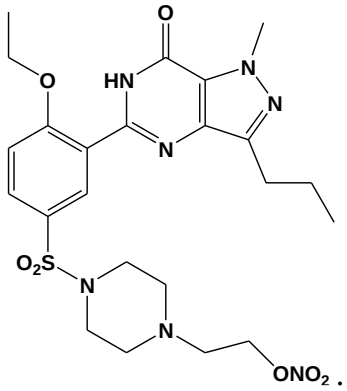
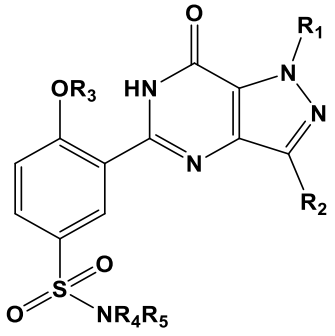
R_8 and R_9 are independently H, or C_1-C_4alkyl optionally substituted with ONO, ONO_2;

R_{10} is C_1-C_4alkyl optionally substituted with F, ONO, ONO_2; C_3-C_6cycloalkyl;

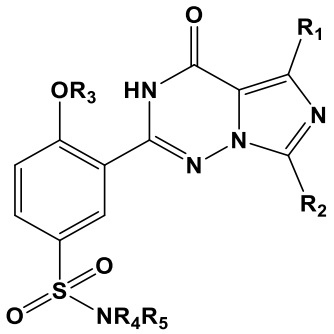
wherein preferably said compound of formula **I** is not



In one aspect, the present disclosure refers to a compound of formula I or formula II



I



II

or pharmaceutically acceptable salt, solvate or hydrate thereof, wherein

said compound of formula **I** and said compound of formula **II** each comprises at least one covalently bound ONO_2 or ONO moiety;

R_1 is C_1-C_3alkyl;

R_2 is H, C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_2alkoxy, or C_2-C_4alkenyl;

R_3 is C_1-C_4alkyl, wherein said C_1-C_4alkyl is optionally substituted with C_1-C_2alkoxy, C_3-C_4cycloalkyl, or C_2-C_4alkenyl;

R_4 and R_5, together with the nitrogen atom to which they are attached, form a heterocyclic ring, wherein said heterocyclic ring is piperidine, and wherein said heterocyclic ring is optionally substituted with independently one or more R_6;

R_6 is C_1-C_6alkyl, wherein said C_1-C_6alkyl is optionally substituted with independently one or more halogen, OH, ONO, ONO_2, C_1-C_3alkoxy, C_1-C_3haloalkoxy, $COOR_7$, NR_8R_9, or $C{=}NR_{10}$;

R_7 is H or C_1-C_4alkyl, wherein said C_1-C_4alkyl is optionally substituted with F, OH, ONO, ONO_2, or NR_8R_9;

R_8 and R_9 are independently H or C_1-C_4alkyl, wherein said C_1-C_4alkyl is optionally substituted with ONO or ONO_2; and

R_{10} is C_3-C_6cycloalkyl or C_1-C_4alkyl, wherein said C_1-C_4alkyl is optionally substituted with F, ONO, or ONO_2.

The present disclosure provides for a pharmaceutical composition comprising at least one of the inventive compounds of formula **I** or formula **II**, or a pharmaceutically acceptable salt, solvate or hydrate thereof, and a pharmaceutically acceptable excipient, adjuvant, or carrier.

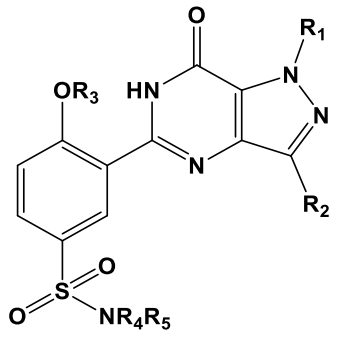
In another aspect, the present disclosure refers to a pharmaceutical composition comprising at least one of the compounds of formula **I** or formula **II** of the present disclosure, or a pharmaceutically acceptable salt, solvate or hydrate thereof, and a pharmaceutically acceptable excipient, adjuvant, or carrier.

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

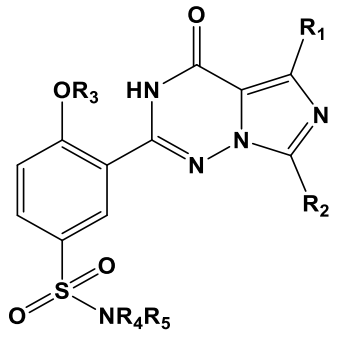
The present disclosure provides for a compound of formula **I** or formula **II**, or a pharmaceutical composition, or a pharmaceutically acceptable salt, solvate or hydrate thereof, for use in a method of treating or preventing a disease alleviated by inhibition of PDE5 in a human or in a non-human mammal, preferably in a human, wherein preferably said disease is selected from glaucoma**,** diabetic retinopathy, age dependent macular degeneration, 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

CLAIMS:

1. A compound of formula I or formula II



I



II

or pharmaceutically acceptable salt, solvate or hydrate thereof, wherein

said compound of formula **I** and said compound of formula **II** each comprises at least one covalently bound ONO_2 or ONO moiety;

R_1 is C_1-C_3alkyl;

R_2 is H, C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_2alkoxy, or C_2-C_4alkenyl;

R_3 is C_1-C_4alkyl, wherein said C_1-C_4alkyl is optionally substituted with C_1-C_2alkoxy, C_3-C_4cycloalkyl, or C_2-C_4alkenyl;

R_4 and R_5, together with the nitrogen atom to which they are attached, form a heterocyclic ring, wherein said heterocyclic ring is piperidine, and wherein said heterocyclic ring is optionally substituted with independently one or more R_6;

R_6 is C_1-C_6alkyl, wherein said C_1-C_6alkyl is optionally substituted with independently one or more halogen, OH, ONO, ONO_2, C_1-C_3alkoxy, C_1-C_3haloalkoxy, $COOR_7$, NR_8R_9, or $C{=}NR_{10}$;

R_7 is H or C_1-C_4alkyl, wherein said C_1-C_4alkyl is optionally substituted with F, OH, ONO, ONO_2, or NR_8R_9;

R_8 and R_9 are independently H or C_1-C_4alkyl, wherein said C_1-C_4alkyl is optionally substituted with ONO or ONO_2; and

R_{10} is C_3-C_6cycloalkyl or C_1-C_4alkyl, wherein said C_1-C_4alkyl is optionally substituted with F, ONO, or ONO_2.

2. The compound according to claim 1, wherein R_1 is methyl or ethyl.

3. The compound according to claim 1, wherein R_1 is ethyl.

4. The compound according to claim 1, wherein R_1 is methyl.

5. The compound according to any of claims 1 to 4, wherein R_2 is C_1-C_3alkyl or C_3-C_6cycloalkyl.

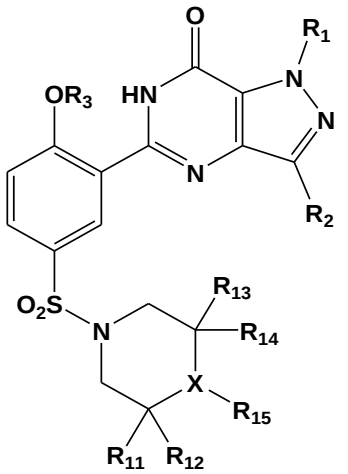
6. The compound according to any one of the claims 1 to 5, wherein R_3 is C_1-C_4alkyl.

7. The compound according to claim 1, wherein said heterocyclic ring is optionally substituted with independently one or two R_6.

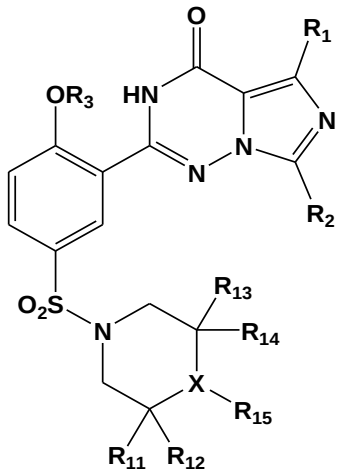
8. The compound according to claim 1, wherein said heterocyclic ring is substituted with independently one or two R_6.

9. The compound according to any one of the claims 1 to 8, wherein R_6 is C_1-C_6alkyl, wherein said C_1-C_6alkyl is optionally substituted with independently one or more OH, ONO, ONO_2, or C_1-C_3alkoxy.

10. The compound according to any one of claims 1 to 9, wherein said compound of formula **I** is a compound of formula **I***, and wherein said compound of formula **II** is a compound of formula **II*,** or independently a pharmaceutically acceptable salt, solvate or hydrate thereof,



I*



II*

wherein R_1, R_2, and R_3 are as defined in any one of the claims 1 to 6; and wherein X is CR_{16};

R_{11}, R_{12}, R_{13}, R_{14} and R_{15} are independently H or C_1-C_6alkyl, wherein said C_1-C_6alkyl is optionally substituted with independently one or more halogen, OH, ONO, ONO_2, C_1-C_3alkoxy, C_1-C_3haloalkoxy, $COOR_{17}$, $NR_{18}R_{19}$, or $C{=}NR_{20}$;

R_{16} is H or C_1-C_6alkyl, wherein said C_1-C_6alkyl is optionally substituted with independently one or more halogen, OH, ONO, ONO_2, C_1-C_3alkoxy, C_1-C_3haloalkoxy, $COOR_{17}$, $NR_{18}R_{19}$, or $C{=}NR_{20}$;

R_{17} is H or C_1-C_4alkyl, wherein said C_1-C_4alkyl is optionally substituted with F, OH, ONO, or ONO_2;

R_{18} and R_{19} are independently H or C_1-C_4alkyl, wherein said C_1-C_4alkyl is optionally substituted with ONO or ONO_2; and

R_{20} is C_1-C_4alkyl, wherein said C_1-C_4alkyl is optionally substituted with F, ONO, or ONO_2;

wherein at least one of said R_{11}, R_{12}, R_{13}, R_{14}, R_{15} and R_{16} comprises independently at least one covalently bound ONO_2 or ONO moiety.

11. The compound according to claim 10, wherein one of said R_{13} and R_{14} is H, and the other of said R_{13} and R_{14} is H or C_1-C_6alkyl, wherein said C_1-C_6alkyl is optionally substituted with independently one or more halogen, OH, ONO, ONO_2, C_1-C_3alkoxy, C_1-C_3haloalkoxy, $COOR_{17}$, $NR_{18}R_{19}$, or $C{=}NR_{20}$;

said R_{15} is C_1-C_6alkyl, wherein said C_1-C_6alkyl is optionally substituted with independently one or more halogen, OH, ONO, ONO_2, C_1-C_3alkoxy, C_1-C_3haloalkoxy, $COOR_{17}$, $NR_{18}R_{19}$, or $C{=}NR_{20}$; and

said R_{16} is H or C_1-C_6alkyl, wherein said C_1-C_6alkyl is optionally substituted with independently one or more halogen, OH, ONO, ONO_2, C_1-C_3alkoxy, C_1-C_3haloalkoxy, $COOR_{17}$, $NR_{18}R_{19}$, or $C{=}NR_{20}$.

12. The compound according to claim 10 or claim 11, wherein one of said R_{13} and R_{14} is H, and the other of said R_{13} and R_{14} is H or C_1-C_6alkyl, wherein said C_1-C_6alkyl is optionally substituted with independently one or more halogen, OH, ONO, ONO_2, C_1-C_3alkoxy, or C_1-C_3haloalkoxy;

said R_{15} is C_1-C_6alkyl, wherein said C_1-C_6alkyl is optionally substituted with independently one or more halogen, OH, ONO, ONO_2, C_1-C_3alkoxy, or C_1-C_3haloalkoxy; and

said R_{16} is H or C_1-C_6alkyl, wherein said C_1-C_6alkyl is optionally substituted with independently one or more halogen, OH, ONO, ONO_2, C_1-C_3alkoxy, or C_1-C_3haloalkoxy.

13. The compound according to any one of claims 10 to 12, wherein
one of said R_{11} and R_{12} is H, and the other of said R_{11} and R_{12} is H or C_1-C_6alkyl, wherein said C_1-C_6alkyl is optionally substituted with independently one or more halogen, OH, ONO, ONO_2, C_1-C_3alkoxy, C_1-C_3haloalkoxy, $COOR_{17}$, $NR_{18}R_{19}$, or $C=NR_{20}$;
one of said R_{13} and R_{14} is H, and the other of said R_{13} and R_{14} is H or C_1-C_6alkyl, wherein said C_1-C_6alkyl is optionally substituted with independently one or more halogen, OH, ONO, ONO_2, C_1-C_3alkoxy, C_1-C_3haloalkoxy, $COOR_{17}$, $NR_{18}R_{19}$, or $C=NR_{20}$;
R_{15} is C_1-C_6alkyl, wherein said C_1-C_6alkyl is optionally substituted with independently one or more halogen, OH, ONO, ONO_2, C_1-C_3alkoxy, C_1-C_3haloalkoxy, $COOR_{17}$, $NR_{18}R_{19}$, or $C=NR_{20}$;
R_{16} is H or C_1-C_6alkyl, wherein said C_1-C_6alkyl is optionally substituted with independently one or more halogen, OH, ONO, ONO_2, C_1-C_3alkoxy, C_1-C_3haloalkoxy, $COOR_{17}$, $NR_{18}R_{19}$, or $C=NR_{20}$;
wherein R_{17} is H or C_1-C_4alkyl, wherein said C_1-C_4alkyl is optionally substituted with OH, ONO, or ONO_2; and
R_{18} and R_{19} are each independently H or C_1-C_4alkyl, wherein said C_1-C_4alkyl is optionally substituted with ONO or ONO_2.

14. The compound according to claim 1, wherein said compound is selected from
(R)-1-(1-((4-ethoxy-3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl)sulfonyl)piperidin-4-yl)ethane-1,2-diyl dinitrate (**1a**);
(S)-1-(1-((4-ethoxy-3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl)sulfonyl)piperidin-4-yl)ethane-1,2-diyl dinitrate (**1b**);
(R)-2-(1-((4-ethoxy-3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl)sulfonyl)piperidin-4-yl)-2-hydroxyethyl nitrate (**1c**);
(S)-2-(1-((4-ethoxy-3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl)sulfonyl)piperidin-4-yl)-2-hydroxyethyl nitrate (**1d**);
(R)-3-(1-((4-ethoxy-3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl)sulfonyl)piperidin-4-yl)-3-hydroxypropyl nitrate;
(S)-3-(1-((4-ethoxy-3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl)sulfonyl)piperidin-4-yl)-3-hydroxypropyl nitrate;
3-(1-((4-ethoxy-3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl)sulfonyl)piperidin-4-yl)-3,5-dihydroxypentyl nitrate (**1g**);

3-(1-((4-ethoxy-3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl)sulfonyl)piperidin-4-yl)-3-hydroxypentane-1,5-diyl dinitrate (**1h**);
2-((1-((4-ethoxy-3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl)sulfonyl)piperidin-4-yl)(hydroxy)methyl)propane-1,3-diyl dinitrate (**1i**);
(R)-1-(1-((4-ethoxy-3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl)sulfonyl)piperidin-4-yl)-2-hydroxyethyl nitrate;
(S)-1-(1-((4-ethoxy-3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl)sulfonyl)piperidin-4-yl)-2-hydroxyethyl nitrate;
(R)-1-(1-((4-ethoxy-3-(5-methyl-4-oxo-7-propyl-3,4-dihydroimidazo[5,1-f][1,2,4]triazin-2-yl)phenyl)sulfonyl)piperidin-4-yl)ethane-1,2-diyl dinitrate (**2a**);
(S)-1-(1-((4-ethoxy-3-(5-methyl-4-oxo-7-propyl-3,4-dihydroimidazo[5,1-f][1,2,4]triazin-2-yl)phenyl)sulfonyl)piperidin-4-yl)ethane-1,2-diyl dinitrate (**2b**);
(R)-2-(1-((4-ethoxy-3-(5-methyl-4-oxo-7-propyl-3,4-dihydroimidazo[5,1-f][1,2,4]triazin-2-yl)phenyl)sulfonyl)piperidin-4-yl)-2-hydroxyethyl nitrate (**2c**);
(S)-2-(1-((4-ethoxy-3-(5-methyl-4-oxo-7-propyl-3,4-dihydroimidazo[5,1-f][1,2,4]triazin-2-yl)phenyl)sulfonyl)piperidin-4-yl)-2-hydroxyethyl nitrate (**2d**);
(R)-3-(1-((4-ethoxy-3-(5-methyl-4-oxo-7-propyl-3,4-dihydroimidazo[5,1-f][1,2,4]triazin-2-yl)phenyl)sulfonyl)piperidin-4-yl)-3-hydroxypropyl nitrate;
(S)-3-(1-((4-ethoxy-3-(5-methyl-4-oxo-7-propyl-3,4-dihydroimidazo[5,1-f][1,2,4]triazin-2-yl)phenyl)sulfonyl)piperidin-4-yl)-3-hydroxypropyl nitrate;
3-(1-((4-ethoxy-3-(5-methyl-4-oxo-7-propyl-3,4-dihydroimidazo[5,1-f][1,2,4]triazin-2-yl)phenyl)sulfonyl)piperidin-4-yl)-3,5-dihydroxypentyl nitrate (**2g**);
3-(1-((4-ethoxy-3-(5-methyl-4-oxo-7-propyl-3,4-dihydroimidazo[5,1-f][1,2,4]triazin-2-yl)phenyl)sulfonyl)piperidin-4-yl)-3-hydroxypentane-1,5-diyl dinitrate (**2h**);
2-((1-((4-ethoxy-3-(5-methyl-4-oxo-7-propyl-3,4-dihydroimidazo[5,1-f][1,2,4]triazin-2-yl)phenyl)sulfonyl)piperidin-4-yl)(hydroxy)methyl)propane-1,3-diyl dinitrate (**2i**);
(R)-1-(1-((4-ethoxy-3-(5-methyl-4-oxo-7-propyl-3,4-dihydroimidazo[5,1-f][1,2,4]triazin-2-yl)phenyl)sulfonyl)piperidin-4-yl)-2-hydroxyethyl nitrate;
(S)-1-(1-((4-ethoxy-3-(5-methyl-4-oxo-7-propyl-3,4-dihydroimidazo[5,1-f][1,2,4]triazin-2-yl)phenyl)sulfonyl)piperidin-4-yl)-2-hydroxyethyl nitrate;
2-((1-((4-ethoxy-3-(5-methyl-4-oxo-7-propyl-3,4-dihydroimidazo[5,1-f][1,2,4]triazin-2-yl)phenyl)sulfonyl)piperidin-4-yl)methyl)propane-1,3-diyl dinitrate (**2m**);
3-(1-((4-ethoxy-3-(5-methyl-4-oxo-7-propyl-3,4-dihydroimidazo[5,1-f][1,2,4]triazin-2-yl)phenyl)sulfonyl)piperidin-4-yl)-2-(hydroxymethyl)propyl nitrate (**2n**);

2-((1-((4-ethoxy-3-(5-methyl-4-oxo-7-propyl-3,4-dihydroimidazo[5,1-f][1,2,4]triazin-2-yl)phenyl)sulfonyl)piperidin-4-yl)methyl)-2-methylpropane-1,3-diyl dinitrate (**2o**); and 3-(1-((4-ethoxy-3-(5-methyl-4-oxo-7-propyl-3,4-dihydroimidazo[5,1-f][1,2,4]triazin-2-yl)phenyl)sulfonyl)piperidin-4-yl)-2-(hydroxymethyl)-2-methylpropyl nitrate (**2p**); or a pharmaceutically acceptable salt, solvate or hydrate thereof.

15. The compound according to claim 1, wherein said compound is 2-((1-((4-ethoxy-3-(5-methyl-4-oxo-7-propyl-3,4-dihydroimidazo[5,1-f][1,2,4]triazin-2-yl)phenyl)sulfonyl)piperidin-4-yl)methyl)-2-methylpropane-1,3-diyl dinitrate (**2o**); or a pharmaceutically acceptable salt, solvate or hydrate thereof.

16. The compound according to claim 1, wherein said compound is 3-(1-((4-ethoxy-3-(5-methyl-4-oxo-7-propyl-3,4-dihydroimidazo[5,1-f][1,2,4]triazin-2-yl)phenyl)sulfonyl)piperidin-4-yl)-2-(hydroxymethyl)-2-methylpropyl nitrate (**2p**); or a pharmaceutically acceptable salt, solvate or hydrate thereof.

17. A pharmaceutical composition comprising at least one of the compounds of formula **I** or formula **II** of any one of the claims 1 to 16, or a pharmaceutically acceptable salt, solvate or hydrate thereof, and a pharmaceutically acceptable excipient, adjuvant, or carrier.

18. The pharmaceutical composition of claim 17, wherein said pharmaceutical composition further comprises at least one sGC stimulator.

19. The pharmaceutical composition of claim 18, wherein said sGC stimulator is selected from the group consisting of riociguat, vericiguat, praliciguat and olinciguat.

20. Use of the compound of formula **I** or formula **II** of any of the claims 1 to 16, or the pharmaceutical composition of any of the claims 17 to 19, in the manufacture of a medicament for the treatment or prevention of a disease in a human or in a non-human mammal, 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, 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, achalasia, sickle cell disease (SCD), diabetic nephropathy, inflammatory diseases, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, diabetic neuropathy, Idiopathic pulmonary fibrosis (IPF), peyronic's disease, glaucoma, diabetic retinopathy, Retinopathia pigmentosa, age dependent macular degeneration or a disease characterized by disorders of gut motility like irritable bowel syndrome, liver fibrosis, Alzheimer's disease, chronic heart failure, and cancer.

21. The use of claim 20, in the manufacture of a medicament for the treatment or prevention of a disease in a human.

22. The use according to claim 20, wherein said cancer is selected from breast, gastrointestinal, lung, skin, prostate, pancreatic, colon, and rectal cancer.

23. The use according to claim 20, wherein 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, diabetic retinopathy, Retinopathia pigmentosa, age dependent macular degeneration, male erectile dysfunction, priapism, female sexual dysfunction and colorectal cancer.

24. The use according to claim 20, wherein said disease is selected from pulmonary artery hypertension (PAH), chronic thromboembolic pulmonary hypertension, diabetic retinopathy, Retinopathia pigmentosa, age dependent macular degeneration, scleroderma, 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.

25. The use of any of claims 20 to 24, wherein said compound or said pharmaceutical composition is to be used in combination with at least one sGC stimulator.

26. The use of claim 25, wherein said sGC stimulator is selected from the group consisting of riociguat, vericiguat, praliciguat and olinciguat.