

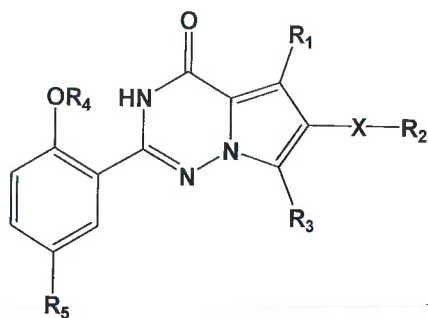
Sildenafil, Tadalafil and Vardenafil which have been described among others, for example, in WO 99/24433, WO 01/60825, EP 995'751 and WO 2011/075655.

Beside the success of the known PDE5 inhibitors, there is still a need for further and in particular more potent PDE5 inhibitors and their pharmaceutical compositions for use in the therapeutic treatment or prophylaxis of diseases associated with a disturbed cGMP balance. Moreover, and in general, there is still a need for compounds and their pharmaceutical compositions being beneficial for use in the therapeutic treatment or prophylaxis of diseases associated with a disturbed cGMP balance.

SUMMARY

We have surprisingly found that the compounds of the present disclosure are very potent and selective inhibitors of PDE5. Furthermore, we have surprisingly found that the compounds of the present disclosure can be tailored to become dual-pharmacology NO-releasing PDE5 inhibitors which are believed to release NO in addition to its PDE 5 inhibition in a more than additive fashion. These dual-pharmacology NO-releasing PDE5 inhibitors are believed to be highly beneficial for the treatment of diabetic patients. Moreover, we have surprisingly found that preferred compounds of the present disclosure show even a significantly higher PDE5 inhibition activity as compared to known PDE5 inhibitors such as sildenafil. As a consequence, the novel pyrrolo triazine compounds of the present disclosure are useful in the therapy and prophylaxis of diseases which are associated with a disturbed cGMP balance. Due to the potent and selective PDE5 inhibition exhibited by compounds of the present disclosure, cGMP levels are elevated, which in turn can give rise to beneficial vasodilatory, anti-vasospastic, anti-platelet, anti-neutrophil, natriuretic and diuretic activities. Furthermore, the tailoring of the inventive compounds to dual-pharmacology NO-releasing PDE5 inhibitors allows the release of nitric oxide for activating the soluble guanylate cyclase as well as the PDE 5 inhibition in a more than additive fashion. Thus, the compounds of the present disclosure have utility in variety of therapeutic areas where a disturbed cGMP balance occurred and/or PDE5 inhibition is thought to be beneficial. Some of the preferred therapeutic areas are wound healing, in particular chronic wound healing, diabetic foot, diabetic foot ulcer, leg ulcer, Raynaud's, male erectile dysfunction, female sexual dysfunction, Alzheimer's disease, diabetes, hair loss, skin aging, vascular aging, pulmonary artery hypertension and chronic heart failure.

Thus, the present disclosure provides for a compound of formula I



or pharmaceutically acceptable salt, solvate or hydrate thereof, wherein

- 5 R₁ is C₁-C₃alkyl optionally substituted with F, C₃-C₆cycloalkyl, C₁-C₃alkoxy;
X represents a bond or C₁-C₃alkylene optionally substituted with OH, ONO, ONO₂;
R₂ is H, OH, ONO, ONO₂, C(O)OH, C(O)OC₁-C₃alkyl, CHO, CN, C₁-C₃alkoxy, OC(O)H,
OC(O)-C₁-C₃alkyl, C(O)N(R₆)OR₇, OC₁-C₃alkylene-C(O)OH, OC₁-C₃alkylene-C(O)OC₁-
C₃alkyl, OC₁-C₃alkylene-C(O)N(R₆)OR₇, S(O₀₋₂)C₁-C₃alkyl, CR₈=N-OR₉, CR₈=N-NR₁₀R₁₁,
10 CR₈=NR₁₂ or CR₈=N-ONO₂;
R₃ is C₁-C₆alkyl optionally substituted with F, OH, ONO, ONO₂, C₁-C₃alkoxy, C₃-C₆cycloalkyl;
C₃-C₆cycloalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl;
R₄ is C₁-C₆alkyl optionally substituted with C₃-C₆cycloalkyl, C₁-C₆alkoxy, F, ONO, ONO₂; C₂-
C₆alkenyl, C₂-C₆alkynyl, C₃-C₆cycloalkyl;
15 R₅ is H, SO₂NR₁₃R₁₄, NHSO₂NR₁₃R₁₄;
R₆ is H or C₁-C₃alkyl;
R₇ is H, C₁-C₃alkyl, C₁-C₃alkoxy, C₁-C₃alkyl substituted with phenyl, benzyl or a heterocyclic
ring, wherein said phenyl, benzyl or said heterocyclic ring are independently optionally
substituted by C₁-C₃alkyl, F;
20 R₈ is H, CH₃ or C₂H₅;
R₉ is H, C₁-C₃alkyl optionally substituted with OH, ONO, ONO₂, CN, COOH, COOC₁-C₃alkyl,
C₁-C₃alkoxy, OC(O)H, OC(O)-C₁-C₃alkyl, C(O)N(R₆)OR₇, OC₁-C₃alkylene-C(O)OH, OC₁-
C₃alkylene-C(O)OC₁-C₃alkyl, OC₁-C₃alkylene-C(O)N(R₆)OR₇, S(O₀₋₂)C₁-C₃alkyl;
R₁₀ and R₁₁ are each independently H, C₁-C₃alkyl optionally substituted with OH, ONO, ONO₂,
25 CN, COOH, COOC₁-C₃, C₁-C₃alkoxy, OC(O)H, OC(O)-C₁-C₃alkyl, C(O)N(R₆)OR₇, OC₁-
C₃alkylene-C(O)OH, OC₁-C₃alkylene-C(O)OC₁-C₃alkyl, OC₁-C₃alkylene-C(O)N(R₆)OR₇, S(O₀₋₂)
C₁-C₃alkyl; or together with the nitrogen atom to which they are attached form a heterocyclic
ring, wherein preferably said heterocyclic ring is selected from aziridine, azetidine, pyrrolidine,

piperidine, morpholine, piperazine and homopiperazine, wherein said heterocyclic ring is optionally substituted with C₁-C₃ alkyl;

R₁₂ is C₁-C₃ alkyl optionally substituted with OH, ONO, ONO₂, CN, COOH, COOC₁-C₃alkyl, C₁-C₃alkoxy, OC(O)H, OC(O)-C₁-C₃alkyl, C(O)N(R₆)OR₇, OC₁-C₃alkylene-C(O)OH, OC₁-C₃alkylene-C(O)OC₁-C₃alkyl, OC₁-C₃alkylene-C(O)N(R₆)OR₇, S(O₀₋₂)C₁-C₃alkyl;

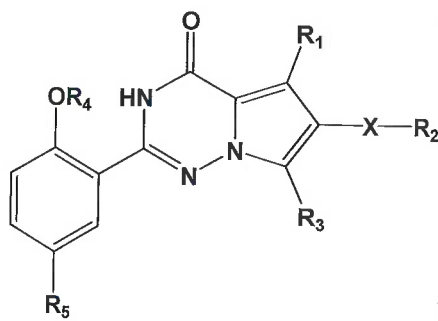
R₁₃ and R₁₄ are each independently H or C₁-C₆alkyl optionally substituted with F, OH, ONO, ONO₂, COOH, C₁-C₃alkoxy, C₃-C₆cycloalkyl; or together with the nitrogen atom to which they are attached form a heterocyclic ring, wherein preferably said heterocyclic ring is selected from aziridine, azetidine, pyrrolidine, piperidine, morpholine, piperazine, homopiperazine, 2,5-diazabicyclo[2,2,1]heptane and 3,7-diazabicyclo[3,3,0]octane, wherein said heterocyclic ring is optionally substituted with R₁₅;

R₁₅ is C₁-C₆alkyl optionally substituted with halogen, OH, ONO, ONO₂, C₁-C₃alkoxy, C₁-C₃haloalkoxy, COOR₁₆, NR₁₇R₁₈, C=NR₁₉, or with a tetrazole group which is optionally substituted with C₁-C₃alkyl; or a heteroaryl ring which is optionally substituted with F, wherein the at least one heteroatom of said heteroaryl ring is nitrogen;

R₁₆ is H, or C₁-C₄alkyl optionally substituted with F, OH, ONO, ONO₂, NR₁₇R₁₈, or with a heteroaryl ring, wherein the at least one heteroatom of said heteroaryl ring is nitrogen, and wherein preferably said heteroaryl ring is selected from pyrrolidine, piperidine, piperazine, morpholine, pyrrole, and imidazole, wherein nitrogen atom is directly bound to C₁-C₄ alkyl;

R₁₇ and R₁₈ are each independently H or C₁-C₄alkyl optionally substituted with ONO, ONO₂; R₁₉ is C₁-C₄alkyl optionally substituted with F, ONO, ONO₂; C₃-C₆cycloalkyl.

In a first aspect, the present disclosure provides for a compound of formula **I**



or pharmaceutically acceptable salt, solvate or hydrate thereof, wherein

- R₁ is C₁-C₃alkyl optionally substituted with F, C₃-C₆cycloalkyl, C₁-C₃alkoxy;
X-R₂ represents C₁-C₃alkylene substituted with ONO, ONO₂, CN, C(O)OH, C(O)OC₁-C₃alkyl, C(O)N(R₆)OR₇, CHO, OC(O)H, OC₁-C₃alkylene-C(O)OH, OC₁-C₃alkylene-C(O)N(R₆)OR₇, OC(O)-C₁-C₃alkyl, CR₈=N-OR₉; C(O)OC₁-C₃alkyl, CHO, C(O)N(R₆)OR₇, S(O₀₋₂)C₁-C₃alkyl,
5 CR₈=N-OR₉, CR₈=N-NR₁₀R₁₁, CR₈=NR₁₂ or CR₈=N-ONO₂;
R₃ is C₁-C₆alkyl optionally substituted with F, OH, ONO, ONO₂, C₁-C₃alkoxy, C₃-C₆cycloalkyl; C₃-C₆cycloalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl;
R₄ is C₁-C₆alkyl optionally substituted with C₃-C₆cycloalkyl, C₁-C₆alkoxy, F, ONO, ONO₂; C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₆cycloalkyl;
10 R₅ is SO₂NR₁₃R₁₄, NHSO₂NR₁₃R₁₄;
R₆ is H or C₁-C₃alkyl;
R₇ is H, C₁-C₃alkyl, C₁-C₃alkoxy, C₁-C₃alkyl substituted with phenyl, benzyl or a heterocyclic ring, wherein said phenyl, benzyl or said heterocyclic ring are independently optionally substituted by C₁-C₃alkyl, F;
15 R₈ is H, CH₃ or C₂H₅;
R₉ is H, C₁-C₃alkyl optionally substituted with OH, ONO, ONO₂, CN, COOH, COOC₁-C₃alkyl, C₁-C₃alkoxy, OC(O)H, OC(O)-C₁-C₃alkyl, C(O)N(R₆)OR₇, OC₁-C₃alkylene-C(O)OH, OC₁-C₃alkylene-C(O)OC₁-C₃alkyl, OC₁-C₃alkylene-C(O)N(R₆)OR₇, S(O₀₋₂)C₁-C₃alkyl;
R₁₀ and R₁₁ are each independently H, C₁-C₃alkyl optionally substituted with OH, ONO, ONO₂, CN, COOH, COOC₁-C₃, C₁-C₃alkoxy, OC(O)H, OC(O)-C₁-C₃alkyl, C(O)N(R₆)OR₇, OC₁-C₃alkylene-C(O)OH, OC₁-C₃alkylene-C(O)OC₁-C₃alkyl, OC₁-C₃alkylene-C(O)N(R₆)OR₇, S(O₀₋₂)C₁-C₃alkyl; or together with the nitrogen atom to which they are attached form a heterocyclic ring, wherein preferably said heterocyclic ring is selected from aziridine, azetidine, pyrrolidine, piperidine, morpholine, piperazine and homopiperazine, wherein said heterocyclic ring is
20 optionally substituted with C₁-C₃ alkyl;
R₁₂ is C₁-C₃ alkyl optionally substituted with OH, ONO, ONO₂, CN, COOH, COOC₁-C₃alkyl, C₁-C₃alkoxy, OC(O)H, OC(O)-C₁-C₃alkyl, C(O)N(R₆)OR₇, OC₁-C₃alkylene-C(O)OH, OC₁-C₃alkylene-C(O)OC₁-C₃alkyl, OC₁-C₃alkylene-C(O)N(R₆)OR₇, S(O₀₋₂)C₁-C₃alkyl;
R₁₃ and R₁₄ are each independently H or C₁-C₆alkyl optionally substituted with F, OH, ONO, ONO₂, COOH, C₁-C₃alkoxy, C₃-C₆cycloalkyl; or together with the nitrogen atom to which they are attached form a heterocyclic ring, wherein preferably said heterocyclic ring is selected from aziridine, azetidine, pyrrolidine, piperidine, morpholine, piperazine, homopiperazine, 2,5-diazabicyclo[2,2,1]heptane and 3,7-diazabicyclo[3,3,0]octane, wherein said heterocyclic ring is
30 optionally substituted with R₁₅;

R₁₅ is C₁-C₆alkyl optionally substituted with halogen, OH, ONO, ONO₂, C₁-C₃alkoxy, C₁-C₃haloalkoxy, COOR₁₆, NR₁₇R₁₈, C=NR₁₉, or with a tetrazole group which is optionally substituted with C₁-C₃alkyl; or a heteroaryl ring which is optionally substituted with F, wherein the at least one heteroatom of said heteroaryl ring is nitrogen;

5 R₁₆ is H, or C₁-C₄alkyl optionally substituted with F, OH, ONO, ONO₂, NR₁₇R₁₈, or with a heteroaryl ring, wherein the at least one heteroatom of said heteroaryl ring is nitrogen, and wherein preferably said heteroaryl ring is selected from pyrrolidine, piperidine, piperazine, morpholine, pyrrole, and imidazole, wherein nitrogen atom is directly bound to C₁-C₄ alkyl;

R₁₇ and R₁₈ are each independently H or C₁-C₄alkyl optionally substituted with ONO, ONO₂;

10 R₁₉ is C₁-C₄alkyl optionally substituted with F, ONO, ONO₂; C₃-C₆cycloalkyl.

In a further aspect, the present disclosure provides for a pharmaceutical composition comprising at least one of the inventive compound of formula I, or a pharmaceutically acceptable salt, solvate or hydrate thereof, and a pharmaceutically acceptable excipient, adjuvant, or carrier.

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In another aspect, the present disclosure provides for a compound of formula I, or a pharmaceutical composition, or a pharmaceutically acceptable salt, solvate or hydrate thereof, for use as a medicament. The present disclosure provides use of the compound of formula I of the present disclosure, or the pharmaceutical composition of the present disclosure, or a pharmaceutically acceptable salt, solvate or hydrate thereof in the manufacture of a medicament for treating a disease selected from the group consisting of wound healing, chronic wound healing, diabetic foot, diabetic foot ulcer, leg ulcer, Raynaud's disease, male erectile dysfunction, female sexual dysfunction, diabetes, hair loss, skin aging, vascular aging, pulmonary artery hypertension; stable, unstable and variant (Prinzmetal) angina; hypertension, pulmonary hypertension, chronic obstructive pulmonary disease,

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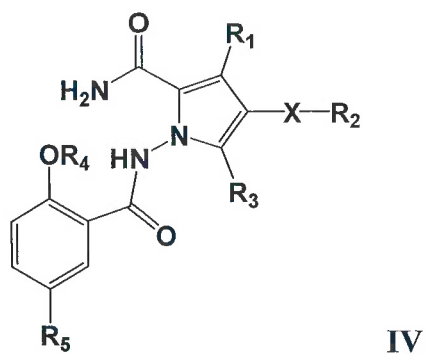
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congestive heart failure, renal failure, atherosclerosis, conditions of reduced blood vessel patency, peripheral vascular disease, vascular disorders, systemic sclerosis (SSc), scleroderma, morphea, inflammatory diseases, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, diabetic neuropathy, Idiopathic pulmonary fibrosis (IPF), peyronic's disease, glaucoma, or a disease characterized by disorders of gut motility like irritable bowel syndrome, liver fibrosis, Alzheimer's disease and chronic heart failure, wherein further preferably said disease is selected from wound healing, chronic wound healing, diabetic foot, diabetic foot ulcer, leg ulcer, diabetic neuropathy, peripheral vascular disease, vascular disorders, Raynaud's disease, systemic sclerosis (SSc), scleroderma, diabetes, pulmonary artery hypertension, male erectile dysfunction, and wherein again further preferably said disease is selected from wound healing, chronic wound healing, diabetic foot, diabetic foot ulcer, leg ulcer and diabetic neuropathy.

In another aspect, the present disclosure provides for use of the compound of formula I as defined herein, or the pharmaceutical composition as defined herein, or a pharmaceutically acceptable salt, solvate or hydrate thereof in the manufacture of a medicament for treating a disease selected from the group consisting of wound healing, chronic wound healing, diabetic foot, diabetic foot ulcer, leg ulcer, Raynaud's disease, male erectile dysfunction, female sexual dysfunction, vascular aging, pulmonary artery hypertension; stable, unstable and variant (Prinzmetal) angina; hypertension, pulmonary hypertension, chronic obstructive pulmonary disease, congestive heart failure, renal failure, atherosclerosis, conditions of reduced blood vessel patency, peripheral vascular disease, vascular disorders, systemic sclerosis (SSc), scleroderma, morphea, inflammatory diseases, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, diabetic neuropathy, Idiopathic pulmonary fibrosis (IPF), peyronic's disease, glaucoma or a disease characterized by disorders of gut motility like irritable bowel syndrome, liver fibrosis, Alzheimer's disease and chronic heart failure, wherein preferably said disease is selected from wound healing, chronic wound healing, diabetic foot, diabetic foot ulcer, leg ulcer, diabetic neuropathy, peripheral vascular disease, vascular disorders such as Raynaud's disease, systemic sclerosis (SSc), scleroderma, pulmonary artery hypertension, male erectile dysfunction, and wherein again further preferably said disease is selected from wound healing, chronic wound healing, diabetic foot, diabetic foot ulcer, leg ulcer and diabetic neuropathy.

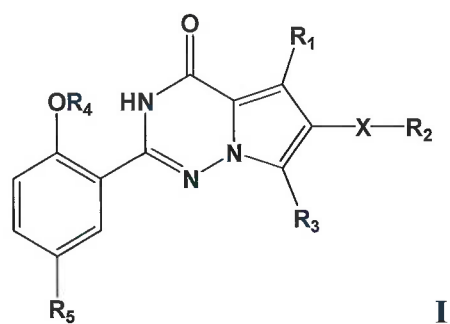
In another aspect, the present disclosure provides for use of the compound of formula I as defined herein, or the pharmaceutical composition as defined herein, or a pharmaceutically acceptable salt, solvate or hydrate thereof for treating hair loss or skin aging.

In again another aspect, the present disclosure provides for a compound of formula **IV**



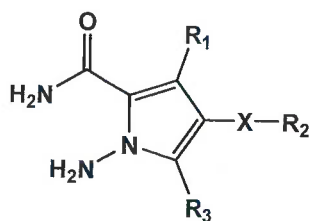
wherein X, R₁, R₂, R₃, R₄, R₅ are defined as for the compound of formula **I**.

- 5 In again another aspect, the present disclosure provides for a process for the preparation of a compound of formula **I**,

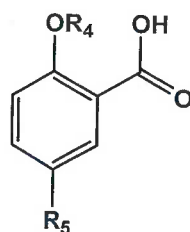


wherein said process comprises:

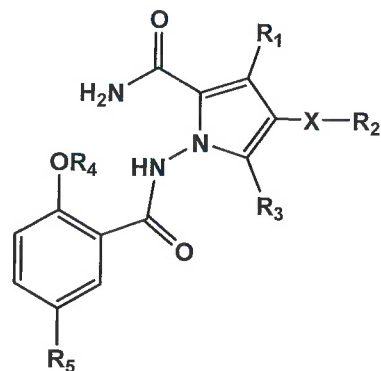
- (a) reaction of a compound of formula **II** with a benzoic acid derivative of formula **III** in
an aprotic or a protic solvent to generate a compound of formula **IV**



II



III



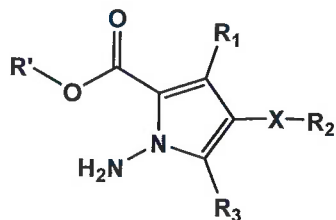
IV

(b) cyclization of said compound of formula **IV** to yield compound of formula **I**,

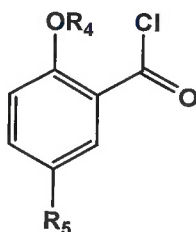
5 wherein X, R₁, R₂, R₃, R₄, and R₅ are defined as for the compound of formula **I**.

In again another aspect, the present disclosure provides for a process for the preparation of a compound of formula **I**, wherein said process comprises

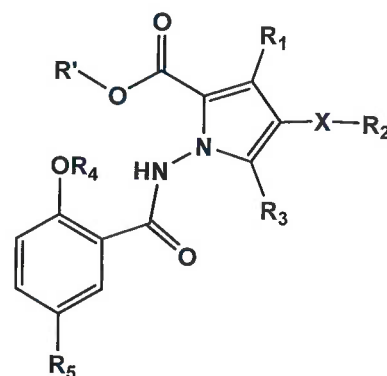
(a) reaction of a compound of formula **VI** with a benzoyl chloride derivative of formula **VIA** to generate a compound of formula **VII**



VI

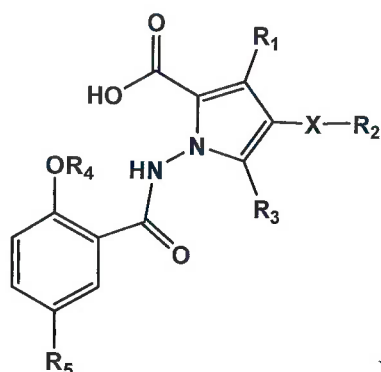


VIA



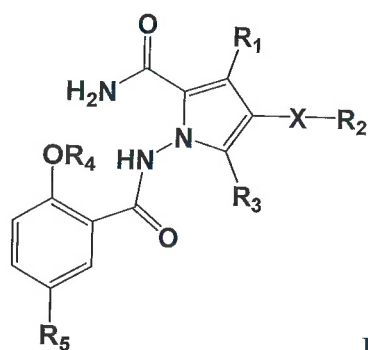
VII

(b) hydrolysis of the ester compound of formula **VII** to an acid derivative of formula **VIII**



VIII

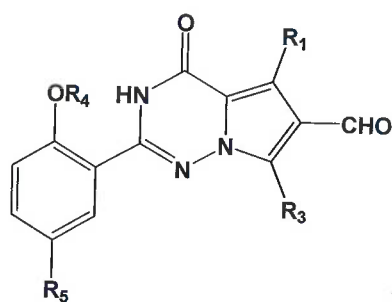
(c) amination of said compound of formula **VIII** to yield a compound of formula **IV**



(d) cyclization of said compound of formula **IV** to yield compound of formula **I**,

wherein X, R₁, R₂, R₃, R₄, and R₅ are defined as for the compound of formula **I**; and wherein R' is C₁-C₄ alkyl, benzyl, 4-alkoxybenzyl.

- 5 The present disclosure provides for a process for the preparation of a compound of formula **I**, wherein said process comprises conversion of compound of formula **IA** to yield compound of formula **I**



- 10 wherein X, R₁, R₂, R₃, R₄, and R₅ are defined as for the compound of formula **I** as defined herein.

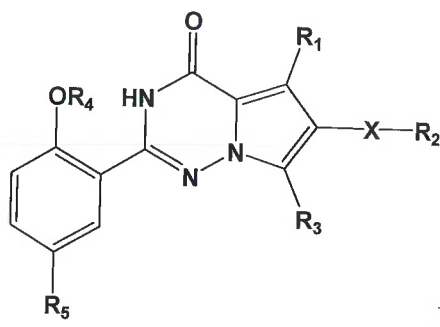
Further aspects and embodiments of the present disclosure will be become apparent as this description continues.

15 DESCRIPTION OF THE FIGURES

FIG. 1: Concentration dependent measurements of cyclic guanosine 3'-5'-monophosphate (cGMP) in human pulmonary artery smooth muscle cells (hPASMC) incubated in presence of the compounds of the inventions or the reference PDE5 inhibitor sildenafil.

CLAIMS:

1. A compound of formula I



or pharmaceutically acceptable salt, solvate or hydrate thereof, wherein

R₁ is C₁-C₃alkyl optionally substituted with F, C₃-C₆cycloalkyl, C₁-C₃alkoxy;

X-R₂ represents C₁-C₃alkylene substituted with ONO, ONO₂, CN, C(O)OH, C(O)OC₁-C₃alkyl, C(O)N(R₆)OR₇, CHO, OC(O)H, OC₁-C₃alkylene-C(O)OH, OC₁-C₃alkylene-C(O)N(R₆)OR₇, OC(O)-C₁-C₃alkyl, CR₈=N-OR₉; C(O)OC₁-C₃alkyl, CHO, C(O)N(R₆)OR₇, S(O₀₋₂)C₁-C₃alkyl, CR₈=N-OR₉, CR₈=N-NR₁₀R₁₁, CR₈=NR₁₂ or CR₈=N-ONO₂;

R₃ is C₁-C₆alkyl optionally substituted with F, OH, ONO, ONO₂, C₁-C₃alkoxy, C₃-C₆cycloalkyl; C₃-C₆cycloalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl;

R₄ is C₁-C₆alkyl optionally substituted with C₃-C₆cycloalkyl, C₁-C₆alkoxy, F, ONO, ONO₂; C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₆cycloalkyl;

R₅ is SO₂NR₁₃R₁₄, NHSO₂NR₁₃R₁₄;

R₆ is H or C₁-C₃alkyl;

R₇ is H, C₁-C₃alkyl, C₁-C₃alkoxy, C₁-C₃alkyl substituted with phenyl, benzyl or a heterocyclic ring, wherein said phenyl, benzyl or said heterocyclic ring are independently optionally substituted by C₁-C₃alkyl, F;

R₈ is H, CH₃ or C₂H₅;

R₉ is H, C₁-C₃alkyl optionally substituted with OH, ONO, ONO₂, CN, COOH, COOC₁-C₃alkyl, C₁-C₃alkoxy, OC(O)H, OC(O)-C₁-C₃alkyl, C(O)N(R₆)OR₇, OC₁-C₃alkylene-C(O)OH, OC₁-C₃alkylene-C(O)OC₁-C₃alkyl, OC₁-C₃alkylene-C(O)N(R₆)OR₇, S(O₀₋₂)C₁-C₃alkyl;

R_{10} and R_{11} are each independently H, C_1 - C_3 alkyl optionally substituted with OH, ONO, ONO_2 , CN, COOH, $COOC_1$ - C_3 , C_1 - C_3 alkoxy, $OC(O)H$, $OC(O)$ - C_1 - C_3 alkyl, $C(O)N(R_6)OR_7$, OC_1 - C_3 alkylene- $C(O)OH$, OC_1 - C_3 alkylene- $C(O)OC_1$ - C_3 alkyl, OC_1 - C_3 alkylene- $C(O)N(R_6)OR_7$, $S(O_0$.

5. The compound according to any one of claims 1 to 4, or pharmaceutically acceptable salt, solvate or hydrate thereof, wherein

R₁₃ and R₁₄ together with the nitrogen atom to which they are attached form a heterocyclic ring, wherein said heterocyclic ring is selected from aziridine, azetidine, pyrrolidine, piperidine, morpholine, piperazine, homopiperazine, 2,5-diazabicyclo-[2,2,1]heptane and 3,7-diazabicyclo[3,3,0]octane, wherein said heterocyclic ring is optionally substituted with R₁₅;

R₁₅ is C₁-C₄alkyl optionally substituted with halogen, OH, ONO, ONO₂, C₁-C₃alkoxy, C₁-C₃haloalkoxy, COOR₁₆, NR₁₇R₁₈, C=NR₁₉;

10 R₁₆ is H, or C₁-C₄alkyl optionally substituted with F, OH, ONO, ONO₂;

R₁₇ and R₁₈ are each independently H or C₁-C₄alkyl optionally substituted with ONO, ONO₂;

R₁₉ is C₁-C₄alkyl optionally substituted with F, ONO, ONO₂.

6. The compound according to any one of claims 1 to 5, or pharmaceutically acceptable salt, solvate or hydrate thereof, wherein

X-R₂ represents C₁-C₃alkylene substituted with CN, C(O)OH, C(O)OC₁-C₃alkyl, C(O)N(R₆)OR₇, CHO, OC(O)H, OC₁-C₃alkylene-C(O)OH, OC₁-C₃alkylene-C(O)N(R₆)OR₇, OC(O)-C₁-C₃alkyl, CR₈=N-OR₉; C(O)OC₁-C₃alkyl, CHO, C(O)N(R₆)OR₇, S(O₀₋₂)C₁-C₃alkyl, CR₈=N-OR₉, CR₈=N-NR₁₀R₁₁, CR₈=NR₁₂ or CR₈=N-ONO₂, wherein preferably said R₈ is H or

20 CH₃, and again further preferably wherein said R₆ is H or CH₃.

7. The compound according to any one of claims 1 to 6, or pharmaceutically acceptable salt, solvate or hydrate thereof, wherein

X-R₂ represents C₁-C₃alkylene substituted with CN, C(O)OH, C(O)OC₁-C₃alkyl, C(O)N(R₆)OR₇, CHO, OC(O)H, OC₁-C₃alkylene-C(O)OH, OC₁-C₃alkylene-C(O)N(R₆)OR₇, OC(O)-C₁-C₃alkyl, CR₈=N-OR₉; C(O)OC₁-C₃alkyl, CHO, C(O)N(R₆)OR₇, CR₈=N-OR₉.

8. The compound according to any one of claims 1 to 7, or pharmaceutically acceptable salt, solvate or hydrate thereof, wherein X-R₂ represents CR₈=N-OR₉, wherein said R₈ is H or CH₃,

30 and wherein said R₉ is H or C₁-C₃ alkyl optionally substituted with OH.

9. The compound according to any one of claims 1 to 8, or pharmaceutically acceptable salt, solvate or hydrate thereof, wherein X-R₂ represents (*E*)-CR₈=N-OR₉, wherein said R₈ is H or CH₃, and wherein said R₉ is H or C₁-C₃ alkyl optionally substituted with OH.
- 5 10. The compound according to claim 1 or pharmaceutically acceptable salt, solvate or hydrate thereof, wherein said compound is selected from
- (*E*)-2-(2-ethoxy-5-((4-methylpiperazin-1-yl)sulfonyl)phenyl)-5-methyl-4-oxo-7-propyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazine-6-carbaldehyde oxime (**1a**);
- (2-(2-ethoxy-5-((4-methylpiperazin-1-yl)sulfonyl)phenyl)-5-methyl-4-oxo-7-propyl-3,4-
- 10 dihydropyrrolo[2,1-*f*][1,2,4]triazin-6-yl)methyl acetate (**1c**);
- 2-(2-ethoxy-5-((4-methylpiperazin-1-yl)sulfonyl)phenyl)-5-methyl-4-oxo-7-propyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylic acid (**1d**);
- N-(benzyloxy)-2-(2-ethoxy-5-((4-methylpiperazin-1-yl)sulfonyl)phenyl)-5-methyl-4-oxo-7-propyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide (**1e**);

- Methyl 2-(2-ethoxy-5-((4-methylpiperazin-1-yl)sulfonyl)phenyl)-5-methyl-4-oxo-7-propyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazine-6-carboxylate (**1f**);
- 2-(2-ethoxy-5-((4-methylpiperazin-1-yl)sulfonyl)phenyl)-N-hydroxy-5-methyl-4-oxo-7-propyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazine-6-carboxamide (**1g**);
- 5 2-((2-(2-ethoxy-5-((4-methylpiperazin-1-yl)sulfonyl)phenyl)-5-methyl-4-oxo-7-propyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazin-6-yl)methoxy)acetic acid (**1h**);
- 2-((2-(2-ethoxy-5-((4-methylpiperazin-1-yl)sulfonyl)phenyl)-5-methyl-4-oxo-7-propyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazin-6-yl)methoxy)-N-hydroxy-N-methylacetamide (**1i**);
- 10 2-(2-ethoxy-5-((4-methylpiperazin-1-yl)sulfonyl)phenyl)-5-methyl-4-oxo-7-propyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazine-6-carbaldehyde (**1j**);
- 5-methyl-2-(5-((4-methylpiperazin-1-yl)sulfonyl)-2-propoxyphenyl)-4-oxo-7-propyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazine-6-carbaldehyde (**1l**);
- 2-(5-((4-(2-hydroxyethyl)piperazin-1-yl)sulfonyl)-2-propoxyphenyl)-5-methyl-4-oxo-7-propyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazine-6-carbaldehyde (**1m**);
- 15 (*E*)-5-methyl-2-(5-((4-methylpiperazin-1-yl)sulfonyl)-2-propoxyphenyl)-4-oxo-7-propyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazine-6-carbaldehyde O-methyl oxime (**1o**);
- 2-(5-((4-(2-hydroxyethyl)piperidin-1-yl)sulfonyl)-2-propoxyphenyl)-5-methyl-4-oxo-7-propyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazine-6-carbaldehyde (**1p**);
- 20 2-(1-((3-(6-formyl-5-methyl-4-oxo-7-propyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazin-2-yl)-4-propoxyphenyl)sulfonyl)piperidin-4-yl)ethyl nitrate (**1q**);
- (*E*)-2-(5-((4-(2-hydroxyethyl)piperidin-1-yl)sulfonyl)-2-propoxyphenyl)-5-methyl-4-oxo-7-propyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazine-6-carbaldehyde oxime (**1r**);
- ethyl-3-(2-(2-ethoxy-5-((4-methylpiperazin-1-yl)sulfonyl)phenyl)-5-methyl-4-oxo-7-propyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazin-6-yl)-3-hydroxypropanoate (**1s**);
- 25 3-(2-(2-ethoxy-5-((4-methylpiperazin-1-yl)sulfonyl)phenyl)-5-methyl-4-oxo-7-propyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazin-6-yl)-N,3-dihydroxypropanamide (**1t**);
- 3-(2-(2-ethoxy-5-((4-methylpiperazin-1-yl)sulfonyl)phenyl)-5-methyl-4-oxo-7-propyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazin-6-yl)-3-hydroxypropanenitrile (**1u**);
- (*E*)-2-(1-((3-(6-((hydroxyimino)methyl)-5-methyl-4-oxo-7-propyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazin-2-yl)-4-propoxyphenyl)sulfonyl)piperidin-4-yl)ethyl nitrate (**1v**);
- 30

- 2-(2-ethoxy-5-((4-(2-hydroxyethyl)piperazin-1-yl)sulfonyl)phenyl)-5-methyl-4-oxo-7-propyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazine-6-carbaldehyde(**1w**);
- (*E*)-2-(2-ethoxy-5-((4-(2-hydroxyethyl)piperazin-1-yl)sulfonyl)phenyl)-5-methyl-4-oxo-7-propyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazine-6-carbaldehyde oxime (**1x**);
- 5 2-(2-ethoxy-5-((4-(2-hydroxyethyl)piperazin-1-yl)sulfonyl)phenyl)-5-methyl-4-oxo-7-propyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazine-6-carbaldehyde O-methyloxime (**1y**);
- (*E*)-2-(2-ethoxy-5-((4-(2-hydroxyethyl)piperazin-1-yl)sulfonyl)phenyl)-5-methyl-4-oxo-7-propyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazine-6-carbaldehyde O-(2-hydroxyethyl) oxime (**1z**);
- 10 2-(2-ethoxy-5-((4-(2-hydroxyethyl)piperazin-1-yl)sulfonyl)phenyl)-5-ethyl-4-oxo-7-propyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazine-6-carbaldehyde(**1aa**);
- (*E*)-2-(2-ethoxy-5-((4-(2-hydroxyethyl)piperazin-1-yl)sulfonyl)phenyl)-5-ethyl-4-oxo-7-propyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazine-6-carbaldehyde oxime (**1ab**);
- (*E*)-2-(2-ethoxy-5-((4-(2-hydroxyethyl)piperazin-1-yl)sulfonyl)phenyl)-5-ethyl-4-oxo-7-propyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazine-6-carbaldehyde O-methyl oxime (**1ac**);
- 15 (*E*)-2-(2-ethoxy-5-((4-(2-hydroxyethyl)piperazin-1-yl)sulfonyl)phenyl)-5-ethyl-4-oxo-7-propyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazine-6-carbaldehyde O-(2-hydroxyethyl) oxime (**1ad**);
- 2-(4-((4-ethoxy-3-(6-formyl-5-methyl-4-oxo-7-propyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazin-2-yl)phenyl)sulfonyl)piperazin-1-yl)ethyl nitrate (**1ae**);
- (*E*)-2-(4-((4-ethoxy-3-(6-((hydroxyimino)methyl)-5-methyl-4-oxo-7-propyl-3,4-
- 20 dihydropyrrolo[2,1-f][1,2,4]triazin-2-yl)phenyl)sulfonyl)piperazin-1-yl)ethyl nitrate (**1af**);
- 2-(4-((4-ethoxy-3-(5-ethyl-6-formyl-4-oxo-7-propyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazin-2-yl)phenyl)sulfonyl)piperazin-1-yl)ethyl nitrate (**1ag**);
- (*E*)-2-(4-((4-ethoxy-3-(5-ethyl-6-((hydroxyimino)methyl)-4-oxo-7-propyl-3,4-
- dihydropyrrolo[2,1-f][1,2,4]triazin-2-yl)phenyl)sulfonyl)piperazin-1-yl)ethyl nitrate (**1ah**);
- 25 (*E*)-2-(4-((4-ethoxy-3-(6-((methoxyimino)methyl)-5-methyl-4-oxo-7-propyl-3,4-
- dihydropyrrolo[2,1-f][1,2,4]triazin-2-yl)phenyl)sulfonyl)piperazin-1-yl)ethyl nitrate (**1ai**);
- (*E*)-2-(4-((4-ethoxy-3-(6-(((2-hydroxyethoxy)imino)methyl)-5-methyl-4-oxo-7-propyl-3,4-
- dihydropyrrolo[2,1-f][1,2,4]triazin-2-yl)phenyl)sulfonyl)piperazin-1-yl)ethyl nitrate (**1ak**);
- (*E*)-2-(2-ethoxy-5-((4-(2-hydroxyethyl)piperidin-1-yl)sulfonyl)phenyl)-5-methyl-4-oxo-7-
- 30 propyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazine-6-carbaldehyde oxime (**1al**);
- (*E*)-2-(1-((4-ethoxy-3-(6-((hydroxyimino)methyl)-5-methyl-4-oxo-7-propyl-3,4-
- dihydropyrrolo[2,1-f][1,2,4]triazin-2-yl)phenyl)sulfonyl)piperidin-4-yl)ethyl nitrate (**1am**);
- (*E*)-2-(2-ethoxy-5-((4-(3-hydroxypropyl)piperazin-1-yl)sulfonyl)phenyl)-5-methyl-4-oxo-7-
- propyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazine-6-carbaldehyde oxime (**1an**);

(*E*)-3-(4-((4-ethoxy-3-(6-((hydroxyimino)methyl)-5-methyl-4-oxo-7-propyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)phenyl)sulfonyl)piperazin-1-yl)propyl nitrate (**1ao**); and

5 (*Z*)-2-(1-((3-(6-((hydroxyimino)methyl)-5-methyl-4-oxo-7-propyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)-4-propoxyphenyl)sulfonyl)piperidin-4-yl)ethyl nitrate (**1aq**).

11. The compound according to claim 1 or pharmaceutically acceptable salt, solvate or hydrate thereof, wherein said compound is selected from

10 (*E*)-2-(5-((4-(2-hydroxyethyl)piperidin-1-yl)sulfonyl)-2-propoxyphenyl)-5-methyl-4-oxo-7-propyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazine-6-carbaldehyde oxime (**1r**); and
(*E*)-2-(1-((3-(6-((hydroxyimino)methyl)-5-methyl-4-oxo-7-propyl-3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazin-2-yl)-4-propoxyphenyl)sulfonyl)piperidin-4-yl)ethyl nitrate (**1v**).

12. A pharmaceutical composition comprising at least one of the compound of formula **I** of
15 any one of the claims 1 to 11, or a pharmaceutically acceptable salt, solvate or hydrate thereof, and a pharmaceutically acceptable excipient, adjuvant, or carrier.

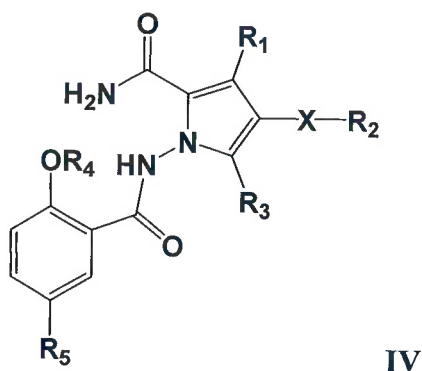
13. The compound of formula **I** of any one of the claims 1 to 11, or the pharmaceutical
20 composition of claim 12, or a pharmaceutically acceptable salt, solvate or hydrate thereof, for use as a medicament.

14. Use of the compound of formula **I** of any one of the claims 1 to 11, or the pharmaceutical
composition of claim 12, or a pharmaceutically acceptable salt, solvate or hydrate thereof in the
25 manufacture of a medicament for treating a disease selected from the group consisting of wound healing, chronic wound healing, diabetic foot, diabetic foot ulcer, leg ulcer, Raynaud's disease, male erectile dysfunction, female sexual dysfunction, vascular aging, pulmonary artery hypertension; stable, unstable and variant (Prinzmetal) angina; hypertension, pulmonary hypertension, chronic obstructive pulmonary disease, congestive heart failure, renal failure, atherosclerosis, conditions of reduced blood vessel patency, peripheral vascular disease, vascular
30 disorders, systemic sclerosis (SSc), scleroderma, morphea, inflammatory diseases, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, diabetic neuropathy, Idiopathic pulmonary fibrosis (IPF), peyronic's disease, glaucoma or a disease characterized by disorders of gut motility like irritable bowel syndrome, liver fibrosis, Alzheimer's disease and chronic heart failure, wherein

preferably said disease is selected from wound healing, chronic wound healing, diabetic foot, diabetic foot ulcer, leg ulcer, diabetic neuropathy, peripheral vascular disease, vascular disorders such as Raynaud's disease, systemic sclerosis (SSc), scleroderma, pulmonary artery hypertension, male erectile dysfunction, and wherein again further preferably said disease is selected from wound healing, chronic wound healing, diabetic foot, diabetic foot ulcer, leg ulcer and diabetic neuropathy.

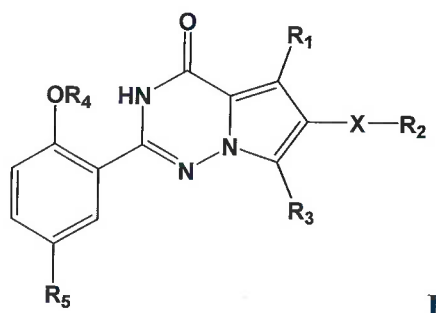
15. Use of the compound of formula **I** of any one of the claims 1 to 11, or the pharmaceutical composition of claim 12, or a pharmaceutically acceptable salt, solvate or hydrate thereof for treating hair loss or skin aging.

16. A compound of formula **IV**



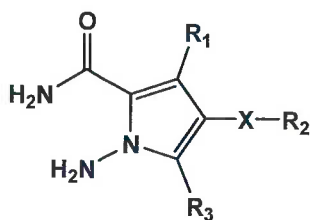
wherein X, R₁, R₂, R₃, R₄, R₅ are defined as for the compound of formula **I** in any one of the claims 1 to 8.

17. A process for the preparation of a compound of formula **I** of any one of the claims 1 to 11,

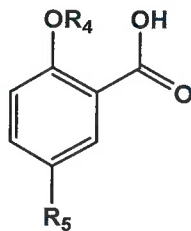


wherein said process comprises:

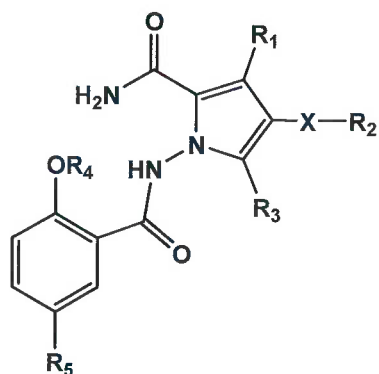
- (a) reaction of a compound of formula **II** with a benzoic acid derivative of formula **III** in an aprotic or a protic solvent to generate a compound of formula **IV**



II



III

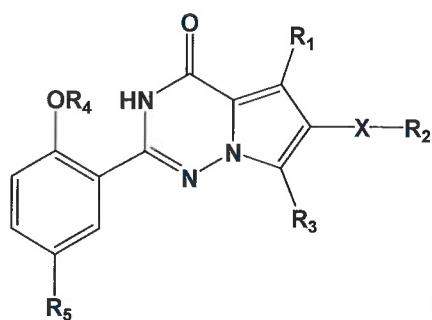


IV

(b) cyclization of said compound of formula **IV** to yield compound of formula **I**,

wherein X, R₁, R₂, R₃, R₄, and R₅ are defined as for the compound of formula **I** in any one of the claims 1 to 11.

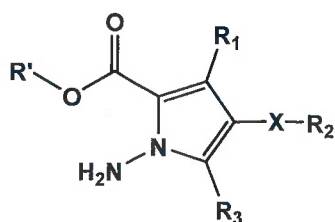
18. A process for the preparation of a compound of formula **I** of any one of the claims 1 to 11,



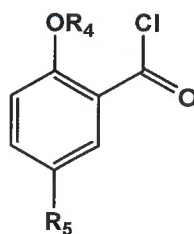
I

wherein said process comprises

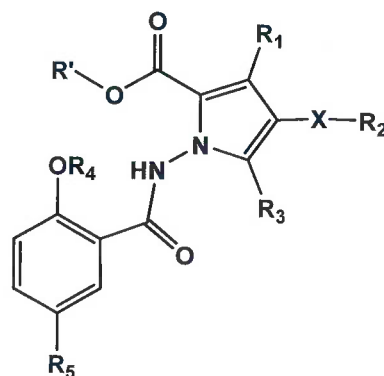
(a) reaction of a compound of formula **VI** with a benzoyl chloride derivative of formula **VIA** to generate a compound of formula **VII**



VI

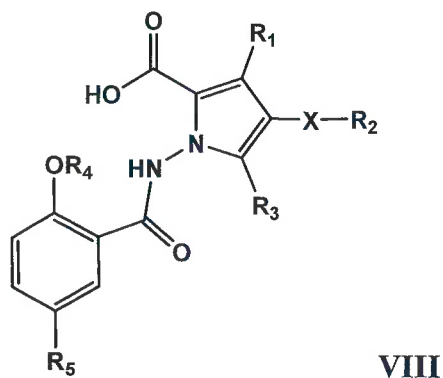


VIA

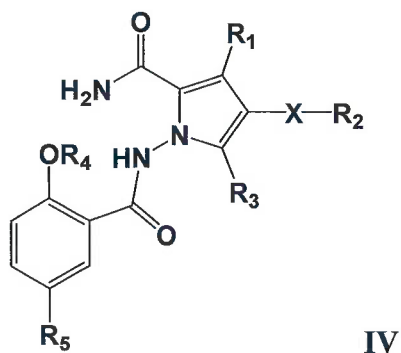


VII

(b) hydrolysis of the ester compound of formula **VII** to an acid derivative of formula **VIII**



(c) amination of said compound of formula **VIII** to yield a compound of formula **IV**



5 (d) cyclization of said compound of formula **IV** to yield compound of formula **I**,

wherein X, R₁, R₂, R₃, R₄, and R₅ are defined as for the compound of formula **I** in any one of the claims 1 to 8; and

wherein R' is C₁-C₄ alkyl, benzyl, 4-alkoxybenzyl.