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(54) Title: THE USE OF SGC STIMULATORS, SGC ACTIVATORS, ALONE AND COMBINATIONS WITH PDE5 INHIBITORS FOR THE TREATMENT OF DIGITAL ULCERS (DU) CONCOMITANT TO SYSTEMIC SCLEROSIS (SSC)

(57) Abstract: Use of s GC stimulators, sGC activators alone, or in combination with PDE5 inhibitors for the prevention and healing of Digital Ulcers which are concomitant to fibrotic diseases, such as systemic sclerosis and scleroderma.

The use of sGC stimulators, sGC activators, alone and combinations with PDE5 inhibitors for the treatment of Digital Ulcers (DU) concomitant to systemic sclerosis (SSc).

The use of sGC stimulators, sGC activators alone, or in combination with PDE5 inhibitors for the prevention and healing of Digital Ulcers which are concomitant to fibrotic diseases, such as systemic sclerosis and scleroderma.

Background of the invention

Systemic Sclerosis and concomitant Digital Ulcers (DU)

The pathogenesis of Systemic Sclerosis (SSc) is still unclear and remains elusive. However, scleroderma is a non-inherited, noninfectious disease and thought to be an autoimmune disease. SSc has a broad variety of symptoms triggered by excessive deposition of extracellular matrix in the dermis resulting in skin fibrosis. In later stages SSc is characterized by progressive tissue fibrosis affecting other internal organs as the gut, the lung or the kidneys. Therefore scleroderma is the hallmark of the disease comprising also e.g. lung fibrosis, renal fibrosis, fibrosis of the heart, the gut or the blood vessels. Besides excessive fibrosis in the skin and internal organs, SSc is also characterized by vasculopathies and microangiopahties. Especially small vessel vasculopathies and concomitant vascular malperfusion and ischemia can cause Raynaud´s phenomena (RP) but also to the formation of digital ulcer (DU). Whereas tissue fibrosis can cause end organ failure and lead to high morbidity and mortality in patients with end-stage SSc, formation of DU substantially reduce the quality of life of SSc patients, impairs hand function and leads to disability. (Harris et al. 2005 - Kelley´s Textbook of Rhematology 7th edition. Elsevier Saunders, Philadelphia PA).

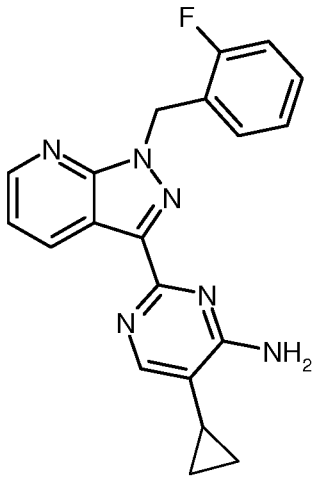
There is still no causative treatment for Systemic Sclerosis (SSc) available and the current therapy is based on suppression of the immune system via corticosteroids, cyclophosphamide, methotrexate. More recently kinase inhibitors and anti-inflammatory drugs are under investigation as immunosuppressant and antifibrotic agents in SSc, but tolerability is limited in SSc patients (Khanna and Denton 2010 - Best. Pract. Res. Clin. Rheumatol. 24:387-400, Ong and Denton 2010 - Curr. Opin. Rheumatol. 22:264-272, Spiera 2011 - Ann. Rheum. Dis. Epub Mar 2011). These therapies either used as stand alone treatment or combined are of limited efficacy and exhibited considerable side effects. Therefore alternative treatment options in SSc which are efficacious and safe are urgently needed. In addition, there is currently no approved treatment for healing of DU but vasoactive drugs as prostacyclin agonists and endothelin antagonists are used.

Antifibrotic effects of cGMP:

The cyclic nucleotides, cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), were discovered decades ago and represent one of the most important second messenger pathway within cells. It is well established that the regulation of intra-cellular cGMP pools have substantial impact on physiology, and pathophysiology and is one basic principle of pharmacological intervention (Evgenov et al. 2006 - Nat. Rev. Drug. Discov. 5(9):755-768). Besides the treatment of cardiovascular, lung or CNS-disorders there is ample evidence that an increase in cGMP is a very effective treatment option for urological disorders as well (Sandner et al. 2009 – Handbook Exper. Pharmacol. 191:507-531). PDE5 inhibitors are the gold-standard for the treatment of erectile dysfunction (ED) but it was shown that PDE5 inhibitors could be useful for the treatment of symptomatic BPH which is characterized by Overactive Bladder (OAB) and Lower Urinary Tract Symptoms (LUTS) (Porst et al. 2008 - Curr. Urol. Rep. 9:295-301; .McVary et al. 2007 - J. Urol. 177:1071-1077, J Urol. 177:1401-1407, Kaplan and Gonzalez. 2007 - Rev. Urol. 9:73-77). The antifibrotic effects of Vardenafil, sGC stimulators and sGC activators is not understood yet. There are some descriptions about antifibrotic effects of Nitric-Oxide which are presumably mediated by cGMP in other organs and PDE5 inhibitors or guanylate cyclase stimulators have shown efficacy in penile fibrosis (Peyronie´s disease) (Ferrini et al. 2006 - B. J. Urol. 97:625-633) and liver fibrosis (Knorr et al. 2008 - Arzneimittelforschung 58:71-80) respectively.

It was not known if the NO/cGMP system is involved in SSc and if cGMP increase provides a treatment option for this disease. We hypothetized that – independent from endogenous NO/cGMP production – sGC stimulators and activators might be an effective treatment option for Systemic Sclerosis (SSc) by reduction of skin fibrosis. In WO2011/147810 we have recently shown that sGC stimulators, sGC activators, alone and combinations with PDE5 inhibitors could directly target skin fibrosis which is one hallmark of Systemic Sclerosis (SSc). This clearly demonstrated that sGC stimulators, sGC activators, alone and combinations with PDE5 inhibitors are an effective future treatment option for SSc. However, it is not known if the vasculopathies in SSc patients which lead e.g. to DU formation which are one of the most bothersome symptoms in SSc, could be also efficiently treated with sGC stimulators, sGC activators, alone and combinations with PDE5 inhibitors. Since these compounds can induce peripheral vasodilation it could be assumed that SSc driven vasculopathies might be reduced, preventing new formation of DU. However, it was unclear if SSc-driven DU could be also healed giving the antifibrotic mode of action of sGC stimulators/sGC activators alone and in combination with PDE5 inhibitors. Therefore, increased blood flow may be counteracted by reduced collagen-synthesis or synthesis of extracellular matrix which is necessary for wound closure and which then may impair wound healing in SSc patients.

We therefore investigated sGC stimulators and sGC activators, i.e. compound of the formula



(27)

and combinations with PDE5 inhibitors thereof on wound healing was in TSK mice an animal model for SSc characterized by excessive skin fibrosis We found in vivo in our animal models that:

- TSK mice have an attenuated wound healing compared to WT mice.
- sGC stimulators or sGC activators, i.e. compounds according to formulae (27) and (3) significantly and dose-dependently accelerated wound healing in the TSK mice.
- sGC stimulators or sGC activators, i.e compounds according to formulae (27) and (3) normalized the healing time to healthy WT control mice. These data suggest that despite the antifibrotic effectof sGC stimulators and sGC activators in SSc, wound healing in SSc could be significantly accelerated and normalized to the levels of healthy control individuals

In summary, we found completely unexpected and for the first time that sGC stimulators or sGC activators i.e. compounds according to formulae (27) and (3), which prevent fibrosis and regress established fibrosis in different animal models of inflammatory and non-inflammatory SSc, could also lead to significantly enhanced wound healing in the TSK-mouse SSc model.

Taken together this data indicate for the first time that sGC stimulators and sGC activators, i.e. compounds according to formulae (27) and (3) could improve wound healing in an SSc. These data also suggest that despite the antifibrotic mode of action, these compounds are able to heal DUs in SSc patients.

Disclosure of the invention

Fibrotic disorders addressed by therapeutic agents of the invention which in particular and with substantial advantage can be treated by the above mentioned sGC stimulators or sGC activators alone or in combination with PDE5 inhibitors comprise but are not limited to Systemic Sclerosis (SSc), Systemic Sclerosis (SSc) concomitant fibrosis and fibrotic diseases.

Fibrotic disorders addressed by therapeutic agents of the invention which in particular and with substantial advantage can be treated by the above mentioned sGC stimulators or sGC activators alone or in combination with PDE5 inhibitors comprise but are not limited to Systemic Sclerosis (SSc) concomitant vasculopathies, to Raynaud´s phenomena (RD) and the formation and healing of digital ulcers (DU)

Systemic Sclerosis (SSc) refers to but is not limited to diffuse Systemic Sclerosis (dSSc), limited Systemic Sclerosis (lSSc), overlap type of Systemic Sclerosis, undifferentiated type of Systemic Sclerosis, Systemic Sclerosis sine scleroderma, skin fibrosis, scleroderma, nephrogenic fibrosing dermopathy (NFD), nephrogenic systemic fibrosis (NSF), keloid formation.

SSc concomitant fibrosis refers to fibrosis of internal organs, comprising but not limited to the gut, the lung, the kidney and the blood vessels.

Fibrotic diseases comprises but are not limited to a condition in which collagen excess - independent of the etiology i.e. autoimmune disorders, chronic graft versus host disease, radiation therapy, intoxications, diabetes, surgery – lead to fibrosis of the skin, gut, liver, lung, heart, bladder, prostate, blood vessels or any other localized or generalized fibrotic condition in tissues.

In the sense of the present invention, the term fibrotic diseases comprises in particular the following terms: hepatic fibrosis, hepatic cirrhosis, pulmonary fibrosis, endomyocardial fibrosis, nephropathy, glomerulonephritis, interstitial renal fibrosis, fibrotic lesions as a consequence of diabetes, bone marrow fibrosis and similar fibrotic diseases, scleroderma, morphea, keloids, hypertrophic scars (including after surgery), naevi, diabetic retinopathy, proliferative vitreoretinopathy and connective tissue diseases (e.g. sarcoidosis

SSc concomitant vasculopathies comprise but are not limited to vascular occlusive diseases vasculitis, micro and macroangiopathies, Raynaud´s Phenomena, digital ischemic lesions, digital ulcer, digital necrotic lesions, gangrene anddigital loss.

In the sense of the present invention, sGC stimulators are nitric oxide (NO) independent and heam-dependent modulators of the soluble guanylate cyclase.

In the sense of the present invention, sGC activators are nitric oxide (NO) and heam- independent modulators of the soluble guanylate cyclase.

A preferred embodiment of the invention is the use of compounds according to compounds disclosed in WO03/097063, WO03/09545, WO04/009589, WO03/004503, WO02/070462, WO2007/045366, WO2007/045369, WO2007/045370, WO2007/045433, WO2007/045367, WO2007/124854, WO2007/128454, WO2008/031513, WO2008/061657, WO2008/119457, WO2008/119458, WO2009/127338, WO2010/079120, WO2010/102717, WO2011/051165, WO2011/147809, WO2011/141409, WO2014/012935, WO2012/059549, WO2012/004259, WO2012/004258, WO2012/059548, WO2012/028647, WO2012/152630, WO 2012/076466, WO2014/068099, WO2014/068104, WO2012/143510, WO2012/139888, WO2012/152629, WO2013/004785, WO2013/104598, WO2013/104597, WO2013/030288, WO2013/104703, WO2013/131923, WO2013/174736, WO2014/012934, WO2014/068095, WO2014/195333, WO2014/128109, WO2014/131760, WO2014/131741, WO2015/018808, WO2015/004105, WO2015/018814, WO98/16223, WO98/16507, WO98/23619, WO00/06569, WO01/19776, WO01/19780, WO01/19778, WO02/042299, WO02/092596, WO02/042300, WO02/042301, WO02/036120, WO02/042302, WO02/070459, WO02/070460, WO02/070461, WO02/070510, WO2012/165399, WO2014/084312, WO2011115804, WO2012003405, WO2012064559, WO2014/047111, WO2014/047325, WO2011/149921, WO2010/065275, WO2011/119518 for the manufacture of a medicament for prevention and healing of Digital Ulcers which are concomitant to fibrotic diseases, such as systemic sclerosis and scleroderma. A preferred embodiment of the invention is the use of compounds according to formulae (1)-(28) for the manufacture of a medicament for prevention and healing of Digital Ulcers which are concomitant to fibrotic diseases, such as systemic sclerosis and scleroderma., as shown below:

2-[1-(2-Fluorbenzyl)-1H-pyrazolo[3,4-b]pyridine-3-yl]-5-(4-morpholinyl)-4,6-pyrimidinediamine (1), disclosed as example 16 in WO 00/06569,

- 2-[1-(2-Fluorobenzyl)-1H-pyrazolo[3,4-b]pyridine-3-yl]-5-(4-pyridinyl)-4-pyrimidine amine (2), disclosed as example 1 in WO 02/42301,
- Methyl-4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridine-3-yl]-5-pyrimidinyl-(methyl)carbamate (3), disclosed as example 8 in WO 03/095451,
- Methyl-4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridine-3-yl]-5-pyrimidinyl-carbamate (4), disclosed as example 5 in WO 03/095451
- 4-({(4-carboxybutyl)[2-(2-{[4-(2-phenylethyl)benzyl]oxy}phenyl)ethyl]amino}methyl) carboxylic acid (5), disclosed as example 8a in WO 01/019780,

- Methyl-{4,6-diamino-2-[5-fluoro-1-(2-fluorbenzyl)-1H-pyrazolo[3,4-b]pyridine-3-yl]pyrimidine-5-yl}carbamate (6), Methyl-{4,6-diamino-2-[5-fluoro-1-(2-fluorbenzyl)-1H-pyrazolo[3,4-b]pyridine-3-yl]pyrimidine-5-yl}methylcarbamate (7), Methyl-{4,6-diamino-2-[5-fluoro-1-(2-fluorbenzyl)-1H-pyrazolo[3,4-b]pyridine-3-yl]pyrimidine-5-yl}(2,2,2-trifluorethyl)carbamate (8), disclosed in WO 2011/147809,

- 5-Chloro-2-(5-chlorothiophene-2-sulfonylamino-N-(4-(morpholine-4-sulfonyl)-phenyl)-benzamid as sodium salt (9), disclosed in WO00/02851,

- 2-(4-Chloro-phenylsulfonylamino)-4,5-dimethoxy-N-(4-(thiomorpholine-4-sulfonyl)-phenyl)-benzamide (10), disclosed in WO00/02851,

- 1-{6-[5-Chloro-2-({4-trans-4-}trifluoromethyl)cyclohexyl]benzyl}oxy)phenyl]pyridine-2-yl}-5-(trifluoromethyl)-1H-pyrazol-4-carboxylic acid (11), disclosed in WO 2009/032249,

- 1-[6-(2-(2-Methyl-4-(4-trifluoromethoxyphenyl)benzyloxy)-phenyl)pyridine-2-yl]-5-trifluoromethyl-pyrazol-4-carboxylic acid (12), disclosed in WO 2009/071504,

- 1[6-(3,4-dichlorophenyl)-2-pyridinyl-5-(trifluoromethyl)-1H-pyrazole-4-caboxylic acid (13), disclosed in WO 2009/068652,

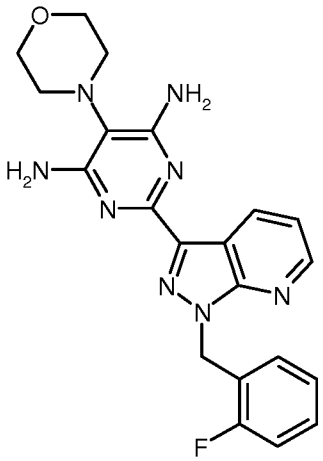
- 1-({2-[3-Chlor-5-(trifluoromethyl)phenyl]-5-methyl-1,3-thiazole-4-yl}methyl)-1H-pyrazole-4-carboxylic acid (14), 4-({2-[3-(Trifluoromethyl)phenyl]-1,3-thiazole-4-yl}methyl)benzoic acid (15) and 1-({2-[2-Fluoro-3-(trifluoromethyl)phenyl]-5-methyl-1,3-thiazole-4-yl}methyl)-1H-pyrazole-4-carboxylic acid (16) disclosed in WO 2009/123316,

- 4-Amino-2-[5-chloro-3(3,3,3-trifluororpropyl)-1H-indazol-1yl]-5,5-dimethyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidine-6-one (17), 4-Amino-2[5-chloro-3-(2,3,6-trifluorbenzyle)-1H-indazol-1yl]-5,5-dimethyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidine-6-one (18), 4-Amino-5,5-dimethyl-2-[3-(2,3,6-trifluorbenzyle)1H-thieno[3,4-c]pyrazol-1-yl]-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidine-6-one (19), 4-Amino-5,5-dimethyl-2-[3-(2,3,6-trifluorbenzyle)-1H-thieno[2,3-d]pyrazole-1-yl]-5,5-dimethyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidine-6-one (20), 4-Amino-5,5-dimethyl-2-[7-(2,3,6-trifluorobenzyle)imidazo[1,5-b]pyridazine-5-yl]-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidine-6-one (21), 4-Amino-2-[6-chloro-3-(2,3,6-trifluorobenzyle)imidazo[1,5-a]pyridine-1-yl]]-5,5-dimethyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidine-6-one (22), 4-Amino-2-[6-fluoro-3-(2,3,6-trifluorobenzyle)imidazo[1,5-a]pyridine-1-yl]]-5,5-dimethyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidine-6-one (23), 4-Amino-2-[6-fluoro-3-(2,3,6-trifluorobenzyl)6-fluoroimidazo[1,5-a]pyridine-1-yl]-5,5-dimethyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidine-6-one (24), 4-Amino-5,5-dimethyl-2-[3-(2,4,6-

trifluorobenzyle)imidazo[1,5-a]pyridine-1-yl]]-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidine-6-one (25), 4-Amino-2-[3-(2-cyclopentylethyl)imidazo[1,5-a]pyridine-1-yl]-5,5-dimethyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidine-6-one (26), disclosed in WO 2010/065275,

- 3-(4-Amino-5-cyclopropylpyrimidine-2-yl)-1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridine (27) known as BAY 41-2272 disclosed as example 1 in WO 00/06568,

- 2-{5-Fluor-1-[(3-fluorpyridine-2-yl)methyl]-1H-pyrazolo[3,4-b]pyridine-3-yl}-5-methyl-5-(trifluormethyl)-4-[(3,3,3-trifluorpropyl)amino]-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidine-6-on (28), disclosed as example 1 in WO 2014/131760.



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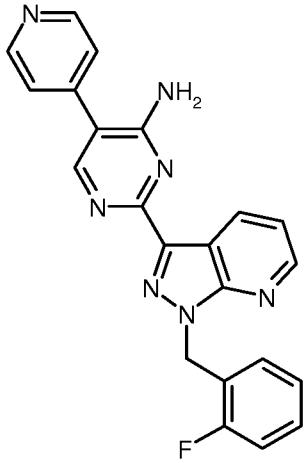

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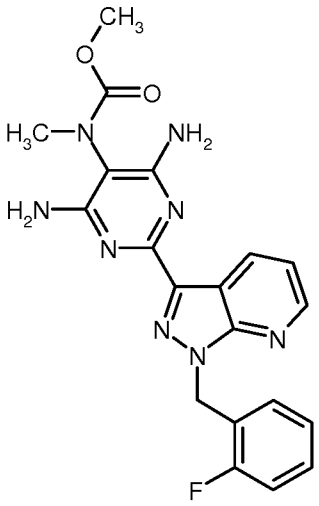

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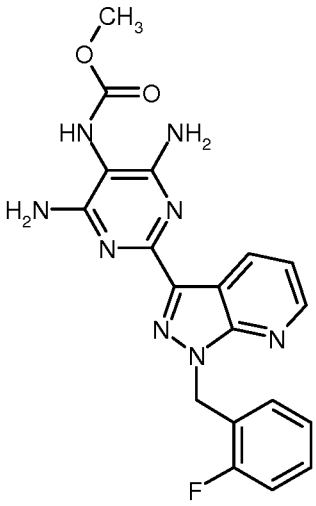

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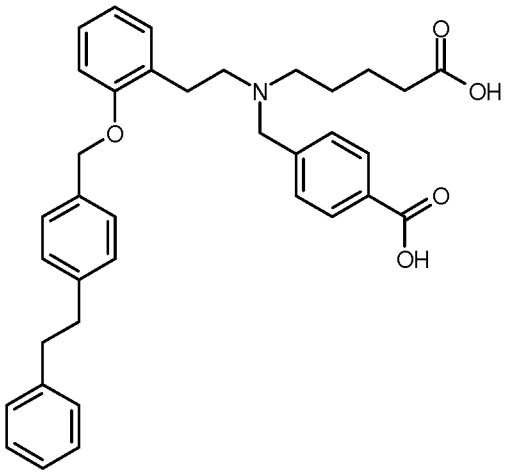

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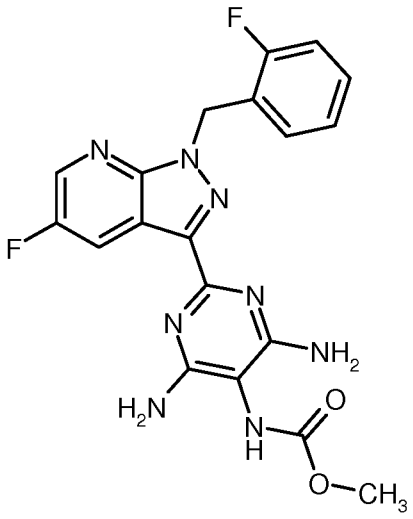

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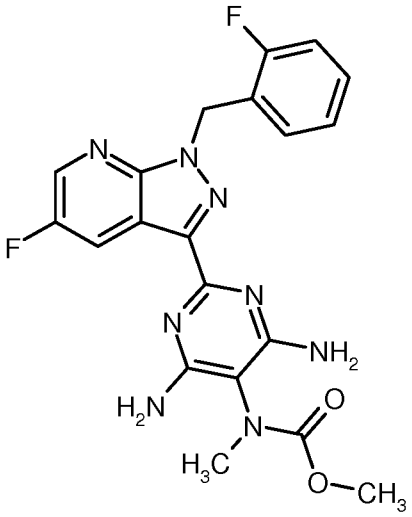

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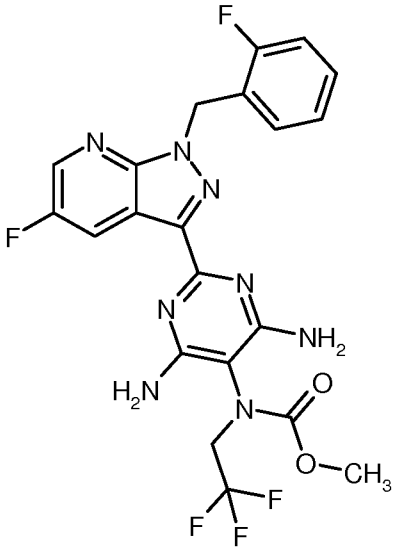

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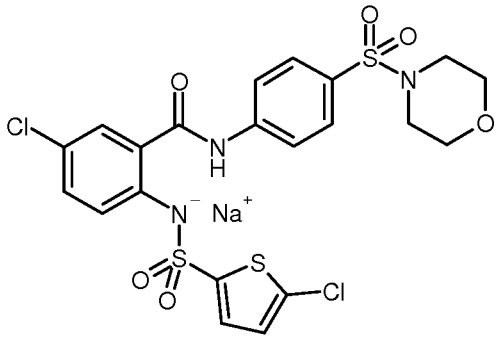

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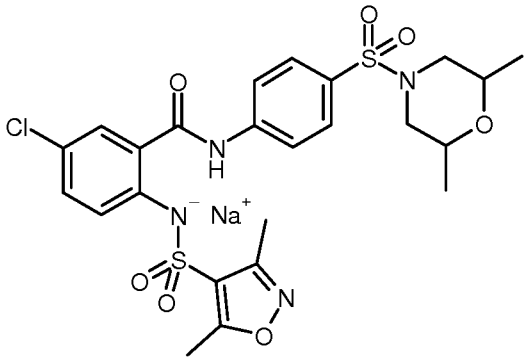

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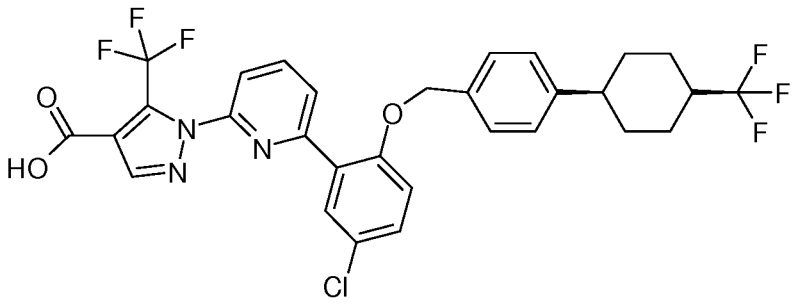

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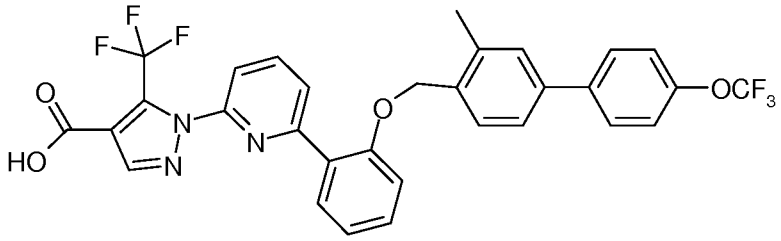

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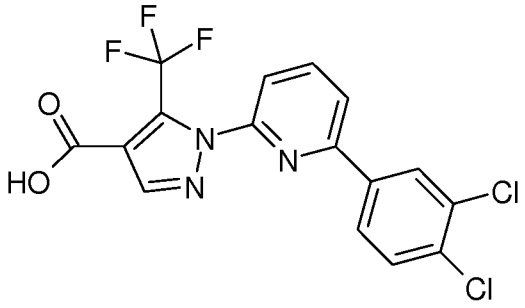

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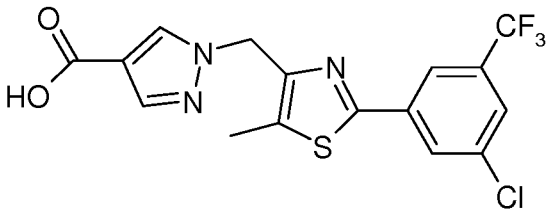

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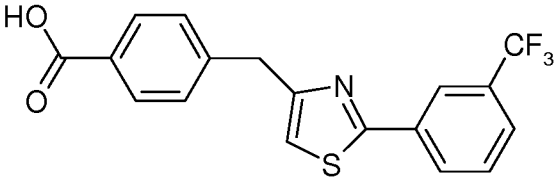

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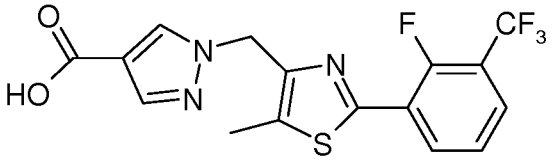

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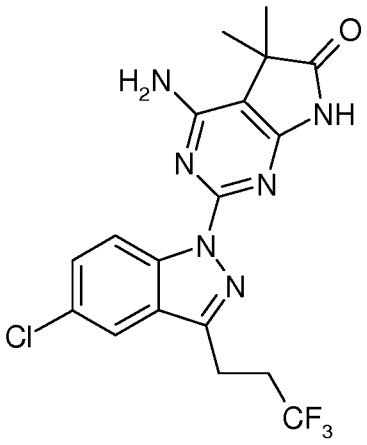

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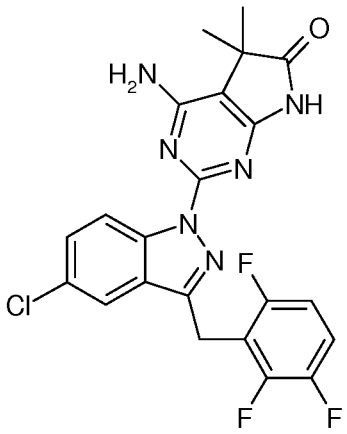

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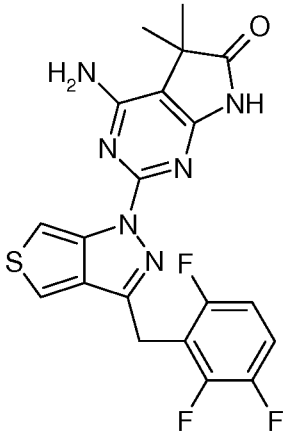

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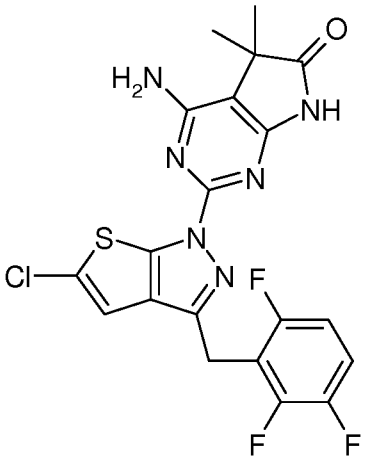

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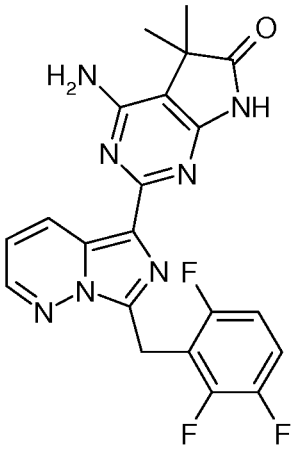

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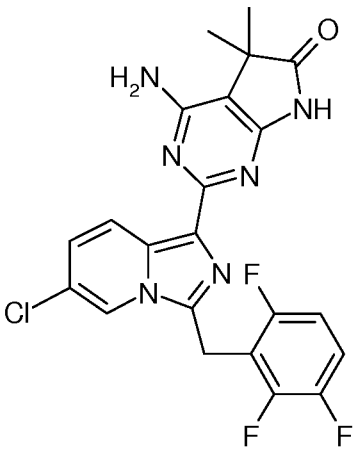

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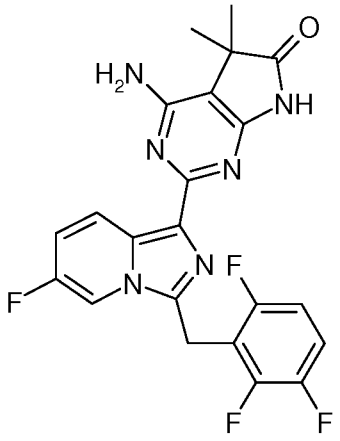

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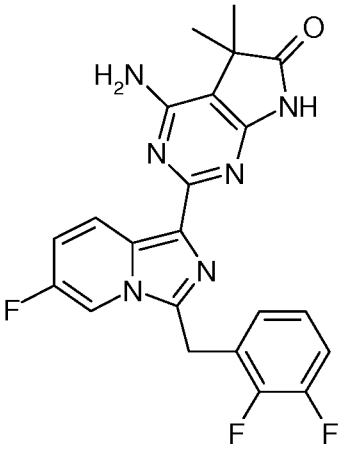

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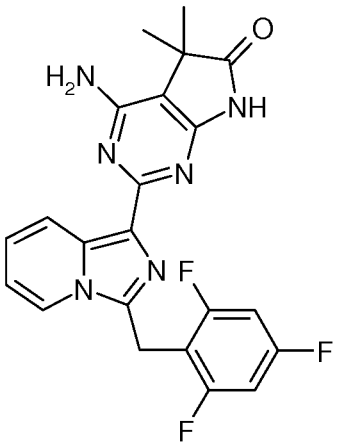

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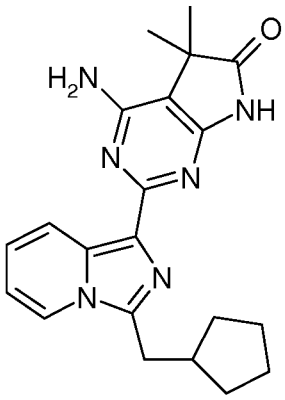

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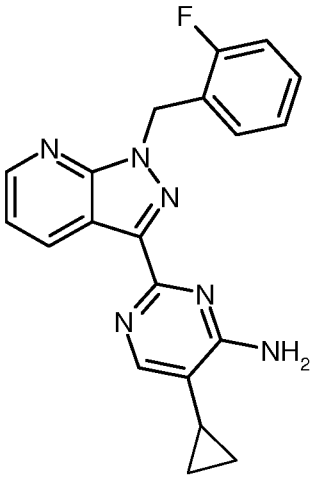

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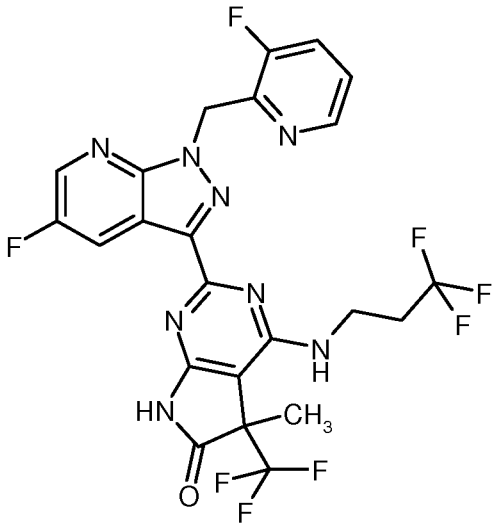

(28)

Compounds according to formulae (1), (2), (3), (4), (6)-(8) and (17)-(27) are known as sGC stimulators. Preferred is the use of compounds according to formulae (1), (2), (3), (4), (6), (7), (27) and (28).

Especially preferred is the use of compounds according to formulae (3), (4), (6), (7) and (28).

Especially preferred is the use of compounds according to formulae (3), (4), (6) and (28).

Especially preferred is the use of compounds according to formulae (3), (7) and (28).

Especially preferred is the use of the compound according to formula (3).

Compounds according to formulae (5) und (9)-(16) are known as sGC activators. Preferred is the use of the compound according to formula (5).

A further embodiment of the invention is the use of the combination of stimulators and/or activators of the soluble guanylate cyclase with PDE5 inhibitors for the manufacture of a medicament for prevention and healing of Digital Ulcers which are concomitant to fibrotic diseases, such as systemic sclerosis and scleroderma.

The use of the following PDE 5 inhibitors is preferred for the combination with sGC stimulators and/or activators:

Tadalafil ((6R,12aR) -2,3,6,7,12,12a – Hexahydro – 2 – methyl – 6 - (3,4-methylene -dioxyphenyl) pyrazino(1',2':1,6) pyrido(3,4-b)indole-1,4-dione), *Vardenafil* (2-(2-Ethoxy-5-(4-ethylpiperazin-1-yl-1-sulfonyl)phenyl)-5-methyl-7-propyl-3H-imidazo (5,1-f) (1,2,4)triazin-4-one), *Sildenafil* (3-[2-

ethoxy-5-(4-methylpiperazin-1-yl)sulfonyl-phenyl]- 7- methy l- 9- propy l-2,4,7,8- tetrazabicyclo [4.3.0]nona -3,8,10-trien-5-one), *Udenafil* 5-[2-propyloxy-5-(1-methyl-2-pyrrolidinylethylamidosulfonyl)phenyl]-methyl-3-propyl-1,6-dihydro-7H-pyrazolo(4,3-d)pyrimidine-7-one, *Dasantafil* 7-(3-Bromo-4-methoxybenzyl)-1-ethyl-8-[[(1,2)-2-hydroxycyclopentyl]amino]-3-(2-hydroxyethyl)-3,7-dihydro-1-purine-2,6-dione, *Avanafil* 4-{[(3-chloro-4-methoxyphenyl)methyl]amino}-2-[(2S)-2-(hydroxymethyl)pyrrolidin-1-yl]-N-(pyrimidin-2-ylmethyl)pyrimidine-5-carboxamide, Mirodenafil, Lodenafil, UK 369.003, UK 371.800, *SLx 2101* of Surface Logix, *LAS 34179*Triazolo[1,2-]xanthine,6-methyl-4-propyl-2-[2-propoxy-5-(4-methylpiperazino)sulfonyl]phenyl or salts, hydrates or hydrates of the salts.

Especially preferred is the use of combinations of compounds according to formulae (1), (2), (3), (4), (6), (7), (27), (28) and /or (5) with vardenafil and/or sildenafil for the manufacture of a medicament in the prevention and healing of Digital Ulcers which are concomitant to fibrotic diseases, such as systemic sclerosis and scleroderma.

Especially preferred is the use of combinations of compounds according to formulae (3), (4), (6), (7), (27), (28) and /or (5) with vardenafil and/or sildenafil for the manufacture of a medicament for the prevention and healing of Digital Ulcers which are concomitant to fibrotic diseases, such as systemic sclerosis and scleroderma.

Especially preferred is the use of compounds according to formulae (3), (4), (6), (7) and/or (28) for the manufacture of a medicament for the prevention and healing of Digital Ulcers which are concomitant to fibrotic diseases, such as systemic sclerosis and scleroderma.

Especially preferred is the use of compounds according to formulae (3), (4) and/or (6) for the manufacture of a medicament for the prevention and healing of Digital Ulcers which are concomitant to fibrotic diseases, such as systemic sclerosis and scleroderma.

Especially preferred is the use of at least one compound according to formulae (3), (4), (6), and/or (7) in combination with vardenafil or sildenafil for the manufacture of a medicament for the prevention and healing of Digital Ulcers which are concomitant to fibrotic diseases, such as systemic sclerosis and scleroderma.

The sGC stimulator such as compound according to formula (3) dose-dependently and significantly accelerated wound healing in the tsk-1 skin fibrosis model in mice. The tsk-1 mouse model is characterized by substantial skin fibrosis reflecting a non-inflammatory driven, stable SSc phenotype. These data imply that the sGC stimulators such as compound according to formula (3) could become an efficacious treatment option for SSc-related vasculopathies, especially for prevention and healing of Digital Ulcer.

The compounds according to the invention can be used alone or in combination with other active substances if necessary. The present invention further relates to medicinal products containing at least one of the compounds according to the invention and one or more further active substances, in particular for the treatment and/or prophylaxis of the aforementioned diseases. As suitable combination active substances, we may mention for example and preferably:

- organic nitrates and NO-donors, for example sodium nitroprusside, nitroglycerin, isosorbide mononitrate, isosorbide dinitrate, molsidomine or SIN-1, and inhalational NO;
- other vasoactive drugs, for examples prostanoids, such as iloprost, beraprost, cicaprost, epoprostenol, treprostinil;
- other vasoactive drugs, for example Rho-kinase inhibitors such as fasudil;
- other vasoactive drugs, for example endothelin receptor antagonists such as bosentan, darusentan, ambrisentan or sitaxsentan, macitentan;
- active substances for lowering blood pressure, for example and preferably from the group of calcium antagonists, such as nifedipine, amlodipine, verapamil or diltiazem;
- active substances for lowering blood pressure, for example and preferably from the group of angiotensin AII antagonists, ACE inhibitors, renin inhibitors, alpha-blockers, beta-blockers, mineralocorticoid receptor antagonists and diuretics; and/or
- antithrombotic agents, for example and preferably from the group of platelet aggregation inhibitors, anticoagulants, thrombin inhibitors or profibrinolytic substances;
- active substances that alter fat metabolism, for example and preferably from the group of thyroid receptor agonists, cholesterol synthesis inhibitors such as for example and preferably HMG-CoA-reductase or squalene synthesis inhibitors, ACAT inhibitors, CETP inhibitors, MTP inhibitors, PPAR-alpha, PPAR-gamma and/or PPAR-delta agonists, cholesterol absorption inhibitors, lipase inhibitors, polymeric bile acid adsorbers, bile acid reabsorption inhibitors and lipoprotein(a) antagonists;
- active substances that are used in fibrotic disorders, for examples and preferable from the group of proteinkinase inhibitors such as sorafenib, regorafenib, imatinib, dasatinib, nilotinib nintedanib, bortezomib and/or pirfenidone;

- active substances that alter inflammatory responses and/or supress immune responses, for example such as, cyclophosphamide, methotrexate, rapamycin, azathioproin, tocilizumab, infliximab, rituximab, adalimumab, belimumab, abatacept, SAR100842, thalidomide derivates;

- active substances working on different pathways, for example pirfenidone, SAR100842, thalidomide derivatives, integrin inhibitors.

Another preferred embodiment of the invention are compounds and/or combinations indicated above for use in the prevention and healing of Digital Ulcers which are concomitant to fibrotic diseases, such as systemic sclerosis and/or scleroderma.

Another preferred embodiment of the invention is the use for the production of a medicament for prevention and healing of Digital Ulcers which are concomitant to fibrotic diseases, such as systemic sclerosis and/or scleroderma comprising an effective amount of a compound and/or a combination as indicated above.

Another preferred embodiment of the invention is the pharmaceutical formulation comprising at least one compound or one combination as indicated above for the use in the prevention and healing of Digital Ulcers which are concomitant to fibrotic diseases, such as systemic sclerosis and/or scleroderma.

Another preferred embodiment of the invention is a kit comprising at least one sGC stimulator and/or activator as indicated above or a combination as indicated above for the use in the prevention and healing of Digital Ulcers which are concomitant to fibrotic diseases, such as systemic sclerosis and/or scleroderma.

A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral e.g., intravenous, intradermal, subcutaneous' oral (e.g.' inhalation)' transdermal (topical) transmucosal and rectal administration. Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, a pharmaceutically acceptable polyol like glycerol, propylene glycol, liquid polyetheylene glycol, and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it

will be preferable to include isotonic agents, for example, sugars, polyalcohols such as maitol sorbitol sodium chloride in the composition.

Oral compositions generally include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed.

Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or con1 starch; a lubricant such as magnesium stearate or sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

For administration by inhalation, the compounds are delivered in the form of an aerosol spray from a pressurized container or dispenser which contains a suitable propellant, e.g.' a gas such as carbon dioxide, or a nebulizer.

Systemic administration can also be by transmucosal or transderrnal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

The compounds can also be prepared in the form of suppositories (e.g., with conventional suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery.

In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Bio degradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid.

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Figures:

Figure 1: Reduction of wound size in WT mice (left) and tsk-1 mice (right) treated with placebo after three days. Data are mean - SEM, n=46 (WT + Placebo) and n=44 (tsk-1 + Placebo), */**/***/****= significant with $p<0.05/0.01/0.001/0.0001$

Figure 2: Reduction of wound size in tsk-1 mice treated with either placebo or compound according to formula (27), (BAY 41-2272) or compound according to formula (3), (BAY 63-2521) after three days. Data are mean - SEM, n=44-46 (Placebo groups), n= 16 (compound according to formula (27) BAY 41-2272 groups) and n=30-32 (compound according to formula (3) BAY 63-2521 groups), */**/***/****= significant with $p<0.05/0.01/0.001/0.0001$; ns = non significant; BAY41 corresponds to BAY41-2227.

Experimental Part

Example A

Wound Healing in Tsk-1 mice versus WT-mice

The tight-skin (Tsk-1) mouse model of SSc was used to evaluate the effects of compound according to formula (27) and (3) (BAY 41-2272 and BAY 63-2521) on wound healing in mice with substantial skin fibrosis. Due to an autosomal dominant mutation namely a tandem duplication of the fibrillin-1 gene, the phenotype of tsk-1 mice is characterized by an increased hypodermal thickness (Beyer et al. 2010). Genotyping of Tsk-1 mice was performed by PCR with the following primers: mutated fibrillin-1/ tsk-1 forward primer: 5' – GTTGGCAACTATACCTGCAT – 3', reverse primer: 5' – CCTTTCCTGGTAACATAGGA – 3'.

The effects of placebo (= vehicle for the test compounds = 0.5 tylose solution) was studied in either WT mice or in Tsk-1 mice. Tsk-1 mice were anaesthetized and carefully shaved 3 days before setting the wounds for exact quantification of the wound size. In order to avoid influences on wound healing by daily handling of the animals, the usual bi-daily gavage treatment was replaced by drug administration in the food. WT mice and Tsk-1 mice received normal mice chow (placebo) which started on the day of shaving. Three days after shaving, mice were carefully anesthetized and round wounds were punched with 4 mm in diameter. 3 days after punching, mice were euthanized and the wound size was assessed. Statistical analysis of data was done by one-way ANOVA followed by Tuckey´s multiple comparison post-hoc analysis

In tsk-1 mice, wound sizes were reduced by 52% ± 2 % after placebo treatment (Figure 1). In contrast, placebo treated WT mice showed a reduction in wound size of 68% ± 2% after 3 days (Figure 1). Therefore, wound healing in tsk-1 mice was partly impaired compared to WT mice and wound closure was significantly attenuated in placebo-treated tsk-1 mice.

Wound Healing in Tsk-1 mice treated with the compound according to formula (27) and (3), (BAY 41-2272 and BAY 63-2521)

The effects of either placebo (= vehicle for the compounds = 0.5% tylose solution), or the compound according to formula (27) or (3), (BAY 41-2272 or BAY 63-2521) were studied in Tsk-1 mice. Tsk-1 mice were anaesthetized and carefully shaved 3 days before setting the wounds for exact quantification of the wound size. In order to avoid influences on wound healing by daily handling of the animals, the bi-daily gavage treatment was replaced by drug administration in the food. Mice received either normal mice chow (placebo) or mice chow, containing 15 and 45 ppm of compound according to formula (27), (BAY 41-2272) or containing 5ppm, 15 ppm and 45 ppm of compound according to formula (3), (BAY 63-2521), respectively. These dosages – as confirmed by an orientating DMPK-study – resulted in similar exposures as 1 and 3 mg/kg of

compound according to formula (27), (BAY 41-2272) BID and 0.3, 1 and 3 mg/kg of compound according to formula (3), (BAY 63-2521) BID, respectively. Treatment groups consist of at least 8 tsk-1 mice per group. Treatment started on the day of shaving to achieve steady state exposure. Three days after shaving, mice were carefully anesthetized and round wounds were punched with 4 mm in diameter. 3 days after punching, mice were euthanized and the wound size was assessed. Statistical analysis of data was done by one-way ANOVA followed by Tuckey´s multiple comparison post-hoc analysis

In the tsk-1 mice wound sizes were dose-dependently and significantly reduced by 64 ± 2% and by 73 ± 2% after treatment with 15 and 45 ppm of compound according to formula (27), (BAY 41-2272), respectively (Figure 2). In addition, in the tsk-1 mice wound sizes were dose-dependently and significantly reduced by 59% ± 4%, 65 ± 3% and 70% ± 2% after treatment with 5, 15 and 45 ppm of compound according to formula (3), (BAY 63-2521), respectively (Figure 2). In addition, treatment with 45 ppm of compound according to formula (27), (BAY 41-2272) and 45 ppm of compound according to formula (3), (BAY 63-2521, Riociguat) normalized wound healing to a similar extent as observed in placebo-treated WT mice (68% ± 2%) (Figure 1, Figure 2). Therefore, compound according to formula (27) and (3), (BAY 41-2272 and BAY 63-2521) accelerated wound healing in compared to placebo treatment in the TSK-mice and lead to a normalization of wound closure as found in healthy control mice.

In summary, these data indicated that:

a) Wound healing in to tsk-1 mice was significantly attenuated compared to WT mice.

b) Wound healing in TSK-1 mice was significantly and dose-dependently improved by treatment with compound according to formula (27), (BAY 41-2272) and/or compound according to formula (3) BAY 63-2521.

- Maximum efficacy lead to a wound closure which was similar to healthy WT mice.

Since Tsk-1 mice are an animal model with extensive skin fibrosis reflecting the conditions in SSc this data indicate that the aforementioned compounds could not only reduce fibrosis but also accelerate wound healing in SSc, implying that these compounds are useful for the treatment of DU in SSc patients.

Claims

1. A sGC stimulator or activator selected from the group comprising 2-[1-(2-Fluorbenzyl)-1H-pyrazolo[3,4-b]pyridine-3-yl]-5-(4-morpholinyl)-4,6-pyrimidinediamine (1), 2-[1-(2-Fluorobenzyl)-1H-pyrazolo[3,4-b]pyridine-3-yl]-5-(4-pyridinyl)-4-pyrimidine amine (2), Methyl-4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridine-3-yl]-5-pyrimidinyl(methyl)carbamate (3), Methyl-4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridine-3-yl]-5-pyrimidinylcarbamate (4), 4-({(4-carboxybutyl)[2-(2-{[4-(2-phenylethyl)benzyl]oxy}phenyl)ethyl]amino}methyl) carboxylic acid (5), Methyl-{4,6-diamino-2-[5-fluoro-1-(2-fluorbenzyl)-1H-pyrazolo[3,4-b]pyridine-3-yl]pyrimidine-5-yl}carbamate (6), Methyl-{4,6-diamino-2-[5-fluoro-1-(2-fluorbenzyl)-1H-pyrazolo[3,4-b]pyridine-3-yl]pyrimidine-5-yl}methylcarbamate (7), Methyl-{4,6-diamino-2-[5-fluoro-1-(2-fluorbenzyl)-1H-pyrazolo[3,4-b]pyridine-3-yl]pyrimidine-5-yl}(2,2,2-trifluorethyl)carbamate (8), 5-Chloro-2-(5-chlorothiophene-2-sulfonylamino-N-(4-(morpholine-4-sulfonyl)-phenyl)-benzamid as sodium salt (9), 2-(4-Chloro-phenylsulfonylamino)-4,5-dimethoxy-N-(4-(thiomorpholine-4-sulfonyl)-phenyl)-benzamide (10), 1-{6-[5-Chloro-2-({4-trans-4-}trifluoromethyl)cyclohexyl]benzyl}oxy)phenyl]pyridine-2-yl}-5-(trifluoromethyl)-1H-pyrazol-4-carboxylic acid (11), 1-[6-(2-(2-Methyl-4-(4-trifluoromethoxyphenyl)benzyloxy)-phenyl)pyridine-2-yl]-5-trifluoromethyl-pyrazol-4-carboxylic acid (12), 1[6-(3,4-dichlorophenyl)-2-pyridinyl-5-(trifluoromethyl)-1H-pyrazole-4-caboxylic acid (13), 1-({2-[3-Chlor-5-(trifluoromethyl)phenyl]-5-methyl-1,3-thiazole-4-yl}methyl)-1H-pyrazole-4-carboxylic acid (14), 4-({2-[3-(Trifluoromethyl)phenyl]-1,3-thiazole-4-yl}methyl)benzoic acid (15) and 1-({2-[2-Fluoro-3-(trifluoromethyl)phenyl]-5-methyl-1,3-thiazole-4-yl}methyl)-1H-pyrazole-4-carboxylic acid (16), 4-Amino-2-[5-chloro-3(3,3,3-trifluororpropyl)-1H-indazol-1yl]-5,5-dimethyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidine-6-one (17), 4-Amino-2[5-chloro-3-(2,3,6-trifluorbenzyle)-1H-indazol-1yl]-5,5-dimethyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidine-6-one (18), 4-Amino-5,5-dimethyl-2-[3-(2,3,6-trifluorbenzyle)1H-thieno[3,4-c]pyrazol-1-yl]-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidine-6-one (19), 4-Amino-5,5-dimethyl-2-[3-(2,3,6-trifluorbenzyle)-1H-thieno[2,3-d]pyrazole-1-yl]-5,5-dimethyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidine-6-one (20), 4-Amino-5,5-dimethyl-2-[7-(2,3,6-trifluorobenzyle)imidazo[1,5-b]pyridazine-5-yl]-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidine-6-one (21), 4-Amino-2-[6-chloro-3-(2,3,6-trifluorobenzyle)imidazo[1,5-a]pyridine-1-yl]]-5,5-dimethyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidine-6-one (22), 4-Amino-2-[6-fluoro-3-(2,3,6-trifluorobenzyle)imidazo[1,5-a]pyridine-1-yl]]-5,5-dimethyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidine-6-one (23), 4-Amino-2-[6-fluoro-3-(2,3,6-trifluorobenzyl)6-

fluoroimidazo[1,5-a]pyridine-1-yl]-5,5-dimethyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidine-6-one (24), 4-Amino-5,5-dimethyl-2-[3-(2,4,6-trifluorobenzyle)imidazo[1,5-a]pyridine-1-yl]]-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidine-6-one (25), 4-Amino-2-[3-(2-cyclopentylethyl)imidazo[1,5-a]pyridine-1-yl]-5,5-dimethyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidine-6-one (26), 3-(4-Amino-5-cyclopropylpyrimidine-2-yl)-1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridine (27), 2-{5-Fluor-1-[(3-fluorpyridine-2-yl)methyl]-1H-pyrazolo[3,4-b]pyridine-3-yl}-5-methyl-5-(trifluormethyl)-4-[(3,3,3-trifluorpropyl)amino]-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidine-6-on (28) for use in the prevention and healing of Digital Ulcers which are concomitant to fibrotic diseases, such as systemic sclerosis and scleroderma.

2. A sGC stimulator selected from the group 2-[1-(2-Fluorbenzyl)-1H-pyrazolo[3,4-b]pyridine-3-yl]-5-(4-morpholinyl)-4,6-pyrimidinediamine (1), 2-[1-(2-Fluorobenzyl)-1H-pyrazolo[3,4-b]pyridine-3-yl]-5-(4-pyridinyl)-4-pyrimidine amine (2), Methyl-4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridine-3-yl]-5-pyrimidinyl-(methyl)carbamate (3), Methyl-4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridine-3-yl]-5-pyrimidinylcarbamate (4), Methyl-{4,6-diamino-2-[5-fluoro-1-(2-fluorbenzyl)-1H-pyrazolo[3,4-b]pyridine-3-yl]pyrimidine-5-yl}carbamate (6), Methyl-{4,6-diamino-2-[5-fluoro-1-(2-fluorbenzyl)-1H-pyrazolo[3,4-b]pyridine-3-yl]pyrimidine-5-yl}methylcarbamate (7), 3-(4-Amino-5-cyclopropylpyrimidine-2-yl)-1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridine (27), 2-{5-Fluor-1-[(3-fluorpyridine-2-yl)methyl]-1H-pyrazolo[3,4-b]pyridine-3-yl}-5-methyl-5-(trifluormethyl)-4-[(3,3,3-trifluorpropyl)amino]-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidine-6-on (28) for use in the prevention and healing of Digital Ulcers which are concomitant to fibrotic diseases, such as systemic sclerosis and scleroderma.

3. A sGC stimulator selected from the group Methyl-4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridine-3-yl]-5-pyrimidinyl(methyl)carbamate (3), Methyl-{4,6-diamino-2-[5-fluoro-1-(2-fluorbenzyl)-1H-pyrazolo[3,4-b]pyridine-3-yl]pyrimidine-5-yl}carbamate (6), Methyl-{4,6-diamino-2-[5-fluoro-1-(2-fluorbenzyl)-1H-pyrazolo[3,4-b]pyridine-3-yl]pyrimidine-5-yl}methylcarbamate (7), 2-{5-Fluor-1-[(3-fluorpyridine-2-yl)methyl]-1H-pyrazolo[3,4-b]pyridine-3-yl}-5-methyl-5-(trifluormethyl)-4-[(3,3,3-trifluorpropyl)amino]-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidine-6-on (28) for use in the prevention and healing of Digital Ulcers which are concomitant to fibrotic diseases, such as systemic sclerosis and scleroderma.

4. Methyl-4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridine-3-yl]-5-pyrimidinyl(methyl)carbamate (3) for use in the prevention and healing of Digital Ulcers which are concomitant to fibrotic diseases, such as systemic sclerosis and scleroderma.

5. Compounds according to claims 1 to 4 for the use in patients suffering from Digital Ulcers which are concomitant to fibrotic diseases, such as systemic sclerosis and scleroderma.

6. Pharmaceutical formulation comprising at least one compound according to claims 1 to 4 for the use in patients suffering from Digital Ulcers which are concomitant to fibrotic diseases, such as systemic sclerosis and scleroderma.

7. Combination of at least one sGC stimulator or activator selected from the group comprising group 2-[1-(2-Fluorbenzyl)-1H-pyrazolo[3,4-b]pyridine-3-yl]-5-(4-morpholinyl)-4,6-pyrimidinediamine (1), 2-[1-(2-Fluorobenzyl)-1H-pyrazolo[3,4-b]pyridine-3-yl]-5-(4-pyridinyl)-4-pyrimidine amine (2), Methyl-4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridine-3-yl]-5-pyrimidinyl(methyl)carbamate (3), Methyl-4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridine-3-yl]-5-pyrimidinylcarbamate (4), Methyl-{4,6-diamino-2-[5-fluoro-1-(2-fluorbenzyl)-1H-pyrazolo[3,4-b]pyridine-3-yl]pyrimidine-5-yl}carbamate (6), Methyl-{4,6-diamino-2-[5-fluoro-1-(2-fluorbenzyl)-1H-pyrazolo[3,4-b]pyridine-3-yl]pyrimidine-5-yl}methylcarbamate (7), 3-(4-Amino-5-cyclopropylpyrimidine-2-yl)-1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridine (27), 2-{5-Fluor-1-[(3-fluorpyridine-2-yl)methyl]-1H-pyrazolo[3,4-b]pyridine-3-yl}-5-methyl-5-(trifluormethyl)-4-[(3,3,3-trifluorpropyl)amino]-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidine-6-on (28) with a PDE5 inhibitor selected form the group comprising Vardenafil, Sildenafil, Tadalafil, Udenafil, Dasantafil, Avanafil, Mirodenafil, Lodenafil, UK 369.003, UK 371.800, SLx2101 and LAS34179) for use in the prevention and healing of Digital Ulcers which are concomitant to fibrotic diseases, such as systemic sclerosis and scleroderma.

8. Combination according to claim 7 in which the sGC stimulator is Methyl-{4,6-diamino-2-[5-fluoro-1-(2-fluorbenzyl)-1H-pyrazolo[3,4-b]pyridine-3-yl]pyrimidine-5-yl}carbamate (6), Methyl-{4,6-diamino-2-[5-fluoro-1-(2-fluorbenzyl)-1H-pyrazolo[3,4-b]pyridine-3-yl]pyrimidine-5-yl}methylcarbamate (7) or 2-{5-Fluor-1-[(3-fluorpyridine-2-yl)methyl]-1H-pyrazolo[3,4-b]pyridine-3-yl}-5-methyl-5-(trifluormethyl)-4-[(3,3,3-trifluorpropyl)amino]-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidine-6-on (28) for use in the prevention and healing of Digital Ulcers which are concomitant to fibrotic diseases, such as systemic sclerosis and scleroderma.

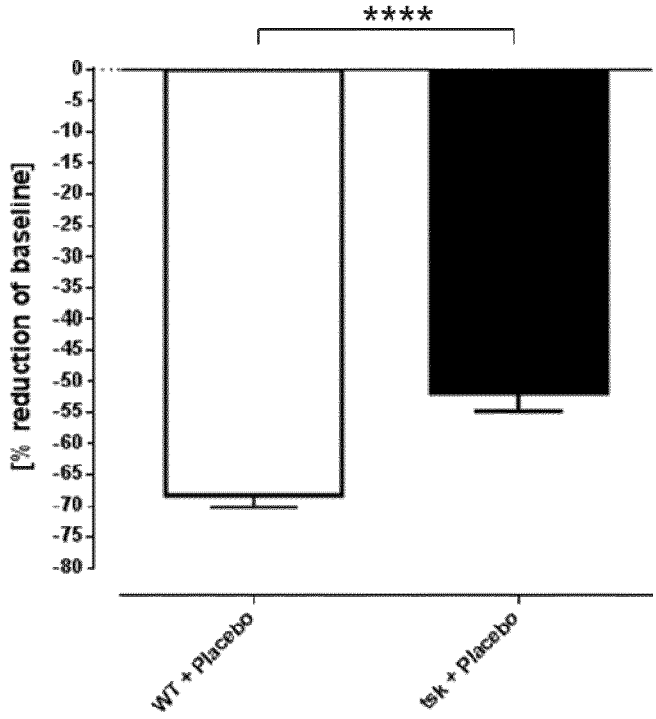
9. Combination according to claims 7 and 8 in which the PDE5 inhibitor is Vardenafil or Sildenafil for use in the prevention and healing of Digital Ulcers which are concomitant to fibrotic diseases, such as systemic sclerosis and scleroderma.

10. Combination according to claims 7 to 10 for the use in patients suffering from Digital Ulcers which are concomitant to fibrotic diseases, such as systemic sclerosis and scleroderma.

11. Pharmaceutical formulation comprising at least one combination according to claims 7 to 9.

12. sGC stimulators and/or sGC activators alone, or in combination with PDE5 inhibitors for use in the prevention and healing of Digital Ulcers which are concomitant to fibrotic diseases, such as systemic sclerosis and scleroderma

Figure 1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-35
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-70
-75
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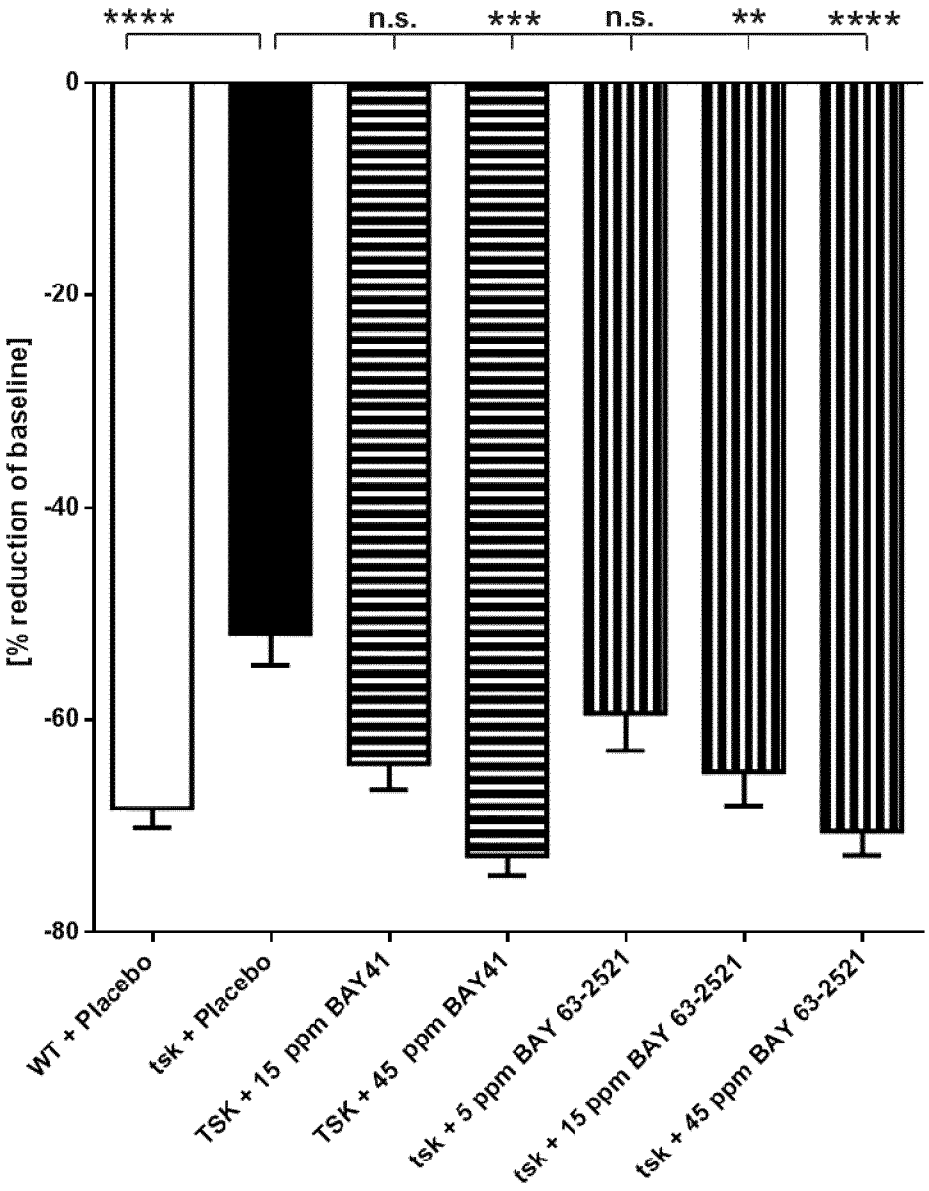
[% reduction of baseline]
WT + Placebo
tsk + Placebo

Figure 2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n.s.
***
n.s.
**
****
0
-20
-40
-60
-80
[% reduction of baseline]
WT + Placebo
tsk + Placebo
TSK + 15 ppm BAY41
TSK + 45 ppm BAY41
tsk + 5 ppm BAY 63-2521
tsk + 15 ppm BAY 63-2521
tsk + 45 ppm BAY 63-2521

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/059734

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/426 A61K31/427 A61K31/4439 A61K31/506 A61K31/519
A61K31/5377 A61K31/635 A61K45/06 A61P17/02
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Anonymous: "Bayer to Evaluate sGC Stimulator Riociguat in Patients With Diffuse Cutaneous Systemic Sclerosis - News Release", Bayer , 13 November 2014 (2014-11-13), XP002759127, Retrieved from the Internet: URL:http://www.epresspack.net/bayer-riociguat/bayer-to-evaluate-sgc-stimulator-riociguat-in-patients-with-diffuse-cutaneous-systemic-sclerosis/ [retrieved on 2016-06-22]	1-6,12
Y	the whole document	7-11

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 June 2016	08/09/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Hoff, Philippe

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Anonymous: "Digital ulcers: sildenafil", Nice , 24 March 2015 (2015-03-24), XP002759128, Retrieved from the Internet: URL:https://www.nice.org.uk/guidance/esuom42/resources/digital-ulcers-sildenafil-54116459119149253 [retrieved on 2016-06-22] the whole document	7-11
X	WO 2011/147810 A1 (BAYER PHARMA AG [DE]; HIRTH-DIETRICH CLAUDIA [DE]; SANDNER PETER [DE];) 1 December 2011 (2011-12-01) cited in the application claims; examples	1-4,7-9, 11,12
X	US 2009/215769 A1 (KRAHN THOMAS [DE] ET AL) 27 August 2009 (2009-08-27) the whole document	1-4,12
X	S. KOTZKI ET AL: "Anodal Iontophoresis of a Soluble Guanylate Cyclase Stimulator Induces a Sustained Increase in Skin Blood Flow in Rats", JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 346, no. 3, 9 July 2013 (2013-07-09), pages 424-431, XP055282639, DOI: 10.1124/jpet.113.205484 the whole document	12
X	DEES CLARA ET AL: "Stimulators of soluble guanylate cyclase (sGC) inhibit experimental skin fibrosis of different aetiologies", ANNALS OF THE RHEUMATIC DISEASES, BRITISH MEDICAL ASSOCIATION, LONDON, GB, vol. 74, no. 8, 1 January 2015 (2015-01-01), pages 1621-1625, XP008180685, ISSN: 0003-4967 whole document and more particularly page 1624, left-hand column, last paragraph	1-6,12
A	US 2009/221573 A1 (KRAHN THOMAS [DE] ET AL) 3 September 2009 (2009-09-03) abstract; claims; examples	1-12

-/--

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BEYER CHRISTIAN ET AL: "Stimulation of soluble guanylate cyclase reduces experimental dermal fibrosis", ANNALS OF THE RHEUMATIC DISEASES, BRITISH MEDICAL ASSOCIATION, LONDON, GB, vol. 71, no. 6, 1 June 2012 (2012-06-01), pages 1019-1026, XP009167097, ISSN: 0003-4967 the whole document	1-12
X,P	SANDNER PETER ET AL: "Stimulators of Soluble Guanylate Cyclase (sGC) Improve Wound Healing in the Tsk-1 Mouse Skin Fibrosis Mode", ARTHRITIS & RHEUMATOLOGY, vol. 67, no. Suppl. 10, ABS.1906, October 2015 (2015-10), XP002759129, & ANNUAL MEETING OF THE AMERICAN-COLLEGE-OF-RHEUMATOLOGY (ACR) AND ASSOCIATION-OF-RHEUMATOLOGY-HEALTH-; SAN FRANCISCO, CA, USA; NOVEMBER 06 -11, 2015 the whole document	1-12
X,P	M. Ollé: "The European League Against Rheumatism (EULAR) - 16th Annual European Congress (June 10-13, 2015 - Rome, Italy).", Drugs of Today, vol. 51, no. 6 June 2015 (2015-06), June 2015 (2015-06), pages 387-392, XP002759130, Retrieved from the Internet: URL:http://www.ncbi.nlm.nih.gov/pubmed/26261853 [retrieved on 2016-06-22] page 390, right-hand column, paragraph 2	1-12

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2016/059734

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. [ ] forming part of the international application as filed:

      [ ] in the form of an Annex C/ST.25 text file.

      [ ] on paper or in the form of an image file.

   b. [ ] furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. [X] furnished subsequent to the international filing date for the purposes of international search only:

      [X] in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      [ ] on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. [X] In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2016/059734

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

2-4, 7-11(completely); 1, 5, 6, 12(partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 2-4, 7-11(completely); 1, 5, 6, 12(partially)

   A sGC stimulator or activator which is a 1H-pyrazolo[3,4-b]pyridine derivative selected from the compounds (1)-(4),(6)-(8),(27) and (28) for use in the prevention and healing of digital ulcers which are concomitant to fibrotic diseases, such as systemic sclerosis and scleroderma

   ---

2. claims: 1, 5, 6, 12(all partially)

   A sGC stimulator or activator which is the compound (5) for use in the prevention and healing of digital ulcers which are concomitant to fibrotic diseases, such as systemic sclerosis and scleroderma

   ---

3. claims: 1, 5, 6, 12(all partially)

   A sGC stimulator or activator which is a (morpholine-4-sulfonyl)-phenyl-benzamid derivative selected from the compounds (9) and (10) for use in the prevention and healing of digital ulcers which are concomitant to fibrotic diseases, such as systemic sclerosis and scleroderma

   ---

4. claims: 1, 5, 6, 12(all partially)

   A sGC stimulator or activator which is a pyridine-2-pyrazole derivative selected from the compounds (11)-(13) for use in the prevention and healing of digital ulcers which are concomitant to fibrotic diseases, such as systemic sclerosis and scleroderma

   ---

5. claims: 1, 5, 6, 12(all partially)

   A sGC stimulator or activator which is a 1,3-thiazole derivative selected from the compounds (14)-(16) for use in the prevention and healing of digital ulcers which are concomitant to fibrotic diseases, such as systemic sclerosis and scleroderma

   ---

6. claims: 1, 5, 6, 12(all partially)

   A sGC stimulator or activator which is a pyrrolo[2,3-d]pyrimidine-6-one derivative selected from the compounds (17)-(26) for use in the prevention and healing of digital ulcers which are concomitant to fibrotic diseases,

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

such as systemic sclerosis and scleroderma

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2016/059734

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		EA 201291309 A1	28-06-2013
		EP 2576548 A1	10-04-2013
		ES 2549979 T3	03-11-2015
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(54)发明名称

单独和与PDE5抑制剂组合的sGC刺激剂、sGC活化剂用于治疗伴随系统性硬化症(SSc)的指溃疡(DU)的用途

(57)摘要

单独或与PDE5抑制剂组合的sGC刺激剂、sGC活化剂用于伴随纤维化疾病诸如系统性硬化症和硬皮病的指溃疡的预防和愈合的用途。

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1.选自以下的sGC刺激剂或活化剂:2-[1-(2-氟苄基)-1H-吡唑并[3,4-b]吡啶-3-基]-5-(4-吗啉基)-4,6-嘧啶二胺(1)、2-[1-(2-氟苄基)-1H-吡唑并[3,4-b]吡啶-3-基]-5-(4-吡啶基)-4-嘧啶胺(2)、4,6-二氨基-2-[1-(2-氟苄基)-1H-吡唑并[3,4-b]吡啶-3-基]-5-嘧啶基(甲基)氨基甲酸甲酯(3)、4,6-二氨基-2-[1-(2-氟苄基)-1H-吡唑并[3,4-b]吡啶-3-基]-5-嘧啶基氨基甲酸甲酯(4)、4-({(4-羧基丁基)[2-(2-{[4-(2-苯基乙基)苄基]氧基}苯基)乙基]氨基}甲基)甲酸(5)、{4,6-二氨基-2-[5-氟-1-(2-氟苄基)-1H-吡唑并[3,4-b]吡啶-3-基]嘧啶-5-基}氨基甲酸甲酯(6)、{4,6-二氨基-2-[5-氟-1-(2-氟苄基)-1H-吡唑并[3,4-b]吡啶-3-基]嘧啶-5-基}甲基氨基甲酸甲酯(7)、{4,6-二氨基-2-[5-氟-1-(2-氟苄基)-1H-吡唑并[3,4-b]吡啶-3-基]嘧啶-5-基}(2,2,2-三氟乙基)氨基甲酸甲酯(8)、作为钠盐的5-氯-2-(5-氯噻吩-2-磺酰基氨基-N-(4-(吗啉-4-磺酰基)-苯基)-苯甲酰胺(9)、2-(4-氯-苯基磺酰基氨基)-4,5-二甲氧基-N-(4-(硫代吗啉-4-磺酰基)-苯基)-苯甲酰胺(10)、1-{6-[5-氯-2-({4-反-4-}三氟甲基)环己基]苄基}氧基)苯基]吡啶-2-基}-5-(三氟甲基)-1H-吡唑-4-甲酸(11)、1-[6-(2-(2-甲基-4-(4-三氟甲氧基苯基)苄基氧基)-苯基)吡啶-2-基]-5-三氟甲基-吡唑-4-甲酸(12)、1-[6-(3,4-二氯苯基)-2-吡啶基]-5-(三氟甲基)-1H-吡唑-4-甲酸(13)、1-({2-[3-氯-5-(三氟甲基)苯基]-5-甲基-1,3-噻唑-4-基}甲基)-1H-吡唑-4-甲酸(14)、4-({2-[3-(三氟甲基)苯基]-1,3-噻唑-4-基}甲基)苯甲酸(15)和1-({2-[2-氟-3-(三氟甲基)苯基]-5-甲基-1,3-噻唑-4-基}甲基)-1H-吡唑-4-甲酸(16)、4-氨基-2-[5-氯-3-(3,3,3-三氟丙基)-1H-吲唑-1-基]-5,5-二甲基-5,7-二氢-6H-吡咯并[2,3-d]嘧啶-6-酮(17)、4-氨基-2-[5-氯-3-(2,3,6-三氟苄基)-1H-吲唑-1-基]-5,5-二甲基-5,7-二氢-6H-吡咯并[2,3-d]嘧啶-6-酮(18)、4-氨基-5,5-二甲基-2-[3-(2,3,6-三氟苄基)-1H-噻吩并[3,4-c]吡唑-1-基]-5,7-二氢-6H-吡咯并[2,3-d]嘧啶-6-酮(19)、4-氨基-5,5-二甲基-2-[3-(2,3,6-三氟苄基)-1H-噻吩并[2,3-d]吡唑-1-基]-5,5-二甲基-5,7-二氢-6H-吡咯并[2,3-d]嘧啶-6-酮(20)、4-氨基-5,5-二甲基-2-[7-(2,3,6-三氟苄基)咪唑并[1,5-b]哒嗪-5-基]-5,7-二氢-6H-吡咯并[2,3-d]嘧啶-6-酮(21)、4-氨基-2-[6-氯-3-(2,3,6-三氟苄基)咪唑并[1,5-a]吡啶-1-基]]-5,5-二甲基-5,7-二氢-6H-吡咯并[2,3-d]嘧啶-6-酮(22)、4-氨基-2-[6-氟-3-(2,3,6-三氟苄基)咪唑并[1,5-a]吡啶-1-基]]-5,5-二甲基-5,7-二氢-6H-吡咯并[2,3-d]嘧啶-6-酮(23)、4-氨基-2-[6-氟-3-(2,3,6-三氟苄基)-6-氟咪唑并[1,5-a]吡啶-1-基]-5,5-二甲基-5,7-二氢-6H-吡咯并[2,3-d]嘧啶-6-酮(24)、4-氨基-5,5-二甲基-2-[3-(2,4,6-三氟苄基)咪唑并[1,5-a]吡啶-1-基]]-5,7-二氢-6H-吡咯并[2,3-d]嘧啶-6-酮(25)、4-氨基-2-[3-(2-环戊基乙基)咪唑并[1,5-a]吡啶-1-基]-5,5-二甲基-5,7-二氢-6H-吡咯并[2,3-d]嘧啶-6-酮(26)、3-(4-氨基-5-环丙基嘧啶-2-基)-1-(2-氟苄基)-1*H*-吡唑并[3,4-*b*]吡啶(27)、2-{5-氟-1-[(3-氟吡啶-2-基)甲基]-1H-吡唑并[3,4-b]吡啶-3-基}-5-甲基-5-(三氟甲基)-4-[(3,3,3-三氟丙基)氨基]-5,7-二氢-6H-吡咯并[2,3-d]嘧啶-6-酮(28),所述sGC刺激剂或活化剂用于伴随纤维化疾病诸如系统性硬化症和硬皮病的指溃疡的预防和愈合。

2.选自以下的sGC刺激剂:2-[1-(2-氟苄基)-1H-吡唑并[3,4-b]吡啶-3-基]-5-(4-吗啉基)-4,6-嘧啶二胺(1)、2-[1-(2-氟苄基)-1H-吡唑并[3,4-b]吡啶-3-基]-5-(4-吡啶基)-4-嘧啶胺(2)、4,6-二氨基-2-[1-(2-氟苄基)-1H-吡唑并[3,4-b]吡啶-3-基]-5-嘧啶基(甲基)氨基甲酸甲酯(3)、4,6-二氨基-2-[1-(2-氟苄基)-1H-吡唑并[3,4-b]吡啶-3-

基]-5-嘧啶基氨基甲酸甲酯(4)、{4,6-二氨基-2-[5-氟-1-(2-氟苄基)-1H-吡唑并[3,4-b]吡啶-3-基]嘧啶-5-基}氨基甲酸甲酯(6)、{4,6-二氨基-2-[5-氟-1-(2-氟苄基)-1H-吡唑并[3,4-b]吡啶-3-基]嘧啶-5-基}甲基氨基甲酸甲酯(7)、3-(4-氨基-5-环丙基嘧啶-2-基)-1-(2-氟苄基)-1*H*-吡唑并[3,4-*b*]吡啶(27)、2-{5-氟-1-[(3-氟吡啶-2-基)甲基]-1H-吡唑并[3,4-b]吡啶-3-基}-5-甲基-5-(三氟甲基)-4-[(3,3,3-三氟丙基)氨基]-5,7-二氢-6H-吡咯并[2,3-d]嘧啶-6-酮(28),所述sGC刺激剂用于伴随纤维化疾病诸如系统性硬化症和硬皮病的指溃疡的预防和愈合。

3.选自以下的sGC刺激剂:4,6-二氨基-2-[1-(2-氟苄基)-1H-吡唑并[3,4-b]吡啶-3-基]-5-嘧啶基(甲基)氨基甲酸甲酯(3)、{4,6-二氨基-2-[5-氟-1-(2-氟苄基)-1H-吡唑并[3,4-b]吡啶-3-基]嘧啶-5-基}氨基甲酸甲酯(6)、{4,6-二氨基-2-[5-氟-1-(2-氟苄基)-1H-吡唑并[3,4-b]吡啶-3-基]嘧啶-5-基}甲基氨基甲酸甲酯(7)、2-{5-氟-1-[(3-氟吡啶-2-基)甲基]-1H-吡唑并[3,4-b]吡啶-3-基}-5-甲基-5-(三氟甲基)-4-[(3,3,3-三氟丙基)氨基]-5,7-二氢-6H-吡咯并[2,3-d]嘧啶-6-酮(28),所述sGC刺激剂用于伴随纤维化疾病诸如系统性硬化症和硬皮病的指溃疡的预防和愈合。

4.4,6-二氨基-2-[1-(2-氟苄基)-1H-吡唑并[3,4-b]吡啶-3-基]-5-嘧啶基(甲基)氨基甲酸甲酯(3),其用于伴随纤维化疾病诸如系统性硬化症和硬皮病的指溃疡的预防和愈合。

5.根据权利要求1至4所述的化合物,其用于患有伴随纤维化疾病诸如系统性硬化症和硬皮病的指溃疡的患者。

6.包含至少一种根据权利要求1至4所述的化合物的药物制剂,所述药物制剂用于患有伴随纤维化疾病诸如系统性硬化症和硬皮病的指溃疡的患者。

7.至少一种sGC刺激剂或活化剂与PDE5抑制剂的组合产品,所述组合产品用于伴随纤维化疾病诸如系统性硬化症和硬皮病的指溃疡的预防和愈合,其中所述sGC刺激剂或活化剂选自:2-[1-(2-氟苄基)-1H-吡唑并[3,4-b]吡啶-3-基]-5-(4-吗啉基)-4,6-嘧啶二胺(1)、2-[1-(2-氟苄基)-1H-吡唑并[3,4-b]吡啶-3-基]-5-(4-吡啶基)-4-嘧啶胺(2)、4,6-二氨基-2-[1-(2-氟苄基)-1H-吡唑并[3,4-b]吡啶-3-基]-5-嘧啶基(甲基)氨基甲酸甲酯(3)、4,6-二氨基-2-[1-(2-氟苄基)-1H-吡唑并[3,4-b]吡啶-3-基]-5-嘧啶基氨基甲酸甲酯(4)、{4,6-二氨基-2-[5-氟-1-(2-氟苄基)-1H-吡唑并[3,4-b]吡啶-3-基]嘧啶-5-基}氨基甲酸甲酯(6)、{4,6-二氨基-2-[5-氟-1-(2-氟苄基)-1H-吡唑并[3,4-b]吡啶-3-基]嘧啶-5-基}甲基氨基甲酸甲酯(7)、3-(4-氨基-5-环丙基嘧啶-2-基)-1-(2-氟苄基)-1*H*-吡唑并[3,4-*b*]吡啶(27)、2-{5-氟-1-[(3-氟吡啶-2-基)甲基]-1H-吡唑并[3,4-b]吡啶-3-基}-5-甲基-5-(三氟甲基)-4-[(3,3,3-三氟丙基)氨基]-5,7-二氢-6H-吡咯并[2,3-d]嘧啶-6-酮(28),所述PDE5抑制剂选自伐地那非、西地那非、他达拉非、乌地那非、Dasantafil、阿伐那非、米罗那非、罗地那非、UK 369.003、UK 371.800、SLx2101和LAS34179。

8.根据权利要求7所述的组合产品,其中所述sGC刺激剂是{4,6-二氨基-2-[5-氟-1-(2-氟苄基)-1H-吡唑并[3,4-b]吡啶-3-基]嘧啶-5-基}氨基甲酸甲酯(6)、{4,6-二氨基-2-[5-氟-1-(2-氟苄基)-1H-吡唑并[3,4-b]吡啶-3-基]嘧啶-5-基}甲基氨基甲酸甲酯(7)或2-{5-氟-1-[(3-氟吡啶-2-基)甲基]-1H-吡唑并[3,4-b]吡啶-3-基}-5-甲基-5-(三氟甲基)-4-[(3,3,3-三氟丙基)氨基]-5,7-二氢-6H-吡咯并[2,3-d]嘧啶-6-酮(28),所述组合

产品用于伴随纤维化疾病诸如系统性硬化症和硬皮病的指溃疡的预防和愈合。

9.根据权利要求7和8所述的组合产品，其中所述PDE5抑制剂是伐地那非或西地那非，所述组合产品用于伴随纤维化疾病诸如系统性硬化症和硬皮病的指溃疡的预防和愈合。

10.根据权利要求7至10所述的组合产品，其用于患有伴随纤维化疾病诸如系统性硬化症和硬皮病的指溃疡的患者。

11.药物制剂，其包含至少一种根据权利要求7至9所述的组合产品。

12.单独或与PDE5抑制剂组合的sGC刺激剂和/或sGC活化剂，其用于伴随纤维化疾病诸如系统性硬化症和硬皮病的指溃疡的预防和愈合。

单独和与PDE5抑制剂组合的sGC刺激剂、sGC活化剂用于治疗伴随系统性硬化症(SSc)的指溃疡(DU)的用途

[0001] 单独或与PDE5抑制剂组合的sGC刺激剂、sGC活化剂用于伴随纤维化疾病诸如系统性硬化症和硬皮病的指溃疡的预防和愈合的用途。

[0002] 发明背景

系统性硬化症和伴随的指溃疡(DU)

系统性硬化症(SSc)的发病机制仍不清楚,且仍然难以捉摸。然而,硬皮病是非遗传性、非感染性疾病,且被认为是自身免疫性疾病。SSc具有通过真皮中细胞外基质的过量沉积(导致皮肤纤维化)触发的多种症状。在后期,SSc的特征在于进行性组织纤维化,影响其它内脏,如肠、肺或肾。因此,硬皮病是该疾病的标志,还包括例如肺纤维化、肾纤维化、心脏、肠或血管的纤维化。除了皮肤和内部器官中的过量纤维化外,SSc的特征还在于血管病变和微血管病变。特别是,小血管血管病变和伴随的血管灌注不良和局部缺血可引起雷诺氏现象(RP),也引起指溃疡(DU)的形成。而组织纤维化可引起终末器官衰竭并且导致具有终末期SSc的患者中的高发病率和死亡率,DU的形成显著降低SSc患者的生活质量、损害手部功能且导致残疾。(Harris等人 2005 - Kelley´s Textbook of Rhematology 第7版 Elsevier Saunders, Philadelphia PA)。

[0003] 还没有可用的系统性硬化症(SSc)的病因治疗,且目前的疗法基于经由皮质类固醇、环磷酰胺、甲氨蝶呤对免疫系统的抑制。更近来,激酶抑制剂和抗炎药作为SSc中的免疫抑制剂和抗纤维化药剂正在研究中,但耐受性在SSc患者中受限(Khanna和Denton 2010 - Best. Pract. Res. Clin. Rheumatol. 24:387-400, Ong and Denton 2010 - Curr. Opin. Rheumatol. 22:264-272, Spiera 2011 - Ann. Rheum. Dis. Epub Mar 2011)。作为独立治疗或组合使用的这些疗法的效力有限并且表现出相当大的副作用。因此,迫切需要在SSc中有效和安全的替代治疗选项。此外,目前还没有批准用于DU的愈合的治疗,但使用血管活性药物作为前列环素激动剂和内皮素拮抗剂。

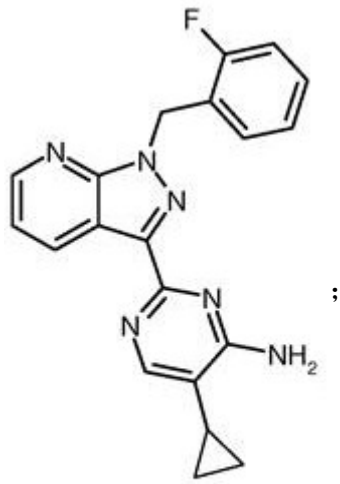
[0004] cGMP的抗纤维化作用:

数十年前发现环核苷酸(环单磷酸腺苷(cAMP)和环单磷酸鸟苷(cGMP)),并且代表细胞内最重要的第二信使途径之一。充分确立的是,细胞内cGMP库的调节对生理学和病理生理学具有重大影响,并且是药理学干预的一个基本原则(Evgenov等人 2006 - Nat. Rev. Drug. Discov. 5(9):755-768)。除了治疗心血管、肺或CNS-病症之外,存在充分的证据证明cGMP的增加对于泌尿道病症同样是一种非常有效的治疗选项(Sandner等人 2009 - Handbook Exper. Pharmacol. 191:507-531)。PDE5抑制剂是用于治疗勃起功能障碍(ED)的金标准,但显示,PDE5抑制剂可以用于治疗特征在于膀胱过度活动(OAB)和下尿路症状(LUTS)的症状性BPH (Porst等人 2008 - Curr. Urol. Rep. 9:295-301; .McVary等人 2007 - J. Urol. 177:1071-1077, J Urol. 177:1401-1407, Kaplan和Gonzalez. 2007 - Rev. Urol. 9:73-77)。尚未理解伐地那非、sGC刺激剂和sGC活化剂的抗纤维化作用。存在一些关于一氧化氮的抗纤维化作用的描述,其据推测由其它器官中的cGMP介导,并且PDE5抑制剂或鸟苷酸环化酶刺激剂已经分别在阴茎纤维化(Peyronie氏病)(Ferrini等人

2006 - B. J. Urol. 97:625-633)和肝纤维化(Knorr等人2008 - Arzneimittelforschung 58:71-80)中显示效力。

[0005] 不知道NO/cGMP系统是否参与SSc且cGMP增加是否为该疾病提供治疗选项。我们假设 - 独立于内源性NO/cGMP产生 - sGC刺激剂和活化剂通过减少皮肤纤维化可能是系统性硬化症(SSc)的有效治疗选项。在WO2011/147810中,我们最近已显示,单独和与PDE5抑制剂组合的sGC刺激剂、sGC活化剂可以直接靶向皮肤纤维化,所述皮肤纤维化是系统性硬化症(SSc)的一种标志。这清楚地表明,单独和与PDE5抑制剂组合的sGC刺激剂、sGC活化剂是SSc的有效的未来治疗选项。然而,不知道SSc患者中的血管病变(其导致例如DU形成(DU为SSc中最麻烦的症状之一))是否也可以用单独和与PDE5抑制剂组合的sGC刺激剂、sGC活化剂进行有效治疗。由于这些化合物可诱导外周血管舒张,所以可以假设SSc驱动的血管病变可能减少,从而防止DU的新形成。然而,考虑到单独和与PDE5抑制剂组合的sGC刺激剂/sGC活化剂的抗纤维化作用模式,不清楚SSc驱动的DU是否也可以愈合。因此,增加的血流量可能被减少的胶原合成或细胞外基质的合成(其是伤口闭合所必不可少的)抵消,而这继而可能削弱SSc患者中的伤口愈合。

[0006] 因此,我们在TSK小鼠(特征在于过量皮肤纤维化的SSc的动物模型)中针对伤口愈合研究sGC刺激剂和sGC活化剂,即下式的化合物,以及其与PDE5抑制剂的组合产品:



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(27)

我们在体内动物模型中发现:

· 与WT小鼠相比,TSK小鼠具有减弱的伤口愈合。

[0007] · sGC刺激剂或sGC活化剂,即根据式(27)和(3)的化合物在TSK小鼠中显著且剂量依赖性地加速伤口愈合。

[0008] · sGC刺激剂或sGC活化剂,即根据式(27)和(3)的化合物使愈合时间正常化至健康WT对照小鼠。这些数据表明,尽管sCC刺激剂和sGC活化剂在SSc中具有抗纤维化作用,但SSc中的伤口愈合可以显著加速,并且正常化至健康对照个体的水平。

[0009] 总之,我们完全意外且首次发现,sGC刺激剂或sGC活化剂,即根据式(27)和(3)的化合物(其在炎性和非炎性SSc的不同动物模型中防止纤维化且退化已确定的纤维化),也可以导致TSK-小鼠SSc模型中的显著增强的伤口愈合。

[0010] 总之,这些数据首次表明,sGC刺激剂和sGC活化剂,即根据式(27)和(3)的化合物

可以改善SSc中的伤口愈合。这些数据还表明，尽管存在抗纤维化作用模式，但这些化合物能够治愈SSc患者中的DU。

[0011] 发明公开内容

本发明的治疗剂所解决的、特别且相当有利地可以通过单独或与PDE5抑制剂组合的上述sGC刺激剂或sGC活化剂治疗的纤维化病症包括但不限于系统性硬化症(SSc)、系统性硬化症(SSc)伴随的纤维化和纤维化疾病。

[0012] 本发明的治疗剂所解决的、特别且相当有利地可以通过单独或与PDE5抑制剂组合的上述sGC刺激剂或sGC活化剂治疗的纤维化病症包括但不限于系统性硬化症(SSc)伴随的血管病变、雷诺氏现象(RD)和指溃疡(DU)的形成和愈合。

[0013] 系统性硬化症(SSc)是指但不限于弥漫性系统性硬化症(dSSc)、局限性系统性硬化症(ISSc)、重叠型系统性硬化症、未分化型系统性硬化症、无硬皮病的系统性硬化症、皮肤纤维化、硬皮病、肾源性纤维化皮肤病变(NFD)、肾源性系统性纤维化(NSF)、瘢痕疙瘩形成。

[0014] SSc伴随的纤维化是指内部器官(包括但不限于肠、肺、肾和血管)的纤维化。

[0015] 纤维化疾病包括但不限于这样的病况，其中胶原蛋白过量(不依赖于病因，即自身免疫性病症、慢性移植物抗宿主病、放射疗法、中毒、糖尿病、手术)导致皮肤、肠、肝、肺、心脏、膀胱、前列腺、血管的纤维化或组织中的任何其它局部或全身性纤维化病况。

[0016] 在本发明的意义上，术语纤维化疾病特别包括以下术语：肝纤维化、肝硬化、肺纤维化、心内膜心肌纤维化、肾病、肾小球性肾炎、间质性肾纤维化、由糖尿病引起的纤维化病变、骨髓纤维化和类似的纤维化疾病、硬皮病、硬斑病、瘢痕疙瘩、肥大性瘢痕(包括手术后)、痣、糖尿病性视网膜病变、增生性玻璃体视网膜病变和结缔组织疾病(例如肉状瘤病)。

[0017] SSc伴随的血管病变包括但不限于血管闭塞性疾病血管炎、微血管病变和大血管病变、雷诺氏现象、指缺血性损伤、指溃疡、指坏死性损伤、坏疽和指损失。

[0018] 在本发明的意义上，sGC刺激剂是一氧化氮(NO)非依赖性和血红素(heam)依赖性的可溶性鸟苷酸环化酶调节剂。

[0019] 在本发明的意义上，sGC活化剂是一氧化氮(NO)和血红素(heam)非依赖性的可溶性鸟苷酸环化酶调节剂。

[0020] 本发明的一个优选实施方案是根据WO03/097063、WO03/09545、WO04/009589、WO03/004503、WO02/070462、WO2007/045366、WO2007/045369、WO2007/045370、WO2007/045433、WO2007/045367、WO2007/124854、WO2007/128454、WO2008/031513、WO2008/061657、WO2008/119457、WO2008/119458、WO2009/127338、WO2010/079120、WO2010/102717、WO2011/051165、WO2011/147809、WO2011/141409、WO2014/012935、WO2012/059549、WO2012/004259、WO2012/004258、WO2012/059548、WO2012/028647、WO2012/152630、WO2012/076466、WO2014/068099、WO2014/068104、WO2012/143510、WO2012/139888、WO2012/152629、WO2013/004785、WO2013/104598、WO2013/104597、WO2013/030288、WO2013/104703、WO2013/131923、WO2013/174736、WO2014/012934、WO2014/068095、WO2014/195333、WO2014/128109、WO2014/131760、WO2014/131741、WO2015/018808、WO2015/004105、WO2015/018814、WO98/16223、WO98/16507、WO98/23619、WO00/06569、WO01/19776、WO01/19780、WO01/19778、WO02/042299、WO02/092596、WO02/042300、WO02/042301、WO02/036120、WO02/042302、WO02/070459、WO02/

070460、WO02/070461、WO02/070510、WO2012/165399、WO2014/084312、WO2011115804、WO2012003405、WO2012064559、WO2014/047111、WO2014/047325、WO2011/149921、WO2010/065275、WO2011/119518中公开的化合物的化合物用于制备用于伴随纤维化疾病诸如系统性硬化症和硬皮病的指溃疡的预防和愈合的药物的用途。本发明的一个优选实施方案是根据式(1)-(28)的化合物用于制备用于伴随纤维化疾病诸如系统性硬化症和硬皮病的指溃疡的预防和愈合的药物的用途，如下所示：

2-[1-(2-氟苄基)-1H-吡唑并[3,4-b]吡啶-3-基]-5-(4-吗啉基)-4,6-嘧啶二胺(1)，其公开为WO 00/06569中的实施例16，

· 2-[1-(2-氟苄基)-1H-吡唑并[3,4-b]吡啶-3-基]-5-(4-吡啶基)-4-嘧啶胺(2)，其公开为WO 02/42301中的实施例1，

· 4,6-二氨基-2-[1-(2-氟苄基)-1H-吡唑并[3,4-b]吡啶-3-基]-5-嘧啶基(甲基)氨基甲酸甲酯(3)，其公开为WO 03/095451中的实施例8，

· 4,6-二氨基-2-[1-(2-氟苄基)-1H-吡唑并[3,4-b]吡啶-3-基]-5-嘧啶基氨基甲酸甲酯(4)，其公开为WO 03/095451中的实施例5，

· 4-({(4-羧基丁基)[2-(2-{[4-(2-苯基乙基)苄基]氧基}苯基)乙基]氨基}甲基)甲酸(5)，其公开为WO 01/019780中的实施例8a，

· {4,6-二氨基-2-[5-氟-1-(2-氟苄基)-1H-吡唑并[3,4-b]吡啶-3-基]嘧啶-5-基}氨基甲酸甲酯(6)、{4,6-二氨基-2-[5-氟-1-(2-氟苄基)-1H-吡唑并[3,4-b]吡啶-3-基]嘧啶-5-基}甲基氨基甲酸甲酯(7)、{4,6-二氨基-2-[5-氟-1-(2-氟苄基)-1H-吡唑并[3,4-b]吡啶-3-基]嘧啶-5-基}(2,2,2-三氟乙基)氨基甲酸甲酯(8)，其公开于WO 2011/147809中，

· 作为钠盐的5-氯-2-(5-氯噻吩-2-磺酰基氨基-N-(4-(吗啉-4-磺酰基)-苯基)-苯甲酰胺(9)，其公开于WO00/02851中，

· 2-(4-氯-苯基磺酰基氨基)-4,5-二甲氧基-N-(4-(硫代吗啉-4-磺酰基)-苯基)-苯甲酰胺 (10)，其公开于WO00/02851中，

· 1-{6-[5-氯-2-({4-反-4-}三氟甲基)环己基]苄基}氧基)苯基]吡啶-2-基}-5-(三氟甲基)-1H-吡唑-4-甲酸(11)，其公开于WO 2009/032249中，

· 1-[6-(2-(2-甲基-4-(4-三氟甲氧基苯基)苄基氧基)-苯基)吡啶-2-基]-5-三氟甲基-吡唑-4-甲酸 (12)，其公开于WO 2009/071504中，

· 1-[6-(3,4-二氯苯基)-2-吡啶基]-5-(三氟甲基)-1H-吡唑-4-甲酸(13)，其公开于WO 2009/068652中，

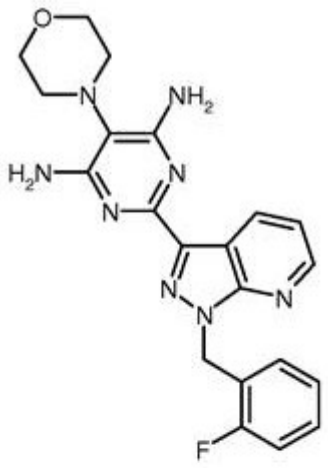
· 1-({2-[3-氯-5-(三氟甲基)苯基]-5-甲基-1,3-噻唑-4-基}甲基)-1H-吡唑-4-甲酸(14)， 4-({2-[3-(三氟甲基)苯基]-1,3-噻唑-4-基}甲基)苯甲酸(15)和1-({2-[2-氟-3-(三氟甲基)苯基]-5-甲基-1,3-噻唑-4-基}甲基)-1H-吡唑-4-甲酸(16)，其公开于WO 2009/123316中，

· 4-氨基-2-[5-氯-3-(3,3,3-三氟丙基)-1H-吲唑-1-基]-5,5-二甲基-5,7-二氢-6H-吡咯并[2,3-d]嘧啶-6-酮(17)、4-氨基-2-[5-氯-3-(2,3,6-三氟苄基)-1H-吲唑-1-基]-5,5-二甲基-5,7-二氢-6H-吡咯并[2,3-d]嘧啶-6-酮 (18)、4-氨基-5,5-二甲基-2-[3-(2,3,6-三氟苄基)-1H-噻吩并[3,4-c]吡唑-1-基]-5,7-二氢-6H-吡咯并[2,3-d]嘧啶-6-酮(19)、4-氨基-5,5-二甲基-2-[3-(2,3,6-三氟苄基)-1H-噻吩并[2,3-d]吡唑-1-基]-5,5-

二甲基-5,7-二氢-6H-吡咯并[2,3-d]嘧啶-6-酮(20)、4-氨基-5,5-二甲基-2-[7-(2,3,6-三氟苄基)咪唑并[1,5-b]哒嗪-5-基]-5,7-二氢-6H-吡咯并[2,3-d]嘧啶-6-酮(21)、4-氨基-2-[6-氯-3-(2,3,6-三氟苄基)咪唑并[1,5-a]吡啶-1-基]]-5,5-二甲基-5,7-二氢-6H-吡咯并[2,3-d]嘧啶-6-酮(22)、4-氨基-2-[6-氟-3-(2,3,6-三氟苄基)咪唑并[1,5-a]吡啶-1-基]]-5,5-二甲基-5,7-二氢-6H-吡咯并[2,3-d]嘧啶-6-酮(23)、4-氨基-2-[6-氟-3-(2,3,6-三氟苄基)6-氟咪唑并[1,5-a]吡啶-1-基]-5,5-二甲基-5,7-二氢-6H-吡咯并[2,3-d]嘧啶-6-酮(24)、4-氨基-5,5-二甲基-2-[3-(2,4,6-三氟苄基)咪唑并[1,5-a]吡啶-1-基]]-5,7-二氢-6H-吡咯并[2,3-d]嘧啶-6-酮(25)、4-氨基-2-[3-(2-环戊基乙基)咪唑并[1,5-a]吡啶-1-基]-5,5-二甲基-5,7-二氢-6H-吡咯并[2,3-d]嘧啶-6-酮(26)，其公开于WO 2010/065275中，

· 已知为BAY 41-2272的3-(4-氨基-5-环丙基嘧啶-2-基)-1-(2-氟苄基)-1*H*-吡唑并[3,4-*b*]吡啶 (27)，其公开为WO 00/06568中的实施例1，

· 2-{5-氟-1-[(3-氟吡啶-2-基)甲基]-1H-吡唑并[3,4-b]吡啶-3-基}-5-甲基-5-(三氟甲基)-4-[(3,3,3-三氟丙基)氨基]-5,7-二氢-6H-吡咯并[2,3-d]嘧啶-6-酮(28)，其公开为WO 2014/131760中的实施例1。



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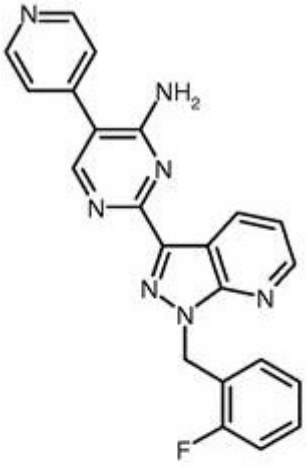

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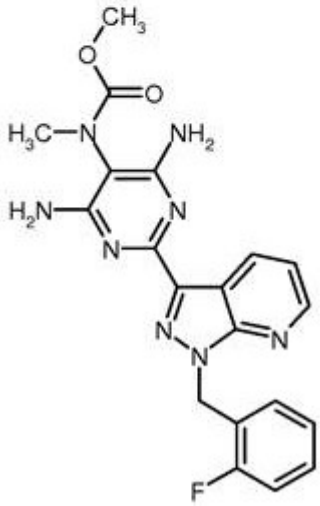

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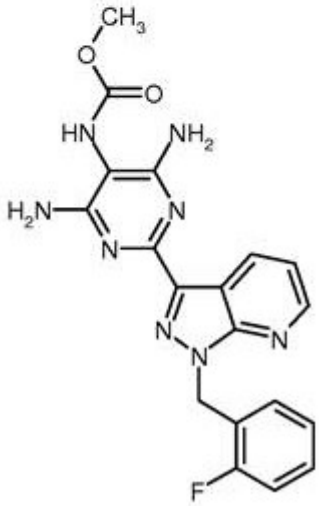

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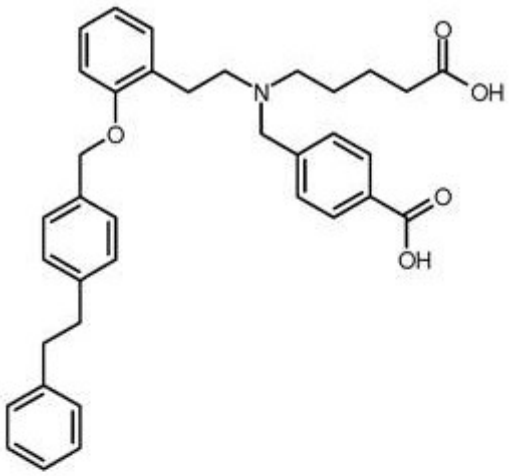

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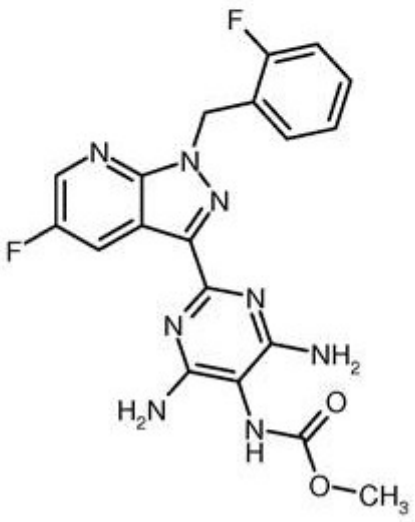

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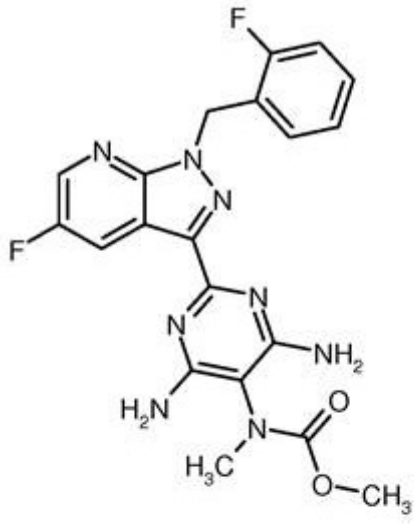

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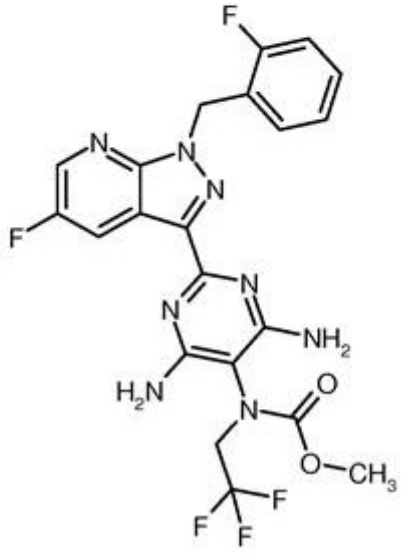

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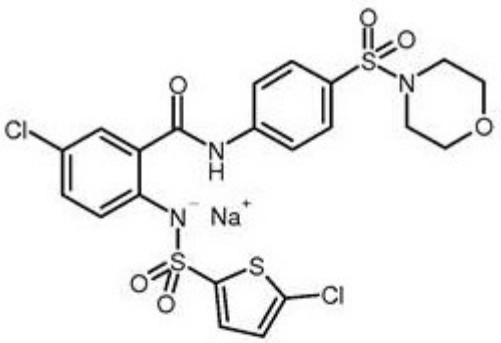

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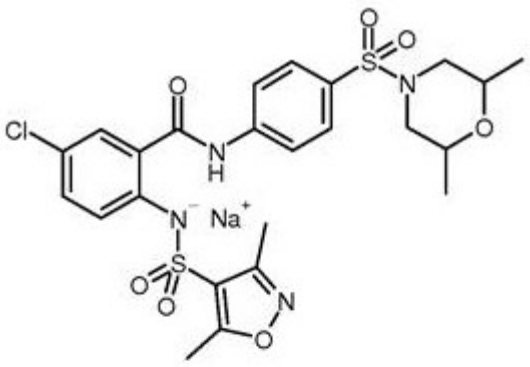

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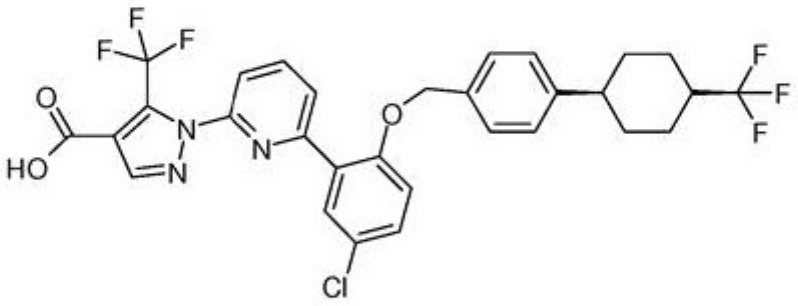

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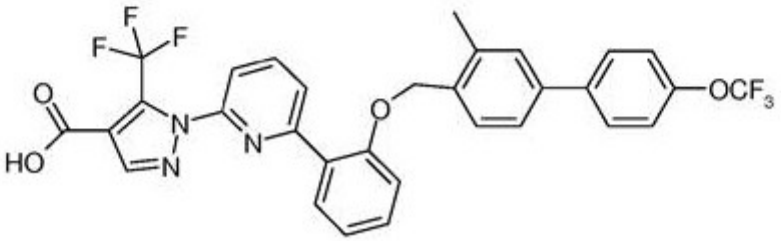

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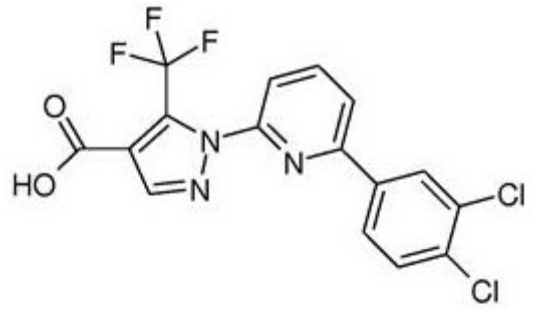

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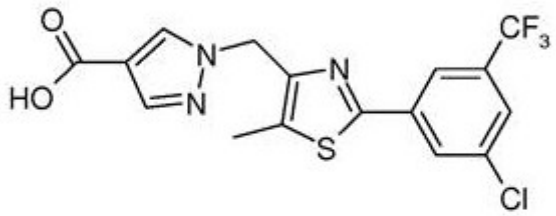

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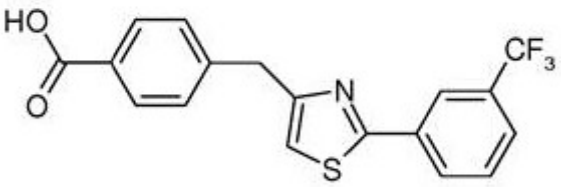

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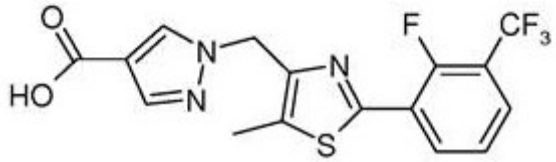

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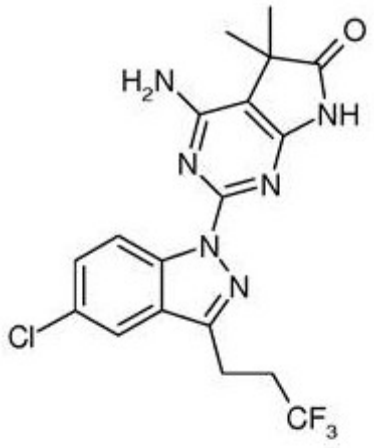

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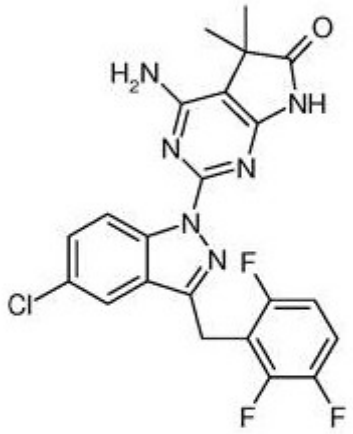

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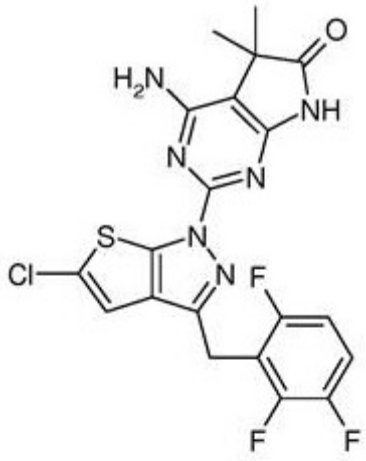

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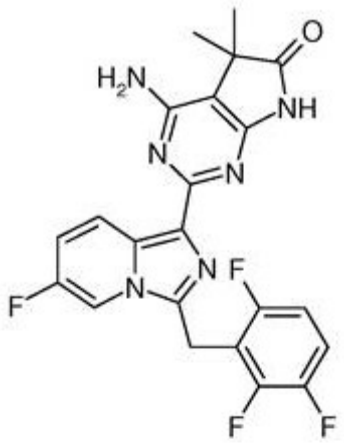

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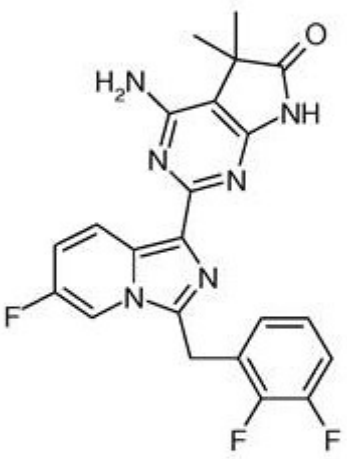

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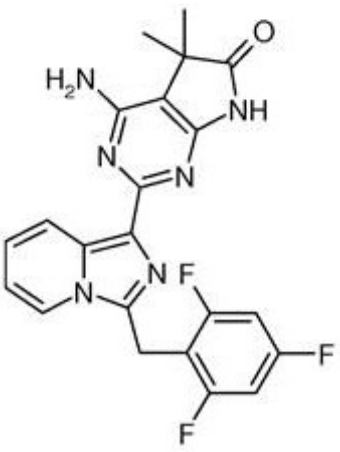

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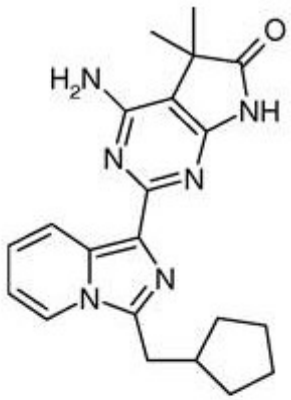

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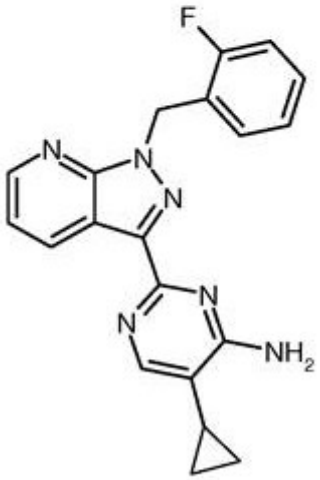

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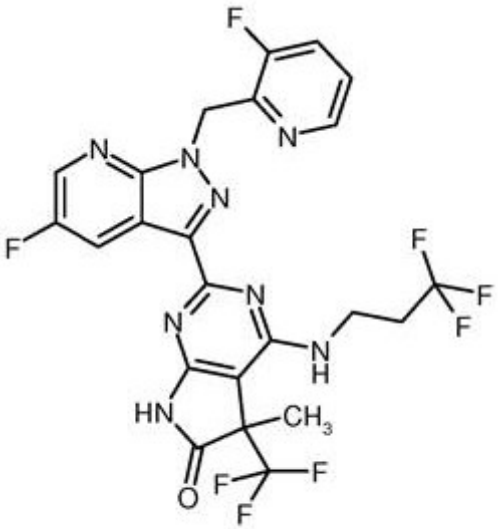

(28)

[0021] 根据式(1)、(2)、(3)、(4)、(6)-(8)和(17)-(27)的化合物已知为sGC刺激剂。优选使用根据式(1)、(2)、(3)、(4)、(6)、(7)、(27)和(28)的化合物。

[0022] 特别优选使用根据式(3)、(4)、(6)、(7)和(28)的化合物。

[0023] 特别优选使用根据式(3)、(4)、(6)和(28)的化合物。

[0024] 特别优选使用根据式(3)、(7)和(28)的化合物。

[0025] 特别优选使用根据式(3)的化合物。

[0026] 根据式(5)和(9)-(16)的化合物已知为sGC活化剂。优选使用根据式(5)的化合物。

[0027] 本发明的另一个实施方案是可溶性鸟苷酸环化酶的刺激剂和/或活化剂与PDE5抑制剂的组合产品用于制备用于伴随纤维化疾病诸如系统性硬化症和硬皮病的指溃疡的预防和愈合的药物的用途。

[0028] 优选使用以下PDE 5抑制剂用于与sGC刺激剂和/或活化剂的组合产品：

他达拉非((6R,12aR)-2,3,6,7,12,12a-六氢-2-甲基-6-(3,4-亚甲基-二氧基苯基)吡嗪并(1',2':1,6)吡啶并(3,4-b)吲哚-1,4-二酮)、伐地那非(2-(2-乙氧基-5-(4-乙基哌嗪-1-基-1-磺酰基)苯基)-5-甲基-7-丙基-3H-咪唑并(5,1-f)(1,2,4)三嗪-4-酮)、西地那非(3-[2-乙氧基-5-(4-甲基哌嗪-1-基)磺酰基-苯基]-7-甲基-9-丙基-2,4,7,8-四氮杂双环[4.3.0]壬-3,8,10-三烯-5-酮)、乌地那非 5-[2-丙基氧基-5-(1-甲基-2-吡咯烷基乙基酰氨基磺酰基)苯基]-甲基-3-丙基-1,6-二氢-7H-吡唑并(4,3-d)嘧啶-7-酮、*Dasantafil* 7-(3-溴-4-甲氧基苄基)-1-乙基-8-[[(1,2)-2-羟基环戊基]氨基]-3-(2-羟基乙基)-3,7-二氢-1-嘌呤-2,6-二酮、阿伐那非 4-{[(3-氯-4-甲氧基苯基)甲基]氨基}-2-[(2S)-2-(羟基甲基)吡咯烷-1-基]-N-(嘧啶-2-基甲基)嘧啶-5-甲酰胺、米罗那非、罗地那非(Lodenafil)、UK 369.003、UK 371.800、Surface Logix的*SLx 2101*、*LAS 34179*三唑并[1,2-]黄嘌呤,6-甲基-4-丙基-2-[2-丙氧基-5-(4-甲基哌嗪子基)磺酰基]苯基或盐、水合物或盐的水合物。

[0029] 特别优选的是根据式(1)、(2)、(3)、(4)、(6)、(7)、(27)、(28)和/或(5)的化合物与伐地那非和/或西地那非的组合产品用于制备用于伴随纤维化疾病诸如系统性硬化症和硬皮病的指溃疡的预防和愈合的药物的用途。

[0030] 特别优选的是根据式(3)、(4)、(6)、(7)、(27)、(28)和/或(5)的化合物与伐地那非和/或西地那非的组合产品用于制备用于伴随纤维化疾病诸如系统性硬化症和硬皮病的指溃疡的预防和愈合的药物的用途。

[0031] 特别优选的是根据式(3)、(4)、(6)、(7)和/或(28)的化合物用于制备用于伴随纤维化疾病诸如系统性硬化症和硬皮病的指溃疡的预防和愈合的药物的用途。

[0032] 特别优选的是根据式(3)、(4)和/或(6)的化合物用于制备用于伴随纤维化疾病诸如系统性硬化症和硬皮病的指溃疡的预防和愈合的药物的用途。

[0033] 特别优选的是至少一种根据式(3)、(4)、(6)和/或(7)的化合物与伐地那非或西地那非的组合产品用于制备用于伴随纤维化疾病诸如系统性硬化症和硬皮病的指溃疡的预防和愈合的药物的用途。

[0034] sGC刺激剂诸如根据式(3)的化合物在小鼠中的tsk-1皮肤纤维化模型中剂量依赖性地且显著地加速伤口愈合。tsk-1小鼠模型的特征在于反映非炎性驱动的、稳定的SSc表型的大量皮肤纤维化。这些数据暗示sGC刺激剂诸如根据式(3)的化合物可以成为SSc相关血管病变的有效治疗选项,特别是用于指溃疡的预防和愈合。

[0035] 如果必要,根据本发明的化合物可以单独使用或与其它活性物质组合使用。本发

明还涉及含有至少一种根据本发明的化合物和一种或多种其它活性物质的药用产品，其特别是用于治疗和/或预防上述疾病。作为合适的组合活性物质，我们可以例如且优选提及：

· 有机硝酸盐和NO-供体，例如硝普钠、硝酸甘油、单硝酸异山梨酯、二硝酸异山梨酯、吗多明或SIN-1和吸入性NO；

· 其它血管活性药物，例如前列腺素类，诸如伊洛前列素、贝前列素、西卡前列素、依前列醇、曲前列环素；

· 其它血管活性药物，例如Rho激酶抑制剂，诸如法舒地尔；

· 其它血管活性药物，例如内皮素受体拮抗剂，诸如波生坦、达卢生坦、安贝生坦或西他生坦、马西替坦；

· 用于降低血压的活性物质，例如且优选自钙拮抗剂，诸如硝苯地平、氨氯地平、维拉帕米或地尔硫卓；

· 用于降低血压的活性物质，例如且优选自血管紧张素AII拮抗剂、ACE抑制剂、肾素抑制剂、α-阻断剂、β-阻断剂、盐皮质激素受体拮抗剂和利尿剂；和/或

· 抗血栓形成剂，例如且优选自血小板聚集抑制剂、抗凝血剂、凝血酶抑制剂或纤维蛋白溶解物质；

· 改变脂肪代谢的活性物质，例如且优选自甲状腺受体激动剂、胆固醇合成抑制剂，诸如例如且优选HMG-CoA还原酶或角鲨烯合成抑制剂、ACAT抑制剂、CETP抑制剂、MTP抑制剂、PPAR-α、PPAR-γ 和/或PPAR-δ激动剂、胆固醇吸收抑制剂、脂肪酶抑制剂、聚合胆汁酸吸附剂、胆汁酸重吸收抑制剂和脂蛋白(a)拮抗剂；

· 用于纤维化病症的活性物质，例如且优选自蛋白激酶抑制剂诸如索拉非尼、瑞戈非尼、伊马替尼、达沙替尼、尼罗替尼、尼达尼布、硼替佐米和/或吡非尼酮；

· 改变炎性反应和/或抑制免疫应答的活性物质，例如诸如环磷酰胺、甲氨蝶呤、雷帕霉素、咪唑硫嘌呤(azathioproin)、托珠单抗、英夫利昔单抗、利妥昔单抗、阿达木单抗、贝利木单抗、阿巴西普、SAR100842、沙利度胺衍生物；

· 作用于不同途径的活性物质，例如吡非尼酮、SAR100842、沙利度胺衍生物、整联蛋白抑制剂。

[0036] 本发明的另一个优选实施方案是如上所示的化合物和/或组合产品，其用于伴随纤维化疾病诸如系统性硬化症和/或硬皮病的指溃疡的预防和愈合。

[0037] 本发明的另一个优选实施方案是用于生产用于伴随纤维化疾病诸如系统性硬化症和/或硬皮病的指溃疡的预防和愈合的药物的用途，所述药物包含有效量的如上所示的化合物和/或组合产品。

[0038] 本发明的另一个优选实施方案是包含如上所示的至少一种化合物或一种组合产品的药物制剂，其用于伴随纤维化疾病诸如系统性硬化症和/或硬皮病的指溃疡的预防和愈合。

[0039] 本发明的另一个优选实施方案是包含至少一种如上所示的sGC刺激剂和/或活化剂或如上所示的组合产品的试剂盒，其用于伴随纤维化疾病诸如系统性硬化症和/或硬皮病的指溃疡的预防和愈合。

[0040] 本发明的药物组合物被配制成与其预期给药途径相容。给药途径的实例包括胃肠外，例如静脉内、皮内、皮下、经口(例如吸入)、透皮(局部)、透粘膜和直肠给药。适于可注射

使用的药物组合物包括无菌水溶液(当为水溶性时)或分散液和用于临时制备无菌可注射溶液或分散液的无菌粉末。载体可以是溶剂或分散介质,其含有例如,水,乙醇,药学上可接受的多元醇如甘油、丙二醇、液态聚乙二醇,及其合适的混合物。可以维持适当的流动性,例如,通过使用包衣诸如卵磷脂,通过在分散液情况下维持所需的粒径和通过使用表面活性剂。可以通过各种抗细菌剂和抗真菌剂实现微生物作用的预防,例如对羟苯甲酸酯类、氯丁醇、酚、抗坏血酸、硫柳汞等。在许多情况下,组合物中优选包括等渗剂,例如糖类,多元醇类诸如甘露醇(maitol)、山梨醇,氯化钠。

[0041] 口服组合物通常包括惰性稀释剂或可食用载体。它们可以被包封在明胶胶囊中或压制成片剂。对于口服治疗给药的目的,活性化合物可以掺入赋形剂,并且以片剂、糖锭剂或胶囊的形式应用。口服组合物也可以使用流体载体制备以用作漱口水,其中流体载体中的化合物经口施用并且漱口和吐出或吞下。

[0042] 药学上相容的粘合剂和/或辅助材料可以作为组合物的一部分包括。片剂、丸剂、胶囊、糖锭剂等可以含有任何下列成分或类似性质的化合物:粘合剂,诸如微晶纤维素、黄蓍胶或明胶;赋形剂诸如淀粉或乳糖,崩解剂诸如藻酸、Primogel或玉米淀粉(con 1 starch);润滑剂诸如硬脂酸镁或sterotes;助流剂诸如胶体二氧化硅;甜味剂诸如蔗糖或糖精;或调味剂诸如薄荷、水杨酸甲酯或橙调味剂。

[0043] 对于通过吸入给药,从含有适当抛射剂例如气体诸如二氧化碳的加压容器或分配器、或喷雾器中以气溶胶喷雾的形式递送化合物。

[0044] 也可以通过透粘膜或透皮方式进行全身给药。对于透粘膜或透皮给药,在制剂中使用适于待渗透屏障的渗透剂。此类渗透剂是本领域中通常已知的,并且对于透粘膜给药包括例如去垢剂、胆酸盐和梭链孢酸衍生物。透粘膜给药可以通过使用鼻喷雾或栓剂而完成。对于透皮给药,将活性化合物配制成本领域通常已知的软膏、药膏(salve)、凝胶或乳膏剂。

[0045] 化合物也可以以用于直肠递送的栓剂(例如具有常规栓剂基质诸如可可脂和其它甘油酯)或保留灌肠剂的形式配制。

[0046] 在一个实施方案中,将活性化合物与保护该化合物免于从身体快速消除的载体一起配制,诸如控释制剂,包括植入物和微胶囊化的递送系统。可以使用生物可降解的生物相容性聚合物,诸如乙烯乙酸乙烯酯、聚酐类、聚乙醇酸、胶原、聚原酸酯类和聚乳酸。

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[0048] 附图：

图1:三天后用安慰剂治疗的WT小鼠(左)和tsk-1小鼠(右)中的伤口大小的减小。数据是平均值- SEM,n=46 (WT + 安慰剂)和n=44 (tsk-1 + 安慰剂),*/**/***/****= 显著的,其中p<0.05/0.01/0.001/0.0001

图2:三天后用安慰剂或根据式(27)的化合物(BAY 41-2272)或根据式(3)的化合物(BAY 63-2521)治疗的tsk-1小鼠中伤口大小的减小。数据是平均值 - SEM, n=44-46 (安慰剂组),n= 16 (根据式(27)的化合物 BAY 41-2272组)和n=30-32 (根据式(3)的化合物BAY 63-2521组),*/**/***/****= 显著的,其中p<0.05/0.01/0.001/0.0001;ns = 不显著的;BAY41对应于BAY41-2227。

[0049] 实验部分

实施例A

Tsk-1小鼠vs.WT-小鼠中的伤口愈合

使用SSc的紧皮(Tsk-1)小鼠模型评估根据式(27)和(3)的化合物(BAY 41-2272和BAY 63-2521)对具有大量皮肤纤维化的小鼠中的伤口愈合的影响。由于常染色体显性突变,即原纤蛋白-1基因的串联重复,tsk-1小鼠的表型的特征在于皮下厚度增加(Beyer等人2010)。用以下引物通过PCR进行Tsk-1小鼠的基因分型:突变的原纤蛋白-1/ tsk-1正向引物:5’ - GTTGGCAACTATACCTGCAT - 3’,反向引物:5’ - CCTTTCCTGGTAACATAGGA - 3’。

[0050] 在WT小鼠或Tsk-1小鼠中研究安慰剂(=测试化合物的媒介物= 0.5侵填体(tylose)溶液)的作用。将Tsk-1小鼠麻醉并仔细剃毛,3天后设置伤口以精确定量伤口大小。为了避免日常处理动物对伤口愈合的影响,将通常的每日两次灌胃治疗替换为食物中的药物给药。WT小鼠和Tsk-1小鼠接受正常小鼠食物(安慰剂),其在剃毛当天开始。剃毛后三天,将小鼠小心麻醉,且以4 mm的直径打开圆形伤口。打开后3天,将小鼠安乐死并评价伤口大小。数据的统计分析通过单因素ANOVA、随后Tuckey氏多重比较事后分析进行。

[0051] 在tsk-1小鼠中,安慰剂治疗后,伤口大小减小52%±2%(图1)。相比之下,安慰剂治疗的WT小鼠在3天后显示伤口大小减小68%±2%(图1)。因此,与WT小鼠相比,tsk-1小鼠的伤口愈合部分受损,并且在安慰剂治疗的tsk-1小鼠中伤口闭合显著减弱。

[0052] 用根据式(27)和(3)的化合物(BAY 41-2272和BAY 63-2521)治疗的Tsk-1小鼠中的伤口愈合

在Tsk-1小鼠中研究安慰剂(=化合物的媒介物= 0.5%侵填体(tylose)溶液)或根据式(27)或(3)的化合物(BAY 41-2272或BAY 63-2521)的作用。将Tsk-1小鼠麻醉并仔细剃毛,3天后设置伤口以精确定量伤口大小。为了避免日常处理动物对伤口愈合的影响,将每日两次灌胃治疗替换为食物中的药物给药。小鼠接受正常小鼠食物(安慰剂)或小鼠食物,小鼠食物分别含有15和45 ppm的根据式(27)的化合物(BAY 41-2272)或含有5 ppm、15 ppm和45 ppm的根据式(3)的化合物(BAY 63-2521)。这些剂量 - 如通过定向DMPK-研究所证实 - 导致分别与1和3 mg/kg的根据式(27)的化合物(BAY 41-2272) BID以及0.3、1和3 mg/kg的根据式(3)的化合物(BAY 63-2521) BID类似的暴露。治疗组由每组至少8只tsk-1小鼠组成。治疗在剃毛当天开始,以达到稳态暴露。剃毛后三天,将小鼠小心麻醉,且以4 mm的直径打开圆形伤口。打开后3天,将小鼠安乐死并评价伤口大小。数据的统计分析通过单因素ANOVA、随后Tuckey氏多重比较事后分析进行。

[0053] 在tsk-1小鼠中,在用15和45ppm根据式(27)的化合物(BAY 41-2272)治疗后,伤口大小分别剂量依赖性地且显著地减小64 ± 2%和73 ± 2%(图2)。此外,在tsk-1小鼠中,在用5、15和45ppm根据式(3)的化合物(BAY 63-2521)治疗后,伤口大小分别剂量依赖性地且显著地减小59%±4%、65 ± 3%和70%±2%(图2)。此外,用45ppm根据式(27)的化合物(BAY 41-2272)和45ppm根据式(3)的化合物(BAY 63-2521,Riociguat)治疗,使伤口愈合正常化至与安慰剂治疗的WT小鼠中观察到的(68%±2%)类似的程度(图1,图2)。因此,在TSK-小鼠中,根据式(27)和(3)的化合物(BAY 41-2272和BAY 63-2521)与安慰剂治疗相比加速伤口愈合,并且导致如在健康对照小鼠中发现的伤口闭合的正常化。

[0054] 总之,这些数据表明:

a) 与WT小鼠相比,tsk-1小鼠的伤口愈合显著减弱。

[0055] b) 通过用根据式(27)的化合物(BAY 41-2272)和/或根据式(3)的化合物BAY 63-2521治疗,显著且剂量依赖性地改善TSK-1小鼠的伤口愈合。

[0056] · 最大效力导致与健康WT小鼠相似的伤口闭合。

[0057] 由于Tsk-1小鼠是具有广泛皮肤纤维化的动物模型(其反映SSc中的病况),该数据表明上述化合物不仅可以减少纤维化,而且加速SSc中的伤口愈合,暗示这些化合物可用于治疗SSc患者中的DU。

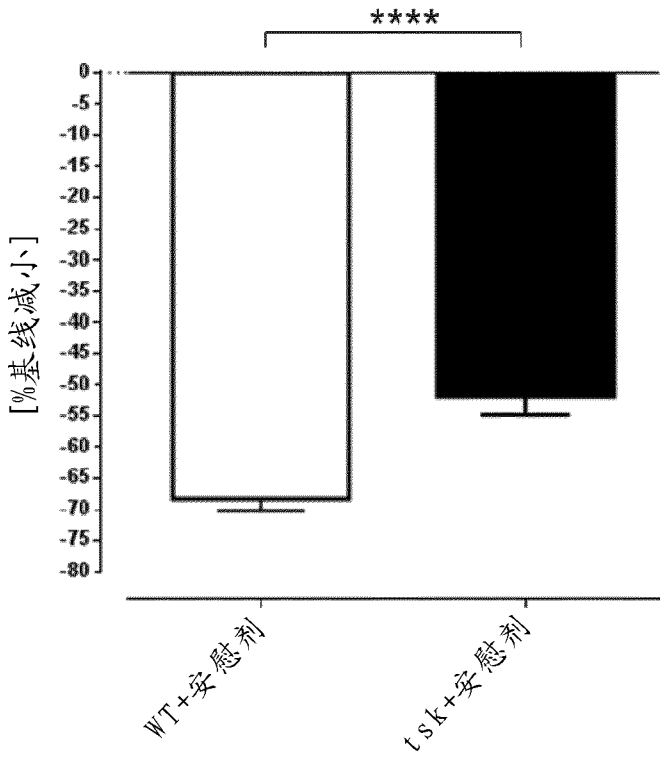
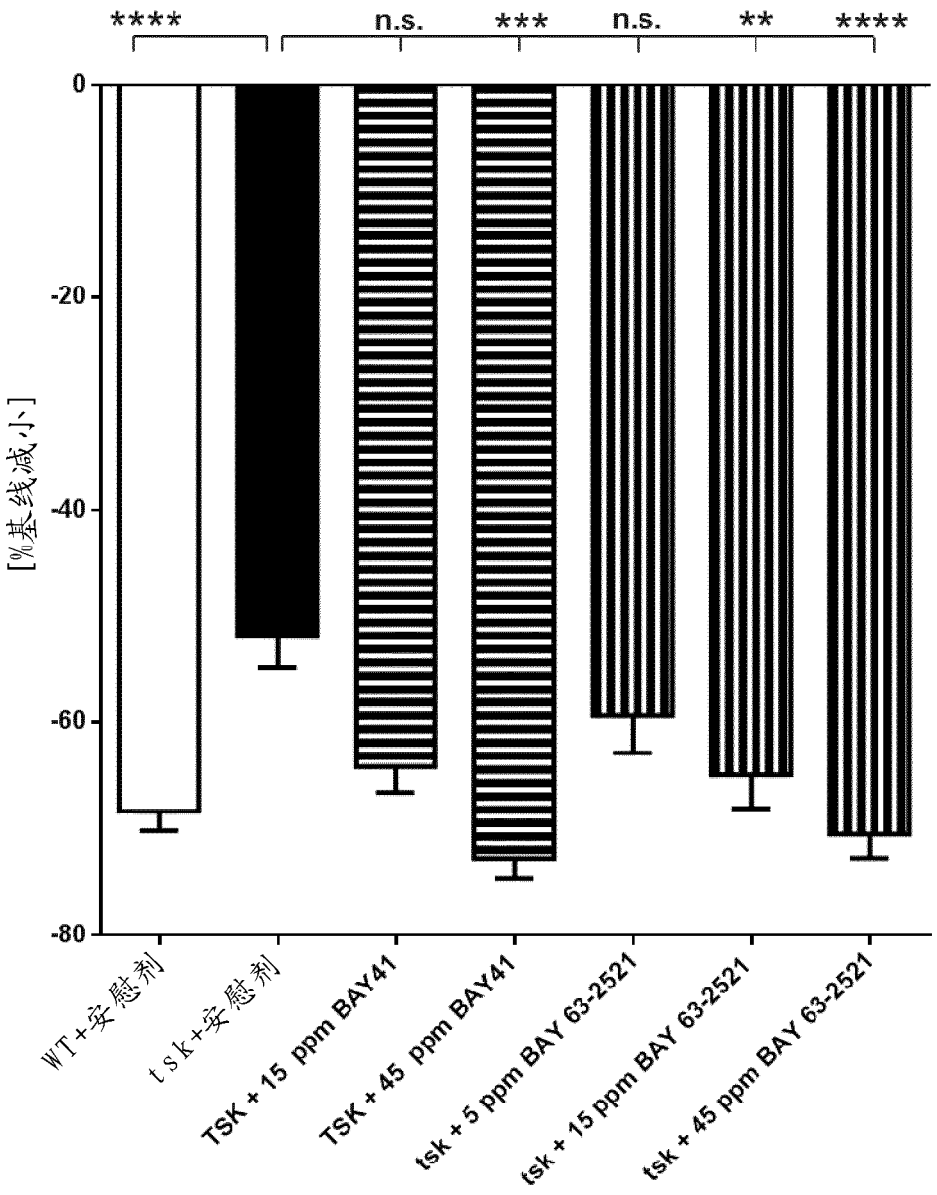


图 1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n.s.
***
n.s.
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0
-20
-40
-60
-80
[%基线减小]
WT+安慰剂
tsk+安慰剂
TSK + 15 ppm BAY41
TSK + 45 ppm BAY41
tsk + 5 ppm BAY 63-2521
tsk + 15 ppm BAY 63-2521
tsk + 45 ppm BAY 63-2521

图 2