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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 pyrazoli. 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**

## 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

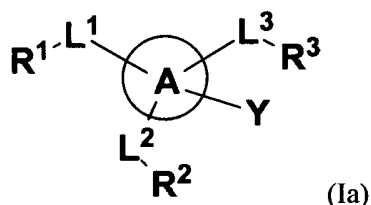
32 in a drive to discover and develop orally available drugs with wide therapeutic windows for  
33 safety and efficacy.

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.

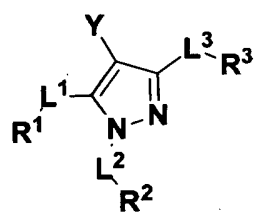
#### 47 BRIEF SUMMARY OF THE INVENTION

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

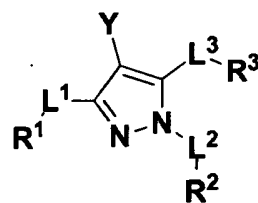


51 or pharmaceutically acceptable salt, ester, solvate, or prodrug thereof; wherein Ring A can be  
52 substituted or unsubstituted pyrazolyl; L<sup>1</sup> and L<sup>3</sup> can be independently a bond, substituted or  
53 unsubstituted alkylene, substituted or unsubstituted heteroalkylene, -S-, -SO-, -SO<sub>2</sub>-, -O-,  
54 -NHSO<sub>2</sub>-, or -NR<sup>4</sup>-; L<sup>2</sup> can be absent, a bond, substituted or unsubstituted alkylene,  
55 substituted or unsubstituted heteroalkylene, -S-, -SO-, -SO<sub>2</sub>-, -O-, -NHSO<sub>2</sub>-, or -NR<sup>4</sup>-; R<sup>1</sup>  
56 and R<sup>3</sup> 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; R<sup>2</sup> 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):



(IIa)



(IIb)

74  
 75 [0009] In some embodiments where the compound can have the structure of Formula (IIa),  
 76  $L^3$  can be a bond, or substituted or unsubstituted alkylene, and  $R^3$  can be substituted or  
 77 unsubstituted aryl, substituted or unsubstituted fused ring aryl, substituted or unsubstituted  
 78 heterocycloalkyl, or substituted or unsubstituted heteroaryl, and Y can be fluorine. In some  
 79 embodiments where the compound can have the structure of Formula (IIa),  $L^3$  can be  
 80  $-C(O)O-$ ,  $R^3$  can be substituted or unsubstituted alkyl, and Y can be fluorine. In some  
 81 embodiments where the compound can have the structure of Formula (IIa),  $L^3$  can be  
 82  $-C(O)NR^5$ ,  $R^5$  can be hydrogen or alkyl,  $R^3$  can be substituted or unsubstituted alkyl, or  
 83 substituted or unsubstituted aryl, and Y can be fluorine. In some embodiments,  $R^3$  can be  
 84 substituted or unsubstituted phenyl. In some embodiments, the heteroaryl can be pyridyl,  
 85 pyridazinyl, pyrimidinyl, thienyl, or furyl. In some embodiments,  $R^3$  can be chloro-  
 86 substituted thienyl. In some embodiments, the heterocycloalkyl can be morpholinyl, oxanyl,  
 87 or oxetanyl. In some embodiments, the fused ring aryl can be benzodioxinyl or naphthyl. In  
 88 some embodiments,  $L^1$  can be a bond,  $-S-$ ,  $-NR^4$ , substituted or unsubstituted alkylene, or  
 89 substituted or unsubstituted heteroalkylene, and  $R^1$  can be hydrogen, substituted or  
 90 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,  $R^1$  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,  $R^1$  can be substituted or  
96 unsubstituted phenyl. In some embodiments,  $L^2$  can be a bond, and  $R^2$  can be hydrogen. In  
97 some embodiments,  $L^2$  can be substituted or unsubstituted alkylene or  $-C(O)-$ , and  $R^2$  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,  $R^2$  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,  $R^2$  can be substituted or unsubstituted phenyl.

108 **[0010]** In some embodiments where the compound can have the structure of Formula (IIb),  
109  $L^3$  can be a bond, or substituted or unsubstituted alkylene,  $R^3$  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),  $L^3$  can be  
113  $-C(O)O-$ ,  $R^3$  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),  $L^3$  can be  
115  $-C(O)NR^5-$ ,  $R^5$  can be hydrogen or alkyl,  $R^3$  can be substituted or unsubstituted alkyl, or  
116 substituted or unsubstituted aryl, and Y can be fluorine. In some embodiments,  $R^3$  can be  
117 substituted or unsubstituted phenyl. In some embodiments, the heteroaryl can be pyridyl,  
118 pyridazinyl, pyrimidinyl, thienyl, or furyl. In some embodiments,  $R^3$  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,  $L^1$  can be a bond,  $-S-$ ,  $-NR^4-$ , substituted or unsubstituted alkylene, or  
122 substituted or unsubstituted heteroalkylene, and  $R^1$  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,  $R^1$  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,  $R^1$  can be substituted or  
129 unsubstituted phenyl. In some embodiments,  $L^2$  can be a bond, and  $R^2$  can be hydrogen. In  
130 some embodiments,  $L^2$  can be substituted or unsubstituted alkylene or  $-C(O)-$ , and  $R^2$  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,  $R^2$  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,  $R^2$  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., -CH<sub>2</sub>O- is equivalent to  
172 -OCH<sub>2</sub>-.

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(C<sub>1</sub>-C<sub>4</sub>)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., C<sub>1</sub>-C<sub>10</sub> 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-butylnyl, and

the higher homologs and isomers. Accordingly, the term "alkyl" can refer to C<sub>1</sub>-C<sub>16</sub> straight chain saturated, C<sub>1</sub>-C<sub>16</sub> branched saturated, C<sub>3</sub>-C<sub>8</sub> cyclic saturated and C<sub>1</sub>-C<sub>16</sub> straight chain or branched saturated aliphatic hydrocarbon groups substituted with C<sub>3</sub>-C<sub>8</sub> cyclic saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, this definition shall include but is not limited to methyl (Me), ethyl (Et), propyl (Pr), butyl (Bu), pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, isopropyl (i-Pr), isobutyl (i-Bu), tert-butyl (t-Bu), sec-butyl (s-Bu), isopentyl, neopentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopropylmethyl, and the like.

[0018] The term "alkylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkyl, as exemplified, but not limited by, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred in the compounds disclosed herein. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms.

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

[0020] Similarly, the term "heteroalkylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from heteroalkyl, as exemplified, but not limited by, -CH<sub>2</sub>-CH<sub>2</sub>-S-CH<sub>2</sub>-CH<sub>2</sub>- and -CH<sub>2</sub>-S-CH<sub>2</sub>-CH<sub>2</sub>-NH-CH<sub>2</sub>-. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula -C(O)<sub>2</sub>R'- represents both -C(O)<sub>2</sub>R'- and -R'C(O)<sub>2</sub>-. 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 -SO<sub>2</sub>R'. 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-piperidiny, 2-piperidiny, 3-  
237 piperidiny, 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 C<sub>2</sub>-C<sub>16</sub> straight chain unsaturated, C<sub>2</sub>-C<sub>11</sub> branched  
242 unsaturated, C<sub>5</sub>-C<sub>8</sub> unsaturated cyclic, and C<sub>2</sub>-C<sub>16</sub> straight chain or branched unsaturated  
243 aliphatic hydrocarbon groups substituted with C<sub>3</sub>-C<sub>8</sub> 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', -CO<sub>2</sub>R', -CONR'R'', -OC(O)NR'R'', -NR''C(O)R',  
 267 -NR'-C(O)NR''R''', -NR''C(O)<sub>2</sub>R', -NR-C(NR'R'')=NR''', -S(O)R', -S(O)<sub>2</sub>R', -S(O)<sub>2</sub>NR'R'',  
 268 -NRSO<sub>2</sub>R', -CN, and -NO<sub>2</sub> 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 halogens), 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., -CF<sub>3</sub> and -CH<sub>2</sub>CF<sub>3</sub>) and acyl (e.g.,  
 281 -C(O)CH<sub>3</sub>, -C(O)CF<sub>3</sub>, -C(O)CH<sub>2</sub>OCH<sub>3</sub>, 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', -CO<sub>2</sub>R', -CONR'R'', -OC(O)NR'R'', -NR''C(O)R',  
 285 -NR'-C(O)NR''R''', -NR''C(O)<sub>2</sub>R', -NR-C(NR'R'')=NR''', -S(O)R', -S(O)<sub>2</sub>R', -S(O)<sub>2</sub>NR'R'',  
 286 -NRSO<sub>2</sub>R', -CN, -NO<sub>2</sub>, -R', -N<sub>3</sub>, -CH(Ph)<sub>2</sub>, fluoro(C<sub>1</sub>-C<sub>4</sub>)alkoxy, and fluoro(C<sub>1</sub>-C<sub>4</sub>)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')<sub>q</sub>-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-(CH<sub>2</sub>)<sub>r</sub>-B-, wherein A and B are independently -CRR'-, -O-,  
309 -NR-, -S-, -S(O)-, -S(O)<sub>2</sub>-, -S(O)<sub>2</sub>NR'-, 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')<sub>s</sub>-X'-(C''R''')<sub>d</sub>-, where s  
313 and d are independently integers of from 0 to 3, and X' is -O-, -NR'-, -S-, -S(O)-, -S(O)<sub>2</sub>-, or  
314 -S(O)<sub>2</sub>NR'-. 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)  
321 represents an alkyl group as defined above having the indicated number of carbon atoms  
322 attached through an oxygen bridge (-O-).
- 323 [0032] The term "alkylthio" (e.g. methylthio, ethylthio, propylthio, cyclohexylthio and the  
324 like) represents an alkyl group as defined above having the indicated number of carbon atoms  
325 attached through a sulfur bridge (-S-).
- 326 [0033] The term "alkylamino" represents one or two alkyl groups as defined above having  
327 the indicated number of carbon atoms attached through an amine bridge. The two alkyl  
328 groups can be taken together with the nitrogen to which they are attached forming a cyclic  
329 system containing 3 to 8 carbon atoms with or without one C<sub>1</sub>-C<sub>16</sub>alkyl, arylC<sub>0</sub>-C<sub>16</sub>alkyl, or  
330 C<sub>0</sub>-C<sub>16</sub>alkylaryl substituent.
- 331 [0034] The term "alkylaminoalkyl" represents an alkylamino group attached through an  
332 alkyl group as defined above having the indicated number of carbon atoms.
- 333 [0035] The term "alkyloxy(alkyl)amino" (e.g. methoxy(methyl)amine,  
334 ethoxy(propyl)amine) represents an alkyloxy group as defined above attached through an  
335 amino group, the amino group itself having an alkyl substituent.
- 336 [0036] The term "alkylcarbonyl" (e.g. cyclooctylcarbonyl, pentylcarbonyl, 3-  
337 hexylcarbonyl) represents an alkyl group as defined above having the indicated number of  
338 carbon atoms attached through a carbonyl group.
- 339 [0037] The term "alkylcarboxy" (e.g. heptylcarboxy, cyclopropylcarboxy, 3-  
340 pentenylcarboxy) represents an alkylcarbonyl group as defined above wherein the carbonyl is  
341 in turn attached through an oxygen.
- 342 [0038] The term "alkylcarboxyalkyl" represents an alkylcarboxy group attached through an  
343 alkyl group as defined above having the indicated number of carbon atoms.
- 344 [0039] The term "alkylcarbonylamino" (e.g. hexylcarbonylamino,  
345 cyclopentylcarbonylaminomethyl, methylcarbonylaminophenyl) represents an alkylcarbonyl  
346 group as defined above wherein the carbonyl is in turn attached through the nitrogen atom of  
347 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,  
350 hydrocarbon substituent, which can be a single ring or multiple rings (preferably from 1 to 3  
351 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-quinoxalyl, 5-  
 371 quinoxalyl, 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, C<sub>1-16</sub>alkyl, arylC<sub>1-16</sub>  
 380 alkyl, C<sub>0-16</sub>alkyloxyC<sub>0-16</sub>alkyl, arylC<sub>0-16</sub>alkyloxyC<sub>0-16</sub>alkyl, C<sub>0-16</sub>alkylthioC<sub>0-16</sub>alkyl,  
 381 arylC<sub>0-16</sub>alkylthioC<sub>0-16</sub>alkyl, C<sub>0-16</sub>alkylaminoC<sub>0-16</sub>alkyl, arylC<sub>0-16</sub>alkylaminoC<sub>0-16</sub>alkyl,  
 382 di(arylC<sub>1-16</sub>alkyl)aminoC<sub>0-16</sub>alkyl, C<sub>1-16</sub>alkylcarbonylC<sub>0-16</sub>alkyl, arylC<sub>1-16</sub>alkylcarbonylC<sub>0-16</sub>  
 383 alkyl, C<sub>1-16</sub>alkylcarboxyC<sub>0-16</sub>alkyl, arylC<sub>1-16</sub>alkylcarboxyC<sub>0-16</sub>alkyl, C<sub>1-16</sub>  
 384 alkylcarbonylaminoC<sub>0-16</sub>alkyl, arylC<sub>1-16</sub>alkylcarbonylaminoC<sub>0-16</sub>alkyl, -C<sub>0-16</sub>alkylCOOR<sub>4</sub>, -  
 385 C<sub>0-16</sub>alkylCONR<sub>5</sub>R<sub>6</sub> wherein R<sub>4</sub>, R<sub>5</sub> and R<sub>6</sub> are independently selected from hydrogen, C<sub>1-</sub>

386 C<sub>11</sub>alkyl, arylC<sub>0</sub>-C<sub>11</sub>alkyl, or R<sub>5</sub> and R<sub>6</sub> 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<sub>1</sub>-  
388 <sub>16</sub>alkyl, arylC<sub>0</sub>-C<sub>16</sub>alkyl, or C<sub>0</sub>-Cl<sub>16</sub>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., phenoxymethyl, 2-pyridyloxymethyl, 3-(1-  
396 naphthyloxy)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<sub>2</sub>)-R', where R' is an alkyl group as defined above. R' can have a specified number of  
404 carbons (e.g., "C<sub>1</sub>-C<sub>4</sub> 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<sup>1</sup>, R<sup>2</sup> or R<sup>3</sup> described herein, e.g., Formula (Ia) and generically referred to as R<sup>n</sup>, 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<sup>n</sup> or -NHCO-R<sup>n</sup>), thioamido (-CSNH-R<sup>n</sup> or -NHCS-R<sup>n</sup>),  
414 carboxyl (-CO<sub>2</sub>-R<sup>n</sup> or -OCOR<sup>n</sup>), carbonyl (-CO-R<sup>n</sup>), urea (-NHCONH-R<sup>n</sup>), thiourea  
415 (-NHCSNH-R<sup>n</sup>), sulfonamido (-NHSO<sub>2</sub>-R<sup>n</sup> or -SO<sub>2</sub>NH-R<sup>n</sup>), ether (-O-R<sup>n</sup>), sulfonyl  
416 (-SO<sub>2</sub>-R<sup>n</sup>), sulfoxyl (-SO-R<sup>n</sup>), carbamoyl (-NHCO<sub>2</sub>-R<sup>n</sup> or -OCONH-R<sup>n</sup>), or amino (-NHR<sup>n</sup>)  
417 linking moieties.

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

- 420 (A) -OH, -NH<sub>2</sub>, -SH, -CN, -CF<sub>3</sub>, -NO<sub>2</sub>, 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, -NH<sub>2</sub>, -SH, -CN, -CF<sub>3</sub>, -NO<sub>2</sub>, 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, -NH<sub>2</sub>, -SH, -CN, -CF<sub>3</sub>, -NO<sub>2</sub>, 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, -NH<sub>2</sub>, -SH, -CN, -CF<sub>3</sub>,  
435 -NO<sub>2</sub>, halogen, -COOH, unsubstituted alkyl, unsubstituted heteroalkyl,  
436 unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, and  
437 unsubstituted heteroaryl.

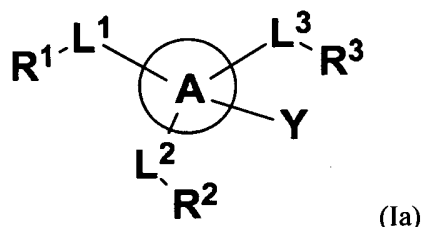
438 [0049] A “size-limited substituent” or “size-limited substituent group,” as used herein,  
439 means a group selected from all of the substituents described above for a “substituent group,”  
440 wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C<sub>1</sub>-C<sub>20</sub> 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 C<sub>4</sub>-C<sub>8</sub> 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 C<sub>1</sub>-C<sub>8</sub> 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 C<sub>5</sub>-  
450 C<sub>7</sub> 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 or pharmaceutically acceptable salt, ester, solvate, or prodrug thereof. Ring A is substituted  
 457 or unsubstituted pyrazolyl.  $L^1$  and  $L^3$  are independently a bond, substituted or unsubstituted  
 458 alkylene, substituted or unsubstituted heteroalkylene, -S-, -SO-, -SO<sub>2</sub>-, -O-, -NHSO<sub>2</sub>-, or -  
 459 NR<sup>4</sup>-.  $L^2$  is absent, a bond, a hydrogen, substituted or unsubstituted alkylene, substituted or  
 460 unsubstituted heteroalkylene, -S-, -SO-, -SO<sub>2</sub>-, -O-, -NHSO<sub>2</sub>-, or -NR<sup>4</sup>-.  $R^1$  and  $R^3$  are  
 461 independently hydrogen, halogen, substituted or unsubstituted alkyl, substituted or  
 462 unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted  
 463 cycloalkenyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted  
 464 heterocycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted fused ring  
 465 aryl, or substituted or unsubstituted heteroaryl.  $R^2$  is absent, hydrogen, halogen, substituted or  
 466 unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted  
 467 cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted  
 468 heterocycloalkyl, substituted or unsubstituted heterocycloalkenyl, substituted or unsubstituted  
 469 aryl, substituted or unsubstituted fused ring aryl, or substituted or unsubstituted heteroaryl.  
 470  $R^4$  is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl,  
 471 substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted  
 472 or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or  
 473 unsubstituted aryl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted  
 474 heterocycloalkenyl, substituted or unsubstituted fused ring aryl, or substituted or  
 475 unsubstituted heteroaryl. Y is a halogen. . In some embodiments,  $R^2$  can be absent provided  
 476  $L^2$  is also absent.

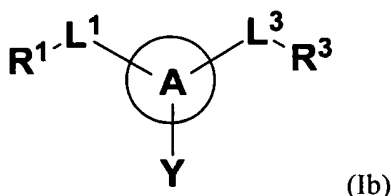
478 [0053] In some embodiments, the compound is a pharmaceutically acceptable salt, ester,  
 479 solvate, or prodrug of a compound of Formula (Ia). In some embodiments, the compound is  
 480 not an ester, not a solvate, and not a prodrug.



481 [0054] Further to any embodiment above, in some embodiments  $L^1$  is -S-, -NR<sup>4</sup>-,  
 482 substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene, where R<sup>4</sup>  
 483 is as described above in regards to formula Ia, and R<sup>1</sup> 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, R<sup>3</sup> is substituted or unsubstituted aryl. In some embodiments, R<sup>3</sup> is  
 487 unsubstituted aryl. In some embodiments, R<sup>3</sup> is unsubstituted phenyl. In some embodiments,  
 488 L<sup>2</sup> is a bond. In some embodiments, L<sup>2</sup> is a bond and R<sup>2</sup> is hydrogen. Y is fluorine.

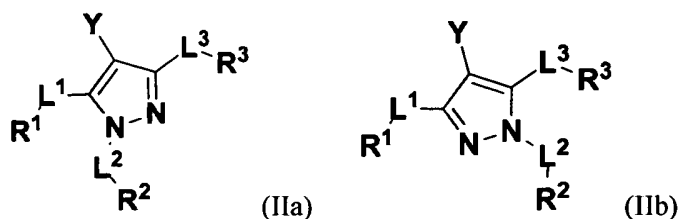
489 [0055] Further to any embodiment above, in some embodiments L<sup>2</sup> is -C(O)-, and R<sup>2</sup> is  
 490 substituted or unsubstituted alkyl, hydrogen, substituted or unsubstituted heteroalkyl,  
 491 substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted  
 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<sup>2</sup> is unsubstituted aryl. In some  
 496 embodiments, R<sup>2</sup> is unsubstituted phenyl.

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



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, R<sup>1</sup> is an unsubstituted pyridyl. In some  
540 embodiments, R<sup>1</sup> is an unsubstituted pyridazinyl. In some embodiments, R<sup>1</sup> is an unsubstituted  
541 pyrimidinyl. In some embodiments, R<sup>1</sup> is an unsubstituted thienyl. In some embodiments, R<sup>1</sup>  
542 is a chloro-substituted thienyl. In some embodiments, R<sup>1</sup> is an unsubstituted furyl. In some  
543 embodiments, R<sup>1</sup> is a substituted or unsubstituted morpholinyl. In some embodiments, R<sup>1</sup> is a  
544 substituted or unsubstituted oxanyl. In some embodiments, R<sup>1</sup> is a substituted or unsubstituted  
545 oxetanyl. In some embodiments, R<sup>1</sup> is an unsubstituted morpholinyl. In some embodiments,  
546 R<sup>1</sup> is an unsubstituted oxanyl. In some embodiments, R<sup>1</sup> is an unsubstituted oxetanyl. In some  
547 embodiments, R<sup>1</sup> is substituted or unsubstituted benzodioxinyl. In some embodiments, R<sup>1</sup> is  
548 substituted or unsubstituted naphthyl. In some embodiments, R<sup>1</sup> is unsubstituted  
549 benzodioxinyl. In some embodiments, R<sup>1</sup> is unsubstituted naphthyl. In some embodiments,  
550 R<sup>1</sup> 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, L<sup>2</sup> is a bond. In some embodiments, R<sup>2</sup> is hydrogen. In  
553 some embodiments, L<sup>2</sup> is substituted or unsubstituted alkylene or -C(O)-, and R<sup>2</sup> 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, R<sup>2</sup> is a substituted or unsubstituted pyridyl. In  
559 some embodiments, R<sup>2</sup> is a substituted or unsubstituted pyridazinyl. In some embodiments, R<sup>2</sup>  
560 is a substituted or unsubstituted pyrimidinyl. In some embodiments, R<sup>2</sup> is a substituted or  
561 unsubstituted thienyl. In some embodiments, R<sup>2</sup> is a substituted or unsubstituted furyl. In some  
562 embodiments, R<sup>2</sup> is an unsubstituted pyridyl. In some embodiments, R<sup>2</sup> is an unsubstituted  
563 pyridazinyl. In some embodiments, R<sup>2</sup> is an unsubstituted pyrimidinyl. In some embodiments,  
564 R<sup>2</sup> is an unsubstituted thienyl. In some embodiments, R<sup>2</sup> is a chloro-substituted thienyl. In  
565 some embodiments, R<sup>2</sup> is an unsubstituted furyl. In some embodiments, R<sup>2</sup> is a substituted or  
566 unsubstituted morpholinyl. In some embodiments, R<sup>2</sup> is a substituted or unsubstituted oxanyl.  
567 In some embodiments, R<sup>2</sup> is a substituted or unsubstituted oxetanyl. In some embodiments, R<sup>2</sup>  
568 is an unsubstituted morpholinyl. In some embodiments, R<sup>2</sup> is an unsubstituted oxanyl. In some  
569 embodiments, R<sup>2</sup> is an unsubstituted oxetanyl. In some embodiments, R<sup>2</sup> is substituted or  
570 unsubstituted benzodioxinyl. In some embodiments, R<sup>2</sup> is substituted or unsubstituted  
571 naphthyl. In some embodiments, R<sup>2</sup> is unsubstituted benzodioxinyl. In some embodiments,

572  $R^2$  is unsubstituted naphthyl. In some embodiments,  $R^2$  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,  $L^3$  is a bond, or substituted or unsubstituted alkylene, and  $R^3$  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,  $R^3$  is  
578 substituted or unsubstituted phenyl, or substituted or unsubstituted thienyl. In some  
579 embodiments,  $R^3$  is unsubstituted phenyl. In some embodiments,  $R^3$  is unsubstituted thienyl.  
580 In some embodiments,  $R^3$  is a chloro-substituted thienyl. In some embodiments,  $R^3$  is  
581 substituted or unsubstituted pyridyl, or substituted or unsubstituted pyridazinyl. In some  
582 embodiments,  $R^3$  is unsubstituted pyridyl. In some embodiments,  $R^3$  is unsubstituted  
583 pyridazinyl. In some embodiments,  $R^3$  is substituted or unsubstituted pyrimidinyl, or  
584 substituted or unsubstituted furyl. In some embodiments,  $R^3$  is unsubstituted pyrimidinyl. In  
585 some embodiments,  $R^3$  is unsubstituted furyl. In some embodiments,  $R^3$  is substituted or  
586 unsubstituted morpholinyl, or substituted or unsubstituted oxanyl, or substituted or  
587 unsubstituted oxetanyl. In some embodiments,  $R^3$  is unsubstituted morpholinyl. In some  
588 embodiments,  $R^3$  is unsubstituted oxanyl. In some embodiments,  $R^3$  is unsubstituted  
589 oxetanyl. In some embodiments,  $R^3$  is substituted or unsubstituted benzodioxinyl, or  
590 substituted or unsubstituted naphthyl. In some embodiments,  $R^3$  is unsubstituted  
591 benzodioxinyl. In some embodiments,  $R^3$  is unsubstituted naphthyl. In some embodiments,  
592  $R^3$  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  $L^3$   
594 is  $-C(O)O-$ , and  $R^3$  is substituted or unsubstituted alkyl, and Y is fluorine.

595 [0066] In some embodiments, the compound has the structure of Formula (IIb) wherein  $L^3$   
596 is  $-C(O)NR^5-$ ,  $R^5$  is hydrogen or alkyl, and  $R^3$  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,  $L^1$  is a bond,  $-S-$ ,  $-NR^4-$ , substituted or unsubstituted  
600 alkylene, or substituted or unsubstituted heteroalkylene, where  $R^4$  is as described in formula  
601 Ia and  $R^1$  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,  $R^1$  is a substituted or  
604 unsubstituted pyridyl. In some embodiments,  $R^1$  is a substituted or unsubstituted pyridazinyl.

605 In some embodiments, R<sup>1</sup> is a substituted or unsubstituted pyrimidinyl. In some embodiments,  
606 R<sup>1</sup> is a substituted or unsubstituted thienyl. In some embodiments, R<sup>1</sup> is a substituted or  
607 unsubstituted furyl. In some embodiments, R<sup>1</sup> is an unsubstituted pyridyl. In some  
608 embodiments, R<sup>1</sup> is an unsubstituted pyridazinyl. In some embodiments, R<sup>1</sup> is an unsubstituted  
609 pyrimidinyl. In some embodiments, R<sup>1</sup> is an unsubstituted thienyl. In some embodiments, R<sup>1</sup>  
610 is a chloro-substituted thienyl. In some embodiments, R<sup>1</sup> is an unsubstituted furyl. In some  
611 embodiments, R<sup>1</sup> is a substituted or unsubstituted morpholinyl. In some embodiments, R<sup>1</sup> is a  
612 substituted or unsubstituted oxanyl. In some embodiments, R<sup>1</sup> is a substituted or unsubstituted  
613 oxetanyl. In some embodiments, R<sup>1</sup> is an unsubstituted morpholinyl. In some embodiments,  
614 R<sup>1</sup> is an unsubstituted oxanyl. In some embodiments, R<sup>1</sup> is an unsubstituted oxetanyl. In some  
615 embodiments, R<sup>1</sup> is substituted or unsubstituted benzodioxinyl. In some embodiments, R<sup>1</sup> is  
616 substituted or unsubstituted naphthyl. In some embodiments, R<sup>1</sup> is unsubstituted  
617 benzodioxinyl. In some embodiments, R<sup>1</sup> is unsubstituted naphthyl. In some embodiments,  
618 R<sup>1</sup> 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, L<sup>2</sup> is a bond or substituted or unsubstituted alkylene. In  
621 some embodiments, L<sup>2</sup> is a bond. In some embodiments, L<sup>2</sup> is unsubstituted alkylene. In  
622 some embodiments, L<sup>2</sup> is substituted alkylene. In some embodiments, R<sup>2</sup> is hydrogen. In  
623 some embodiments, R<sup>2</sup> is substituted or unsubstituted alkyl, or substituted or unsubstituted  
624 aryl. Further to any particular L<sup>2</sup>, in some embodiments R<sup>2</sup> is substituted or unsubstituted  
625 alkyl, or substituted or unsubstituted aryl. In some embodiments, R<sup>2</sup> is unsubstituted alkyl.  
626 In some embodiments, R<sup>2</sup> is unsubstituted aryl. In some embodiments, R<sup>3</sup> is unsubstituted  
627 phenyl. In some embodiments, R<sup>2</sup> is substituted alkyl. In some embodiments, R<sup>2</sup> 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, L<sup>2</sup> is substituted or unsubstituted alkylene or -C(O)-,  
631 and R<sup>2</sup> 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, R<sup>2</sup> is a substituted or unsubstituted pyridyl. In  
636 some embodiments, R<sup>2</sup> is a substituted or unsubstituted pyridazinyl. In some embodiments, R<sup>2</sup>  
637 is a substituted or unsubstituted pyrimidinyl. In some embodiments, R<sup>2</sup> is a substituted or  
638 unsubstituted thienyl. In some embodiments, R<sup>2</sup> is a substituted or unsubstituted furyl. In some

embodiments,  $R^4$  is an unsubstituted pyridyl. In some embodiments,  $R^4$  is an unsubstituted pyridazinyl. In some embodiments,  $R^2$  is an unsubstituted pyrimidinyl. In some embodiments,  $R^2$  is an unsubstituted thienyl. In some embodiments,  $R^2$  is a chloro-substituted thienyl. In some embodiments,  $R^2$  is an unsubstituted furyl. In some embodiments,  $R^2$  is a substituted or unsubstituted morpholinyl. In some embodiments,  $R^2$  is a substituted or unsubstituted oxanyl. In some embodiments,  $R^2$  is a substituted or unsubstituted oxetanyl. In some embodiments,  $R^2$  is an unsubstituted morpholinyl. In some embodiments,  $R^2$  is an unsubstituted oxanyl. In some embodiments,  $R^2$  is an unsubstituted oxetanyl. In some embodiments,  $R^2$  is substituted or unsubstituted benzodioxinyl. In some embodiments,  $R^2$  is substituted or unsubstituted naphthyl. In some embodiments,  $R^2$  is unsubstituted benzodioxinyl. In some embodiments,  $R^2$  is unsubstituted naphthyl. In some embodiments,  $R^2$  is substituted or unsubstituted phenyl. In some embodiments, Y is fluorine.

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

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

**Table A.**

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

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

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



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

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

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 ( $^3\text{H}$ ),  
 680 iodine-125 ( $^{125}\text{I}$ ), or carbon-14 ( $^{14}\text{C}$ ). 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, acetoxymethyl, 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  $\mu\text{M}$ , 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,  $0.1-1 \mu\text{M}$ ,  $1-10 \mu\text{M}$ , 10-100  $\mu\text{M}$ , 100-200  $\mu\text{M}$ , 200-500  
732  $\mu\text{M}$ , or even 500-1000  $\mu\text{M}$ . In some embodiments, the inhibitory activity is in the range of  
733 about 1-10 nM, 10-100 nM,  $0.1-1 \mu\text{M}$ ,  $1-10 \mu\text{M}$ , 10-100  $\mu\text{M}$ , 100-200  $\mu\text{M}$ , 200-500  $\mu\text{M}$ , or  
734 even 500-1000  $\mu\text{M}$ . 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  $\text{IC}_{50}$  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,  $0.1-1 \mu\text{M}$ ,  $1-10 \mu\text{M}$ , 10-100  $\mu\text{M}$ , 100-200  $\mu\text{M}$ , 200-500  $\mu\text{M}$ , or even  
745 500-1000  $\mu\text{M}$ , preferably about 1-10 nM, 10-100 nM, or  $0.1-1 \mu\text{M}$ . 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*  
782 *Thromb Haemost*, 3:1917-1923. Very recently, it was demonstrated that dabigatran etexilate,  
783 a DTI recently FDA-approved (see e.g., Hughes, B., 2010, *Nat Rev Drug Discov*, 9:903-906)  
784 for DVT indications, inhibited both the invasion and metastasis of malignant breast tumors.  
785 See e.g., DeFeo, K.*et al.*, 2010, *Thrombosis Research*, 125 (Supplement 2): S188-S188;  
786 Defeo, K., *et al.*, 2010, *Cancer Biol Ther*, 10:1001-1008. Thus, dabigatran etexilate  
787 treatment led to a 50% reduction in tumor volume at 4 weeks with no weight loss in treated  
788 mice. Dabigatran etexilate also reduced tumor cells in the blood and liver micrometastases  
789 by 50-60%. These investigators concluded that dabigatran etexilate can be beneficial in not  
790 only preventing thrombotic events in cancer patients, but also as adjunct therapy to treat  
791 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 CCl<sub>4</sub>-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*  
812 *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, Biochemica 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 DiaPharma. 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  $\mu$ 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 IC<sub>50</sub> 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 IC<sub>50</sub> 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 -NHSO<sub>3</sub>H, -COOH and  
971 -P(O)(OH)<sub>2</sub>, 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 pharmaceutical 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/m<sup>2</sup> times 1.8 = the corresponding oral dosage in milligrams ("mg").  
1161 As to oncology applications, the parenteral dosage in mg/m<sup>2</sup> 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 LD<sub>50</sub> (the amount of compound  
1279 lethal in 50% of the population) and ED<sub>50</sub> (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 ED<sub>50</sub> 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

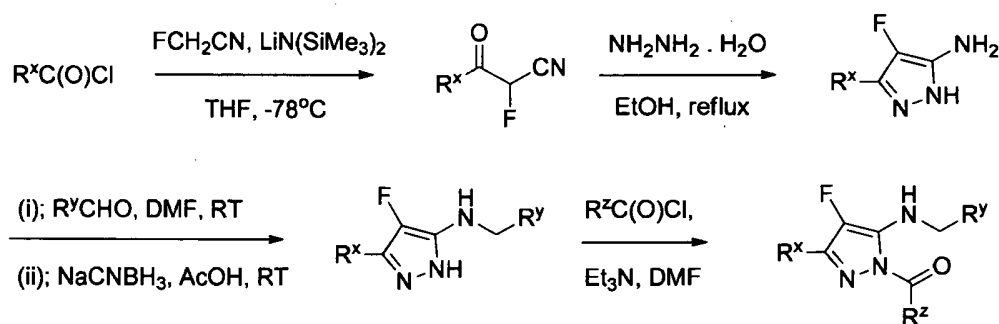
1292 [0157] The examples below are meant to illustrate certain embodiments of the invention and  
1293 not to limit the scope of the invention. Abbreviations used herein have their conventional  
1294 meaning in the art, unless indicated otherwise. Specific abbreviations include the following:  
1295 Å = Ångström; Ac<sub>2</sub>O = 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;  $\delta$  =  
 1300 chemical shift (given in ppm, unless otherwise indicated); EDCI = 1-ethyl-3-(3-  
 1301 dimethylaminopropyl)carbodiimide; eq = equivalent; Et<sub>2</sub>O = diethyl ether; Et<sub>3</sub>N =  
 1302 triethylamine; EtOAc = ethyl acetate; EtOH = ethanol; g = gram; h (or hr) = hour; HOBt =  
 1303 hydroxybenzotriazole; HPLC = high performance liquid chromatography; Hz = Hertz; IC<sub>50</sub> =  
 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]<sup>+</sup> = parent mass spectrum peak plus H<sup>+</sup>; MS = mass  
 1307 spectrum; ms = molecular sieves; MP = melting point; Me<sub>2</sub>NH = dimethylamine; MeOH =  
 1308 methanol; mg = milligram; mL = milliliter; mM = millimolar; mmol = millimole; min =  
 1309 minute;  $\mu$ L = microliter;  $\mu$ M = micromolar; ng = nanogram; nM = nanomolar; NMR =  
 1310 nuclear magnetic resonance; ppm = parts per million; q = quartet; R<sub>f</sub> = retention factor; RT  
 1311 = room temperature; s = singlet; t = triplet; TFA = trifluoroacetic acid; THF =  
 1312 tetrahydrofuran; TLC = thin layer chromatography.

1313

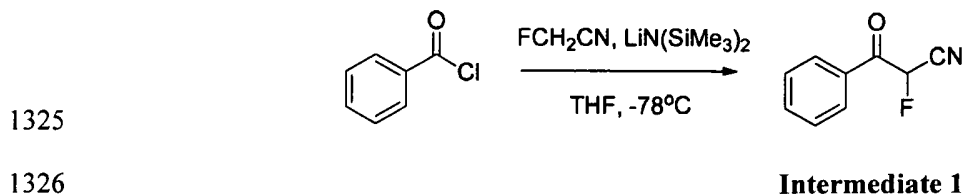
1314 *Example 1 - Preparation of Intermediate 1*

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<sup>x</sup>”, “R<sup>y</sup>”,  
 1317 and “R<sup>z</sup>” 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.



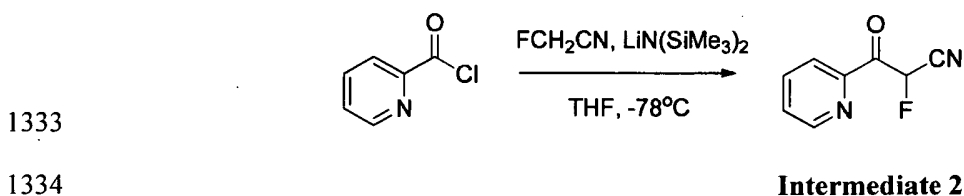
1323 [0159] The synthesis of Intermediate 1 followed General Procedure 1 following.

1324 **General Procedure 1**



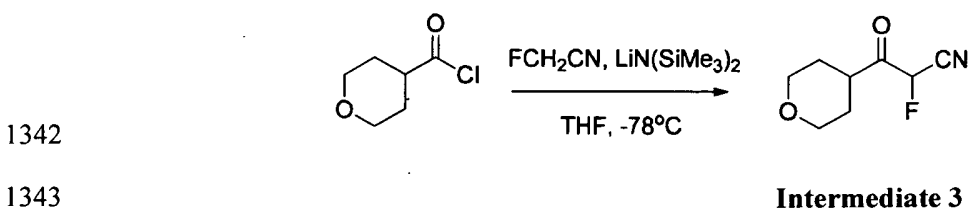
1327 To a cold (-78 °C) solution of benzoyl chloride (5.0 mmol, 1.0 eq) and fluoroacetonitrile  
1328 (278 µL, 5.0 mmol, 1.0 eq) in dry THF (15 mL) was added a solution of LHMDS in THF (1  
1329 M, 10 mL, 10.0 mmol, 2.0 eq). The mixture was allowed to reach room temperature, and 1N  
1330 HCl was added dropwise achieving pH 2. The mixture was concentrated under reduced  
1331 pressure to afford intermediate 1 in a form pure enough for the next step.

1332 *Example 2 - Preparation of Intermediate 2*



1335 [0160] General Procedure 1 was followed to obtain Intermediate 2. Thus, to a cold (-78  
1336 °C) solution of picolinoyl chloride (5.0 mmol, 1.0 eq) and fluoroacetonitrile (278 µL, 5.0  
1337 mmol, 1.0 eq) in dry THF (15 mL) was added a solution of LHMDS in THF (1 M, 10 mL,  
1338 10.0 mmol, 2.0 eq). The mixture was allowed to reach room temperature, and 1N HCl was  
1339 added dropwise achieving pH 2. The mixture was concentrated under reduced pressure to  
1340 afford intermediate 2 in a form pure enough for the next step.

1341 *Example 3 - Preparation of Intermediate 3*



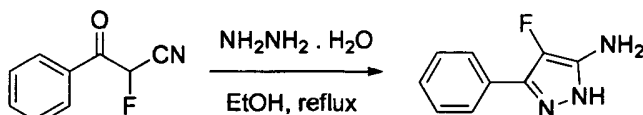
1344 [0161] General Procedure 1 was followed to obtain Intermediate 3. Thus, to a cold (-78  
1345 °C) solution of pyran-4-carbonyl chloride (5.0 mmol, 1.0 eq) and fluoroacetonitrile (278 µL,  
1346 5.0 mmol, 1.0 eq) in dry THF (15 mL) was added a solution of LHMDS in THF (1 M, 10  
1347 mL, 10.0 mmol, 2.0 eq). The mixture was allowed to reach room temperature, and 1N HCl

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

*Example 4 - Preparation of Intermediate 4*

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

**General Procedure 2**

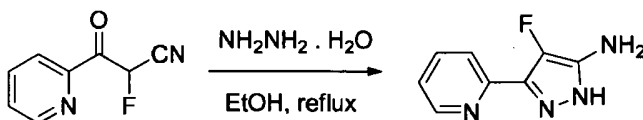


**Intermediate 1**

**Intermediate 4**

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

*Example 5 - Preparation of Intermediate 5*

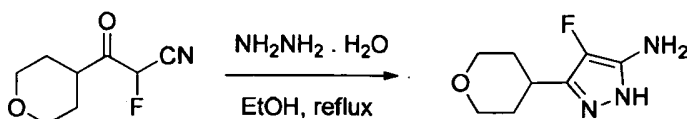


**Intermediate 2**

**Intermediate 5**

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

*Example 6 - Preparation of Intermediate 6*



**Intermediate 3**

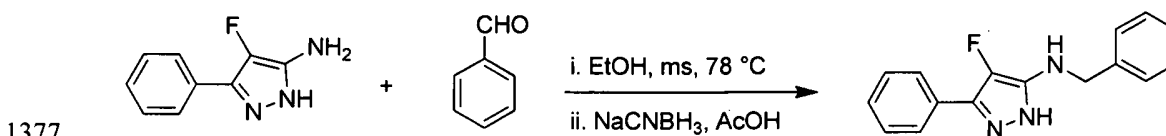
**Intermediate 6**

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

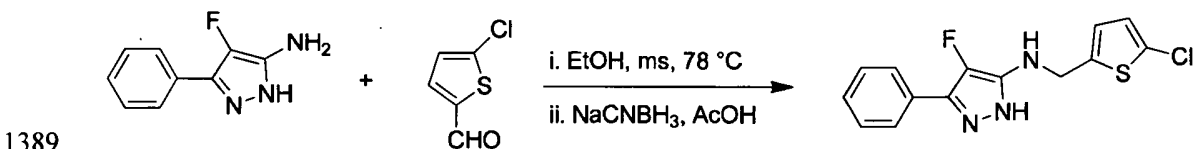


1373 *Example 7 - Preparation of Intermediate 7*

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 (4Å powder) was refluxed for 8 h. Then was added a  
1381 catalytic quantity of AcOH, NaCNBH<sub>3</sub> (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 NaHCO<sub>3</sub> (2 × 20 mL), water (20 mL), brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>,  
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 CHCl<sub>3</sub> as the eluent to afford Intermediate 7.

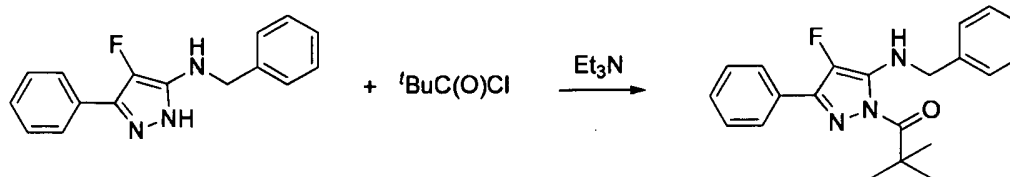
1388 *Example 8 - Preparation of Intermediate 8*1390 **Intermediate 4****Intermediate 8**

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.

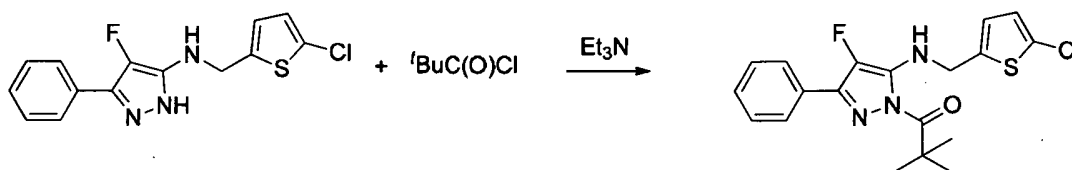
1395

1396 **General Procedure 4**

1397

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

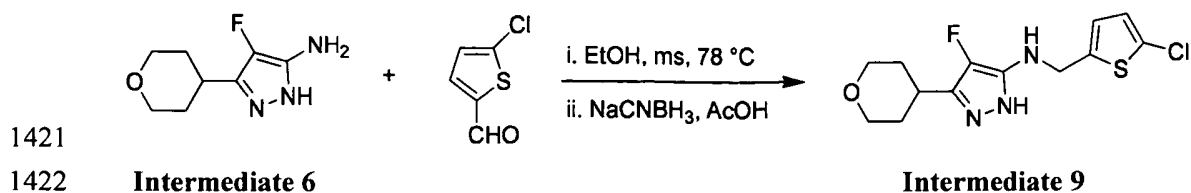
1399 **[0170]** Pivaloyl chloride was added to a solution of Intermediate 7 in triethylamine (3 mL)  
 1400 at RT and stirred for 5 h. The reaction mixture was diluted with water (5 mL) and extracted  
 1401 with EtOAc (20 mL). The organic layer washed with water (2 × 5 mL), saturated aqueous  
 1402 NaHCO<sub>3</sub> (5 mL), brine (5 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The  
 1403 crude compound was purified by column chromatography over silica gel (100-200 mesh) by  
 1404 using a gradient mixture of 0-30% EtOAc-hexane as the eluent to afford Compound 23  
 1405 (33%). MP 105-106°C; <sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) δ 7.77 (d, J = 7.4 Hz, 2H), 7.56-7.60 (m, 1H),  
 1406 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);  
 1407 MS: 352 [M + H]<sup>+</sup>.

1408 **Example 10 - Preparation of Compound 10**

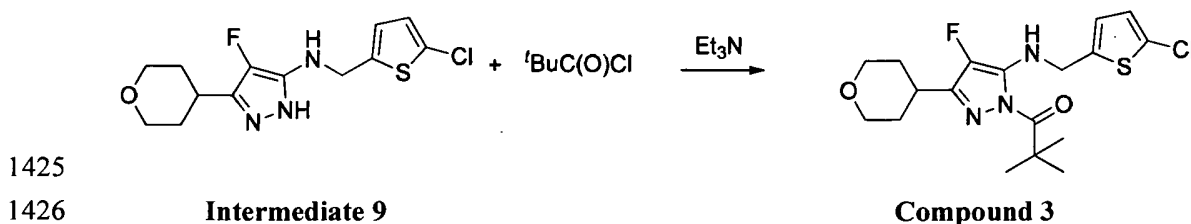
1409

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

1411 **[0171]** General Procedure 4 was followed to convert Intermediate 8 to Compound 10.  
 1412 Thus, pivaloyl chloride was added to a solution of Intermediate 8 in triethylamine (3 mL) at  
 1413 RT and stirred for 5 h. The reaction mixture was diluted with water (5 mL) and extracted with  
 1414 EtOAc (20 mL). The organic layer washed with water (2 × 5 mL), saturated aqueous  
 1415 NaHCO<sub>3</sub> (5 mL), brine (5 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The  
 1416 crude compound was purified by column chromatography over silica gel (100-200 mesh) by  
 1417 using a gradient mixture of 0-30% EtOAc-hexane as the eluent to afford Compound 10  
 1418 (35%). <sup>1</sup>H NMR: (CDCl<sub>3</sub>) δ 7.8-7.9 (m, 2H), 7.40-7.48 (m, 3H), 7.10-7.18 (m, 1H), 6.74-  
 1419 6.81 (m, 2H), 4.63 (d, J = 6.2 Hz, 2H), 1.53 (s, 9H); MS: 392 [M + H]<sup>+</sup>.

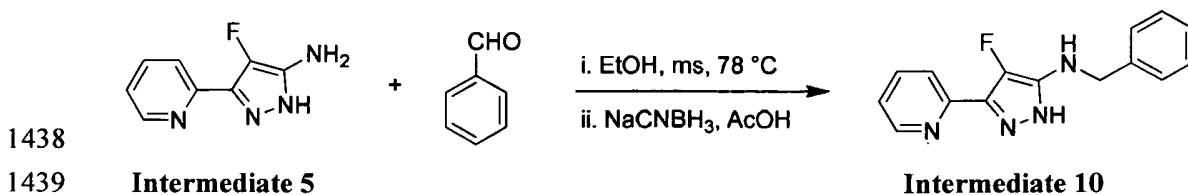
1420 *Example 11 - Preparation of Intermediate 9*

1423 [0172] General Procedure 3 was followed to convert Intermediate 6 to Intermediate 9

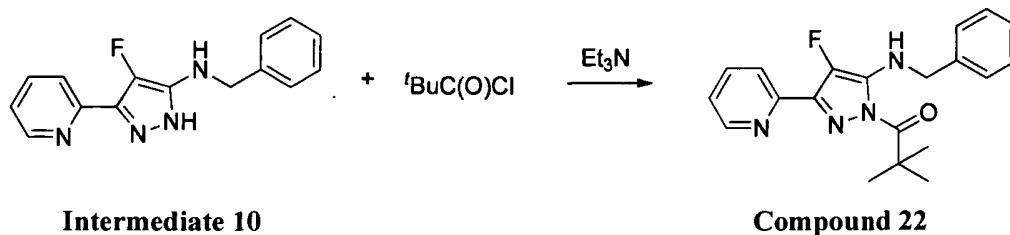
1424 *Example 12 - Preparation of Compound 3*

1427 [0173] General Procedure 4 was followed to convert Intermediate 9 to Compound 3.

1428 Thus, pivaloyl chloride was added to a solution of Intermediate 9 in triethylamine (3 mL) at  
 1429 RT and stirred for 5 h. The reaction mixture was diluted with water (5 mL) and extracted with  
 1430 EtOAc (20 mL). The organic layer washed with water (2 × 5 mL), saturated aqueous  
 1431 NaHCO<sub>3</sub> (5 mL), brine (5 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The  
 1432 crude compound was purified by column chromatography over silica gel (100-200 mesh) by  
 1433 using a gradient mixture of 0-30% EtOAc-hexane as the eluent to afford Compound 3 (46%).  
 1434 <sup>1</sup>H NMR: (CDCl<sub>3</sub>) δ 7.03 (t, J = 7.0 Hz, 1H), 6.75 (br s, 2H), 4.54 (d, J = 6.2 Hz, 2H), 4.01 –  
 1435 4.06 (m, 2H), 3.50 – 3.57 (m, 2H), 2.89 – 2.93 (m, 1H), 1.87 – 1.91 (m, 4H), 1.44 (s, 9H);  
 1436 MS: 400 [M + H]<sup>+</sup>.

1437 *Example 13 - Preparation of Intermediate 10*

1440 [0174] General Procedure 3 was followed to convert Intermediate 5 to Intermediate 10

1441 *Example 14 - Preparation of 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 NaHCO<sub>3</sub> (5 mL), brine (5 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, 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%). <sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) 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]<sup>+</sup>.

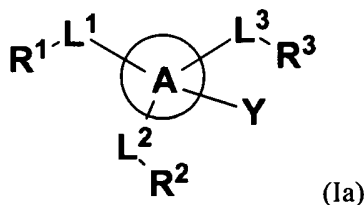
1453

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 (1a):



1461 or pharmaceutically acceptable salt, ester, solvate, or prodrug thereof;

1462 wherein

1463 Ring A is substituted or unsubstituted pyrazolyl;

1464 L<sup>1</sup> and L<sup>3</sup> are independently a bond, substituted or unsubstituted alkylene, substituted  
1465 or unsubstituted heteroalkylene, -S-, -SO-, -SO<sub>2</sub>-, -O-, -NHSO<sub>2</sub>-, or -NR<sup>4</sup>-;

1466 L<sup>2</sup> is absent, a bond, substituted or unsubstituted alkylene, substituted or unsubstituted  
1467 heteroalkylene, -S-, -SO-, -SO<sub>2</sub>-, -O-, -NHSO<sub>2</sub>-, or -NR<sup>4</sup>-;

1468 R<sup>1</sup> and R<sup>3</sup> are independently hydrogen, halogen, substituted or unsubstituted alkyl,  
1469 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or  
1470 unsubstituted cycloalkenyl, substituted or unsubstituted heterocycloalkyl, substituted or  
1471 unsubstituted heterocycloalkenyl, substituted or unsubstituted aryl, substituted or  
1472 unsubstituted fused ring aryl, or substituted or unsubstituted heteroaryl;

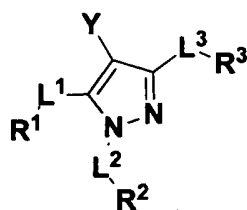
1473 R<sup>2</sup> is absent, hydrogen, halogen, substituted or unsubstituted alkyl, substituted or  
1474 unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted  
1475 cycloalkenyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted  
1476 heterocycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted fused ring  
1477 aryl, or substituted or unsubstituted heteroaryl, provided that when L<sup>2</sup> is absent, R<sup>2</sup> is absent;

1478 R<sup>4</sup> is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted  
1479 heteroalkyl, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene,  
1480 substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl,  
1481 substituted or unsubstituted aryl, substituted or unsubstituted cycloalkenyl, substituted or  
1482 unsubstituted heterocycloalkenyl, and substituted or unsubstituted fused ring aryl or  
1483 substituted or unsubstituted heteroaryl; and

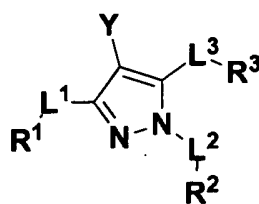
1484 Y is a halogen.

1485 2. The compound according to claim 1, wherein L<sup>2</sup> and R<sup>2</sup> are absent.

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



(IIa)



(IIb)

1490 4. The compound according to claim 3, with structure of Formula (IIa), wherein  
1491 L<sup>3</sup> is a bond, or substituted or unsubstituted alkylene, and R<sup>3</sup> 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<sup>3</sup> is -C(O)O-, R<sup>3</sup> 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<sup>3</sup> is -C(O)NR<sup>5</sup>-, R<sup>5</sup> is hydrogen or alkyl, R<sup>3</sup> is substituted or unsubstituted alkyl, or  
1498 substituted or unsubstituted aryl, and Y is fluorine.

1499 7. The compound according to claim 4, wherein R<sup>3</sup> 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<sup>3</sup> is chloro-substituted thienyl.

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

1506 11. The compound according to claim 4, wherein said fused ring aryl is  
1507 benzodioxinyl or naphthyl.

1508 12. The compound according to any of claims 4 to 11, wherein L<sup>1</sup> is a bond, -S-,  
1509 -NR<sup>4</sup>-, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene,  
1510 and R<sup>1</sup> 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.

1513 13. The compound according to claim 12, wherein said heteroaryl is pyridyl,  
1514 pyridazinyl, pyrimidinyl, thienyl, or furyl.

1515 14. The compound according to claim 13, wherein R<sup>1</sup> is chloro-substituted thienyl.

- 1516           15.    The compound according to claim 12, wherein said heterocycloalkyl is  
1517 morpholinyl, 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 R<sup>1</sup> is substituted or  
1521 unsubstituted phenyl.
- 1522           18.    The compound according to claim 4, wherein L<sup>2</sup> is a bond, and R<sup>2</sup> is  
1523 hydrogen.
- 1524           19.    The compound according to claim 4, wherein L<sup>2</sup> is substituted or unsubstituted  
1525 alkylene or -C(O)-, and R<sup>2</sup> 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 R<sup>2</sup> 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 morpholinyl, 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 R<sup>2</sup> is substituted or  
1540 unsubstituted phenyl.
- 1541           25.    The compound according to claim 3, with structure of Formula (IIb), wherein  
1542 L<sup>3</sup> is a bond, or substituted or unsubstituted alkylene, R<sup>3</sup> 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 L<sup>3</sup> is -C(O)O-, R<sup>3</sup> is substituted or unsubstituted alkyl, and Y is fluorine.
- 1547           27.    The compound according to claim 3, with structure of Formula (IIb), wherein  
1548 L<sup>3</sup> is -C(O)NR<sup>5</sup>-, R<sup>5</sup> is hydrogen or alkyl, R<sup>3</sup> 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 -NR<sup>4</sup>-, 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 R<sup>2</sup> 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 R<sup>2</sup> 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。