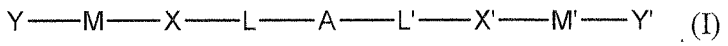
inhibitors. Therefore, when patients are anti-coagulated with these agents, adverse effects associated with overdosing, particularly significant or fatal bleeds, are much more dangerous than the side effects associated with administration of unfractionated heparin. The lack of reversal agent therefore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

**[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~~embodiment, 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;

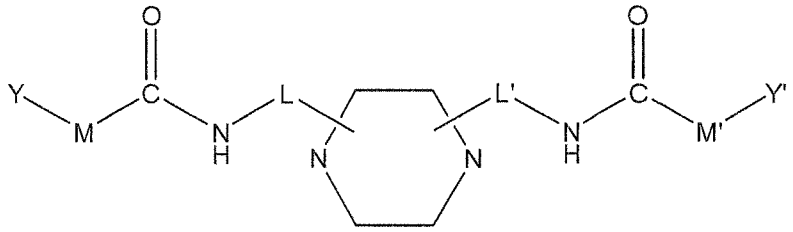
M and M' are the same or different and are absent or is a linker that attaches X to Y and X' to Y', respectively; and

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.

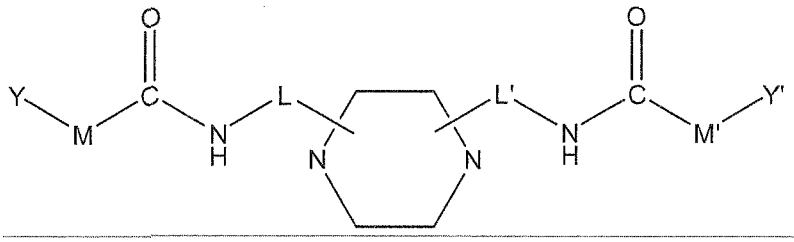
**[0015]** In some embodiments, A is a heterocyclic moiety. In other embodiments, A is a heterocyclic moiety and L and L' are a substituted or unsubstituted alkylene chain. In still other embodiments, A is a heterocyclic moiety, L and L' are a substituted or unsubstituted alkylene chain, and X and X' 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 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. In an aspect, there is provided a compound of formula II:

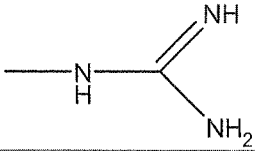


(II)

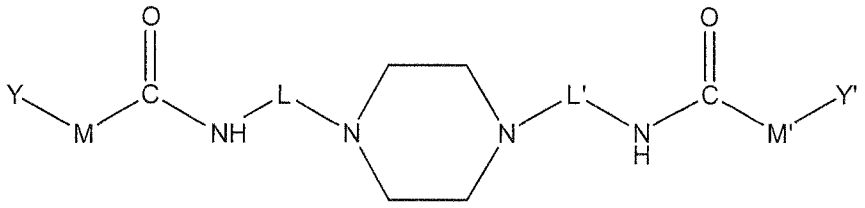
or a pharmaceutically acceptable salt thereof,

wherein L and L' are each a substituted or unsubstituted alkylene chain,

wherein M and M' are each a substituted alkylene chain, and

wherein Y and Y' are each .

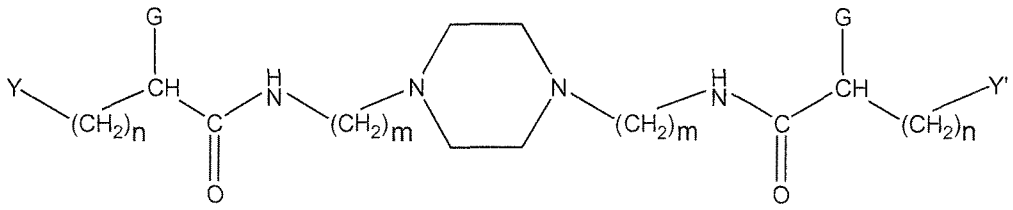
**[0017]** In another embodiment of the present disclosure, the inhibitor is a compound represented by the formula III or a pharmaceutically acceptable salt thereof:




(III)

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

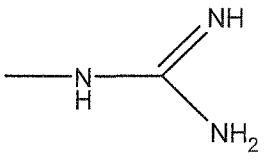
**[0018]** In yet another embodiment of the present disclosure, the inhibitor is a compound represented by the formula (IV) or pharmaceutically acceptable salt thereof:




(IV)

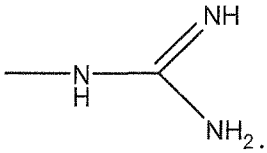
wherein Y and Y′ are as described herein and n is 3 to 5, m is 3 to 6 and G is selected from $-NH_2$ and OH. Most preferably, G is amino.

**[0019]** Yet another embodiment of the 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 $-NH_2$.

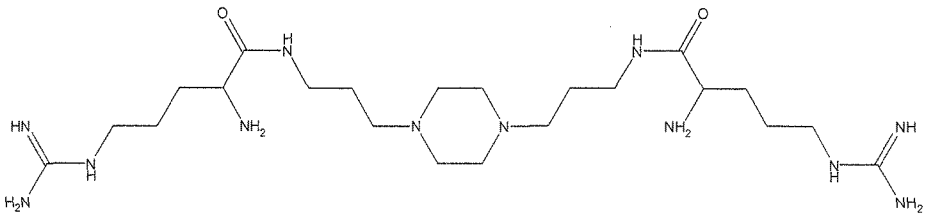
**[0020]** Most preferably G is $-NH_2$ and Y and Y′ are




.

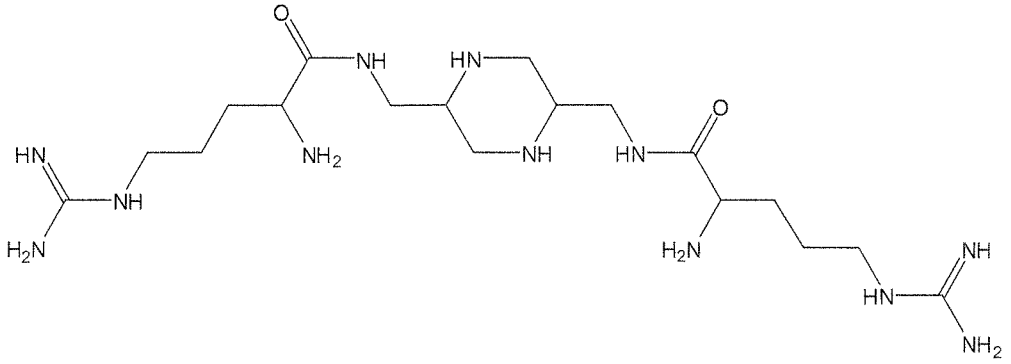
**[0021]** In ~~aspects~~embodiments, the compound provided is di-arginine piperazine (DAP), depicted in formula V, or a related compound, depicted in formula VI, or pharmaceutically acceptable salts of either compound:

(V)




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

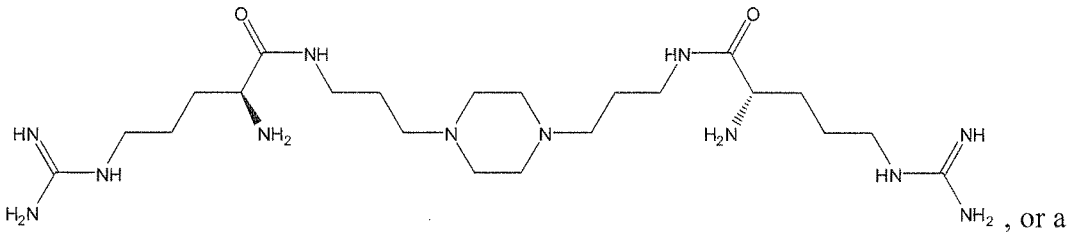
(VI)



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

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

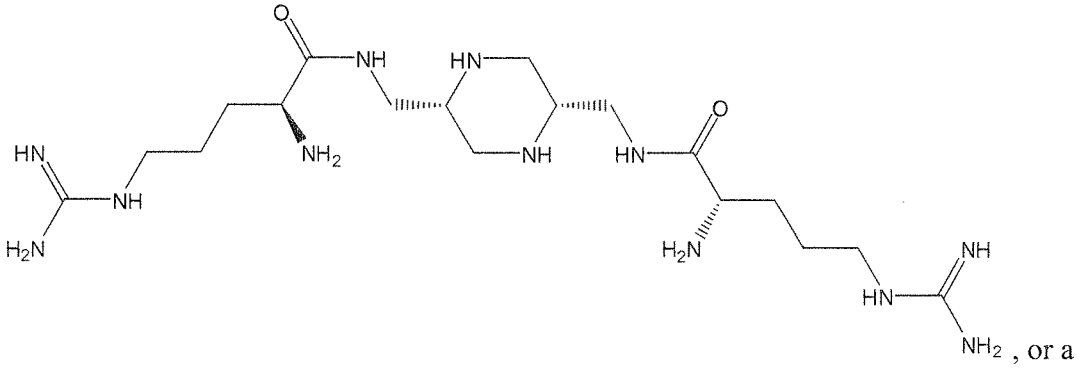
(VII)



pharmaceutically acceptable salt thereof.

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

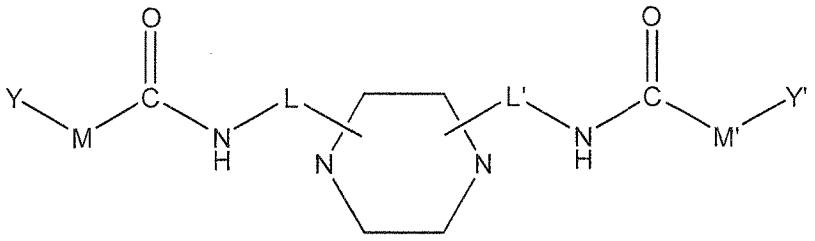
(VIII)



pharmaceutically acceptable salt thereof.

WHAT IS CLAIMED IS:

1. A compound of formula II:

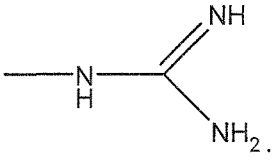


(II)

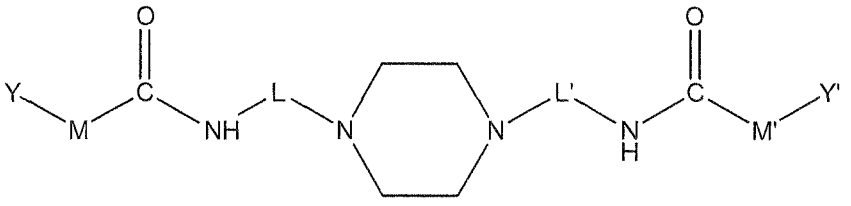
or a pharmaceutically acceptable salt thereof,

wherein L and L' are each a substituted or unsubstituted alkylene chain,

wherein M and M' are each a substituted alkylene chain, and

wherein Y and Y' are each .

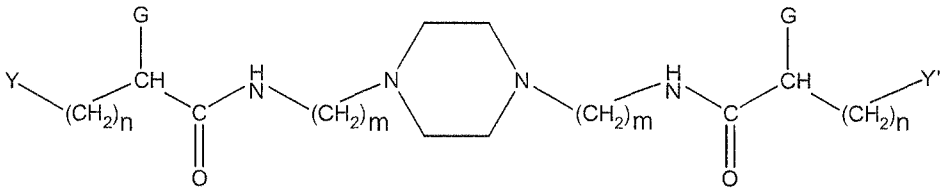
2. The compound of claim 1, wherein the compound is represented by formula III:



(III)

or a pharmaceutically acceptable salt thereof.

3. The compound of claim 2, wherein the compound is represented by formula IV:



(IV)

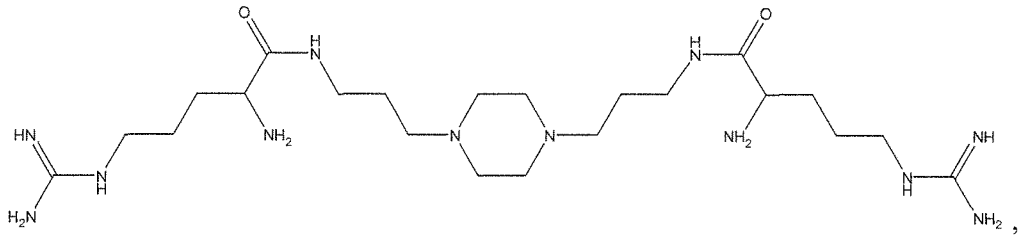
or a pharmaceutically acceptable salt thereof,

wherein n is 3 to 5, m is 3 to 6 and G is selected from $-NH_2$ and OH.

4. The compound of claim 3, wherein G is amino.

5. The compound of claim 1, wherein the compound is represented by formula V

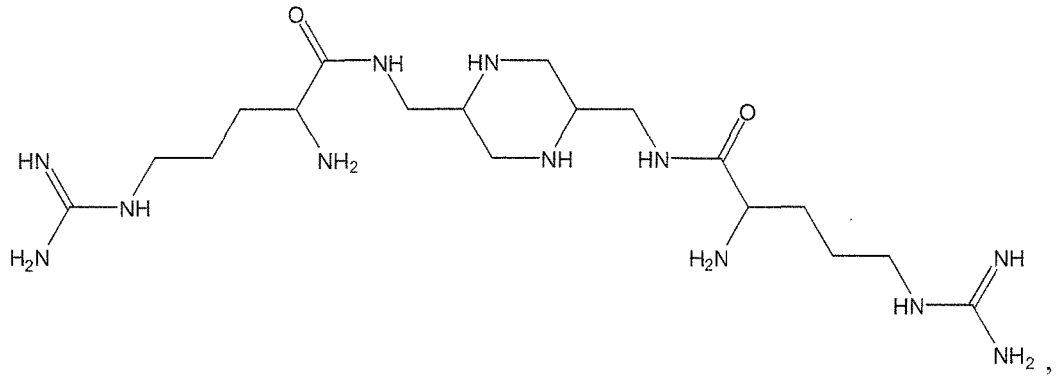
(V)



or a pharmaceutically acceptable salt thereof.

6. The compound of claim 1, wherein the compound is represented by formula VI

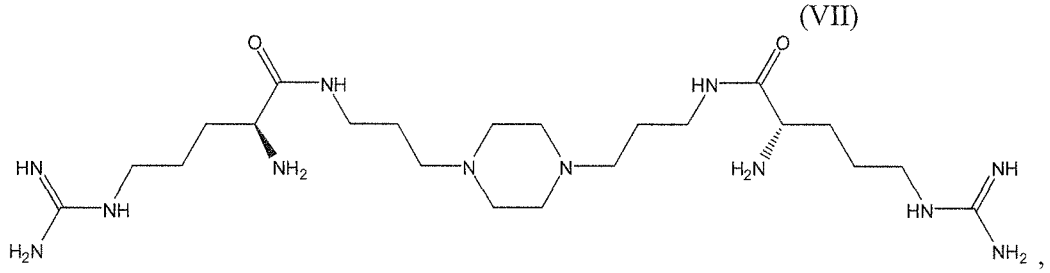
(VI)



or a pharmaceutically acceptable salt thereof.

7. The compound of claim 1, wherein the compound is represented by formula VII

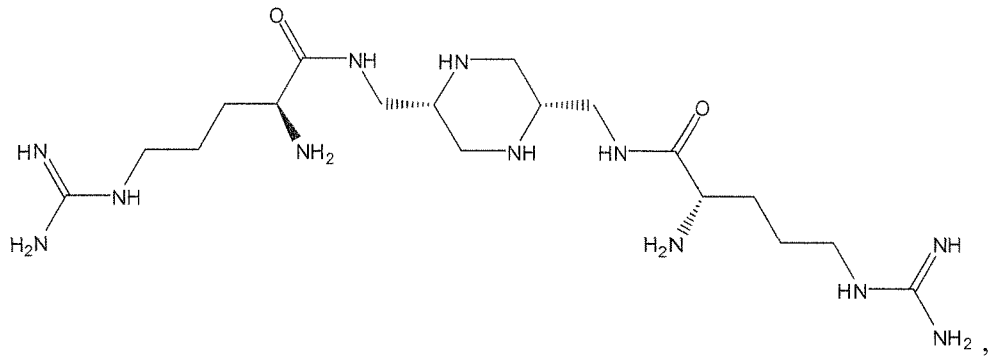
(VII)



or a pharmaceutically acceptable salt thereof.

8. The compound of claim 1, wherein the compound is represented by formula VIII

(VIII)



or a pharmaceutically acceptable salt thereof.

9. A pharmaceutical composition comprising the compound of any one of claims 1-8 and a pharmaceutically acceptable carrier.

10. The pharmaceutical composition of claim 9, wherein the composition is adapted for enteral administration.

11. The pharmaceutical composition of claim 10, wherein the composition is adapted for oral administration.

12. The pharmaceutical composition of claim 9, wherein the composition is adapted for parenteral administration.

13. The pharmaceutical composition of claim 12, wherein the composition is adapted for intravenous or subcutaneous administration.

14. Use of a compound of any one of claims 1-8 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.

15. The use of claim 14, 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.

16. The use of claim 15, wherein the coagulation inhibitor is a factor Xa inhibitor.

17. The use of claim 16, wherein the factor Xa inhibitor is selected from the group consisting of rivaroxaban, apixaban, edoxaban, and fondaparinux.

18. The use of claim 14, wherein the subject is a mammal.

19. The use of claim 18, wherein the subject is a human.

20. The use of claim 14, wherein the complete or partial reversal of an anticoagulant effect of a coagulation inhibitor is measured by anti-factor Xa activity assay.

21. The use of claim 14, wherein the subject in need thereof is a subject in whom acute or planned reversal of anticoagulation is indicated.

22. The use of claim 21, 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.

23. The use of claim 21, 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.

24. The use of claim 15, 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.

25. The use of claim 14, wherein the 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.

26. The use of claim 25, wherein the 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.

27. The use of claim 14, wherein the medicament comprises at least one additional therapeutic agent.

28. The use of claim 27, wherein the at least one additional therapeutic agent is vitamin K.

29. A diagnostic kit comprising the compound of any one of claims 1-8.

30. The kit of claim 29, wherein the kit is used for determining an anticoagulant concentration in blood.

WHAT IS CLAIMED IS:

1. A compound of formula I

Y——M——X——L——A——L'——X'——M'——Y' (I)

or a pharmaceutically acceptable salt thereof, 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 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.

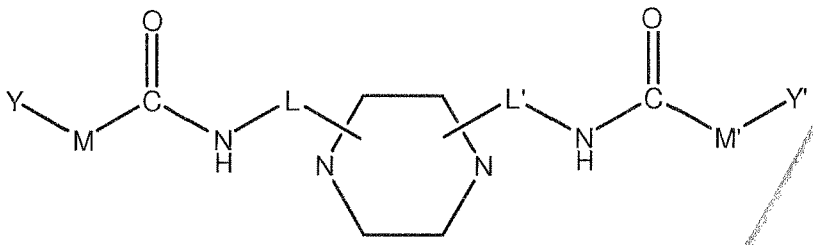
2. The compound of claim 1, wherein A is a non-aromatic, heterocyclic ring or a linear moiety, and wherein the ring or the linear moiety contain reactive functional groups that can form a bond to X and/or X', when present, or Y and/or Y'.

3. The compound of claim 2, wherein A is a piperazine or diketopiperazine.

4. The compound of any one of claims 1-3, wherein X and X', when present, is a functional group that attaches linker L to Y and linker L' to Y', respectively, and wherein the functional group is selected from the group consisting of esters, amides, and ketones.

5. The compound of any one of claims 1-4, wherein L and/or L' is a substituted or unsubstituted alkylene chain that is $C_1$ to $C_6$.

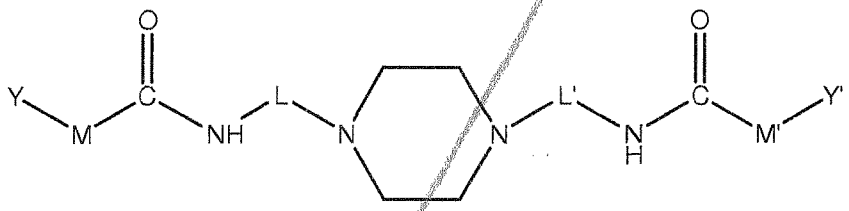
6. The compound of claim 1, wherein the compound is represented by formula II:



(II)

or a pharmaceutically acceptable salt thereof.

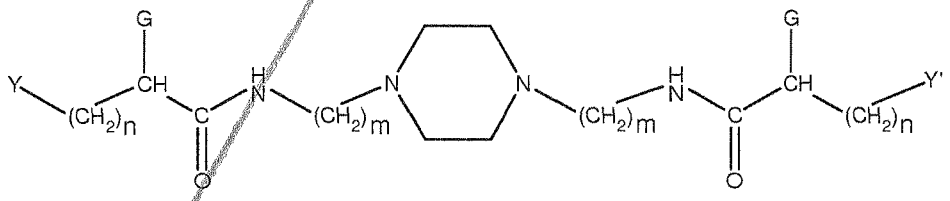
7. The compound of claim 6, wherein the compound is represented by formula III:



(III)

or a pharmaceutically acceptable salt thereof.

8. The compound of claim 7, wherein the compound is represented by formula IV:



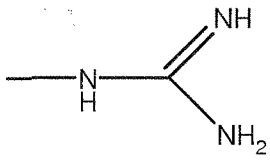
(IV)

or a pharmaceutically acceptable salt thereof,

wherein n is 3 to 5, m is 3 to 6 and G is selected from $-NH_2$ and OH.

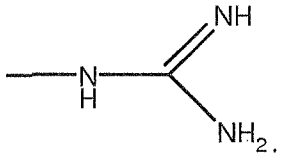
9. The compound of claim 8, wherein G is amino.

10. The compound of any one of claims 1-9, wherein Y and Y' are independently selected from



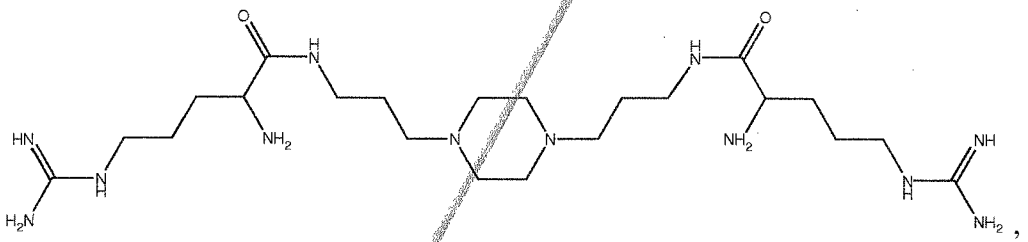
and -$NH_2$.

11. The compound of claim 10, wherein Y and Y' is



12. A compound of formula V

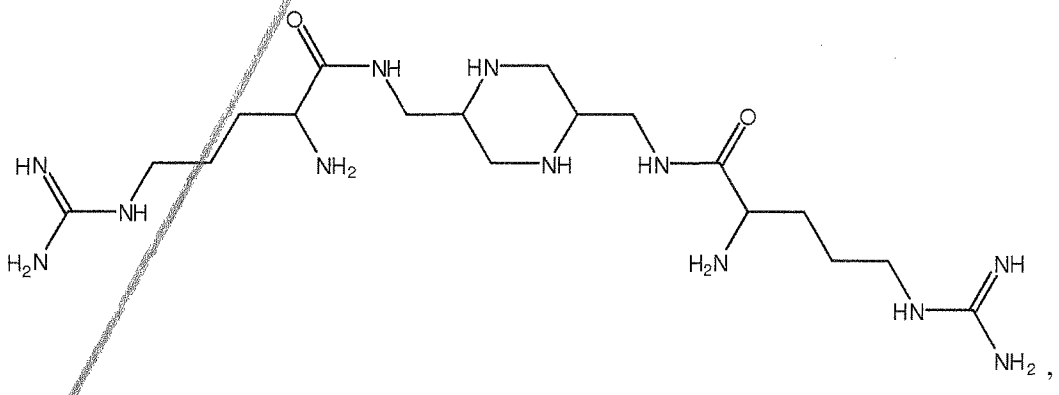
(V)



or a pharmaceutically acceptable salt thereof.

13. A compound of formula VI

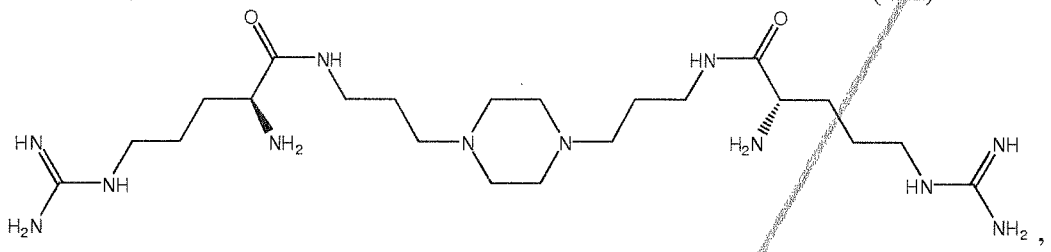
(VI)



or a pharmaceutically acceptable salt thereof.

14. A compound of formula VII

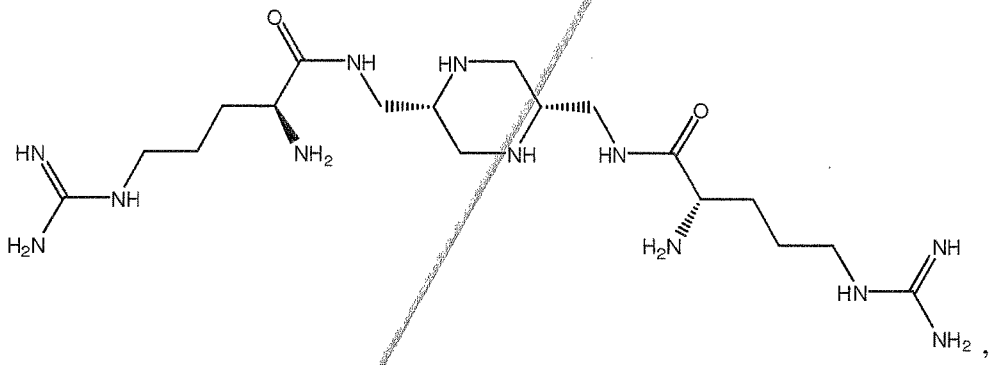
(VII)



or a pharmaceutically acceptable salt thereof.

15. A compound of formula VIII

(VIII)



or a pharmaceutically acceptable salt thereof.

16. A pharmaceutical composition comprising the compound of any one of claims 1-15 and a pharmaceutically acceptable carrier.

17. The pharmaceutical composition of claim 16, wherein the composition is adapted for enteral administration.

18. The pharmaceutical composition of claim 17, wherein the composition is adapted for oral administration.

19. The pharmaceutical composition of claim 16, wherein the composition is adapted for parenteral administration.

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

21. 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 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 of claim 22, wherein the coagulation inhibitor is a factor Xa inhibitor.

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

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

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

27. The use 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 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 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 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 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 of claim 21, wherein the 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 of claim 32, wherein the 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 of claim 21, wherein the medicament comprises at least one additional therapeutic agent.

35. The use 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.