7(11):603-609). 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; 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.

Beside the success of the known PDE5 inhibitors, there is still a need for further and in particular 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 a disturbed cGMP balance.

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. Compounds however, which stimulate sGC and inhibit PDE5 at the same time however have not been described.

SUMMARY

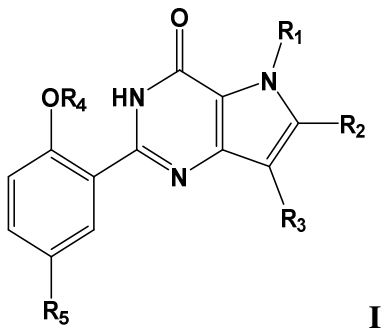
We have surprisingly found that the compounds of the present disclosure are dual-pharmacology NO-releasing PDE5 inhibitors believed to release NO in addition to its PDE5 inhibition in a more than additive, thus, synergistic fashion. We have further surprisingly found that the compounds of the present disclosure are highly bound to plasma proteins when they reach blood circulation. Such strongly bound compounds cannot exhibit their biological activity, making them especially prone to local application and local action. The synergistic increase of cGMP results in highly potent vasodilatation, angiogenesis and inhibition of endothelial dysfunction (see Fig. 1). Thus, the dual-pharmacology NO-releasing PDE5 inhibitors of the present disclosure are expected to be especially beneficial in treating disorders where NO production is diminished such as in conditions of endothelial dysfunction. Furthermore, the

disclosed dual-pharmacology NO-releasing PDE5 inhibitors are further believed to be highly beneficial for the treatment of diabetic patients.

Moreover, we have surprisingly found that the compounds of the present disclosure show even a significantly higher efficacy to elevate intracellular cGMP. as compared to known PDE5 inhibitors such as sildenafil or mirodenafil. In addition we discovered a very high plasma protein binding with several compounds of the disclosure, making them especially prone to local applications and local actions. As a consequence, the novel pyrrolo pyrimidone 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 in combination with stimulation of soluble guanylate cyclase exhibited by compounds of the present disclosure, cGMP levels are elevated, which in turn can give rise to beneficial vasodilatory, anti-vasospastic, anti-platelet, natriuretic and diuretic activities. Furthermore, the dual-pharmacology NO-releasing PDE5 inhibitors allows the release of nitric oxide for activating the soluble guanylate cyclase as well as the PDE5 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 pulmonary artery hypertension (PAH), chronic thromboembolic pulmonary hypertension, male erectile dysfunction, priapism, female sexual dysfunction, wound healing, in particular chronic wound healing, diabetic foot, diabetic foot ulcer, leg ulcer, Raynaud's, male erectile dysfunction, Alzheimer's disease, livedoid vasculopathy, thromboangitis obliterans, chronic anal fissure, skin fibrosis, diabetes, hair loss, skin aging, vascular aging, pulmonary artery hypertension and chronic heart failure. The compounds of the disclosure are especially suited for local drug application as depicted in Fig. 2.

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



I

or pharmaceutically acceptable salt, solvate or hydrate thereof, wherein

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};

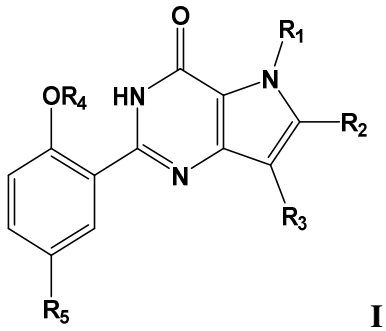
R_{15} is C_1-C_6alkyl optionally substituted with halogen, OH, ONO, ONO_2, C_1-C_3alkoxy, C_1-C_3haloalkoxy, $COOR_{16}$, $NR_{17}R_{18}$, $C{=}NR_{19}$, or with a tetrazole moiety which is optionally substituted with C_1-C_3alkyl; or a heteroaryl ring which is optionally substituted with F, wherein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

at least one of R_1, R_2, R_3, R_4, or R_5 independently of each other comprises at least one ONO_2 or ONO moiety;

R_1 is C_1-C_3alkyl optionally substituted with F, C_3-C_6cycloalkyl, C_1-C_3alkoxy, ONO, ONO_2;

R_2 is H, C_1-C_3alkyl optionally substituted with OH, ONO, ONO_2; C(O)OH, $C(O)OC_1$-C_3alkyl, CHO, CN, $C(O)N(R_6)OR_7$, $CR_8{=}N\text{-}OR_9$, $CR_8{=}N\text{-}NR_{10}R_{11}$, $CR_8{=}NR_{12}$, $CR_8{=}N\text{-}ONO_2$, C_1-C_3alkoxy; C_1-C_3alkylene-Y, wherein Y is ONO, ONO_2, C(O)OH, $C(O)OC_1$-C_3alkyl, CHO, CN, OH, OC(O)H, $OC(O)\text{-}C_1$-C_3alkyl, $C(O)N(R_6)OR_7$, OC_1-C_3alkylene-C(O)OH, OC_1-C_3alkylene-$C(O)OC_1$-C_3alkyl, OC_1-C_3alkylene-$C(O)N(R_6)OR_7$, $S(O_{0\text{-}2})C_1$-C_3alkyl, $CR_8{=}N\text{-}OR_9$, $CR_8{=}N\text{-}NR_{10}R_{11}$, $CR_8{=}NR_{12}$ or $CR_8{=}N\text{-}ONO_2$;

R_3 is C_1-C_4alkyl optionally substituted with F, OH, ONO, ONO_2, C_1-C_3alkoxy, C_3-C_6cycloalkyl; C_3-C_6cycloalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl;

R_4 is C_1-C_6alkyl optionally substituted with C_3-C_6cycloalkyl, C_1-C_6alkoxy, F, ONO, ONO_2; C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl;

R_5 is H, $SO_2NR_{13}R_{14}$, $NHSO_2NR_{13}R_{14}$;

R_6 is H or C_1-C_3alkyl;

R_7 is H, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkyl substituted with phenyl, benzyl or a heterocyclic ring, wherein said phenyl, benzyl or said heterocyclic ring are independently optionally substituted by C_1-C_3alkyl, F;

R_8 is H, CH_3 or C_2H_5;

R_9 is H, C_1-C_3alkyl optionally substituted with OH, ONO, ONO_2, CN, COOH, $COOC_1$-C_3alkyl, C_1-C_3alkoxy, OC(O)H, OC(O)-C_1-C_3alkyl, $C(O)N(R_6)OR_7$, OC_1-C_3alkylene-C(O)OH, OC_1-C_3alkylene-C(O)OC_1-C_3alkyl, OC_1-C_3alkylene-$C(O)N(R_6)OR_7$, $S(O_{0-2})C_1$-C_3alkyl;

R_{10} and R_{11} are each independently H, C_1-C_3alkyl optionally substituted with OH, ONO, ONO_2, CN, COOH, $COOC_1$-C_3, C_1-C_3alkoxy, OC(O)H, OC(O)-C_1-C_3alkyl, $C(O)N(R_6)OR_7$, OC_1-C_3alkylene-C(O)OH, OC_1-C_3alkylene-C(O)OC_1-C_3alkyl, OC_1-C_3alkylene-$C(O)N(R_6)OR_7$, $S(O_{0-2})C_1$-C_3alkyl;, 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 and homopiperazine, wherein said heterocyclic ring is optionally substituted with C_1-C_3 alkyl;

R_{12} is C_1-C_3 alkyl optionally substituted with OH, ONO, ONO_2, CN, COOH, $COOC_1$-C_3alkyl, C_1-C_3alkoxy, OC(O)H, OC(O)-C_1-C_3alkyl, $C(O)N(R_6)OR_7$, OC_1-C_3alkylene-C(O)OH, OC_1-C_3alkylene-C(O)OC_1-C_3alkyl, OC_1-C_3alkylene-$C(O)N(R_6)OR_7$, $S(O_{0-2})C_1$-C_3alkyl;

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 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),

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.

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

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 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 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.

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

Further examples of the present disclosure will be become apparent as this description continues.

DESCRIPTION OF THE FIGURES

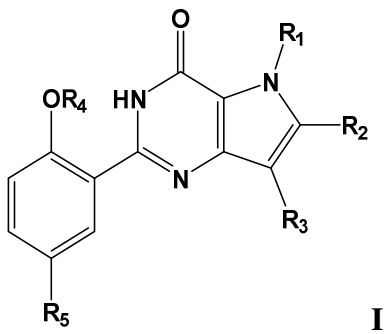
FIG. 1: PDE5 inhibition and activation of soluble guanylate cyclase from one molecule

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

FIG. 3: 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 and mirodenafil.

CLAIMS:

1. A compound of formula **I**



I

or pharmaceutically acceptable salt, solvate or hydrate thereof, wherein

at least one of R_1, R_2, R_3, R_4, or R_5 independently of each other comprises at least one ONO_2 or ONO moiety;

R_1 is C_1-C_3alkyl optionally substituted with F, C_3-C_6cycloalkyl, C_1-C_3alkoxy, ONO, ONO_2;

R_2 is H, C_1-C_3alkyl optionally substituted with OH, ONO, ONO_2; C(O)OH, C(O)OC_1-C_3alkyl, CHO, CN, C(O)N(R_6)OR_7, CR_8=N-OR_9, CR_8=N-N$R_{10}R_{11}$, CR_8=NR_{12}, CR_8=N-ONO_2, C_1-C_3alkoxy; C_1-C_3alkylene-Y, wherein Y is ONO, ONO_2, C(O)OH, C(O)OC_1-C_3alkyl, CHO, CN, OH, OC(O)H, OC(O)-C_1-C_3alkyl, C(O)N(R_6)OR_7, OC_1-C_3alkylene-C(O)OH, OC_1-C_3alkylene-C(O)OC_1-C_3alkyl, OC_1-C_3alkylene-C(O)N(R_6)OR_7, S(O_{0-2})C_1-C_3alkyl, CR_8=N-OR_9, CR_8=N-$NR_{10}R_{11}$, CR_8=NR_{12} or CR_8=N-ONO_2;

R_3 is C_1-C_4alkyl optionally substituted with F, OH, ONO, ONO_2, C_1-C_3alkoxy, C_3-C_6cycloalkyl; C_3-C_6cycloalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl;

R_4 is C_1-C_6alkyl optionally substituted with C_3-C_6cycloalkyl, C_1-C_6alkoxy, F, ONO, ONO_2; C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl;

R_5 is H, $SO_2NR_{13}R_{14}$, $NHSO_2NR_{13}R_{14}$;

R_6 is H or C_1-C_3alkyl;

R_7 is H, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkyl substituted with phenyl, benzyl or a heterocyclic ring, wherein said phenyl, benzyl or said heterocyclic ring are independently optionally substituted by C_1-C_3alkyl, F;

R_8 is H, CH_3 or C_2H_5;

R_9 is H, C_1-C_3alkyl optionally substituted with OH, ONO, ONO_2, CN, COOH, $COOC_1$-C_3alkyl, C_1-C_3alkoxy, OC(O)H, OC(O)-C_1-C_3alkyl, $C(O)N(R_6)OR_7$, OC_1-C_3alkylene-C(O)OH, OC_1-C_3alkylene-C(O)OC_1-C_3alkyl, OC_1-C_3alkylene-$C(O)N(R_6)OR_7$, $S(O_{0-2})C_1$-C_3alkyl;

R_{10} and R_{11} are each independently H, C_1-C_3alkyl optionally substituted with OH, ONO, ONO_2, CN, COOH, $COOC_1$-C_3, C_1-C_3alkoxy, OC(O)H, OC(O)-C_1-C_3alkyl, $C(O)N(R_6)OR_7$, OC_1-C_3alkylene-C(O)OH, OC_1-C_3alkylene-C(O)OC_1-C_3alkyl, OC_1-C_3alkylene-$C(O)N(R_6)OR_7$, $S(O_{0-2})C_1$-C_3alkyl;, 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 and homopiperazine, wherein said heterocyclic ring is optionally substituted with C_1-C_3 alkyl;

R_{12} is C_1-C_3 alkyl optionally substituted with OH, ONO, ONO_2, CN, COOH, $COOC_1$-C_3alkyl, C_1-C_3alkoxy, OC(O)H, OC(O)-C_1-C_3alkyl, $C(O)N(R_6)OR_7$, OC_1-C_3alkylene-C(O)OH, OC_1-C_3alkylene-C(O)OC_1-C_3alkyl, OC_1-C_3alkylene-$C(O)N(R_6)OR_7$, $S(O_{0-2})C_1$-C_3alkyl;

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.

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, C_1-C_3alkyl optionally substituted with OH, ONO, ONO_2; C(O)OH, C(O)OC_1-C_3alkyl, CHO, CN, CR_8=N-OR_9,

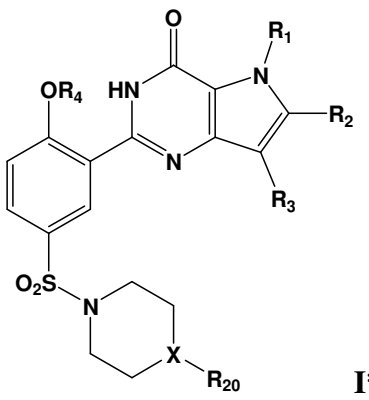
CR_8=N-$NR_{10}R_{11}$, CR_8=NR_{12}, CR_8=N-ONO_2, C_1-C_3alkoxy; C_1-C_3alkylene-Y, wherein Y is ONO, ONO_2, CHO, CN, OH, OC(O)H, OC_1-C_3alkylene-C(O)OH, OC_1-C_3alkylene-C(O)N(R_6)OR_7, OC(O)-C_1-C_3alkyl, C(O)OC_1-C_3alkyl, C(O)N(R_6)OR_7, CR_8=N-OR_9, CR_8=N-$NR_{10}R_{11}$, CR_8=NR_{12} or CR_8=N-ONO_2, wherein preferably said R_6 and R_8 are independently of each other H or CH_3.

4. The compound according to any one of the claims 1 to 3, wherein R_3 is C_1-C_4alkyl optionally substituted with OH, ONO, ONO_2, C_1-C_3alkoxy; C_2-C_4alkenyl.

5. The compound according to any one of the claims 1 to 4, wherein R_4 is C_1-C_4alkyl optionally substituted with C_1-C_3alkoxy, F, ONO, ONO_2; C_2-C_4alkenyl.

6. The compound according to any one of claims 1 to 5, wherein R_{13} and R_{14} together with the nitrogen atom to which they are attached form a heterocyclic ring, wherein said heterocyclic ring is selected from piperidine and piperazine, and wherein said heterocyclic ring is substituted with R_{15}; wherein R_{15} is C_1-C_4alkyl 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}; and wherein
R_{16} is H, or C_1-C_4alkyl optionally substituted with F, OH, ONO, ONO_2;
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.

7. The compound according to any one of claims 1 to 5, wherein said compound of formula **I** is a compound of formula **I*,** or pharmaceutically acceptable salt, solvate or hydrate thereof, wherein at least one of R_1, R_2, R_3, R_4, or R_{20} independently of each other 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 2 to 5; and wherein

X is CR_{21} or N;

R_{20} is C_1-C_4alkyl optionally substituted with halogen, OH, ONO, ONO_2, C_1-C_3alkoxy, C_1-C_3haloalkoxy, $COOR_{25}$, $NR_{26}R_{27}$, $C{=}NR_{28}$;

R_{21} is H or C_1-C_4alkyl optionally substituted with halogen, OH, ONO, ONO_2, C_1-C_3alkoxy, C_1-C_3haloalkoxy, $COOR_{25}$, $NR_{26}R_{27}$, $C{=}NR_{28}$;

R_{25} is H, or C_1-C_4alkyl optionally substituted with F, OH, ONO, ONO_2;

R_{26} and R_{27} are each independently H or C_1-C_4alkyl optionally substituted with ONO, ONO_2;

R_{28} is C_1-C_4alkyl optionally substituted with F, ONO, ONO_2.

8. The compound according to claim 7, wherein

R_1 is C_1-C_3alkyl;

R_2 is H, C_1-C_3alkyl optionally substituted with OH, ONO, ONO_2; CHO, CN, $CR_8{=}N\text{-}OR_9$, $CR_8{=}N\text{-}NR_{10}R_{11}$, C_1-C_3alkoxy; C_1-C_3alkylene-Y, wherein Y is ONO, ONO_2, CHO, CN, OH, OC(O)H, $C(O)OC_1$-C_3alkyl, $CR_8{=}N\text{-}OR_9$, $CR_8{=}N\text{-}NR_{10}R_{11}$, or $CR_8{=}N\text{-}ONO_2$, wherein R_6 and R_8 are independently of each other H or CH_3; R_9 is H, C_1-C_3alkyl optionally substituted with OH, ONO, ONO_2, CN, COOH, C_1-C_3alkoxy, OC(O)H, OC(O)-C_1-C_3alkyl; R_{10} and R_{11} are each independently H, C_1-C_3alkyl optionally substituted with OH, ONO, ONO_2, CN, COOH, C_1-C_3alkoxy, OC(O)H, OC(O)-C_1-C_3alkyl;

R_3 is C_1-C_4alkyl optionally substituted with OH, ONO, ONO_2, C_1-C_3alkoxy;

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 halogen, OH, ONO, ONO_2, C_1-C_3alkoxy, $COOR_{25}$, $NR_{26}R_{27}$;

R_{21} is H or C_1-C_4alkyl optionally substituted with halogen, OH, ONO, ONO_2, C_1-C_3alkoxy, $COOR_{25}$, $NR_{26}R_{27}$;

wherein R_{25} is H, or C_1-C_4alkyl optionally substituted with OH, ONO, ONO_2;

R_{26} and R_{27} are each independently H or C_1-C_4alkyl optionally substituted with ONO, ONO_2.

9. The compound according to claim 7, wherein

R_1 is C_1-C_2alkyl;

R_2 is H, C_1-C_3alkyl optionally substituted with OH, ONO, ONO_2; CHO, $CR_8{=}N\text{-}OR_9$, C_1-C_3alkoxy; C_1-C_3alkylene-Y, wherein Y is ONO, ONO_2, CN, or $CR_8{=}N\text{-}OR_9$, wherein R_8 is H or CH_3; R_9 is H, C_1-C_3alkyl optionally substituted with OH, ONO, ONO_2;

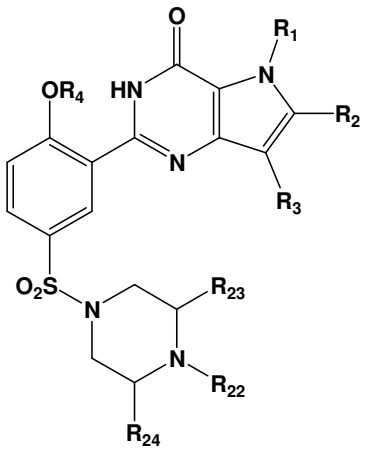
R_3 is C_2-C_3alkyl optionally substituted with OH, ONO, ONO_2;

R_4 is C_2-C_3alkyl optionally substituted with ONO, ONO_2;

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

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

10. The compound according to any one of claims 1 to 5, wherein said compound of formula **I** is a compound of formula **I**,** or pharmaceutically acceptable salt, solvate or hydrate thereof, wherein at least one of R_1, R_2, R_3, R_4, 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 9; and wherein

R_{22} is H or C_1-C_4alkyl optionally substituted with halogen, OH, ONO, ONO_2, C_1-C_3alkoxy, C_1-C_3haloalkoxy, $COOR_{25}$, $NR_{26}R_{27}$, $C{=}NR_{28}$;

R_{23} and R_{24} are each independently C_1-C_4alkyl optionally substituted with halogen, OH, ONO, ONO_2, C_1-C_3alkoxy, C_1-C_3haloalkoxy, $COOR_{25}$, $NR_{26}R_{27}$, $C{=}NR_{28}$;

R_{25} is H, or C_1-C_4alkyl optionally substituted with F, OH, ONO, ONO_2;

R_{26} and R_{27} are each independently H or C_1-C_4alkyl optionally substituted with ONO, ONO_2;

R_{28} is C_1-C_4alkyl optionally substituted with F, ONO, ONO_2.

11. The compound according to claim 10, 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.

12. 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)-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 (**3p**);
(S)-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 (**3q**).

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

14. Use of the compound of formula **I** of any one of the claims 1 to 12, or the pharmaceutical composition of claim 13, in the manufacture of a medicament for 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.

15. Use of the compound of formula **I** of any one of the claims 1 to 12 or the pharmaceutical composition of claim 13, in the manufacture of a medicament for 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.

16. The compound of formula **I** of any one of the claims 1 to 12 or the pharmaceutical composition of claim 13, for use as a medicament.