

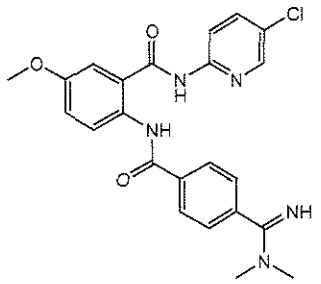
Compound A.

Since treatment for diseases such as acute coronary syndromes might require co-administration of an anticoagulant agent and an antiplatelet agent, a combination would allow for increased efficacy as well as superior patient compliance during chronic treatment. However, some current anticoagulants therapies are not suitable for combination therapy. For example, warfarin, a currently available anticoagulant for chronic use, requires dose titration using international normalized ratio (INR) clotting assays to avoid excessive blood thinning and the risk of bleeding. Therefore it cannot be used as a combination with an antiplatelet agent at a fixed dose. Further, while some anticoagulant agents and antiplatelet agents may be suitable for combination therapy, they do not provide sufficient therapeutic benefit. For example, a recent clinical study examined patients on fondaparinux (an anticoagulant agent) and either aspirin or clopidogrel. The patients continued to experience thrombotic events over the course of the study. (Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators, et al, *N. Engl. J. Med.* **2006**, 354(14):1464-76).

Thus, there is a need for combination therapies that combine a fixed dose of anticoagulant agent with an antiplatelet agent that have enhanced efficacy. Further, there is a need for combination therapies for patients having thrombotic disease(s) with other co-existing conditions, such as high blood pressure or inflammation.

SUMMARY OF THE ~~INVENTION~~DISCLOSURE

This ~~invention~~disclosure provides methods and pharmaceutical compositions of combined therapies comprising a factor Xa inhibitor, having the following structure:



which has the chemical name, [2-({4-[(dimethylamino)iminomethyl]phenyl}carbonylamino)-5-methoxyphenyl]-N-(5-chloro(2-pyridyl))carboxamide and is referred to throughout as "Compound A".

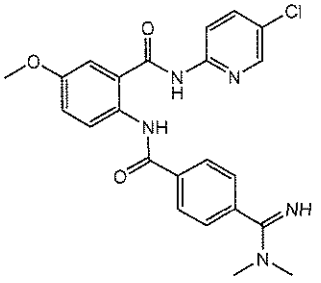
This compound has been shown to have the ability to treat conditions associated with undesired thrombosis. A patient undergoing treatment for undesired thrombosis are often in need of receiving additional cardiac and/or vascular therapy.

Compound A has been shown to have predictable levels of anticoagulation as measured by pharmacodynamic assays. This is more thoroughly described in Examples 2 and 3. Thus, it is contemplated that Compound A can surprisingly and unexpectedly be used in a fixed, non-dose-titrated manner in combination with other therapeutic agents for the treatment of thrombotic disease. It is further contemplated that Compound A when provided in combination with certain other therapeutic agents shows a synergistic effect illustrated by superior efficacy or safety profile.

The present ~~invention~~disclosure provides novel methods for treating a condition in a mammal characterized by undesired thrombosis, comprising administering to said mammal a therapeutically effective amount of the Compound A, [2-({4-[(dimethylamino)iminomethyl]phenyl}carbonylamino)-5-methoxyphenyl]-N-(5-chloro(2-pyridyl))carboxamide, or a pharmaceutically acceptable salt thereof, and a therapeutically effective amount of another therapeutic agent. The other therapeutically effective agent is selected from an antiplatelet agent, an anticoagulant agent, an inflammatory agent, a blood pressure lowering agent and combinations thereof. In one embodiment, Compound A and the other therapeutic agent can be combined with another agent selected from a thrombin

inhibitor, a thrombolytic agent, an antiarrhythmic agent, a cholesterol or triglyceride agent and combinations thereof.

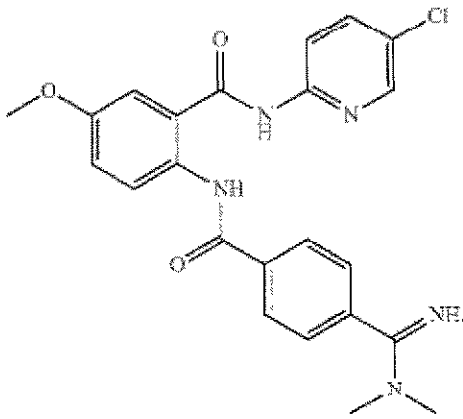
The ~~invention~~disclosure is also directed to pharmaceutical compositions comprising a compound of the following formula:



which has the chemical name, [2-({4-[(dimethylamino)iminomethyl]phenyl}carbonylamino)-5-methoxyphenyl]-N-(5-chloro(2-pyridyl))carboxamide and another therapeutic agent, including, an antiplatelet agent, an anticoagulant agent, an inflammatory agent, and combinations thereof.

In a first aspect, there is provided the use of a therapeutically effective amount of

(1) [2-({4-[(dimethylamino)iminomethyl]phenyl}carbonylamino)-5-methoxyphenyl]-N-(5-chloro(2-pyridyl))carboxamide, of the formula:



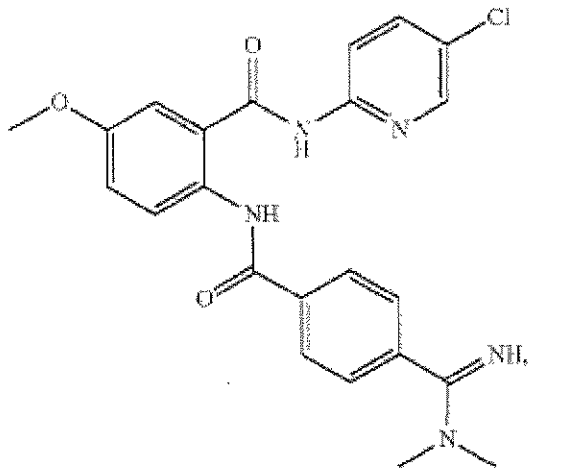
or a pharmaceutically acceptable salt thereof; and

(2) a $P2Y_{12}$ receptor antagonist,

in the manufacture of a medicament for treating a condition in a mammal characterized by undesired thrombosis.

In a second aspect, there is provided a kit, comprising:

(1) a first container, wherein said container comprises [2-({4-[(dimethylamino)iminomethyl]phenyl}carbonylamino)-5-methoxyphenyl]-N-(5-chloro(2-pyridyl))carboxamide, of the formula:



or a pharmaceutically acceptable salt thereof; and

(2) a second container, wherein said container comprises a $P2Y_{12}$ receptor antagonist.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 and Figure 2 show the correlation of Compound A plasma concentration and inhibition of thrombin generation in human studies.

Figure 3 shows the correlation of Compound A plasma concentration and anti-factor Xa units in a human study.

DETAILED DESCRIPTION OF THE INVENTION

This invention relates to methods and compositions for treating a condition in a mammal characterized by undesired thrombosis using a combination of Compound A with another therapeutic agent. Prior to describing this invention in more detail, the following terms will first be defined.

WHAT IS CLAIMED IS:

1. A method for treating a condition in a mammal characterized by undesired thrombosis comprising administering to said mammal a therapeutically effective amount of

(1) [2-({4-[(dimethylamino)iminomethyl]phenyl}carbonylamino)-5-methoxyphenyl]-N-(5-chloro(2-pyridyl))carboxamide, or a pharmaceutically acceptable salt thereof; and

(2) a therapeutic agent selected from the group consisting of an antiplatelet agent, an anticoagulant agent, an anti-inflammatory agent, a blood-pressure lowering agent, and combinations thereof.

2. The method of claim 1, comprising administering to said mammal a therapeutically effective amount of the following two therapeutic agents:

(1) [2-({4-[(dimethylamino)iminomethyl]phenyl}carbonylamino)-5-methoxyphenyl]-N-(5-chloro(2-pyridyl))carboxamide, or a pharmaceutically acceptable salt thereof; and

(2) an antiplatelet agent.

3. The method of claim 2, wherein the antiplatelet agent is selected from the group consisting of a GP IIb/IIIa receptor antagonist, a $P2Y_{12}$ receptor antagonist, a phosphodiesterase III inhibitor, a thromboxane synthase inhibitor, a thromboxane A2 receptor antagonist, a thrombin receptor antagonist, and an inhibitor of p Selectin.

4. The method of claim 2, wherein the antiplatelet agent is selected from the group consisting of abciximab, eptifibatide, tirofiban, acetylsalicylic acid, cangrelor, ticagrelor, clopidogrel, ticlopidine, prasugrel, dipyridamole, aggrenox, ifetroban, cilostazol, isbogrel, furegrelate, ramatroban, ridogrel, terbogrel, ethyl (1R,3aR,4aR,6R, 8aR, 9S, 9aS)-9-((E)-2-(5-(3-fluorophenyl)pyridin-2-yl)vinyl)-1-methyl-3-oxododecahydronaphtho[2,3-C] furan-6-ylcarbamate, 3-{6-[(4-chlorophenylsulfonyl)amino]-2-methyl-5,6,7,8-tetrahydronaphth-1-yl}propionic acid and ozagrel.

5. The method of claim 4, wherein the antiplatelet agent is eptifibatide.

6. The method of claim 4, wherein the antiplatelet agent is clopidogrel.

7. The method of claim 1 comprising administering to said mammal a therapeutically effective amount of the following two therapeutic agents:

(1) [2-({4-[(dimethylamino)iminomethyl]phenyl}carbonylamino)-5-methoxyphenyl]-N-(5-chloro(2-pyridyl))carboxamide, or a pharmaceutically acceptable salt thereof; and

(2) an anticoagulant agent.

8. The method of claim 7, wherein the anticoagulant agent is selected from the group consisting of specific inhibitors of thrombin, factor IXa, factor XIa, factor XIIa or factor VIIa, synthetic pentasaccharides, low molecular weight heparin, anti-tissue factor antibody and combinations thereof.

9. The method of claim 7, wherein the anticoagulant agent is an injectable anticoagulant agent.

10. The method of claim 7, wherein the anticoagulant agent is selected from the group consisting of bivalirudin, dabigatran, argatroban, lepirudin, warfarin, phenocoumarol, fondaparinux, danaparoid, enoxaparin, dalteparin and unfractionated heparin.

11. The method of claim 10, wherein the anticoagulant agent is enoxaparin.

12. The method of claim 1, comprising administering to said mammal a therapeutically effective amount of the following two therapeutic agents:

(1) [2-({4-[(dimethylamino)iminomethyl]phenyl}carbonylamino)-5-methoxyphenyl]-N-(5-chloro(2-pyridyl))carboxamide, or a pharmaceutically acceptable salt thereof; and

(2) an anti-inflammatory agent.

13. The method of claim 12, wherein the anti-inflammatory agent is selected from the group consisting of a non-steroidal anti-inflammatory agent, a tumor necrosis factor antagonist, an interleukin 1 receptor antagonist, a cyclooxygenase-2 inhibitor and a rheumatoid arthritis agent.

14. The method of claim 12, wherein the anti-inflammatory agent is selected from the group consisting of acetylsalicylic acid, piroxicam, indomethacin, mesalamine, sulfasalazine, methotrexate, leflunomide, etanercept, infliximab, adalimubab, and anakinra.

15. The method of claim 14, wherein the anti-inflammatory agent is acetylsalicylic acid.

16. The method of claim 1, comprising administering to said mammal a therapeutically effective amount of the following two therapeutic agents:

(1) [2-({4-[(dimethylamino)iminomethyl]phenyl}carbonylamino)-5-methoxyphenyl]-N-(5-chloro(2-pyridyl))carboxamide, or a pharmaceutically acceptable salt thereof; and

(2) a blood pressure lowering agent.

17. The method of claim 16, wherein the blood pressure lowering agent is selected from the group consisting of a diuretic, a beta blocker, an angiotensin converting enzyme inhibitor, an angiotensin 2 receptor antagonist, and a calcium channel blocker.

18. The method of claim 16, wherein the blood pressure lowering agent is selected from the group consisting of verapamil, diltiazem, amiodarone, metoprolol, and carvedilol.

19. The method of any one of claims 1 to 18, wherein at least one of [2-({4-[(dimethylamino)iminomethyl]phenyl}carbonylamino)-5-methoxyphenyl]-N-(5-chloro(2-pyridyl))carboxamide, or a pharmaceutically acceptable salt thereof, and the therapeutic agent is administered in a sub-therapeutic dosage.

20. The method of any one of claims 1 to 18, wherein both of [2-({4-[(dimethylamino)iminomethyl]phenyl}carbonylamino)-5-methoxyphenyl]-N-(5-chloro(2-pyridyl))carboxamide, or a pharmaceutically acceptable salt thereof, and the therapeutic agent are administered in sub-therapeutic dosages.

21. The method of any one of claims 1 to 18, wherein [2-({4-[(dimethylamino)iminomethyl]phenyl}carbonylamino)-5-methoxyphenyl]-N-(5-chloro(2-pyridyl))carboxamide, or a pharmaceutically acceptable salt thereof, and the therapeutic agent are administered simultaneously.

22. The method of any one of claims 1 to 18, wherein [2-({4-[(dimethylamino)iminomethyl]phenyl}carbonylamino)-5-methoxyphenyl]-N-(5-chloro(2-pyridyl))carboxamide, or a pharmaceutically acceptable salt thereof, and the therapeutic agent are administered sequentially.

23. The method of any one of claims 1 to 22, wherein the pharmaceutical acceptable salt of [2-({4-[(dimethylamino)iminomethyl]phenyl}carbonylamino)-5-methoxyphenyl]-N-(5-chloro(2-pyridyl))carboxamide is the maleate salt.

24. The method of any one of claims 1 to 22, wherein the method further comprises administering to said mammal a therapeutically effective amount of:

(3) a third therapeutic agent selected from another antiplatelet agent, another anticoagulant agent, a thrombin inhibitor, a thrombolytic agent, an anti-arrhythmic agent, a blood pressure lowering agent, a cholesterol or triglyceride lowering agent.

25. The method of any one of claims 1 to 20, wherein the condition is selected from the group consisting of:

acute coronary syndrome, myocardial infarction, unstable angina, refractory angina, occlusive coronary thrombus occurring post-thrombolytic therapy or post-coronary angioplasty, a thrombotically mediated cerebrovascular syndrome, embolic stroke, thrombotic stroke, transient ischemic attacks, venous thrombosis, deep venous thrombosis, pulmonary embolus, coagulopathy, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, thromboangiitis obliterans, thrombotic disease

associated with heparin-induced thrombocytopenia, thrombotic complications associated with extracorporeal circulation, thrombotic complications associated with instrumentation, and thrombotic complications associated with the fitting of prosthetic devices.

26. A pharmaceutical composition, comprising the following two therapeutic agents:

(1) [2-({4-[(dimethylamino)iminomethyl]phenyl}carbonylamino)-5-methoxyphenyl]-N-(5-chloro(2-pyridyl))carboxamide, or a pharmaceutically acceptable salt thereof;

(2) a therapeutic agent selected from the group consisting of an antiplatelet agent, an anticoagulant agent, an anti-inflammatory agent, a blood pressure-lowering agent, and combinations thereof; and

a pharmaceutically acceptable carrier.

27. The pharmaceutical composition of claim 26, comprising the following two therapeutic agents:

(1) [2-({4-[(dimethylamino)iminomethyl]phenyl}carbonylamino)-5-methoxyphenyl]-N-(5-chloro(2-pyridyl))carboxamide, or a pharmaceutically acceptable salt thereof;

(2) an antiplatelet agent;

and a pharmaceutically acceptable carrier.

28. The pharmaceutical composition of claim 27, wherein the antiplatelet agent is selected from the group consisting of a GP IIb/IIIa receptor antagonist, a $P2Y_{12}$ receptor antagonist, a phosphodiesterase III inhibitor, a thromboxane synthase inhibitor, a thromboxane A2 receptor antagonist, a thrombin receptor antagonist, and an inhibitor of p Selectin.

29. The pharmaceutical composition of claim 27, wherein the antiplatelet agent is selected from the group consisting of: abciximab, eptifibatide, tirofiban, acetylsalicylic acid, cangrelor, ticagrelor, clopidogrel, ticlopidine, prasugrel, dipyridamole, aggrenox, ifetroban, cilostazol, isbogrel, furegrelate, ramatroban, ridogrel, terbogrel, ethyl (1R,3aR,4aR,6R, 8aR, 9S, 9aS)-9-((E)-2-(5-(3-fluorophenyl)pyridin-2-yl)vinyl)-1-methyl-

3-oxododecahydronaphtho[2,3-C] furan-6-ylcarbamate, 3-{6-[(4-chlorophenylsulfonyl)amino]-2-methyl-5,6,7,8-tetrahydronaphth-1-yl}propionic acid and ozagrel.

30. The pharmaceutical composition of claim 29, wherein the antiplatelet agent is eptifibatide.

31. The pharmaceutical composition of claim 29, wherein the antiplatelet agent is clopidogrel.

32. The pharmaceutical composition of claim 26, comprising the following two therapeutic agents:

(1) [2-({4-[(dimethylamino)iminomethyl]phenyl}carbonylamino)-5-methoxyphenyl]-N-(5-chloro(2-pyridyl))carboxamide, or a pharmaceutically acceptable salt thereof; and

(2) an anticoagulant agent;

and a pharmaceutically acceptable carrier.

33. The pharmaceutical composition of claim 32, wherein the anticoagulant agent is selected from the group consisting of specific inhibitors of thrombin, factor IXa, factor Xa, factor XIIa, factor XIa or factor VIIa, synthetic pentasaccharide, low molecular weight heparin, anti tissue factor antibodies and combinations thereof.

34. The pharmaceutical composition of claim 32, wherein the anticoagulant agent is an injectable anticoagulant agent.

35. The pharmaceutical composition of claim 32, wherein the anticoagulant agent is selected from the group consisting of bivalirudin, dabigatran, argatroban, lepirudin, warfarin, phenocoumarol, fondaparinux, danaparoid, enoxaparin, dalteparin and unfractionated heparin.

36. The pharmaceutical composition of claim 35, wherein the anticoagulant agent is enoxaparin.

37. The pharmaceutical composition of claim 26, comprising the following two therapeutic agents:

(1) [2-({4-[(dimethylamino)iminomethyl]phenyl}carbonylamino)-5-methoxyphenyl]-N-(5-chloro(2-pyridyl))carboxamide, or a pharmaceutically acceptable salt thereof; and

(2) an anti-inflammatory agent;

and a pharmaceutically acceptable carrier.

38. The pharmaceutical composition of claim 37, wherein the anti-inflammatory agent is selected from the group consisting of a non-steroidal anti-inflammatory agent, a tumor necrosis factor antagonist, a interleukin 1 receptor antagonist, a cyclooxygenase-2 inhibitor and a rheumatoid arthritis agent.

39. The pharmaceutical composition of claim 37, wherein the anti-inflammatory agent is selected from the group consisting of acetylsalicylic acid, piroxicam, indomethacin, mesalamine, sulfasalazine, methotrexate, leflunomide, etanercept, infliximab, adalimubab, and anakinra.

40. The pharmaceutical composition of claim 37, wherein the anti-inflammatory agent is acetylsalicylic acid.

41. The pharmaceutical composition of claim 26, comprising the following two therapeutic agents:

(1) [2-({4-[(dimethylamino)iminomethyl]phenyl}carbonylamino)-5-methoxyphenyl]-N-(5-chloro(2-pyridyl))carboxamide, or a pharmaceutically acceptable salt thereof; and

(2) a blood pressure lowering agent;

and a pharmaceutically acceptable carrier.

42. The pharmaceutical composition of claim 41, wherein the blood pressure lowering agent is selected from the group consisting of a diuretic, a beta blocker, an angiotensin converting enzyme inhibitor, an angiotensin 2 receptor antagonist and a calcium channel blocker.

43. The pharmaceutical composition of claim 41, wherein the blood pressure lowering agent is selected from the group consisting of verapamil, diltiazem, amiodarone, metoprolol, and carvedilol.

44. The pharmaceutical composition of any one of claims 26 to 43, wherein at least one of the therapeutic agents is present in a sub-therapeutic dosage.

45. The pharmaceutical composition of any one of claims 26 to 43, wherein both of the therapeutic agents are present in sub-therapeutic dosages.

46. The pharmaceutical composition of any one of claims 26 to 43, wherein the pharmaceutical acceptable salt of [2-({4-[(dimethylamino)iminomethyl]phenyl}carbonylamino)-5-methoxyphenyl]-N-(5-chloro(2-pyridyl))carboxamide is the maleate salt.

47. The pharmaceutical composition of any one of claims 26 to 43, further comprising:

(3) a third therapeutic agent selected from another antiplatelet agent, another anti-coagulant, a thrombin inhibitor, a thrombolytic agent, an anti-arrhythmic agent, a blood pressure lowering agent, a cholesterol or triglyceride lowering agent.

48. A kit, comprising:

(1) a first container, wherein said container contains [2-({4-[(dimethylamino)iminomethyl]phenyl}carbonylamino)-5-methoxyphenyl]-N-(5-chloro(2-pyridyl))carboxamide, or a pharmaceutically acceptable salt thereof; and

(2) a second container, wherein said container contains another therapeutic agent selected from the group consisting of antiplatelet agents, anticoagulant agents, anti-inflammatory agents and blood pressure lowering agents.

49. The kit of claim 48, further comprising:

(3) a package insert stating that the two therapeutic agents can be used together.

50. The kit of claim 48, wherein the pharmaceutically acceptable salt of [2-({4-[(dimethylamino)iminomethyl]phenyl}carbonylamino)-5-methoxyphenyl]-N-(5-chloro(2-pyridyl))carboxamide is the maleate salt.

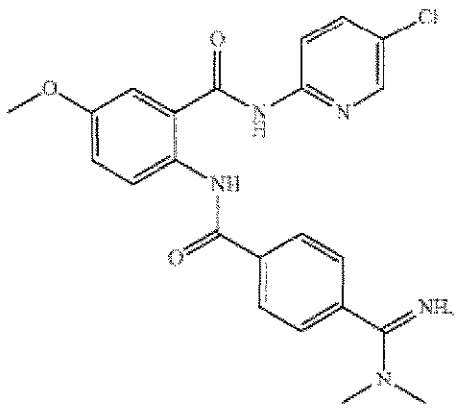
51. The kit of claim 48, wherein at least one of the therapeutic agents is present in a sub-therapeutic dosage.

52. The kit of claim 48, wherein both of the therapeutic agents are present in sub-therapeutic dosages.

What is claimed is:

1. Use of a therapeutically effective amount of

(1) [2-({4-[(dimethylamino)iminomethyl]phenyl}carbonylamino)-5-methoxyphenyl]-N-(5-chloro(2-pyridyl))carboxamide, of the formula:



or a pharmaceutically acceptable salt thereof; and

(2) a $P2Y_{12}$ receptor antagonist,

in the manufacture of a medicament for treating a condition in a mammal characterized by undesired thrombosis.

2. The use of claim 1, wherein the $P2Y_{12}$ receptor antagonist is selected from the group consisting of cangrelor, ticagrelor, clopidogrel, ticlopidine, and prasugrel.

3. The use of claim 2, wherein the $P2Y_{12}$ receptor antagonist is clopidogrel.

4. The use of claim 1, wherein at least one of [2-({4-[(dimethylamino)iminomethyl]phenyl}carbonylamino)-5-methoxyphenyl]-N-(5-chloro(2-pyridyl))carboxamide, or a pharmaceutically acceptable salt thereof, and the $P2Y_{12}$ receptor antagonist is in a sub-therapeutic dosage.

5. The use of claim 1, wherein both of [2-({4-[(dimethylamino)iminomethyl]phenyl}carbonylamino)-5-methoxyphenyl]-N-(5-chloro(2-pyridyl))carboxamide, or a pharmaceutically acceptable salt thereof, and the $P2Y_{12}$ receptor antagonist are in sub-therapeutic dosages.

6. The use of claim 1, wherein [2-({4-[(dimethylamino)iminomethyl]phenyl}carbonylamino)-5-methoxyphenyl]-N-(5-chloro(2-pyridyl))carboxamide, or a pharmaceutically acceptable salt thereof, and the $P2Y_{12}$ receptor antagonist are to be administered simultaneously.

7. The use of claim 1, wherein [2-({4-[(dimethylamino)iminomethyl]phenyl}carbonylamino)-5-methoxyphenyl]-N-(5-chloro(2-pyridyl))carboxamide, or a pharmaceutically acceptable salt thereof, and the $P2Y_{12}$ receptor antagonist are to be administered sequentially.

8. The use of claim 1, wherein the pharmaceutical acceptable salt of [2-({4-[(dimethylamino)iminomethyl]phenyl}carbonylamino)-5-methoxyphenyl]-N-(5-chloro(2-pyridyl))carboxamide is the maleate salt.

9. The use of claim 1, wherein the medicament further comprises a therapeutically effective amount of:

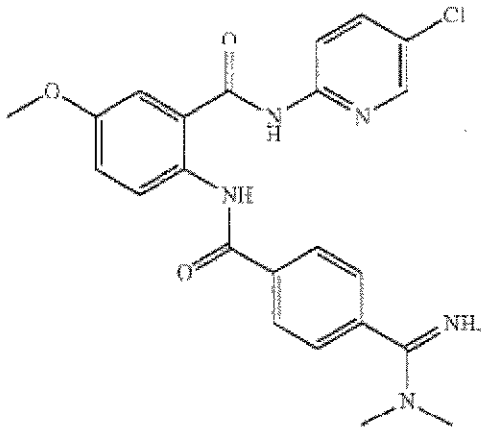
(3) a third therapeutic agent selected from an antiplatelet agent, an anticoagulant agent, a thrombin inhibitor, a thrombolytic agent, an anti-arrhythmic agent, a blood pressure lowering agent, a cholesterol or triglyceride lowering agent.

10. The use of claim 1, wherein the condition is selected from the group consisting of:

acute coronary syndrome, myocardial infarction, unstable angina, refractory angina, occlusive coronary thrombus occurring post-thrombolytic therapy or post-coronary angioplasty, a thrombotically mediated cerebrovascular syndrome, embolic stroke, thrombotic stroke, transient ischemic attacks, venous thrombosis, deep venous thrombosis, pulmonary embolus, coagulopathy, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, thromboangiitis obliterans, thrombotic disease associated with heparin-induced thrombocytopenia, thrombotic complications associated with extracorporeal circulation, thrombotic complications associated with instrumentation, and thrombotic complications associated with the fitting of prosthetic devices.

11. A pharmaceutical composition, comprising two therapeutic agents:

(1) [2-({4-[(dimethylamino)iminomethyl]phenyl}carbonylamino)-5-methoxyphenyl]-N-(5-chloro(2-pyridyl))carboxamide, of the formula:



or a pharmaceutically acceptable salt thereof;

(2) a $P2Y_{12}$ receptor antagonist; and

a pharmaceutically acceptable carrier.

12. The pharmaceutical composition of claim 11, wherein the $P2Y_{12}$ receptor antagonist is selected from the group consisting of cangrelor, ticagrelor, clopidogrel, ticlopidine, and prasugrel.

13. The pharmaceutical composition of claim 12, wherein the $P2Y_{12}$ receptor antagonist is clopidogrel.

14. The pharmaceutical composition of claim 11, wherein at least one of the therapeutic agents is present in a sub-therapeutic dosage.

15. The pharmaceutical composition of claim 11, wherein both of the therapeutic agents are present in sub-therapeutic dosages.

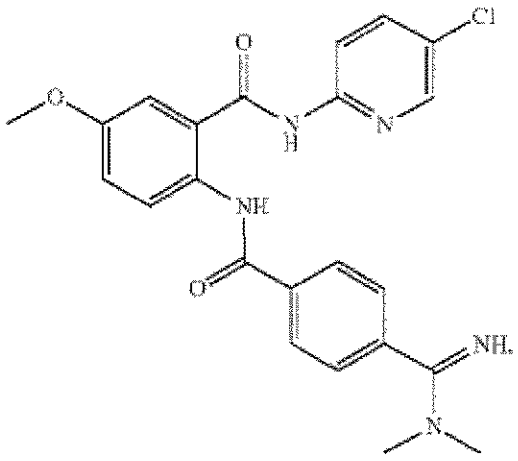
16. The pharmaceutical composition of claim 11, wherein the pharmaceutical acceptable salt of [2-({4-[(dimethylamino)iminomethyl]phenyl}carbonylamino)-5-methoxyphenyl]-N-(5-chloro(2-pyridyl))carboxamide is the maleate salt.

17. The pharmaceutical composition of claim 11, further comprising:

(3) a third therapeutic agent selected from an antiplatelet agent, an anti-coagulant, a thrombin inhibitor, a thrombolytic agent, an anti-arrhythmic agent, a blood pressure lowering agent, a cholesterol or triglyceride lowering agent.

18. A kit, comprising:

(1) a first container, wherein said container comprises [2-({4-[(dimethylamino)iminomethyl]phenyl}carbonylamino)-5-methoxyphenyl]-N-(5-chloro(2-pyridyl))carboxamide, of the formula:



or a pharmaceutically acceptable salt thereof; and

(2) a second container, wherein said container comprises a $P2Y_{12}$ receptor antagonist.

19. The kit of claim 18, further comprising:

(3) a package insert stating that the two therapeutic agents can be used together.

20. The kit of claim 18, wherein the pharmaceutically acceptable salt of [2-({4-[(dimethylamino)iminomethyl]phenyl}carbonylamino)-5-methoxyphenyl]-N-(5-chloro(2-pyridyl))carboxamide is the maleate salt.

21. The kit of claim 18, wherein at least one of the therapeutic agents is present in a sub-therapeutic dosage.

22. The kit of claim 18, wherein both of the therapeutic agents are present in sub-therapeutic dosages.

23. The kit of claim 18, wherein the $P2Y_{12}$ receptor antagonist is selected from the group consisting of cangrelor, ticagrelor, clopidogrel, ticlopidine, and prasugrel.

24. The kit of claim 18, wherein the $P2Y_{12}$ receptor antagonist is clopidogrel.