, or prodrug thereof.
934 In some embodiments, the compound is set forth in Table A herein.

935 [0109] The term “pharmaceutically acceptable salts” is meant to include salts of the active
936 compounds that are prepared with relatively nontoxic acids or bases, depending on the
937 particular substituents found on the compounds described herein. When compounds
938 disclosed herein contain relatively acidic functionalities, base addition salts can be obtained
939 by contacting the neutral form of such compounds with a sufficient amount of the desired
940 base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base
941 addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium
942 salt, or a similar salt. When compounds disclosed herein contain relatively basic

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

957 [0110] Compounds disclosed herein can exist as salts, such as with pharmaceutically
958 acceptable acids. Accordingly, the compounds contemplated herein include such salts.
959 Examples of such salts include hydrochlorides, hydrobromides, sulfates, methanesulfonates,
960 nitrates, maleates, acetates, citrates, fumarates, tartrates (e.g., (+)-tartrates, (-)-tartrates, or
961 mixtures thereof including racemic mixtures), succinates, benzoates, and salts with amino
962 acids such as glutamic acid. These salts can be prepared by methods known to those skilled
963 in the art.

964 [0111] The neutral forms of the compounds are preferably regenerated by contacting the
965 salt with a base or acid and isolating the parent compound in the conventional manner. The
966 parent form of the compound differs from the various salt forms in certain physical
967 properties, such as solubility in polar solvents.

968 [0112] Pharmaceutically acceptable salts of the compounds above, where a basic or acidic
969 group is present in the structure, are also included within the scope of compounds
970 contemplated herein. When an acidic substituent is present, such as -NHSO₃H, -COOH and
971 -P(O)(OH)₂, there can be formed the ammonium, sodium, potassium, calcium salt, and the
972 like, for use as the dosage form. Basic groups, such as amino or basic heteroaryl radicals, or
973 pyridyl and acidic salts, such as hydrochloride, hydrobromide, acetate, maleate, palmoate,
974 methanesulfonate, p-toluenesulfonate, and the like, can be used as the dosage form.

975 [0113] Also, in the embodiments in which R-COOH is present, pharmaceutically
976 acceptable esters can be employed, e. g. , methyl, ethyl, tert-butyl, pivaloyloxymethyl, and
977 the like, and those esters known in the art for modifying solubility or hydrolysis
978 characteristics for use as sustained release or prodrug formulations.

979 A. **Formulations**

980 [0114] The compounds disclosed herein can be prepared and administered in a wide variety
981 of oral, parenteral, and topical dosage forms. Thus, the compounds can be administered by
982 injection (e.g. intravenously, intramuscularly, intracutaneously, subcutaneously,
983 intraduodenally, or intraperitoneally). Also, the compounds described herein can be
984 administered by inhalation, for example, intranasally. Additionally, the compounds disclosed
985 herein can be administered transdermally. It is also envisioned that multiple routes of
986 administration (e.g., intramuscular, oral, transdermal) can be used to administer the
987 compounds disclosed herein. In some embodiments, the compounds disclosed herein can be
988 administered orally as tablets, aqueous or oily suspensions, lozenges, troches, powders,
989 granules, emulsions, capsules, syrups or elixirs. The composition for oral use can contain one
990 or more agents selected from the group of sweetening agents, flavoring agents, coloring
991 agents and preserving agents in order to produce pharmaceutically elegant and palatable
992 preparations. Accordingly, there are also provided pharmaceutical compositions comprising
993 a pharmaceutically acceptable carrier or excipient and one or more compounds disclosed
994 herein.

995 [0115] In some embodiments, tablets contain the acting ingredient in admixture with non-
996 toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets.
997 These excipients can be, for example, (1) inert diluents, such as calcium carbonate, lactose,
998 calcium phosphate, carboxymethylcellulose, or sodium phosphate; (2) granulating and
999 disintegrating agents, such as corn starch or alginic acid; (3) binding agents, such as starch,
1000 gelatin or acacia; and (4) lubricating agents, such as magnesium stearate, stearic acid or talc.
1001 These tablets can be uncoated or coated by known techniques to delay disintegration and
1002 absorption in the gastrointestinal tract and thereby provide a sustained action over a longer
1003 period. For example, a time delay material such as glyceryl monostearate or glyceryl
1004 distearate can be employed.

1005 [0116] For preparing pharmaceutical compositions from the compounds disclosed herein,
1006 pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations
1007 include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A

1008 solid carrier can be one or more substance that can also act as diluents, flavoring agents,
1009 binders, preservatives, tablet disintegrating agents, or an encapsulating material.

1010 [0117] A compound disclosed herein, in the form of a free compound or a
1011 pharmaceutically-acceptable pro-drug, metabolite, analogue, derivative, solvate or salt, can
1012 be administered, for in vivo application, parenterally by injection or by gradual perfusion
1013 over time. Administration can be intravenously, intraperitoneally, intramuscularly,
1014 subcutaneously, intracavity, or transdermally. For *in vitro* studies the compounds can be
1015 added or dissolved in an appropriate biologically acceptable buffer and added to a cell or
1016 tissue.

1017 [0118] In powders, the carrier is a finely divided solid in a mixture with the finely divided
1018 active component. In tablets, the active component is mixed with the carrier having the
1019 necessary binding properties in suitable proportions and compacted in the shape and size
1020 desired.

1021 [0119] The powders and tablets preferably contain from 5% to 70% of the active compound.
1022 Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin,
1023 dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low
1024 melting wax, cocoa butter, and the like. The term “preparation” is intended to include the
1025 formulation of the active compound with encapsulating material as a carrier providing a
1026 capsule in which the active component with or without other carriers, is surrounded by a
1027 carrier, which is thus in association with it. Similarly, cachets and lozenges are included.
1028 Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms
1029 suitable for oral administration.

1030 [0120] For preparing suppositories, a low melting wax, such as a mixture of fatty acid
1031 glycerides or cocoa butter, is first melted and the active component is dispersed
1032 homogeneously therein, as by stirring. The molten homogeneous mixture is then poured into
1033 convenient sized molds, allowed to cool, and thereby to solidify.

1034 [0121] Liquid form preparations include solutions, suspensions, and emulsions, for example,
1035 water or water/propylene glycol solutions. For parenteral injection, liquid preparations can
1036 be formulated in solution in aqueous polyethylene glycol solution.

1037 [0122] When parenteral application is needed or desired, particularly suitable admixtures for
1038 the compounds disclosed herein are injectable, sterile solutions, preferably oily or aqueous
1039 solutions, as well as suspensions, emulsions, or implants, including suppositories. In

1040 particular, carriers for parenteral administration include aqueous solutions of dextrose, saline,
1041 pure water, ethanol, glycerol, propylene glycol, peanut oil, sesame oil, polyoxyethylene-block
1042 polymers, and the like. Ampoules are convenient unit dosages. The compounds disclosed
1043 herein can also be incorporated into liposomes or administered via transdermal pumps or
1044 patches. Pharmaceutical admixtures suitable for use in the pharmaceuticals compositions and
1045 methods disclosed herein include those described, for example, in PHARMACEUTICAL
1046 SCIENCES (17th Ed., Mack Pub. Co., Easton, PA) and WO 96/05309, the teachings of both of
1047 which are hereby incorporated by reference.

1048 [0123] In some embodiments, preparations for parenteral administration include sterile
1049 aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous
1050 solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and
1051 injectable organic esters such as ethyl oleate. Aqueous carriers include water,
1052 alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media.
1053 Parenteral vehicles include sodium chloride solution, Ringer's dextrose, dextrose and sodium
1054 chloride, lactated Ringer's intravenous vehicles include fluid and nutrient replenishers,
1055 electrolyte replenishers (such as those based on Ringer's dextrose), and the like. Preservatives
1056 and other additives can also be present such as, for example, antimicrobials, anti-oxidants,
1057 chelating agents, growth factors and inert gases and the like.

1058 [0124] Aqueous solutions suitable for oral use can be prepared by dissolving the active
1059 component in water and adding suitable colorants, flavors, stabilizers, and thickening agents
1060 as desired. Aqueous suspensions suitable for oral use can be made by dispersing the finely
1061 divided active component in water with viscous material, such as natural or synthetic gums,
1062 resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending
1063 agents.

1064 [0125] Also included are solid form preparations that are intended to be converted, shortly
1065 before use, to liquid form preparations for oral administration. Such liquid forms include
1066 solutions, suspensions, and emulsions. These preparations can contain, in addition to the
1067 active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners,
1068 dispersants, thickeners, solubilizing agents, and the like.

1069 [0126] The pharmaceutical preparation is preferably in unit dosage form. In such form the
1070 preparation is subdivided into unit doses containing appropriate quantities of the active
1071 component. The unit dosage form can be a packaged preparation, the package containing
1072 discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or

1073 ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it
1074 can be the appropriate number of any of these in packaged form.

1075 [0127] The quantity of active component in a unit dose preparation can be varied or adjusted
1076 from 0.1 mg to 10000 mg, more typically 1.0 mg to 1000 mg, most typically 10 mg to 500
1077 mg, according to the particular application and the potency of the active component. The
1078 composition can, if desired, also contain other compatible therapeutic agents.

1079 [0128] Some compounds can have limited solubility in water and therefore can require a
1080 surfactant or other appropriate co-solvent in the composition. Such co-solvents include:
1081 Polysorbate 20, 60, and 80; Pluronic F-68, F-84, and P-103; cyclodextrin; and polyoxyl 35
1082 castor oil. Such co-solvents are typically employed at a level between about 0.01 % and
1083 about 2% by weight.

1084 [0129] Viscosity greater than that of simple aqueous solutions can be desirable to decrease
1085 variability in dispensing the formulations, to decrease physical separation of components of a
1086 suspension or emulsion of formulation, and/or otherwise to improve the formulation. Such
1087 viscosity building agents include, for example, polyvinyl alcohol, polyvinyl pyrrolidone,
1088 methyl cellulose, hydroxy propyl methylcellulose, hydroxyethyl cellulose, carboxymethyl
1089 cellulose, hydroxy propyl cellulose, chondroitin sulfate and salts thereof, hyaluronic acid and
1090 salts thereof, and combinations of the foregoing. Such agents are typically employed at a
1091 level between about 0.01% and about 2% by weight.

1092 [0130] The compositions disclosed herein can additionally include components to provide
1093 sustained release and/or comfort. Such components include high molecular weight, anionic
1094 mucomimetic polymers, gelling polysaccharides, and finely-divided drug carrier substrates.
1095 These components are discussed in greater detail in U.S. Pat. Nos. 4,911,920; 5,403,841;
1096 5,212,162; and 4,861,760. The entire contents of these patents are incorporated herein by
1097 reference in their entirety for all purposes.

1098 [0131] By the present, there are provided methods for ameliorating wound healing and for
1099 mediating tissue repair (including but not limited to treatment of peripheral and coronary
1100 vascular disease). According to these methods, a subject having a wound or in need of tissue
1101 repair, is treated at the site of the wound or damaged tissue or treated systemically, with a
1102 compound disclosed herein in the form of a free compound or a pharmaceutically-acceptable
1103 prodrug, metabolite, analogue, derivative, solvate or salt.

1104 [0132] Generally, the terms "treating", "treatment" and the like are used herein to mean
1105 affecting a subject, tissue or cell to obtain a desired pharmacologic and/or physiologic effect.
1106 The effect can be prophylactic in terms of completely or partially preventing a disease or
1107 disorder or sign or symptom thereof, and/or can be therapeutic in terms of a partial or
1108 complete cure for a disorder and/or adverse effect attributable to it. "Treating" as used herein
1109 covers any treatment of, or prevention of a disease or disorder in a vertebrate, a mammal,
1110 particularly a human, and includes: (a) preventing the disease or disorder from occurring in a
1111 subject that can be predisposed to the disease or disorder, but has not yet been diagnosed as
1112 having it; (b) inhibiting the disease or disorder, i. e. , arresting its development; or (c)
1113 relieving or ameliorating the disease or disorder, i. e. , cause regression of the disease or
1114 disorder.

1115 [0133] There are provided various pharmaceutical compositions useful for ameliorating
1116 diseases and disorders, including thrombosis. In some embodiments, the disease or disorder
1117 is a thrombotic disorder. In some embodiments, the disease or disorder is acute coronary
1118 syndrome, venous thromboembolism, arterial thromboembolism or cardiogenic
1119 thromboembolism. In some embodiments, the disease or disorder is fibrosis. In some
1120 embodiments, the disease or disorder is Alzheimer's Disease. In some embodiments, the
1121 disease or disorder is multiple sclerosis. In some embodiments, the disease or disorder is
1122 pain. In some embodiments, the disease or disorder is cancer. The pharmaceutical
1123 compositions according to one embodiment are prepared by formulating a compound
1124 disclosed herein in the form of a free compound or a pharmaceutically-acceptable pro-drug,
1125 metabolite, analogue, derivative, solvate or salt, either alone or together with other
1126 pharmaceutical agents, suitable for administration to a subject using carriers, excipients and
1127 additives or auxiliaries. Frequently used carriers or auxiliaries include magnesium carbonate,
1128 titanium dioxide, lactose, mannitol and other sugars, talc, milk protein, gelatin, starch,
1129 vitamins, cellulose and its derivatives, animal and vegetable oils, polyethylene glycols and
1130 solvents, such as sterile water, alcohols, glycerol and polyhydric alcohols. Intravenous
1131 vehicles include fluid and nutrient replenishers.

1132 [0134] Preservatives include antimicrobial, anti-oxidants, chelating agents and inert gases.
1133 Other pharmaceutically acceptable carriers include aqueous solutions, non-toxic excipients,
1134 including salts, preservatives, buffers and the like, as described, for instance, in Remington's
1135 Pharmaceutical Sciences, 15th ed. Easton: Mack Publishing Co. , 1405-1412, 1461-1487
1136 (1975) and The National Formulary XIV., 14th ed. Washington: American Pharmaceutical
1137 Association (1975), the contents of which are hereby incorporated by reference. The pH and

1138 exact concentration of the various components of the pharmaceutical composition are
1139 adjusted according to routine skills in the art. *See e.g.*, Goodman and Gilman (eds.), 1990,
1140 THE PHARMACOLOGICAL BASIS FOR THERAPEUTICS (7th ed.).

1141 [0135] The pharmaceutical compositions are preferably prepared and administered in dose
1142 units. Solid dose units are tablets, capsules and suppositories. For treatment of a subject,
1143 depending on activity of the compound, manner of administration, nature and severity of the
1144 disease or disorder, age and body weight of the subject, different daily doses can be used.

1145 [0136] Under certain circumstances, however, higher or lower daily doses can be
1146 appropriate. The administration of the daily dose can be carried out both by single
1147 administration in the form of an individual dose unit or else several smaller dose units and
1148 also by multiple administrations of subdivided doses at specific intervals.

1149 [0137] The pharmaceutical compositions contemplated herein can be administered locally
1150 or systemically in a therapeutically effective dose. Amounts effective for this use will, of
1151 course, depend on the severity of the disease or disorder and the weight and general state of
1152 the subject. Typically, dosages used *in vitro* can provide useful guidance in the amounts
1153 useful for *in situ* administration of the pharmaceutical composition, and animal models can be
1154 used to determine effective dosages for treatment of particular disorders.

1155 [0138] Various considerations are described, e. g. , in Langer, 1990, *Science*, 249: 1527;
1156 Goodman and Gilman's (eds.), 1990, *Id.*, each of which is herein incorporated by reference
1157 and for all purposes. Dosages for parenteral administration of active pharmaceutical agents
1158 can be converted into corresponding dosages for oral administration by multiplying
1159 parenteral dosages by appropriate conversion factors. As to general applications, the
1160 parenteral dosage in mg/m² times 1.8 = the corresponding oral dosage in milligrams ("mg").
1161 As to oncology applications, the parenteral dosage in mg/m² times 1.6 = the corresponding
1162 oral dosage in mg. An average adult weighs about 70 kg. *See e.g.*, Miller-Keane, 1992,
1163 ENCYCLOPEDIA & DICTIONARY OF MEDICINE, NURSING & ALLIED HEALTH, 5th Ed., (W. B.
1164 Saunders Co.), pp. 1708 and 1651.

1165 [0139] The method by which the compound disclosed herein can be administered for oral
1166 use would be, for example, in a hard gelatin capsule wherein the active ingredient is mixed
1167 with an inert solid diluent, or soft gelatin capsule, wherein the active ingredient is mixed with
1168 a co-solvent mixture, such as PEG 400 containing Tween-20. A compound disclosed herein
1169 can also be administered in the form of a sterile injectable aqueous or oleaginous solution or

1170 suspension. The compound can generally be administered intravenously or as an oral dose of
1171 0.1 ug to 20 mg/kg given, for example, every 3 - 12 hours.

1172 [0140] Formulations for oral use can be in the form of hard gelatin capsules wherein the
1173 active ingredient is mixed with an inert solid diluent, for example, calcium carbonate,
1174 calcium phosphate or kaolin. They can also be in the form of soft gelatin capsules wherein
1175 the active ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin
1176 or olive oil.

1177 [0141] Aqueous suspensions normally contain the active materials in admixture with
1178 excipients suitable for the manufacture of aqueous suspension. Such excipients can be (1)
1179 suspending agent such as sodium carboxymethyl cellulose, methyl cellulose,
1180 hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and
1181 gum acacia; (2) dispersing or wetting agents which can be (a) naturally occurring phosphatide
1182 such as lecithin; (b) a condensation product of an alkylene oxide with a fatty acid, for
1183 example, polyoxyethylene stearate ; (c) a condensation product of ethylene oxide with a long
1184 chain aliphatic alcohol, for example, heptadecaethylenoxycetanol; (d) a condensation product
1185 of ethylene oxide with a partial ester derived from a fatty acid and hexitol such as
1186 polyoxyethylene sorbitol monooleate, or (e) a condensation product of ethylene oxide with a
1187 partial ester derived from fatty acids and hexitol anhydrides, for example polyoxyethylene
1188 sorbitan monooleate.

1189 [0142] The pharmaceutical compositions can be in the form of a sterile injectable aqueous
1190 or oleagenous suspension. This suspension can be formulated according to known methods
1191 using those suitable dispersing or wetting agents and suspending agents that have been
1192 mentioned above. The sterile injectable preparation can also a sterile injectable solution or
1193 suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a
1194 solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed
1195 are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed
1196 oils are conventionally employed as a solvent or suspending medium. For this purpose, any
1197 bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty
1198 acids such as oleic acid find use in the preparation of injectables.

1199 [0143] A compound disclosed herein can also be administered in the form of suppositories
1200 for rectal administration of the drug. These compositions can be prepared by mixing the drug
1201 with a suitable non-irritating excipient that is solid at ordinary temperature but liquid at the

1202 rectal temperature and will therefore melt in the rectum to release the drug. Such materials
1203 include cocoa butter and polyethylene glycols.

1204 [0144] The compounds disclosed herein as used in the methods disclosed herein can also be
1205 administered in the form of liposome delivery systems, such as small unilamellar vesicles,
1206 large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a
1207 variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

1208 [0145] For topical use, creams, ointments, jellies, solutions or suspensions, etc. , containing
1209 the compounds disclosed herein, are employed.

1210 [0146] In addition, some of the compounds disclosed herein can form solvates with water
1211 or common organic solvents. Such solvates are encompassed within the scope of the
1212 methods contemplated herein.

1213 **B. Effective Dosages**

1214 [0147] Pharmaceutical compositions provided herein include compositions wherein the
1215 active ingredient is contained in a therapeutically effective amount, i.e., in an amount
1216 effective to achieve its intended purpose. The actual amount effective for a particular
1217 application will depend, *inter alia*, on the condition being treated. For example, when
1218 administered in methods to treat thrombosis, such compositions will contain an amount of
1219 active ingredient effective to achieve the desired result (e.g. decreasing the extent of the
1220 thrombosis).

1221 [0148] The dosage and frequency (single or multiple doses) of compound administered can
1222 vary depending upon a variety of factors, including route of administration; size, age, sex,
1223 health, body weight, body mass index, and diet of the recipient; nature and extent of
1224 symptoms of the disease being treated (e.g., the disease responsive to inhibition of thrombin);
1225 presence of other diseases or other health-related problems; kind of concurrent treatment; and
1226 complications from any disease or treatment regimen. Other therapeutic regimens or agents
1227 can be used in conjunction with the methods and compounds disclosed herein.

1228 [0149] For any compound described herein, the therapeutically effective amount can be
1229 initially determined from a variety of techniques known in the art, e.g., biochemical
1230 characterization of inhibition of thrombin, cell culture assays, and the like. Target
1231 concentrations will be those concentrations of active compound(s) that are capable of
1232 decreasing thrombin enzymatic activity as measured, for example, using the methods
1233 described.

1234 [0150] Therapeutically effective amounts for use in humans can be determined from animal
1235 models. For example, a dose for humans can be formulated to achieve a concentration that
1236 has been found to be effective in animals. The dosage in humans can be adjusted by
1237 monitoring thrombin inhibition and adjusting the dosage upwards or downwards, as described
1238 above.

1239 [0151] Dosages can be varied depending upon the requirements of the patient and the
1240 compound being employed. The dose administered to a patient, in the context of the methods
1241 disclosed herein, should be sufficient to affect a beneficial therapeutic response in the patient
1242 over time. The size of the dose also will be determined by the existence, nature, and extent of
1243 any adverse side effects. Generally, treatment is initiated with smaller dosages, which are
1244 less than the optimum dose of the compound. Thereafter, the dosage is increased by small
1245 increments until the optimum effect under circumstances is reached. In some embodiments
1246 of a method disclosed herein, the dosage range is 0.001% to 10% w/v. In some
1247 embodiments, the dosage range is 0.1% to 5% w/v.

1248 [0152] Dosage amounts and intervals can be adjusted individually to provide levels of the
1249 administered compound effective for the particular clinical indication being treated. This will
1250 provide a therapeutic regimen that is commensurate with the severity of the individual's
1251 disease state.

1252 [0153] Utilizing the teachings provided herein, an effective prophylactic or therapeutic
1253 treatment regimen can be planned that does not cause substantial toxicity and yet is entirely
1254 effective to treat the clinical symptoms demonstrated by the particular patient. This planning
1255 should involve the careful choice of active compound by considering factors such as
1256 compound potency, relative bioavailability, patient body weight, presence and severity of
1257 adverse side effects, preferred mode of administration, and the toxicity profile of the selected
1258 agent.

1259 [0154] Accordingly, in some embodiments, dosage levels of the compounds disclosed
1260 herein as used in the present methods are of the order of e.g., about 0.1 mg to about 1 mg,
1261 about 1 mg to about 10 mg; about 0.5 mg to about 20 mg per kilogram body weight, an
1262 average adult weighing 70 kilograms, with a preferred dosage range between about 0.1 mg to
1263 about 20 mg per kilogram body weight per day (from about 0.7 mg to about 1.4 gm per
1264 patient per day). The amount of the compound disclosed herein that can be combined with the
1265 carrier materials to produce a single dosage will vary depending upon the host treated and the
1266 particular mode of administration. For example, a formulation intended for oral

1267 administration to humans can contain about 5 ug to 1 g of a compound disclosed herein with
1268 an appropriate and convenient amount of carrier material that can vary from about 5 to 95
1269 percent of the total composition. Dosage unit forms will generally contain between from
1270 about 0.1 mg to 500 mg of a compound disclosed herein.

1271 [0155] It will be understood, however, that the specific dose level for any particular patient
1272 will depend upon a variety of factors including the activity of the specific compound
1273 employed, the age, body weight, general health, sex, diet, time of administration, route of
1274 administration, rate of excretion, drug combination and the severity of the particular disease
1275 undergoing therapy.

1276 **C. Toxicity**

1277 [0156] The ratio between toxicity and therapeutic effect for a particular compound is its
1278 therapeutic index and can be expressed as the ratio between LD₅₀ (the amount of compound
1279 lethal in 50% of the population) and ED₅₀ (the amount of compound effective in 50% of the
1280 population). Compounds that exhibit high therapeutic indices are preferred. Therapeutic
1281 index data obtained from *in vitro* assays, cell culture assays and/or animal studies can be used
1282 in formulating a range of dosages for use in humans. The dosage of such compounds
1283 preferably lies within a range of plasma concentrations that include the ED₅₀ with little or no
1284 toxicity. The dosage can vary within this range depending upon the dosage form employed
1285 and the route of administration utilized. See, e.g. Fingl *et al.*, *In: THE PHARMACOLOGICAL*
1286 *BASIS OF THERAPEUTICS*, Ch.1, p.1, 1975. The exact formulation, route of administration, and
1287 dosage can be chosen by the individual practitioner in view of the patient's condition and the
1288 particular method in which the compound is used. For *in vitro* formulations, the exact
1289 formulation and dosage can be chosen by the individual practitioner in view of the patient's
1290 condition and the particular method in which the compound is used.

1291 **VII. Examples**

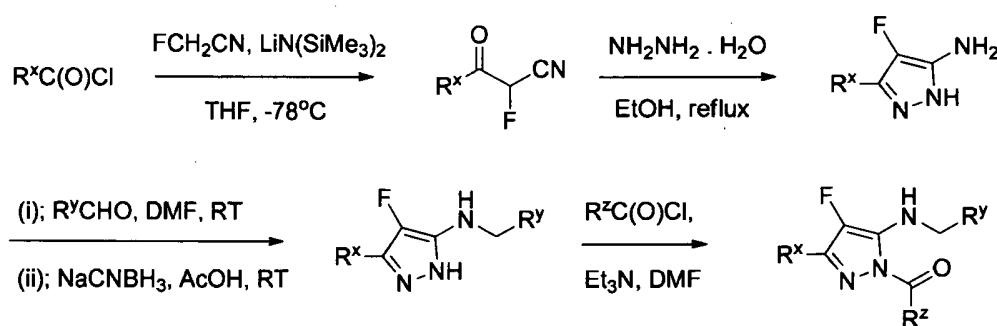
1292 [0157] The examples below are meant to illustrate certain embodiments of the invention and
1293 not to limit the scope of the invention. Abbreviations used herein have their conventional
1294 meaning in the art, unless indicated otherwise. Specific abbreviations include the following:
1295 Å = Ångström; Ac₂O = acetic anhydride; AcOH = acetic acid; aq = aqueous; Bt =
1296 benzotriazole; BOC = *N-tert*-butoxycarbonyl; br = broad; *t*-BuOH = *tert*-butanol; °C = degree
1297 Celsius; d = doublet; DABCO = 1,4-diazabicyclo[2.2.2]octane; DCE = 1,2-dichloroethane;
1298 DCM = dichloromethane; dd = doublet of doublets; DIEA = diethylisopropylamine; DMAP =

1299 4-dimethylaminopyridine; DMF = *N,N*-dimethylformamide; DMSO = dimethylsulfoxide; δ =
 1300 chemical shift (given in ppm, unless otherwise indicated); EDCI = 1-ethyl-3-(3-
 1301 dimethylaminopropyl)carbodiimide; eq = equivalent; Et₂O = diethyl ether; Et₃N =
 1302 triethylamine; EtOAc = ethyl acetate; EtOH = ethanol; g = gram; h (or hr) = hour; HOBr =
 1303 hydroxybenzotriazole; HPLC = high performance liquid chromatography; Hz = Hertz; IC₅₀ =
 1304 inhibitory concentration at 50% inhibition; *J* = coupling constant (given in Hz, unless
 1305 otherwise indicated); LC = liquid chromatography; LHMDS = lithium hexamethyldisilazide;
 1306 m = multiplet; M = molar; [M+H]⁺ = parent mass spectrum peak plus H⁺; MS = mass
 1307 spectrum; ms = molecular sieves; MP = melting point; Me₂NH = dimethylamine; MeOH =
 1308 methanol; mg = milligram; mL = milliliter; mM = millimolar; mmol = millimole; min =
 1309 minute; μ L = microliter; μ M = micromolar; ng = nanogram; nM = nanomolar; NMR =
 1310 nuclear magnetic resonance; ppm = parts per million; q = quartet; R_f = retention factor; RT
 1311 = room temperature; s = singlet; t = triplet; TFA = trifluoroacetic acid; THF =
 1312 tetrahydrofuran; TLC = thin layer chromatography.

1313

1314 *Example 1 - Preparation of Intermediate 1*

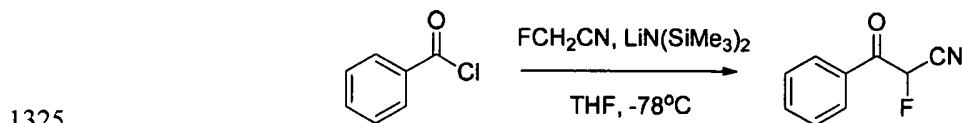
1315 [0158] **General Scheme I.** A synthetic scheme useful for synthesis of compounds
 1316 described herein is disclosed in General Scheme I following, wherein the terms “R^x”, “R^y”,
 1317 and “R^z” are independently hydrogen, substituted or unsubstituted alkyl, substituted or
 1318 unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted
 1319 heterocycloalkyl, substituted or unsubstituted heterocycloalkenyl, substituted or unsubstituted
 1320 aryl, or substituted or unsubstituted heteroaryl, or other groups obvious to those skilled in the
 1321 art.



1322

1323 [0159] The synthesis of Intermediate 1 followed General Procedure 1 following.

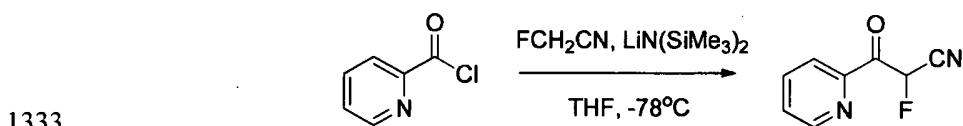
1324 **General Procedure 1**



1326 **Intermediate 1**

1327 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.

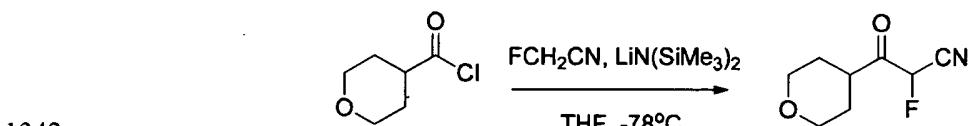
1332 *Example 2 - Preparation of Intermediate 2*



1334 **Intermediate 2**

1335 [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.

1341 *Example 3 - Preparation of Intermediate 3*



1343 **Intermediate 3**

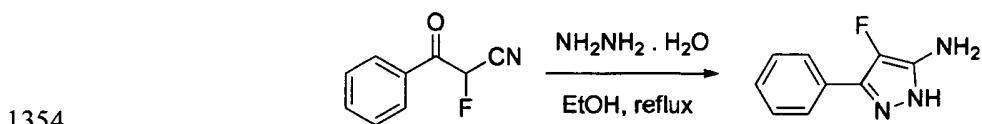
1344 [0161] General Procedure 1 was followed to obtain Intermediate 3. Thus, to a cold (-78°C) solution of pyran-4-carbonyl chloride (5.0 mmol, 1.0 eq) and fluoroacetonitrile (278 μL , 5.0 mmol, 1.0 eq) in dry THF (15 mL) was added a solution of LHMDS in THF (1 M, 10 mL, 10.0 mmol, 2.0 eq). The mixture was allowed to reach room temperature, and 1N HCl

1348 was added dropwise achieving pH 2. The mixture was concentrated under reduced pressure
 1349 to afford intermediate 3 in a form pure enough for the next step.

1350 *Example 4 - Preparation of Intermediate 4*

1351 [0162] The synthesis of Intermediate 4 followed the procedure of General Procedure 2
 1352 following.

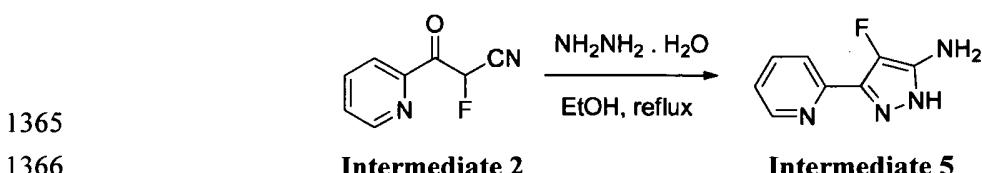
1353 **General Procedure 2**



1355 **Intermediate 1** **Intermediate 4**

1356 [0163] To a solution of intermediate 1 (5.0 mmol) in ethanol (15 mL) was added hydrazine
 1357 monohydrate (582 μ L, 12.0 mmol, 2.4 eq). The reaction was heated at reflux for 18 h. The
 1358 reaction mixture was allowed to cool to room temperature, and the solvent was evaporated
 1359 under reduced pressure. The residue was dissolved in dichloromethane (DCM) and washed
 1360 with water. The organic phase was concentrated to give a crude product that was purified by
 1361 silica column, yielding intermediate 4 as a light brown solid (0.56 g, 55%). 1 H NMR (400
 1362 MHz, DMSO-d₆) δ (ppm): 4.80 (s, 2H), 7.28–7.32 (m, 1H), 7.41–7.45 (m, 2H), 7.62–7.64 (m,
 1363 2H), 11.88 (s, 1H).

1364 *Example 5 - Preparation of Intermediate 5*

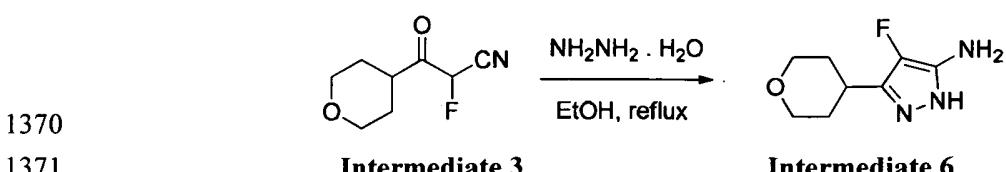


1366 **Intermediate 2** **Intermediate 5**

1367 [0164] General Procedure 2 was followed to convert Intermediate 2 to Intermediate 5

1368

1369 *Example 6 - Preparation of Intermediate 6*



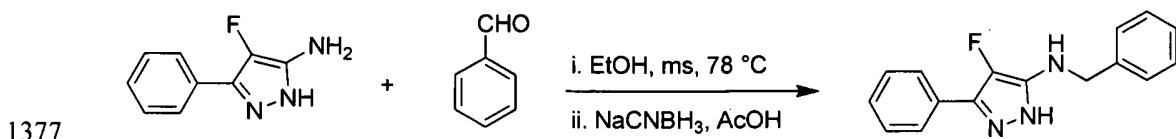
1371 **Intermediate 3** **Intermediate 6**

1372 [0165] General Procedure 2 was followed to convert Intermediate 3 to Intermediate 6

1373 *Example 7 - Preparation of Intermediate 7*

1374 [0166] The synthesis of Intermediate 7 followed the procedure of General Procedure 3
1375 following.

1376 **General Procedure 3**

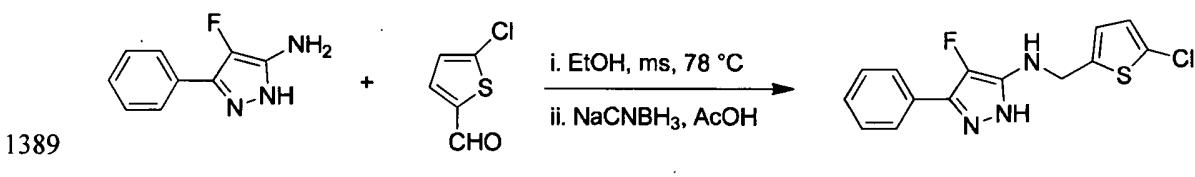


1378 **Intermediate 4**

Intermediate 7

1379 [0167] A solution of intermediate 4 (12.4 mmol) and benzaldehyde (24.8 mmol, 2 eq) in
1380 EtOH (20 mL) with molecular sieves (4 \AA powder) was refluxed for 8 h. Then was added a
1381 catalytic quantity of AcOH, NaCnBH₃ (1.6 g, 24.8 mmol, 2 eq) at 0 °C with stirring for 15 h
1382 at RT. The solvent was distilled off, and the residue was dissolved in EtOAc (200 mL) and
1383 filtered through a Celite® pad to remove inorganic materials. The filtrate was washed with
1384 saturated aqueous NaHCO₃ (2 \times 20 mL), water (20 mL), brine (20 mL), dried over Na₂SO₄,
1385 filtered and concentrated *in vacuo*. The resultant compound was purified by column
1386 chromatography over silica gel (100-200 mesh) by using a solvent gradient of 0-10% MeOH-
1387 CHCl₃ as the eluent to afford Intermediate 7.

1388 *Example 8 - Preparation of Intermediate 8*



1390 **Intermediate 4**

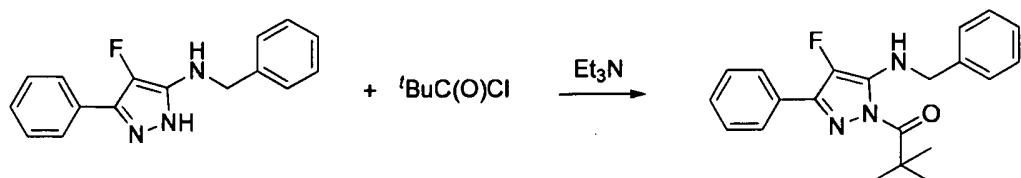
Intermediate 8

1391 [0168] General Procedure 3 was followed to convert Intermediate 4 to Intermediate 8

1392 *Example 9 - Preparation of Compound 23*

1393 [0169] The synthesis of Compound 23 followed the procedure of General Procedure 4
1394 following.

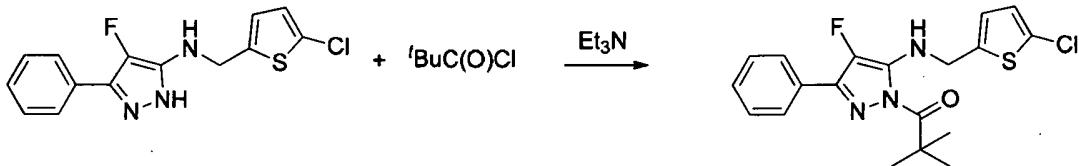
1395

1396 **General Procedure 4**

1397

1398 **Intermediate 7****Compound 23**

1399 [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 \times 5 mL), saturated aqueous NaHCO₃ (5 mL), brine (5 mL), dried over Na₂SO₄, 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; ¹H NMR: (DMSO-d₆) 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]⁺.

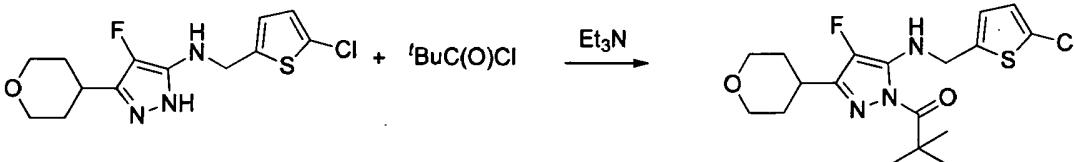
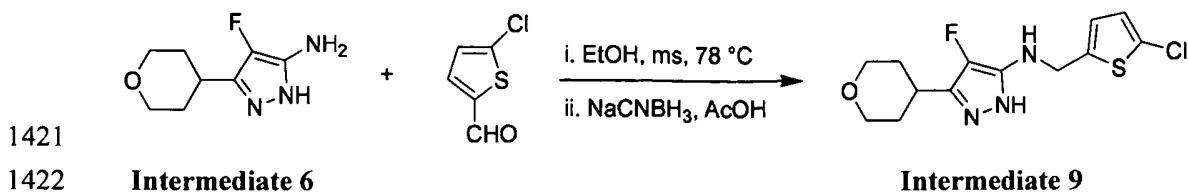
1408 *Example 10 - Preparation of Compound 10*

1409

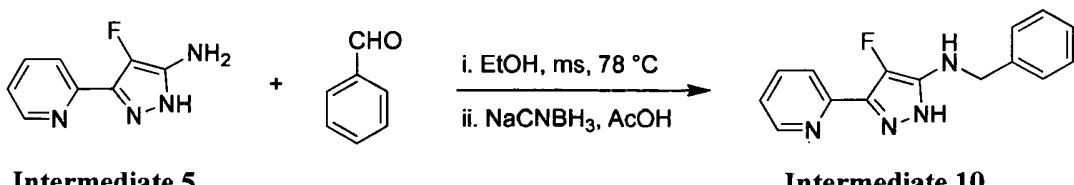
1410 **Intermediate 8****Compound 10**

1411 [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 \times 5 mL), saturated aqueous NaHCO₃ (5 mL), brine (5 mL), dried over Na₂SO₄, 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%). ¹H NMR: (CDCl₃) 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]⁺.

1420 *Example 11 - Preparation of Intermediate 9*

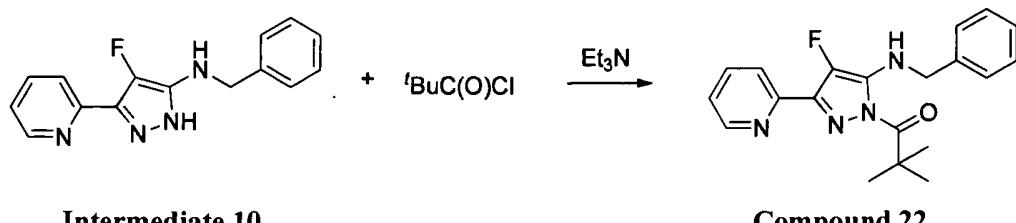


Compound 3



Intermediate 10

1441 *Example 14 - Preparation of Compound 22*



1442

1443 **Intermediate 10**

Compound 22

1444 [0175] General Procedure 4 was followed to convert Intermediate 10 to Compound 22.
 1445 Thus, pivaloyl chloride was added to a solution of Intermediate 10 in triethylamine (3 mL) at
 1446 RT and stirred for 5 h. The reaction mixture was diluted with water (5 mL) and extracted with
 1447 EtOAc (20 mL). The organic layer washed with water (2 × 5 mL), saturated aqueous
 1448 NaHCO₃ (5 mL), brine (5 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The
 1449 crude compound was purified by column chromatography over silica gel (100-200 mesh) by
 1450 using a gradient mixture of 0-30% EtOAc-hexane as the eluent to afford Compound 22
 1451 (40%). ¹H NMR: (DMSO-d₆) δ 8.6 (m, 1H), 7.83 – 7.91 (m, 2H), 7.55 (m, 1H), 7.25 – 7.45
 1452 (m, 6H), 4.52 - 4.54 (m, 2H), 1.48 (s, 9H); MS: 353.03 [M + H]⁺.

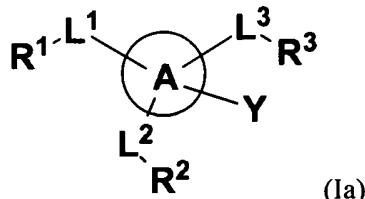
1453

1454 [0176] The contents of all references, patents, and published applications cited herein are
 1455 hereby incorporated by reference in their entirety and for all purposes.

1456 [0177] While the invention has been described in detail with reference to certain preferred
 1457 embodiments thereof, it will be understood that modifications and variations are within the
 1458 spirit and scope of that which is described and claimed.

1459 WHAT IS CLAIMED IS:

1460 1. A compound with structure of Formula (Ia):



1461

1462 or pharmaceutically acceptable salt, ester, solvate, or prodrug thereof;

1463 wherein

1464 Ring A is substituted or unsubstituted pyrazolyl;

1465 L^1 and L^3 are independently a bond, substituted or unsubstituted alkylene, substituted
1466 or unsubstituted heteroalkylene, -S-, -SO-, -SO₂-, -O-, -NHSO₂-, or -NR⁴-;

1467 L^2 is absent, a bond, substituted or unsubstituted alkylene, substituted or unsubstituted
1468 heteroalkylene, -S-, -SO-, -SO₂-, -O-, -NHSO₂-, or -NR⁴-;

1469 R^1 and R^3 are independently hydrogen, halogen, substituted or unsubstituted alkyl,
1470 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
1471 unsubstituted cycloalkenyl, substituted or unsubstituted heterocycloalkyl, substituted or
1472 unsubstituted heterocycloalkenyl, substituted or unsubstituted aryl, substituted or
1473 unsubstituted fused ring aryl, or substituted or unsubstituted heteroaryl;

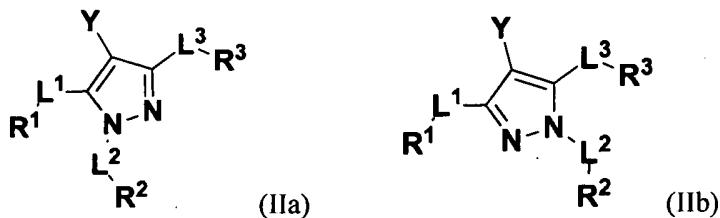
1474 R^2 is absent, hydrogen, halogen, substituted or unsubstituted alkyl, substituted or
1475 unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted
1476 cycloalkenyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted
1477 heterocycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted fused ring
1478 aryl, or substituted or unsubstituted heteroaryl, provided that when L^2 is absent, R^2 is absent;

1479 R^4 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted
1480 heteroalkyl, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene,
1481 substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl,
1482 substituted or unsubstituted aryl, substituted or unsubstituted cycloalkenyl, substituted or
1483 unsubstituted heterocycloalkenyl, and substituted or unsubstituted fused ring aryl or
1484 substituted or unsubstituted heteroaryl; and

1485 Y is a halogen.

1486 2. The compound according to claim 1, wherein L^2 and R^2 are absent.

1487 3. The compound according to claim 1, with structure of Formula (IIa) or
1488 Formula (IIb):



1490 4. The compound according to claim 3, with structure of Formula (IIa), wherein
1491 L^3 is a bond, or substituted or unsubstituted alkylene, and R^3 is substituted or unsubstituted
1492 aryl, substituted or unsubstituted fused ring aryl, substituted or unsubstituted
1493 heterocycloalkyl, or substituted or unsubstituted heteroaryl, and Y is fluorine.

1494 5. The compound according to claim 3, with structure of Formula (IIa), wherein
1495 L^3 is $-C(O)O-$, R^3 is substituted or unsubstituted alkyl, and Y is fluorine.

1496 6. The compound according to claim 3, with structure of Formula (IIa), wherein
1497 L^3 is $-C(O)NR^5-$, R^5 is hydrogen or alkyl, R^3 is substituted or unsubstituted alkyl, or
1498 substituted or unsubstituted aryl, and Y is fluorine.

1499 7. The compound according to claim 4, wherein R³ is substituted or unsubstituted
1500 phenyl.

1501 8. The compound according to claim 4, wherein said heteroaryl is pyridyl,
1502 pyridazinyl, pyrimidinyl, thienyl, or furyl.

1503 9. The compound according to claim 8, wherein R^3 is chloro-substituted thienyl.

1504 10. The compound according to claim 4, wherein said heterocycloalkyl is
1505 morpholiny, oxanyl, or oxetanyl.

11. The compound according to claim 4, wherein said fused ring aryl is
benzodioxinyl or naphthyl.

1508 12. The compound according to any of claims 4 to 11, wherein L^1 is a bond, $-S-$,
1509 $-NR^4-$, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene,
1510 and R^1 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl,
1511 substituted or unsubstituted fused ring aryl, substituted or unsubstituted heteroaryl, or
1512 substituted or unsubstituted heterocycloalkyl.

13. The compound according to claim 12, wherein said heteroaryl is pyridyl, pyridazinyl, pyrimidinyl, thienyl, or furyl.

14. The compound according to claim 13, wherein R¹ is chloro-substituted thiaryl.

1516 15. The compound according to claim 12, wherein said heterocycloalkyl is
1517 morpholiny, oxanyl, or oxetanyl.

1518 16. The compound according to claim 12, wherein said fused ring aryl is
1519 benzodioxinyl or naphthyl.

1520 17. The compound according to claim 12, wherein R¹ is substituted or
1521 unsubstituted phenyl.

1522 18. The compound according to claim 4, wherein L² is a bond, and R² is
1523 hydrogen.

1524 19. The compound according to claim 4, wherein L² is substituted or unsubstituted
1525 alkylene or -C(O)-, and R² is hydrogen, substituted or unsubstituted alkyl, substituted or
1526 unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted
1527 cycloalkenyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted
1528 heterocycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted fused ring
1529 aryl, or substituted or unsubstituted heteroaryl.

1530 20. The compound according to claim 19, wherein said heteroaryl is pyridyl,
1531 pyridazinyl, pyrimidinyl, thienyl, or furyl.

1532 21. The compound according to claim 19, wherein R² is substituted or
1533 unsubstituted alkyl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted
1534 heterocycloalkyl.

1535 22. The compound according to claim 21, wherein said heterocycloalkyl is
1536 morpholiny, oxanyl, or oxetanyl.

1537 23. The compound according to claim 19, wherein said fused ring aryl is
1538 benzodioxinyl or naphthyl.

1539 24. The compound according to claim 19, wherein R² is substituted or
1540 unsubstituted phenyl.

1541 25. The compound according to claim 3, with structure of Formula (IIb), wherein
1542 L³ is a bond, or substituted or unsubstituted alkylene, R³ is substituted or unsubstituted aryl,
1543 substituted or unsubstituted fused ring aryl, substituted or unsubstituted heterocycloalkyl, or
1544 substituted or unsubstituted heteroaryl, and Y is fluorine.

1545 26. The compound according to claim 3, with structure of Formula (IIb), wherein
1546 L³ is -C(O)O-, R³ is substituted or unsubstituted alkyl, and Y is fluorine.

1547 27. The compound according to claim 3, with structure of Formula (IIb), wherein
1548 L³ is -C(O)NR⁵-, R⁵ is hydrogen or alkyl, R³ is substituted or unsubstituted alkyl, or
1549 substituted or unsubstituted aryl, and Y is fluorine.

1550 28. The compound according to claim 25, wherein R^3 is substituted or
1551 unsubstituted phenyl.

1552 29. The compound according to claim 25, wherein said heteroaryl is pyridyl,
1553 pyridazinyl, pyrimidinyl, thienyl, or furyl.

1554 30. The compound according to claim 29, wherein R^3 is chloro-substituted thienyl.

1555 31. The compound according to claim 25, wherein said heterocycloalkyl is
1556 morpholinyl, oxanyl, or oxetanyl.

1557 32. The compound according to claim 25, wherein said fused ring aryl is
1558 benzodioxinyl or naphthyl.

1559 33. The compound according to any of claims 25 to 32, wherein L^1 is a bond, -S-,
1560 -NR⁴-, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene,
1561 and R^1 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl,
1562 substituted or unsubstituted fused ring aryl, substituted or unsubstituted heteroaryl, or
1563 substituted or unsubstituted heterocycloalkyl.

1564 34. The compound according to claim 33, wherein said heteroaryl is pyridyl,
1565 pyridazinyl, pyrimidinyl, thienyl, or furyl.

1566 35. The compound according to claim 34, wherein R^1 is chloro-substituted thienyl.

1567 36. The compound according to claim 33, wherein said heterocycloalkyl is
1568 morpholinyl, oxanyl, or oxetanyl.

1569 37. The compound according to claim 33, wherein said fused ring aryl is
1570 benzodioxinyl or naphthyl.

1571 38. The compound according to claim 33, wherein R^1 is substituted or
1572 unsubstituted phenyl.

1573 39. The compound according to claim 25, wherein L^2 is a bond, and R^2 is
1574 hydrogen.

1575 40. The compound according to claim 25, wherein L^2 is substituted or
1576 unsubstituted alkylene or -C(O)-, and R^2 is hydrogen, substituted or unsubstituted alkyl,
1577 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
1578 unsubstituted cycloalkenyl, substituted or unsubstituted heterocycloalkyl, substituted or
1579 unsubstituted heterocycloalkenyl, substituted or unsubstituted aryl, substituted or
1580 unsubstituted fused ring aryl, or substituted or unsubstituted heteroaryl.

1581 41. The compound according to claim 40, wherein said heteroaryl is pyridyl,
1582 pyridazinyl, pyrimidinyl, thienyl, or furyl.

1583 42. The compound according to claim 40, wherein R² is substituted or
1584 unsubstituted alkyl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted
1585 heterocycloalkyl.

1586 43. The compound according to claim 42, wherein said heterocycloalkyl is
1587 morpholinyl, oxanyl, or oxetanyl.

1588 44. The compound according to claim 40, wherein said fused ring aryl is
1589 benzodioxinyl or naphthyl.

1590 45. The compound according to claim 40, wherein R² is substituted or
1591 unsubstituted phenyl.

1592 46. The compound according to any of claims 1 to 45 as set forth in Table A.

1593 47. A pharmaceutical composition comprising a compound according to any of
1594 claims 1 to 45, or a compound as set forth in Table A, and a pharmaceutically acceptable
1595 excipient.

1596 48. A method for treating a disease or disorder in a subject, comprising
1597 administering a compound according to any of claims 1 to 46 or a pharmaceutical
1598 composition according to claim 47, to a subject in need thereof in an amount effective to treat
1599 said disease or disorder.

1600 49. The method according to claim 48, wherein said disease or disorder is a
1601 thrombotic disorder.

1602 50. The method according to claim 49, wherein said thrombotic disorder is acute
1603 coronary syndrome, venous thromboembolism, arterial thromboembolism or cardiogenic
1604 thromboembolism.

1605 51. The method according to claim 48, wherein said disease or disorder is fibrosis.

1606 52. The method according to claim 48, wherein said disease or disorder is
1607 Alzheimer's Disease.

1608 53. The method according to claim 48, wherein said disease or disorder is multiple
1609 sclerosis.

1610 54. The method according to claim 48, wherein said disease or disorder is pain.

1611 55. The method according to claim 48, wherein said disease or disorder is cancer.

1612 56. A method for preventing a disease or disorder in a subject, comprising
1613 administering a compound according to any of claims 1 to 46 or a pharmaceutical
1614 composition according to claim 47, to a subject in need thereof in an amount effective to
1615 prevent said disease or disorder.

1616 57. The method according to claim 56, wherein said disease or disorder is a
1617 thrombotic disorder.

1618 58. The method according to claim 56, wherein said thrombotic disorder is acute
1619 coronary syndrome, venous thromboembolism, arterial thromboembolism or cardiogenic
1620 thromboembolism.

1621 59. The method according to claim 56, wherein said thrombotic disorder is
1622 disseminated intravascular coagulation.

1623 60. The method according to claim 56, wherein said thrombotic disorder involves
1624 the presence or the potential formation of a blood clot thrombus.

摘要

本发明尤其提供了可用于抑制凝血酶的多取代芳族化合物，所述化合物包括被取代的吡唑基。另外提供了药物组合物。另外提供了治疗和预防疾病或病症的方法，所述疾病或病症顺从于通过抑制凝血酶进行治疗或预防。