This invention provides aryl and heteroaryl compounds, methods of their preparation, pharmaceutical compositions comprising the compounds, and their use in treating human or animal disorders. The compounds of the invention may be useful as antagonists, or partial antagonist of factor IX and/or factor XI and thus, may be used to inhibit the intrinsic pathway of blood coagulation. The compounds may be useful in a variety of applications including the management, treatment and/or control of diseases caused in part by the intrinsic clotting pathway utilizing factor IX and/or XI.
Fig. 2

From Fig. 1

Factor Xa

Phospholipid

Factor Va

Prothrombin

Thrombus (crosslinked fibrin clot)

Fibrin

Fibrinogen

Factor XIII

Factor Xlla
ARYL AND HETERARYL COMPOUNDS, COMPOSITIONS, AND METHODS OF USE

STATEMENT OF RELATED APPLICATIONS

[0001] This application claims priority as a divisional application under 35 USC § 120 to U.S. application Ser. No. 11/069,621, which was filed on Mar. 1, 2005, which claims priority as a continuation in part application to U.S. application Ser. No. 10/913,168 filed on Aug. 6, 2004, which in turn claims priority under 35 USC 119 to the following U.S. Provisional Patent Applications: Ser. No. 60/493,879, filed Aug. 8, 2003, entitled “Aryl and Heteroaryl Compounds as Antiviral agents”; Ser. No. 60/493,878, filed Aug. 8, 2003, entitled “Aryl and Heteroaryl Compounds and Methods to Modulate Red Blood Cell Production”; Ser. No. 60/493,903, filed Aug. 8, 2003, entitled “Aryl and Heteroaryl Compounds and Methods to Modulate Coagulation”, the entirety of all are herein incorporated by reference.

FIELD OF THE INVENTION

[0002] This invention relates to aryl and heteroaryl compounds and compositions that may be antagonists of the intrinsic clotting pathway by binding to, and inhibiting the function of factor XI or of both factors XI and IX, and methods of use for such compounds and compositions.

BACKGROUND OF THE INVENTION

[0003] Hemostasis, the arrest of bleeding from an injured blood vessel, requires the coordinated endeavors of vascular, platelet, and plasma factors to eventually form a hemostatic seal or a blood clot. In normal hemostasis, collective activity of these factors is counterbalanced by regulatory mechanisms to limit the accumulation of platelets and fibrin in the area of injury.

[0004] Upon injury to a blood vessel, vascular factors reduce blood flow from the blood vessel by local vasoconstriction and compression of injured vessels. At the same time, platelets adhere to the site of vessel wall injury and form aggregates called hemostatic plugs, which form the first key element of the hemostatic seal. Platelets also release factors that provide surface membrane sites and components for the formation of enzyme/cofactor complexes in blood coagulation reactions. Through a series of interacting and propagating zymogen activations, the activated form of one plasma factor catalyzes the activation of the next plasma factor. This cascade of blood coagulation reactions eventually forms a fibrin clot. The fibrin clot, an insoluble fibrin matrix that radiates from and anchors the hemostatic plug, is the second key element of the hemostatic seal.

[0005] Specifically, the cascade of blood coagulation reactions discussed involves two interdependent pathways, an intrinsic pathway and an extrinsic pathway. Both pathways ultimately catalyzes the proteolytic activation of factor X to factor Xa.

[0006] Damage to the blood vessel or a negatively charged surface initiates blood clotting by the intrinsic pathway. As seen in FIG. 1, the major components of the intrinsic pathway include factor VIII, a non-enzymatic co-factor, and factors IX and XI, zymogen serine proteases. The initiation of the intrinsic pathway results in the activation of factor XI to Xla. Factor Xla, as well as the presence of the factor VIIa/tissue factor complex involved in the extrinsic pathway, catalyzes the activation of factor IX to factor IXa. The presence of factor IXa, in combination with the activated form of factor VIII on an appropriate phospholipid surface, results in the formation of a tenase complex (10). The tenase complex catalyzes the formation of factor Xa from its zymogen, factor X.

[0007] Exposure of blood to injured tissue initiates blood clotting by the extrinsic pathway. As is shown in FIG. 1, the major components of the extrinsic pathway are factor VII, a zymogen serine protease, and tissue factor, a membrane bound protein. Tissue factor serves as the requisite non-enzymatic co-factor for factor VII. The initiation of the extrinsic pathway is thought to be an autocatalytic event resulting from the activation of factor VII by trace levels of activated factor VII (factor VIIa), both of which are bound to newly exposed tissue factor on membrane surfaces at sites of vascular damage (20). The factor VIIa/tissue factor complex directly catalyzes the formation of factor Xa from factor X.

[0008] Once the initial intrinsic or extrinsic cascade results in the activation of factor X, factor Xa catalyzes the penultimate step in the blood coagulation cascade, the formation of serine protease thrombin. As seen in FIG. 2, thrombin formation occurs when a prothrombinase complex, comprising of factor Xa, the non-enzymatic co-factor Va and the substrate prothrombin, is assembled on an appropriate phospholipid surface (30). Once formed, thrombin functions as part of a feedback loop, controlling the activation of factors V and VIII. It additionally catalyzes both the activation of factor VIII and the conversion of fibrinogen to fibrin. Finally, the factor VIIIa interacts with fibrin to catalyze the formation of a thrombus, or crosslinked fibrin clot.

[0009] In normal hemostasis, the process of clot formation (blood coagulation) and clot dissolution (fibrinolysis) is delicately balanced. A slight imbalance between the processes of clot formation and dissolution can lead to excessive bleeding or thrombosis. Many significant disease states are related to abnormal hemostasis. With respect to the coronary arterial vasculature, abnormal thrombus formation due to the rupture of an established atherosclerotic plaque is the major cause of acute myocardial infarction and unstable angina. Moreover, treatment of an occlusive coronary thrombus by either thrombolytic therapy or percutaneous transluminal coronary angioplasty (PTCA) is often accompanied by an acute thrombotic reocclusion of the affected vessel which requires immediate resolution. With respect to the venous vasculature, a high percentage of patients undergoing major surgery in the lower extremities or the abdominal area suffer from thrombus formation in the venous vasculature which can result in reduced blood flow to the affected extremity and a predisposition to pulmonary embolism. Disseminated intravascular coagulopathy commonly occurs within both vascular systems during septic shock, certain viral infections and cancer and is characterized by the rapid consumption of coagulation factors and systemic coagulation which results in the formation of life-threatening thrombi occurring throughout the vasculature leading to widespread organ failure.

[0010] Pathogenic thrombosis in the arterial vasculature is a major clinical concern in today’s medicine. It is the leading cause of acute myocardial infarction which is one of the
leading causes of death in the western world. Recurrent arterial thrombosis also remains one of the leading causes of failure following enzymatic or mechanical recanalization of occluded coronary vessels using thrombolytic agents or percutaneous transluminal coronary angioplasty (PTCA), respectively [Ross, A. M., Thrombosis in Cardiovascular Disease, p. 327, W.B. Saunders Co. (Fuster, V. and Verstraete, M. edn. 1991); Calif, R. M. and Willerson, J. T., Id. at p 389]. In contrast to thrombotic events in the venous vasculature, arterial thrombosis is the result of a complex interaction between fibrin formation resulting from the blood coagulation cascade and cellular components, particularly platelets, which make up a large percentage of arterial thrombi. Heparin, the most widely used clinical anticoagulant administered intravenously, has not been shown to be universally effective in the treatment or prevention of acute arterial thrombosis or rethrombosis [Prins, M. H. and Hirsh, J., J. Am. Coll. Cardiol., 67: 3A (1991)].

[0011] Besides the unpredictable, recurrent thrombotic reocclusion which commonly occurs following PTCA, a profound restenosis of the recanalized vessel occurs in 30 to 40% of patients 1 to 6 months following this procedure [Califf, R. M. et al., J. Am. Coll. Cardiol., 17: 2B (1991)]. These patients require further treatment with either a repeat PTCA or coronary artery bypass surgery to relieve the newly formed stenosis. Restenosis of a mechanically damaged vessel is not a thrombotic process but instead is the result of a hyperproliferative response in the surrounding smooth muscle cells which over time results in a decreased luminal diameter of the affected vessel due to increased muscle mass. As for arterial thrombosis, there is currently no effective pharmacological treatment for the prevention of vascular restenosis following mechanical recanalization.

[0012] Numerous strategies have been developed for the treatment of thrombotic disorders. Many antithrombotic therapies are based on interference in the hemostatic system. This approach carries the inherent risk of bleeding, since the hemostatic system is no longer fully responsive to potential injury. Therefore, antithrombotic benefits are normally associated with antihemostatic risks. In attempts to improve the benefit-to-risk ratio, antithrombotic agents are continuously being developed. Various antithrombotic strategies include administering general inhibitors of thrombin formation such as heparin or vitamin K antagonists; administering specific thrombin inhibitors; administering specific factor Xa inhibitors; and administering inhibitors of platelet activation and adhesion.

[0013] Evaluation of current antithrombotic strategies in terms of antithrombotic benefits versus antihemostatic risks reveals that the benefit-to-risk ratio tends to be more favorable for strategies that interfere with one specific step rather than in a more general phase of the hemostatic system [L. A. Harker, Biomedical Progress vol 8, 1995, 17-26]. For example, the development of inhibitors specific for factor Xa is an improvement from general and specific thrombin inhibitors. But, this approach blocks the common (intrinsic and extrinsic) pathway of thrombin generation (see FIG. 1), and thereby thrombin-dependent platelet activation. Thus, a need exists for more specific anti-thrombotic agents that selectively inhibit one single hemostatic pathway, while leaving other pathways unaffected.

SUMMARY OF THE INVENTION

[0014] The present invention provides compounds of Formula (I or X), pharmaceutical compositions, and methods for the treatment of cardiovascular diseases. Embodiments of the present invention provide compounds of Formula (I or X) as depicted below. Embodiments of the present invention also provide methods for the preparation of compounds of Formula (I or X) and pharmaceutical compositions comprising compounds of Formula (I or X).

[0015] In another embodiment, the present invention provides methods for the use of compounds of Formula (I or X) and pharmaceutical compositions comprising compounds of Formula (I or X) in treating human or animal disorders.

[0016] Compounds of Formula (I or X) may be useful as modulators of the intrinsic clotting pathway by inhibiting the biological activity of factor XI and/or both factor IX and factor XI. Compounds of Formula (I or X) may be useful in a variety of applications including management, treatment, control, and/or as an adjunct of diseases in humans caused in part by the intrinsic clotting pathway utilizing factor XI/IX. Such diseases or disease states include cardiopulmonary bypass, stroke, myocardial infarction, deep vein thrombosis associated with surgical procedures or long periods of confinement, acute and chronic inflammation and clotting associated with hemodialysis.

BRIEF DESCRIPTION OF THE FIGURES

[0017] The present invention will be described with reference to the accompanying drawings, wherein:

[0018] FIG. 1 is a diagram depicting the steps involved in the intrinsic and extrinsic blood clotting cascades, from time of trauma to the activation of factor X.

[0019] FIG. 2 is a diagram depicting the steps following initial intrinsic and extrinsic blood clotting cascades, beginning with the formation of Xa and culminating in the formation of a thrombus.

DETAILED DESCRIPTION

[0020] Two blood coagulation pathways are associated with normal hemostasis: intrinsic and extrinsic. These two coagulation pathways converge in the formation of factor Xa (FIGS. 1 & 2). But, these two coagulation pathways are interdependent because complete elimination of the intrinsic pathway can lead to uncontrolled bleeding. For example, Type B hemophiliacs completely lack factor IX or factor IX function and have a phenotype characterized by a severe bleeding disorder. Thus, the direct factor VIIIi/tissue factor activation of factor X, which bypasses the need for factor VIII and factor IX, is insufficient for normal hemostasis. Conversely, formation of the factor VIIIi/IXa phospholipid factor X activator (tenase complex) (20) is essential for normal hemostasis.

[0021] Selective inhibition of the intrinsic pathway of coagulation with a factor XI antagonist or a dual factor XI/IX antagonist can provide a method to inhibit the clotting cascade associated with some surgery, stroke, myocardial infarction and hemodialysis while leaving the clotting pathway associated with external lesions such as trauma or abscess intact. Factor XI and IX are primarily associated with the intrinsic clotting pathway. Antagonists which have
activity to factor XI or dual activity to factor XI/XI may have a therapeutic benefit in diseases associated with intrinsic pathway clotting by inhibiting intravascular thrombosis. Additionally, antagonists of factor XI or dual antagonists of factor XI/XI may not have the side effect of unwanted or uncontrollable bleeding by impairing extravascular hemo-
stasis associated with wound healing.

[0022] Some point mutations in factor IX partially inhibit its function and result in a mild or moderate phenotype manifested as a non-life threatening bleeding disorder [Bo-
wen, D. J., J. Clin. Pathol. Mol. Pathol. 55:1-18 (2002)]. These point mutations cause factor IX to behave as if it were subject to a partial antagonist. In the presence of a partial antagonist, factor IX should maintain some activity, even at saturation levels of the partial antagonist. As a result of the point mutations in factor IX, its activity is reduced along with clotting associated with the intrinsic pathway, but some residual activity remains that leaves the extrinsic pathway intact. Additionally, an antibody directed against the gamma-carboxyglutamic acid domain of Factor XI demonstrated efficacy in animal models of thrombosis without an increase in bleeding times [Refino, C. J., et al. Thromb Haemost. 82(3) 1188-1195 (1999)].

[0023] The present invention provides compounds of Formula (1 or X), pharmaceutical compositions, and methods to inhibit the clotting activities of factor XI and/or both factor IX and factor XI. Inhibition of hemostasis with agents that may selectively inhibit the intrinsic pathway of factor X activation may leave the extrinsic pathway intact and allow the formation of small, but hemostatically important amounts of factor Xa and thrombin.

[0024] Embodiments of the present invention provide compounds of Formula (I or X) as depicted below. Embodi-
ments of the present invention also provide methods of the preparation of compounds of Formula (I or X) and pharmaceutical compositions comprising compounds of Formula (I or X).

[0025] In another embodiment, the present invention provides methods for the use of compounds of Formula (I or X) and pharmaceutical compositions comprising compounds of Formula (I or X) in treating human or animal disorders. Compounds of the Formula (I or X) may be useful as modulators of the intrinsic clotting pathway by inhibiting the biological activities of factor XI and/or both factor IX and factor XI. Compounds of Formula (I or X) may be useful in a variety of applications including management, treatment, control, and/or as an adjunct of diseases in humans caused in part by the intrinsically clotting pathway utilizing factors XI/XI. Such diseases or disease states include cardiopulmonary bypass, stroke, myocardial infarction, deep vein thrombosis associated with surgical procedures or long periods of confinement, acute and chronic inflammation and clotting associated with hemodialysis.

[0026] In a first aspect, the present invention provides a compound comprising at least one moiety of the Formula (I or X).

[0027] In one aspect, the present invention provides compounds which are represented by Formula I:

\[
\text{Ar}_2-K
\]  

wherein

[0028] \( \text{Ar}_2 \) comprises an aryl, heteroaryl, fused cycloalkyl-
ary, fused cycloalkylheteroaryl, fused heterocyclylary, or fused heterocyclylheteroaryl group optionally substituted 1 to 7 times. In an embodiment, \( \text{Ar}_2 \) comprises an aryl, heteroaryl, or fused arylheterocyclyl group optionally substituted 1 to 7 times. In another embodiment, \( \text{Ar}_2 \) comprises a phenyl, naphthyl, pyridyl, indolyl, isoquinolyl, pyrimidyl, tetrahydroisoquinolyl, quinoxazolyl, or quinazolyl group optionally substituted 1 to 7 times. In another embodiment, \( \text{Ar}_2 \) comprises a substituted phenyl, 2-naphthyl, 2-pyridyl, 3-isouinolyl, 2-pyrimidyl, 2-quinazolyl, or 3-tetrahydroiso-
quinolyl group having 1 to 5 substituents wherein the substituents independently comprise:

[0029] a) i-fluoro;

[0030] b) -chloro;

[0031] c) -bromo;

[0032] d) -iodo;

[0033] e) -cyano;

[0034] f) -nitro;

[0035] g) -perfluoroalkyl;

[0036] h) -T,R,R2;

[0037] i) -alkyl;

[0038] j) -aryl;

[0039] k) -heteroaryl;

[0040] l) -heterocyclyl;

[0041] m) -cycloalkyl;

[0042] n) -alkylene-aryl;

[0043] o) -alkylene-arylene-aryl;

[0044] p) -alkylene-arylene-alkyl;

[0045] q) -arylene-alkyl;

[0046] r) -arylene-aryl;

[0047] s) -arylene-heteroaryl;

[0048] t) -heteroarylene-aryl;

[0049] u) -heteroarylene-heteroaryl;

[0050] v) -heteroarylene-heterocyclyl;

[0051] w) -arylene-heterocyclyl;

[0052] x) -arylene-arylene-alkyl;

[0053] y) -T,-aryl;

[0054] z) -T,-aryl;

[0055] aa) -T,-alkylene-aryl;

[0056] bb) -T,-alkylene-arylene-aryl;

[0057] cc) -T,-alkylene-heteroaryl;

[0058] dd) -T,-alkylene-heteroaryl;

[0059] ee) -T,-cycloalkylene-arylene-aryl;

[0060] ff) -T,-cycloalkylene-heteroaryl;

[0061] gg) -T,-heterocyclylene-arylene-aryl;

[0062] hh) -T,-heterocyclylene-heteroaryl;
[0063] ii) -T1-arylene-alkyl;
[0064] jj) -T1-arylene-alkenyl;
[0065] kk) -T1-arylene-arylene-aryl;
[0066] ll) -T1-arylene-T2-aryl;
[0067] mm) -T1-arylene-arylene-aryl;
[0068] nn) -T1-arylene-arylene-alkyl;
[0069] oo) -arylene-T1-arylene-aryl;
[0070] pp) -arylene-T1-alkyl;
[0071] qq) -arylene-T1-alkylene-aryl;
[0072] rr) -T1-alkylene-T2-aryl;
[0073] ss) -T1-alkylene-aryl;
[0074] tt) -alkylene-T1-heteroaryl;
[0075] uu) -alkylene-T1-cycloalkyl;
[0076] vv) -alkylene-T1-heterocycyl;
[0077] ww) -alkylene-T1-arylene-alkyl;
[0078] xx) -alkylene-T1-alkylene-aryl;
[0079] yy) -alkylene-T1-alkyl;
[0080] zz) -alkylene-T1-R20;
[0081] a) -alkylene-T1-R32;
[0082] b) -alkylene-cycloalkyl;
[0083] c) -alkylene-alkylene-aryl;
[0084] d) -alkylene-aryl;
[0085] e) -alkylene-cycloalkyl;
[0086] f) -alkylene-arylene-aryl;
[0087] g) -alkylene-cycloalkyl-T2-aryl;
[0088] h) -alkylene-arylene-aryl;
[0089] i) -arylene-alkyl;
[0090] j) -arylene-aryl;

and wherein T1 comprises -CH2-, -O-, -N(R21)-, -CON(R21)-, -N(R22)-, -N(R23)-, -OC(O)N(R24)-, -N(R25)-SO2-, -SO2N(R26)-, -C(O)-O-, -O-C(O)-, -S-, -S(O)-, -S(O2)-, -N(R27)-SO2N(R28)-; wherein T2 comprises a direct bond, -CH2-, -O-, -N(R24)-, -CON(R25)-, -N(R26)-CON(R27)-, -N(R28)-C(O)-, -OC(O)N(R29)-, -N(R24)-SO2-, -SO2N(R25)-, -C(O)-O-, -O-C(O)-, -S-, -S(O)-, -S(O2)-, -N(R26)-SO2N(R27)-; wherein R24 and R26 independently comprise: hydrogen, -alkyl, -alkenyl, -alkylene-cycloalkyl, -alkylen-heterocycyl, -aryl, -heteroaryl, -arylene-alkyl, -alkylene-arylene-aryl, -alkylene-arylene-alkylene-aryl, -alkylene-arylene-arylene-aryl, or alkylene-arylene-O-arylene, or alkylene-arylene-O-alkylene-aryl; and

[0091] In another embodiment, Ar2 comprises a substituted phenyl, 2-naphthyl, 2-pyridyl, 3-isoquinolyl, 2-pyrimidyl or 2-quinazolyl group having 1 to 5 substituents independently comprising:

a) -fluoro;
b) -chloro;
c) -bromo;
d) -iodo;
e) -cyano;
f) -nitro;
g) -perfluoroalkyl;
h) -T1-R20;
i) -alkyl;
j) -aryl;
k) -arylene-alkyl;
l) -aryl;
m) -T1-arylene-aryl;
n) -T1-arylene-aryl;
o) -T1-arylene-alkylene-aryl;
p) -arylene-T1-alkyl;
q) -hydrogen;

wherein T1 comprises -CH2-, -O-, -N(R23)-, -CON(R24)-, or -N(R25)-C(O)-; wherein R20 and R24 independently comprise: -hydrogen, -alkyl, or -aryl.

[0092] K comprises a group of the formula

![Chemical Structure](image-url)
wherein

[c] c is equal to 0, 1, or 2; wherein the values of 0, 1, and 2 comprise a direct bond, —CH₂—, and —CH₂—CH₂—, optionally substituted 1 to 4 times with a substituent group, wherein said substituent group(s) or the term substituted refers to groups comprising: —alkyl, —aryl, —alkenyl-aryl, —arylene-alkenyl-aryl, —O-aryl, or —hydroxy-aryl. In an embodiment, c is equal to 0 or 1. In another embodiment, c is equal to 0.

[G] G comprises: —hydrogen, —CO₂H, —CH₃, —OR, —C(O)R, —C(O)—N—O—R₂, —C(O)(R₁)(R₃), —C(O)—NH—NH—, an acid isostere, or an ester isostere, wherein R₁ and R₂ independently comprise: —hydrogen, —alkyl, —alkoxy, —alkoxyhydroxy, —aryl-N,N'-dialkyl-aminooxy, —alkyl-aminooxy-aryl, —arylene-alkenyl-aryl, or when R₁ and R₂ are bonded to a nitrogen group in G, R₁ and R₂ may be taken together to form a ring having the formula —(CH₂)ₓ—Z—(CH₂)ᵧ—, wherein m and n are, independently, 1, 2, 3, or 4; Z comprises: —CH₂—, —C(O)—, —O—, —N(H)—, —S—, —N(C(O)OR)—, wherein Rₐ comprises hydrogen, aryl, alkyl, or alkylene-aryl. In an embodiment, G comprises: —hydrogen, —CO₂H, —CH₃, —OR, or —hydroxy-aryl. In an embodiment, G comprises: —CO₂H, or an ester isostere, wherein R₁ comprises: —alkyl, —alkenyl-aryl, or —hydroxy-aryl.


eroaryl, —S(O)₂-alkyl, —S(O)₂-aryl, —S(O)₂-heteroaryl, —S(O)₂-alkylene-aryl, —S(O)₂-alkylene-heteroaryl, —S(O)₂-NH-alkyl, —S(O)₂-NH-alkylene-aryl, —S(O)₂-NH-alkylene-heteroaryl, —S(O)₂-NH-hetaryl, or —S(O)₂-NH-hetaryl;

[0102] R₁₀ and R₁₁ may be taken together to form a ring having the formula —(CH₂)ₘ-Z₂-(CH₂)ₙ— bonded to the nitrogen or carbon atom to which R₁₀ and R₁₁ are attached, wherein m and n are independently, 1, 2, 3, or 4; Z₂ independently comprises —CH₂—, —C(O)—,
—O—, —N(H)—, —S—, —S(O)—, —S(O)₂—,
—CON(H)—, —NH₂(O)—, —NH₂(O)N(H)—,
—NH₂(SO₂)—, —S(O)₂N(H)—, —(O)CO—,
—N₂(SO₂)N₁₂—, —OC(O)—, —N(R₁₂)—,
—N(C(O)R₁₂)—, —N(C(O)NH₂R₁₂)—, or
—N(C(O)OR₁₂)—; or

[0103] R₁₀ and R₁₁ may be taken together, with the nitrogen or carbon atom to which they are attached, to form a heterocyclyl or heteroaryl ring.

[0104] R₁₂ comprises hydrogen, aryl, alkyl, or alkylene-aryl;

[0105] In an embodiment, X comprises: —N(R₉)—,
—CON(R₉)—, or —N(R₉)CON(R₉)—,
wherein R₉ and R₉ independently comprise: hydrogen, alkyl, aryl, alkenyl, alkylenyl, or alkylethenyl.

[0106] Ar₃ comprises an aryl, heteroaryl, fused cycloalkylaryl, fused cycloalkylenheteroaryl, fused heterocyclylaryl, or fused heterocyclylenheteroaryl group optionally substituted 1 to 7 times. In an embodiment, Ar₃ comprises a mono- or bicyclic aryl or heteroaryl group optionally substituted 1 to 7 times. In another embodiment, Ar₃ comprises a phenyl, pyridyl, indolyl, napththyl, thiophenyl, thiazole, or benzothiazole group optionally substituted 1 to 7 times. In another embodiment, Ar₃ comprises a phenyl group having 1 to 5 substituents, wherein the substituents independently comprise:

a) -fluoro;
b) -chloro;
c) -bromo;
d) -iodo;
e) -cyano;
f) -nitro;
g) -perfluoroalkyl;
h) -D₁₁-R₁₁;
i) -alkyl;
j) -aryl;
k) -heteroaryl;
l) -heterocyclyl;
m) -cycloalkyl;

[0107] Rᵣ and Rₛ may be taken together, with the nitrogen or carbon atom to which they are attached, to form a heteroaryl or heteroarylenheteroaryl ring.
fi) -alkylene-D-, heteroarylene-alkyl;
ggi) -alkylene-D-, alkyne-arylene-alkyl;
hi) -alkylene-D-, alkyne-heteroarylene-alkyl;
ii) -alkylene-D-, alkyl;
jj) -alkylene-D-, R1α;
kk) -arylene-D-, R1α;
ll) -heteroarylene-D-, R1α;
mm) -D-, alkyl;
nn) -D-, alkyl-

and wherein Rs and Rios independently comprise: -hydrogen, -alkyl, -aryl, -heteroaryl, -arylene-alkyl, -heteroarylene-alkyl, -alkylene-aryl, -alkylene-arylene-alkyl, or -arylene-heteroarylene-alkyl.

d) comprises -CH\(_2\)-, -alkylene-, -alkenylene-, -alkylene-S-, -S-alkylene-, -alkylene-O-, -O-alkylene-, -alkylene-S(O)\(_2\), -S(O)\(_2\)-alkylene, -O-, -N(R1\(_{15}\)), -C(O), -CON(R1\(_{16}\)), -CON(R1\(_{17}\)), -N(R1\(_{15}\))CON(R1\(_{16}\)), -N(R1\(_{15}\))CON(R1\(_{17}\)), -N(R1\(_{15}\))CON(R1\(_{16}\)), -N(R1\(_{15}\))C(O)\(_{13}\), -OC(O)\(_{13}\)N(R1\(_{15}\)), -N(R1\(_{15}\))SO\(_2\), -SO\(_2\)N(R1\(_{18}\)), -C(O)-, -O-, -C(O)-, -S-, -S(O)\(_{13}\), -N(R1\(_{15}\))SO\(_2\)-N(R1\(_{18}\)), and wherein R18 and R19 independently comprise: -hydrogen, -alkyl, -aryl, -arylene-aryl, -alkylene-aryl, or -arylene-arylene-aryl.

In another embodiment, Ar1 comprises a mono-substituted phenyl group wherein the substituent comprises: -aryl, -arylene-aryl, -D-, arylene-arylene-aryl, or -arylene-D-, alkyl; wherein D comprises -O-, -N(R1\(_{15}\)), -CON(R1\(_{16}\)), or -N(R1\(_{15}\))C(O)-, and wherein R15 comprises: -hydrogen; -alkyl; or -aryl.

In another embodiment, Ar1 comprises a phenyl group substituted with at least one of the following substituents:

a) -D-, R1\(_{14}\);
b) -alkyl;
[0134] wherein Q and W independently comprise:

-CH\(_2\)_\(-\) O \(-\) N\((R_{2a})\)
-CH\(_2\)_\(-\) CON\((R_{2b})\)
-N\((R_{2b})\)CON\((R_{2c})\)
-N\((R_{2c})\)CO\(-\)
-OC\((O)N\((R_{2a})\)
-N\((R_{2a})\)SO\(_2\)
-SO\(_2\)NR\((R_{2a})\)
-CON\((R_{2b})\)
-CON\((R_{2c})\)

wherein R\(_{2a}\), R\(_{2b}\), R\(_{2c}\), and R\(_{2d}\) independently comprise: hydrogen, alkyl, aryl, arylenalkyl, arylenephenyl, or arylene-arylene-alkyl.

[0135] In another embodiment, the compounds are represented by Formula (I), in which c is equal to 0; G comprises: hydrogen or \(-\)CO\(_2\)H; V comprises: \(-\)CH\(_2\); or a direct bond; X comprises: \(-\)CON\((R_{4a})\)
-CON\((R_{4b})\)
-N\((R_{4c})\)
wherein R\(_{4a}\) comprises: hydrogen; Ar\(_{1}\) comprises a mono-substituted phenyl group wherein the substituent comprises: -aryl, -arylenalkyl, -D, -aryl -D, -alkylene-arylene-alkyl, or -D, -alkylene-D-alkyl, wherein D, comprises \(-\)O, or \(-\)N\((R_{11})\)
wherein R\(_{11}\) comprises: hydrogen, alkyl, or -aryl; and Ar\(_{2}\) comprises a substituted phenyl, 2-naphthyl, 2-pyridyl, 3-isoquinolinyl, 2-pyrimidyl or 2-quinoxazolyl group having 1 to 5 substituents independently comprising: hydrogen, fluoro, chloro, bromo, iodo, cyano, nitro, perfluoroalkyl, \(-\)CH\(_2\), -alkyl, -aryl, -alkylene-arylene-alkyl, -alkylene-arylene-alkyl, or -alkylene-arylene-alkyl, wherein T, comprises \(-\)CH\(_2\)O, \(-\)O, \(-\)N\((R_{2d})\)
-CON\((R_{2c})\)

wherein R\(_{2d}\) comprises: hydrogen, alkyl, or -aryl. The alkyl, aryl, and arylene groups in Ar\(_{1}\), and Ar\(_{2}\) may be optionally substituted 1 to 4 times with a substituent group, wherein said substituent group(s) or the term substituted refers to groups comprising: hydrogen, fluoro, chloro, bromo, iodo, cyano, nitro, or perfluoroalkyl.

[0136] In another embodiment, the instant invention relates to a compound of Formula (X),

\[
\text{R}_{101}^3 \text{R}_{103}^3 \text{R}_{104}^3 \text{Y}
\]

wherein R\(_{101}\) is selected from the group consisting of \(-\)H, or \(-\)CH\(_2\)-thienyl wherein the thienyl group in \(-\)CH\(_2\)-thienyl is optionally substituted with \(-\)Br or \(-\)CH\(_3\);

R\(_{102}\) is selected from the group consisting of \(-\)CO\(_2\)H, \(-\)CO\(_2\)CH\(_3\), \(-\)CO\(_2\)O-t-butyl, \(-\)CO\(_2\)NH\(_2\)-OCH\(_2\)-phenyl, \(-\)CO\(_2\)NH\(_2\)-OCH\(_2\)-phenyl, \(-\)CO\(_2\)NH\(_2\)-OCH\(_2\)-phenyl, \(-\)CO\(_2\)NH\(_2\)-OCH\(_2\)-phenyl, \(-\)CO\(_2\)NH\(_2\)-OCH\(_2\)-phenyl, \(-\)CO\(_2\)NH\(_2\)-OCH\(_2\)-phenyl, \(-\)CO\(_2\)NH\(_2\)-OCH\(_2\)-phenyl, \(-\)CO\(_2\)NH\(_2\)-OCH\(_2\)-phenyl, and \(-\)CO\(_2\)NH\(_2\)-OCH\(_2\)-phenyl.

R\(_{103}\) is selected from the group consisting of \(-\)H, \(-\)CH\(_2\)-thienyl, \(-\)CH\(_2\)-phenyl, \(-\)CH\(_2\)-furanyl, \(-\)thienyl, and benzoquinolin wherein each of the above possibilities for R\(_{103}\) except \(-\)H are optionally substituted with one or more members selected from group consisting of \(-\)H, \(-\)CH\(_3\), \(-\)CF\(_3\), \(-\)Cl, \(-\)Br, \(-\)F, \(-\)C(O)CH\(_3\), \(-\)CH\(_2\)CH\(_3\), \(-\)CH\(_2\)OH, \(-\)CH(CH\(_3\))\(_2\), and a pharmaceutically acceptable salt, ester, or prodrug thereof.

[0137] In another embodiment, the instant invention relates to a compound of Formula (X),

\[
\text{R}_{101}^3 \text{R}_{103}^3 \text{R}_{104}^3 \text{Y}
\]

wherein R\(_{101}\) is selected from the group consisting of \(-\)H, or \(-\)CH\(_2\)-thienyl wherein the thienyl group in \(-\)CH\(_2\)-thienyl is optionally substituted with \(-\)Br or \(-\)CH\(_3\);

R\(_{102}\) is selected from the group consisting of \(-\)CO\(_2\)H, \(-\)CO\(_2\)CH\(_3\), \(-\)CO\(_2\)O-t-butyl, \(-\)CO\(_2\)NH\(_2\)-OCH\(_2\)-phenyl, \(-\)CO\(_2\)NH\(_2\)-OCH\(_2\)-phenyl, \(-\)CO\(_2\)NH\(_2\)-OCH\(_2\)-phenyl, \(-\)CO\(_2\)NH\(_2\)-OCH\(_2\)-phenyl, \(-\)CO\(_2\)NH\(_2\)-OCH\(_2\)-phenyl, \(-\)CO\(_2\)NH\(_2\)-OCH\(_2\)-phenyl, \(-\)CO\(_2\)NH\(_2\)-OCH\(_2\)-phenyl, \(-\)CO\(_2\)NH\(_2\)-OCH\(_2\)-phenyl, and \(-\)CO\(_2\)NH\(_2\)-OCH\(_2\)-phenyl.

R\(_{103}\) is selected from the group consisting of \(-\)H, \(-\)CH\(_2\)-thienyl, \(-\)CH\(_2\)-phenyl, \(-\)CH\(_2\)-furanyl, \(-\)thienyl, and benzoquinolin wherein each of the above possibilities for R\(_{103}\) except \(-\)H are optionally substituted with one or more members selected from group consisting of \(-\)H, \(-\)CH\(_3\), \(-\)CF\(_3\), \(-\)Cl, \(-\)Br, \(-\)F, \(-\)C(O)CH\(_3\), \(-\)CH\(_2\)CH\(_3\), \(-\)CH\(_2\)OH, \(-\)CH(CH\(_3\))\(_2\), \(-\)CH\(_2\)CH\(_3\), \(-\)propenyl, \(-\)3,3-dimethyl-butenyl, \(-\)isopropenyl, \(-\)phenyl, \(-\)phenylene-methyl, \(-\)phenylene-propyl, \(-\)phenylene-trifluoromethyl, \(-\)phenylene-chloride, \(-\)cyclopentyl, \(-\)cyclopentene, \(-\)cyclopentadiene, \(-\)and \(-\)furanyl;

R\(_{104}\) is selected from the group consisting of \(-\)O-cyclohexylene-ethyl, \(-\)O-cyclohexylene-t-butyl, \(-\)O-cyclohexylene-1-propyl, \(-\)O-phenylene-t-butyl, \(-\)phenylene-t-butyl, and \(-\)C(O)-phenylene-t-butyl;

and Y is selected from the group consisting of \(-\)H, \(-\)methylenecyclopentyl, \(-\)amino-cyclohexyl, \(-\)methylene-thienylene-methyl, \(-\)methylene-thienylene-bromide, and \(-\)tetrahydropyranyl;

or a pharmaceutically acceptable salt, ester, or prodrug thereof.
The instant invention also relates to a compound of Formula (X),

\[ \text{Formula (X)} \]

wherein \( R_{103} \) is selected from the group consisting of \(-\text{H}, \) or \(-\text{CH}_2\)-thienyl wherein the thienyl group in \(-\text{CH}_2\)-thienyl is optionally substituted with \(-\text{Br} \) or \(-\text{CH}_3\); \( R_{102} \) is selected from the group consisting of \(-\text{C(O)OH}, \) \(-\text{C(O)OCH}_3\), \(-\text{C(O)O-t-butyl}, \) \(-\text{C(O)NH-OCH}_2\)-phenyl, \(-\text{C(O)NHCl}, \) and \(-\text{C(O)NH}_{2}\text{SO}_{2}\text{CH}_3\); \( R_{103} \) is selected from the group consisting of \(-\text{H}, \) \(-\text{CH}_2\)-thienyl, \(-\text{CH}_2\)-phenyl, \(-\text{CH}_2\)-furanyl, thienyl, and benzothienyl wherein each of the above possibilities for \( R_{103} \) except \(-\text{H} \) are optionally substituted with one or more members selected from group consisting of \(-\text{H}, \) \(-\text{CH}_3\), \(-\text{CF}_3\), \(-\text{Cl}, \) \(-\text{Br}, \) \(-\text{F}, \) \(-\text{C(O)CH}_3\), \(-\text{CH}_2\text{CH}_3\), \(-\text{CH}==\text{CH}_2\)-CH_2OH, \(-\text{CH}(\text{CH}_3)_2\), \(-\text{CH}_2\text{CH}_2\text{CH}_3\), or a pharmaceutically acceptable salt, ester, or prodrug thereof.

Another embodiment is a compound wherein \( R_{104} \) is

\[ \text{Structure of } R_{104} \]

and wherein \( R_{103} \) is optionally substituted \(-\text{CH}_2\)-2-yl-thienyl or optionally substituted \(-\text{CH}_2\)-phenyl. Moreover, another embodiment relates to compounds wherein \( R_{101} \) is \(-\text{H} \) and compounds wherein \( Y \) is selected from the group consisting of
Another embodiment for $Y$ is when it is -methylene-cyclopentyl.

In another embodiment, the instant invention relates to a pharmaceutical composition comprising a therapeutically effective amount of the compound of Formula (X)

$$
\text{H}_2\text{C} - \text{S} - \text{Br}, \text{ and} \text{Br, and}
$$

An R$_{101}$ is selected from the group consisting of $-$H, or $-$CH$_2$-thienyl wherein the thienyl group in $-$CH$_2$-thienyl is optionally substituted with $-$Br or $-$CH$_3$;

R$_{102}$ is selected from the group consisting of $-$C(O)OH, $-$C(O)OCH$_3$, $-$C(O)O-t-buty, $-$C(O)NH-OCH$_2$-phenyl, $-$C(O)NH$_2$, and $-$C(O)NH$_2$CH$_3$;

R$_{103}$ is selected from the group consisting of $-$H, $-$CH$_2$-thienyl, $-$CH$_2$-phenyl, $-$CH$_2$-furanyl, thienyl, and benzothienyl wherein each of the above possibilities for R$_{103}$ except $-$H are optionally substituted with one or more members selected from group consisting of

- H, CH$_3$, CF$_3$, Cl, Br, F,
- C(O)CH$_3$, CH$_2$CH$_3$, CH=CH$_2$, CH$_2$OH,
- CH(CH$_3$)$_2$, CH$_2$CH$_2$CH$_3$, and
- t-Butyl, CH$_3$, O,

and Y is selected from the group consisting of H,
or a pharmaceutically acceptable salt, ester, or prodrug thereof, and one or more pharmaceutically acceptable carriers, excipients, or diluents.

[0141] Other embodiments are pharmaceutical compositions wherein $R_{104}$ is

![Chemical structure](image1)

and wherein $R_{103}$ is optionally substituted $-\text{CH}_2-2\text{-yl-thienyl}$ or optionally substituted $-\text{CH}_2\text{-phenyl}$.

Another embodiment is when $R_{103}$ is optionally substituted $-\text{CH}_2-2\text{-yl-thienyl}$.

[0142] Other embodiments are when the pharmaceutical composition has a compound of formula (X) as above when $R_{101}$ is $\text{H}$, or when $Y$ is selected from the group consisting of

![Chemical structures](image2)

and more particularly when $Y$ is $\text{-methylene-cyclopentyl}$.

[0143] The present invention also relates to a method for the inhibition of the normal biological function of factor IX comprising administering to a subject a compound of Formula (X)

![Chemical structure](image3)

wherein $R_{101}$ is selected from the group consisting of $-\text{H}$, or $-\text{CH}_2\text{-thienyl}$ wherein the thienyl group in $-\text{CH}_2\text{-thienyl}$ is optionally substituted with $-\text{Br}$ or $-\text{CH}_3$, $R_{102}$ is selected from the group consisting of $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{OCH}_3$, $-\text{C}(\text{O})\text{Ot-butyl}$, $-\text{C}(\text{O})\text{NH}-\text{OCH}_2\text{-phenyl}$, $-\text{C}(\text{O})\text{NHOH}$, and $-\text{C}(\text{O})\text{NEISO}_2\text{CH}_3$; $R_{103}$ is selected from the group consisting of $-\text{H}$, $-\text{CH}_2\text{-thienyl}$, $-\text{CH}_2\text{-phenyl}$, $-\text{CH}_2\text{-furanyl}$, thienyl, and benzothienyl wherein each of the above possibilities for $R_{103}$ except $-\text{H}$ are optionally substituted with one or more members selected from group consisting of $-\text{H}$, $-\text{CH}_3$, $-\text{CF}_3$, $-\text{Cl}$, $-\text{Br}$, $-\text{F}$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}==\text{CH}_2$, $-\text{CH}_2\text{OH}$, $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}_2\text{CH}_3$, and $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$.
and Y is selected from the group consisting of H, or a pharmaceutically acceptable salt, ester, or prodrug thereof.

[0144] In another embodiment, the instant invention relates to a method for the inhibition of the normal biological function of factor IX, wherein the compound of formula (X) is delivered as part of a pharmaceutical composition.

[0145] In another embodiment, the method for the inhibition of the normal biological function of factor IX uses a compound of formula (X) wherein R_{104} is

$$\text{t-Butyl} \quad \text{O}$$

or, wherein R_{103} is optionally substituted —CH$_2$-yl-thienyl or optionally substituted —CH$_2$-phenyl.

[0146] Another embodiment is the method for the inhibition of the normal biological function of factor IX wherein a compound of formula (X) is administered and R_{101} is —H, or wherein Y is selected from the group consisting of

Another method for the inhibition of the normal biological function of factor IX is administering a compound when Y is —methylene-cyclopentyl.

[0147] In another embodiment, the instant invention comprises a method of treating stroke, myocardial infarction, an aneurysm, or thrombosis comprising administering to a subject a compound of Formula (X)
and \(Y\) is selected from the group consisting of \(H\), or a pharmaceutically acceptable salt, ester, or prodrug thereof.

[0148] In another embodiment, the method of treating the above enumerated diseases comprises administering a compound of formula (X) as part of a pharmaceutical composition.

In another embodiment, the method of treating the above enumerated diseases comprises administering a compound of formula (X) wherein \(R_{104}\) is

or wherein \(R_{104}\) is optionally substituted —\(CH_2\)-yl-thienyl or optionally substituted —\(CH_2\)-phenyl. In an embodiment, \(R_{101}\) is —\(H\).

[0149] One method of treating the above enumerated diseases uses a compound that is selected from the group consisting of

[0150] 2(S)\{-[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-amino\} -3-(5-phenyl-thiophen-2-yl)-propionic acid,

[0151] 2(S)\{-[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-amino\} -3-[5-(4-trifluoromethyl-phenyl)-thiophen-2-yl]-propionic acid,

[0152] 2(S)\{-[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-amino\} -3-[5-cyclopent-1-etyl-thiophen-2-yl]-propionic acid methyl ester,

[0153] 2(S)\{-[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-amino\} -3-(5-cyclopent-1-etyl-thiophen-2-yl)-propionic acid,

[0154] 2(S)\{-[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-amino\} -3-(5-cyclopent-thiophen-2-yl)-propionic acid methyl ester,

[0155] 2(S)\{-[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-amino\} -3-(5-cyclopent-thiophen-2-yl)-propionic acid,

[0156] 2(S)\{-[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-amino\} -3-[5-furan-3-yl-thiophen-2-yl]-propionic acid,

[0157] 2(S)\{-[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-amino\} -3-[5-(4-isopropyl-phenyl)-thiophen-2-yl]-propionic acid,

[0158] 2(S)\{-[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-amino\} -3-(5-vinyl-thiophen-2-yl)-propionic acid,

[0159] 2(S)\{-[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-amino\} -3-(5-p-toly-thiophen-2-yl)-propionic acid,

[0160] 2(S)\{-[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-amino\} -3-[5-(4-chloro-phenyl)-thiophen-2-yl]-propionic acid,

[0161] 2(S)\{-[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-amino\} -3-(5-ethyl-thiophen-2-yl)-propionic acid,

[0162] 2(S)\{-[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-amino\} -3-furan-2-yl-propionic acid,

[0163] 2(S)\{-[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-amino\} -3-[2-trifluoromethyl-ethyl]-propionic acid,

[0164] \{5-Bromo-thiophen-2-ylmethyl\}\{-[7-(4-tert-butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-amino\}-acetic acid tert-butyl ester,

[0165] 2(S)\{-[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-amino\} -3-(3,5-difluorophenyl)-propionic acid,

[0166] \{7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl\}\{-5-methyl-thiophen-2-ylmethyl-amino\}-acetic acid,

[0167] \{5-Bromo-thiophen-2-ylmethyl\}\{-[7-(4-tert-butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-amino\}-acetic acid methyl ester,

[0168] \{4-Bromo-thiophen-2-ylmethyl\}\{-[7-(4-tert-butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-amino\}-acetic acid,

[0169] \{5-Bromo-thiophen-2-ylmethyl\}\{-[7-(4-tert-butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-amino\}-acetic acid,

[0170] Benzo[b]thiophen-3-yl\{-[7-(4-tert-butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-amino\}-acetic acid,

[0171] 2(S)\{-[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-amino\} -3-(4-fluoro-phenyl)-propionic acid,

[0172] 2(S)\{-[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-amino\} -3-(5-propenyl-thiophen-2-yl)-propionic acid,
[0173] 2(S)-[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isquinoline-3-carbonyl]-amino]-3-(5-propyliothien-2-yI)-propionic acid,

[0174] 2(S)-[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isquinoline-3-carbonyl]-amino]-3-(5,3-dimethyl-but-1-enyl)-thiophen-2-yl)-propionic acid,

[0175] 2(S)-[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isquinoline-3-carbonyl]-amino]-3-(5-hydroxymethyl-thiophen-2-yI)-propionic acid methyl ester,

[0176] 2(S)-[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isquinoline-3-carbonyl]-amino]-3-(5-hydroxymethyl-thiophen-2-yI)-propionic acid,

[0177] 2(S)-[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isquinoline-3-carbonyl]-amino]-3-(5-methylthiophen-2-yI)-propionic acid,

[0178] 2(S)-[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isquinoline-3-carbonyl]-amino]-3-(5-isopropenylthiophen-2-yI)-propionic acid,

[0179] 2(S)-[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isquinoline-3-carbonyl]-amino]-3-(5-isopropylthiophen-2-yI)-propionic acid,

[0180] 3-(5-Bromo-thiophen-2-yI)-2(R)-[7-(4-tert-butyl-phenoxy)-1-cyclopentylmethyl-isquinoline-3-carbonyl]-amino]-propionic acid,

[0181] 2(R)-[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isquinoline-3-carbonyl]-amino]-3-(5-chlorothiophen-2-yI)-propionic acid,

[0182] 2(S)-[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isquinoline-3-carbonyl]-amino]-3-(5-chlorofuran-2-yI)-propionic acid,

[0183] 2(S)-[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isquinoline-3-carbonyl]-amino]-3-(2,5-dichlorothiophen-3-yI)-propionic acid,

[0184] 3-(5-Bromo-thiophen-2-yI)-[7-(4-tert-butyl-phenoxy)-1-cyclopentylmethyl-isquinoline-3-carbonyl]-amino]-acetic acid,

[0185] 3-(5-Bromo-furan-2-yI)-2(S)-[7-(4-tert-butyl-phenoxy)-1-cyclopentylmethyl-isquinoline-3-carbonyl]-amino]-propionic acid,

[0186] 3-(5-Bromo-thiophen-2-yI)-2(S)-[7-(4-trans-tert-butyl-cyclohexyloxy)-1-cyclopentylmethyl-isquinoline-3-carbonyl]-amino]-propionic acid,

[0187] 3-(5-Bromo-thiophen-2-yI)-2(S)-[7-(4-trans-tert-butyl-cyclohexyloxy)-1-cyclopentylmethyl-isquinoline-3-carbonyl]-amino]-propionic acid,

[0188] 2(S)-[7-(4-trans-tert-Butyl-cyclohexyloxy)-1-cyclopentylmethyl-isquinoline-3-carbonyl]-amino]-3-(5-isopropenyl-thiophen-2-yI)-propionic acid,

[0189] 2(S)-[7-(4-trans-tert-Butyl-cyclohexyloxy)-1-cyclopentylmethyl-isquinoline-3-carbonyl]-amino]-3-(5-isopropyl-thiophen-2-yI)-propionic acid,

[0190] 2(S)-[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isquinoline-3-carbonyl]-amino]-3-(5-isopropenyl-furan-2-yI)-propionic acid,

[0191] 2(S)-[1-Cyclopentylmethyl-7-(4-isopropyl-cyclohexyloxy)-isquinoline-3-carbonyl]-amino]-3-(5-isopropyl-thiophen-2-yI)-propionic acid,

[0192] 2(R)-[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isquinoline-3-carbonyl]-amino]-3-(5-propyliothien-2-yI)-propionic acid,

[0193] 2(S)-[7-(4-tert-Butyl-phenoxy)-isquinoline-3-carbonyl]-amino]-3-(5-isopropyl-thiophen-2-yI)-propionic acid,

[0194] 2(S)-[1-Cyclopentylmethyl-7-(4-trans-ethyl-cyclohexyloxy)-isquinoline-3-carbonyl]-amino]-3-(5-isopropyl-thiophen-2-yI)-propionic acid,

[0195] 2(S)-[1-Cyclopentylmethyl-7-(4-isopropyl-phenoxy)-isquinoline-3-carbonyl]-amino]-3-(5-isopropyl-thiophen-2-yI)-propionic acid,

[0196] 2(S)-[7-(4-tert-Butyl-phenoxy)-1-(tetrahydro-pyran-4-yI)-isquinoline-3-carbonyl]-amino]-3-(5-isopropyl-thiophen-2-yI)-propionic acid,

[0197] 2(S)-[6-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isquinoline-3-carbonyl]-amino]-3-(5-isopropyl-thiophen-2-yI)-propionic acid,

[0198] 2(S)-[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isquinoline-3-carbonyl]-amino]-3-(5-isopropyl-thiophen-2-yI)-propionic acid,

[0199] 2(S)-[7-(4-tert-Butyl-benzoyl)-1-cyclopentylmethyl-isquinoline-3-carbonyl]-amino]-3-(5-isopropyl-thiophen-2-yI)-propionic acid,

[0200] 3-(5-Acetyl-thiophen-2-yI)-2(S)-[7-(4-tert-butyl-phenoxy)-1-cyclopentylmethyl-isquinoline-3-carbonyl]-amino]-propionic acid,

[0201] 7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isquinoline-3-carboxylic acid [1-(5-isopropyl-thiophen-2-yI)-methyl]-2(R)-methanesulfonylamino-2-oxo-ethyl]-amide,

[0202] 7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isquinoline-3-carboxylic acid [1-(5-isopropyl-thiophen-2-yI)-methyl]-2(S)-methanesulfonylamino-2-oxo-ethyl]-amide,

[0203] 7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isquinoline-3-carboxylic acid [1-benzyloxy-carbamoyl-2-(5-isopropyl-thiophen-2-yI)-ethyl]-amide, and


[0205] In another embodiment, the method of treating the above-enumerated diseases comprises the administration of formula (X) wherein Y is selected from the group consisting of

![Chemical Structure](image-url)
In another embodiment, the method of treating the above-mentioned diseases comprises the administration of formula (X) wherein Y is -methylene-cyclopentyl.

[0206] Also included within the scope of the invention are the individual enantiomers of the compounds represented by Formula (I or X) above as well as any wholly or partially racemic mixtures thereof. The present invention also covers the individual enantiomers of the compounds represented by formulas above as mixtures with diastereoisomers thereof in which one or more stereocenters are inverted.

[0207] Compounds of the present invention are listed in Table 1 below.

<table>
<thead>
<tr>
<th>EX.</th>
<th>Compound</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>![Image]</td>
<td>2(S)-7-(4-tert-Butyl phenoxy)-1-cyclopentylmethyl isoquinoline-3-carbonyl amino-3-(5-phenyl thiophen-2-yl)-propionic acid</td>
</tr>
<tr>
<td>2</td>
<td>![Image]</td>
<td>2(S)-7-(4-tert-Butyl phenoxy)-1-cyclopentylmethyl isoquinoline-3-carbonyl amino-3-(5-cyclopent-1-enyl-thiophen-2-yl)-propionic acid methyl ester</td>
</tr>
<tr>
<td>3</td>
<td>![Image]</td>
<td>2(S)-7-(4-tert-Butyl phenoxy)-1-cyclopentylmethyl isoquinoline-3-carbonyl amino-3-(5-cyclopent-1-enyl-thiophen-2-yl)-propionic acid methyl ester</td>
</tr>
<tr>
<td>EX.</td>
<td>Compound</td>
<td>Name</td>
</tr>
<tr>
<td>-----</td>
<td>----------</td>
<td>------</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Compound 4" /></td>
<td>2(S)-[[7-(4-tert-Butyl-phenoxo)y]-1-cyclopropylmethyl-isoquinoline-3-carbonyl]-amino)-3-(5-cyclopent-1-enyl-thiophen-2-yl)-propionic acid</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Compound 5" /></td>
<td>2(S)-[[7-(4-tert-Butyl-phenoxo)y]-1-cyclopropylmethyl-isoquinoline-3-carbonyl]-amino)-3-(5-cyclopentyl-thiophen-2-yl)-propionic acid methyl ester</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="Compound 6" /></td>
<td>2(S)-[[7-(4-tert-Butyl-phenoxo)y]-1-cyclopropylmethyl-isoquinoline-3-carbonyl]-amino)-3-(5-cyclopentyl-thiophen-2-yl)-propionic acid</td>
</tr>
<tr>
<td>EX.</td>
<td>Compound</td>
<td>Name</td>
</tr>
<tr>
<td>-----</td>
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</tr>
<tr>
<td>7</td>
<td><img src="image" alt="Compound 7" /></td>
<td>2(S)-{(1-tert-Butylphenoxymethyl)-cyclopropylmethylisoquinoline-3-carbonyl}-1-amino)-3-(5-fluor-3-ylthiophen-2-yl)-propionic acid</td>
</tr>
<tr>
<td>8</td>
<td><img src="image" alt="Compound 8" /></td>
<td>2(S)-{(1-tert-Butylphenoxymethyl)-cyclopropylmethylisoquinoline-3-carbonyl}-1-amino)-3-(5-fluor-3-ylthiophen-2-yl)-propionic acid</td>
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<tr>
<td>9</td>
<td><img src="image" alt="Compound 9" /></td>
<td>2(S)-{(1-tert-Butylphenoxymethyl)-cyclopropylmethylisoquinoline-3-carbonyl}-1-amino)-3-(5-fluor-3-ylthiophen-2-yl)-propionic acid</td>
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<tr>
<td>EX.</td>
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<tr>
<td>10</td>
<td><img src="image1.png" alt="Chemical Structure 1" /></td>
<td>2(S)-[(7-(4-tert-Butyl-phenoxo)-1-cyclopropylmethyl-isoquinoline-3-carbonyl]-amino)-3-(5-p-tolyl-thiophen-2-yl)-propionic acid</td>
</tr>
<tr>
<td>11</td>
<td><img src="image2.png" alt="Chemical Structure 2" /></td>
<td>2(S)-[(7-(4-tert-Butyl-phenoxo)-1-cyclopropylmethyl-isoquinoline-3-carbonyl]-amino)-3-[5-(4-chloro-phenyl)-thiophen-2-yl]-propionic acid</td>
</tr>
<tr>
<td>12</td>
<td><img src="image3.png" alt="Chemical Structure 3" /></td>
<td>2(S)-[(7-(4-tert-Butyl-phenoxo)-1-cyclopropylmethyl-isoquinoline-3-carbonyl]-amino)-3-(5-ethyl-thiophen-2-yl)-propionic acid</td>
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TABLE 1-continued

<table>
<thead>
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<th>EX.</th>
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<tr>
<td>13</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>2(S)-[(7-(4-tert-Butyl-phenoxycarbonyl)-1-cyclopropylmethyl-isooquinoline-3-carboxyl)amino]-3-furane-2-yl-propionic acid</td>
</tr>
<tr>
<td>14</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>2(S)-[(7-(4-tert-Butyl-phenoxycarbonyl)-1-cyclopropylmethyl-isooquinoline-3-carboxyl)amino]-3-(2-trifluoromethyl-phenyl)-propionic acid</td>
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<tr>
<td>15</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>(5-Bromo-thiophen-2-ylmethyl)-[7-(4-tert-butyphenoxycarbonyl)-1-cyclopropylmethyl-isooquinoline-3-carboxyl]amino]-acetic acid tert-butyl ester</td>
</tr>
<tr>
<td>16</td>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>2(S)-[(7-(4-tert-Butyl-phenoxycarbonyl)-1-cyclopropylmethyl-isooquinoline-3-carboxyl)amino]-3-(3,5-difluorophenyl)-propionic acid</td>
</tr>
<tr>
<td>EX.</td>
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</tr>
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<td>----------</td>
<td>------</td>
</tr>
<tr>
<td>17</td>
<td><img src="image17.png" alt="ChemicalStructure17" /></td>
<td>((7-(4\text{-}tert\text{-}butyl\text{-}phenoxy})\text{-}1\text{-}cyclopropyl\text{-}methyl\text{-}isoquinoline\text{-}3\text{-}carbonyl}\text{-}(5\text{-}methyl\text{-}thiophen\text{-}2\text{-}ylmethyl\text{-}amino)\text{-}acetic acid</td>
</tr>
<tr>
<td>18</td>
<td><img src="image18.png" alt="ChemicalStructure18" /></td>
<td>((5\text{-}bromo\text{-}thiophen\text{-}2\text{-}ylmethyl)\text{-}7\text{-}(4\text{-}tert\text{-}butyl\text{-}phenoxy)\text{-}3\text{-}cyclopropyl\text{-}methyl\text{-}isoquinoline\text{-}3\text{-}carbonyl\text{-}amino)\text{-}acetic acid methyl ester</td>
</tr>
<tr>
<td>19</td>
<td><img src="image19.png" alt="ChemicalStructure19" /></td>
<td>((4\text{-}bromo\text{-}thiophen\text{-}2\text{-}ylmethyl)\text{-}7\text{-}(4\text{-}tert\text{-}butyl\text{-}phenoxy)\text{-}3\text{-}cyclopropyl\text{-}methyl\text{-}isoquinoline\text{-}3\text{-}carbonyl\text{-}amino)\text{-}acetic acid</td>
</tr>
<tr>
<td>20</td>
<td><img src="image20.png" alt="ChemicalStructure20" /></td>
<td>((5\text{-}bromo\text{-}thiophen\text{-}2\text{-}ylmethyl)\text{-}7\text{-}(4\text{-}tert\text{-}butyl\text{-}phenoxy)\text{-}1\text{-}cyclopropyl\text{-}methyl\text{-}isoquinoline\text{-}3\text{-}carbonyl\text{-}amino)\text{-}acetic acid</td>
</tr>
<tr>
<td>EX.</td>
<td>Compound</td>
<td>Name</td>
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<td>-----</td>
<td>----------</td>
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<tr>
<td>21</td>
<td><img src="image1.png" alt="Chemical Structure 21" /></td>
<td>Benzof[b]thiophen-3-yl-[[7-(4-tert-butyl-phenoxyl)-1-cyclopropylmethylisquinoline-3-carboxyl]-amino]-acetic acid</td>
</tr>
<tr>
<td>22</td>
<td><img src="image2.png" alt="Chemical Structure 22" /></td>
<td>(S)-[[7-(4-tert-Butylphenoxyl)-1-cyclopropylmethylisquinoline-3-carboxyl]-amino]-3-(4-fluoro-phenyl)-propionic acid</td>
</tr>
<tr>
<td>23</td>
<td><img src="image3.png" alt="Chemical Structure 23" /></td>
<td>(S)-[[7-(4-tert-Butylphenoxyl)-1-cyclopropylmethylisquinoline-3-carboxyl]-amino]-3-(5-propynyl-thiophen-2-yl)-propionic acid</td>
</tr>
<tr>
<td>24</td>
<td><img src="image4.png" alt="Chemical Structure 24" /></td>
<td>(S)-[[7-(4-tert-Butylphenoxyl)-1-cyclopropylmethylisquinoline-3-carboxyl]-amino]-3-(5-propyly-thiophen-2-yl)-propionic acid</td>
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TABLE 1-continued

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<th>EX.</th>
<th>Compound</th>
<th>Name</th>
</tr>
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<tbody>
<tr>
<td>25</td>
<td>[2(S)-7-(4-tert-Butyl phenoxy)-1-cyclopentylmethyl isoquinoline-3-carbonyl amino-3-(5-hydroxymethyl thiophen-2-yl)-propionic acid]</td>
<td>Chiral</td>
</tr>
<tr>
<td>26</td>
<td>[2(S)-7-(4-tert-Butyl phenoxy)-1-cyclopentylmethyl isoquinoline-3-carbonyl amino-3-(5-hydroxymethyl thiophen-2-yl)-propionic acid methyl ester]</td>
<td>Chiral</td>
</tr>
<tr>
<td>EX.</td>
<td>Compound</td>
<td>Name</td>
</tr>
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<td>------</td>
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<tr>
<td>27</td>
<td><img src="https://via.placeholder.com/150" alt="Chemical Structure" /></td>
<td>2(S)-[(7-(4-tert-Butyl-phenoxo)-1-cyclopropylmethyl-isoquinoline-3-carboxyl)-amino]-3-(5-hydroxymethyl-thiophen-2-yl)-propionic acid</td>
</tr>
<tr>
<td>28</td>
<td><img src="https://via.placeholder.com/150" alt="Chemical Structure" /></td>
<td>2(S)-[(7-(4-tert-Butyl-phenoxo)-1-cyclopropylmethyl-isoquinoline-3-carboxyl)-amino]-3-(5-methyl-thiophen-2-yl)-propionic acid</td>
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<tr>
<td>29</td>
<td><img src="https://via.placeholder.com/150" alt="Chemical Structure" /></td>
<td>2(S)-[(7-(4-tert-Butyl-phenoxo)-1-cyclopropylmethyl-isoquinoline-3-carboxyl)-amino]-3-(5-isopropenyl-thiophen-2-yl)-propionic acid</td>
</tr>
</tbody>
</table>
TABLE 1-continued

<table>
<thead>
<tr>
<th>EX.</th>
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<tbody>
<tr>
<td>30</td>
<td><img src="image1" alt="structure1" /></td>
<td>2(S)-[7-(4-tert-Butyl-phenoxoy)-1-cyclopropylmethyl-isoquinoline-3-carboxyl]-amino]-3-(5-isopropylthiophen-2-yl)-propionic acid</td>
</tr>
<tr>
<td>31</td>
<td><img src="image2" alt="structure2" /></td>
<td>3-(5-Bromo-thiophen-2-yl)-2(R)-[7-(4-tert-butyl-phenoxoy)-1-cyclopropylmethyl-isoquinoline-3-carboxyl]-amino]-propionic acid</td>
</tr>
<tr>
<td>32</td>
<td><img src="image3" alt="structure3" /></td>
<td>2(R)-[7-(4-tert-Butyl-phenoxoy)-1-cyclopropylmethyl-isoquinoline-3-carboxyl]-amino]-3-(5-chlorothiophen-2-yl)-propionic acid</td>
</tr>
<tr>
<td>EX.</td>
<td>Compound</td>
<td>Name</td>
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</tr>
<tr>
<td>33</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>2(S)-[(7-(4-tert-Butyl-phenoxo)-1-cyclopentylmethyl-isoquinoline-3-carboxyl)-amino]-3-(5-chloro-furan-2-yl)-propionic acid</td>
</tr>
<tr>
<td>34</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>2(S)-[(7-(4-tert-Butyl-phenoxo)-1-cyclopentylmethyl-isoquinoline-3-carboxyl)-amino]-3-(2,5-dichlorothiophen-3-yl)-propionic acid</td>
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<tr>
<td>35</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>(5-Bromo-thiophen-2-yl)-[(7-(4-tert-butyl-phenoxo)-1-cyclopentylmethyl-isoquinoline-3-carboxyl)-amino]-acetic acid</td>
</tr>
<tr>
<td>EX.</td>
<td>Compound</td>
<td>Name</td>
</tr>
<tr>
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<tr>
<td>36</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>3-(5-Bromo-furan-2-yl)-2(S)-N-[7-(4-tert-butylocyclohexyloxy)-1-cyclopropylmethyliodoquinoline-3-carboxy]-amino]-propionic acid</td>
</tr>
<tr>
<td>37</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>3-(5-Bromo-thiophen-2-yl)-2(S)-N-[6-(4-tert-butylocyclohexyloxy)-1-cyclopropylmethyliodoquinoline-3-carboxy]-amino]-propionic acid</td>
</tr>
<tr>
<td>38</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>3-(5-Bromo-4-thiophen-2-yl)-2(S)-N-[7-(4-tert-butylocyclohexyloxy)-1-cyclopropylmethyliodoquinoline-3-carboxy]-amino]-propionic acid</td>
</tr>
<tr>
<td>39</td>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>2(S)-N-[7-(4-tert-butylocyclohexyloxy)-1-cyclopropylmethyliodoquinoline-3-carboxy]-amino]-3-(5-isopropenylthiophen-2-yl)-propionic acid</td>
</tr>
<tr>
<td>EX.</td>
<td>Compound</td>
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</tr>
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<tr>
<td>40</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>Chiral 2(8S)-[7-(4-trans-tert-Butylcyclohexyloxy)-1-cyclohexylmethylisoquinoline-3-carbonyl]-amino)-3-(5-isopropylthiophen-2-yl)-propionic acid</td>
</tr>
<tr>
<td>41</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>Chiral 2(8S)-[7-(4-trans-Butylphenoxo)-1-cyclohexylmethylisoquinoline-3-carbonyl]-amino)-3-(5-isopropyl-furan-2-yl)-propionic acid</td>
</tr>
<tr>
<td>42</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>Chiral 2(8S)-[1-Cyclohexylmethyl-7-(4-isopropyl-cyclohexyloxy)-isoquinoline-3-carbonyl]-amino)-3-(5-isopropyl-thiophen-2-yl)-propionic acid</td>
</tr>
<tr>
<td>EX.</td>
<td>Compound</td>
<td>Name</td>
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<td>-----</td>
<td>----------</td>
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</tr>
<tr>
<td>43</td>
<td><img src="image1.png" alt="Chemical Structure" /></td>
<td>2(R)-[7-(4-tert-Butyl-phenoxo)-1-cyclopentanylmethyl-isoquinoline-3-carbonyl]-amino]-3-(5-isopropyl-thiophen-2-yl)-propionic acid</td>
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<tr>
<td>44</td>
<td><img src="image2.png" alt="Chemical Structure" /></td>
<td>2(S)-[7-(4-tert-Butyl-phenoxo)-isoquinoline-3-carbonyl]-amino]-3-(5-isopropyl-thiophen-2-yl)-propionic acid</td>
</tr>
<tr>
<td>45</td>
<td><img src="image3.png" alt="Chemical Structure" /></td>
<td>2(S)-[1-Cyclopentylmethyl-7-(4-trans-ethyl-cyclohexyl-oxy)-isoquinoline-3-carbonyl]-amino]-3-(5-isopropyl-thiophen-2-yl)-propionic acid</td>
</tr>
</tbody>
</table>
### TABLE 1-continued

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<tr>
<td>46</td>
<td><img src="image1" alt="Compound 46" /></td>
<td>Chiral 2(S)-[(1-Cyclopropylmethyl)-7-(4-isopropyl-phenoxoy)-isoquinoline-3-carboxy]-amino]-3-(5-isopropyl-thiophen-2-yl)-propionic acid</td>
</tr>
<tr>
<td>47</td>
<td><img src="image2" alt="Compound 47" /></td>
<td>Chiral 2(S)-[(7-(4-tert-Butyl-phenoxoy)-1-(tetrahydro-pyran-4-y)-isoquinoline-3-carboxy]-amino]-3-(5-isopropyl-thiophen-2-yl)-propionic acid</td>
</tr>
<tr>
<td>48</td>
<td><img src="image3" alt="Compound 48" /></td>
<td>Chiral 2(S)-[(6-(4-tert-Butyl-phenoxoy)-1-cyclopropylmethyl-isoquinoline-3-carboxy]-amino]-3-(5-isopropyl-thiophen-2-yl)-propionic acid</td>
</tr>
</tbody>
</table>
TABLE 1-continued

<table>
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<td>49</td>
<td><img src="image1.png" alt="Chemical Structure" /></td>
<td>2-(S)-(7-(4-tert-Butyl-phenyl)-1-cyclopropylnethyl)-isosquoline-3-carboxylic acid (S)-3-(5-isopropyl-thiophen-2-yl)-propionic acid</td>
</tr>
<tr>
<td>50</td>
<td><img src="image2.png" alt="Chemical Structure" /></td>
<td>2-(S)-(7-(4-tert-Butyl-benzoyl)-1-cyclopropylnethyl)-isosquoline-3-carboxylic acid (S)-3-(5-isopropyl-thiophen-2-yl)-propionic acid</td>
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<td>51</td>
<td><img src="image3.png" alt="Chemical Structure" /></td>
<td>3-(5-Acetyl-thiophen-2-yl)-2-(S)-(7-(4-tert-Butyl-phenyl)-1-cyclopropylnethyl)-isosquoline-3-carboxylic acid (S)-3-(5-isopropyl-thiophen-2-yl)-propionic acid</td>
</tr>
<tr>
<td>52</td>
<td><img src="image4.png" alt="Chemical Structure" /></td>
<td>7-(4-tert-Butyl-phenoxyl)-1-cyclopropylnethyl)-isosquoline-3-carboxylic acid (S)-3-(5-isopropyl-thiophen-2-yl)-propionic acid (S)-methanesulfonfylaminino-2-oxo-ethyl]-amide</td>
</tr>
<tr>
<td>EX.</td>
<td>Compound</td>
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<td>----------</td>
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</tr>
<tr>
<td>53</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>Chiral 7-(4-tert-Butyl-phenoxy)-1-cyclopropylmethylisoquinoline-3-carboxylic acid 1-(5-isopropyl-thiophen-2-ylmethyl)-2(S)-methanesulfonylthiophene-2-oxo-ethoxy-amide</td>
</tr>
<tr>
<td>54</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>Chiral 7-(4-tert-Butyl-phenoxy)-1-cyclopropylmethylisoquinoline-3-carboxylic acid 1-benzyloxycarbamoyl 2-(5-isopropyl-thiophen-2-yl)-ethyl-amide</td>
</tr>
<tr>
<td>55</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>Chiral 7-(4-tert-Butyl-phenoxy)-1-cyclopropylmethylisoquinoline-3-carboxylic acid 1-hydroxycarbamoyl 2-(5-isopropyl-thiophen-2-yl)-ethylamide</td>
</tr>
</tbody>
</table>

[0208] Incomplete valences for heteroatoms such as oxygen and nitrogen in the chemical structures listed in Table 1 are assumed to be completed by hydrogen.

[0209] In another aspect, the present invention comprises a pharmaceutical composition comprising the compound of Formula (I or X) and one or more pharmaceutically acceptable carriers, excipients, or diluents.

[0210] As used herein, the term “alkyl” refers to a straight or branched chain hydrocarbon having from one to ten carbon atoms, optionally substituted with substituents selected from the group consisting of halo, lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, silyloxy optionally substituted by alkoxy, alkyl, or aryl, silyl optionally substituted by alkoxy, alkyl, or aryl,
nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. Such an “alkyl” group may containing one or more O, S, S(O), or S(O)_2 atoms.

Examples of “alkyl” as used herein include, but are not limited to, methyl, n-butyl, t-butyl, n-pentyl, isobutyl, and isoamyl, and the like.

[0212] As used herein, the term “alkylene” refers to a straight or branched chain divalent hydrocarbon radical having from one to ten carbon atoms, optionally substituted with substituents selected from the group consisting of halo, lower alkyl, lower alkoxy, lower alkyloxynyl, lower alkylsulfenyl, lower alkylsulfonyl, or haloxy, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, silyloxy optionally substituted by alkyl, alkyl, or aryl, silyl optionally substituted by alkoxo, alkyl, or aryl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. Such an “alkylene” group may containing one or more O, S, S(O), or S(O)_2 atoms. Examples of “alkylene” as used herein include, but are not limited to, methylene, ethylene, and the like.

[0213] As used herein, the term “alkenyl” refers to a hydrocarbon radical having from two to ten carbons and at least one carbon-carbon double bond, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkyloxynyl, lower alkylsulfinyl, lower alkylsulfenyl, lower alkylsulfonxy, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonxy optionally substituted by alkyl, silyloxy optionally substituted by alkyl, alkyl, or aryl, silyl optionally substituted by alkoxo, alkyl, or aryl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. Such an “alkenyl” group may containing one or more O, S, S(O), or S(O)_2 atoms.

[0214] As used herein, the term “alkenylene” refers to a straight or branched chain divalent hydrocarbon radical having from two to ten carbon atoms and one or more carbon-carbon double bonds, optionally substituted with substituents selected from the group consisting of halo, lower alkyl, lower alkoxy, lower alkyloxynyl, lower alkylsulfinyl, lower alkylsulfenyl, lower alkylsulfonxy, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonxy optionally substituted by alkyl, silyloxy optionally substituted by alkyl, alkyl, or aryl, silyl optionally substituted by alkoxo, alkyl, or aryl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. Such an “alkenylene” group may containing one or more O, S, S(O), or S(O)_2 atoms. Examples of “alkenylene” as used herein include, but are not limited to, ethene-1,2-diyi, propene-1,3-diyi, methylene-1,1-diyi, and the like.

[0215] As used herein, the term “alkynyl” refers to a hydrocarbon radical having from two to ten carbons and at least one carbon-carbon triple bond, optionally substituted with substituents selected from the group consisting of halo, lower alkyl, lower alkoxy, lower alkyloxynyl, lower alkylsulfinyl, lower alkylsulfenyl, lower alkylsulfonxy, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonxy optionally substituted by alkyl, silyloxy optionally substituted by alkyl, alkyl, or aryl, silyl optionally substituted by alkoxo, alkyl, or aryl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. Such an “alkynyl” group may containing one or more O, S, S(O), or S(O)_2 atoms.

[0216] As used herein, the term “alkynylene” refers to a straight or branched chain divalent hydrocarbon radical having from two to ten carbon atoms and one or more carbon-carbon triple bonds, optionally substituted with substituents selected from the group consisting of halo, lower alkyl, lower alkoxy, lower alkyloxynyl, lower alkylsulfinyl, lower alkylsulfenyl, lower alkylsulfonxy, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonxy optionally substituted by alkyl, silyloxy optionally substituted by alkyl, alkyl, or aryl, silyl optionally substituted by alkyl, alkyl, or aryl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. Such an “alkynylene” group may containing one or more O, S, S(O), or S(O)_2 atoms. Examples of “alkynylene” as used herein include, but are not limited to, ethyne-1,2-diyi, propyne-1,3-diyi, and the like.

[0217] As used herein, “cycloalkyl” refers to an aliphatic hydrocarbon group optionally possessing one or more degrees of unsaturation, consisting from three to twelve carbon atoms, optionally substituted with substituents selected from the group consisting of halo, lower alkyl, lower alkoxy, lower alkyloxynyl, lower alkylsulfinyl, lower alkylsulfenyl, lower alkylsulfonxy, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonxy optionally substituted by alkyl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. “Cycloalkyl” includes by way of example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl, and the like.

[0218] As used herein, the term “cycloalkylene” refers to an aliphatic hydrocarbon radical having from three to twelve carbon atoms and optionally possessing one or more degrees of unsaturation, optionally substituted with substituents selected from the group consisting of halo, lower alkyl, lower alkoxy, lower alkyloxynyl, lower alkylsulfinyl, lower alkylsulfenyl, lower alkylsulfonxy, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonxy optionally substituted by alkyl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. Examples of “cycloalkylene” as used herein include, but are not limited to, cyclopropen-1,1-diyi, cyclobuten-1,2-diyi, cyclohexen-1,2-diyi, cyclohexen-1,3-diyi, cyclohex-1,4-diyi, cyclohept-1,4-diyi, cyclooct-1,5-diyi, and the like.

[0219] As used herein, the term “heterocyclic” or the term “heterocyclyl” refers to a three to twelve-membered heterocyclic ring optionally possessing one or more degrees of unsaturation, containing one or more heteroatomic substitutions selected from S, SO, SO_2, or N, optionally substituted with substituents selected from the group consisting of halo, lower alkyl, lower alkoxy, lower alkyloxynyl, lower alkylsulfinyl, lower alkylsulfenyl, lower alkylsulfonxy, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonxy optionally substituted by alkyl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being
allowed. Such a ring may be optionally fused to one or more of another "heterocyclic" ring(s) or cycloalkyl ring(s). Examples of "heterocyclic" include, but are not limited to, tetrahydrofuran, 1,4-dioxane, 1,3-dioxane, pipеридине, pyрролине, морфолине, пиразине, and the like.

[0220] As used herein, the term "heterocyclylene" refers to a three to twelve-membered heterocyclic ring diradical optionally having one or more degrees of unsaturation containing one or more heteroatoms selected from S, SO, SO₂, O, or N, optionally substituted with substituents selected from the group consisting of halo, lower alkyl, lower alkoxy, lower alkythiolanyl, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carboxamyl optionally substituted by alkyl, amino sulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or lower perfluoralkyl, multiple degrees of substitution being allowed. Such a ring may be optionally fused to one or more benzene rings or to one or more of another "heterocyclic" rings or cycloalkyl rings.

Examples of "heterocyclylene" include, but are not limited to, tetrahydrofuran-2,5-diyl, morpholine-2,3-diyl, pyran-2,4-diyl, 1,4-dioxane-2,3-diyl, 1,3-dioxane-2,4-diyl, piperidine-2,4-diyl, piperridine-1,4-diyl, pyrroolidine-1,3-diyl, morpholine-2,4-diyl, piperazine-1,4-diyl, and the like.

[0221] As used herein, the term "aryl" refers to a benzene ring or to an optionally substituted benzene ring system fused to one or more optionally substituted benzene rings, optionally substituted with substituents selected from the group consisting of halo, lower alkyl, lower alkoxy, lower alkylthio, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, di(lower alkylamino)alkyl, aminoalkyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carboxamyl optionally substituted by alkyl, amino sulfonyl optionally substituted by alkyl, acyl, ary, heteroaryl, acyl amino, acyloxy, aryloxy, heteroaryloxy, alkoxy carbonyl, silyloxy optionally substituted by alkoxyl, acyl, or sily optionally substituted by alkoxyl, alkyl, or aryl, nitro, cyano, halogen, or lower perfluoralkyl, multiple degrees of substitution being allowed. Examples of aryl include, but are not limited to, phenyl, 2-naphthyl, 1-naphthyl, 1-anthracenyl, and the like.

[0222] As used herein, the term "arylene" refers to a benzene ring diradical or to a benzene ring system diradical fused to one or more optionally substituted benzene rings, optionally substituted with substituents selected from the group consisting of halo, lower alkyl, lower alkoxy, lower alkylthio, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, di(lower alkylamino)alkyl, aminoalkyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carboxamyl optionally substituted by alkyl, amino sulfonyl optionally substituted by alkyl, acyl, ary, heteroaryl, acyl amino, acyloxy, aryloxy, heteroaryloxy, alkoxy carbonyl, silyloxy optionally substituted by alkoxyl, alkyl, or aryl, sily optionally substituted by alkoxyl, alkyl, or aryl, nitro, cyano, halogen, or lower perfluoralkyl, multiple degrees of substitution being allowed. Examples of "arylene" include, but are not limited to, benzene-1,4-diyl, naphthalene-1,8-diyl, and the like.

[0223] As used herein, the term "heteroaryl" refers to a five- to seven-membered aromatic ring, or to a polycyclic heterocyclic aromatic ring, containing one or more nitrogen, oxygen, or sulfur heteroatoms, where N-oxides and sulfur monoxides and sulfur dioxides are permissible heteroaromatic substitutions, optionally substituted with substituents selected from the group consisting of halo, lower alkyl, lower alkoxy, lower alkylthiyl, lower alkylsulfanyl, lower alkylsulfenyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carboxamyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, ary, heteroaryl, acyloxy, aryloxy, heteroaryloxy, alkoxy carbonyl, silyloxy optionally substituted by alkoxyl, alkyl, or aryl, sily optionally substituted by alkoxyl, alkyl, or aryl, nitro, cyano, halogen, or lower perfluoralkyl, multiple degrees of substitution being allowed. For polycyclic aromatic ring systems, one or more of the rings may contain one or more heteroatoms. Examples of "heteroaryl" used herein are furan, thiophene, pyrrole, imidazole, pyrazole, triazole, tetrazole, thiazole, oxazole, isoxazole, oxadiazole, thiazolizole, isothiazole, pyridine, pyridazine, pyrimidine, quinoline, isoquinoline, quinazoline, benzofuran, benzo Thiophene, indole, and indazole, and the like.

[0224] As used herein, the term "heterocyclylene" refers to a five- to seven-membered aromatic ring diradical, or to a polycyclic heterocyclic aromatic ring diradical, containing one or more nitrogen, oxygen, or sulfur heteroatoms, where N-oxides and sulfur monoxides and sulfur dioxides are permissible heteroaromatic substitutions, optionally substituted with substituents selected from the group consisting of halo, lower alkyl, lower alkoxy, lower alkylthiyl, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carboxamyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, ary, heteroaryl, acyloxy, aryloxy, heteroaryloxy, alkoxy carbonyl, silyloxy optionally substituted by alkoxyl, alkyl, or aryl, sily optionally substituted by alkoxyl, alkyl, or aryl, nitro, cyano, halogen, or lower perfluoralkyl, multiple degrees of substitution being allowed. For polycyclic aromatic ring systems diradicals, one or more of the rings may contain one or more heteroatoms. Examples of "heterocyclylene" used herein are furan-2,5-diyl, thiophene-2,4-diyl, 1,3,4-oxadiazole-2,5-diyl, 1,3,4-thiadiazole-2,5-diyl, 1,3-thiazole-2,5-diyl, pyridine-2,4-diyl, pyridine-2,3-diyl, pyridine-2,5-diyl, pyrimidine-2,4-diyl, pyrimidine-2,3-diyl, and the like.

[0225] As used herein, the term "fused cycloalkylaryl" refers to a cycloalkyl group fused to an aryl group, the two having two atoms in common, and wherein the aryl group is the point of substitution. Examples of "fused cycloalkylaryl" used herein include 5-indanyl, 5,6,7,8-tetrahydro-2-naphthyl, and the like.

[0226] As used herein, the term "fused cycloalkylarylene" refers to a fused cycloalkylaryl, wherein the aryl group is divalent. Examples include
As used herein, the term “fused arylcycloalkyl” refers to an aryl group fused to a cycloalkyl group, the two having two atoms in common, and wherein the cycloalkyl group is the point of substitution. Examples of “fused arylcycloalkyl” used herein include 1-indanyl, 2-indanyl, 1-(1,2,3,4-tetrahydronaphthyl), and the like.

As used herein, the term “fused heterocyclylaryl” refers to a heterocyclyl group fused to an aryl group, the two having two atoms in common, and wherein the aryl group is the point of substitution. Examples of “fused heterocyclylaryl” used herein include 3,4-methylenedioxy-1-phenyl, and the like.

As used herein, the term “fused heterocyclylarylene” refers to a heterocyclylaryl, wherein the aryl group is divalent. Examples include 5-aza-6-indanyl, and the like.

As used herein, the term “fused cycloalkylheteroaryl” refers to a cycloalkyl group fused to a heteroaryl group, the two having two atoms in common, and wherein the heteroaryl group is the point of substitution. Examples of “fused cycloalkylheteroaryl” used herein include 2-(1,3-benzodioxolyl), and the like.
As used herein, the term "fused heteroaryl-cycloalkyl" refers to a heteroaryl group fused to a cycloalkyl group, the two having two atoms in common, and wherein the cycloalkyl group is the point of substitution. Examples of "fused heteroaryl-cycloalkyl" used herein include 5-aza-1-indanyl, and the like.

As used herein, the term "fused heteroaryl-cycloalkylene" refers to a fused heteroaryl-cycloalkyl, wherein the cycloalkyl group is divalent. Examples include

As used herein, the term "fused heterocyclyl-heteroaryl" refers to a heterocyclyl group fused to a heteroaryl group, the two having two atoms in common, and wherein the heteroaryl group is the point of substitution. Examples of "fused heterocyclyl-heteroaryl" used herein include 1,2,3,4-tetrahydro-beta-carbolin-8-yl, and the like.

As used herein, the term "fused heterocyclyl-heteroaryl-cycloalkyl" refers to a heterocyclyl group fused to a heterocyclyl-heteroaryl, wherein the heteroaryl group is divalent. Examples include

As used herein, the term "fused heterocyclyl-heteroaryl-cycloalkylene" refers to a fused heterocyclyl-heteroaryl-cycloalkyl, wherein the heterocyclyl group is divalent. Examples include

As used herein, the term "fused heterocyclyl-heteroaryl-dicarboxamide" refers to a dicarboxamide group fused to a heterocyclyl-heteroaryl group, wherein the two having two atoms in common and wherein the carboxamide group is the point of substitution. Examples of "fused heterocyclyl-heteroaryl-dicarboxamide" used herein include 5-aza-2,3-dihydrobenzo[furan-2-yl, and the like.

As used herein, the term "fused heterocyclyl-heteroaryl-dicarboxamide-cycloalkyl" refers to a heterocyclyl-heteroaryl-dicarboxamide group fused to a cycloalkyl group, wherein the two having two atoms in common and wherein the cycloalkyl group is the point of substitution. Examples of "fused heterocyclyl-heteroaryl-dicarboxamide-cycloalkyl" used herein include 5-aza-2,3-dihydrobenzo[furan-2-yl, and the like.

As used herein, the term "fused heterocyclyl-heteroaryl-dicarboxamide-cycloalkylene" refers to a fused heterocyclyl-heteroaryl-dicarboxamide-cycloalkyl, wherein the cycloalkyl group is divalent. Examples include

As used herein, the term "acid isostere" refers to a substituent group that may ionize at physiological pH to bear a negative charge. Examples of such "acid isosteres" include but are not limited to heteroaryl groups such as but not limited to isoxazol-3-ol-5-yl, 1H-tetrazole-5-yl, or 2H-tetrazole-5-yl. Such acid isosteres include but are not limited to heterocyclyl groups such as but not limited to imidazolidine-2,4-dione-5-yl, imidazolidine-2,4-dione-1-yl, 1,3-thiazolidine-2,4-dione-5-yl, or 5-hydroxy-4H-pyran-4-one-2-yl, 1,2,5-thiadiazolidin-3-one-1,1-dioxide-4-yl, or 1,2,5-thiadiazolidin-3-one-1,1-dioxide-5-yl.

As used herein, the term "ester isostere" refers to a substituent group that can be metabolically stable and can retain the selectivity and affinity of a corresponding ester toward a target protein. Examples of such "ester isosteres" include but are not limited to heteroaryl groups such as, but not limited to, 1,3-oxazole-5-yl, 1,3-oxazole-2-yl, 1,2,3-oxadiazole-5-yl, 1,2,4-oxadiazole-5-yl, 1,3,4-oxadiazole-5-yl, 1,2,3-thiadiazole-5-yl, 1,2,4-thiadiazole-5-yl, 1,3,4-thiadiazole-5-yl, 5-alkyl-1,3-oxazole-2-yl, 2-alkyl-1,3-oxazole-5-yl, 4-alkyl-1,2,3-oxadiazole-5-yl, 3-alkyl-1,2,4-
oxadiazole-5-yl, 2-alkyl-1,3,4-oxadiazole-5-yl, 4-alkyl-1,2,3-thiadiazole-5-yl, 3-alkyl-1,2,4-thiadiazole-5-yl, 2-alkyl-1,3,4-thiadiazole-5-yl, 1,2,4-triazole-1-yl, 3-alkyl-1,2,4-triazole-1-yl, tetrazole-1-yl, and 1-alkyl-tetrazole-5-yl; aryl groups such as, but not limited to, 3,5-difluoro-4-alkoxyphenyl; and heterocyclic groups such as, but not limited to, 1-alkyl-imidazolidine-2,4-dione-5-yl, imidazolidine-2,4-dione-1-yl, 3-alkyl-1,3-thiazolidine-2,4-dione-5-yl, and 5-alkoxy-4H-pyrano-4-on-2-yl. The alkyl groups in the heterocyclic, aryl, and heteroaryl groups of the ester isosteres may be replaced with a phenyl or alkylphenyl group.

As used herein, the term “direct bond”, where part of a structural variable specification, refers to the direct joining of the substituents flanking (preceding and succeeding) the variable taken as a “direct bond”.

As used herein, the term “alkoxy” refers to the group R₃O—, where R₃ is alkyl.

As used herein, the term “alkenylalkoxy” refers to the group R₃O—, where R₃ is alkenyl.

As used herein, the term “alkynyloxy” refers to the group R₃O—, where R₃ is alkynyl.

As used herein, the term “alkylsulfanyloxy” refers to the group R₃S—, where R₃ is alkyl.

As used herein, the term “alkenylsulfanyloxy” refers to the group R₃S—, where R₃ is alkenyl.

As used herein, the term “alkynylsulfanyloxy” refers to the group R₃S—, where R₃ is alkynyl.

As used herein, the term “alkylsulfanyl” refers to the group R₃S(O)—, where R₃ is alkyl.

As used herein, the term “alkenylsulfanyl” refers to the group R₃S(O)—, where R₃ is alkenyl.

As used herein, the term “alkynylsulfanyl” refers to the group R₃S(O)—, where R₃ is alkynyl.

As used herein, the term “alkylsulfonyl” refers to the group R₃SO₂—, where R₃ is alkyl.

As used herein, the term “alkenylsulfonyl” refers to the group R₃SO₂—, where R₃ is alkenyl.

As used herein, the term “alkynylsulfonyl” refers to the group R₃SO₂—, where R₃ is alkynyl.

As used herein, the term “acyl” refers to the group R₃C(O)—, where R₃ is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, or heterocyclyl.

As used herein, the term “aryl” refers to the group R₃C(O)—, where R₃ is aryl.

As used herein, the term “heteroaryl” refers to the group R₃C(O)—, where R₃ is heteroaryl.

As used herein, the term “alkoxycarbonyloxy” refers to the group R₃OC(O)—, where R₃ is alkyl.

As used herein, the term “acyloxy” refers to the group R₃C(O)O—, where R₃ is alkyl, alkynyl, alkynyl, cycloalkyl, cycloalkenyl, or heterocyclyl.

As used herein, the term “aryloxy” refers to the group R₃C(O)O—, where R₃ is aryl.
Whenever the terms “alkyl” or “aryl” or either of their prefix roots appear in a name of a substituent (e.g. arylalkoxyaryloxy) they shall be interpreted as including those limitations given above for “alkyl” and “aryl”. Designated numbers of carbon atoms (e.g. C_{1-10}) shall refer independently to the number of carbon atoms in an alkyl, alkenyl or alkynyl or cyclic alkyl moiety or to the alkyl portion of a larger substituent in which the term “alkyl” appears as its prefix root.

As used herein, the term “oxo” shall refer to the substituent —O.

As used herein, the term “halogen” or “halo” shall include iodine, bromine, chlorine and fluorine.

As used herein, the term “mercapto” shall refer to the substituent —SH.

As used herein, the term “carboxy” shall refer to the substituent —COOH.

As used herein, the term “cyano” shall refer to the substituent —CN.

As used herein, the term “aminosulfonyl” shall refer to the substituent —SO_{2}NH_{2}.

As used herein, the term “carbamoyl” shall refer to the substituent —C(O)NH_{2}.

As used herein, the term “sulfanyl” shall refer to the substituent —S—.

As used herein, the term “sulfenyl” shall refer to the substituent —S(O)—.

As used herein, the term “sulfonyl” shall refer to the substituent —S(O)_{2}—.

The compounds can be prepared according to the following reaction Schemes (in which variables are as defined before or are defined) using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are themselves known to those of ordinary skill in this art, but are not mentioned in greater detail.

The present invention also provides a method for the synthesis of compounds useful as intermediates in the preparation of compounds of Formula (I or X) along with methods for the preparation of compounds of Formula (I or X).

Scheme XIV describes the synthesis of a compound of formula (66). R_{85} and R_{86} may be groups such as but not limited to hydrogen, alkyl, or -alkylene-aryl. R_{81} may be a group such as the side chain of a natural or unnatural amino acid. R_{82} may be a group such as aryl, heteroaryl, alkyl, or cycloalkyl. R_{84} may be a group such as but not limited to alkyl, aryl, heteroaryl, cycloalkyl, -alkylene-cycloalkyl, or -alkylene-aryl.

Compound (62) represents a nitrogen containing fused heterocyclaryl ring system which may be synthesized by methods known in the art, such as acid catalyzed condensation of the corresponding amino acid with a carbonyl compound R_{85}C(O)R_{86} followed by protection at nitrogen with a protecting group such as but not limited to BOC. (62) may be treated with a peptide coupling agent such as DIC or HBTU, in the presence or absence of a base such as DIEA, in a solvent such as DMF of DCM, and an amino ester such as (63), to provide (64). An amine similar in structure to (63) may also be used to provide (64) without a methoxycarbonyl functionality. The phenol functionality of (64) may be functionalized by treatment of (64) with a primary or secondary alcohol in a solvent such as THF, with dialkyl azodicarboxylate and triphenylphosphine at a temperature of from −20°C to 25°C, to give (65) where R_{83} is alkyl, substituted alkyl, or cycloalkyl. (64) may also be treated with a aryl or heteroaryl boronic acid and copper (II) acetate to afford (65) where R_{83} is aryl or heteroaryl. The PG_{1} group of (65) may be removed as appropriate; the nitrogen thus freed may be functionalized with R_{83}, where R_{83} represents groups such as but not limited to a alkyl-sulfenyl group, a alkoxycarbonyl group, or an acyl or alkanoyl group. The methyl ester of the intermediate may be removed by treatment with, for example, lithium hydroxide in aqueous THF—methanol at a temperature of from 0°C to 25°C, to afford (66).
Scheme XV depicts the synthesis of a compound of formula (70). \( R_{85}, R_{82}, \) and \( R_{84} \) have the meanings described for Scheme XIV. The phenolic functionality of (67) may be functionalized as in Scheme XIV, and the \( PG_1 \) protecting group may be removed with a reagent such as TFA, where PG1 is tBOC. (68) may be treated with a reagent such as dichlorodicyanoquinone (DDQ) in a solvent such as toluene, at a temperature of from 25°C to 110°C, to afford the acid (69) after hydrolysis of the ester with a reagent such as lithium hydroxide in a solvent such as aqueous THF. In manner similar to that described in Scheme XIV, the acid (69) may be coupled with an amino ester or other amine and the ester, if present, may be hydrolyzed with aqueous alkali to afford (70).

Scheme XVI describes the synthesis of intermediates and further compounds of Formula I. The acid (69) may be coupled with a functionalized bromoaryl alanine ester, or other similar bromoaromatic substituted amine, under conditions described previously to afford (71). (71) may be transformed to (72) employing conditions described in Scheme II. Similarly, (69) may be coupled with a hydroxyaryl alanine ester, or other similar hydroxyaryl or hydroxyheteroaryl substituted amine, to give (73), which may be functionalized as described in Scheme III to provide (74).
[0287] Scheme XVII describes synthesis of compounds of formula (79). R_{85}, R_{82}, and R_{81} have the meanings as described for Scheme XIV. PG_{2} represents a hydroxyl protecting group. An N-acylated amino acid ester (75) may be treated with a reagent such as oxalyl chloride in a solvent such as DCM, at a temperature of from 0°C to 25°C, to afford an imidoyl chloride intermediate, which is treated with a reagent such as but not limited to FeCl_{3} in DCM, followed by treatment with sulfuric acid in methanol to afford the cyclized product; concomitant removal of PG_{2} (where PG_{2} is tert-butyl or benzyl) may occur, to afford (76). Where PG_{2} is not removed during these above steps, it may be removed, where PG_{2} is tert-butyl, by treatment with TFA or HCl in dioxane. (76) may be dehydrogenated by treatment with Pd/C in xylene at a temperature of from 25°C to 130°C, or by treatment with copper (II) acetate in DCM, to afford (77). The phenolic function of (77) may be functionalized as for Scheme XIV; as well, the product (78) after ester hydrolysis may be coupled with an amine or amino acid ester to give, after hydrolysis, the acid (79).

[0288] The term “amino-protecting group” as used herein refers to substituents of the amino group commonly employed to block or protect the amino functionality while reacting other functional groups on the compound. Examples of such amino-protecting groups include the formyl group, the triyl group, the phthalimidoc group, the trichloroacetetyl group, the chloroacetetyl, bromaacetetyl and iodacetetyl groups, urethane-type blocking groups such as benzylxycarbonyl, 4-phenylbenzoxycarbonyl, 2-methylbenzoxycarbonyl, 4-methoxybenzoxycarbonyl, 4-fluorobenzoxycarbonyl, 4-chlorobenzoxycarbonyl, 3-chlorobenzoxycarbonyl, 2-chlorobenzoxycarbonyl, 2,4-dichlorobenzoxycarbonyl, 4-bromobenzoxycarbonyl, 3-bromobenzoxycarbonyl, 4-nitrobenzoxycarbonyl, 4-cyanobenzoxycarbonyl, 2-(4-xenyl)iso-propoxyxycarbonyl, 1.1-diphenylketh-1-ylxycarbonyl, 1.1-diphenylketh-1-ylxycarbonyl, 2-phenylprop-2-yloxyxycarbonyl, 2-(p-toluyl)prop-2-yloxyxycarbonyl, cyclopentanyloxycarbonyl, 1-methylcyclopentanyloxycarbonyl, cyclohexanyloxycarbonyl, 1-methylcyclohexanyloxycarbonyl, 2-methylcyclohexanyloxycarbonyl, 2-(4-tolylsulfonyl)ethoxycarbonyl, 2-(methylsulfonyl)ethoxycarbonyl, 2-(triphenylphosphinoo)ethoxycarbonyl, 9-fluorenylmethoxycarbonyl ("FOMOC"), t-butoxycarbonyl ("BOC"), 2-(trimethylsilyl)ethoxycarbonyl, allyloxycarbonyl, 1-(trimethylsilylmethyl)prop-1-enyloxoxycarbonyl, 5-benzisoxalylmethoxycarbonyl, 4-acetoxybenzoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-ethynyl-2-propoxyxycarbonyl, cyclopropylmethoxycarbonyl, 4-(decyloxy)benzyloxycarbonyl, isobornyloxycarbonyl, 1-piperidylxycarbonyl and the like, the benzoylmethylsulfonyl group, the 2-(nitrophenylsulfenyl group, the diphenylphosphinooxide group and like amino-protecting...
groups. The species of amino-protecting group employed is not critical as long as the derivatized amino group is stable to the condition of subsequent reaction(s) on other positions of the compound of Formula (1 or X) and can be removed at the desired point without disrupting the remainder of the molecule. Commonly used amino-protecting groups are the alkyloxy carbonyl, the t-butoxy carbonyl, 9-fluorenyl methoxy carbonyl, and the trityl groups. Similar amino-protecting groups used in the cephalosporin, penicillin and peptide art are also embraced by the above terms. The related term “protected amino” or “protected amino group” defines an amino group substituted with an amino-protecting group discussed above.

[0289] The term “hydroxyl protecting group” as used herein refers to substituents of the alcohol group commonly employed to block or protect the alcohol functionality while reacting other functional groups on the compound. Examples of such alcohol protecting groups include the 2-tetrahydro propyl group, 2-ethoxyethyl group, the trityl group, the trichloracetate group, urethane-type blocking groups such as benzyl oxycarbonyl, and the trialkylsilyl group, examples of such being trimethylsilyl, tert-butyldimethylsilyl, phenyldimethylsilyl, triisopropylsilyl and triethylsilyl. The choice of alcohol-protecting group employed is not critical so long as the derivatized alcohol group is stable to the condition of subsequent reaction(s) on other positions of the compound of the formulae and can be removed at the desired point without disrupting the remainder of the molecule. The related term “protected hydroxyl” or “protected alcohol” defines a hydroxyl group substituted with a hydroxyl-protecting group as discussed above.

[0290] The term “carboxyl protecting group” as used herein refers to substituents of the carboxyl group commonly employed to block or protect the —OH functionality while reacting other functional groups on the compound. Examples of such carboxyl protecting groups include the 2-tetrahydro propyl group, 2-ethoxyethyl group, the trityl group, the allyl group, the trimethylsilyl ethoxymethyl group, the 2,2,2-trichloroethoxy group, the benzyl group and the trialkylsilyl group, examples of such being trimethylsilyl, tert-butyldimethylsilyl, phenyldimethylsilyl, triisopropylsilyl and triethylsilyl. The choice of carboxyl-protecting group employed is not critical as long as the derivatized alcohol group is stable to the condition of subsequent reaction(s) on other positions of the compound of the formulae and can be removed at the desired point without disrupting the remainder of the molecule. The related term “protected carboxyl” defines a carboxyl group substituted with a carboxyl-protecting group as discussed above.


[0292] The invention further provides pharmaceutical compositions comprising the factor XI or dual Factor IX/XI modulating compounds of the invention. The term “pharmaceutical composition” is used herein to denote a composition that may be administered to a mammalian host, e.g., orally, topically, parenterally, by inhalation spray, or rectally, in unit dosage formulations containing conventional non-toxic carriers, diluents, adjuvants, vehicles and the like. The term “parenteral” as used herein, includes subcutaneous injections, intravenous, intramuscular, intracerebral injection, or by infusion techniques.

[0293] The term “factor IX” is used herein to refer to blood coagulation factor IX, including both activated and non-activated forms thereof.

[0294] The term “therapeutically effective amount” is used herein to denote that amount of a drug or pharmaceutical agent that will elicit the therapeutic response of an animal or human that is being sought.

[0295] The pharmaceutical compositions containing a compound of the invention may be in a form suitable for oral use, for example, as tablets, powders, capsules, elixirs, for oral administration, or as a solution, or suspension, or other water or oil-in-water or oil-in-oil emulsions, or as a cream or gel, or a suppository or similar dosage form, or by parenteral administration, for example, by injection or instillation. Compositions intended for oral use may be prepared according to any known method, and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, color agents, and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets may contain the active ingredient in admixture with non-toxic pharmaceutically-acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or calcium sulfate; granulating and disintegrating agents, for example corn starch or alginic acid; binding agents, for example, starch, gelatin or acacia; and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in U.S. Pat. Nos. 4,356,108; 4,166, 452; and 4,265,874, to form osmotic therapeutic tablets for controlled release.

[0296] Formulations for oral use may also be presented as hard gelatin capsules where the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or a soft gelatin capsule wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

[0297] Aqueous suspensions may contain the active compound in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide such as lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example, heptadecaethylen oxoxyetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol
anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

[0298] Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as a liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or ceteryl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

[0299] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active compound in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example, sweetening, flavoring, and coloring agents may also be present.

[0300] The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example, olive oil or arachis oil, or a mineral oil, for example a liquid paraffin, or a mixture thereof. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monolaurate, and condensation products of said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monolaurate. The compositions may also contain sweetening and flavoring agents.

[0301] Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known methods using suitable dispersing or wetting agents and suspending agents described above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1.3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer’s solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conveniently employed as solvent or suspending medium. For this purpose, any bland fixed oil may be employed using synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[0302] The compositions may also be in the form of suppositories for rectal administration of the compounds of the invention. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will melt in the rectum to release the drug. Such materials include cocoa butter and polyethylene glycols, for example.

[0303] For topical use, creams, ointments, jellies, solutions of suspensions, etc., containing the compounds of the invention are contemplated. For the purpose of this application, topical applications shall include mouth washes and gargles. The compounds of the present invention may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multimamellar vesicles. Liposomes may be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines. Also provided by the present invention are prodrugs of the invention.

[0304] Pharmaceutically-acceptable salts of the compounds of the present invention, where a basic or acidic group is present in the structure, are also included within the scope of the invention. The term “pharmaceutically acceptable salts” refers to non-toxic salts of the compounds of this invention which are generally prepared by reacting the free base with a suitable organic or inorganic acid or by reacting the acid with a suitable organic or inorganic base. Representative salts include the following salts: Acetate, Benzenesulfonate, Benzoate, Bisulfate, Bisulfate, Bitartrate, Borate, Bromide, Calcium Edetate, Camysylate, Carbonate, Chloride, Clavulanate, Citrate, Dihydrochloride, Edetate, Edisylate, Estolate, Elylate, Fumarate, Gluconate, Glutarate, Glycollylarsanilate, Hexylresorcinate, Hydramamine, Hydrobromide, Hydrochloride, Hydroxy naphtoate, Iodide, Isotionate, Lactate, Lactobionate, Laurate, Maleate, Maleate, Mandelate, Methanesulfonate, Methylbromide, Methylenebume, Methylsulfate, Monopotassium Maleate, Mucate, Napsylate, Nitrate, N-methylguancine, Oxalate, Pamoate (Embonate), Palmitate, Pantothenate, Phosphate/diphosphate, Polyalglutonate, Potassium, Salicylate, Sodium, Stearate, Subacetae, Succinate, Tamate, Tartrate, TEOlate, TOSylate, Triethiodide, Trimethylammonium and Valerate. When an acidic substituent is present, such as —COOH, there can be formed the ammonium, morpholinium, sodium, potassium, barium, calcium salt, and the like, for use as the dosage form. When a basic group is present, such as amino or a basic heterocyclic radical, such as pyridyl, an acidic salt, such as hydrochloride, hydrobromide, phosphate, sulfate, trifluoroacetate, trifluoroacetate, acetate, oxlate, maleate, pyruvate, malonate, succinate, citrate, tartrate, fumarate, mandelate, benzoate, cinnamate, methanesulfonate, ethanesulfonate, picrate and the like, and include acids related to the pharmaceutically-acceptable salts listed in the Journal of Pharmaceutical Science, 66, 2 (1977) p. 1-19.

[0305] Other salts which are not pharmaceutically acceptable may be useful in the preparation of compounds of the invention and these form a further aspect of the invention.

[0306] In addition, some of the compounds of Formula (I or X) may form solvates with water or common organic solvents. Such solvates are also encompassed within the scope of the invention.

[0307] Thus, in another aspect of the present invention, there is provided a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I or X), or a pharmaceutically acceptable salt, solvate, or prodrug thereof; and one or more pharmaceutically acceptable carriers, excipients, or diluents. In an embodiment of the pharmaceutical composition, the compound of Formula (I or X) is an antagonist of factor XI or an
antagonist of factor IX/XI activity. In another embodiment of the pharmaceutical composition, the compound of Formula (I or X) is a partial antagonist of factor XI activity or of both factor IX/XI activity, wherein a partial antagonist comprises a compound that inhibits less than complete activity at a physiologically tolerable dose. In another embodiment of the pharmaceutical composition, the compound of Formula (I or X) is a partial antagonist of factor XI activity or of factor IX/XI activity, wherein the compound of Formula (I or X) inhibits up to 80% of factor XI or factor IX/XI activity. In another embodiment of the pharmaceutical composition, the compound of Formula (I or X) is a partial antagonist of factor XI activity or of factor IX/XI activity, wherein the compound of Formula (I or X) inhibits up to 50% of factor XI or factor IX/XI activity. In another embodiment of the pharmaceutical composition, the compound of Formula (I or X) antagonizes blood clotting mediated by factor XI or IX/XI.

[0308] In another aspect of the present invention, there is provided a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I or X), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, and one or more pharmaceutically acceptable carriers, excipients, or diluents, wherein said therapeutically effective amount of Formula (I or X) preferentially inhibits the intrinsic clotting cascade as compared to the extrinsic clotting cascade. In an embodiment of the pharmaceutical composition, said therapeutically effective amount of Formula (I or X) inhibits the intrinsic clotting cascade by greater than 80% and inhibits the extrinsic clotting cascade by less than 50%. In another embodiment of the pharmaceutical composition, said therapeutically effective amount of Formula (I or X) comprises an amount sufficient to achieve and maintain a sustained blood level that at least partially antagonizes factor XI or factor IX/XI biological activity. In another embodiment, said sustained blood level comprises a concentration ranging from about 0.01 μM to 2 mM. In another embodiment, said sustained blood level comprises a concentration ranging from about 0.05 μM to 100 μM. In another embodiment, said sustained blood level comprises a concentration ranging from about 0.1 μM to about 30 μM.

[0309] In another aspect of the present invention, there is provided a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I or X), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, and one or more pharmaceutically acceptable carriers, excipients, or diluents, wherein said therapeutically effective amount comprises a sufficient amount of the compound of Formula (I or X) to at least partially inhibit the biological activity of factor XI or factor IX/XI in a subject, a sufficient amount of the compound of Formula (I or X) for at least partial amelioration of at least one factor XI- or factor IX/XI-mediated disease, or a sufficient amount of the compound of Formula (I or X) to at least partially inhibit the intrinsic clotting cascade in a subject. In an embodiment of the pharmaceutical composition, said factor XI- or factor IX/XI-mediated disease comprises stroke. In another embodiment of the pharmaceutical composition, said factor XI- or factor IX/XI-mediated disease comprises deep vein thrombosis. In another embodiment of the pharmaceutical composition, said factor XI- or factor IX/XI-mediated disease comprises deep vein thrombosis, wherein said thrombosis is associated with surgical procedures, long periods of confinement, acquired or inherited pro-coagulant states including anti-phospholipid antibody syndrome, protein C deficiency and protein S deficiency, or acute and chronic inflammation including recurrent miscarriage or Systemic Lupus Erythematosus (SLE). In another embodiment, said factor XI- or factor IX/XI-mediated disease comprises excessive clotting associated with the treatment of kidney diseases by hemodialysis and/or venous hemofiltration. In another embodiment, said factor XI- or factor IX/XI-mediated disease comprises cardiovascular disease. In another embodiment, said factor XI- or factor IX/XI-mediated disease comprises cardiovascular disease, wherein said cardiovascular disease comprises myocardial infarction, arrhythmia, or aneurysm.

[0310] In another aspect, the present invention provides a pharmaceutical composition comprising a therapeutically effective amount of the compound of Formula (I or X), and one or more pharmaceutically acceptable carriers, excipients, or diluents, wherein said pharmaceutical composition is used to replace or supplement compounds that reduce clotting.

[0311] In another aspect, the present invention provides a pharmaceutical composition comprising a therapeutically effective amount of the compound of Formula (I or X), and one or more pharmaceutically acceptable carriers, excipients, or diluents, further comprising one or more therapeutic agents.

[0312] In another aspect, the present invention provides a method for the inhibition of the normal biological function of factor XI or factor IX/XI comprising administering to a subject in need thereof a compound of Formula (I or X). In an embodiment of the method, said compound of Formula (I or X) is an antagonist of factor XI or factor IX/XI activity. In another embodiment of the method, said compound of Formula (I or X) antagonizes blood clotting mediated by factor XI or factor IX/XI. In another embodiment of the method, said compound of Formula (I or X) is administered in an amount sufficient to partially antagonize the biological activity of factor XI or factor IX/XI in said subject. In another embodiment of the method, said compound of Formula (I or X) is an antagonist of factor XI or factor IX/XI activity. In another embodiment of the method, said compound of Formula (I or X) antagonizes blood clotting mediated by factor XI or factor IX/XI. In another embodiment of the method, said compound of Formula (I or X) is administered in an amount sufficient to partially antagonize the biological activity of factor XI or factor IX/XI in said subject. In another embodiment of the method, said pharmaceutical composition is administered in the form of an oral dosage or parenteral dosage unit. In another embodiment of the method, said compound of Formula (I or X) is administered as a dose in a range from about 0.01 to 1,000 mg/kg of body weight per day. In another embodiment of the method, said compound of Formula (I or X) is administered as a dose in a range from about 0.1 to 100 mg/kg of body weight per day. In another embodiment of the method, said compound of Formula (I or X) is administered as a dose in a range from about 0.5 to 10 mg/kg of body weight per day.
In another embodiment, said compound of Formula (I or X) is used to replace or supplement compounds that reduce clotting.

[0313] In another aspect, the present invention provides a method for the inhibition of the normal biological function of factor XI or factor IX/XI comprising administering to a subject in need thereof a compound of Formula (I or X), wherein said compound of Formula (I or X) is administered to said subject as a pharmaceutical composition comprising a therapeutically effective amount of said compound of Formula (I or X) and one or more pharmaceutically acceptable carriers, excipients, or diluents. In an embodiment of the method, said therapeutically effective amount of the compound of Formula (I or X) comprises a sufficient amount of the compound of Formula (I or X) to at least partially inhibit the intrinsic clotting cascade in said subject. In another embodiment of the method, said therapeutically effective amount of the compound of Formula (I or X) preferentially inhibits the intrinsic clotting cascade as compared to the extrinsic clotting cascade. In another embodiment of the method, said therapeutically effective amount of the compound of Formula (I or X) inhibits the intrinsic clotting cascade by greater than 80% and inhibits the extrinsic clotting cascade by less than 50%. In another embodiment of the method, said therapeutically effective amount of the compound of Formula (I or X) comprises an amount sufficient to achieve and maintain a sustained blood level that at least partially antagonizes factor XI or factor IX/XI biological activity. In another embodiment, said sustained blood level comprises a concentration ranging from about 0.01 μM to 2 mM. In another embodiment, said sustained blood level comprises a concentration ranging from about 0.05 μM to 100 μM. In another embodiment, said sustained blood level comprises a concentration ranging from about 0.1 μM to about 30 μM. In another embodiment of the method, said pharmaceutical composition further comprises one or more therapeutic agents.

[0314] In another aspect, the present invention provides a method for the inhibition of the normal biological function of factor XI or factor IX/XI comprising administering to a subject in need thereof a compound of Formula (I or X), wherein said compound of Formula (I or X) is a partial antagonist of factor XI or factor IX/XI, wherein a partial antagonist comprises a compound that inhibits less than complete activity at a physiologically tolerable dose. In an embodiment of the method, said compound of Formula (I or X) inhibits up to 95% of factor XI or factor IX/XI activity. In another embodiment of the method, said compound of Formula (I or X) inhibits up to 80% of factor XI or factor IX/XI activity. In another embodiment of the method, said compound of Formula (I or X) inhibits up to 50% of factor XI or factor IX/XI activity.

[0315] In another aspect, the present invention provides a method for the inhibition of the normal biological function of factor XI or factor IX/XI comprising administering to a subject in need thereof a compound of Formula (I or X), wherein said compound of Formula (I or X) is administered to said subject as a pharmaceutical composition comprising a therapeutically effective amount of said compound of Formula (I or X) and one or more pharmaceutically acceptable carriers, excipients, or diluents, wherein said therapeutically effective amount of the compound of Formula (I or X) comprises a sufficient amount of the compound of Formula (I or X) for treatment or prevention of factor XI- or factor IX/XI-mediated diseases. In an embodiment of the method, said factor XI- or factor IX/XI-mediated disease comprises stroke. In another embodiment of the method, said factor XI- or factor IX/XI-mediated disease comprises deep vein thrombosis. The thrombosis may be associated with surgical procedures, long periods of confinement, acquired or inherited pro-coagulant states including anti-phospholipid antibody syndrome, protein C deficiency and protein S deficiency, or acute and chronic inflammation including recurrent miscarriage or Systemic Lupus Erythematosus (SLE). In another embodiment of the method, said factor XI- or factor IX/XI-mediated disease comprises cardiovascular disease. The cardiovascular disease may be associated myocardial infarction, arrhythmia, or aneurysm.

[0316] In a further aspect of the present invention, the factor XI or dual factor IX/XI modulators of the invention are utilized in adjuvant therapeutic or combination therapeutic treatments with other known therapeutic agents.

[0317] The term “treatment” as used herein, refers to the full spectrum of treatments for a given disorder from which the patient is suffering, including alleviation of one, most of all symptoms resulting from that disorder, to an outright cure for the particular disorder or prevention of the onset of the disorder.

[0318] The following is a non-exhaustive listing of adjuvants and additional therapeutic agents which may be utilized in combination with the factor IXa antagonists of the present invention:

[0319] 1. Analgesics: Aspirin

[0320] 2. NSAIDs (Nonsteroidal anti-inflammatory drugs): Ibuprofen, Naproxen, Diclofenac

[0321] 3. DMARDs (Disease-Modifying Antirheumatic drugs): Methotrexate, gold preparations, hydroxychloroquine, sulfasalazine

[0322] 4. Biologic Response Modifiers, DMARDs: Etanercept, Infliximab, Glucocorticoids

[0323] In another embodiment, the present invention provides a method of treating or preventing a factor IXa mediated diseases, the method comprising administering to a subject in need thereof, a therapeutically effective amount of a compound of Formula (I or X) alone or in combination with therapeutic agents selected from the group consisting of antibiotics, hormones, biologic response modifers, analgesics, NSAIDs, DMARDs, glucocorticoids, thrombolytic agents, antidepressants, and anticonvulsants.

[0324] The compound of Formula (I or X) of the present invention, may be administered at a dosage level of from about 0.01 to 1000 mg/kg of the body weight of the subject being treated. In another embodiment, The compound of Formula (I or X) of the present invention, may be administered at a dosage range between 0.01 and 100 mg/kg. In another embodiment, the compound of Formula (I or X) of the present invention, may be administered at a dosage range between 0.5 to 10 mg/kg of body weight per day. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage will vary
depending upon the host treated and the particular mode of administration. For example, a formulation intended for oral administration to humans may contain 1 mg to 2 grams of a compound of Formula (I or X) with an appropriate and convenient amount of carrier material which may vary from about 5 to 95 percent of the total composition. Dosage unit forms will generally contain between from about 5 mg to about 500 mg of active ingredient. This dosage may be individualized by the clinician based on the specific clinical condition of the subject being treated. Thus, it will be understood that the specific dosage level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The general procedures used in the methods of the present invention are described below.

Common names and definitions for resin reagents used in the disclosure are:

| Merrifield | p-Chloromethyl polystyrene |
| Hydroxy-Merrifield | p-Hydroxymethyl polystyrene |
| Wang | (4-Hydroxymethyl)phenoxy)methyl polystyrene |
| Wang carbonate | (4-p-nitrophenyl carbonate) phenoxymethyl polystyrene |
| Rink Resin | (2,4-Dimethoxyphenyl)Fmoc-aminomethyl) phenox polystyrene resin |
| Wang Brono Resin | (4-(4-Bromomethyl)phenoxymethyl polystyrene |
| THP Resin | 3,4-Dihydro-2H-pyran-2-ylmethoxymethyl polystyrene |

Aldehyde resin can refer to the following:

- 4-Benzylxoybenzaldehyde polystyrene
- 3-Benzylxoybenzaldehyde polystyrene
- 4-(4-Formyl-3-methoxyphenoxo)butyryl-aminomethyl polystyrene
- 2-(4-Formyl-3-methoxyphenoxo)ethyl polystyrene
- 2-(3,5-dimethoxy-4-formylphenoxo)ethoxy-methyl polystyrene
- 2-(3,5-dimethoxy-4-formylphenoxo)ethoxy polystyrene
- (3-Formylindolyl)acetamidomethyl polystyrene
- (4-Formyl-3-methoxyphenoxy) grafted (polyethylene- glycol)-polystyrene; or
- (4-Formyl-3-methoxyphenoxy)methylpolystyrene.

Abbreviations used in the Examples are as follows:

- APCI=atmospheric pressure chemical ionization
- BOC=tert-butoxycarbonyl
- BOP=(1-benzotriazol-1-yl)tris(dimethylamino)phosphonium hexafluorophosphate
- d=day
- DIAD=diisopropyl azodicarboxylate
- DCC=dicyclohexylcarbodiimide
- DCE=1,2-dichloroethane
- DCM=dichloromethane
- DIC=diisopropylcarbodiimide
- DIEA=diisopropylethylamine
- DMA=N,N-dimethylacetamide
- DMAP=dimethylamino pyridine
- DME=1,2-dimethoxyethane
- DMF=N,N-dimethylformamide
- DMPU=1,3-dimethylpropylene urea
- DMSO=dimethyl sulfoxide
- EDC=1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
- EDTA=ethylenediamine tetraacetic acid
- ELISA=enzyme-linked immunosorbent assay
- ESI=electrospray ionization
- ether=diethyl ether
- EtOAc=ethyl acetate
- FBS=fetal bovine serum
- g=gram
- h=hour
- HBTU=O-benzotriazol-1-yl-N,N,N',N''-tetramethyluronium hexafluorophosphate
- HMPA=hexamethylphosphoric triamide
- HOBr=1-hydroxybenzotriazole
- Hz=herz
- i.v.=intravenous
- kD=kiloDalton
- L=liter
- LAH=lithium aluminum hydride
- LDA=lithium diisopropylamide
- LPS=lipopolysaccharide
- M=molar
- m/z=mass to charge ratio
- mbar=millibar
- MeOH=methanol
- mg=milligram
- min=minute
- ml=milliliter
- mM=millimolar
- mmol=millimole
- mol=mole
- mp=melting point
- MS=mass spectrometry
- N=normal
NMM = N-methylmorpholine, 4-methylmorpholine
NMR = nuclear magnetic resonance spectroscopy
P.O. = per oral
PBS = phosphate buffered saline solution
PMA = phorbol myristate acetate
ppm = parts per million
psi = pounds per square inch
R_r = relative TLC mobility
RT = room temperature
s.c. = subcutaneous
SPA = scintillation proximity assay
TEA = triethylamine
TFE = trifluoroacetic acid
THF = tetrahydrofuran
THP = tetrahydropyran
TLC = thin layer chromatography
TMSBr = bromotrimethylsilane, trimethylsilyl bromide
T_r = retention time

General Procedure A
[0336] To a solution of a carboxylic acid (1.0 mmol) in DMF was added an amino acid methyl ester (1.2 mmol), HBTU (1.1 mmol), and DIEA (4.0 mmol) and the mixture was stirred overnight. After completion of the reaction, sufficient amount of water was added and the mixture was extracted with ethyl acetate. The organic layer washed with water, brine, dried (Na_2SO_4), and concentrated under reduced pressure to afford the amide. The crude product was purified by flash chromatography (silica, Hexanes:EtOAc) to afford the pure product.

General Procedure B
[0337] To a mixture of phenol (1 mmol) and aryl or heteroaryl fluoride (2 mmol) in DMF was added solid potassium carbonate (5 mmol), and the mixture was heated at 80°C for 12 h. After completion of the reaction, sufficient amount of water was added, and the mixture was extracted with ethyl acetate. The organic layer washed with water, brine, dried (Na_2SO_4), and concentrated under reduced pressure to obtain crude product. The crude material obtained was purified by flash chromatography (silica, Hexanes:EtOAc) to afford the desired ether.

General Procedure C
[0338] To a solution of an ester in THF—CH_2OH (4:1), 2 N lithium hydroxide solution (5 eq) was added, and the resulting reaction mixture was stirred at 60°C for 30 minutes and then warmed to rt. After completion of the reaction, the mixture was acidified with 2N HCl, extracted with ethyl acetate, the organic layer washed with brine, dried over (Na_2SO_4), and the solvent was removed under reduced pressure to afford the product.

General Procedure D
[0339] To a solution of an aryl bromide or heteroaryl bromide (1 mmol) in DME or toluene were added a boronic acid (2 eq), Pd(PPh_3)_4 (ca. 10 mol %), 2N Na_2CO_3 solution (3 mmol). The mixture was heated at 75°C for 12 h. After completion of the reaction, solvent was evaporated under reduced pressure and the residue was purified by column chromatography to provide the desired ester. The resulting ester was hydrolyzed as described in procedure C yielding the acid.

General Procedure E
[0340] To a solution of an aniline or amine (1.0 mmol) in DCE (10 mL) was added an aldehyde (2.0-2.2 mmol), acetic acid (3.0 mmol) and sodium triacetoxoborohydride (2.5 mmol) or sodium cyanoborohydride and the mixture was stirred overnight. After completion of the reaction, 50 mL of DCM was added and the organic layer was washed with saturated sodium bicarbonate solution and brine, and then dried over Na_2SO_4. The solvent was removed in vacuum to afford the product, which was purified by flash chromatography.

General Procedure F
[0341] To a solution of an aniline or amine (1.0 mmol) in DCM (10 mL) was added a sulfonyl chloride (1.0 mmol), pyridine (10.0 mmol), and the mixture was stirred overnight. After completion of the reaction, 50 mL of DCM was added and the organic layer was washed with 1N HCl, saturated sodium bicarbonate solution, and brine, and then dried over Na_2SO_4. The solvent was removed in vacuum to afford the sulfonyl amide, which was purified by flash chromatography.

General Procedure G
[0342] A flask was charged with phenol or aniline (1.0 equiv), Cu(OAc)_2 (1.0 equiv), arylboronic acid (1.0-3.0), and powdered 4 A molecular sieves. The reaction mixture was stirred and diluted with CH_2Cl_2 to yield a solution approximately 0.1 M in phenol or aniline, and the Et,N (5.0 equiv) is added. After stirring the colored heterogeneous mixture for 24 h at 25°C, under ambient atmosphere, the resulting slurry was filtered and the diaryl ether or diaryl amine was isolated from the organic filtrate by flash chromatography.

General Procedure H
[0343] To a solution of a phenol (1.0 mmol) in DMF (5 mL) was added an alkyl halide (1.2 mmol) (a catalytic amount of NaI is added for alkyl chlorides), and potassium carbonate (2.5 mmol) and the mixture heated at 70°C overnight. After completion of the reaction, 5 mL of ethyl acetate and 5 mL of water was added. The organic layer was washed with water, and then dried over Na_2SO_4. The solvent was removed in vacuum to afford the ether, which was purified by flash chromatography.

General Procedure I
[0344] To a solution of ester in THF was added lithium hydroxide (3-4 eq), water, and methanol. The ratio of THF/water/methanol is 4:1:1. The reaction mixture was stirred at rt for 1-1.5 h. A 10% solution of citric acid was added to adjust the pH between 6-7. Ethyl acetate was added and the organic layer is separated. The aqueous layer was extracted with ethyl acetate twice. The combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure to give the product.
General Procedure J

To a stirring solution of an aniline (2 mmol) dissolved in DCM containing pyridine (4 mmol) was added acid chloride (2.5 mmol) at 0°C. The reaction mixture was stirred at rt for 3 h, extracted with DCM, washed with 1M HCl and brine, and evaporation followed by column chromatography purification gave the amide.

General Procedure K

To a stirring solution of amine or aniline (1 mmol) dissolved in DCM containing triethyl amine (4 mmol), was added a chloroformate (1.5 mmol) at rt. The reaction mixture was stirred for 1-1.5 h. The reaction mixture was concentrated and purified by chromatography to give the carbonate.

General Procedure I.

To a stirring solution of amine or aniline (1 mmol) dissolved in DCM containing DIFAM (4 mmol) was added an isocyanate (1.5 mmol) at rt. The reaction mixture was stirred for 1-1.5 h. The reaction mixture was concentrated and purified by chromatography to give the urea.

General Procedure M

A solution of an aryl bromide or heteroaryl bromide (1 mmol) and Pd(PPh₃)₄ (10 mol %) in anhydrous dioxane was degassed by bubbling N₂ gas into the solution for 10 min. To this was added alkynyl tin (1.2 mmol) and the solution was degassed for an additional 10 min and then heated at 80°C overnight under N₂ atmosphere. The reaction was cooled to rt and KF solution was added and the reaction mixture was stirred for 50 min. The precipitated solid was filtered and the solid residue on the filter funnel was washed with copious amounts ethyl acetate to strip the product. The filtrate was concentrated and purified by flash column chromatography (silica, Hex:EtOAc) to provide the corresponding coupled product. This was hydrolyzed as described in the general procedure C to yield the acid.

General Procedure N

To a solution of an alkeno in anhydrous methanol or ethyl acetate was added Pd/C (10 wt %) and the reaction was stirred for 2-18 h under an atmosphere of H₂ gas (1 atm). For some alkeno substrates, the reaction was performed under 3-4 atm pressure of H₂ gas. The reaction mixture was filtered on a celite pad and washed with methanol. The filtrate was concentrated under reduced pressure to afford the desired reduced product.

The above general methods are for illustration only. Alternate conditions that may optionally be used include: Use of alternative solvents, alternative stoichiometries of reagents, alternative reaction temperatures and alternative methods of purification.

EXAMPLES

LC-MS data was obtained using gradient elution on a parallel MUX™️ system, running four Waters 1525 binary HPLC pumps, equipped with a Mux-UV 2488 multichannel UV-Vis detector (recording at 215 and 254 nm) and a Leap Technologies HTS PAL Auto sampler using a Sepax GP-C18 4.6x50 mm column. A three minute gradient was run from 25% B (97.5% acetonitrile, 2.5% water, 0.05% TFA) and 75% A (97.5% water, 2.5% acetonitrile, 0.05% TFA) to 100% B. The system is interfaced with a Waters Micromass ZQ mass spectrometer using electrospray ionization. All MS data was obtained in the positive mode unless otherwise noted. 1H NMR data was obtained on a Varian 400 MHz spectrometer.

Example E-1

7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isouquinoline-3-carboxylic acid

[0352]

[0353] To a stir of solution of H-Tyr(O-tert-Bu)-OMe HCl (15 g, 52.1 mmol), NEt₃ (13.1 g, 129.7 mmol) in 400 mL of DCM at 0°C. The reaction mixture was stirred for 2.0 h, filtered, and the filtrate was concentrated followed by column chromatography purification to give 19 g of amide, which was used for further step without purification.

[0354] LCMS: 438 (M+1)⁺

[0355] To a stirring solution of above amide (19 g, 52.1 mmol) in 400 mL of anhydrous DCM at 0°C. The reaction mixture was added oxalyl chloride (7.9 g, 63.1 mmol). The reaction mixture was brought to rt and stirring continued for another one hour. Then the reaction mixture was cooled to −10°C and to it anhydrous FeCl₃ (10.1 g, 62.3 mmol) was added portion wise. The stirring was continued for 12 h at rt and the reaction mixture was treated with 200 mL of 2.0 M HCl for 2 h. The organic layer was separated washed with water and brine, dried over Na₂SO₄ and concentrated under reduced pressure. Methanol (400 mL) and conc. H₂SO₄ (10 mL) was added to the foamy residue and reaction was heated to reflux for 12 h, methanol was evaporated and the crude product was extracted with ethyl acetate (2x100 mL). The aqueous layer was basified with NH₄OH (pH=9) and extracted with DCM (2x100 mL). The organic layer washed with water and brine and dried over Na₂SO₄. Evaporation of the solvent gave 7.0 g of 1-cyclopentyloxymethyl-7-hydroxy-3,4-dihydro-isouquinoline-3-carboxylic acid methyl ester.

[0356] LCMS: 288 (M+1)⁺

[0357] The above compound (7 g, 24.3 mmol) was dissolved in 200 mL of DCM, then 8.8 g (48.6 mmol) of copper (I) acetate and 12.3 g (121 mmol) of NEt₃ was added. The resulting mixture was stirred at rt for 2.0 h, filtered, and the filtrate was concentrated followed by column chromatogra-
phy using ethyl acetate and hexane to give 6.6 g of 1-cyclopentylmethyl-7-hydroxy-isouquinoline-3-carboxylic acid methyl ester.

**Example E-2**

3-(5-bromo-thiophene-2-yl)-2(S)-[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isouquinoline-3-carbonyl-amino]-propionic acid methyl ester

**Example E-3**

7-(trans-4-tert-Butyl-cyclohexyloxy)-1-cyclopentylmethyl-isouquinoline-3-carboxylic acid

**Example E-4**

6-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isouquinoline-3-carboxylic acid

[0358] LCMS: 286 (M+1)*

[0359] 3.0 g (10.5 mmol) of above phenol, 2.7 g (15.7 mmol) of 4-tert-butyl phenylboronic acid, 1.9 g (10.5 mmol) of copper (II) acetate and 1 g of crushed 4 Å molecular sieves were taken up in 115 mL of DCM. To this stirring solution 5.3 g (115 mmol) of NEt₃ was added and stirring was continued for 12 h. Filtration and evaporation of the solvent followed by column chromatography using hexane and ethyl acetate as eluant gave 1.5 g of 7-(4-tert-butyl-phenoxy)-1-cyclopentylmethyl-isouquinoline-3-carboxylic acid methyl ester.

[0360] LCMS: 418 (M+1)*

[0361] To a stirring solution of 1.5 g (3.6 mmol) of ester in 9.0 mL of THF and 2.16 mL of MeOH was added 2.16 mL of 2 N LiOH at rt. Stirring was continued for 30 min and the mixture was acidified with 1.0 N HCl (pH<3) and extracted with 2×25 mL of ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated to give 1.37 g of title compound as a light yellow solid.

[0362] ¹H-NMR (400 MHz, CDCl₃): δ 8.47 (s, 1H), 7.98 (d, 1H), 7.59 (s, 1H), 7.53 (dd, 1H), 7.46 (d, 2H), 7.05 (d, 2H), 3.15 (d, 2H), 2.55 (m, 1H), 1.67 (m, 4H), 1.53 (m, 2H), 1.36 (s, 9H), 1.30 (m, 2H). LCMS: 404 (M+1)*

**Example E-2**

3-(5-bromo-thiophene-2-yl)-2(S)-[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isouquinoline-3-carbonyl-amino]-propionic acid methyl ester

[0364] The title compound was prepared by treatment of Compound E-1 with (2S)-amino-3-(5-bromo-thiophen-2-yl)-propionic acid methyl ester HCl prepared from commercially available (2S)-amino-3-(5-bromo-thiophen-2-yl)-propionic acid according to general procedure A.

[0366] 0.7 g (2.5 mmol) of 1-cyclopentylmethyl-7-hydroxy-isouquinoline-3-carboxylic acid methyl ester (prepared in example E-1), 3.0 g (5.0 mmol) of triphenyl phosphine polystyrene resin (1.10 mmol/g) and 0.42 g (2.7 mmol) of cis-4-tert-butylecyclohexanol were taken in 25 mL of DCM. To this was added DIAD (0.6 g, 3.0 mmol) at 0°C. The reaction mixture was shaken for 2 h. Filtration and evaporation of the solvent followed by column chromatography using hexane/ethyl acetate gave 0.75 g of product, which was hydrolyzed as described in general procedure C to afford 669 mg of the title compound as a light yellow solid.

[0367] LCMS: 410 (M+1)*

[0369] 12.5 g (54.3 mmol) of 2-amino-3-(3-hydroxy-phenyl)-propionic acid methyl ester was reacted with cyclopentyl acetic acid (6.97 g, 54.3 mmol) as described in general procedure A. The compound was purified using gradient elution with ethyl acetate in hexanes to yield 9.1 g of 2-(2-(cyclopentyl-acetamido)-3-(3-hydroxy-phenyl)-propionic acid methyl ester.

[0370] LCMS 307 (M+1)*

[0371] A portion of the material from the previous step (4.0 g, 13.1 mmol) was dissolved in 120 mL anhydrous DCM, and to this was added 4-tert-butylphenyl boronic acid
(2.0 eq., 26.2 mmol, 4.66 g), copper (II) acetate (1.1 eq., 14.4 mmol, 2.62 g), and 2.0 g of powdered 4 Å molecular sieves. To the stirring mixture was added triethylamine (3.0 eq., 39.3 mmol, 5.5 ml) and the reaction carried out according to general procedure G. Chromatographic purification on silica eluting with ethyl acetate in hexanes afforded 2.50 g of 3-(2-cyclopentyl-acetylaminio)-propionic acid methyl ester.

[0372] LCMS: 439 (M+1)+.

[0373] 1.77 g (4.07 mmol) of 3-(4-tert-butyl-phenoxy)-phenyl)-2-(2-cyclopentyl-acetylaminio)-propionic acid methyl ester was dissolved in 40 ml anhydrous toluene and phosphorl chloride was added and the mixture heated at 90°C for several hours and then cooled. The solvent and excess reagent was removed and the residue was purified via column chromatography on silica eluting with 20-30% ethyl acetate in hexanes to afford 380 mg of the cyclized product, 6-(4-tert-butyl-phenoxy)-1-cyclopentylmethyl-3,4-dihydroisoquinoline-3-carboxylic acid methyl ester.

[0374] LCMS 421 (M+1)+.

[0375] The product of the previous reaction (380 mg, 0.91 mmol) was dissolved in 9 ml dry DCM and triethylamine (5.0 eq., 4.53 mmol, 0.63 ml) and copper (II) acetate (2.2 eq., 1.99 mmol, 362 mg) was added and the mixture stirred at rt for several hours. The solution was concentrated and purified via column chromatography on silica eluting with ethyl acetate/hexanes to afford 378 mg of 6-(4-tert-butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carboxylic acid methyl ester.

[0376] LCMS 419 (M+1)+.

[0377] The above material was taken in its entirety (378 mg, 0.905 mmol) and hydrolyzed according to general procedure C to afford the title compound as a white solid (365 mg).

[0378] LCMS 405 (M+1)+.

Example E-5

2(R)-Amino-3-(5-isopropyl-thiophen-2-yl)-propionic acid methyl ester HCl

[0379]

[0380] To a suspension of (2R)-amino-3-(5-bromo-thiophen-2-yl)-propionic acid methyl ester HCl (14.0 g, 46.59 mmol) (prepared from commercially available (2R)-amino-3-(5-bromo-thiophen-2-yl)-propionic acid in DCM (250 mL) was added NaHCO₃ (9.78 g, 116.49 mmol), water (100 mL). The solution was stirred for 10 min and Boc-anhydride (12.20 g, 55.91 mmol) was added. The reaction was stirred overnight. The organic layer was separated and washed with brine, dried (Na₂SO₄) and concentrated under reduced pressure to give 17.0 g of 3-(5-bromo-thiophen-2-yl)-2(R)-tert-butoxycarbonylamino-propionic acid methyl ester.

[0381] 15.0 g (41.17 mmol) of 3-(5-bromo-thiophen-2-yl)-2(R)-tert-butoxycarbonylamino-propionic acid methyl ester was treated with tributyl-isopropenyl-stannane (17.88 g, 54.07 mmol) and Pd(PPh₃)₄ (4.8 g, 4.15 mmol) as described in the general procedure M to afford 8.50 g of 2(R)-tert-butoxycarbonylamino-3-(5-isopropenyl-thiophen-2-yl)-propionic acid methyl ester.

[0382] 8.50 g of 2(R)-tert-butoxycarbonylamino-3-(5-isopropenyl-thiophen-2-yl)-propionic acid methyl ester was treated with Pd/C and H₂ gas (1 atm) by the general procedure N to afford 8.20 g of 2(R)-tert-butoxycarbonylamino-3-(5-isopropenyl-thiophen-2-yl)-propionic acid methyl ester. This ester was treated with HCl/dioxane (4.0 M) to afford 7.10 g of title compound.

Example E-6

2(S)-Amino-3-(5-isopropenyl-thiophen-2-yl)-propionic acid methyl ester HCl

[0383]

[0384] The title compound was prepared by analogous procedure used to prepare Compound E-5.

Example E-7

7-(4-tert-Butyl-phenoxy)-1-(tetrahydro-pyran-4-yl)-isoquinoline-3-carboxylic acid

[0385]

[0386] The title compound was synthesized by analogous procedure used to prepare Compound E-1 with the exception that tetrahydro-pyran-4-carbonyl chloride was used instead of cyclopentylacetyl chloride.
Example E-8
1-Cyclopentylmethyl-7-(4-isopropyl-cyclohexyloxy)-isoquinoline-3-carboxylic acid

[0387]

[0388] To a solution of Compound E-1 (1.0 mmol) in THF was added 4-isopropyl cyclohexanol (1.5 mmol), triphenyl phosphine polystyrene resin (1.10 mmol/g, 2.50 mmol), and DIAD (2 mmol) at 0°C. The reaction was warmed to rt and stirred for 4 h. The reaction mixture was filtered and concentrated. The crude product was purified by flash column chromatography (silica, Hexanes/EtOAc to afford 1-cyclopentylmethyl-7-(4-isopropyl-cyclohexyloxy)-isoquinoline-3-carboxylic acid methyl ester. This ester was hydrolyzed by the general procedure C to afford the title compound.

Example E-9
1-Cyclopentylmethyl-7-(4-trans-ethyl-cyclohexyloxy)-isoquinoline-3-carboxylic acid

[0389]

[0390] The title compound was prepared by analogous procedure used to prepare Compound E-8 with the exception that 4-Cis-4-ethyl-cyclohexanol was used.

Example E-10
7-(4-tert-Butylphenoxy)-isoquinoline-3-carboxylic acid

[0391]

[0392] To a solution of (3S)-7-hydroxy-3,4-dihydro-1H-isoquinoline-2,3-dicarboxylic acid 2-tert-butyl ester (1.47 g, 5.0 mmol) in dry DMF (25 mL) at ambient temperature, was added iodomethane (1.2 eq., 6.0 mmol, 0.37 mL) and disopropylethylamine (1.5 eq. 7.5 mmol, 1.31 mL) in succession, and the reaction mixture was stirred at rt for 3-4 hours, at which point LC/MS analysis showed the presence of product. The reaction mixture was poured into 50 mL of water and extracted with DCM (3x50 mL) and the combined DCM extracts were washed with water (3x50 mL) and brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica (ethyl acetate/hexanes) to afford (3S)-7-hydroxy-3,4-dihydro-1H-isoquinoline-2,3-dicarboxylic acid 2-tert-butyl ester 3-methyl ester (1.13 g).

[0393] LCMS: 308 (M+1)*.

[0394] The above phenol (1.20 g, 3.91 mmol) was reacted with 4-(tert-butyl)phenylboronic acid (1.6 eq., 6.26 mmol, 1.11 g), copper (II) acetate (1.0 eq. 3.91 mmol, 710 mg) as described in general procedure G. Flash column chromatography on silica (ethyl acetate/hexanes) provided 750 mg of the desired product, (3S)-7-(4-tert-butylphenoxy)-3,4-dihydro-1H-isoquinoline-2,3-dicarboxylic acid 2-tert-butyl ester 3-methyl ester.

[0395] LCMS: 440 (M+1)*

[0396] A portion of the material described above (400 mg, 0.91 mmol) was placed in a dry 4 dram vial containing a magnetic stir bar, and was treated with a 4N solution of anhydrous HCl in 1,4-dioxane (1.0 mL, 4.0 mmol, 4.4 eq). The reaction was stirred at ambient temperature for 1 hour, until complete by T.L.C. The solvent and residual HCl was removed under vacuum and the crude product, (3S)-7-(4-tert-butylphenoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methyl ester hydrochloride, was used without further purification.

[0397] LCMS: 340 (M+1)*

[0398] The above crude product was dissolved in 18 mL of dry toluene and DDQ (3.0 eq., 2.73 mmol, 620 mg) was added in a single portion. The mixture was heated at reflux for 2 hours then cooled to rt and concentrated under reduced pressure. The crude residue was placed directly atop a silica gel column and eluted with a mixture of ethyl acetate and hexanes to furnish 229 mg of, 7-(4-tert-butylphenoxy)-isoquinoline-3-carboxylic acid methyl ester. A portion of the ester (208 mg, 0.62 mmol) was hydrolyzed as described in general procedure C to afford 199 mg of the title compound as a white solid.

[0399] ¹H-NMR (400 MHz, CDCl₃): 8 8.47 (s, 1H), 7.98 (d, 1H), 7.59 (s, 1H), 7.53 (dd, 1H), 7.46 (d, 2H), 7.05 (d, 2H), 3.15 (d, 2H), 2.35 (m, 1H), 1.67 (m, 4H), 1.53 (m, 2H), 1.36 (s, 9H), 1.30 (m, 2H). LCMS: 322 (M+1)*.
Example E-11

\[
\text{([5-Bromo-thiophen-2-ylmethyl]-amino)-acetic acid tert-butyl ester}
\]

The title compound was prepared by treatment of 5-bromo-thiophene-2-carboxaldehyde with amino-acetic acid tert-butyl ester by the general procedure E.

Example E-12

\[
\text{([5-Bromo-thiophen-2-ylmethyl]-amino)-acetic acid methyl ester}
\]

The title compound was prepared by treatment of 5-bromo-thiophene-2-carboxaldehyde with amino-acetic acid methyl ester by the general procedure E.

Example E-13

\[
\text{([4-Bromo-thiophen-2-ylmethyl]-amino)-acetic acid methyl ester}
\]

The title compound was prepared by treatment of 5-bromo-thiophene-2-carboxaldehyde with amino-acetic acid methyl ester by the general procedure E.

Example E-14

\[
\text{([5-Methyl-thiophen-2-ylmethyl]-amino)-acetic acid methyl ester}
\]

The title compound was prepared by treatment of 5-methyl-thiophene-2-carboxaldehyde with amino-acetic acid methyl ester by the general procedure E.

Example 1

\[
\text{2(S)-[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl}-isoquinoline-3-carbonyl]-amino\text{-3-(5-phenylthiophen-2-yl)-propionic acid}}
\]

Example 2

\[
\text{2(S)-[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl}-isoquinoline-3-carbonyl]-amino\text{-3-[5-trifluoromethyl-phenyl]thiophen-2-yl]-propionic acid}
\]

Example 3

\[
\text{2(S)-[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl}-isoquinoline-3-carbonyl]-amino\text{-3-[5-cyclopent-1-enyl-thiophen-2-yl]-propionic acid}}
\]

Example 4

\[
\text{2(S)-[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl}-isoquinoline-3-carbonyl]-amino\text{-3-[5-cyclopent-1-enyl-thiophen-2-yl]-propionic acid}}
\]

Example 5

\[
\text{2(S)-[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl}-isoquinoline-3-carbonyl]-amino\text{-3-[5-cyclopentyl-thiophen-2-yl]-propionic acid methyl ester}}
\]

Example 6

The title compound was prepared by the treatment of Example 3 with Pd/C and H₂ gas (1 atm) by the general procedure N.

Example 7

\[
\text{LCMS: 640 (M+1)⁺}
\]
Example 6

2(S)-[(7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl)-amino]-3-(5-cyclo-pentyl-thiophen-2-yl)-propionic acid

[0418] The title compound was prepared by hydrolysis of Example 5 by the general procedure C.

[0419] LCMS: 626 (M+1)*

Example 7

2(S)-[(7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl)-amino]-3-(5-furan-3-yl-thiophen-2-yl)-propionic acid

[0420] The title compound was prepared by treatment of Compound E-2 with furan-3-boronic acid to afford 2(S)-[(7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl)-amino]-3-(5-furan-3-yl-thiophen-2-yl)-propionic acid methyl ester. The ester was hydrolyzed by the general procedure C to obtain the title compound.

[0421] LCMS: 624 (M+1)*

Example 8

2(S)-[(7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl)-amino]-3-[5-(4-isopropylphenyl)-thiophen-2-yl]propionic acid

[0422] The title compound was prepared by treatment of Compound E-2 with 4-isopropylphenylboronic acid to yield 2(S)-[(7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl)-amino]-3-[5-(4-isopropylphenyl)-thiophen-2-yl]propionic acid methyl ester. The ester was hydrolyzed by the general procedure C to afford the title compound.

[0423] LCMS: 676 (M+1)*

Example 9

2(S)-[(7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl)-amino]-3-(5-vinylthiophen-2-yl)-propionic acid

[0424] The title compound was prepared by treatment of Compound E-2 with tributyl vinyl stannane and Pd(PPh₃)₄ by the general procedure M to afford 2(S)-[(7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl)-amino]-3-(5-vinylthiophen-2-yl)-propionic acid methyl ester. The ester was hydrolyzed by the general procedure C to afford the title compound.

[0425] LCMS: 584 (M+1)*

Example 10

2(S)-[(7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl)-amino]-3-(5-p-tolylthiophen-2-yl)-propionic acid

[0426] The title compound was prepared by treatment of Compound E-2 with 4-methylphenylboronic acid by the general procedure D to afford 2(S)-[(7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl)-amino]-3-(5-p-tolylthiophen-2-yl)-propionic acid methyl ester. The ester was hydrolyzed by the general procedure C to afford the title compound.

[0427] LCMS: 648 (M+1)*

Example 11

2(S)-[(7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl)-amino]-3-[5-(4-chloro-phenyl)-thiophen-2-yl]-propionic acid

[0428] The title compound was prepared by treatment of Compound E-2 with 4-chlorophenylboronic acid by the general procedure D to afford 2(S)-[(7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl)-amino]-3-[5-(4-chloro-phenyl)-thiophen-2-yl]-propionic acid methyl ester. The ester was hydrolyzed by the general procedure C to afford the title compound.

[0429] LCMS: 668 (M+1)*

Example 12

2(S)-[(7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl)-amino]-3-(5-ethylthiophen-2-yl)-propionic acid

[0430] The title compound was prepared by the treatment of Example 9 with Pd/C and H₂ (1 atm) by the general procedure N.

[0431] LCMS: 586 (M+1)*

Example 13

2(S)-[(7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl)-amino]-3-furan-2-yl-propionic acid

[0432] Compound E-1 (0.050 g; 0.012 mmol) was reacted with (2S)-amino-3-furan-2-yl-propionic acid methyl ester HCl (0.038 g, 0.018 mmol, prepared from commercially available (2S)-amino-3-furan-2-yl-propionic acid) as described in general procedure A to afford 0.066 g of 2(S)-[(7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl)-amino]-3-furan-2-yl-propionic acid methyl ester.

[0433] The resulting ester was hydrolyzed by the general procedure C to afford 0.060 g of the title compound.

[0434] LCMS: 542 (M+1)*

Example 14

2(S)-[(7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl)-amino]-3-(2-trifluoromethyl-phenyl)-propionic acid

[0435] The title compound was prepared by analogous procedure used to prepare Example 13 with the exception that 2(S)-Amino-3-(2-trifluoromethyl-phenyl)-propionic acid methyl ester HCl (prepared from commercially available 2(S)-Amino-3-(2-trifluoromethyl-phenyl)-propionic acid) was used.

[0436] The resulting ester was hydrolyzed by the general procedure C to afford the title compound.

[0437] LCMS: 620 (M+1)*
Example 15

\{(5-Bromo-thiophen-2-ylmethyl)-7-(4-tert-butyl-phenoxo)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-amino\}-acetic acid tert-butyl ester

[0438] Compound E-11 (0.060 g, 0.195 mmol) was treated with Compound E-1 (0.079 g, 0.195 mmol) by the general procedure A to afford 36 mg of the title compound.

[0439] LCMS: 693 (M+1)*

Example 16

2(S)-\{[7-(4-tert-Butyl-phenoxo)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-amino\}-3-(3,5-difluorophenyl-propionic acid

[0440] The title compound was prepared by analogous procedure used to prepare Example 13 with the exception that 2(S)-Amino-3-(3,5-difluorophenyl)-propionic acid methyl ester HCl (prepared from commercially available 2(S)-Amino-3-(3,5-difluorophenyl)-propionic acid) was used.

[0441] The resulting ester was hydrolyzed by the general procedure C to afford the title compound.

[0442] LCMS: 588 (M+1)*

Example 17

\{[7-(4-tert-butyl-phenoxo)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-5-methyl-thiophen-2-ylmethyl]-amino\}-acetic acid

[0443] Compound E-14 was treated with Compound E-1 by the general procedure A to yield \{[7-(4-tert-butyl-phenoxo)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-5-methyl-thiophen-2-ylmethyl]-amino\}-acetic acid methyl ester, which upon hydrolysis by the general procedure C gave the title compound.

[0444] LCMS: 572 (M+1)*

Example 18

\{(5-Bromo-thiophen-2-ylmethyl)-7-(4-tert-butyl-phenoxo)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-amino\}-acetic acid methyl ester

[0445] Compound E-12 was treated with Compound E-1 by the general procedure E to afford the title compound.

[0446] LCMS: 651 (M+1)*

Example 19

\{(4-Bromo-thiophen-2-ylmethyl)-7-(4-tert-butyl-phenoxo)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-amino\}-acetic acid

[0447] Compound E-13 was treated with Compound E-1 by the general procedure A to yield \{(4-Bromo-thiophen-2-ylmethyl)-7-(4-tert-butyl-phenoxo)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-amino\}-acetic acid methyl ester which upon hydrolysis by the general procedure C gave the title compound.

[0448] LCMS: 637 (M+1)*

Example 20

\{(5-Bromo-thiophen-2-ylmethyl)-7-(4-tert-butyl-phenoxo)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-amino\}-acetic acid

[0449] Example 18 was hydrolyzed by the general procedure C to afford the title compound.

[0450] LCMS: 637 (M+1)*

Example 21

Benz[o]thiophen-3-yl-[7-(4-tert-butyl-phenoxo)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-amino\}-acetic acid

[0451] The title compound was prepared by analogous procedure used to prepare Example 13 with the exception that amino-benz[o]thiophen-3-yl-acetic acid methyl ester HCl (obtained from commercially available amino-benz[o] thiophen-3-yl-acetic acid) was used.

[0452] The resulting ester was hydrolyzed by the general procedure C to afford the title compound.

[0453] LCMS: 594 (M+1)*

Example 22

2(S)-\{[7-(4-tert-butyl-phenoxo)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-amino\}-3-(4-fluorophenyl)-propionic acid

[0454] The title compound was prepared by analogous procedure use to prepare Example 13 with the exception that 2(S)-amino-3-(4-fluoro-phenyl)-propionic acid methyl ester HCl (obtained from commercially available 2(S)-amino-3-(4-fluoro-phenyl)-propionic acid) was used.

[0455] The resulting ester was hydrolyzed by the general procedure C to afford the title compound.

[0456] LCMS: 570 (M+1)*

Example 23

2(S)-\{[7-(4-tert-Butyl-phenoxo)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-amino\}-3-(5-propenylthiophen-2-yl)-propionic acid

[0457] Compound E-2 was treated with tributyl-propenylstannane by the general procedure M to yield 2(S)-\{[7-(4-tert-Butyl-phenoxo)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-amino\}-3-(5-propenylthiophen-2-yl)-propionic acid methyl ester. The ester was hydrolyzed by the general procedure C to afford the title compound.

[0458] LCMS: 598 (M+1)*

Example 24

2(S)-\{[7-(4-tert-Butyl-phenoxo)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-amino\}-3-(5-propenylthiophen-2-yl)-propionic acid

[0459] The title compound was prepared by treatment of 2(S)-\{[7-(4-tert-Butyl-phenoxo)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-amino\}-3-(5-propenylthiophen-2-yl)-propionic acid methyl ester (prepared in Example 23) with Pd/C and H₂ (1 atm) by the general procedure N to
afford 2(S)-[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl-amino]-3-(5-propylthiophen-2-yl)-propionic acid methyl ester. The ester was hydrolyzed by the general procedure C to afford the title compound.

Example 25

2(S)-[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl-amino]-3-(5,3,3-dimethyl-but-1-enyl)-thiophen-2-yl)-propionic acid

Example 26

2(S)-[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl-amino]-3-[5-(3,3-dimethyl-but-1-enyl)-thiophen-2-yl]-propionic acid methyl ester. The ester was hydrolyzed by the general procedure C to afford the title compound.

Example 27

2(S)-[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl-amino]-3-[5-(5-propylthiophen-2-yl)-propionic acid methyl ester]

Example 28

2(S)-[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl-amino]-3-[5-(methyl-thiophen-2-yl)-propionic acid methyl ester]

Example 29

2(S)-[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl-amino]-3-(5-isopropylthiophen-2-yl)-propionic acid methyl ester

Example 30

2(S)-[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl-amino]-3-(5-isopropylthiophen-2-yl)-propionic acid methyl ester

Example 31

3-(5-bromo-thiophene-2-yl)-2(R)-[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl-amino]-propionic acid methyl ester

Compound E-1 (0.150 g, 0.37 mmol) was reacted with (2R)-amino-3-(5-bromo-thiophen-2-yl)-propionic acid methyl ester (Example 26).
methyl ester HCl (0.145 g, 0.482 mmol), prepared from commercially available (2R)-amino-3-(5-bromo-thiophen-2-yl)-propionic acid) as described in general procedure A to afford 0.180 g of 3-(5-bromo-thiophen-2-yl)-2(R)-[[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isouquinoline-3-carbonyl]-amino]-propionic acid methyl ester. This resulting ester was hydrolyzed by the general procedure C to afford 0.158 g of the title compound.

[0477] LCMS: 637 (M+1)*

Example 32

2(R)-[[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isouquinoline-3-carbonyl]-amino]-3-(5-chlorothiophen-2-yl)-propionic acid

[0478] Compound E-1 was treated with 2(R)-amino-3-(5-chlorothiophen-2-yl)-propionic acid methyl ester (obtained from commercially available 2(R)-amino-3-(5-chlorothiophen-2-yl)-propionic acid) by the general procedure A to obtain 2(R)-[[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isouquinoline-3-carbonyl]-amino]-3-(5-chlorothiophen-2-yl)-propionic acid methyl ester. The ester was hydrolyzed by the general procedure C to obtain the title compound.

[0479] LCMS: 592 (M+1)*

Example 33

2(S)-[[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isouquinoline-3-carbonyl]-amino]-3-(5-chlorofuran-2-yl)-propionic acid

[0480] Compound E-1 was treated with 2(S)-amino-3-(5-chlorofuran-2-yl)-propionic acid methyl ester HCl (obtained from commercially available 2(S)-amino-3-(5-chlorofuran-2-yl)-propionic acid) by the general procedure A to obtain 2(S)-[[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isouquinoline-3-carbonyl]-amino]-3-(5-chlorofuran-2-yl)-propionic acid methyl ester. The ester was hydrolyzed by the general procedure C to obtain the title compound.

[0481] LCMS: 576 (M+1)*

Example 34

2(S)-[[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isouquinoline-3-carbonyl]-amino]-3-(2,5-dichlorothiophen-3-yl)-propionic acid

[0482] Compound E-1 was treated with 2(S)-amino-3-(2,5-dichlorothiophen-3-yl)-propionic acid methyl ester HCl (obtained from commercially available 2(S)-amino-3-(2,5-dichlorothiophen-3-yl)-propionic acid) by the general procedure A to obtain 2(S)-[[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isouquinoline-3-carbonyl]-amino]-3-(2,5-dichlorothiophen-3-yl)-propionic acid methyl ester. The ester was hydrolyzed by the general procedure C to obtain the title compound.

[0483] LCMS: 626 (M+1)*

Example 35

(5-Bromo-thiophen-2-yl)-[[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isouquinoline-3-carbonyl]-amino]-acetic acid

[0484] Compound E-1 was treated with amino-(5-bromo-thiophen-2-yl)-acetic acid methyl ester (obtained from commercially available amino-(5-bromo-thiophen-2-yl)-acetic acid) by the general procedure A to obtain (5-Bromo-thiophen-2-yl)-[[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isouquinoline-3-carbonyl]-amino]-acetic acid methyl ester. The ester was hydrolyzed by the general procedure C to obtain the title compound.

[0485] LCMS: 622 (M+1)*

Example 36

3-(5-Bromo-furan-2-yl)-2(S)-[[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isouquinoline-3-carbonyl]-amino]-propionic acid

[0486] Compound E-1 was treated with 2(S)-amino-(5-bromo-furan-2-yl)-propionic acid methyl ester HCl (obtained from commercially available 2(S)-amino-(5-bromo-furan-2-yl)-propionic acid) by the general procedure A to obtain 3-(5-Bromo-furan-2-yl)-2(S)-[[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isouquinoline-3-carbonyl]-amino]-propionic acid methyl ester. The ester was hydrolyzed by the general procedure C to obtain the title compound.

[0487] LCMS: 620 (M+1)*

Example 37

3-(5-Bromo-thiophen-2-yl)-2(S)-[[7-(4-trans-tert-butyl-cyclohexyloxy)-1-cyclopentylmethyl-isouquinoline-3-carbonyl]-amino]-propionic acid

[0488] Compound E-3 was treated with 2(S)-amino-3-(5-bromo-thiophen-2-yl)-propionic acid methyl ester HCl (prepared from commercially available 2(S)-amino-3-(5-bromo-thiophen-2-yl)-propionic acid) by the general procedure A to obtain 3-(5-Bromo-thiophen-2-yl)-2(S)-[[7-(4-trans-tert-butyl-cyclohexyloxy)-1-cyclopentylmethyl-isouquinoline-3-carbonyl]-amino]-propionic acid methyl ester. The ester was hydrolyzed by the general procedure C to afford the title compound.

[0489] LCMS: 642 (M+1)*

Example 38

3-(5-Bromo-thiophen-2-yl)-2(S)-[[6-(4-tert-butyl-phenoxy)-1-cyclopentylmethyl-isouquinoline-3-carbonyl]-amino]-propionic acid

[0490] Compound E-4 was treated with 2(S)-amino-3-(5-bromo-thiophen-2-yl)-propionic acid methyl ester HCl (prepared from commercially available 2(S)-amino-3-(5-bromo-thiophen-2-yl)-propionic acid) by the general procedure A to afford 3-(5-Bromo-thiophen-2-yl)-2(S)-[[6-(4-tert-butyl-phenoxy)-1-cyclopentylmethyl-isouquinoline-3-carbonyl]-amino]-propionic acid methyl ester. This ester was hydrolyzed by the general procedure C to afford the title compound.

[0491] LCMS: 636 (M+1)*

Example 39

2(S)-[[7-(4-trans-tert-butyl-cyclohexyloxy)-1-cyclopentylmethyl-isouquinoline-3-carbonyl]-amino]-3-(5-isopropenyl-thiophen-2-yl)-propionic acid

[0492] 3-(5-Bromo-thiophen-2-yl)-2(S)-[[7-(4-trans-tert-butyl-cyclohexyloxy)-1-cyclopentylmethyl-isouquinoline-3-carbonyl]-amino]-propionic acid
carbonyl-amino)-propionic acid methyl ester (prepared in Example 37) was treated with tributyl-isopropenyl-stannane and Pd(PPh3)4 by the general procedure M to afford 2(S)-[[7-(4-trans-tert-butyl-cyclohexyloxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl-amino]-3-(5-isopropyl-thiophen-2-yl)-propionic acid methyl ester. This ester was hydrolyzed by the general procedure C to afford the title compound.

Example 40

2(S)-[[7-(4-trans-tert-butyl-cyclohexyloxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl-amino]-3-(5-isopropyl-thiophen-2-yl)-propionic acid

Example 41

2(S)-[[7-(4-trans-tert-butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl-amino]-3-(5-isopropyl-furan-2-yl)-propionic acid

Example 42

2(S)-[[1-cyclopentylmethyl-7-(4-isopropyl-cyclohexyloxy)-isoquinoline-3-carbonyl-amino]-3-(5-isopropyl-thiophen-2-yl)-propionic acid

The title compound was prepared by treatment of Compound E-8 (1 mmol) with E-6 (1.20 mmol) by the general procedure A to yield 2(S)-[[1-cyclopentylmethyl-7-(4-isopropyl-cyclohexyloxy)-isoquinoline-3-carbonyl-amino]-3-(5-isopropyl-thiophen-2-yl)-propionic acid methyl ester. The ester was hydrolyzed by the general procedure C to afford the title compound.

Example 43

2(R)-[[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl-amino]-3-(5-isopropyl-thiophen-2-yl)-propionic acid

Example 44

2(S)-[[7-(4-tert-Butyl-phenoxy)-isoquinoline-3-carbonyl-amino]-3-(5-isopropyl-thiophen-2-yl)-propionic acid

The title compound was prepared by the treatment of Compound E-10 (1 mmol) with Compound E-6 (1.2 mmol) by the general procedure A to afford 2(S)-[[7-(4-tert-Butyl-phenoxy)-isoquinoline-3-carbonyl-amino]-3-(5-isopropyl-thiophen-2-yl)-propionic acid methyl ester. This ester was hydrolyzed by the general procedure C to afford title compound.

Example 45

2(S)-[[1-Cyclopentylmethyl-7-(4-trans-ethyl-cyclohexyloxy)-isoquinoline-3-carbonyl-amino]-3-(5-isopropyl-thiophen-2-yl)-propionic acid

The title compound was prepared by treatment of Compound E-9 (1 mmol) with Compound E-6 (1.20 mmol) by the general procedure A to yield 2(S)-[[1-cyclopentylmethyl-7-(4-ethyl-cyclohexyloxy)-isoquinoline-3-carbonyl-amino]-3-(5-isopropyl-thiophen-2-yl)-propionic acid methyl ester. The ester was hydrolyzed by the general procedure C to afford the title compound.

Example 46

2(S)-[[1-Cyclopentylmethyl-7-(4-isopropyl-phenoxy)-isoquinoline-3-carbonyl-amino]-3-(5-isopropyl-thiophen-2-yl)-propionic acid

1-cyclopentylmethyl-7-hydroxy-isoquinoline-3-carboxylic acid methyl ester (prepared in example E-1) was
treated with 4-isopropylphenylboronic acid by the general procedure G to yield 7-(4-isopropyl-phenoxy)-1-cyclopentylmethoxy-isouquinoline-3-carboxylic acid methyl ester. This ester was hydrolyzed by the general procedure C to afford 7-(4-isopropyl-phenoxy)-1-cyclopentylmethyl-isouquinoline-3-carboxylic acid. This acid was coupled with Compound E-6 by the general procedure A to yield 2(S)-[7-(4-isopropyl-phenox-y)-1-cyclopentylmethyl-isoquino-line-3-carbonyl]-amino]-3-(5-isopropyl-thiophen-2-yl)-propionic acid methyl ester. This ester was hydrolyzed by the general procedure C to afford the title compound.

[0509] LCMS: 586 (M+1)*

Example 47

2(S)-[7-(4-tet-butyl-phenox-y)-1-(tetrahydro-pyr-an-4-yl)-isouquinoline-3-carbonyl]-amino]-3-(5-isopropyl-thiophen-2-yl)-propionic acid

[0510] This was prepared by the treatment of Compound E-7 with Compound E-6 to afford 2(S)-[7-(4-tet-butyl-phenox-y)-1-(tetrahydro-pyr-an-4-yl)-isouquinoline-3-carbonyl]-amino]-3-(5-isopropyl-thiophen-2-yl)-propionic acid methyl ester. The ester was hydrolyzed by the general procedure C to afford the title compound.

[0511] LCMS: 602 (M+1)*

Example 48

2(S)-[6-(4-tet-butyl-phenox-y)-1-cyclopentylmethoxy-isouquinoline-3-carbonyl]-amino]-3-(5-isopropyl-thiophen-2-yl)-propionic acid

[0512] 3-(5-Bromo-thiophen-2-yl)-2(S)-[6-(4-tet-butyl-phenox-y)-1-cyclopentylmethyl-isouquinoline-3-carbonyl]-amin o]-propionic acid methyl ester (prepared in Example 38) was treated with tributylisopropenylstannane and Pd(PPh₃)₄ as described in the general procedure M to afford 2(S)-[6-(4-tet-butyl-phenox-y)-1-cyclopentylmethyl-isouquinoline-3-carbonyl]-amin o]-3-(5-isopropyl-thiophen-2-yl)-propionic acid methyl ester. This was treated with Pd/C and H₂ (1 atm) by the general procedure N to afford 2(S)-[6-(4-tet-butyl-phenox-y)-1-cyclopentylmethyl-isouquinoline-3-carbonyl]-amin o]-3-(5-isopropyl-thiophen-2-y l)-propionic acid methyl ester. This ester was hydrolyzed by the general procedure C to afford the title compound.

[0513] LCMS: 600 (M+1)*

Example 49

2(S)-[7-(4-tet-butyl-phenyl)-1-cyclopentylmethyl-isouquinoline-3-carbonyl]-amino]-3-(5-isopropyl-thiophen-2-yl)-propionic acid

[0514] 1-cyclopentylmethyl-7-hydroxy-isouquinoline-3-carboxylic acid methyl ester (prepared in Example E-1) was hydrolyzed by the general procedure C to afford 1-cyclopentylmethyl-7-hydroxy-isouquinoline-3-carboxylic acid. This acid (1 mmol) was coupled with Compound E-6 to afford 2(S)-[1-cyclopentylmethyl-7-hydroxy-isouquinoline-3-carbonyl]-amin o]-3-(5-isopropyl-thiophen-2-yl)-propionic acid methyl ester.

[0515] To a stirring solution of above phenol (1 mmol), Et₃N (2 mmol) and DMAP (cat.) in DCM was added, followed by excess trifluoromethanesulfonic anhydride (2 mmol) at 0°C. The reaction was stirred at rt for 30 min. The organic layer was separated, washed with citric acid, water, brine, dried (Na₂SO₄) and concentrated under reduced pressure to give the desired triflate which was used without further purification for the next step.

[0516] The above triflate (1 mmol) was treated with 4-tert-butyphosphonic acid (2 mmol), Pd(PPh₃)₄ (0.05 mmol) and 2Na₂CO₃ (3 mmol) solution by the general procedure D to afford 2(S)-[7-(4-tet-butyl-phenox-y)-1-cyclopentylmethyl-isouquinoline-3-carbonyl]-amin o]-3-(5-isopropyl-thiophen-2-yl)-propionic acid methyl ester. This ester was hydrolyzed by the general procedure C to afford the title compound.

[0517] LCMS: 584 (M+1)*

Example 50

2(S)-[7-(4-tet-butyl-benzoyl)-1-cyclopentylmethyl-isouquinoline-3-carbonyl]-amin o]-3-(5-isopropyl-thiophen-2-yl)-propionic acid

[0518] The triflate of Example 49 (1 mmol), 4-tet-butylyphosphonic acid (1.40 mmol), PdCl₂ (dppe) (10 mol %), potassium carbonate (3 mmol), and crushed NaI (3 mmol) were added to a flame dried flask. The flask was flushed with CO gas and then charged with anisole. The mixture was heated at 80°C for 48 h under an atmosphere of CO. The reaction mixture was cooled to rt, filtered, and washed with EtOAc. The organic layer was washed with water, brine, dried, and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica, Hexanes:EtOAc) to give pure 2(S)-[7-(4-tet-butyl-benzoyl)-1-cyclopentylmethyl-isouquinoline-3-carbonyl]-amin o]-3-(5-isopropyl-thiophen-2-yl)-propionic acid methyl ester. The ester was hydrolyzed by the general procedure C to afford the title compound.

[0519] LCMS: 612 (M+1)*

Example 51

3-(5-Acetyl-thiophen-2-yl)-2(S)-[7-(4-tet-butyl-phenox-y)-1-cyclopentylmethyl-isouquinoline-3-carbonyl]-amin o]-propionic acid

[0520] Compound E-2 (1.0 g, 1.53 mmol) was treated with tributyl-(1-ethoxy-vinyl)-stannane (0.83 g, 2.3 mmol), and Pd(PPh₃)₄ (0.177 g, 0.15 mmol) by the general procedure M to yield 0.600 g of 3-(5-Acetyl-thiophen-2-yl)-2(S)-[7-(4-tet-butyl-phenox-y)-1-cyclopentylmethyl-isouquinoline-3-carbonyl]-amin o]-propionic acid methyl ester. The ester (20 mg) was hydrolyzed by the general procedure C to afford the title compound.

[0521] LCMS: 600 (M+1)*

Example 52

7-(4-tet-butyl-phenox-y)-1-cyclopentylmethyl-isouquinoline-3-carboxylic acid [1-(5-isopropyl-thiophen-2-yl)methyl](2R)-methanesulfonylamino-2-oxo-ethylamide

[0522] To a solution of Example 43 (0.150 g, 0.250 mmol) in DCM was added oxalyl chloride (0.063 g, 0.50 mmol) and
the solution was stirred for 45 min. The solution was concentrated and the solid was dried under vacuum. The solid was dissolved in DCM and methanesulfonyamide (0.070 g, 0.750 mmol) was added followed by the NEt3 (0.100 mL, 0.750 mmol) and the reaction was stirred for 2 h. The solution was concentrated and purified by flash chromatography (silica, DCM:MeOH) to afford 7 mg of title compound.

LCMS: 677 (M+1)*

Example 53

7-(4-tert-Butyl-phenoxo)-1-cyclopentylmethyl-isoquinoline-3-carboxylic acid [1-(5-isopropyl-thiophen-2-ylmethyl)-(2S)-methanesulfonylamino-2-oxo-ethyl]-amide

To a solution of Example 50 (0.105 g, 0.17 mmol) in THF was added CDI (0.085 g, 0.526 mmol) and the reaction was stirred at rt for 6 h. To this was added a solution of methanesulfonyamide (0.035 g, 0.36 mmol) and DBU (0.040 g, 0.26 mmol) in THF and the reaction was heated at 60°C for 3 h and stirred at rt for 3 h. The solution was concentrated under reduced pressure and the crude product was purified by the same procedure as used in Example 52 to afford 8 mg of the title compound.

LCMS: 677 (M+1)*

Example 54

7-(4-tert-Butyl-phenoxo)-1-cyclopentylmethyl-isoquinoline-3-carboxylic acid [1-benzoxycarbamoyl-2-(5-isopropyl-thiophen-2-yl)-ethyl]-amide

A solution of Example 43 (0.090 g, 0.150 mmol) in DMF was treated with o-Benzylhydroxylamine hydrochloride (27 mg, 0.165 mmol), HBTU (0.063 g, 0.165 mmol), and DIEA (0.150 mL, 0.829 mmol) by the general procedure A. The crude product was purified by flash chromatography (silica, Hexanes:EtOAc) to afford 74 mg of title compound.

LCMS: 705 (M+1)*

Example 55

7-(4-tert-Butyl-phenoxo)-1-cyclopentylmethyl-isoquinoline-3-carboxylic acid [1-hydroxyoxycarbamoyl-2-(5-isopropyl-thiophen-2-yl)-ethyl]-amide

Example 54 (68 mg, 0.09 mmol) was treated with H2 (1 atm) and Pd/C by the general procedure N. The crude product was purified by flash chromatography (silica, CH2Cl2:CH3OH) to afford 6 mg of title compound.

LCMS: 615 (M+1)*

Biological Assay

[0530] The following assay methods may be used to identify compounds of Formula (I or X) that are effective in antagonizing the function of factor IX. Compounds of Formula (I or X) are effective in antagonizing the function of factor IX may be as inhibitors of the intrinsic clotting pathway.

Factor IXa Assay

[0531] To determine the IC50 of compounds of Formula (I or X) relative to factor IXa, 12 μL solutions of compounds of Formula (I or X) at various concentrations (2% DMSO final concentration) were incubated for 10 min at room temp. with a 24 μL solution of FIXa (HCXIA-0050 Haemotologo Technologies Inc. Essex Junction, Vt.; 3.9 units/mL) in buffer containing 80% Ethylene glycol, 10 mM CaCl2, 200 mM NaCl, and 100 mM Tris (pH 7.4) where the 24 μL solution of FIXa had an activity of 3.9 units/mL. The reaction was started by the addition of 12 μL of 0.5 mM FIXa substrate (Pefia-1048 from Pentapharm Basel, Switzerland; methyl sulfonyl-D-cyclohexylglycyl-glycyl-arginine-7-amino-4-methylcoumarid monoacetate, available from Centerchem, Inc.). After incubating the reaction for 10 min at room temp, the plate was read in a SpectraMax Gemini fluorescence plate reader with an excitation wavelength of 340 nm and an emission wavelength of 440 nm. From the varying concentrations of test compound, IC50's are then calculated.

Factor XIa Assay

[0532] To determine the IC50 of compounds of Formula (I or X) relative to factor XIa, 20 μL solutions of compounds of Formula (I or X) at various concentrations (2% DMSO final concentration) were incubated for 10 min at room temp. with a 10 μL solution of FXIa (HCXIA-0160 from Haemotologo Technologies Inc. Essex Junction, Vt.) in buffer containing 50 mM Tris (pH 7.4) and 150 mM NaCl where the 10 μL solution of FXIa had an activity of 2 units/mL, and 150 μL of buffer. The reaction was started by the addition of 20 μL of 10 mM FXIa substrate (Pefia-3371 from Pentapharm Basel; Switzerland; Pyr-Phg-Ang-pNA monoacetate, available from Centerchem, Inc.). After incubating the reaction for 10 min at room temp, the plate was read in a SpectraMax UV/vis plate reader at 405 nm.

FXIa In Vitro Clotting Assay

[0533] Compounds of Formula (I or X) of the present invention were evaluated for their inhibition of clotting in plasma to which exogenous Factor IXa was added. 20 μL solutions of compounds of Formula (I or X) at various concentrations having 2% DMSO were incubated with 30 μL FIXa (HCXIA-0160 from Haemotologo Technologies Inc. Essex Junction, Vt.) 3.2 units/mL in assay buffer containing 20 mM HEPES (pH 7.4) and 150 mM NaCl, 50 μL of 1:64 dilution of ALEXIN (trinity biosciences) in assay buffer, and 50 μL reconstituted human citrated plasma (Sigma) for 10 min at 37°C. The reaction was started by the addition of 50 μL of 40 mM CaCl2 in assay buffer. The plate was read in kinetic mode at 405 nm and 37°C immediately after addition of calcium. The plate was read for 5-10 min (depending on clot time) in 10 sec intervals on a SpectraMax UV/vis plate reader.

FXIa In Vitro Clotting Assay

[0534] Compounds of Formula (I or X) of the present invention were evaluated for their inhibition of clotting in plasma to which exogenous Factor XIa was added. 20 μL solutions of compounds of Formula (I or X) at various concentrations having 2% DMSO were incubated with 50 μL FXIa (HCXIA-0160 from Haemotologo Technologies
In assays to determine inhibitory activity, Factor IXa was incubated at 37°C for 10 min with various candidates at concentrations ranging from 1:64 dilution to 1:1 dilution of ALEXIN (trinity biosciences) in assay buffer, and 50 μL of reconstituted human citrated plasma (Sigma) for 10 min at 37°C. The reaction was started by the addition of 50 μL of 40 mM CaCl₂ in assay buffer. The plate was read in kinetic mode at 405 nm and 37°C immediately after addition of calcium. The plate was read for 5-10 min (depending on clot time) in 10 sec intervals on a Spectromax UV/Vis plate reader.

[0535] The Examples in Table 1 either inhibit Factor IX in the Factor IXa Fluorescence assay, inhibit Factor XI in the Factor XIa Chromogenic assay, inhibit Factor IX in the Factor IXa in vitro clotting assay, or inhibit Factor XI in the in vitro clotting assay with an IC₅₀ of less than 30 μM. Various Examples in Table 1 may also have IC₅₀'s below 30 μM in more than one of the above-mentioned assays.

[0536] While the invention has been described and illustrated with reference to certain preferred embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the preferred dosages as set forth herein may be applicable as a consequence of variations in the responsiveness of the mammal being treated for factor IXa-mediated disease(s). Likewise, the specific pharmacological responses observed may vary according to and depending on the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. Moreover, all compounds that are recited in the written description are contemplated as possibilities for any of the recited methods, processes, compositions, and/or compounds as appear in the written description and the appended claims.

We claim:

I. A pharmaceutical composition comprising the compound of Formula (X)

![Chemical Structure](image)

wherein R₁₀₃ is selected from the group consisting of —H, or —CH₂-thienyl wherein the thienyl group in —CH₂-thienyl is optionally substituted with —Br or —CH₂;

R₁₀₂ is selected from the group consisting of —C(O)OOH, —C(O)OCH₃, —C(O)O-t-butyl, —C(O)NH—OCH₂—phenyl, —C(O)NH—OH, and —C(O)NH—OCH₂—phenyl;

R₁₀₁ is selected from the group consisting of —H, —CH₂-thienyl, —CH₂-phenyl, —CH₄-furanyl, thienyl, and benzothienyl wherein each of the above possibilities for R₁₀₃ except —H are optionally substituted with one or more members selected from the group consisting of —H, —CH₃, —CF₃, —Cl, —Br, —F, —C(O)CH₂, —CH₂CH₃, —CH₂═CH₂, —CH₂OH, —CH(CH₃)₂, —CH₂CH₂CH₃,

and Y is selected from the group consisting of

![Chemical Structures](image)
or a pharmaceutically acceptable salt, ester, or prodrug thereof.

2. The pharmaceutical composition according to claim 1, wherein \( R_{104} \) is

[Diagram of compound]

3. The pharmaceutical composition according to claim 1, wherein \( R_{103} \) is optionally substituted —CH\(_2\)-2-yl-thienyl or optionally substituted —CH\(_2\)-phenyl.

4. The pharmaceutical composition according to claim 1, wherein \( R_{103} \) is optionally substituted —CH\(_2\)-2-yl-thienyl.

5. The pharmaceutical composition according to claim 4, wherein \( R_{101} \) is H.

6. The pharmaceutical composition according to claim 1, wherein Y is selected from the group consisting of

[Diagram of compound]

7. The pharmaceutical composition according to claim 1, wherein Y is methylene-cyclopentyl.

8. The pharmaceutical composition according to claim 1, wherein the pharmaceutical composition is prepared in a dose in a range of from about 0.01 to 1,000 mg/kg of body weight per day.

9. The pharmaceutical composition of claim 1, wherein the compound of Formula (X) is an antagonist of factor XI or factor IX/XI activity.

10. The pharmaceutical composition of claim 9, wherein the compound of Formula (X) is a partial antagonist of both factor XI and factor IX/IX activity, wherein a partial antagonist comprises a compound that inhibits less than complete activity at a physiological dose.

11. The pharmaceutical composition of claim 9, comprising a therapeutically effective amount of the compound of Formula (X), wherein said therapeutically effective amount of Formula (X) preferentially inhibits the intrinsic clotting cascade as compared to the extrinsic clotting cascade.

12. The pharmaceutical composition of claim 11, wherein said therapeutically effective amount of Formula (X) comprises an amount sufficient to achieve and maintain a sustained blood level that at least partially antagonizes factor XI or factor IX/XI biological activity.

13. The pharmaceutical composition of claim 1, wherein the compound of Formula (X) is an antagonist of factor IX activity.

14. The pharmaceutical composition of claim 13, wherein the compound of Formula (X) is a partial antagonist of factor IX activity, wherein a partial antagonist comprises a compound that inhibits less than complete activity at a physiological dose.

15. The pharmaceutical composition of claim 1, comprising a therapeutically effective amount of the compound of Formula (X), wherein said therapeutically effective amount comprises a sufficient amount of the compound of Formula (X) to at least partially inhibit the biological activity of factor IX in a subject.

16. The pharmaceutical composition of claim 1, comprising a therapeutically effective amount of the compound of Formula (X), wherein said therapeutically effective amount comprises a sufficient amount of the compound of Formula (X) to at least partially inhibit the biological activity of factor IX in a subject.

17. The pharmaceutical composition of claim 16, wherein said therapeutically effective amount of Formula (X) preferentially inhibits the intrinsic clotting cascade as compared to the extrinsic clotting cascade.

18. The pharmaceutical composition of claim 1, wherein said therapeutically effective amount of Formula (X) comprises a sufficient amount of the compound of Formula (X) for at least partial amelioration of at least one factor IX-mediated disease.

19. The pharmaceutical composition of claim 1 in the form of an oral dosage or parenteral dosage unit.

20. A method comprising administering to a subject a compound of Formula (X)

[Diagram of compound]

wherein \( R_{101} \) is selected from the group consisting of —H, or —CH\(_2\)-thienyl wherein the thienyl group in —CH\(_2\)-thienyl is optionally substituted with —Br or —CH\(_3\);

\( R_{102} \) is selected from the group consisting of —C(O)OH, —C(O)CH\(_3\), —C(O)O-t-buty1, —C(O)NH—CH\(_2\)_phenyl, —C(O)NH—CH\(_2\)_phenyl, and —C(O)NH—SO\(_2\)CH\(_3\);

\( R_{103} \) is selected from the group consisting of —H, —CH\(_3\)_thienyl, —CH\(_2\)_phenyl, —CH\(_2\)furanyl, thienyl, and benzothienyl wherein each of the above possibilities for \( R_{103} \) except —H are optionally substituted with one or more members selected from group consisting of
or a pharmaceutically acceptable salt, ester, or prodrug thereof.

21. The method according to claim 20, wherein the compound of Formula (X) is delivered as a part of a pharmaceutical composition comprising a therapeutically effective amount of said compound of Formula (X) and one or more pharmaceutically acceptable carriers, excipients, or diluents.

22. The method according to claim 20, wherein $R_{104}$ is

$$
\text{t-Butyl - } \begin{array}{c}
\text{O} \\
\text{H}_2 \\
\text{C}
\end{array}
$$

23. The method according to claim 22, wherein $R_{101}$ is $-H$.

24. The method according to claim 20, wherein $R_{103}$ is optionally substituted $-\text{CH}_2$-$2$-$\text{yl}$-$\text{thienyl}$ or optionally substituted $-\text{CH}_2$-$\text{phenyl}$.

25. The method according to claim 20, wherein $Y$ is selected from the group consisting of

$$
\begin{array}{c}
\text{H}_2 \\
\text{C}
\end{array}
$$

26. The method according to claim 20, wherein $Y$ is $-\text{methylene-cyclopentyl}$.

27. The method according to claim 20, wherein the compound of Formula (X) is selected from the group consisting of

2(S)-[[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethylisoquinoline-3-carbonyl-amino]-3-(5-phenylthiophen-2-yl)-propionic acid,

2(S)-[[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethylisoquinoline-3-carbonyl-amino]-3-[5-(4-trifluoromethyl-phenyl)-thiophen-2-yl]-propionic acid,

2(S)-[[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethylisoquinoline-3-carbonyl-amino]-3-(5-cyclopent-1-enyl-thiophen-2-yl)-propionic acid methyl ester,

2(S)-[[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethylisoquinoline-3-carbonyl-amino]-3-(5-cyclopent-1-enyl-thiophen-2-yl)-propionic acid methyl ester,

2(S)-[[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethylisoquinoline-3-carbonyl-amino]-3-(5-cyclopentylthiophen-2-yl)-propionic acid methyl ester,

2(S)-[[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethylisoquinoline-3-carbonyl-amino]-3-(5-cyclopentylthiophen-2-yl)-propionic acid methyl ester,
2(S)-[[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-amino]-3-(5-furan-3-yl-thiophen-2-yl)-propionic acid,

2(S)-[[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-amino]-3-[5-(4-isopropyl-phenyl)-thiophen-2-yl]-propionic acid,

2(S)-[[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-amino]-3-[5-(vinyl-thiophen-2-yl)]-propionic acid,

2(S)-[[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-amino]-3-[5-(p-toly1-thiophen-2-yl)]-propionic acid,

2(S)-[[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-amino]-3-[5-(4-chloro-phenyl)-thiophen-2-yl]-propionic acid,

2(S)-[[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-amino]-3-[5-(ethyl-thiophen-2-yl)]-propionic acid,

2(S)-[[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-amino]-3-[5-2-furan-2-yl-propionic acid,

2(S)-[[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-amino]-3-[2-trifluoromethyl-phenyl]-propionic acid,

{(5-Bromo-thiophen-2-ylmethyl)[7-(4-tert-buty1-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-amino}-acetic acid tert-butyl ester,

2(S)-[[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-amino]-3-[3,5-difluorophenyl]-propionic acid,

[[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-[5-methyl-thiophen-2-ylmethyl-aminol]-acetic acid,

{(5-Bromo-thiophen-2-ylmethyl)[7-(4-tert-buty1-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-amino}-acetic acid methyl ester,

{(4-Bromo-thiophen-2-ylmethyl)[7-(4-tert-buty1-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-amino}-acetic acid,

{(5-Bromo-thiophen-2-ylmethyl)[7-(4-tert-butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-amino}-acetic acid,

Benzo[b]thiophen-3-yl-[[7-(4-tert-butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-amino]-acetic acid,

2(S)-[[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-amino]-3-[5-(4-fluoro-phenyl)]-propionic acid,

2(S)-[[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-amino]-3-[5-(propenyl-thiophen-2-yl)]-propionic acid,

2(S)-[[7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-amino]-3-[5-(propyl-thiophen-2-yl)]-propionic acid,
2(R)—[(7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-
isoquinoline-3-carbonyl]-amino]-3-(5-isopropyl-
thiophen-2-yl)-propionic acid,
2(S)—[(7-(4-tert-Butyl-phenoxy)-isoquinoline-3-carbonyl]-amino]-3-(5-isopropyl-thiophen-2-yl)-propionic acid,
2(S)—[(1-Cyclopentylmethyl-7-(4-trans-ethyl-cyclohexy-
loxy)-isoquinoline-3-carbonyl]-amino]-3-(5-isopropyl-
thiophen-2-yl)-propionic acid,
2(S)—[(1-Cyclopentylmethyl-7-(4-isopropyl-phenoxy)-
isoquinoline-3-carbonyl]-amino]-3-(5-isopropyl-
thiophen-2-yl)-propionic acid,
2(S)—[(7-(4-tert-Butyl-phenoxy)-1-(tetrahydro-pyran-4-
yl)-isoquinoline-3-carbonyl]-amino]-3-(5-isopropyl-
thiophen-2-yl)-propionic acid,
2(S)—[(6-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-
isoquinoline-3-carbonyl]-amino]-3-(5-isopropyl-
thiophen-2-yl)-propionic acid,
2(S)—[(7-(4-tert-Butyl-phenyl)-1-cyclopentylmethyl-
isoquinoline-3-carbonyl]-amino]-3-(5-isopropyl-
thiophen-2-yl)-propionic acid,
2(S)—[(7-(4-tert-Butyl-benzyl)-1-cyclopentylmethyl-
isoquinoline-3-carbonyl]-amino]-3-(5-isopropyl-
thiophen-2-yl)-propionic acid,
3-(5-Acetyl-thiophen-2-yl)-2(S)—[(7-(4-tert-butyl-pheno-
xy)-1-cyclopentylmethyl-isoquinoline-3-carbonyl]-
amino]-propionic acid,
7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquino-
line-3-carboxylic acid [1-(5-isopropyl-thiophen-2-yl-
ethyl)-2(R)-methanesulfonilamino-2-oxo-ethyl]-amide, and
7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquino-
line-3-carboxylic acid [1-(5-isopropyl-thiophen-2-yl-
ethyl)-2(S)-methanesulfonilamino-2-oxo-ethyl]-amide,
7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquino-
line-3-carboxylic acid [1-benzoylcarbamoyl-2-(5-
isopropyl-thiophen-2-yl)-ethyl]-amide, and
7-(4-tert-Butyl-phenoxy)-1-cyclopentylmethyl-isoquino-
line-3-carboxylic acid [1-hydroxycarbamoyl-2-(5-
isopropyl-thiophen-2-yl)-ethyl]-amide.
28. The method according to claim 20, wherein said compound of formula (X) inhibits up to 95% of factor IX activity.
30. The method of claim 20, wherein the compound of Formula (X) is an antagonist of factor IX activity.
31. The method of claim 20, wherein said compound of Formula (X) is a partial antagonist of factor IX, wherein a partial antagonist comprises a compound that inhibits less than complete activity at a physiological dose.
32. The method of claim 20, wherein the compound of Formula (X) antagonizes blood clotting mediated by factor IX.
33. The method of claim 20, wherein said compound of Formula (X) is administered in an amount sufficient to partially antagonize the biological activity of factor IX in said subject.
34. The method of claim 21, wherein said therapeutically effective amount of the compound of Formula (X) comprises a sufficient amount of the compound of Formula (X) to at least partially inhibit the intrinsic clotting cascade in said subject.
35. The method of claim 21, wherein said therapeutically effective amount of Formula (X) preferentially inhibits the intrinsic clotting cascade as compared to the extrinsic clotting cascade.
36. The method of claim 21, wherein said therapeutically effective amount of the compound of Formula (X) comprises a sufficient amount of the compound of Formula (X) for treatment or prevention of factor IX-mediated diseases.
37. The method of claim 20, wherein said pharmaceutical composition is administered in the form of an oral dosage or parenteral dosage unit.
38. The method of claim 20, wherein said compound of Formula (X) is administered as a dose in a range from about 0.01 to 1,000 mg/kg of body weight per day.
39. The method of claim 36, wherein said factor IX-mediated disease comprises stroke.
40. The method of claim 36, wherein said factor IX-mediated disease comprises deep vein thrombosis.
41. The method of claim 40, wherein said thrombosis is associated with surgical procedures, long periods of confinement, acquired or inherited pro-coagulant states including anti-phospholipid antibody syndrome, protein C deficiency and protein S deficiency, or acute and chronic inflammation including recurrent miscarriage or Systemic Lupus Erythmatosis (SLE).
42. The method of claim 36, wherein said factor IX-mediated disease comprises clotting associated with the treatment of kidney disease by hemodialysis and/or venous hemolification.
43. The method of claim 36, wherein said factor IX-mediated disease comprises cardiovascular disease.
44. The method of claim 43, wherein said cardiovascular disease comprises myocardial infarction, arrhythmia, or aneurysm.
45. The method of claim 20, wherein said compound of Formula (X) is used to replace or supplement compounds that reduce clotting.
46. The method of claim 21, wherein said pharmaceutical composition further comprises one or more therapeutic agents.
47. A method for the inhibition of the normal biological function of factor XI or factor IX/XI comprising the method of claim 20.
48. A method to inhibit blood clotting comprising the method of claim 20.

* * * * *