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(54) Title: FLUORINATED OXAZOLIDINONE DERIVATIVES

(57) Abstract: The invention relates to fluorinated compounds and their use in the field of blood coagulation. Novel fluorinated oxazolidinone derivatives of rivaroxaban and pharmaceutically acceptable salts or solvates thereof and their use as medicinally active compounds for the treatment and prevention of disorders are described.



## FLUORINATED OXAZOLIDINONE DERIVATIVES

### RELATED APPLICATIONS

5           This application claims priority to U.S. provisional application Nos. 61/620,623 and 61/697,695, respectively filed on April 5, 2012 and September 6, 2012, which are incorporated herein by reference.

10           Thromboembolic disorders are a group of disorders characterized by inflammation of the veins and formation of blood clots (thrombus). The disorders develop as a result of changes in the venous blood flow (it becomes sluggish) due to infection, damage, or increased coagulability (blood clotting) of the blood. Thromboembolic disease can be a serious complication of surgery. Rivaroxaban, also known as (S)-5-chloro-N-{[2-oxo-3-[4-(3-oxomorpholin-4-yl)

15   phenyl]oxazolidin-5-yl]methyl} thiophene-2-carboxamide, is an oral anticoagulant invented and manufactured by Bayer; in a number of countries it is marketed as Xarelto®. In the United States, it is marketed by Janssen Pharmaceutica. It is an orally active direct factor Xa inhibitor. U.S. Patent Nos. 7,157,456; 7,592,339; and 7,585,860 describe rivaroxaban and its use.

20           Despite the beneficial activities of rivaroxaban, there is a continuing need for new compounds to treat thromboembolic disorders.

### DETAILED DESCRIPTION OF THE INVENTION

25           For purposes of the present invention, the following definitions will be used (unless expressly stated otherwise):

          The term "a compound of the invention" or "compounds of the invention" refers to a compound(s) disclosed herein e.g., a compound(s) of the invention includes a compound(s) of any of the formulae described herein including formulae I, II, III, IV, V, VI, VII, VIII, IX, X, XI, or XII and/or a compound(s) explicitly disclosed herein. Whenever the term is used in the

30   context of the present invention it is to be understood that the reference is being made to the free base and the corresponding pharmaceutically acceptable salts or solvates thereof, provided that such is possible and/or appropriate under the circumstances.

          The term "pharmaceutical" or "pharmaceutically acceptable" when used herein as an adjective, means substantially non-toxic and substantially non-deleterious to the recipient.

By "pharmaceutical formulation" it is further meant that the carrier, solvent, excipient(s) and salt must be compatible with the active ingredient of the formulation (e.g. a compound of the invention). It is understood by those of ordinary skill in this art that the terms "pharmaceutical formulation" and "pharmaceutical composition" are generally  
5 interchangeable, and they are so used for the purposes of this application.

Some of the compounds of the present invention may exist in unsolvated as well as solvated forms such as, for example, hydrates.

"Solvate" means a solvent addition form that contains either a stoichiometric or non stoichiometric amounts of solvent. Some compounds have a tendency to trap a fixed molar  
10 ratio of solvent molecules in the crystalline solid state, thus forming a solvate. If the solvent is water the solvate formed is a hydrate, when the solvent is alcohol, the solvate formed is an alcoholate. Hydrates are formed by the combination of one or more molecules of water with one of the substances in which the water retains its molecular state as H<sub>2</sub>O, such combination being able to form one or more hydrate. In the hydrates, the water molecules are attached  
15 through secondary valencies by intermolecular forces, in particular hydrogen bridges. Solid hydrates contain water as so-called crystal water in stoichiometric ratios, where the water molecules do not have to be equivalent with respect to their binding state. Examples of hydrates are sesquihydrates, monohydrates, dihydrates or trihydrates. Equally suitable are the hydrates of salts of the compounds of the invention

20 The compounds described herein can have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom can be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. Many geometric isomers of olefins, C=N double bonds, and the like can also be  
25 present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and can be isolated as a mixture of isomers or as separate isomeric forms. All chiral, diastereomeric, racemic, and geometric isomeric forms of a structure are intended, unless specific stereochemistry or isomeric form is specifically indicated. All  
30 processes used to prepare compounds of the present invention and intermediates made therein are considered to be part of the present invention. All tautomers of shown or described compounds are also considered to be part of the present invention. Furthermore, the invention also includes metabolites of the compounds described herein.

Physiologically acceptable, i.e. pharmaceutically compatible, salts can be salts of the compounds of the invention with inorganic or organic acids. Preference is given to salts with inorganic acids, such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid or sulphuric acid, or to salts with organic carboxylic or sulphonc acids, such as, for example, 5 acetic acid, trifluoroacetic acid, propionic acid, maleic acid, fumaric acid, malic acid, citric acid, tartaric acid, lactic acid, benzoic acid, or methanesulphonic acid, ethanesulphonic acid, benzenesulphonic acid, toluenesulphonic acid or naphthalenedisulphonic acid.

Other pharmaceutically compatible salts which may be mentioned are salts with customary bases, such as, for example, alkali metal salts (for example sodium or potassium 10 salts), alkaline earth metal salts (for example calcium or magnesium salts) or ammonium salts, derived from ammonia or organic amines, such as, for example, diethylamine, triethylamine, ethyldiisopropylamine, procaine, dibenzylamine, N-methylmorpholine, dihydroabietylamine or methylpiperidine.

When any variable (*e.g.*, X) occurs more than one time in any constituent or formula 15 for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with one or more X moieties, then X at each occurrence is selected independently from the definition of X. Also, combinations of substituents and/or variables are permissible, but only if such combinations result in stable compounds within a designated atom's normal valency.

20 As used herein, the term "treat," "treating," or "treatment" herein, is meant decreasing the symptoms, markers, and/or any negative effects of a condition in any appreciable degree in a patient who currently has the condition. In some embodiments, treatment may be administered to a subject who exhibits only early signs of the condition for the purpose of decreasing the risk of developing the disease, disorder, and/or condition.

25 As used herein, the term "prevent," "prevention," or "preventing" refers to any method to partially or completely prevent or delay the onset of one or more symptoms or features of a disease, disorder, and/or condition. Prevention may be administered to a subject who does not exhibit signs of a disease, disorder, and/or condition.

30 As used herein, "subject" means a human or animal (in the case of an animal, more typically a mammal). In one aspect, the subject is a human.

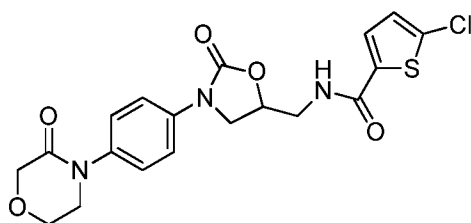
As used herein, the term a "fluorinated derivative" is a derivative compound that the same chemical structure as the original compound, except that at least one atom is replaced with a fluorine atom or with a group of atoms containing at least one fluorine atom.

The problem to be solved by the present invention is the identification of novel compounds for the treatment and/or prevention of diseases or disorders that are influenced by positively inhibiting factor Xa e.g., thromboembolic disorders. Although drugs for thromboembolic disorders are available, these anti-coagulant drugs are often not suitable for patients for a variety of reasons. Many of the available anti-coagulant drugs are associated with bleeding complications. For example, side effects of the anti-coagulant rivaroxaban include coughing up blood, nosebleeds, unusual weakness and blood in the urine. Additional adverse effects of rivaroxaban include back pain, itching, and headaches. Patients on rivaroxaban also have been known to have elevated liver enzymes, elevated bilirubin levels, and low blood platelets. The present invention provides the solution of new fluorinated oxazolidinone derivatives for the treatment and/or prevention of diseases and disorders. The fluorinated compounds described herein have the advantage of providing improved potency, selectivity, tissue penetration, half-life, and/or metabolic stability.

#### Compounds of the Invention

The present invention relates to novel fluorinated oxazolidinone derivatives and their use. The present invention relates the synthesis of fluorinated oxazolidinone derivatives.

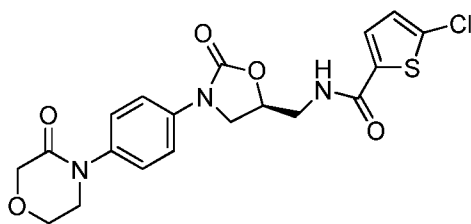
In one aspect, the invention provides a compound of formula I:



(I) or a pharmaceutically acceptable salt or solvate

thereof, wherein the compound of formula I is a fluorinated derivative, wherein at least one atom is replaced with F or with a group of atoms containing at least one F.

In one aspect, the invention provides a compound of formula II:



(II) or a pharmaceutically acceptable salt or solvate

thereof, wherein the compound of formula II is a fluorinated derivative wherein at least one atom is replaced with F or with a group of atoms containing at least one F.

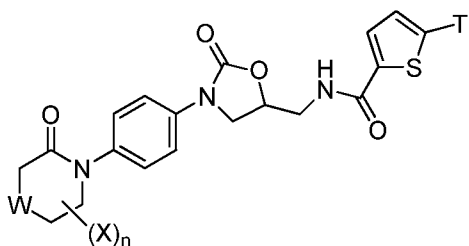
While all of the compounds of this invention are useful, certain classes are preferred. The following paragraphs describe certain preferred classes of a compound of formula I or II, wherein:

- a) at least one hydrogen atom is replaced with F;
- 5 b) two hydrogen atoms are each replaced with F;
- c) three hydrogen atoms are each replaced with F;
- d) one or more hydrogen atoms are replaced with F or a group of atoms selected from CF<sub>3</sub>, CHF<sub>2</sub>, CH<sub>2</sub>F, OCF<sub>3</sub>, OCHF<sub>2</sub>, and OCH<sub>2</sub>F;
- e) one hydrogen atom is replaced with F;
- 10 f) one or more hydrogen atoms are replaced with F or a group of atoms selected from CF<sub>3</sub>, CHF<sub>2</sub>, CH<sub>2</sub>F, OCF<sub>3</sub>, OCHF<sub>2</sub>, and OCH<sub>2</sub>F;
- g) one or more hydrogen atoms are replaced with a group of atoms selected from CF<sub>3</sub>, CHF<sub>2</sub>, CH<sub>2</sub>F, OCF<sub>3</sub>, OCHF<sub>2</sub>, and OCH<sub>2</sub>F;
- 15 h) one or more hydrogen atoms are replaced with a group of atoms selected from CF<sub>3</sub>, CHF<sub>2</sub>, and CH<sub>2</sub>F;
- i) one hydrogen atom is replaced with CF<sub>3</sub>;
- j) one or more hydrogen atoms are replaced with a group of atoms selected from OCF<sub>3</sub>, OCHF<sub>2</sub>, and OCH<sub>2</sub>F;
- 20 k) one hydrogen atom is replaced with OCF<sub>3</sub>;
- l) the chlorine atom is replaced with F or a group of atoms selected from CF<sub>3</sub>, CHF<sub>2</sub>, CH<sub>2</sub>F, OCF<sub>3</sub>, OCHF<sub>2</sub>, and OCH<sub>2</sub>F;
- m) the chlorine atom is replaced with F;
- n) the chlorine atom is replaced with a group of atoms selected from CF<sub>3</sub>, CHF<sub>2</sub>, CH<sub>2</sub>F, OCF<sub>3</sub>, OCHF<sub>2</sub>, and OCH<sub>2</sub>F;
- 25 o) the chlorine atom is replaced with a group of atoms selected from CF<sub>3</sub>, CHF<sub>2</sub>, and CH<sub>2</sub>F;
- p) the chlorine atom is replaced with CF<sub>3</sub>;
- q) the chlorine atom is replaced with a group of atoms selected from OCF<sub>3</sub>, OCHF<sub>2</sub>, and OCH<sub>2</sub>F;
- 30 r) the chlorine atom is replaced with OCF<sub>3</sub>;
- s) one heteroatom is replaced with a group of atoms selected from CF<sub>2</sub>, CHF, CH(CF<sub>3</sub>), CH(OCF<sub>3</sub>), CH(OCHF<sub>2</sub>), and CH(OCH<sub>2</sub>F);

- t) the heteroatom is an oxygen atom and said oxygen atom is replaced with a group of atoms selected from  $\text{CF}_2$ ,  $\text{CHF}$ ,  $\text{CH}(\text{CF}_3)$ ,  $\text{CH}(\text{OCF}_3)$ ,  $\text{CH}(\text{OCHF}_2)$ , and  $\text{CH}(\text{OCH}_2\text{F})$ ;
- u) the oxygen atom of the morpholinone ring is replaced with a group of atoms selected from  $\text{CF}_2$ ,  $\text{CHF}$ ,  $\text{CH}(\text{CF}_3)$ ,  $\text{CH}(\text{OCF}_3)$ ,  $\text{CH}(\text{OCHF}_2)$ , and  $\text{CH}(\text{OCH}_2\text{F})$ ;
- 5 v) the oxygen atom of the morpholinone ring is replaced with a group of atoms selected from  $\text{CF}_2$ ,  $\text{CHF}$ , and  $\text{CH}(\text{CF}_3)$ ;
- w) the oxygen atom of the morpholinone ring is replaced with a group of atoms selected from  $\text{CH}(\text{OCF}_3)$ ,  $\text{CH}(\text{OCHF}_2)$ , and  $\text{CH}(\text{OCH}_2\text{F})$ ; and
- x) the oxygen atom of the morpholinone ring is replaced with  $\text{CF}_2$ .

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In one aspect, the invention provides a compound of formula III:

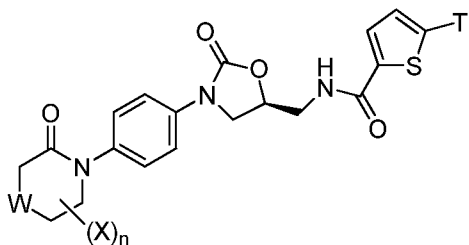


(III) or a pharmaceutically acceptable salt or solvate

thereof, wherein T is selected from Cl, F,  $\text{CF}_3$ ,  $\text{CHF}_2$ ,  $\text{CH}_2\text{F}$ ,  $\text{OCF}_3$ ,  $\text{OCHF}_2$ , and  $\text{OCH}_2\text{F}$ ; each X is independently selected from H, F,  $\text{CF}_3$ ,  $\text{CHF}_2$ ,  $\text{CH}_2\text{F}$ ,  $\text{OCF}_3$ ,  $\text{OCHF}_2$ , and  $\text{OCH}_2\text{F}$ ;

15 W is selected from O,  $\text{CF}_2$ ,  $\text{CHF}$ ,  $\text{CH}(\text{CF}_3)$ ,  $\text{CH}(\text{OCF}_3)$ ,  $\text{CH}(\text{OCHF}_2)$ , and  $\text{CH}(\text{OCH}_2\text{F})$ ; and n is 0, 1, 2, or 3, provided that when W is O and T is Cl, then X is not H (when n=1), each X is not H (when n=2), and each X is not H (when n=3).

In one aspect, the invention provides a compound of formula IV:



(IV) or a pharmaceutically acceptable salt or solvate

20 thereof, wherein T is selected from Cl, F,  $\text{CF}_3$ ,  $\text{CHF}_2$ ,  $\text{CH}_2\text{F}$ ,  $\text{OCF}_3$ ,  $\text{OCHF}_2$ , and  $\text{OCH}_2\text{F}$ ; each X is independently selected from H, F,  $\text{CF}_3$ ,  $\text{CHF}_2$ ,  $\text{CH}_2\text{F}$ ,  $\text{OCF}_3$ ,  $\text{OCHF}_2$ , and  $\text{OCH}_2\text{F}$ ; W is selected from O,  $\text{CF}_2$ ,  $\text{CHF}$ ,  $\text{CH}(\text{CF}_3)$ ,  $\text{CH}(\text{OCF}_3)$ ,  $\text{CH}(\text{OCHF}_2)$ , and  $\text{CH}(\text{OCH}_2\text{F})$ ; and n is 0, 1, 2 or 3, provided that when W is O and T is Cl, then X is not H (when n=1), each X is not H (when n=2), and each X is not H (when n=3).

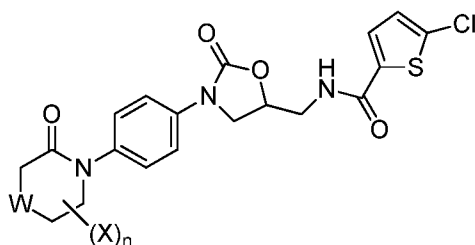
The following paragraphs describe certain preferred classes of a compound of formula III or IV, wherein:

- a-1) T is F;
- a-2) T is CF<sub>3</sub>;
- 5 a-3) T is CHF<sub>2</sub>;
- a-4) T is CH<sub>2</sub>F;
- a-5) T is OCF<sub>3</sub>;
- a-6) T is OCHF<sub>2</sub>;
- a-7) T is OCH<sub>2</sub>F;
- 10 a-8) X is F;
- a-9) X is F and W is O;
- a-10) X is F, W is O, and n is 1;
- a-11) n is 2, each X is F, and W is O;
- a-12) n is 2 and one X is F and the remaining X is H, and W is O.
- 15 a-13) n is 0 and W is CF<sub>2</sub>; and
- a-14) n is 0 and W is CHF.

It is understood that the above classes may be combined to form additional classes, as for example the combination of selections for two or more substituents. Illustrative combinations of examples are:

- 20 a-15) the combination of any one of classes a-1, a-2, a-3, a-4, a-5, a-6, or a-7 with classes a-8, a-9, a-10, a-11, a-12, a-13, or a-14.

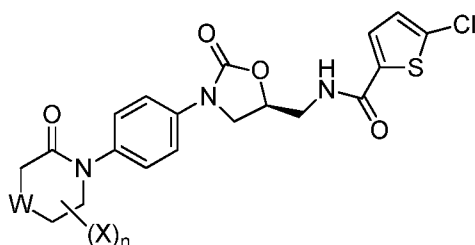
In one aspect, the invention provides a compound of formula V:



(V) or a pharmaceutically acceptable salt or solvate

- 25 thereof, wherein each X is independently selected from H, F, CF<sub>3</sub>, CHF<sub>2</sub>, CH<sub>2</sub>F, OCF<sub>3</sub>, OCHF<sub>2</sub>, and OCH<sub>2</sub>F; W is selected from O, CF<sub>2</sub>, CHF, CH(CF<sub>3</sub>), CH(OCF<sub>3</sub>), CH(OCHF<sub>2</sub>), and CH(OCH<sub>2</sub>F); and n is 0, 1, 2, or 3, provided that when W is O, then X is not H (when n=1), each X is not H (when n=2), and each X is not H (when n=3).

In one aspect, the invention provides a compound of formula VI:



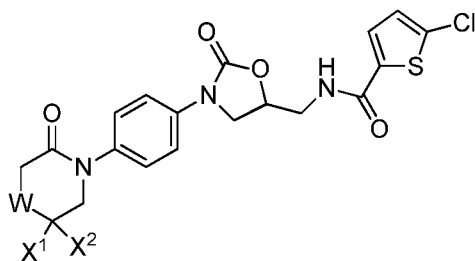
(VI) or a pharmaceutically acceptable salt or solvate

thereof, wherein each X is independently selected from H, F, CF<sub>3</sub>, CHF<sub>2</sub>, CH<sub>2</sub>F, OCF<sub>3</sub>, OCHF<sub>2</sub>, and OCH<sub>2</sub>F; W is selected from O, CF<sub>2</sub>, CHF, CH(CF<sub>3</sub>), CH(OCF<sub>3</sub>), CH(OCHF<sub>2</sub>), and CH(OCH<sub>2</sub>F); and n is 0, 1, 2 or 3, provided that when W is O, then X is not H (when n=1), each X is not H (when n=2), and each X is not H (when n=3).

The following paragraphs describe certain preferred classes of a compound of formula V or VI, wherein:

- b-1) X is F;
- b-2) X is F and W is O;
- 10 b-3) X is F, W is O, and n is 1;
- b-4) n is 2, each X is F, and W is O;
- b-5) n is 2, one X is F and the remaining X is H, and W is O;
- b-6) n is 0 and W is CF<sub>2</sub>;
- b-7) n is 0 and W is CHF.
- 15 b-8) the compound is the free base;
- b-9) the compound is a pharmaceutically acceptable salt;
- b-10) the compound is a solvate; and
- b-11) the compound is a hydrate.

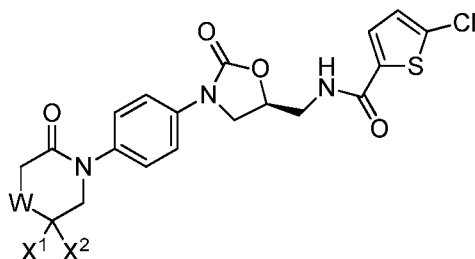
20 In one aspect, the invention provides a compound of formula VII:



(VII) or a pharmaceutically acceptable salt or solvate

thereof, wherein each X<sup>1</sup> and X<sup>2</sup> is independently selected from H, F, CF<sub>3</sub>, CHF<sub>2</sub>, CH<sub>2</sub>F, OCF<sub>3</sub>, OCHF<sub>2</sub>, and OCH<sub>2</sub>F; and W is selected from O, CF<sub>2</sub>, CHF, CH(CF<sub>3</sub>), CH(OCF<sub>3</sub>), CH(OCHF<sub>2</sub>), and CH(OCH<sub>2</sub>F), provided that when W is O, then X<sup>1</sup> and X<sup>2</sup> are not both H.

In one aspect, the invention provides a compound of formula VIII:



(VIII) or a pharmaceutically acceptable salt or

solvate thereof, wherein each  $X^1$  and  $X^2$  is independently selected from H, F,  $CF_3$ ,  $CHF_2$ ,  $CH_2F$ ,  $OCF_3$ ,  $OCHF_2$ , and  $OCH_2F$ ; and W is selected from O,  $CF_2$ , CHF,  $CH(CF_3)$ ,

- 5  $CH(OCF_3)$ ,  $CH(OCHF_2)$ , and  $CH(OCH_2F)$ , provided that when W is O, then  $X^1$  and  $X^2$  are not both H.

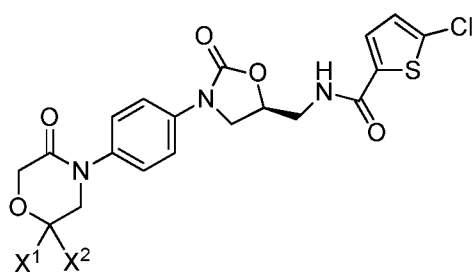
The following paragraphs describe certain preferred classes of a compound of formula VII or VIII, wherein:

- c-1)  $X^1$  and  $X^2$  is independently selected from H, F,  $CF_3$ ,  $CHF_2$ , and  $CH_2F$ , provided that  
 10  $X^1$  and  $X^2$  are not both H;  
 c-2) one of  $X^1$  or  $X^2$  is F and the remaining  $X^1$  or  $X^2$  is H;  
 c-3) both of  $X^1$  and  $X^2$  are F;  
 c-4) W is O;  
 c-5) W is  $CF_2$ ;  
 15 c-6) the compound is the free base;  
 c-7) the compounds is a pharmaceutically acceptable salt;  
 c-8) the compound is a solvate;  
 c-9) the compound is a hydrate.

- 20 It is understood that the above classes may be combined to form additional classes, as for example the combination of selections for two or more substituents. Illustrative combinations of examples are:

c-6) the combination of any one of classes c-1, c-2, or c-3 with classes c-4 or c-5.

- 25 In one aspect, the invention provides a compound of formula IX:



(IX) or a pharmaceutically acceptable salt or solvate

thereof, wherein each  $X^1$  and  $X^2$  is independently selected from H, F,  $CF_3$ ,  $CHF_2$ ,  $CH_2F$ ,  $OCF_3$ ,  $OCHF_2$ , and  $OCH_2F$ , provided that  $X^1$  and  $X^2$  are not both H.

The following paragraphs describe certain preferred classes of a compound of formula

5 X or IX, wherein:

d-1) each  $X^1$  and  $X^2$  is independently selected from H, F,  $CF_3$ ,  $CHF_2$ , and  $CH_2F$ , provided that  $X^1$  and  $X^2$  are not both H;

d-2) one of  $X^1$  or  $X^2$  is F and the remaining  $X^1$  or  $X^2$  is H;

d-3) both of  $X^1$  and  $X^2$  are F;

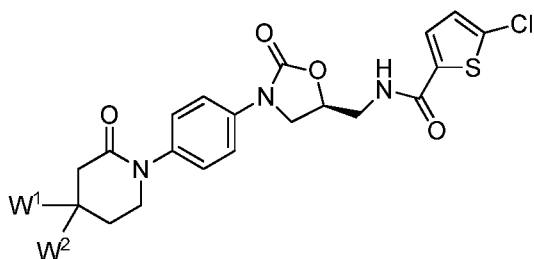
10 d-4) the compound is the free base;

d-5) the compounds is a pharmaceutically acceptable salt;

d-6) the compound is a solvate; and

d-7) the compound is a hydrate.

15 In one aspect, the invention provides a compound of formula X:



(X) or a pharmaceutically acceptable salt or

solvate thereof, wherein each  $W^1$  and  $W^2$  are selected from H, F,  $CF_3$ ,  $CHF_2$ ,  $CH_2F$ ,  $OCF_3$ ,  $OCHF_2$ , and  $OCH_2F$ .

The following paragraphs describe certain preferred classes of a compound of formula

20 X, wherein:

e-1) at least one of  $W^1$  or  $W^2$  is not H;

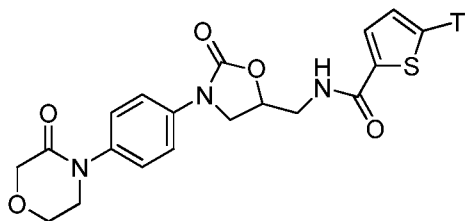
e-2) each  $W^1$  and  $W^2$  is independently selected from H, F,  $CF_3$ ,  $CHF_2$ , and  $CH_2F$ ;

e-3) one of  $W^1$  or  $W^2$  is F and the remaining  $W^1$  or  $W^2$  is H;

e-4)  $W^1$  and  $W^2$  are both F; and

- e-5) each  $W^1$  and  $W^2$  is independently selected from H,  $OCF_3$ ,  $OCHF_2$ , and  $OCH_2F$ .  
 e-6) the compound is the free base;  
 e-7) the compounds is a pharmaceutically acceptable salt;  
 e-8) the compound is a solvate;  
 5 e-9) the compound is a hydrate.

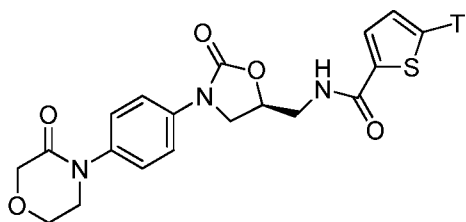
In one aspect, the invention provides a compound of formula XI:



(XI) or a pharmaceutically acceptable salt or solvate thereof, wherein T is selected from F,  $CF_3$ ,  $CHF_2$ ,  $CH_2F$ ,  $OCF_3$ ,  $OCHF_2$ , and  $OCH_2F$ .

10

In one aspect, the invention provides a compound of formula XII:



(XII) or a pharmaceutically acceptable salt or solvate thereof, wherein T is selected from F,  $CF_3$ ,  $CHF_2$ ,  $CH_2F$ ,  $OCF_3$ ,  $OCHF_2$ , and  $OCH_2F$ .

The following paragraphs describe certain preferred classes of a compound of formula

15 X or IX, wherein:

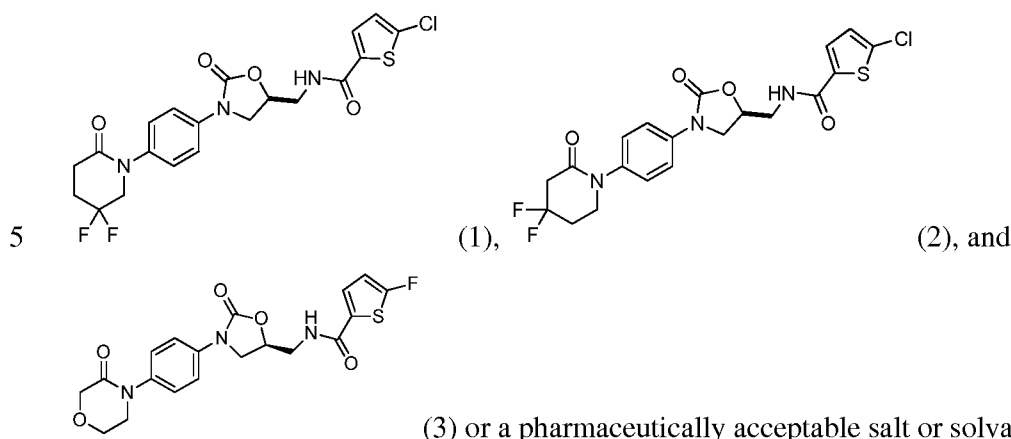
- f-1) T is F;  
 f-2) T is  $CF_3$ ;  
 f-3) T is  $CH_2F$ ;  
 f-4) T is  $CHF_2$ ;  
 20 f-5) T is  $OCF_3$ ;  
 f-6) T is  $OCHF_2$ ; and  
 f-7) T is  $OCH_2F$ .  
 f-8) T is  $CF_3$ ,  $CHF_2$ , or  $CH_2F$ ;  
 f-9) T is F or  $CF_3$ ;  
 25 f-10) T is  $OCF_3$ ,  $OCHF_2$ , or  $OCH_2F$   
 f-11) the compound is the free base;

f-12) the compounds is a pharmaceutically acceptable salt;

f-13) the compound is a solvate;

f-14) the compound is a hydrate.

In one aspect, the invention provides a compound selected from



(3) or a pharmaceutically acceptable salt or solvate thereof. In

one aspect, the invention provides compound 1, 2, or 3. In one aspect, the invention provides a pharmaceutically acceptable salt of compound 1, 2, or 3. In one aspect, the invention provides a solvate of compound 1, 2, or 3. In one aspect, the invention provides a hydrate of compound 1, 2, or 3.

The present invention relates to pharmaceutical compositions comprising one of the compounds of the invention as an active ingredient. In one aspect, the invention provides a pharmaceutical composition comprising at least one compound of formulae I, II, III, IV, V, VI, VII, VIII, IX, X, XI, or XII or a pharmaceutically acceptable salt or solvate thereof and one or more pharmaceutically acceptable carrier or excipients. In one aspect, the invention provides a pharmaceutical composition comprising compound 1, 2, or 3 or a pharmaceutically acceptable salt or solvate thereof and one or more pharmaceutically acceptable carrier or excipients.

The present invention also comprehends deuterium labeled compounds, which are identical to those recited in formulae I, II, III, IV, V, VI, VII, VIII, IX, X, XI, or XII but for the fact that one or more hydrogen atoms is replaced by a deuterium atom having an abundance of deuterium at that position that is substantially greater than the natural abundance of deuterium, which is 0.015%.

The term "deuterium enrichment factor" as used herein means the ratio between the deuterium abundance and the natural abundance of a deuterium. In one aspect, a compound of the invention has a deuterium enrichment factor for each deuterium atom of at least 3500 (52.5% deuterium incorporation at each deuterium atom), at least 4000 (60% deuterium

incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation).

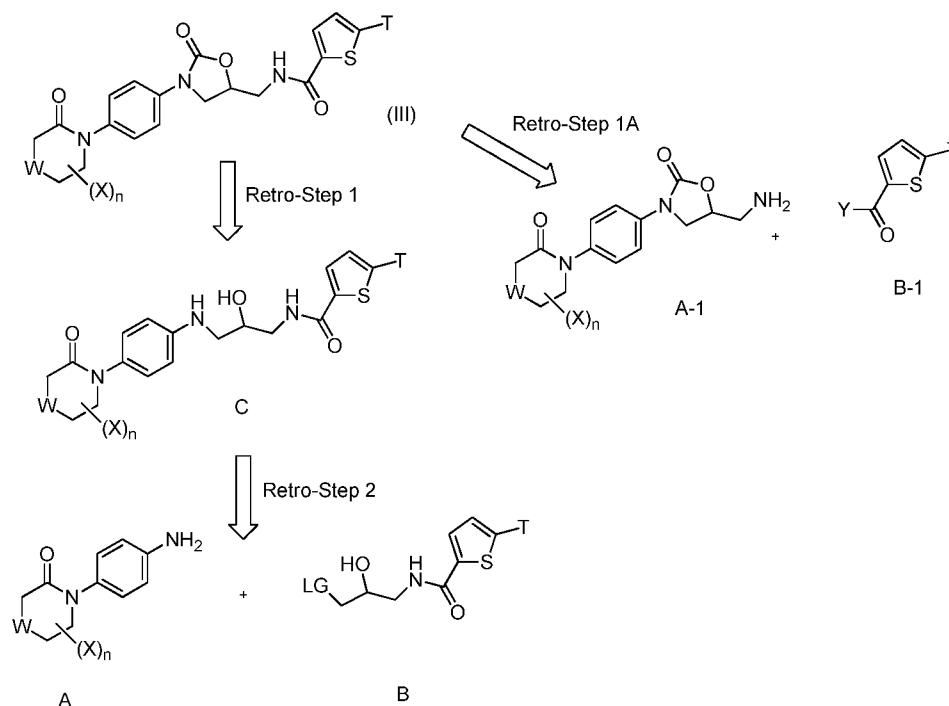
A compound of the invention or a pharmaceutically acceptable salt or solvate thereof that contains the aforementioned deuterium atom(s) is within the scope of the invention.

Further, substitution with heavier deuterium, i.e.,  $^2\text{H}$ , can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements.

The present invention relates to a method of synthesizing a compound of the invention or a pharmaceutically acceptable salt or solvate thereof. A compound of the invention can be synthesized using a variety of methods known in the art. The schemes and description below depict general routes for the preparation of a compound of the invention.

Scheme 1 outlines a retrosynthetic analysis for preparing compounds of the invention.

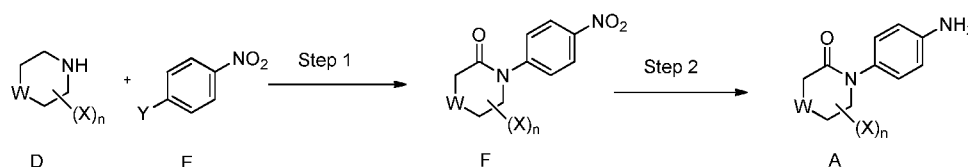
Scheme 1



The retrosynthesis is directed to compounds of formula III. It is understood that formulae IV, VI, VII, VIII, IX, X, XI, and XII are subsets of formula III. Thus, preparations described for a compound of formula III can also be applied for the preparation of a compound of formulae IV, VI, VII, VIII, IX, X, XI, and XII. The retrosynthesis in Scheme 1 depicts two possible routes to compounds of formula III.

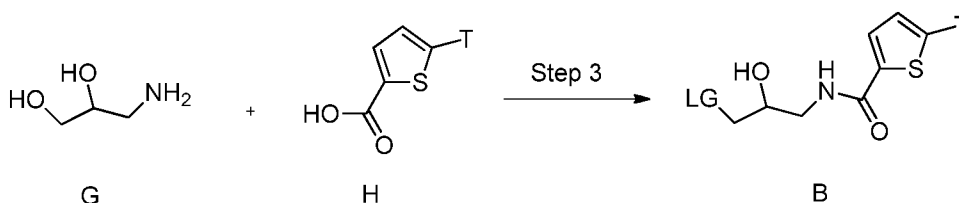
The preparation of compounds of formula III using Retro-Steps 1 and 2 is described in Schemes 2-4. The preparations outlined in Schemes 2 and 3 below begin with commercially available compounds.

Scheme 2



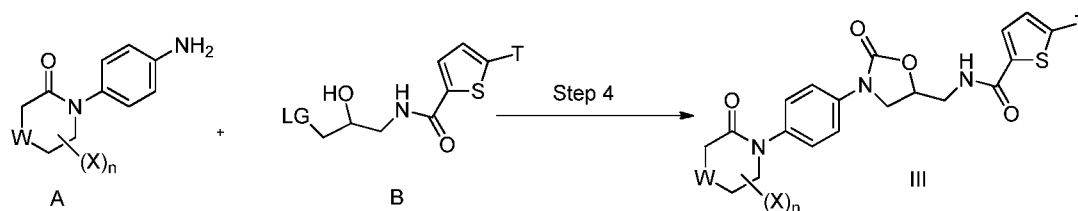
Scheme 2 shows the preparation of Compound A. In Step 1 of Scheme 2, Compound D is coupled to Compound E. For example, Compounds D and E can be coupled via a palladium coupling reaction between the secondary amine of Compound D and the group Y on Compound E. Y is e.g., a halogen. In Step 1, after the coupling reaction, the position adjacent to the nitrogen atom is oxidized to form a carbonyl to produce Compound F. For example, the oxidation step can be carried out using ruthenium oxide and sodium iodate. In Step 2, the nitro group of Compound F is reduced to produce Compound A. For example, the Step 2 reduction can be carried out using palladium catalyzed hydrogenation conditions.

Scheme 3



Scheme 3 shows the preparation of Compound B. In Step 3, Compound G is coupled to Compound H. For example, the amine of Compound G can be coupled to the carboxylic acid of Compound H using HATU and iPr<sub>2</sub>NEt in DMF. In Step 3, after the coupling reaction, the primary hydroxyl group is converted to a leaving group (LG) to form Compound B. For example, leaving group formation can be carried out using HBr, Ac<sub>2</sub>O in MeOH and AcOH.

Scheme 4



Scheme 4 shows the final step for the preparation of a compound of formula III. In Step 4, the nucleophilic primary amine of Compound A displaces the leaving group on Compound B. For example, leaving group displacement can be carried out using 2,4,6-collidine, EtOH, NaI in toluene. The oxazolidine group is formed to produce a compound of formula III. The oxazolidinone group can be formed using CDI.

For Retro-Step 1A, Compounds A-1 and B-1 are coupled. For example, Compounds A-1 and B-1 are coupled in pyridine. Compounds A-1 and B-1 are commercially available compounds.

Deuterium labeled compounds can be prepared using any of a variety of art-recognized techniques. For example, deuterium labeled compounds of formula I, II, III, IV, V, VI, VII, VIII, IX, X, XI, or XII of this invention can generally be prepared by carrying out the procedures described above and/or in the Examples described herein, by substituting a readily available deuterium labeled reagent for a non-deuterium labeled reagent.

### Methods of Use

The present invention relates to methods for the use of compounds of the invention. The compounds of the invention have a useful pharmacological activity spectrum and are therefore particularly suitable for the prophylaxis and/or treatment of disorders.

In one aspect, compounds of the invention act in particular as anticoagulants and can therefore be employed in medicaments for the prophylaxis and/or therapy of thromboembolic disorders. For the purpose of the present invention, "thromboembolic disorders" include, in particular, serious disorders such as myocardial infarct, angina pectoris (including unstable angina), reocclusions and restenoses after angioplasty or aortocoronary bypass, stroke, transitory ischaemic attacks, peripheral arterial occlusion disorders, pulmonary embolisms or deep venous thromboses.

In one aspect, compounds of invention are suitable for treating disseminated intravascular coagulation (DIC). In one aspect, compounds of the invention are also suitable for the prophylaxis and/or treatment of atherosclerosis and arthritis, and additionally also for

the prophylaxis and/or treatment of Alzheimer's disease and cancer.

In one aspect, compounds of the invention act in particular as selective inhibitors of the blood coagulation factor Xa and do not inhibit, or only inhibit at considerably higher concentrations, other serine proteases as well, such as thrombin, plasmin or trypsin.

5 In one aspect, inhibitors of the blood coagulation factor Xa in which the IC<sub>50</sub> values for the factor Xa inhibition are lower by a factor of 100, preferably by a factor of 500, in particular by a factor of 1000, than the IC<sub>50</sub> values for the inhibition of other serine proteases, in particular thrombin, plasmin and trypsin, are referred to as being "selective."

10 In one aspect, compounds of the invention can furthermore be used for preventing coagulation ex vivo, for example for banked blood or biological samples which contain factor Xa.

In one aspect, the invention provides medicaments and pharmaceutical compositions comprising at least one compound of the invention together with one or more pharmacologically acceptable auxiliaries or excipients, which medicaments and  
15 pharmaceutical compositions can be used for the indications mentioned above.

In one aspect, the invention provides a method for the prophylaxis and/or treatment of disorders of the human or animal body, in particular of the abovementioned disorders, using the compounds of the invention.

20 In one aspect, the invention provides a method for preventing blood coagulation in vitro, in particular in banked blood or biological samples which contain factor Xa, which method is characterized in that compounds of the invention.

In one aspect, the invention provides a method of treating or preventing a thromboembolic disorder in a subject comprising administering to the subject in need thereof an effective amount of a compound of the invention or a pharmaceutically acceptable salt or  
25 solvate thereof.

In one aspect, the invention provides a method for preventing thromboembolism in a subject comprising administering to the subject in need thereof an effective amount of a compound of the invention or a pharmaceutically acceptable salt or solvate thereof. In one aspect, the method prevents venous thromboembolism. In one aspect, the method prevents  
30 pulmonary embolism. In one aspect, the method prevents deep vein thrombosis.

In one aspect, the invention provides a method of preventing a disorder due to thrombus formation selected from the group consisting of myocardial infarct, unstable angina, stroke, transitory ischaemic attacks, peripheral arterial occlusive disorders, pulmonary embolisms and deep vein thromboses in a subject comprising administering to the subject in

need thereof an effective amount of a compound of the invention or a pharmaceutically acceptable salt or solvate thereof. In one aspect, the disorder is stroke. In one aspect, the disorder is myocardial infarct. In one aspect, the disorder is unstable angina. In one aspect, the disorder is peripheral arterial occlusive disorder. In one aspect, the disorder is pulmonary embolism. In one aspect, the disorder is deep venous thrombosis.

In one aspect, the invention provides a method of treating a disorder selected from the group consisting of myocardial infarct, unstable angina, stroke, transitory ischaemic attacks, peripheral arterial occlusive disorders, pulmonary embolisms, and deep venous thromboses in a subject comprising administering to the subject in need thereof an effective amount of a compound of the invention or a pharmaceutically acceptable salt or solvate thereof. In one aspect, the method treats pulmonary embolism. In one aspect, the method treats deep vein thrombosis. In one aspect, the method treats myocardial infarct. In one aspect, the method treats stroke.

In one aspect, the invention provides a method of treating or preventing disorders, wherein the disorders are influenced positively by inhibition of factor Xa in a subject, comprising administering to the subject in need thereof an effective amount of a compound of the invention or a pharmaceutically acceptable salt or solvate thereof.

In one aspect, the invention provides a method of treating disseminated intravascular coagulation (DIC) in a subject, comprising administering to the subject in need thereof an effective amount of any compound of the invention or a pharmaceutically acceptable salt or solvate thereof.

In one aspect, the invention provides a method of treating or preventing disorders such as atherosclerosis, arthritis, Alzheimer's disease or cancer in a subject, comprising administering to the subject in need thereof an effective amount of a compound of the invention or a pharmaceutically acceptable salt or solvate thereof. In one aspect, the disorder is atherosclerosis.

In one aspect, the invention provides method for preventing the coagulation of blood in vitro, in particular in the case of banked blood or biological samples containing factor Xa, characterized in that a compound of the invention is added.

In one aspect, the invention provides a method for inhibiting thrombus formation in a subject comprising administering to the subject in need thereof an effective amount of a compound of the invention or a pharmaceutically acceptable salt or solvate thereof. In one aspect, the subject has a thromboembolism. In one aspect, the thromboembolism is a venous

thromboembolism. In one aspect, the venous thromboembolism comprises pulmonary embolism. In one aspect, the venous thromboembolism comprises deep vein thrombosis.

In one aspect, the invention provides a medical device containing a compound of the invention or a pharmaceutically acceptable salt or solvate thereof. In one aspect, the device is  
5 a stent.

All customary administration forms are suitable for administration of the compounds according to the invention. Administration is preferably carried out orally, lingually, sublingually, buccally, rectally or parenterally (i.e. bypassing the intestinal tract, that is intravenously, intraarterially, intracardially, intracutaneously, subcutaneously, transdermally,  
10 intraperitoneally or intramuscularly). In one aspect, oral and intravenous administration are suitable. In one aspect, oral administration is suitable.

The compounds of the invention can be converted in a known manner into the customary formulations, such as tablets, sugar-coated tablets, pills, granules, aerosols, syrups, emulsions, suspensions and solutions, using inert non-toxic pharmaceutically suitable  
15 excipients or solvents. Here, the therapeutically active compound should in each case be present in a concentration of from about 0.1 to 95% by weight, preferably from 0.5 to 90% by weight, in particular from 1 to 85% by weight, of the total mixture, i.e. in amounts which are sufficient in order to achieve the dosage range indicated.

In spite of this, if appropriate, it may be necessary to depart from the amounts  
20 mentioned, namely depending on the body weight or on the type of administration route, on the individual response to the medicament, on the manner of its formulation and the time or interval at which administration takes place. Thus, in some cases it may be adequate to manage with less than the abovementioned minimum amount, while in other cases the upper limit mentioned must be exceeded. In the case of the administration of relatively large  
25 amounts, it may be advisable to divide these into several individual administrations over the course of the day.

The formulations are prepared, for example, by extending the active compounds with solvents and/or excipients, if appropriate using emulsifiers and/or dispersants, it being possible, for example if the diluent used is water, optionally to use organic solvents as  
30 auxiliary solvents.

In general it has proved advantageous in the case of intravenous administration to administer amounts from approximately 0.001 to 10 mg/kg, preferably approximately 0.01 to 10 mg/kg, in particular approximately 0.1 to 8 mg/kg, of body weight to achieve effective results.

In general, it has proved advantageous in the case of oral administration to administer amounts from approximately 0.01 to 50 mg/kg, preferably approximately 0.1 to 10 mg/kg, in particular approximately 0.5 to 8 mg/kg, of body weight to achieve effective results.

In spite of this, if appropriate, it may be necessary in the case of intravenous or oral administration to depart from the amounts mentioned, namely depending on the body weight or on the type of administration route, on the individual response to the medicament, on the manner of its formulation and the time or interval at which administration takes place. Thus, in some cases it may be adequate to manage with less than the abovementioned minimum amount, while in other cases the upper limit mentioned must be exceeded. In the case of the administration of relatively large amounts, it may be advisable to divide these over the course of the day, namely into several individual doses or as a continuous infusion.

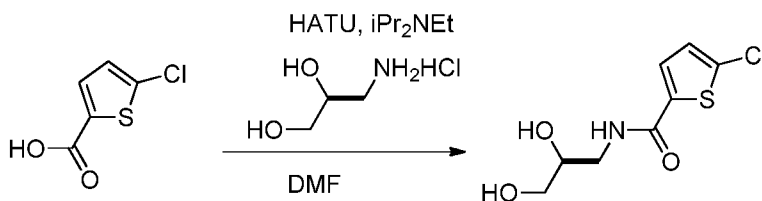
Compared to the conventional preparations for treating thromboembolic disorders, the compounds of the invention are distinguished in particular by the fact that a greater therapeutic range is achieved by the selective inhibition of factor Xa. For the patient, this means a lower risk of bleeding, and for the treating physician, this means that the patient is easier to adjust. Moreover--owing to the mechanism--the onset of action is more rapid.

The following Examples are illustrative and should not be interpreted in any way so as to limit the scope of the invention.

## EXAMPLES

Example 1. Synthesis of (*S*)-5-chloro-*N*-((3-(4-(4,4-difluoro-2-oxopiperidin-1-yl)phenyl)-2-oxooxazolidin-5-yl)methyl)thiophene-2-carboxamide

(*S*)-5-chloro-*N*-(2,3-dihydroxypropyl)thiophene-2-carboxamide

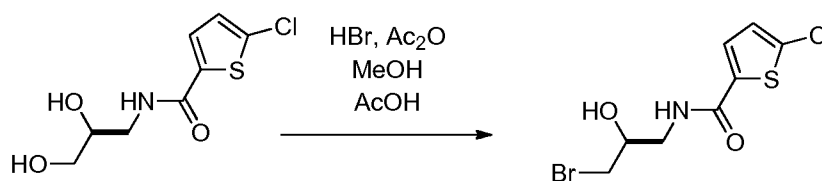


Under nitrogen, to 5-chlorothiophene-2-carboxylic acid (1.0 g, 0.62 mmol, 1.0 equiv) in DMF (1.5 mL) at −5 °C was added *i*-Pr<sub>2</sub>NEt (214 μL, 1.23 mmol, 2.00 equiv) and HATU (351 mg, 0.923 mmol, 1.50 equiv). After stirring for 5 min at −5 °C, (*S*)-3-aminopropane-1,2-diol (56 mg, 0.62 mmol, 1.0 equiv) was added and the reaction mixture was warm to 23 °C. After stirring for 16 hr at 23 °C, the reaction mixture was concentrated in vacuo and the

residue was purified by chromatography on alumina eluting with CH<sub>2</sub>Cl<sub>2</sub>/MeOH to afford 85 mg of the title compound as light brown solid (59%). *R<sub>f</sub>* = 0.45 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9:1 (v/v)).

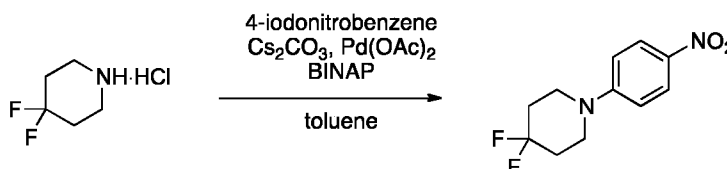
NMR Spectroscopy: <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>, 23 °C, δ): 8.53 (br, 1H), 7.68 (d, *J* = 4.0 Hz, 1H), 7.17 (d, *J* = 4.0 Hz, 1H), 4.81 (d, *J* = 5.2 Hz, 1H), 4.55 (dd, *J* = 5.6 Hz, 5.6 Hz, 1H), 3.62–3.57 (m, 1H), 3.38–3.30 (m, 3H), 3.15–3.08 (m, 1H).

(*S*)-*N*-(3-bromo-2-hydroxypropyl)-5-chlorothiophene-2-carboxamide



Under air, to (*S*)-5-chloro-*N*-(2,3-dihydroxypropyl)thiophene-2-carboxamide (500 mg, 2.12 mmol, 1.00 equiv) in AcOH (1.2 mL) at 23 °C was added 30%wt HBr in AcOH (2.5 mL) and acetic anhydride (0.2 mL). After stirring for 3 h at 65 °C, the reaction mixture was cool to 23 °C and was diluted with MeOH (3.75 mL). After further stirring for 2 h at 65 °C and 16 hr at 23 °C, the reaction mixture was concentrated in vacuo. The residue was dissolved in diethyl ether (20 mL) and washed with saturated NaHCO<sub>3</sub> and water. The combined organic phases were washed with brine and dried (Na<sub>2</sub>SO<sub>4</sub>). The filtrate was concentrated in vacuo to afford 304 mg of the title compound as an off-white solid (48% yield). *R<sub>f</sub>* = 0.50 (hexanes/EtOAc 1:1 (v/v)). NMR Spectroscopy: <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>, 23 °C, δ): 8.63 (br, 1H), 7.68 (d, *J* = 4.0 Hz, 1H), 7.18 (d, *J* = 4.0 Hz, 1H), 5.43 (br s, 1H), 3.83 (br s, 1H), 3.55–3.52 (m, 1H), 3.45–3.31 (m, 2H), 3.26–3.19 (m, 1H).

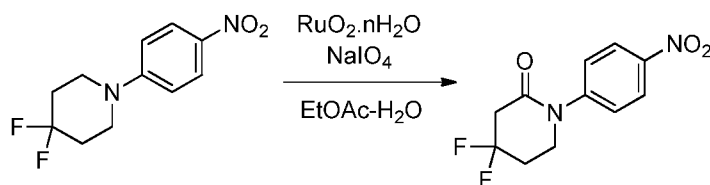
4,4-difluoro-1-(4-nitrophenyl)piperidine



Under nitrogen, to 4,4-difluoropiperidine hydrochloride (508 mg, 3.22 mmol, 1.00 equiv) in toluene (10 mL) at 23 °C was added BINAP (301 mg, 0.484 mmol, 0.150 equiv), 4-iodonitrobenzene (784 mg, 3.86 mmol, 1.20 equiv), Pd(OAc)<sub>2</sub> (72 mg, 0.32 mmol, 0.10 equiv), and cesium carbonate (2.60 g, 8.05 mmol, 2.50 equiv). After stirring for 12 hr at 95 °C, the reaction mixture was warmed to 23 °C and H<sub>2</sub>O (10 mL) was added. The phases were separated and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined

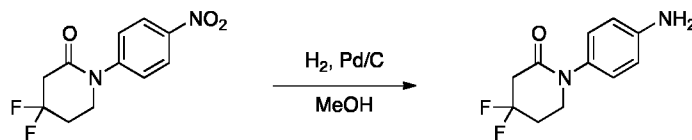
organic phases were washed with brine (30 mL) and dried (MgSO<sub>4</sub>). The filtrate was concentrated in vacuo and the residue was purified by chromatography on silica gel eluting with hexanes/EtOAc to afford 590 mg of the title compound as a yellow solid (76% yield).  $R_f$  = 0.15 (hexanes/EtOAc 9:1 (v/v)). NMR Spectroscopy: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, 23 °C, δ): 8.14 (d,  $J$  = 7.2 Hz, 2H), 6.87 (d,  $J$  = 7.2 Hz, 2H), 3.64–3.56 (m, 4H), 2.20–2.00 (m, 4H). <sup>19</sup>F NMR (281 MHz, CDCl<sub>3</sub>, 23 °C, δ): –97.83 (m, 2F).

#### 4,4-difluoro-1-(4-nitrophenyl)piperidin-2-one



Under air, to RuO<sub>2</sub>•nH<sub>2</sub>O (58 mg, 0.44 mmol, 0.20 equiv) in H<sub>2</sub>O (10 mL) at 23 °C was added NaIO<sub>4</sub> (1.87 g, 8.76 mmol, 4.00 equiv). After stirring for 3 min at 23 °C, EtOAc (10 mL) and 4,4-difluoro-1-(4-nitrophenyl)piperidine (530 mg, 2.19 mmol, 1.00 equiv) were added. After stirring for 4 hr at 23 °C, the reaction mixture was filtered through a pad of Celite and the filtrate was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (30 mL) and dried (MgSO<sub>4</sub>). The filtrate was concentrated in vacuo and the residue was purified by chromatography on silica gel eluting with hexanes/EtOAc to afford 450 mg of the title compound as a colorless solid (80% yield).  $R_f$  = 0.20 (hexanes/EtOAc 7:3 (v/v)). NMR Spectroscopy: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, 23 °C, δ): 8.28 (d,  $J$  = 7.2 Hz, 2H), 7.47 (d,  $J$  = 7.2 Hz, 2H), 3.85 (t, 6.3 Hz, 2H), 3.15 (t, 14.4 Hz, 2H), 2.59–2.39 (m, 2H). <sup>19</sup>F NMR (281 MHz, CDCl<sub>3</sub>, 23 °C, δ): –94.67 (m, 2F).

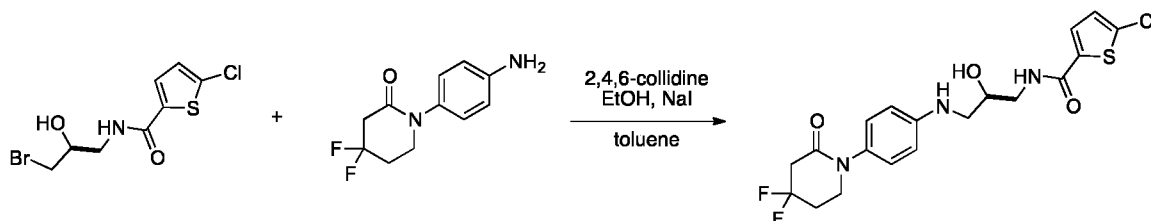
#### 1-(4-aminophenyl)-4,4-difluoropiperidin-2-one



Under air, 4,4-difluoro-1-(4-nitrophenyl)piperidin-2-one (286 mg, 1.12 mmol, 1.00 equiv) in MeOH (11 mL) at 23 °C was added 10%wt Pd/C (119 mg, 0.112 mmol, 0.100 equiv) and H<sub>2</sub> gas (1 atm) was introduced. After stirring for 2 hr at 23 °C, the reaction mixture was filtered through a pad of Celite and the filtrate was concentrated in vacuo. The residue was purified by chromatography on silica gel eluting with hexanes/EtOAc to afford 190 mg of the title compound as a colorless solid (75% yield).  $R_f$  = 0.19 (hexanes/EtOAc 3:7 (v/v)). NMR Spectroscopy: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, 23 °C, δ): 6.99 (d,  $J$  = 7.2 Hz, 2H), 6.68 (d,

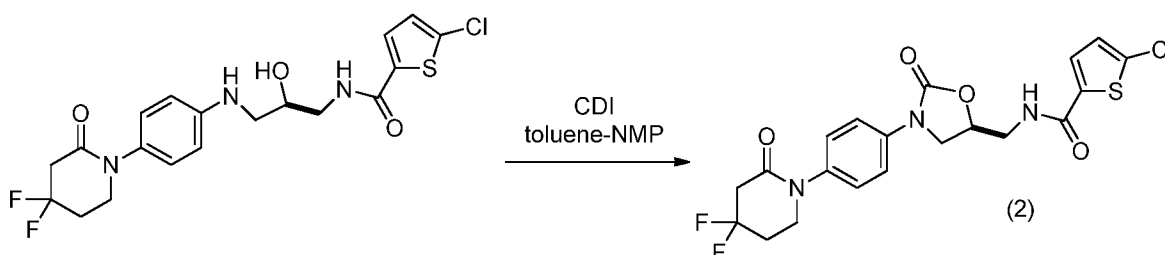
$J = 7.2$  Hz, 2H), 3.70 (t,  $J = 6.3$  Hz, 2H), 3.06 (t,  $J = 14.4$  Hz, 2H), 2.49–2.29 (m, 2H).  $^{19}\text{F}$  NMR (281 MHz,  $\text{CDCl}_3$ , 23 °C,  $\delta$ ): –95.04 (m, 2F).

(*R*)-5-chloro-*N*-(3-((4-(4,4-difluoro-2-oxopiperidin-1-yl)phenyl)amino)-2-hydroxypropyl)thiophene-2-carboxamide



Under nitrogen, to (*S*)-*N*-(3-bromo-2-hydroxypropyl)-5-chlorothiophene-2-carboxamide (249 mg, 1.10 mmol, 1.10 equiv) in toluene (2.0 mL) at 23 °C was added 1-(4-aminophenyl)-5,5-difluoropiperidin-2-one (299 mg, 1.00 mmol, 1.00 equiv), 2,4,6-collidine (119  $\mu\text{L}$ , 0.900 mmol, 0.900 equiv), NaI (150 mg, 1.00 mmol, 1.00 equiv), and EtOH (44  $\mu\text{L}$ , 0.75 mmol, 0.75 equiv). After stirring for 2 hr at 100 °C, the reaction mixture was warmed to 23 °C and concentrated in vacuo. The residue was purified by chromatography on silica gel eluting with hexanes/EtOAc to afford 92 mg of the title compound as a colorless solid (21% yield) and 100 mg of the starting material was recovered (33%).  $R_f = 0.10$  (hexanes/EtOAc 1:9 (v/v)). NMR Spectroscopy:  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ , 23 °C,  $\delta$ ): 7.53 (d,  $J = 3.9$  Hz, 1H), 7.01 (d,  $J = 3.9$  Hz, 1H), 6.99 (d,  $J = 7.2$  Hz, 2H), 6.69 (d,  $J = 7.2$  Hz, 2H), 4.00–3.95 (m, 1H), 3.78–3.62 (m, 2H), 3.58–3.38 (m, 2H), 3.30–2.95 (m, 4H), 2.54–2.39 (m, 2H).  $^{19}\text{F}$  NMR (281 MHz,  $\text{CD}_3\text{OD}$ , 23 °C,  $\delta$ ): –104.03 (m, 2F).

(*S*)-5-chloro-*N*-((3-(4-(4,4-difluoro-2-oxopiperidin-1-yl)phenyl)-2-oxooxazolidin-5-yl)methyl)thiophene-2-carboxamide (2)



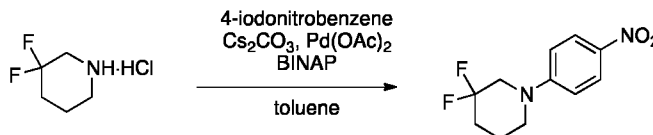
To (*R*)-5-chloro-*N*-(3-((4-(4,4-difluoro-2-oxopiperidin-1-yl)phenyl)amino)-2-hydroxypropyl)thiophene-2-carboxamide (92 mg, 0.21 mmol, 1.0 equiv) in toluene–NMP

(0.93 mL–0.14 mL) at 23 °C was added CDI (40 mg, 0.25 mmol, 1.2 equiv). After stirring for 30 min at 80 °C and then for 30 min at 100 °C, the reaction mixture was cooled to 23 °C and H<sub>2</sub>O was added (1 mL). The phases were separated and the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 1 mL). The combined organic phases were washed with brine (3 mL) and dried (Na<sub>2</sub>SO<sub>4</sub>). The filtrate was concentrated in vacuo and the residue was purified by preparative TLC eluting with CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95:5 (v/v) to afford 30 mg of the title compound as a colorless solid (30% yield).

$R_f$  = 0.25 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95:5 (v/v)). NMR Spectroscopy: <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD, 23 °C,  $\delta$ ): 7.62 (d,  $J$  = 7.2 Hz, 2H), 7.52 (d,  $J$  = 3.9 Hz, 1H), 7.29 (d,  $J$  = 7.2 Hz, 2H), 7.01 (d,  $J$  = 3.9 Hz, 1H), 4.89–4.80 (m, 1H), 4.30–4.14 (m, 1H), 3.93 (dd,  $J$  = 9.6 Hz, 5.7 Hz, 1H), 3.81–3.70 (m, 3H), 3.35–3.25 (m, 1H), 3.09 (t,  $J$  = 14.1 Hz, 2H), 2.55–2.44 (m, 2H). <sup>19</sup>F NMR (281 MHz, CD<sub>3</sub>OD, 23 °C,  $\delta$ ): –96.60 (m, 2F).

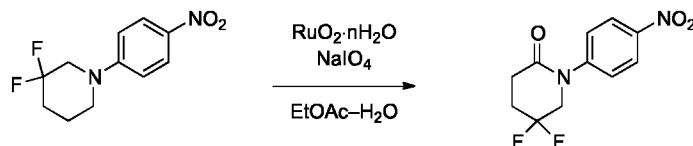
Example 2. Synthesis of (*S*)-5-chloro-*N*-((3-(4-(5,5-difluoro-2-oxopiperidin-1-yl)phenyl)-2-oxooxazolidin-5-yl)methyl)thiophene-2-carboxamide

3,3-difluoro-1-(4-nitrophenyl)piperidine



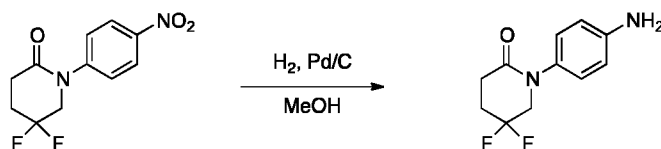
Under nitrogen, to 3,3-difluoropiperidine hydrochloride (552 mg, 3.50 mmol, 1.00 equiv) in toluene (10 mL) at 23 °C was added BINAP (327 mg, 0.530 mmol, 0.150 equiv), 4-iodonitrobenzene (853 mg, 4.20 mmol, 1.20 equiv), Pd(OAc)<sub>2</sub> (79 mg, 0.35 mmol, 0.10 equiv), and cesium carbonate (2.90 g, 8.80 mmol, 2.50 equiv). After stirring for 19 hr at 95 °C, the reaction mixture was warmed to 23 °C and H<sub>2</sub>O (10 mL) was added. The phases were separated and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (30 mL) and dried (MgSO<sub>4</sub>). The filtrate was concentrated in vacuo and the residue was purified by chromatography on silica gel eluting with hexanes/EtOAc to afford 628 mg of the title compound as a yellow solid (74% yield).  $R_f$  = 0.14 (hexanes/EtOAc 9:1 (v/v)). NMR Spectroscopy: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, 23 °C,  $\delta$ ): 8.13 (d,  $J$  = 7.2 Hz, 2H), 6.85 (d,  $J$  = 7.2 Hz, 2H), 3.65 (t,  $J$  = 11.4 Hz, 2H), 3.52–3.42 (m, 2H), 2.21–2.01 (m, 2H), 1.97–1.85 (m, 2H). <sup>19</sup>F NMR (281 MHz, CDCl<sub>3</sub>, 23 °C,  $\delta$ ): –101.69 (m, 2F).

## 5,5-difluoro-1-(4-nitrophenyl)piperidin-2-one



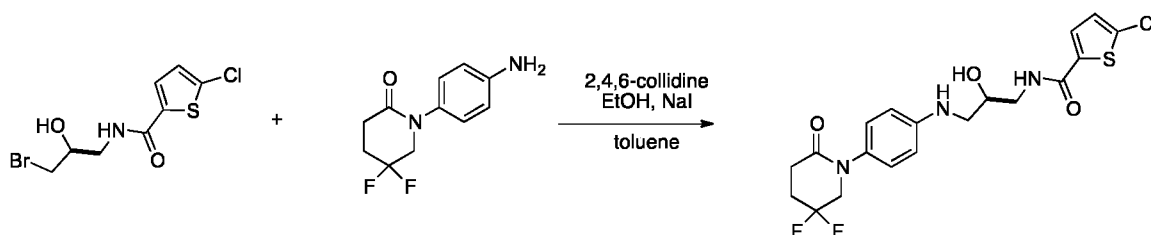
Under air, to  $\text{RuO}_2 \cdot n\text{H}_2\text{O}$  (103 mg, 0.771 mmol, 0.200 equiv) in  $\text{H}_2\text{O}$  (10 mL) at 23 °C was added  $\text{NaIO}_4$  (2.20 g, 10.3 mmol, 4.00 equiv). After stirring for 3 min at 23 °C, EtOAc (10 mL) and 3,3-difluoro-1-(4-nitrophenyl)piperidine (625 mg, 2.58 mmol, 1.00 equiv) were added. After stirring for 2 hr at 23 °C, the reaction mixture was filtered through a pad of Celite and the filtrate was extracted with EtOAc ( $3 \times 10$  mL). The combined organic phases were washed with brine (30 mL) and dried ( $\text{MgSO}_4$ ). The filtrate was concentrated in vacuo and the residue was purified by chromatography on silica gel eluting with hexanes/EtOAc to afford 563 mg of the title compound as a colorless solid (85% yield).  $R_f = 0.20$  (hexanes/EtOAc 7:3 (v/v)). NMR Spectroscopy:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ , 23 °C,  $\delta$ ): 8.25 (d,  $J = 7.2$  Hz, 2H), 7.46 (d,  $J = 7.2$  Hz, 2H), 4.02 (t,  $J = 11.4$  Hz, 2H), 2.82–2.76 (m, 2H), 2.57–2.37 (m, 2H).  $^{19}\text{F}$  NMR (281 MHz,  $\text{CDCl}_3$ , 23 °C,  $\delta$ ): –100.42 (m, 2F).

## 1-(4-aminophenyl)-5,5-difluoropiperidin-2-one



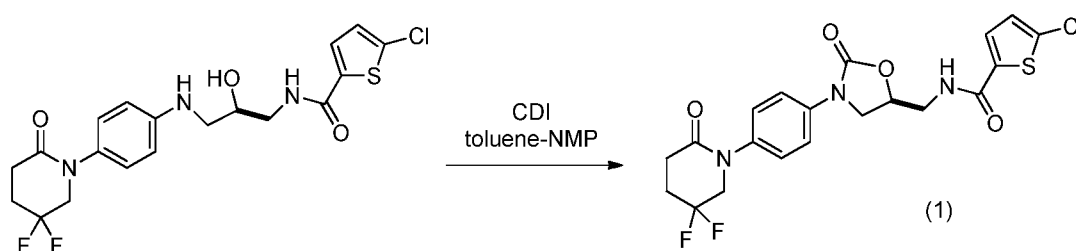
Under air, 5,5-difluoro-1-(4-nitrophenyl)piperidin-2-one (563 mg, 2.20 mmol, 1.00 equiv) in MeOH (11 mL) at 23 °C was added 10%wt Pd/C (234 mg, 0.220 mmol, 0.100 equiv) and  $\text{H}_2$  gas (1 atm) was introduced. After stirring for 2.5 hr at 23 °C, the reaction mixture was filtered through a pad of Celite and the filtrate was concentrated in vacuo. The residue was purified by chromatography on silica gel eluting with hexanes/EtOAc to afford 370 mg of the title compound as a colorless solid (74% yield).  $R_f = 0.16$  (hexanes/EtOAc 3:7 (v/v)). NMR Spectroscopy:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ , 23 °C,  $\delta$ ): 7.01 (d,  $J = 7.2$  Hz, 2H), 6.69 (d,  $J = 7.2$  Hz, 2H), 3.89 (t,  $J = 11.4$  Hz, 2H), 3.74 (br s, 2H), 2.78–2.68 (m, 2H), 2.51–2.31 (m, 2H).  $^{19}\text{F}$  NMR (281 MHz,  $\text{CDCl}_3$ , 23 °C,  $\delta$ ): –101.58 (m, 2F).

(*R*)-5-chloro-*N*-(3-((4-(5,5-difluoro-2-oxopiperidin-1-yl)phenyl)amino)-2-hydroxypropyl)thiophene-2-carboxamide



Under nitrogen, to (*S*)-*N*-(3-bromo-2-hydroxypropyl)-5-chlorothiophene-2-carboxamide (179 mg, 0.600 mmol, 1.20 equiv), prepared as described in Example 1, in toluene (1.0 mL) at 23 °C was added 1-(4-aminophenyl)-4,4-difluoropiperidin-2-one (113 mg, 0.500 mmol, 1.00 equiv), 2,4,6-collidine (60 µL, 0.45 mmol, 0.90 equiv), NaI (75 mg, 0.50 mmol, 1.0 equiv), and EtOH (22 µL, 0.38 mmol, 0.75 equiv). After stirring for 3 hr at 100 °C, the reaction mixture was warmed to 23 °C and *n*-BuOH (230 µL) was added. After stirring for 1 hr, the precipitates were collected by filtration and washed with toluene (3 × 1 mL) and H<sub>2</sub>O (3 × 1 mL) to afford 120 mg of the title compound as a colorless solid (54% yield). *R<sub>f</sub>* = 0.10 (hexanes/EtOAc 1:9 (v/v)). NMR Spectroscopy: <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD, 23 °C, δ): 8.59–8.48 (m, 1H), 7.53 (d, *J* = 3.9 Hz, 1H), 7.01 (d, *J* = 3.9 Hz, 1H), 6.99 (d, *J* = 7.2 Hz, 2H), 6.68 (d, *J* = 7.2 Hz, 2H), 4.00–3.89 (m, 3H), 3.58–3.38 (m, 2H), 3.30–3.05 (m, 2H), 2.75–2.65 (m, 2H), 2.52–2.32 (m, 2H). <sup>19</sup>F NMR (281 MHz, CD<sub>3</sub>OD, 23 °C, δ): –96.82 (m, 2F).

(*S*)-5-chloro-*N*-((3-(4-(5,5-difluoro-2-oxopiperidin-1-yl)phenyl)-2-oxooxazolidin-5-yl)methyl)thiophene-2-carboxamide (1)

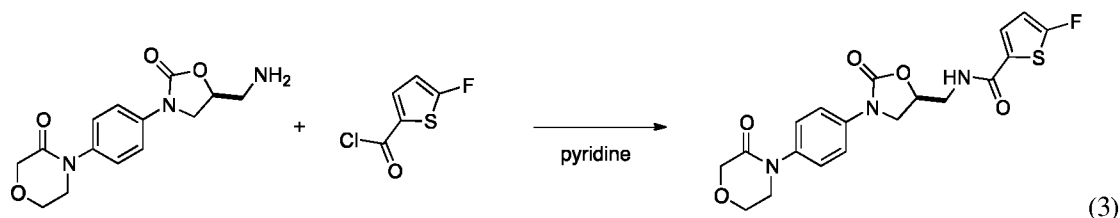


To (*R*)-5-chloro-*N*-(3-((4-(5,5-difluoro-2-oxopiperidin-1-yl)phenyl)amino)-2-hydroxypropyl)thiophene-2-carboxamide (120 mg, 0.270 mmol, 1.00 equiv) in toluene–NMP (1.2 mL–0.18 mL) at 23 °C was added CDI (53 mg, 0.32 mmol, 1.2 equiv). After stirring for

30 min at 80 °C and then for 2 hr at 100 °C, the reaction mixture was cooled to 23 °C. The precipitates were collected by filtration and washed with toluene (3 × 1 mL) and H<sub>2</sub>O (3 × 1 mL) to afford 63 mg of the title compound as a colorless solid (49% yield).  $R_f = 0.28$

(CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95:5 (v/v)). NMR Spectroscopy: <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>, 23 °C,  $\delta$ ): 9.00–8.91 (m, 1H), 7.67 (d,  $J = 3.9$  Hz, 1H), 7.53 (d,  $J = 7.2$  Hz, 2H), 7.28 (d,  $J = 7.2$  Hz, 2H), 7.18 (d,  $J = 3.9$  Hz, 1H), 4.88–4.78 (m, 1H), 4.21–4.11 (m, 1H), 4.03 (t,  $J = 12.6$  Hz, 2H), 3.90–3.78 (m, 1H), 3.61–3.54 (m, 2H), 3.45–3.25 (m, 1H), 2.68–2.35 (m, 3H). <sup>19</sup>F NMR (281 MHz, DMSO-*d*<sub>6</sub>, 23 °C,  $\delta$ ): –99.82 (m, 2F).

10 Example 3. Synthesis of (*S*)-5-fluoro-*N*-((2-oxo-3-(4-(3-oxomorpholino)phenyl)oxazolidin-5-yl)methyl)thiophene-2-carboxamide (3)



Under nitrogen, to (*S*)-4-(4-(5-(aminomethyl)-2-oxooxazolidin-3-yl)phenyl)morpholin-3-one (189 mg, 0.648 mmol, 1.00 equiv) (commercially available) in pyridine (5.5 mL) at 0 °C was added 5-fluorothiophene-2-carbonyl chloride (160 mg, 0.972 mmol, 1.50 equiv). After stirring for 60 min at 23 °C, H<sub>2</sub>O (10 mL) was added to the reaction mixture and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 10 mL). The combined organic phases were washed with brine (30 mL) and dried (MgSO<sub>4</sub>). The filtrate was concentrated in vacuo and the residue was purified by chromatography on silica gel eluting with CH<sub>2</sub>Cl<sub>2</sub>/MeOH to afford 100 mg of the title compound as colorless solid (37%).

NMR Spectroscopy: <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>, 23 °C,  $\delta$ ): 8.93 (t,  $J = 6.0$  Hz, 1H), 7.60–7.52 (m, 3H), 7.41 (d,  $J = 9.3$  Hz, 2H), 6.79 (dd,  $J = 4.5$  Hz, 2.1 Hz, 1H), 4.88–4.79 (m, 1H), 4.24–4.14 (m, 3H), 3.99–3.94 (m, 2H), 3.87–3.81 (m, 1H), 3.75–3.69 (m, 2H), 3.63–3.58 (m, 2H).

Example 4. Testing for anti-coagulation activity

The compounds of the present invention were tested for anti-coagulation activity in whole human blood by measuring prothrombin time (PT) and activated partial thromboplastin time (aPTT) as follows.

Blood samples, anticoagulated with trisodium citrate (3.8%, w/v) at a ratio of 9 parts whole blood, 1 part trisodium citrate, were collected from 5 healthy human volunteers. Syringes were prepared with 2mL of trisodium citrate (3.8%, w/v). Blood was collected into the syringes to a final volume of 20mL. Samples were centrifuged at 3000rpm for 15 minutes. The plasma samples were then transferred to appropriately labeled tubes.

The following reagents were used on this study:

10 For PT: PT-Fibrinogen HS PLUS (Instrumentation Laboratory)  
For APTT: SynthASil (Instrumentation Laboratory)  
Dimethylsulfoxide (DMSO), (Sigma)

The test items were diluted to a concentration of 30 mM with DMSO for the first experiment. They were then stored at -20°C in the dark. During the second experiment, the test items were thawed and then further diluted to obtain final concentrations of 3 µM, 1 µM, 0.3 µM and 0.1 µM in plasma and 1% (w/v) DMSO.

Samples were incubated for 10 minutes at 37 C and then assayed for PT and APTT using the Instrumentation Laboratory ACL Advance Coagulometer. The samples were analyzed in triplicate. Quality control material was run throughout the analysis and all values obtained were within the laboratory criteria.

Sample results were tabulated and plotted using MS EXCEL 2007. The concentration of each test item required to double the PT and APTT clotting times for the vehicle control were estimated by interpolation. This is defined as the CT2 and is reported as µM test item.

For the compound of Example 1, the mean CT2 obtained for PT was 1.97 µM with SD of 0.37 µM. The CT2 obtained for APTT was 5.37 µM with SD of 0.62 µM.

For the compound of Example 2, the mean CT2 obtained for PT was 7.75 µM with SD of 1.79 µM. The mean CT2 obtained for APTT was 17.26 µM with SD of 2.84 µM.

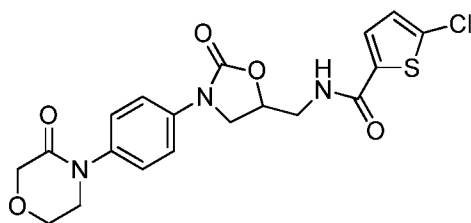
For the compound of Example 3, the mean CT2 obtained for PT was 0.90 µM with SD of 0.06 µM. The mean CT2 obtained for APTT was 2.70 µM with SD of 0.20 µM.

## CLAIMS

What is claimed:

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1. A compound of formula I:

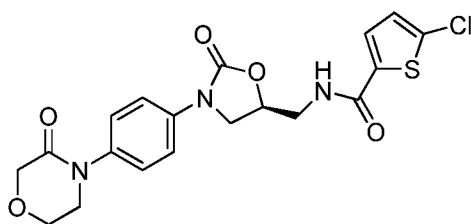


(I) or a pharmaceutically acceptable salt or solvate

thereof, wherein the compound of formula I is a fluorinated derivative, wherein at least one atom is replaced with F or with a group of atoms containing at least one F.

10

2. A compound of formula II:



(II) or a pharmaceutically acceptable salt or solvate

thereof, wherein the compound of formula II is a fluorinated derivative wherein at least one atom is replaced with F or with a group of atoms containing at least one F.

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3. The compound of claim 1 or 2, wherein at least one hydrogen atom is replaced with F.

4. The compound of claim 1 or 2, wherein two hydrogen atoms are each replaced with F.

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5. The compound of claim 1 or 2, wherein three hydrogen atoms are each replaced with F.

6. The compound of claim 1 or 2, wherein one or more hydrogen atoms are replaced with F or a group of atoms selected from CF<sub>3</sub>, CHF<sub>2</sub>, CH<sub>2</sub>F, OCF<sub>3</sub>, OCHF<sub>2</sub>, and OCH<sub>2</sub>F.

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7. The compound of claim 6, wherein one hydrogen atom is replaced with F.

8. The compound of claim 6, wherein one or more hydrogen atoms are replaced with F or a group of atoms selected from CF<sub>3</sub> and OCF<sub>3</sub>.

5 9. The compound of claim 6, wherein one or more hydrogen atoms are replaced with a group of atoms selected from CF<sub>3</sub>, CHF<sub>2</sub>, CH<sub>2</sub>F, OCF<sub>3</sub>, OCHF<sub>2</sub>, and OCH<sub>2</sub>F.

10. The compound of claim 9, wherein one or more hydrogen atoms are replaced with a group of atoms selected from CF<sub>3</sub>, CHF<sub>2</sub>, and CH<sub>2</sub>F.

10

11. The compound of claim 10, wherein one hydrogen atom is replaced with CF<sub>3</sub>.

12. The compound of claim 9, wherein one or more hydrogen atoms are replaced with a group of atoms selected from OCF<sub>3</sub>, OCHF<sub>2</sub>, and OCH<sub>2</sub>F.

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13. The compound of claim 12, wherein one hydrogen atom is replaced with OCF<sub>3</sub>.

14. The compound of claim 1 of 2, wherein the chlorine atom is replaced with F or a group of atoms selected from CF<sub>3</sub>, CHF<sub>2</sub>, CH<sub>2</sub>F, OCF<sub>3</sub>, OCHF<sub>2</sub>, and OCH<sub>2</sub>F.

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15. The compound of claim 14, wherein the chlorine atom is replaced with F.

16. The compound of claim 14, wherein the chlorine atom is replaced with a group of atoms selected from CF<sub>3</sub>, CHF<sub>2</sub>, CH<sub>2</sub>F, OCF<sub>3</sub>, OCHF<sub>2</sub>, and OCH<sub>2</sub>F.

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17. The compound of claim 16, wherein the chlorine atom is replaced with a group of atoms selected from CF<sub>3</sub>, CHF<sub>2</sub>, and CH<sub>2</sub>F.

18. The compound of claim 17, wherein the chlorine atom is replaced with CF<sub>3</sub>.

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19. The compound of claim 16, wherein the chlorine atom is replaced with a group of atoms selected from OCF<sub>3</sub>, OCHF<sub>2</sub>, and OCH<sub>2</sub>F.

20. The compound of claim 19, wherein the chlorine atom is replaced with OCF<sub>3</sub>.

21. The compound of claim 1 or 2, wherein one heteroatom is replaced with a group of atoms selected from CF<sub>2</sub>, CHF, CH(CF<sub>3</sub>), CH(OCF<sub>3</sub>), CH(OCHF<sub>2</sub>), and CH(OCH<sub>2</sub>F).

22. The compound of claim 21, wherein the heteroatom is an oxygen atom and said oxygen atom is replaced with a group of atoms selected from CF<sub>2</sub>, CHF, CH(CF<sub>3</sub>), CH(OCF<sub>3</sub>), CH(OCHF<sub>2</sub>), and CH(OCH<sub>2</sub>F).

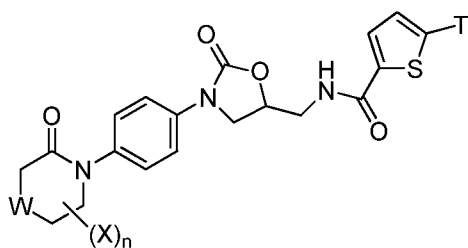
23. The compound of claim 22, wherein the oxygen atom of the morpholinone ring is replaced with a group of atoms selected from CF<sub>2</sub>, CHF, CH(CF<sub>3</sub>), CH(OCF<sub>3</sub>), CH(OCHF<sub>2</sub>), and CH(OCH<sub>2</sub>F).

24. The compound of claim 23, wherein the oxygen atom of the morpholinone ring is replaced with a group of atoms selected from CF<sub>2</sub>, CHF, and CH(CF<sub>3</sub>).

25. The compound of claim 23, wherein the oxygen atom of the morpholinone ring is replaced with a group of atoms selected from CH(OCF<sub>3</sub>), CH(OCHF<sub>2</sub>), and CH(OCH<sub>2</sub>F).

26. The compound of claim 24, wherein the oxygen atom of the morpholinone ring is replaced with CF<sub>2</sub>.

27. A compound of formula III:

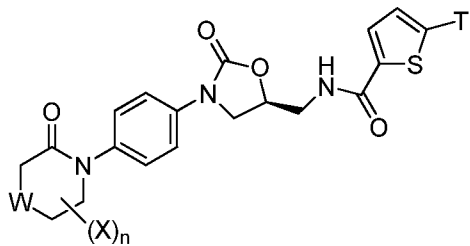


(III) or a pharmaceutically acceptable salt or solvate

thereof, wherein

T is selected from Cl, F, CF<sub>3</sub>, CHF<sub>2</sub>, CH<sub>2</sub>F, OCF<sub>3</sub>, OCHF<sub>2</sub>, OCH<sub>2</sub>F;  
 each X is independently selected from H, F, CF<sub>3</sub>, CHF<sub>2</sub>, CH<sub>2</sub>F, OCF<sub>3</sub>, OCHF<sub>2</sub>, OCH<sub>2</sub>F;  
 W is selected from O, CF<sub>2</sub>, CHF, CH(CF<sub>3</sub>), CH(OCF<sub>3</sub>), CH(OCHF<sub>2</sub>), CH(OCH<sub>2</sub>F); and  
 n is 0, 1, 2, or 3, provided that when W is O and T is Cl, then X is not H (when n=1), each X is not H (when n=2), and each X is not H (when n=3).

28. A compound of formula IV:



(IV) or a pharmaceutically acceptable salt or solvate

thereof, wherein

- 5 T is selected from Cl, F, CF<sub>3</sub>, CHF<sub>2</sub>, CH<sub>2</sub>F, OCF<sub>3</sub>, OCHF<sub>2</sub>, and OCH<sub>2</sub>F;  
 each X is independently selected from H, F, CF<sub>3</sub>, CHF<sub>2</sub>, CH<sub>2</sub>F, OCF<sub>3</sub>, OCHF<sub>2</sub>, and OCH<sub>2</sub>F;  
 W is selected from O, CF<sub>2</sub>, CHF, CH(CF<sub>3</sub>), CH(OCF<sub>3</sub>), CH(OCHF<sub>2</sub>), and CH(OCH<sub>2</sub>F); and  
 n is 0, 1, 2 or 3, provided that when W is O and T is Cl, then X is not H (when n=1), each X  
 is not H (when n=2), and each X is not H (when=3).

10

29. The compound of claim 27 or 28, wherein T is F.

30. The compound of claim 27 or 28, wherein T is CF<sub>3</sub>.

15 31. The compound of claim 27 or 28, wherein T is CHF<sub>2</sub>.

32. The compound of claim 27 or 28, wherein T is CH<sub>2</sub>F.

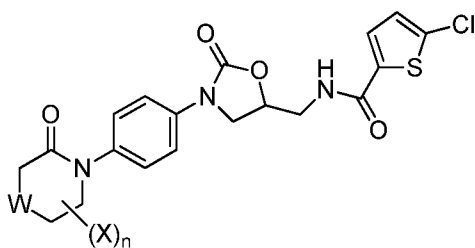
33. The compound of claim 27 or 28, wherein T is OCF<sub>3</sub>.

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34. The compound of claim 27 or 28, wherein T is OCHF<sub>2</sub>.

35. The compound of claim 27 or 28, wherein T is OCH<sub>2</sub>F.

25 36. A compound of formula V:



(V) or a pharmaceutically acceptable salt or solvate

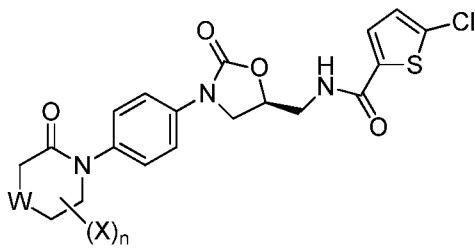
thereof, wherein

each X is independently selected from H, F, CF<sub>3</sub>, CHF<sub>2</sub>, CH<sub>2</sub>F, OCF<sub>3</sub>, OCHF<sub>2</sub>, and OCH<sub>2</sub>F;

W is selected from O, CF<sub>2</sub>, CHF, CH(CF<sub>3</sub>), CH(OCF<sub>3</sub>), CH(OCHF<sub>2</sub>), and CH(OCH<sub>2</sub>F); and

- 5 n is 0, 1, 2, or 3, provided that when W is O, then X is not H (when n=1), each X is not H (when n=2), and each X is not H (when n=3).

37. A compound of formula VI:



(VI) or a pharmaceutically acceptable salt or solvate

thereof, wherein

each X is independently selected from H, F, CF<sub>3</sub>, CHF<sub>2</sub>, CH<sub>2</sub>F, OCF<sub>3</sub>, OCHF<sub>2</sub>, and OCH<sub>2</sub>F;

W is selected from O, CF<sub>2</sub>, CHF, CH(CF<sub>3</sub>), CH(OCF<sub>3</sub>), CH(OCHF<sub>2</sub>), and CH(OCH<sub>2</sub>F); and

n is 0, 1, 2 or 3, provided that when W is O, then X is not H (when n=1), each X is not H (when n=2), and each X is not H (when n=3).

38. The compound of any one of claims 27-37, wherein X is F.

39. The compound of claim 38, wherein X is F and W is O.

40. The compound of claim 39, wherein X is F, W is O, and n is 1.

41. The compound of claim 39, wherein n is 2, each X is F, and W is O.

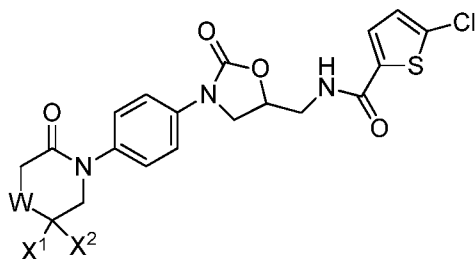
42. The compound of claim 39, wherein n is 2, one X is F and the remaining X is H, and W is O.

43. The compound of any one of claims 27-37, wherein n is 0 and W is CF<sub>2</sub>.

44. The compound of any one of claims 27-37, wherein n is 0 and W is CHF.

5

45. A compound of formula VII:



(VII) or a pharmaceutically acceptable salt or solvate

thereof, wherein

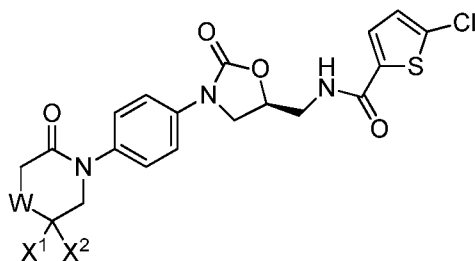
each X<sup>1</sup> and X<sup>2</sup> is independently selected from H, F, CF<sub>3</sub>, CHF<sub>2</sub>, CH<sub>2</sub>F, OCF<sub>3</sub>, OCHF<sub>2</sub>, and

10 OCH<sub>2</sub>F; and

W is selected from O, CF<sub>2</sub>, CHF, CH(CF<sub>3</sub>), CH(OCF<sub>3</sub>), CH(OCHF<sub>2</sub>), and CH(OCH<sub>2</sub>F),

provided that when W is O, then X<sup>1</sup> and X<sup>2</sup> are not both H.

46. A compound of formula VIII:



15

(VIII) or a pharmaceutically acceptable salt or

solvate thereof, wherein

each X<sup>1</sup> and X<sup>2</sup> is independently selected from H, F, CF<sub>3</sub>, CHF<sub>2</sub>, CH<sub>2</sub>F, OCF<sub>3</sub>, OCHF<sub>2</sub>, and

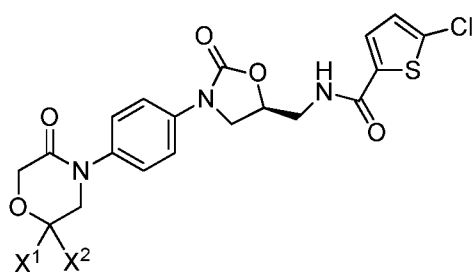
OCH<sub>2</sub>F; and

W is selected from O, CF<sub>2</sub>, CHF, CH(CF<sub>3</sub>), CH(OCF<sub>3</sub>), CH(OCHF<sub>2</sub>), and CH(OCH<sub>2</sub>F),

20

provided that when W is O, then X<sup>1</sup> and X<sup>2</sup> are not both H.

47. A compound of formula IX:



(IX) or a pharmaceutically acceptable salt or solvate

thereof, wherein each  $X^1$  and  $X^2$  is independently selected from H, F,  $CF_3$ ,  $CHF_2$ ,  $CH_2F$ ,  $OCF_3$ ,  $OCHF_2$ , and  $OCH_2F$ , provided that  $X^1$  and  $X^2$  are not both H.

- 5 48. The compound of claim 47, wherein each  $X^1$  and  $X^2$  is independently selected from H, F,  $CF_3$ ,  $CHF_2$ , and  $CH_2F$ , provided that  $X^1$  and  $X^2$  are not both H.

49. The compound of claim 45 or 46, wherein each  $X^1$  and  $X^2$  is independently selected from H, F,  $CF_3$ ,  $CHF_2$ , and  $CH_2F$ , provided that when W is O, then  $X^1$  and  $X^2$  are not both H.

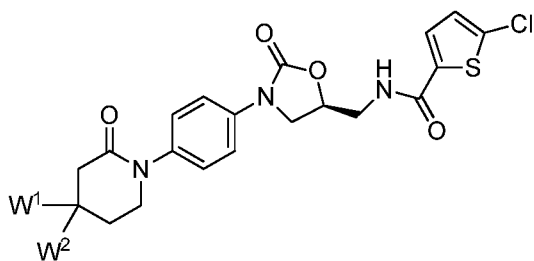
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50. The compound of any one of claims 45-47, wherein one of  $X^1$  or  $X^2$  is F and the remaining  $X^1$  or  $X^2$  is H.

51. The compound of any one of claims 45-47, wherein both of  $X^1$  and  $X^2$  are F.

15

52. A compound of formula X:



(X) or a pharmaceutically acceptable salt or

solvate thereof, wherein each  $W^1$  and  $W^2$  are selected from H, F,  $CF_3$ ,  $CHF_2$ ,  $CH_2F$ ,  $OCF_3$ ,  $OCHF_2$ , and  $OCH_2F$ .

20

53. The compound of claim 52, wherein at least one of  $W^1$  or  $W^2$  is not H.

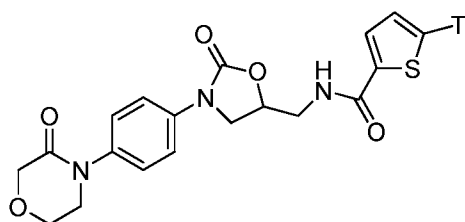
54. The compound of claim 52, wherein each  $W^1$  and  $W^2$  is independently selected from H, F,  $CF_3$ ,  $CHF_2$ , and  $CH_2F$ .

55. The compound of claim 54, wherein one of  $W^1$  or  $W^2$  is F and the remaining  $W^1$  or  $W^2$  is H.

56. The compound of claim 54, wherein  $W^1$  and  $W^2$  are both F.

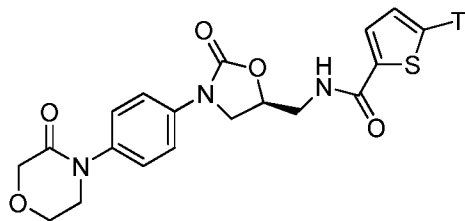
57. The compound of claim 52, wherein each  $W^1$  and  $W^2$  is independently selected from H,  $OCF_3$ ,  $OCHF_2$ , and  $OCH_2F$ .

58. A compound of formula XI:



(XI) or a pharmaceutically acceptable salt or solvate thereof, wherein T is selected from F,  $CF_3$ ,  $CHF_2$ ,  $CH_2F$ ,  $OCF_3$ ,  $OCHF_2$ , and  $OCH_2F$ .

59. A compound of formula XII:



(XII) or a pharmaceutically acceptable salt or solvate thereof, wherein T is selected from F,  $CF_3$ ,  $CHF_2$ ,  $CH_2F$ ,  $OCF_3$ ,  $OCHF_2$ , and  $OCH_2F$ .

60. The compound of claim 58 or 59, wherein T is F.

61. The compound of claim 58 or 59, wherein T is  $CF_3$ .

62. The compound of claim 58 or 59, wherein T is  $CH_2F$ .

63. The compound of claim 58 or 59, wherein T is  $CHF_2$ .

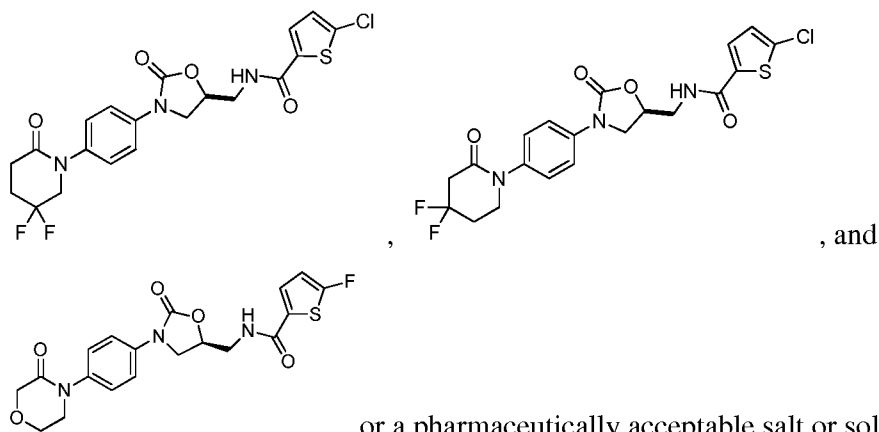
64. The compound of claim 58 or 59, wherein T is  $OCF_3$ .

65. The compound of claim 58 or 59, wherein T is  $\text{OCHF}_2$ .

66. The compound of claim 58 or 59, wherein T is  $\text{OCH}_2\text{F}$ .

5

67. A compound selected from



10 68. The compound of any one of claims 1-67, wherein said compound is the free base.

69. The compound of any one of claims 1-67, wherein the compound is the pharmaceutically acceptable salt.

15 70. The compound of any one of claims 1-67, wherein the compound is a solvate.

71. The compound of any one of claims 1-67, wherein the compound is a hydrate.

20 72. A pharmaceutical composition comprising at least one compound of any one of claims 1-67 or a pharmaceutically acceptable salt or solvate thereof and one or more pharmaceutically acceptable carrier or excipients.

73. A method of treating or preventing a thromboembolic disorder in a subject comprising administering to the subject in need thereof an effective amount of a compound of any one of  
25 claims 1-67 or a pharmaceutically acceptable salt or solvate thereof.

74. A method for preventing thromboembolism in a subject comprising administering to the subject in need thereof an effective amount of a compound of any one of claims 1-67 or a pharmaceutically acceptable salt or solvate thereof.

5 75. The method of claim 74, wherein the method prevents venous thromboembolism.

76. The method of claim 74, wherein the method prevents pulmonary embolism.

77. The method of claim 74, wherein the method prevents deep vein thrombosis.

10

78. A method of preventing a disorder due to thrombus formation selected from the group consisting of myocardial infarct, unstable angina, stroke, transitory ischaemic attacks, peripheral arterial occlusive disorders, pulmonary embolisms and deep vein thromboses in a subject comprising administering to the subject in need thereof an effective amount of a  
15 compound of any one of claims 1-67 or a pharmaceutically acceptable salt or solvate thereof.

79. The method of claim 78, wherein the disorder is stroke.

80. The method of claim 78, wherein the disorder is myocardial infarct.

20

81. The method of claim 78, wherein the disorder is unstable angina.

82. The method of claim 78, wherein the disorder is peripheral arterial occlusive disorder.

25 83. The method of claim 78, wherein the disorder is pulmonary embolism.

84. The method of claims 78, wherein the disorder is deep venous thrombosis.

85. A method of treating a disorder selected from the group consisting of myocardial  
30 infarct, unstable angina, stroke, transitory ischaemic attacks, peripheral arterial occlusive disorders, pulmonary embolisms, and deep venous thromboses in a subject comprising administering to the subject in need thereof an effective amount of a compound of any one of claims 1-67 or a pharmaceutically acceptable salt or solvate thereof.

86. The method of claim 85, wherein the method treats pulmonary embolism.
87. The method of claim 85, wherein the method treats deep vein thrombosis.
- 5 88. The method of claim 85, wherein the method treats myocardial infarct.
89. The method of claim 85, wherein the method treats stroke.
90. A method of treating or preventing disorders, wherein the disorders are influenced  
10 positively by inhibition of factor Xa in a subject, comprising administering to the subject in  
need thereof an effective amount of a compound of any one of claims 1-67 or a  
pharmaceutically acceptable salt or solvate thereof.
91. A method of treating disseminated intravascular coagulation (DIC) in a subject,  
15 comprising administering to the subject in need thereof an effective amount of any compound  
of any one of claims 1-67 or a pharmaceutically acceptable salt or solvate thereof.
92. A method of treating or preventing disorders such as atherosclerosis, arthritis,  
Alzheimer's disease or cancer in a subject, comprising administering to the subject in need  
20 thereof an effective amount of a compound of any one of claims 1-67 or a pharmaceutically  
acceptable salt or solvate thereof.
93. The method of claim 92, wherein the disorder is atherosclerosis.
- 25 94. A method for preventing the coagulation of blood in vitro, in particular in the case of  
banked blood or biological samples containing factor Xa, characterized in that a compound of  
any one of claims 1-67 is added.
95. A method for inhibiting thrombus formation in a subject comprising administering to  
30 the subject in need thereof an effective amount of a compound of any one of claims 1-67 or a  
pharmaceutically acceptable salt or solvate thereof.
96. The method of claim 95, wherein the subject has a throembolism.

97. The method of claim 95, wherein the thromboembolism is a venous thromboembolism.

98. The method of claim 95, wherein the venous thromboembolism comprises pulmonary embolism.

99. The method of claim 98, wherein the venous thromboembolism comprises deep vein thrombosis.

100. The method of any one of claims 73-99, wherein the subject is a human.

101. A method of synthesizing a compound of any one of claims 1-67 or a pharmaceutically acceptable salt or solvate thereof.

102. A medical device containing a compound of any one of claims 1-67 or a pharmaceutically acceptable salt or solvate thereof.

103. The medical device according to claim 102, wherein the device is a stent.