approach and strategies directed to promote inhibition of PDE5 activity have been applied and suggested as therapeutic tools, in particular, in neuronal and cardiovascular conditions and cancer. Moreover, the introduction of PDE5 inhibitors has revolutionized the treatment of male erectile dysfunction (MED) (Dobhal T, Kaur S, Prakash Sharma O, Hari Kumar SL, Critical Review in Pharmaceutical Sciences (2012) 1(3):13-27). Several PDE5 inhibitors are on the market and are characterized particularly for MED or pulmonary hypertension (PH), in particular pulmonary artery hypertension (PAH) (Papapetropoulos A, Hobbs AJ, Topouzis S, British Journal of Pharmacology (2015) 172:1397–1414; Monica FZ, Murad F, Bian K, OA Biochemistry (2014) Mar 11; 2(1):3; Beedimani RS, Kalmath B, Int J Pharm Bio Sci (2014) 5(2): 530-539; Wronski S, Cent European J Urol (2014) 67: 314-318; Barone I et al. Oncotarget (2017) 8(58): 99179-99202; Vighi E et al. Oncotarget (2018) 9(4): 5301-5320; Huang W et al. Gastroenterology 2019;157:672–681; and references cited therein). Most prominent examples of PDE5 inhibitors are Sildenafil, Tadalafil, Vardenafil and Mirodenafil which have been described among others, for example, in WO 99/24433, WO 01/60825, EP 995'751 and WO 2011/075655. Recently, a novel class of very potent PDE5 inhibitors has been described (WO 2017/085056 A1).

Beside the success of the known PDE5 inhibitors, there is still a need for further and more effective drugs 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 cGMP disbalance.

Endothelial dysfunction leads to an imbalance of vasodilator and vasoconstrictor mediators shifted towards the latter. One key mechanism remains impaired endothelial NO generation and associated, reduced activation of soluble guanylyl cyclase (sGC) in adjacent smooth muscle cells. Strategies to increase disturbed cGMP levels by enhancing cGMP in vascular smooth muscle by improving cGMP synthesis and inhibiting its degradation have been described. Examples are combinations of sGC stimulators or activators in combination with PDE5 inhibitors, for example WO 2010/081647 or US2002/0182162.

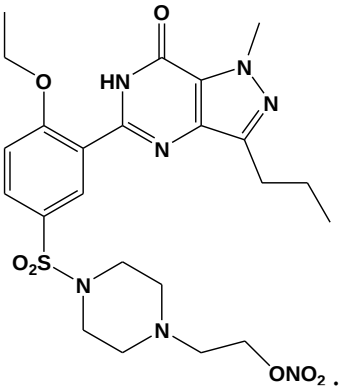
SUMMARY

We have surprisingly found that dual-pharmacology compounds of the present disclosure designed as NO-releasing PDE5 inhibitors believed to release NO in addition to its PDE5 inhibition modulate cGMP levels in a more than additive, thus, synergistic fashion. We have further surprisingly found that the compounds of the present disclosure are highly bound to

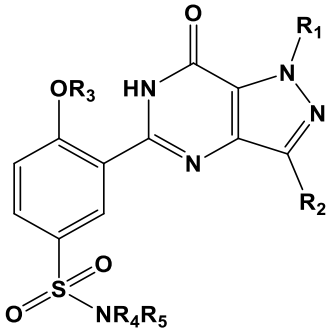
R_8 and R_9 are independently H, or C_1-C_4alkyl optionally substituted with ONO, ONO_2;

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

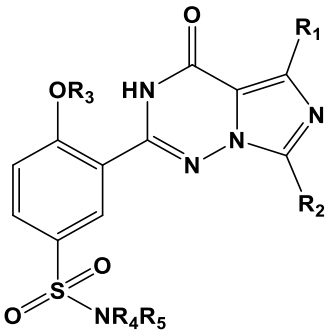
wherein preferably said compound of formula **I** is not



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 are each independently H or C_1-C_6alkyl, wherein said C_1-C_6alkyl is optionally substituted with F, OH, ONO, ONO_2, COOH, C_1-C_3alkoxy, or C_3-C_6cycloalkyl;

or together with the nitrogen atom to which they are attached R_4 and R_5 form a heterocyclic ring~~, wherein preferably said heterocyclic ring is selected from aziridine, azetidine, pyrollidine, piperidine, morpholine, piperazine, homo-piperazine, 2,5- diazabicyclo[2,2,1]heptane and 3,7-diazabicyclo[3,3,0]octane~~, wherein said heterocyclic ring is optionally substituted with independently one or more R_6;

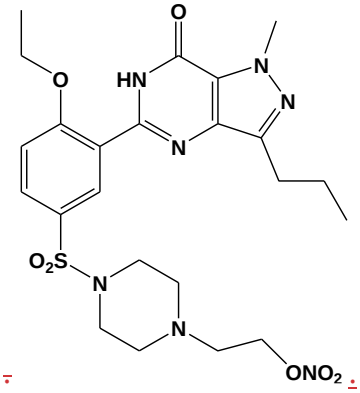
R_6 is C_1-C_6alkyl, wherein said C_1-C_6alkyl is optionally substituted with independently one or more halogen, OH, ONO, ONO_2, C_1-C_3alkoxy, C_1-C_3haloalkoxy, $COOR_7$, NR_8R_9, or $C{=}NR_{10}$;

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; ~~C_3-C_6cycloalkyl,~~

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



~~,~~ .

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~~, and wherein preferably said pharmaceutical composition further comprises at least one sGC stimulator, wherein further preferably said sGC stimulator is selected from the group consisting of riociguat, vericiguat, praliciguat and olinciguat~~.

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

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, by disorders of gut motility like irritable bowel syndrome, liver fibrosis, Alzheimer's disease, chronic heart failure and cancer such as breast and gastrointestinal cancers, non-small cell lung cancer, skin cancers such as melanoma, head and neck cancer, myeloma and head and

neck squamous cell carcinoma, colon and rectal cancers such as colorectal cancer, and prostate and pancreatic cancers, and in particular colorectal cancer.

~~In another aspect, the present disclosure refers to the compound of formula **I** or formula **II** as described herein, or the pharmaceutical composition as described herein, 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, 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, age dependent macular degeneration, Retinopathia pigmentosa, or a disease characterized by disorders of gut motility like irritable bowel syndrome, liver fibrosis, Alzheimer's disease, chronic heart failure, and cancer, preferably breast, gastrointestinal, lung, skin, prostate, pancreatic, colon, rectal cancer.~~

~~In another aspect, the present disclosure refers to the use of the compound of formula **I** or formula **II** as described herein, or the pharmaceutical composition as described herein, in the manufacture of a medicament for the treatment or prevention of a disease alleviated by inhibition of PDE5 in a human or in a non-human mammal, preferably in a human, where in 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, 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, age dependent macular degeneration, Retinopathia pigmentosa, or a disease characterized by disorders~~

~~of gut motility like irritable bowel syndrome, liver fibrosis, Alzheimer's disease, chronic heart failure, and cancer, preferably breast, gastrointestinal, lung, skin, prostate, pancreatic, colon, rectal cancer.~~

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 in a human or in a non-human mammal, preferably in a human, wherein 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 failure, atherosclerosis, conditions of reduced blood vessel patency, peripheral vascular disease, vascular disorders, systemic sclerosis (SSc), scleroderma, morphea, achalasia, sickle cell disease (SCD), inflammatory diseases, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, diabetic neuropathy, Idiopathic pulmonary fibrosis (IPF), peyronic's disease, 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 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, and cancer such as breast and gastrointestinal cancers, non-small cell lung cancer, skin cancers such as melanoma, head and neck cancer, myeloma and head and neck squamous cell carcinoma, colon and rectal cancers such as colorectal cancer, and prostate and pancreatic cancers, and in particular colorectal cancer.

~~In another aspect, the present disclosure refers to the compound of formula **I** or formula **II** as described herein, or the pharmaceutical composition as described herein, 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, 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, preferably breast, gastrointestinal, lung, skin, prostate, pancreatic, colon, rectal cancer, 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, skin aging, 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, and wherein again further preferably 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, skin aging, 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.~~

In another aspect the present disclosure refers to the use of the compound of formula **I** or formula **II** as described herein, or the pharmaceutical composition as described herein, in the manufacture of a medicament for the treatment or prevention of 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, 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~~, preferably breast, gastrointestinal, lung, skin, prostate, pancreatic, colon, rectal cancer, 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, skin aging, 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, and wherein again further preferably 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, skin aging, 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~~.

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

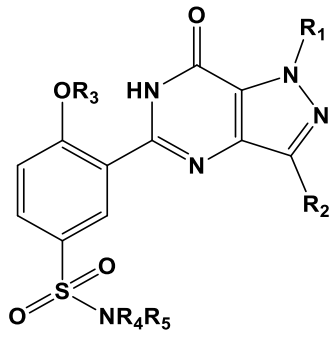
DESCRIPTION OF THE FIGURES

FIG. 1: PDE5 inhibition and activation of soluble guanylate cyclase from one molecule.

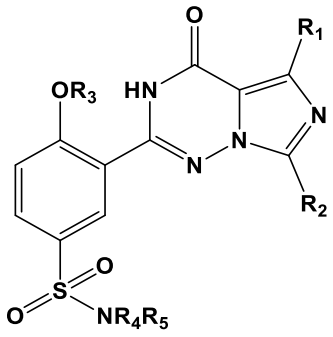
FIG. 2: Dual-pharmacology NO-releasing PDE5 inhibitors addressing disturbed cGMP balance in diseases with disturbed cGMP balance.

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 are each independently H or C_1-C_6alkyl, wherein said C_1-C_6alkyl is optionally substituted with F, OH, ONO, ONO_2, COOH, C_1-C_3alkoxy, or C_3-C_6cycloalkyl;

or together with the nitrogen atom to which they are attached R_4 and R_5 form a heterocyclic ring~~, wherein preferably said heterocyclic ring is selected from aziridine, azetidine, pyrollidine, piperidine, morpholine, piperazine, homo-piperazine, 2,5-diazabicyclo[2,2,1]heptane and 3,7-diazabicyclo[3,3,0]octane~~, wherein said heterocyclic ring is optionally substituted with independently one or more R_6;

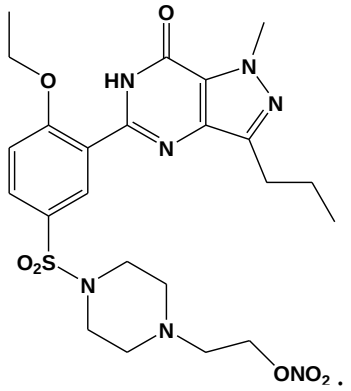
R_6 is C_1-C_6alkyl, wherein said C_1-C_6alkyl is optionally substituted with independently one or more halogen, OH, ONO, ONO_2, C_1-C_3alkoxy, C_1-C_3haloalkoxy, $COOR_7$, NR_8R_9, or $C{=}NR_{10}$;

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; ~~C_3-C_6cycloalkyl,~~

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



2. The compound according to claim 1, wherein R_4 and R_5 together with the nitrogen atom to which they are attached form a heterocyclic ring, wherein said heterocyclic ring is selected from aziridine, azetidine, pyrollidine, piperidine, morpholine, piperazine, homo-piperazine, 2,5-diazabicyclo[2,2,1]heptane and 3,7-diazabicyclo[3,3,0]octane, wherein said heterocyclic ring is optionally substituted with independently one or more R_6.

~~2.~~3. The compound according to claim 1 or claim 2, wherein R_1 is methyl or ethyl~~, preferably methyl~~.

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

~~3.~~5. The compound according to ~~claim 1 or claim 2~~any of claims 1 to 4, wherein R_2 is C_1-C_3alkyl or C_3-C_6cycloalkyl.

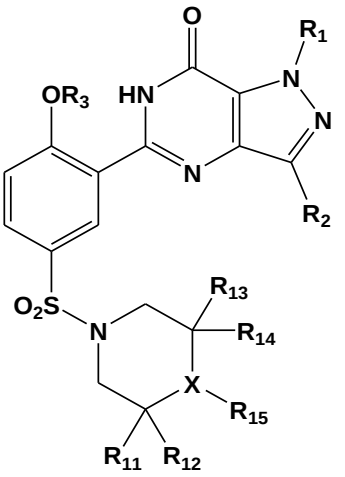
~~4.~~6. The compound according to any one of the claims 1 to ~~3~~5, wherein R_3 is C_1-C_4alkyl.

~~5.~~7. The compound according to any one of the claims 1 to ~~4~~6, wherein R_4 and R_5 together with the nitrogen atom to which they are attached form a heterocyclic ring, wherein said heterocyclic ring is selected from piperidine, piperazine and homopiperazine, wherein said heterocyclic ring is optionally substituted with independently one or more R_6~~, preferably optionally substituted with independently one or two R_6~~.

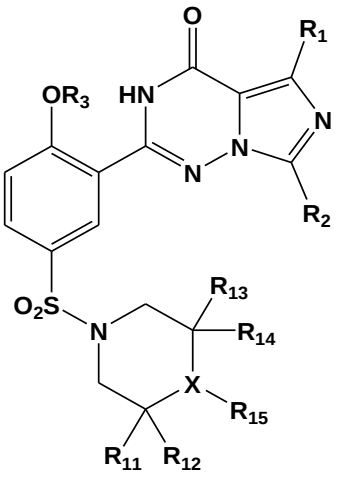
8. The compound according to claim 7, wherein said heterocyclic ring is optionally substituted with independently one or two R_6.

6.9. The compound according to any one of the claims 1 to 58, 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.

7.10. The compound according to any one of claims 1 to 69, 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 46; and wherein

X is CR_{16} or N;

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 $C{=}NR_{20}$;

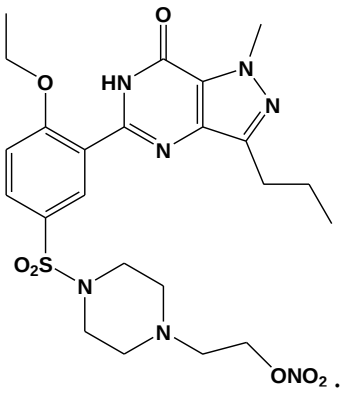
R_{17} is H, or C_1-C_4alkyl, wherein said C_1-C_4alkyl is optionally substituted with F, OH, ONO, or ONO_2;

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,

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



8.11. The compound according to claim 710, 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 $C=NR_{20}$.

9.12. The compound according to claim 710 or claim 811, 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.

10.13. The compound according to any one of claims 7 to 910 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.

~~11.~~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 ~~Enantiomer A (**1e**)~~;

(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 ~~Enantiomer B (**1f**)~~;

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 ~~Enantiomer A (**1k**)~~;

(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 ~~Enantiomer B (**1l**)~~;

(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 ~~Enantiomer A (**2e**)~~;

(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 ~~Enantiomer B (**2f**)~~;

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 ~~Enantiomer A (**2k**)~~;

(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 ~~Enantiomer B (**2l**)~~;

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.

~~12.~~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 ~~11~~16, or a pharmaceutically acceptable salt, solvate or hydrate thereof, and a pharmaceutically acceptable excipient, adjuvant, or carrier~~, and wherein preferably said pharmaceutical composition further comprises at least one sGC stimulator, wherein further preferably said sGC stimulator is selected from the group consisting of riociguat, vericiguat, praliciguat and olinciguat~~.

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.

~~13. The compound of formula **I** or formula **II** of any one of the claims 1 to 11, or the pharmaceutical composition of claim 12, 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, achalasia, sickle cell disease (SCD), diabetic nephropathy, inflammatory diseases, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, diabetic neuropathy, Idiopathic pulmonary fibrosis (IPF), peyronie's disease, glaucoma, diabetic retinopathy, age dependent macular degeneration, Retinopathia pigmentosa, or a disease characterized by disorders of gut motility like irritable bowel syndrome, liver fibrosis, Alzheimer's disease, chronic heart failure, and cancer, preferably breast, gastrointestinal, lung, skin, prostate, pancreatic, colon, rectal cancer.

14. The compound of formula **I** or formula **II** of any one of the claims 1 to 11 or the pharmaceutical composition of claim 12, 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, achalasia, sickle cell disease (SCD), diabetic nephropathy, inflammatory diseases, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, diabetic neuropathy, Idiopathic pulmonary fibrosis (IPF), peyronie'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, preferably breast, gastrointestinal, lung, skin, prostate, pancreatic, colon, rectal cancer, 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, skin aging, 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, and wherein again further preferably 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, skin aging, 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.

15. The compound of formula **I** or formula **II** for use, or the pharmaceutical composition for use of claim 13 or claim 14, wherein said compound or said pharmaceutical composition is used in combination with at least one sGC stimulator, and wherein preferably said sGC stimulator is selected from the group consisting of riociguat, vericiguat, praliciguat and olinciguat.

16. Use of the compound of formula **I** or formula **II** of any of the claims 1 to 11, or the pharmaceutical composition of claim 12, in the manufacture of a medicament for the treatment or prevention of a disease alleviated by inhibition of PDE5 in a human or in a non-human mammal, preferably in a human, where in 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, achalasia, sickle cell disease (SCD), diabetic nephropathy, inflammatory diseases, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, diabetic neuropathy, Idiopathic pulmonary fibrosis (IPF), peyronie's disease, glaucoma, diabetic retinopathy, age dependent macular degeneration, Retinopathia pigmentosa, or a disease characterized by disorders of gut motility like irritable bowel syndrome, liver fibrosis, Alzheimer's disease, chronic heart failure, and cancer, preferably breast, gastrointestinal, lung, skin, prostate, pancreatic, colon, rectal cancer.

~~17~~20. Use of the compound of formula **I** or formula **II** of any of the claims 1 to ~~11~~16, or the pharmaceutical composition of ~~claim 12~~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~~, 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, 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~~, preferably breast, gastrointestinal, lung, skin, prostate, pancreatic, colon, rectal cancer, 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, skin aging, 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, and wherein again further preferably 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, skin aging, 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~~.

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.

~~18~~25. The use of ~~claim 16 or claim 17~~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~~, and wherein preferably said sGC stimulator is selected from the group consisting of riociguat, vericiguat, praliciguat and olinciguat~~.

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