R_{13} and R_{14} are each independently H or C_1-C_6alkyl optionally substituted with F, OH, ONO, ONO_2, COOH, C_1-C_3alkoxy, C_3-C_6cycloalkyl; 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, pyrollidine, 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 R_{15};

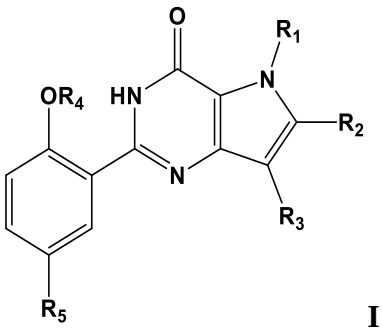
R_{15} is C_1-C_6alkyl optionally substituted with halogen, OH, ONO, ONO_2, C_1-C_3alkoxy, C_1-C_3haloalkoxy, $COOR_{16}$, $NR_{17}R_{18}$, $C=NR_{19}$, or with a tetrazole moiety which is optionally substituted with C_1-C_3alkyl; or a heteroaryl ring which is optionally substituted with F, wherein the at least one heteroatom of said heteroaryl ring is nitrogen;

R_{16} is H, or C_1-C_4alkyl optionally substituted with F, OH, ONO, ONO_2, $NR_{17}R_{18}$, 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 C_1-C_4 alkyl;

R_{17} and R_{18} are each independently H or C_1-C_4alkyl optionally substituted with ONO, ONO_2;

R_{19} is C_1-C_4alkyl optionally substituted with F, ONO, ONO_2; C_3-C_6cycloalkyl.

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



I

or pharmaceutically acceptable salt, solvate or hydrate thereof, wherein

R_5 comprises at least one ONO_2 or ONO moiety;

R_1 is C_1-C_3alkyl optionally substituted with F;

R_2 is H, C_1-C_3alkyl optionally substituted with OH, CHO, CN, CR_8=N-OR_9;

R_3 is C_1-C_4alkyl optionally substituted with F, C_1-C_3alkoxy, C_3-cycloalkyl;

R_4 is C_1-C_6alkyl optionally substituted with C_1-C_6alkoxy;

R_5 is $SO_2NR_{13}R_{14}$;

R_8 is H, CH_3 or C_2H_5;

R_9 is H, C_1-C_3alkyl optionally substituted with OH;

R_{13} and R_{14} are together with the nitrogen atom to which they are attached form a heterocyclic ring, wherein said heterocyclic ring is selected from piperidine and piperazine, wherein said heterocyclic ring is substituted with at least one R_{15}; and

R_{15} is independently selected from C_1-C_6alkyl optionally substituted with OH, ONO, ONO_2.

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

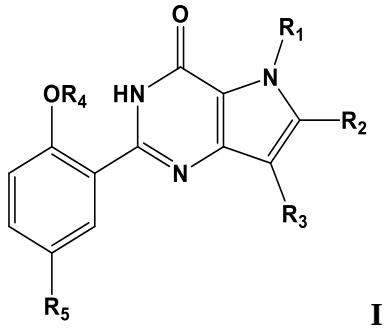
The present disclosure provides for a compound of formula **I**, or a pharmaceutical composition, or a pharmaceutically acceptable salt, solvate or hydrate thereof, for use as a medicament.

In another aspect, the present disclosure provides for the compound of formula **I** as described herein or the pharmaceutical composition as described herein, for use as a medicament.

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 in a method of treating or preventing a disease alleviated by inhibition of PDE5 in a human or in a non-human mammal, preferably in a human, wherein preferably said disease is selected from wound healing, chronic wound healing, diabetic foot, diabetic foot ulcer, leg ulcer, Raynaud's disease, male erectile dysfunction, priapism, female sexual dysfunction, hair loss, skin aging, vascular aging, pulmonary artery hypertension; livedoid vasculopathy, thromboangitis obliterans, chronic anal fissure, skin fibrosis, 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),

CLAIMS:

1. A compound of formula **I**



I

or pharmaceutically acceptable salt, solvate or hydrate thereof, wherein

R_5 comprises at least one ONO_2 or ONO moiety;

R_1 is C_1-C_3alkyl optionally substituted with F;

R_2 is H, C_1-C_3alkyl optionally substituted with OH, CHO, CN, CR_8=N-OR_9;

R_3 is C_1-C_4alkyl optionally substituted with F, C_1-C_3alkoxy, C_3-cycloalkyl;

R_4 is C_1-C_6alkyl optionally substituted with C_1-C_6alkoxy;

R_5 is $SO_2NR_{13}R_{14}$;

R_8 is H, CH_3 or C_2H_5;

R_9 is H, C_1-C_3alkyl optionally substituted with OH;

R_{13} and R_{14} are together with the nitrogen atom to which they are attached form a heterocyclic ring, wherein said heterocyclic ring is selected from piperidine and piperazine, wherein said heterocyclic ring is substituted with at least one R_{15}; and

R_{15} is independently selected from C_1-C_6alkyl optionally substituted with OH, ONO, ONO_2

.

2. The compound according to claim 1, wherein R_1 is C_1-C_3alkyl.

3. The compound according to claim 1 or claim 2, wherein R_2 is H.

4. The compound according to claim 1 or claim 2, wherein R_2 is CHO.

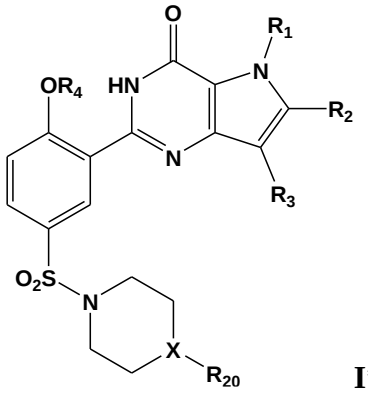
5. The compound according to claim 1 or claim 2, wherein R_2 is CH=N-OR_9, and wherein R_9 is H.

6. The compound according to any one of the claims 1 to 5, wherein R_3 is C_1-C_4alkyl.

7. The compound according to any one of the claims 1 to 6, wherein R_4 is C_1-C_4alkyl optionally substituted with C_1-C_3alkoxy.

8. The compound according to any one of claims 1 to 7, wherein R_{15} is C_1-C_4alkyl optionally substituted with OH, ONO, ONO_2.

9. The compound according to any one of claims 1 to 7, wherein said compound of formula **I** is a compound of formula **I*,** or pharmaceutically acceptable salt, solvate or hydrate thereof, wherein R_{20} comprises at least one ONO_2 or ONO moiety;



I*

wherein R_1, R_2, R_3, and R_4, are as defined in claims 1 to 7; and wherein

X is CR_{21} or N;

R_{20} is C_1-C_4alkyl optionally substituted with OH, ONO, ONO_2;

R_{21} is H or C_1-C_4alkyl optionally substituted with OH, ONO, ONO_{28}; and

.

10. The compound according to claim 9, wherein

R_1 is C_1-C_3alkyl;

R_2 is H, C_1-C_3alkyl optionally substituted with OH; CHO, CN, CR_8=N-OR_9; R_9 is H, C_1-C_3alkyl optionally substituted with OH;

R_3 is C_1-C_4alkyl;

R_4 is C_1-C_4alkyl optionally substituted with C_1-C_3alkoxy, F, ONO, ONO_2;

R_{20} is C_1-C_4alkyl optionally substituted with OH, ONO, ONO_2; and

R_{21} is H or C_1-C_4alkyl optionally substituted with halogen, OH, ONO, ONO_2.

11. The compound according to claim 9, wherein

R_1 is C_1-C_2alkyl;

R_2 is H, C_1-C_3alkyl optionally substituted with OH; CHO, CR_8=N-OR_9; R_9 is H, C_1-C_3alkyl optionally substituted with OH;

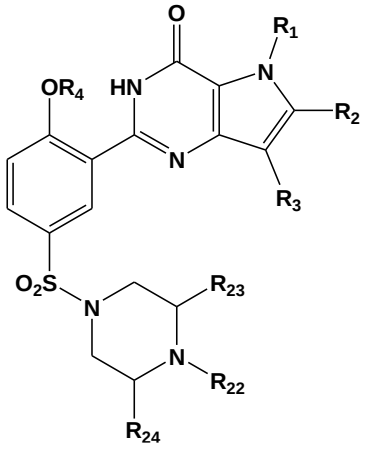
R_3 is C_2-C_3alkyl;

R_4 is C_2-C_3alkyl;

R_{20} is C_1-C_3alkyl substituted with one, two or three substituents selected from OH, ONO and ONO_2; and

R_{21} is H or C_1-C_3alkyl substituted with one or two substituents selected from OH, ONO and ONO_2.

12. The compound according to any one of claims 1 to 7, wherein said compound of formula **I** is a compound of formula **II**,** or pharmaceutically acceptable salt, solvate or hydrate thereof, wherein at least one of R_{22}, R_{23} or R_{24} independently of each other comprises at least one ONO_2 or ONO moiety;



II*

wherein R_1, R_2, R_3, and R_4, are as defined in claims 2 to 11; and wherein

R_{22} is H or C_1-C_4alkyl optionally substituted with OH, ONO, ONO_2; and

R_{23} and R_{24} are each independently C_1-C_4alkyl optionally substituted with OH, ONO, ONO_2.

13. The compound according to claim 12, wherein said

R_{22} is C_1-C_2alkyl, preferably methyl;

R_{23} and R_{24} are each independently C_1-C_3alkyl substituted with OH, ONO, ONO_2, wherein preferably R_{23} and R_{24} are each independently C_1-C_3alkyl substituted with ONO, ONO_2.

14. The compound according to claim 1, wherein said compound is selected from

(E)-2-(4-((3-(5-ethyl-6-((hydroxyimino) methyl)-4-oxo-7-propyl-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-2-yl)-4-propoxyphenyl)sulfonyl)piperazin-1-yl)ethyl nitrate (**1a**);
2-(1-((3-(5-ethyl-4-oxo-7-propyl-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-2-yl)-4-propoxyphenyl)sulfonyl)piperidin-4-yl)ethyl nitrate (**1b**);
(E)-2-(1-((3-(5-ethyl-6-((hydroxyimino) methyl)-4-oxo-7-propyl-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-2-yl)-4-propoxyphenyl)sulfonyl)piperidin-4-yl)ethyl nitrate (**1c**);
3-(1-((3-(5-ethyl-4-oxo-7-propyl-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-2-yl)-4-propoxyphenyl)sulfonyl)piperidin-4-yl)propyl nitrate (**1d**);
(E)-3-(1-((3-(5-ethyl-6-((hydroxyimino) methyl)-4-oxo-7-propyl-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-2-yl)-4-propoxyphenyl)sulfonyl)piperidin-4-yl)propyl nitrate (**1e**);
2-(4-((3-(5-ethyl-6-formyl-4-oxo-7-propyl-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-2-yl)-4-propoxyphenyl)sulfonyl)piperazin-1-yl)ethyl nitrate (**1f**);
2-(1-((3-(5-ethyl-6-formyl-4-oxo-7-propyl-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-2-yl)-4-propoxyphenyl)sulfonyl)piperidin-4-yl)ethyl nitrate (**1g**);
3-(1-((3-(5-ethyl-6-formyl-4-oxo-7-propyl-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-2-yl)-4-propoxyphenyl)sulfonyl)piperidin-4-yl)propyl nitrate (**1h**);
2-(4-((3-(5-ethyl-4-oxo-7-propyl-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-2-yl)-4-propoxyphenyl)sulfonyl)piperazin-1-yl)ethyl nitrate (**1i**);
(R)-1-(1-((3-(5-ethyl-4-oxo-7-propyl-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-2-yl)-4-propoxyphenyl)sulfonyl)piperidin-4-yl)ethane-1,2-diyl dinitrate (**1k**);
(S)-1-(1-((3-(5-ethyl-4-oxo-7-propyl-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-2-yl)-4-propoxyphenyl)sulfonyl)piperidin-4-yl)ethane-1,2-diyl dinitrate (**1l**);
((2R,6S)-4-((3-(5-ethyl-4-oxo-7-propyl-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-2-yl)-4-propoxyphenyl)sulfonyl)-1-methylpiperazine-2,6-diyl)bis(ethane-2,1-diyl) dinitrate (**1m**);
(1-((3-(5-ethyl-4-oxo-7-propyl-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-2-yl)-4-propoxyphenyl)sulfonyl)piperidine-4,4-diyl)bis(ethane-2,1-diyl) dinitrate (**1n**);
((2S,6S)-4-((3-(5-ethyl-4-oxo-7-propyl-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-2-yl)-4-propoxyphenyl)sulfonyl)-1-methylpiperazine-2,6-diyl)bis(ethane-2,1-diyl) dinitrate (**1o**);
3-(1-((3-(5-ethyl-4-oxo-7-propyl-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-2-yl)-4-propoxyphenyl)sulfonyl)piperidin-4-yl)-3-hydroxypentane-1,5-diyl dinitrate (**1p**);
2-(1-((3-(5-ethyl-4-oxo-7-propyl-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-2-yl)-4-propoxyphenyl)sulfonyl)piperidin-4-yl)-2-hydroxypropane-1,3-diyl dinitrate (**1q**);
(E)-2-(1-((4-ethoxy-3-(6-((hydroxyimino) methyl)-5-methyl-4-oxo-7-propyl-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-2-yl)phenyl)sulfonyl)piperidin-4-yl)ethyl nitrate (**2a**);

3-(1-((4-ethoxy-3-(5-methyl-4-oxo-7-propyl-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-2-yl)phenyl)sulfonyl)piperidin-4-yl)propyl nitrate (**2b**);
2-(1-((4-ethoxy-3-(5-methyl-4-oxo-7-propyl-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-2-yl)phenyl)sulfonyl)piperidin-4-yl)ethyl nitrate (**2c**);
2-(4-((4-ethoxy-3-(5-methyl-4-oxo-7-propyl-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-2-yl)phenyl)sulfonyl)piperazin-1-yl)ethyl nitrate (**2d**);
2-(1-((4-ethoxy-3-(6-formyl-5-methyl-4-oxo-7-propyl-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-2-yl)phenyl)sulfonyl)piperidin-4-yl)ethyl nitrate (**2e**);
(E)-3-(4-((4-ethoxy-3-(6-((hydroxyimino)methyl)-5-methyl-4-oxo-7-propyl-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-2-yl)phenyl)sulfonyl)piperazin-1-yl)propyl nitrate (**2f**);
(E)-2-(4-((4-ethoxy-3-(6-((hydroxyimino)methyl)-5-methyl-4-oxo-7-propyl-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-2-yl)phenyl)sulfonyl)piperazin-1-yl)ethyl nitrate (**2g**);
2-(1-((3-(5-methyl-4-oxo-7-propyl-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-2-yl)-4-propoxyphenyl)sulfonyl)piperidin-4-yl)ethyl nitrate (**3a**);
2-(4-((3-(5-methyl-4-oxo-7-propyl-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-2-yl)-4-propoxyphenyl)sulfonyl)piperazin-1-yl)ethyl nitrate (**3b**);
(E)-2-(1-((3-(6-((hydroxyimino)methyl)-5-methyl-4-oxo-7-propyl-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-2-yl)-4-propoxyphenyl)sulfonyl)piperidin-4-yl)ethyl nitrate (**3c**);
3-(4-((3-(5-methyl-4-oxo-7-propyl-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-2-yl)-4-propoxyphenyl)sulfonyl)piperazin-1-yl)propyl nitrate (**3d**);
(E)-2-(4-((3-(6-((hydroxyimino)methyl)-5-methyl-4-oxo-7-propyl-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-2-yl)-4-propoxyphenyl)sulfonyl)piperazin-1-yl)ethyl nitrate (**3e**);
(E)-3-(4-((3-(6-((hydroxyimino)methyl)-5-methyl-4-oxo-7-propyl-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-2-yl)-4-propoxyphenyl)sulfonyl)piperazin-1-yl)propyl nitrate (**3f**);
(R)-1-(1-((3-(5-methyl-4-oxo-7-propyl-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-2-yl)-4-propoxyphenyl)sulfonyl)piperidin-4-yl)ethane-1,2-diyl dinitrate (**3g**);
(S)-1-(1-((3-(5-methyl-4-oxo-7-propyl-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-2-yl)-4-propoxyphenyl)sulfonyl)piperidin-4-yl)ethane-1,2-diyl dinitrate (**3h**);
(1-((3-(5-methyl-4-oxo-7-propyl-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-2-yl)-4-propoxyphenyl)sulfonyl)piperidine-4,4-diyl)bis(methylene) dinitrate (**3i**);
(1-((3-(5-methyl-4-oxo-7-propyl-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-2-yl)-4-propoxyphenyl)sulfonyl)piperidin-4-yl)methyl nitrate (**3k**);
(R)-2-hydroxy-2-(1-((3-(5-methyl-4-oxo-7-propyl-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-2-yl)-4-propoxyphenyl)sulfonyl)piperidin-4-yl)ethyl nitrate (**3l**);

2-hydroxy-1-(1-((3-(5-methyl-4-oxo-7-propyl-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-2-yl)-4-propoxyphenyl)sulfonyl)piperidin-4-yl)ethyl nitrate isomer a (**3m**);
2-hydroxy-1-(1-((3-(5-methyl-4-oxo-7-propyl-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-2-yl)-4-propoxyphenyl)sulfonyl)piperidin-4-yl)ethyl nitrate isomer b (**3n**);
(R,E)-1-(1-((3-(6-((hydroxyimino)methyl)-5-methyl-4-oxo-7-propyl-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidin-2-yl)-4-propoxyphenyl)sulfonyl)piperidin-4-yl)ethane-1,2-diyl dinitrate (**3o**);
(*S*,*E*)-1-(1-((3-(6-((hydroxyimino)methyl)-5-methyl-4-oxo-7-propyl-4,5-dihydro-3*H*-pyrrolo[3,2-*d*]pyrimidin-2-yl)-4-propoxyphenyl)sulfonyl)piperidin-4-yl)ethane-1,2-diyl dinitrate (**3p**); and
(*R*,*E*)-2-hydroxy-2-(1-((3-(6-((hydroxyimino)methyl)-5-methyl-4-oxo-7-propyl-4,5-dihydro-3*H*-pyrrolo[3,2-*d*]pyrimidin-2-yl)-4-propoxyphenyl)sulfonyl)piperidin-4-yl)ethyl nitrate (**3q**).

15. A pharmaceutical composition comprising at least one of the compound of formula **I** of any one of the claims 1 to 14, or a pharmaceutically acceptable salt, solvate or hydrate thereof, and a pharmaceutically acceptable excipient, adjuvant, or carrier.

16. The compound of formula **I** of any one of the claims 1 to 14, or the pharmaceutical composition of claim 15, for use in a method of treating or preventing a disease alleviated by inhibition of PDE5 in a human or in a non-human mammal, preferably in a human, wherein preferably said disease is selected from wound healing, chronic wound healing, diabetic foot, diabetic foot ulcer, leg ulcer, Raynaud's disease, male erectile dysfunction, priapism, female sexual dysfunction, hair loss, skin aging, vascular aging, pulmonary artery hypertension; livedoid vasculopathy, thromboangitis obliterans, chronic anal fissure, skin fibrosis, 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.

17. The compound of formula **I** of any one of the claims 1 to 14 or the pharmaceutical composition of claim 15, for use in a method of treating or preventing a disease in a human or in

a non-human mammal, preferably in a human, wherein said disease is selected from wound healing, chronic wound healing, diabetic foot, diabetic foot ulcer, leg ulcer, Raynaud's disease, male erectile dysfunction, priapism, female sexual dysfunction, hair loss, skin aging, vascular aging, pulmonary artery hypertension; livedoid vasculopathy, thromboangitis obliterans, chronic anal fissure, skin fibrosis, 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, livedoid vasculopathy, thromboangitis obliterans, chronic anal fissure, skin fibrosis, systemic sclerosis (SSc), scleroderma, pulmonary artery hypertension (PAH), chronic thromboembolic pulmonary hypertension, male erectile dysfunction, priapism and female sexual dysfunction, and wherein again further preferably said disease is selected from pulmonary artery hypertension (PAH), chronic thromboembolic pulmonary hypertension, male erectile dysfunction, priapism and female sexual dysfunction, livedoid vasculopathy, thromboangitis obliterans, chronic anal fissure, skin fibrosis, wound healing, chronic wound healing, diabetic foot, diabetic foot ulcer, leg ulcer, diabetic neuropathy and pressure ulcer.