inhibitors. Therefore, when patients are anti-coagulated with these agents, adverse effects associated with overdosing, particularly significant or fatal bleeds, are much more dangerous than the side effects associated with administration of unfractionated heparin. The lack of reversal agent therefore limits the use of these drugs.

[0012] For these reasons, there is a longstanding, strong, unmet clinical need for new anti-coagulation reversal agents.

SUMMARY ~~OF THE INVENTION~~

[0013] Inhibitors of heparin, heparin fragments, fondaparinux and other factor Xa or factor IIa inhibitors has been developed. The general structure of the anti-coagulant reversal agents of interest is: **R-Z-R'**, where R and R' are positively charged agents at physiologic pH and can be the same or different molecules and Z is a hydrophobic cyclic or fused ring compound. More specifically, the inhibitor is represented by a compound of formula I or a pharmaceutically acceptable salt thereof. In an aspect, there is provided a compound of formula I or a pharmaceutically acceptable salt thereof:



(I)

wherein:

A is a substituted or unsubstituted aromatic or non-aromatic, carbocyclic or heterocyclic ring or a linear moiety;

L and L' are the same or different and are linkers;

X and X' are the same or different and are absent or are a functional group that attaches the linker L to M and the linker L' to M', respectively;

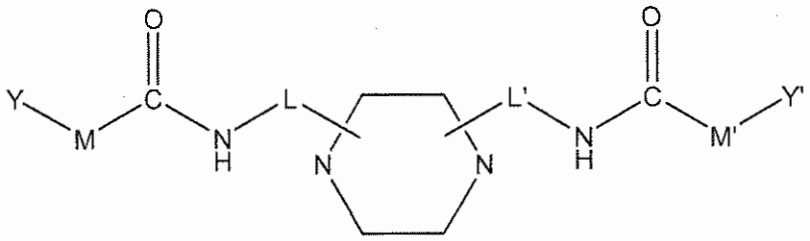
M and M' are the same or different and are absent or is a linker that attaches X to Y and X' to Y', respectively; and

Y and Y' are the same or different and are a moiety containing one or more cationic atoms or groups or one or more groups that become cationic under physiological conditions.

[0014] The compounds can be symmetrical or asymmetrical; that is, one or more of L, L', X, X', M, M', Y, or Y' can be the same or different. The compounds can be chiral (i.e., contain one or more chiral centers) or achiral.

[0015] In some embodiments, A is a heterocyclic moiety. In other embodiments, A is a heterocyclic moiety and L and L' are a substituted or unsubstituted alkylene chain. In still other embodiments, A is a heterocyclic moiety, L and L' are a substituted or unsubstituted alkylene chain, and X and X' are –NH-C(=O)-. In still other embodiments, A is a heterocyclic moiety, L and L' are a substituted or unsubstituted alkylene chain, X and X' are –NH-C(=O)-, and M and M' are a substituted alkylene chain. In still other embodiments, A is a heterocyclic moiety, L and L' are a substituted or unsubstituted alkylene chain, X is –NH-C(=O)-, M and M' are a substituted alkylene chain, and Y and Y' are a guanidine moiety. In particular embodiments, A is a 1,4 or 2,5 disubstituted piperazine ring.

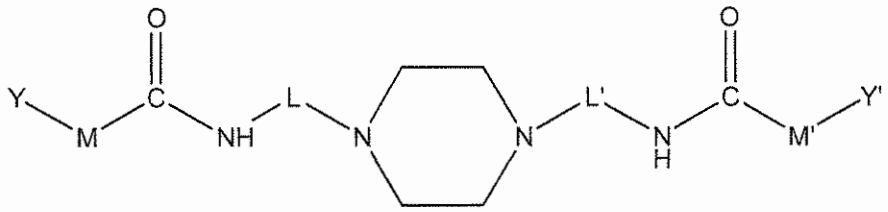
[0016] In another embodiment of the ~~invention~~ present disclosure, the inhibitor is a compound represented by the formula II or a pharmaceutically acceptable salt thereof:



(II)

wherein each of L, L', M, M', Y and Y' are as described herein.

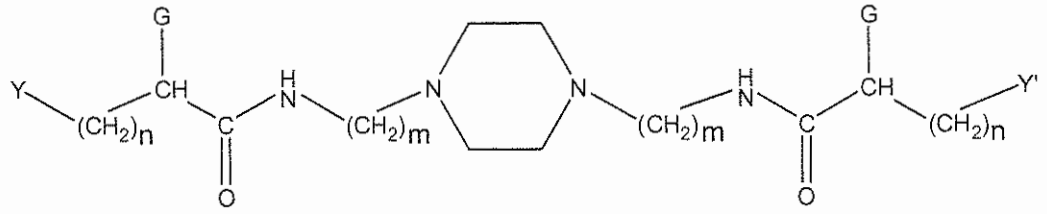
[0017] In another embodiment of the ~~invention~~ present disclosure, the inhibitor is a compound represented by the formula III or a pharmaceutically acceptable salt thereof:



(III)

wherein L, L', M, M', Y and Y' are as described herein.

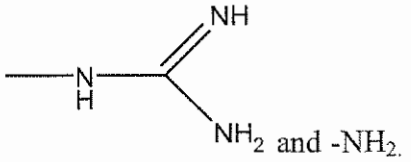
[0018] In yet another embodiment of the ~~invention~~ present disclosure, the inhibitor is a compound represented by the formula (IV) or pharmaceutically acceptable salt thereof:



(IV)

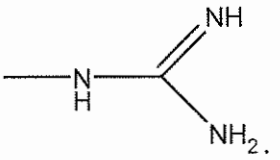
wherein Y and Y′ are as described herein and n is 3 to 5, m is 3 to 6 and G is selected from – NH_2 and OH. Most preferably, G is amino.

[0019] Yet another embodiment of the ~~invention~~ present disclosure, the inhibitor is a compound represented by any of formula II, III or IV and Y and Y′ are independently selected from the group consisting of



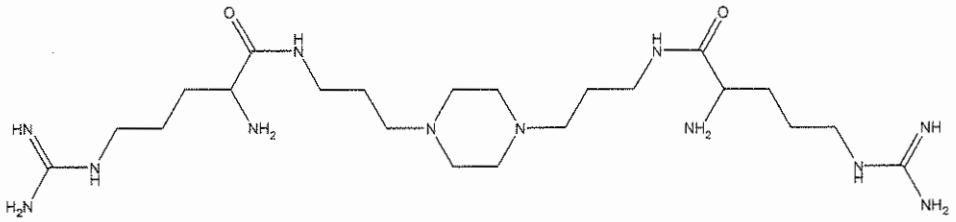
and -NH_2.

[0020] Most preferably G is –NH_2 and Y and Y′ are



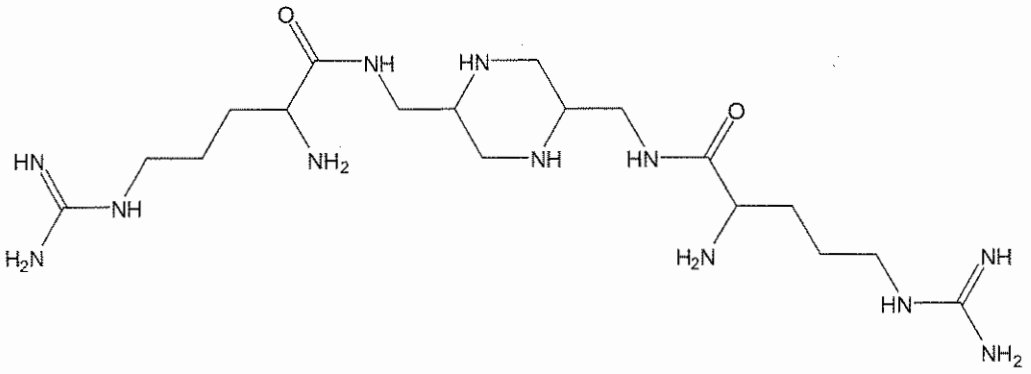
[0021] In ~~the preferred embodiment~~aspects, the compound provided is di-arginine piperazine (DAP), depicted in formula V, or a related compound, depicted in formula VI, or pharmaceutically acceptable salts of either compound:

(V)



2-Amino-5-guanidino-pentanoic acid (3-{4-[3-(2-amino-5-guanidino-pentanoylamino)-propyl]-piperazin-1-yl}-propyl)-amide; or

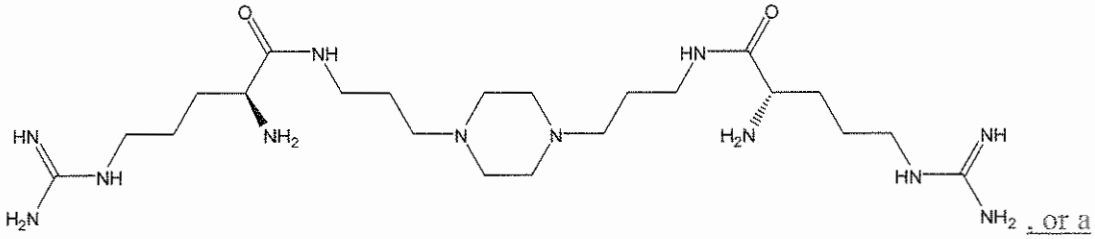
(VI)



2-Amino-5-guanidino-pentanoic acid {5-[(2-amino-5-guanidino-pentanoylamino)-methyl]-piperazin-2-ylmethyl}-amide.

[0022] In ~~a specific embodiment~~another aspect, there is provided the compound of formula V which is a stereoisomer as depicted in formula VII:

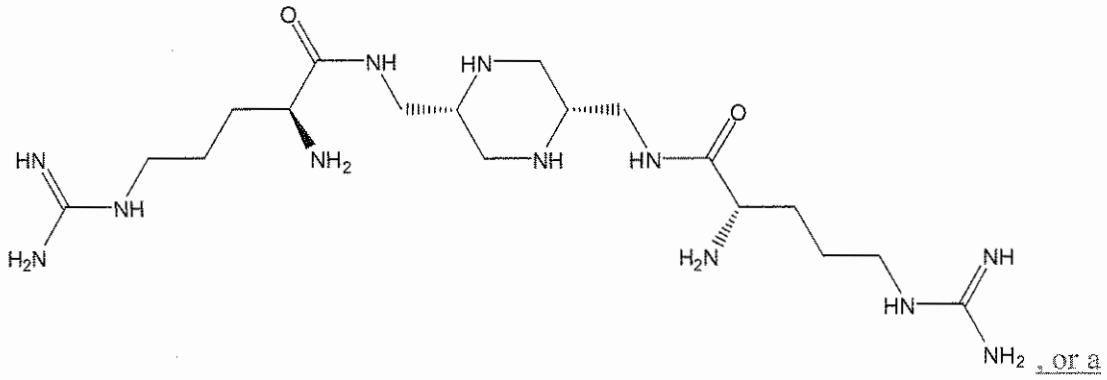
(VII)



, or a pharmaceutically acceptable salt thereof.

[0023] In another ~~specific embodiment~~aspect, there is provided the compound of formula VI which is a stereoisomer as depicted in formula VIII:

(VIII)



, or a pharmaceutically acceptable salt thereof.

[0024] In another aspect, there is provided a pharmaceutical composition comprising the compound as disclosed herein and a pharmaceutically acceptable carrier. The compounds of the ~~invention~~ present disclosure can be administered in a pharmaceutical composition as an aqueous solution as a bolus and/or intravenous infusion, subcutaneous injection, or orally. In the preferred embodiment, the compounds are administered by injection (intravenous, intramuscular or subcutaneous) in a carrier such as distilled sterile water, saline, buffered saline, or another pharmaceutically acceptable excipient for injection. In some embodiments, the inhibitor may be administered orally, to a mucosal surface (nasal, pulmonary, vaginal, rectal or buccal) or by depot.

[0025] The compounds of the ~~invention~~ present disclosure may be administered in pharmaceutical composition to the patient in need of reversal of heparin, LMWH or other thrombin inhibitor-mediated anticoagulation in an effective amount to restore normal coagulation and hemostasis. The pharmaceutical compositions including the compound of the ~~inventions~~ present disclosure are suitable for hospital use or in non-emergency home reversal. It is administered to the patient in need of reversal of heparin, LMWH or other thrombin inhibitor mediated anticoagulation in an effective amount to restore coagulation. The compounds and pharmaceutical compositions described herein can also be used to reduce the activity of heparin-binding growth factors and/or for reversing completely or in part a combination of one or more Factor IIa and/or Factor Xa anticoagulant agents.

[0026] Thus, the compounds of the ~~invention~~ present disclosure can be used in a method of completely or partially reversing an anticoagulant effect of a coagulation inhibitor. In an aspect, there is provided the use of a compound as disclosed herein or pharmaceutically acceptable salt thereof in the manufacture of a medicament for completely or partially reversing an anticoagulant effect of a coagulation inhibitor in a subject in need thereof. The compounds of the ~~invention~~ present disclosure can also be used as a part of a diagnostic kit, e.g., a diagnostic kit for determining concentration of an anticoagulant in the blood. In another aspect, there is provided a diagnostic kit comprising the compound as disclosed herein.

[0027] Examples demonstrate that DAP directly bound rivaroxaban, apixaban, unfractionated heparin, fondaparinux, and LMWH, reversing anticoagulant activity. DAP reversed oral rivaroxaban and subcutaneous LMWH anticoagulation *in vivo* as measured by aPTT and subcutaneous fondaparinux as measured by Xa activity in rats. DAP reversal, confirmed by statistically significant reduction in blood loss in tail rat transection assay, was shown for apixaban, dabigatran, edoxaban, and rivaroxaban. DAP completely reversed apixaban and rivaroxaban at a dose mass ratio of about 10:1 DAP:anticoagulant

20. The pharmaceutical composition of claim 19, wherein the composition is adapted for intravenous or subcutaneous administration.

21. ~~A method of completely or partially reversing an anticoagulant effect of a coagulation inhibitor comprising administering to a subject in need thereof a therapeutically effective amount~~ Use of a compound of any one of claims 1-15 or pharmaceutically acceptable salt thereof in the manufacture of a medicament for completely or partially reversing an anticoagulant effect of a coagulation inhibitor in a subject in need thereof.

22. The ~~method~~ use of claim 21, wherein the coagulation inhibitor is selected from the group consisting of an unfractionated heparin, low molecular weight heparin (LMWH), Factor IIa inhibitor, and Factor Xa inhibitor.

23. The use ~~method~~ of claim 22, wherein the coagulation inhibitor is a factor Xa inhibitor.

24. The use ~~method~~ of claim 23, wherein the factor Xa inhibitor is selected from the group consisting of rivaroxaban, apixaban, edoxaban, and fondaparinux.

25. The use ~~method~~ of claim 21, wherein the subject is a mammal.

26. The use ~~method~~ of claim 25, wherein the subject is a human.

27. The use ~~method~~ of claim 21, wherein the complete or partial reversal of an anticoagulant effect of a coagulation inhibitor is measured by anti-factor Xa activity assay.

28. The use ~~method~~ of claim 21, wherein the subject in need thereof is a subject in whom acute or planned reversal of anticoagulation is indicated.

29. The use ~~method~~ of claim 28, wherein the subject in whom acute or planned reversal of anticoagulation is indicated is a subject suffering from anticoagulant overdose, a subject suffering from hemorrhage, a subject requiring planned surgical intervention, a subject undergoing an invasive or non-invasive procedure

requiring a biopsy, a subject undergoing a procedure wherein a procedural error may result in hemorrhage if the subject remains anticoagulated, or a subject requiring spinal or epidural anesthesia.

30. The use ~~method~~ of claim 28, wherein the subject in need thereof is a subject receiving anticoagulation for stroke prevention, cardiac surgical and diagnostic procedures, cardiac arrhythmias, deep vein thrombosis (DVT) prevention, pulmonary embolism, or generally for the prevention of pathologic blood clots.

31. The use ~~method~~ of claim 22, wherein the coagulation inhibitor is a LMWH, and wherein the LMWH is selected from the group consisting of bemiparin, certoparin, dalteparin, enoxaparin, nadroparin, parnaparin, reviparin, and tinzaparin.

32. The use ~~method~~ of claim 21, wherein the ~~compound or the pharmaceutically acceptable salt thereof~~ medicament is to be administered at a dose mass ratio of between about 0.01:1 to about 1000:1 of the compound or the pharmaceutically acceptable salt thereof to anticoagulant.

33. The use ~~method~~ of claim 32, wherein the ~~compound or the pharmaceutically acceptable salt thereof~~ medicament is to be administered at a dose mass ratio of about 10:1 of the compound or the pharmaceutically acceptable salt thereof to anticoagulant.

34. The use ~~method~~ of claim 21, wherein the medicament ~~method~~ comprises ~~administering~~ at least one additional therapeutic agent.

35. The use ~~method~~ of claim 34, wherein the at least one additional therapeutic agent is vitamin K.

36. A diagnostic kit comprising the compound of any one of claims 1-15.

37. The kit of claim 36, wherein the kit is used for determining an anticoagulant concentration in blood.