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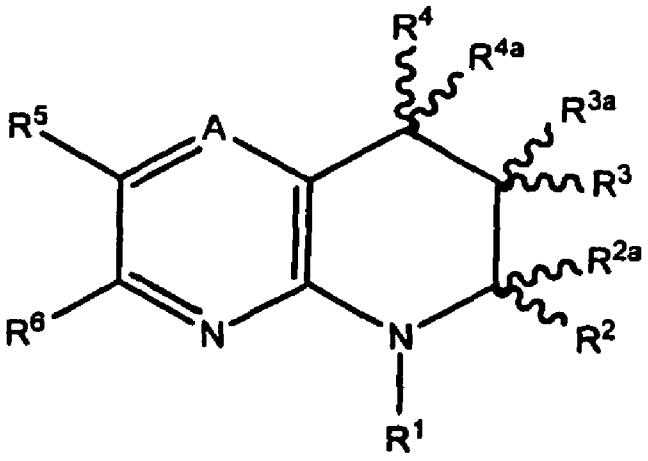
(54) Title: FUSED PIPERIDINES AS IP RECEPTOR AGONISTS FOR THE TREATMENT OF PULMONARY ARTERIAL HYPERTENSION (PAH) AND RELATED DISORDERS



(I)

(57) Abstract: The present invention provides heterocyclic derivatives which activate the IP receptor, processes for preparing them, pharmaceutical compositions comprising said derivatives and uses thereof. Activating the IP receptor signaling pathway is useful to treat many forms of PAH, pulmonary fibrosis and exert beneficial effects in fibrotic conditions of various organs in animal models and in patients. Formula (I):

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FUSED PIPERIDINES AS IP RECEPTOR AGONISTS FOR THE TREATMENT OF PULMONARY ARTERIAL HYPERTENSION (PAH) AND RELATED DISORDERS

Background of the Invention

Prostacyclin (or PGI2) is a member of the family of lipid molecules known as eicosanoids. It is a potent vasodilator, antiproliferative, anti-thrombotic agent that mediates its effects as an agonist of the IP receptor. The IP receptor is a G-protein coupled receptor that, upon activation by prostacyclin, stimulates the formation of cyclic adenosine monophosphate (cAMP). Prostacyclin counteracts the vasoconstrictor and pro-thrombotic activity of endothelin.

Pulmonary arterial hypertension (PAH) is a life-threatening disease characterized by a progressive pulmonary vasculopathy leading to right ventricular hypertrophy. Exogenous administration of an agonist of the IP receptor has become an important strategy in the treatment of PAH. (See, e.g., Tuder et al., Am. J. Respir. Crit. Care. Med., 1999, 159: 1925-1932; Humbert et al, J. Am. Coll. Cardiol., 2004, 43:13S-24S; Rosenzweig, Expert Opin. Emerging Drugs, 2006, 11 :609-619; McLaughlin et al, Circulation, 2006, 114:1417-1431; Rosenkranz, Clin. Res. Cardiol., 2007, 96:527-541; Driscoll et al, Expert Opin. Pharmacother., 2008, 9:65-81.).

The prostacyclin analogue epoprostenol (flolan) is at least as effective as transplantation in terms of survival. Despite this, it is not used as frontline therapy due to significant tolerability, convenience and cost issues. Instead, patients with PAH are often treated first with either endothelin receptor antagonists (e.g. bosentan) and/or PDE5 inhibitors (e.g. sildenafil), which are better tolerated but can have limited efficacy. Prostacyclin analogues are used mainly as add-on treatment as severity of the disease progresses and tolerability and convenience become less of an issue.

Two key issues prevent current prostacyclin analogues being used as frontline therapy in PAH. Firstly, they are very unstable with an extremely short half-life, meaning they must be constantly infused via an in-dwelling intra venous (i.v.) catheter that is both inconvenient for the patient and also associated with a significant risk of infection and sepsis. Secondly, they are associated with significant side effects including nausea, jaw pain, headache and other side effects associated with systemic hypotension.

One solution to these issues is iloprost, which is available as a nebulised formulation that has reduced tolerability issues, but the short half life results in a 6-9 times daily dosing regime. More recently, researchers made efforts to generate stable, orally available IP receptor agonists. These ligands would improve patient convenience and compliance, but high levels of

systemic drug is required to achieve pharmacodynamic effects in the lung; thus, possibly generating similar side effects to those observed with i.v. flolan.

The present invention describes stable, highly selective IP receptor agonists that are suitable for oral and inhaled delivery. The present invention offers a significant improvement over existing prostacyclin analogues and enables their use in less-severe patients. In addition, long term activation of the IP receptor has been shown to reverse remodeling associated with PAH; therefore, earlier intervention with the present invention may have significant effects on disease progression and potentially may show reversal.

In addition, pharmaceutical research has considerable interest in developing IP receptor agonists for the treatment of pulmonary fibrosis. IP deficient mice have been shown to be more susceptible to bleomycin-induced lung fibrosis than wild-type animals (Lovgren AK et al. (2006) *Am J Physiol Lung Cell Mol Physiol.* 291:L144-56), and the IP receptor agonist iloprost increases survival in bleomycin-treated mice (Zhu et al (2010) Respir Res. 11(1):34).

Furthermore, IP receptor signaling has been shown to exert beneficial effects in fibrotic conditions of various organs in animal models and in patients. Benefits of IP receptor agonist were shown for fibrosis of the heart, lung, skin, pancreas and liver, and in systemic sclerosis. (Gayraud M (2007) *Joint Bone Spine*. 74(1):e1-8; Hirata Y et al (2009) *Biomed Pharmacother*. 63(10):781-6; Kaneshige T et al (2007) *J Vet Med Sci.* 69(12):1271-6; Sahsivar MO et al (2009) *Shock* 32(5):498-502; Sato N et al (2010) *Diabetes* 59(4):1092-100; Shouval DS et al (2008) *Clin Exp Rheumatol.* 26(3 Suppl 49):S105-7; Spargias K et al (2009) *Circulation*. 120(18):1793-9; Stratton R et al (2001) *J Clin Invest.* 108(2):241-50; Takenaka M et al (2009) Prostaglandins Leukot Essent Fatty Acids. 80(5-6):263-7; Watanabe M et al (2009) *Am J Nephrol.* 30(1):1-11; Yano T et al (2005) *Am J Pathol.* 166(5):1333-42; Zardi EM et al (2007) *Expert Opin Biol Ther.* 7(6):785-90; Zardi EM et al (2006) *In Vivo* 20(3):377-80; Rehberger P et al (2009) *Acta Derm Venereol.* 89(3):245-9). Fibrotic conditions can occur in most organs secondary to chronic inflammation indications throughout the body and are likely to share common causes.

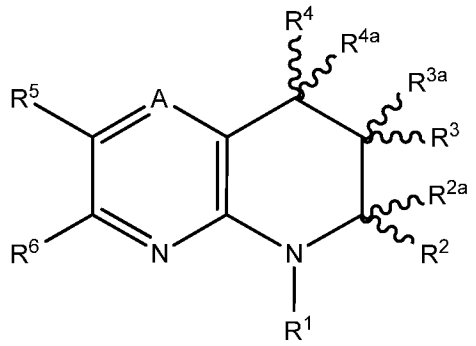
Therefore, antifibrotic agents such as IP receptor agonists of the present invention are of potential benefit in all indications that are associated with fibrotic tissue remodeling.

There is considerable interest in developing agonists of the IP receptor for use in the treatment of other diseases, such as atherothrombosis, preeclampsia. It is highly desirable to develop a stable, inhaled agonists of the IP receptor, which may lead to improved management of PAH.

The invention pertains to the compounds, methods for using them, and uses thereof as described herein. Examples of compounds of the invention include the compounds according to

any of Formula I, or a pharmaceutically acceptable salt thereof, and the compounds of the examples.

In a first aspect, there is provided a compound of Formula I:



(I)

or a pharmaceutically acceptable salt thereof, wherein

A is N or CR';

R' is H, C_1-C_8 alkyl optionally substituted by one or more halogen atoms;

R^1 is selected from H; C_1-C_8 alkyl optionally substituted by one or more halogen atoms, OH, C_1-C_4 alkoxy, C_3-C_7 cycloalkyl or C_3-C_7 cycloalkyloxy; -(C_2-C_4 alkyl)-$NR^{19}R^{21}$ and C_3-C_7 cycloalkyl; or

R^1 is -X-Y; or

R^1 is -W-R^7-X-Y; or

R^1 is –$S(O)_2$-X-Y; or

R^1 is –$S(O)_2$-W-R^7-X-Y;

R^2 is selected from H; C_1-C_8 alkyl optionally substituted by one or more halogen atoms, OH, C_1-C_4 alkoxy, C_3-C_7 cycloalkyl or C_3-C_7 cycloalkyloxy; -(C_1-C_4 alkyl)-$NR^{19}R^{21}$ and C_3-C_7 cycloalkyl; or

R^2 is -X-Y; or

R^2 is -W-R^7-X-Y; or

R^2 is –$S(O)_2$- X-Y; or

R^2 is –$S(O)_2$-W-R^7-X-Y;

R^{2a} is selected from H; C_1-C_8 alkyl optionally substituted by one or more halogen atoms, OH, C_1-C_4 alkoxy, C_3-C_7 cycloalkyl or C_3-C_7 cycloalkyloxy; and C_3-C_7 cycloalkyl; or

R^2 and R^{2a} taken together are oxo;

wherein either R^1 or R^2 is -X-Y, -W-R^7-X-Y, –$S(O)_2$- X-Y; or –$S(O)_2$-W-R^7-X-Y;

R^3 is selected from H; OH; C_1-C_8 alkyl optionally substituted by one or more halogen atoms, OH, C_1-C_4 alkoxy, C_3-C_7 cycloalkyl or C_3-C_7 cycloalkyloxy; C_1-C_4 alkoxy; OR'; -(C_0-C_4alkyl)-$NR^{19}R^{21}$; CN; halogen and C_3-C_7 cycloalkyl;

R^{3a} is selected from H; C_1-C_8 alkyl optionally substituted by one or more halogen atoms, OH, C_1-C_4 alkoxy, C_3-C_7 cycloalkyl or C_3-C_7 cycloalkyloxy; and C_3-C_7 cycloalkyl; or

R^3 and R^{3a} taken together are oxo;

R^4 is selected from H; OH; C_1-C_8 alkyl optionally substituted by one or more halogen atoms, OH, C_1-C_4 alkoxy, C_3-C_7 cycloalkyl or C_3-C_7 cycloalkyloxy; C_1-C_4 alkoxy; OR'; -(C_0-C_4alkyl)-$NR^{19}R^{21}$; CN; halogen and C_3-C_7 cycloalkyl;

R^{4a} is selected from H; C_1-C_8 alkyl optionally substituted by one or more halogen atoms, OH, C_1-C_4 alkoxy, C_3-C_7 cycloalkyl or C_3-C_7 cycloalkyloxy; and C_3-C_7 cycloalkyl; or

R^4 and R^{4a} taken together are oxo;

R^5 and R^6 are independently selected from -(C_0-C_4 alkyl)-C_6-C_{14} aryl and -(C_0-C_4 alkyl)-4 to 14 membered heteroaryl, wherein the aryl and heteroaryl are each optionally substituted by one or more Z substituents;

W is C_1-C_8 alkylene optionally substituted by hydroxy, halogens or C_1-C_4 alkyl;

X is C_1-C_8 alkylene optionally substituted by hydroxy, halogens or C_1-C_4 alkyl;

Y is tetrazolyl;

R^7 is a divalent moiety represented by -O-, -S-, -NHC(O)-, -CH_2=CH_2-, -C_6-C_{14} aryl-D-; -3 to 14 membered heterocyclyl-D-, wherein the heterocyclyl contains at least one heteroatom selected from N, O and S, wherein D is O, S, NH or not present;

Z is independently OH, aryl, O-aryl, benzyl, O-benzyl, C_1-C_6 alkyl optionally substituted by one or more OH groups or NH_2 groups, C_1-C_6 alkyl optionally substituted by one or more halogen atoms, C_1-C_6 alkoxy optionally substituted by one or more OH groups, C_1-C_6 alkoxy optionally substituted by one or more halogen, C_1-C_6 alkoxy optionally substituted by C_1-C_4 alkoxy, $NR^{18}(SO_2)R^{21}$, $(SO_2)NR^{19}R^{21}$, $(SO_2)R^{21}$, $NR^{18}C(O)R^{21}$, $C(O)NR^{19}R^{21}$, $NR^{18}C(O)NR^{19}R^{21}$, $NR^{18}C(O)OR^{19}$, $NR^{19}R^{21}$, $C(O)OR^{19}$, $C(O)R^{19}$, SR^{19}, OR^{19}, oxo, CN, NO_2, halogen or a 3 to 14 membered heterocyclyl, wherein the heterocyclyl contains at least one heteroatom selected from N, O and S;

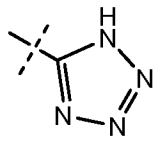
R^{18} is independently H or C_1-C_6 alkyl;

R^{19} and R^{21} are each independently H; C_1-C_8 alkyl; C_3-C_8 cycloalkyl; C_1-C_4 alkoxy-C_1-C_4 alkyl; (C_0-C_4 alkyl)-aryl optionally substituted by one or more groups selected from C_1-C_6 alkyl, C_1-C_6 alkoxy and halogen; (C_0-C_4 alkyl)- 3- to 14-membered heterocyclyl, the heterocyclyl including one or more heteroatoms selected from N, O and S, optionally substituted by one or more

groups selected from halogen, oxo, C_1-C_6 alkyl and $C(O)C_1$-C_6 alkyl; (C_0-C_4 alkyl)-O-aryl optionally substituted by one or more groups selected from C_1-C_6 alkyl, C_1-C_6 alkoxy and halogen; and (C_0-C_4 alkyl)- O-3- to 14-membered heterocyclyl, the heterocyclyl including one or more heteroatoms selected from N, O and S, optionally substituted by one or more groups selected from halogen, C_1-C_6 alkyl or $C(O)C_1$-C_6 alkyl; wherein the alkyl groups are optionally substituted by one or more halogen atoms, C_1-C_4 alkoxy, $C(O)NH_2$, $C(O)NHC_1$-C_6 alkyl or $C(O)N(C_1$-C_6 alkyl$)_2$; or

R^{19} and R^{21} together with the nitrogen atom to which they attached form a 5- to 10-membered heterocyclyl, the heterocyclyl including one or more further heteroatoms selected from N, O and S, the heterocyclyl being optionally substituted by one or more substituents selected from OH; halogen; aryl; 5- to 10-membered heterocyclyl including one or more heteroatoms selected from N, O and S; $S(O)_2$-aryl; $S(O)_2$-C_1-C_6 alkyl; C_1-C_6 alkyl optionally substituted by one or more halogen atoms; C_1-C_6 alkoxy optionally substituted by one or more OH groups or C_1-C_4 alkoxy; and $C(O)OC_1$-C_6 alkyl, wherein the aryl and heterocyclyl substituent groups are themselves optionally substituted by C_1-C_6 alkyl, C_1-C_6 haloalkyl or C_1-C_6 alkoxy.

The term ‘tetrazolyl’ as used herein includes within its scope both possible tautomers



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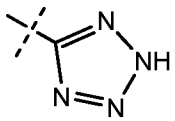

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Various embodiments of the invention are described herein. It will be recognized that features specified in each embodiment may be combined with other specified features to provide further embodiments.

In an embodiment (i) of the invention as described anywhere herein, A is N.

In an embodiment (ii) of the invention as described anywhere herein, A is CR'.

In an embodiment (iii) of the invention as described anywhere herein, A is CR', wherein R' is H.

In an embodiment (iv) of the invention as described anywhere herein,

either R^1 or R^2 is -X-Y or -W-R^7-X-Y;

W is C_1-C_6 alkyl or alkylene optionally substituted by hydroxy, halogens or C_1-C_4 alkyl;

X is C_1-C_6 alkyl or alkylene optionally substituted by hydroxy, halogens or C_1-C_4 alkyl;

R' is H, C_1-C_4 alkyl optionally substituted by one or more halogen atoms;

R^7 is a divalent moiety represented by -C_6-C_{14} aryl-D-; -3 to 14 membered heterocyclyl-D-, wherein the heterocyclyl contains at least one heteroatom selected from N, O and S, wherein D is O.

In an embodiment (v) of the invention as described anywhere herein,

either R^1 or R^2 is -X-Y;

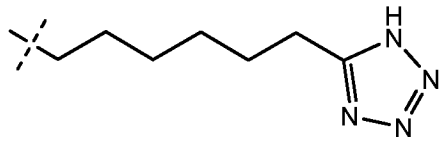
X is C_1-C_6 alkyl or alkylene optionally substituted by hydroxy, halogens or C_1-C_4 alkyl.

In an embodiment (vi) of the invention as described anywhere herein,

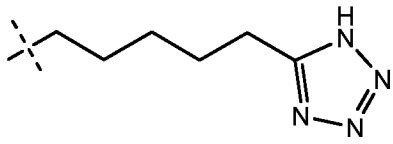
either R^1 or R^2 is -$(CH_2)_m$-tetrazolyl;

m is 1, 2, 3, 4, 5, 6, 7 or 8.

In an embodiment (vii) of the invention as described anywhere herein, either R^1 or R^2 is



or



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In an embodiment (viii) of the invention as described anywhere herein,

R^2 and R^{2a} are independently selected from H and C_1-C_4 alkyl optionally substituted by one or more halogen atoms or OH; or R^2 and R^{2a} taken together are oxo;

R^3 and R^{3a} are independently selected from H; C_1-C_4 alkyl optionally substituted by one or more halogen atoms or OH; and OH; or R^3 and R^{3a} taken together are oxo;

R^4 and R^{4a} are independently selected from H; C_1-C_4 alkyl optionally substituted by one or more halogen atoms or OH; and OH; or R^4 and R^{4a} taken together are oxo.

In an embodiment (ix) of the invention as described anywhere herein, wherein

R^2 and R^{2a} are H; or

R^2 and R^{2a} taken together are oxo;

R^3 and R^{3a} are independently selected from H and OH;
R^4 and R^{4a} are independently selected from H and OH.

In an embodiment (x) of the invention as described anywhere herein, wherein
R^5 and R^6 are independently selected from C_6-C_{14} aryl and 5 to 6 membered heteroaryl, wherein the heteroaryl contains at least one heteroatom selected from N, O and S, wherein the aryl and heteroaryl are each optionally substituted by one or more Z substituents.

In an embodiment (xi) of the invention as described anywhere herein, wherein
R^5 and R^6 are independently selected from phenyl; 2-pyridyl, 3-pyridyl, or 4-pyridyl,
wherein the phenyl, 2-pyridyl, 3-pyridyl, and 4-pyridyl are each optionally substituted by one or more Z substituents.

In an embodiment (xii) of the invention as described anywhere herein, wherein
R^5 is phenyl; 2-pyridyl, 3-pyridyl, or 4-pyridyl, and
R^6 is phenyl; 2-pyridyl, 3-pyridyl, or 4-pyridyl,
wherein the phenyl, 2-pyridyl, 3-pyridyl, and 4-pyridyl are each optionally substituted by one or more Z substituents.

In an embodiment (xiii) of the invention as described anywhere herein, wherein
R^5 and R^6 are independently selected from phenyl optionally substitued by OH, C_1-C_4 alkyl optionally substituted by one or more OH groups or NH_2 groups; C_1-C_4 alkyl optionally substituted by one or more halogen atoms; C_1-C_4 alkoxy optionally substituted by one or more OH groups or C_1-C_4 alkoxy; $NR^{19}R^{21}$; $C(O)OR^{19}$; $C(O)R^{19}$; SR^{19}; OR^{19}; CN; NO_2; and halogen.

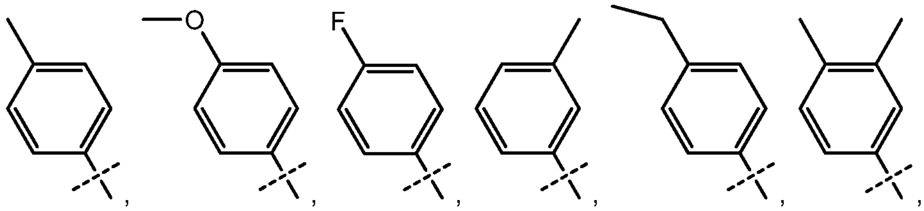
In an embodiment (xiv) of the invention as described anywhere herein, wherein
R^5 and R^6 are independently selected from phenyl optionally substituted by C_1-C_4 alkyl optionally substituted by one or more OH groups or NH_2 groups; C_1-C_4 alkyl optionally substituted by one or more halogen atoms; C_1-C_4 alkoxy optionally substituted by one or more OH groups or C_1-C_4 alkoxy; and halogen.

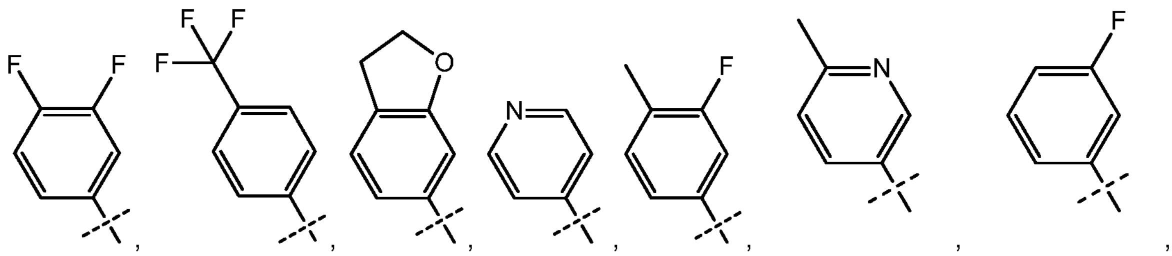
In an embodiment (xv) of the invention as described anywhere herein, wherein
R^5 and R^6 are independently selected from phenyl optionally substituted by C_1-C_4 alkoxy or halogen, and C_1-C_4 alkyl optionally substituted by one or more halogen atoms.

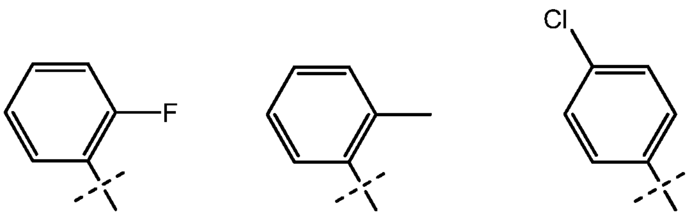
In an embodiment (xvi) of the invention as described anywhere herein, wherein

R^5 and R^6 are independently selected from phenyl optionally substituted by methyl, ethyl, trifluoromethyl, methoxy or halogen.

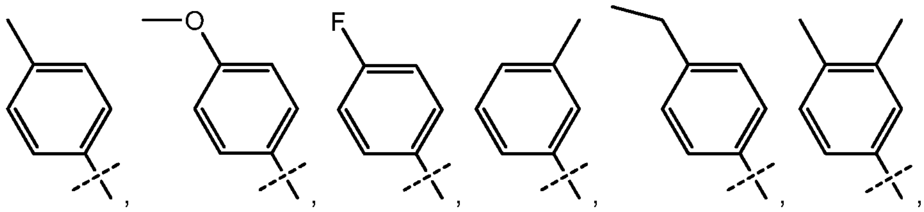
In an embodiment (xvii) of the invention as described anywhere herein, wherein

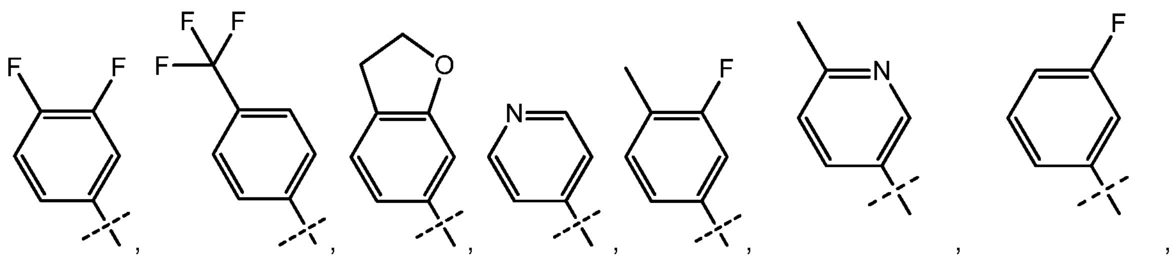
R^5 is 

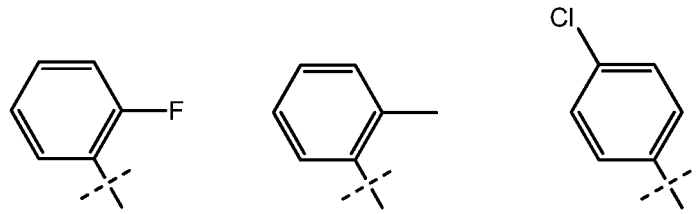




, or ; and

R^6 is 





, or .

In an embodiment (xviii) of the invention as described anywhere herein, wherein

R^3, R^{3a}, R^4 and R^{4a} are independently selected from H, OH, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_3-C_6 cycloalkyl, cyano and halogen.

In an embodiment (xix) of the invention as described anywhere herein, wherein

R^3, R^{3a}, R^4 and R^{4a} are independently H, OH, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_3-C_5 cycloalkyl and halogen.

In an embodiment (xx) of the invention as described anywhere herein, wherein

R^3, R^{3a}, R^4 and R^{4a} are independently selected from H, OH, methyl, ethyl, isopropyl, tert-butyl, methoxy, ethoxy, propoxy, butoxy, cyclopropyl, fluorine, bromine and chlorine.

In an embodiment (xxi) of the invention as described anywhere herein, wherein

Z is independently selected from OH, C_6-aryl, O-C_6-aryl, benzyl, O-benzyl, C_1-C_4 alkyl optionally substituted by one or more OH groups or NH_2 groups, C_1-C_4 alkyl optionally substituted by one or more halogen atoms, C_1-C_4 alkoxy optionally substituted by one or more OH groups or C_1-C_4 alkoxy, $NR^{18}(SO_2)R^{21}$, $(SO_2)NR^{19}R^{21}$, $(SO_2)R^{21}$, $NR^{18}C(O)R^{21}$, $C(O)NR^{19}R^{21}$, $NR^{18}C(O)NR^{19}R^{21}$, $NR^{18}C(O)OR^{19}$, $NR^{19}R^{21}$, $C(O)OR^{19}$, $C(O)R^{19}$, SR^{19}, OR^{19}, oxo, CN, NO_2, halogen and a 4 to 6 membered heterocyclyl, wherein the heterocyclyl contains at least one heteroatom selected from N, O and S;

R^{18} is H or C_1-C_4 alkyl;

R^{19} and R^{21} are each independently selected from H; C_1-C_4 alkyl; C_3-C_6 cycloalkyl; C_1-C_4 alkoxy-C_1-C_4 alkyl; (C_0-C_4 alkyl)-aryl optionally substituted by one or more groups selected from C_1-C_4 alkyl, C_1-C_4 alkoxy and halogen; (C_0-C_4 alkyl)- 4- to 6-membered heterocyclyl, the heterocyclyl including one or more heteroatoms selected from N, O and S, optionally substituted by one or more groups selected from halogen, oxo, C_1-C_4 alkyl and $C(O)C_1$-C_4 alkyl; (C_0-C_4 alkyl)-O-aryl optionally substituted by one or more groups selected from C_1-C_6 alkyl, C_1-C_6

alkoxy and halogen; and (C_0-C_4 alkyl)- O-3- to 14-membered heterocyclyl, the heterocyclyl including one or more heteroatoms selected from N, O and S, optionally substituted by one or more groups selected from halogen, C_1-C_6 alkyl or C(O)C_1-C_6 alkyl; wherein the alkyl groups are optionally substituted by one or more halogen atoms, C_1-C_4 alkoxy, C(O)NH_2, C(O)NHC_1-C_6 alkyl or C(O)N(C_1-C_6 alkyl)$_2$; or

R^{19} and R^{21} together with the nitrogen atom to which they are attached form a 5- to 6-membered heterocyclyl, the heterocyclyl including one or more further heteroatoms selected from N, O and S, the heterocyclyl being optionally substituted by one or more substituents selected from OH; halogen; aryl; 5- to 6-membered heterocyclyl including one or more heteroatoms selected from N, O and S; S(O)$_2$-aryl; S(O)$_2$-C_1-C_6 alkyl; C_1-C_6 alkyl optionally substituted by one or more halogen atoms; C_1-C_4 alkoxy optionally substituted by one or more OH groups or C_1-C_4 alkoxy; and C(O)OC_1-C_6 alkyl, wherein the aryl and heterocyclyl substituent groups are themselves optionally substituted by C_1-C_6 alkyl, C_1-C_6 haloalkyl or C_1-C_6 alkoxy.

In an embodiment (xxii) of the invention as described anywhere herein, wherein

Z is independently OH, C_1-C_4 alkyl optionally substituted by one or more OH groups or NH_2 groups, C_1-C_4 alkyl optionally substituted by one or more halogen atoms, C_1-C_4 alkoxy optionally substituted by one or more OH groups or C_1-C_4 alkoxy, $NR^{19}R^{21}$, C(O)OR^{19}, C(O)R^{19}, SR^{19}, OR^{19}, CN, NO_2, or halogen;

R^{19} and R^{21} are each independently H; C_1-C_4 alkyl; C_3-C_6 cycloalkyl; or C_1-C_4 alkoxy-C_1-C_4 alkyl, wherein all alkyls are optionally substituted with halogens.

In an embodiment (xxiii) of the invention as described anywhere herein, wherein

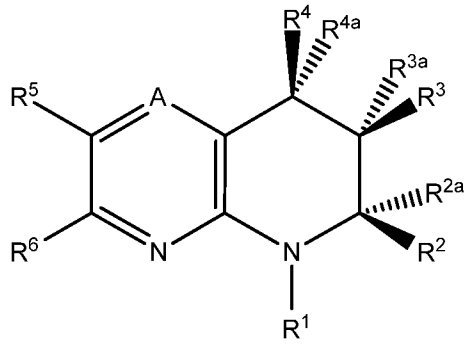
Z is independently OH, C_1-C_4 alkyl optionally substituted by one or more OH groups or NH_2 groups, C_1-C_4 alkyl optionally substituted by one or more halogen atoms, C_1-C_4 alkoxy optionally substituted by one or more OH groups or C_1-C_4 alkoxy, C(O)OR^{19}, C(O)R^{19}, OR^{19}, CN, or halogen;

R^{19} is H; C_1-C_4 alkyl; C_3-C_6 cycloalkyl; or C_1-C_4 alkoxy-C_1-C_4 alkyl, wherein all alkyl are optionally substituted with halogens.

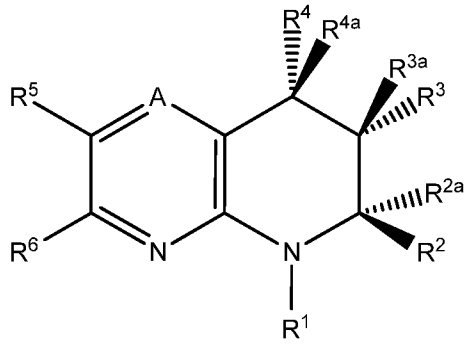
In an embodiment (xxiv) of the invention as described anywhere herein, wherein

Z is independently, C_1-C_4 alkyl optionally substituted by one or more halogen atoms, C_1-C_4 alkoxy or halogen;

In an embodiment (xxv) of the invention as described anywhere herein, wherein the compound of formula (I) has the following stereochemistry:



(I)',



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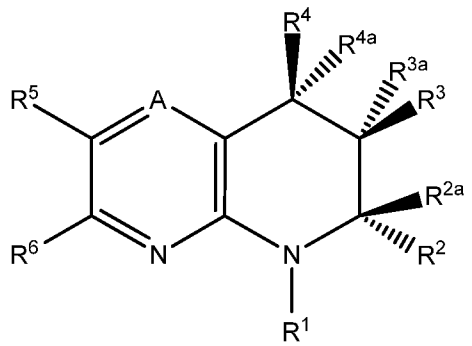

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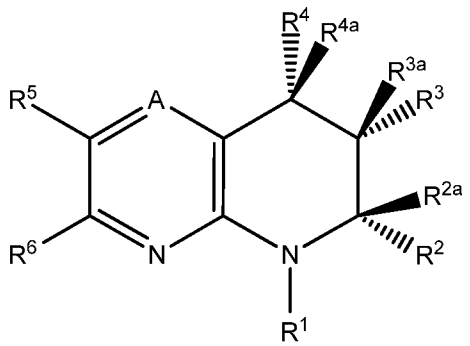


(I)''''.

In an embodiment (xxvi) of the invention as described anywhere herein, wherein the compound is selected from

5-(6-(1H-Tetrazol-5-yl)hexyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazine;

5-(5-(2H-Tetrazol-5-yl)pentyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazine;

5-(6-(1H-Tetrazol-5-yl)hexyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[3,2-b]pyrazin-7-ol;

(rac or R or S)-5-(6-(1H-tetrazol-5-yl)hexyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-8-ol;

5-(6-(1H-tetrazol-5-yl)hexyl)-2,3-di-p-tolyl-7,8-dihydropyrido[2,3-b]pyrazin-6(5H)-one;

(rac or R or S)-5-(6-(1H-tetrazol-5-yl)hexyl)-7-hydroxy-2,3-di-p-tolyl-7,8-dihydropyrido[2,3-b]pyrazin-6(5H)-one;

(rac or R or S)- 5-(5-(1H-tetrazol-5-yl)pentyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol;

(rac or R or S)5-(5-(1H-tetrazol-5-yl)pentyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-8-ol;
5-(5-(1H-tetrazol-5-yl)pentyl)-2,3-di-p-tolyl-7,8-dihydropyrido[2,3-b]pyrazin-6(5H)-one;
(rac or R or S)-5-(5-(1H-tetrazol-5-yl)pentyl)-7-hydroxy-2,3-di-p-tolyl-7,8-dihydropyrido[2,3-b]pyrazin-6(5H)-one;
6-(5-(1H-Tetrazol-5-yl)pentyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazine;
6-(5-(1H-Tetrazol-5-yl)pentyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol;
6-(5-(1H-Tetrazol-5-yl)pentyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-8-ol;
6-(4-(1H-Tetrazol-5-yl)butyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazine;
6-(4-(1H-Tetrazol-5-yl)butyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol;
6-(4-(1H-Tetrazol-5-yl)butyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-8-ol;
6-(5-(1H-Tetrazol-5-yl)pentyl)-5-methyl-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazine;
6-(5-(1H-Tetrazol-5-yl)pentyl)-5-methyl-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol;
6-(5-(1H-Tetrazol-5-yl)pentyl)-5-methyl-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-8-ol;
6-(4-(1H-Tetrazol-5-yl)butyl)-5-methyl-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazine;
6-(4-(1H-Tetrazol-5-yl)butyl)-5-methyl-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol;
6-(4-(1H-Tetrazol-5-yl)butyl)-5-methyl-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-8-ol;
6-(5-(1H-Tetrazol-5-yl)pentyl)-5-isopropyl-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazine;
6-(5-(1H-Tetrazol-5-yl)pentyl)-5-isopropyl-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol;
6-(5-(1H-Tetrazol-5-yl)pentyl)-5-isopropyl-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-8-ol;
6-(4-(1H-Tetrazol-5-yl)butyl)-5-isopropyl-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazine;
6-(4-(1H-Tetrazol-5-yl)butyl)-5-isopropyl-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol;
6-(4-(1H-Tetrazol-5-yl)butyl)-5-isopropyl-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-8-ol;
or a pharmaceutically acceptable salt thereof.

In an embodiment (xxvii) of the invention as described anywhere herein, wherein the compound is selected from
5-(6-(1H-Tetrazol-5-yl)hexyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazine;
5-(5-(1H-Tetrazol-5-yl)pentyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazine;
5-(6-(1H-Tetrazol-5-yl)hexyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol;

(R)-5-(6-(1H-tetrazol-5-yl)hexyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol;
(S)-5-(6-(1H-tetrazol-5-yl)hexyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol;
rac-5-(5-(1H-Tetrazol-5-yl)pentyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[3,2-b]pyrazin-7-ol;
(R)-5-(5-(1H-Tetrazol-5-yl)pentyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol; and
(S)-5-(5-(1H-Tetrazol-5-yl)pentyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol;
or a pharmaceutically acceptable salt thereof.

In an embodiment (xxviii) of the invention as described anywhere herein, wherein
the compound is selected from
5-(6-(1H-Tetrazol-5-yl)hexyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazine;
5-(5-(2H-Tetrazol-5-yl)pentyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazine; and
5-(6-(1H-Tetrazol-5-yl)hexyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[3,2-b]pyrazin-7-ol;
or a pharmaceutically acceptable salt thereof.

It is understood that any and all embodiments of the present invention may be taken in conjunction with any other embodiment to describe additional embodiments of the present invention. Furthermore, any elements of an embodiment are meant to be combined with any and all other elements from any of the embodiments to describe additional embodiments. It is understood by those skilled in the art that combinations of substituents where not possible are not an aspect of the present invention.

Definitions

Terms used in the specification have the following meanings:

"Optionally substituted" means the group referred to can be substituted at one or more positions by any one or any combination of the radicals listed thereafter.

“Optionally substituted by one or more Z groups” denotes that the relevant group may include one or more substituents, each independently selected from the groups included within the definition of Z. Thus, where there are two or more Z group substituents, these may be the same or different.

"Halo" or "halogen", as used herein, may be fluorine, chlorine, bromine or iodine.

"C_1-C_8-Alkyl", as used herein, denotes straight chain or branched alkyl having 1-8 carbon atoms. If a different number of carbon atoms is specified, such as C_6 or C_3, then the definition is to be amended accordingly, such as "C_1-C_4-Alkyl" will represent methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl.

"C_1-C_8-Alkoxy", as used herein, denotes straight chain or branched alkoxy having 1-8 carbon atoms. If a different number of carbon atoms is specified, such as C_6 or C_3, then the definition is to be amended accordingly, such as "C_1-C_4-Alkoxy" will represent methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy and tert-butoxy.

"C_1-C_4-Haloalkyl", as used herein, denotes straight chain or branched alkyl having 1-4 carbon atoms with at least one hydrogen substituted with a halogen. If a different number of carbon atoms is specified, such as C_6 or C_3, then the definition is to be amended accordingly, such as "C_1-C_4-Haloalkyl" will represent methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl that have at least one hydrogen substituted with halogen, such as where the halogen is fluorine: CF_3CF_2-, $(CF_3)_2CH$-, CH_3-CF_2-, CF_3CF_2-, CF_3, CF_2H-, $CF_3CF_2CHCF_3$ or $CF_3CF_2CF_2CF_2$-.

The term "C_1-C_8 alkylene" is a straight or branched alkylene (divalent alkyl chain) having 1 to 8 carbon atoms, for example, methylene, ethylene, 1-methylethylene, 2-methylethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, heptamethylene, and octamethylene.

"C_3-C_{15} Cycloalkyl ", as used herein, denotes a carbocyclic group having 3- to 15-ring carbon atoms that is saturated or partially saturated, such as a C_3-C_8-cycloalkyl. Examples of C_3-C_{15}-carbocyclic groups include but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl or a bicyclic group, such as bicyclooctyl, bicyclononyl including indanyl and indenyl and bicyclodecyl. If a different number of carbon atoms is specified, such as C_6, then the definition is to be amended accordingly.

“aryl” or “C_6-C_{15}-Aromatic carbocyclic group", as used herein, denotes an aromatic group having 6- to 15-ring carbon atoms. Examples of C_6-C_{15}-aromatic carbocyclic groups include, but are not limited to, phenyl, phenylene, benzenetriyl, naphthyl, naphthylene, naphthalenetriyl or anthrylene. If a different number of carbon atoms is specified, such as C_{10}, then the definition is to be amended accordingly.

“4- to 8-Membered heterocyclyl”, “5- to 6- membered heterocyclyl”, “3- to 10-membered heterocyclyl”, “3- to 14-membered heterocyclyl”, “4- to 14-membered heterocyclyl” and “5- to 14-membered heterocyclyl”, refers, respectively, to 4- to 8-membered, 5- to 6-membered, 3- to 10-membered, 3- to 14-membered, 4- to 14-membered and 5- to 14-membered heterocyclic rings containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur, which may be saturated, partially saturated or unsaturated (aromatic). The heterocyclyl includes single ring groups, fused ring groups and bridged groups. Examples of such heterocyclyl include, but are not limited to furan, pyrrole, pyrrolidine, pyrazole, imidazole,

triazole, isotriazole, tetrazole, thiadiazole, isothiazole, oxadiazole, pyridine, piperidine, oxazole, isoxazole, pyrazine, pyridazine, pyrimidine, piperazine, pyrrolidinone, morpholine, triazine, oxazine, tetrahyrofuran, tetrahydrothiophene, tetrahydrothiopyran, tetrahydropyran, 1,4-dioxane, 1,4-oxathiane, indazole, quinoline, indole, 8-aza-bicyclo[3.2.1]octane, 2,3-dihydrobenzofuran or thiazole.

"Heteroaryl" is a subset of heterocyclyl, wherein the heterocyclyl is completely unsaturated (aromatic). Examples of such groups are pyridine and pyrazine.

The term “hydroxy” or “hydroxyl” includes groups with an –OH.

The term “heteroatom” includes atoms of any element other than carbon or hydrogen. Preferred heteroatoms are nitrogen, oxygen, sulfur and phosphorus. In one embodiment, “heteroatom” includes nitrogen, sulfur and oxygen.

The term “carboxy” refers to carboxylic acid.

The term “alkoxycarboxy” refers to an ester.

The term "carbamoyl" is $–C(O)NH_2$. The terms "monoalkylcarbamoyl" and "dialkylcarbamoyl" are carbamoyl, wherein the hydrogen or hydrogens on the nitrogen are substituted with C_1-C_8 alkyl as described above.

In a second aspect, the invention provides a compound as defined in the first aspect, or a pharmaceutically acceptable salt thereof, as defined anywhere herein for use as a medicament.

Activating the IP receptor has been shown to have a beneficial effect or treat the following diseases or disorders:

PAH selected from: idiopathic PAH; familial PAH; PAH associated with a collagen vascular disease selected from: scleroderma, CREST syndrome, systemic lupus erythematosus (SLE), rheumatoid arthritis, Takayasu's arteritis, polymyositis, and dermatomyositis; PAH associated with a congenital heart disease selected from: atrial septic defect (ASD), ventricular septic defect (VSD) and patent ductus arteriosus in an individual; PAH associated with portal hypertension; PAH associated with HIV infection; PAH associated with ingestion of a drug or toxin; PAH associated with hereditary hemorrhagic telangiectasia; PAH associated with splenectomy; PAH associated with significant venous or capillary involvement; PAH associated with pulmonary veno-occlusive disease (PVOD); and PAH associated with pulmonary capillary hemangiomatosis (PCH); Raynaud’s phenomenon, including Raynaud’s disease and Raynaud’s syndrome; fibrotic diseases, including pulmonary fibrosis, systemic sclerosis/scleroderma,

hepatic fibrosis/cirrhosis, renal fibrosis; thrombotic diseases associated with excessive platelet aggregation, coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, ischemia-reperfusion injury, restenosis, atrial fibrillation, blood clot formation, atherosclerosis, atherothrombosis, asthma, a symptom of asthma, a diabetic-related disorder, diabetic peripheral neuropathy, diabetic nephropathy, diabetic retinopathy, glaucoma or other disease of the eye with abnormal intraocular pressure, hypertension, preeclampsia, inflammation, prophylaxis against unwanted side effects of COX-1, COX-2 and non-selective COX inhibitors, psoriasis, psoriatic arthritis, rheumatoid arthritis, Crohn's disease, transplant rejection, multiple sclerosis, systemic lupus erythematosus (SLE), ulcerative colitis, ischemia-reperfusion injury, restenosis, atherosclerosis, acne, type 1 diabetes, type 2 diabetes, sepsis and chronic obstructive pulmonary disorder (COPD).

Hence, in a third aspect of the invention, there is provided a compound as defined in the first aspect, or a pharmaceutically acceptable salt thereof, for use in the treatment of a disorder selected from the aforementioned diseases and disorders.

In an embodiment of the third aspect of the invention, there is provided a compound as defined in the first aspect, or a pharmaceutically acceptable salt thereof, for use in the treatment of PAH as described above.

In a fourth aspect of the present invention, there is provided the use of a compound as defined in the first aspect and in any of the aforementioned embodiments, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of pulmonary arterial hypertension.

An embodiment of the fourth aspect of the present invention provides for the use of a compound as defined in the first aspect and in any of the aforementioned embodiments, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of PAH selected from: idiopathic PAH; familial PAH; PAH associated with a collagen vascular disease selected from: scleroderma, CREST syndrome, systemic lupus erythematosus (SLE), rheumatoid arthritis, Takayasu's arteritis, polymyositis, and dermatomyositis; PAH associated with a congenital heart disease selected from: atrial septic defect (ASD), ventricular septic defect (VSD) and patent ductus arteriosus in an individual; PAH associated with portal hypertension; PAH associated with HIV infection; PAH associated with ingestion of a drug or

toxin; PAH associated with hereditary hemorrhagic telangiectasia; PAH associated with splenectomy; PAH associated with significant venous or capillary involvement; PAH associated with pulmonary veno-occlusive disease (PVOD); and PAH associated with pulmonary capillary hemangiomatosis (PCH).

In a fifth aspect, the present invention provides a method for the prevention or treatment of an IP receptor mediated condition or disease, particularly PAH, comprising administering an effective amount of at least one compound as described herein to a subject in need of such treatment. Such IP receptor mediated conditions or diseases are selected from: idiopathic PAH; familial PAH; PAH associated with a collagen vascular disease selected from: scleroderma, CREST syndrome, systemic lupus erythematosus (SLE), rheumatoid arthritis, Takayasu's arteritis, polymyositis, and dermatomyositis; PAH associated with a congenital heart disease selected from: atrial septic defect (ASD), ventricular septic defect (VSD) and patent ductus arteriosus in an individual; PAH associated with portal hypertension; PAH associated with HIV infection; PAH associated with ingestion of a drug or toxin; PAH associated with hereditary hemorrhagic telangiectasia; PAH associated with splenectomy; PAH associated with significant venous or capillary involvement; PAH associated with pulmonary veno-occlusive disease (PVOD); and PAH associated with pulmonary capillary hemangiomatosis (PCH).

Other IP receptor mediated conditions or diseases are selected from platelet aggregation, coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, ischemia-reperfusion injury, restenosis, atrial fibrillation, blood clot formation, atherosclerosis, atherothrombosis, asthma, a symptom of asthma, a diabetic-related disorder, diabetic peripheral neuropathy, diabetic nephropathy, diabetic retinopathy, glaucoma or other disease of the eye with abnormal intraocular pressure, hypertension, inflammation, psoriasis, psoriatic arthritis, rheumatoid arthritis, Crohn's disease, transplant rejection, multiple sclerosis, systemic lupus erythematosus (SLE), ulcerative colitis, ischemia-reperfusion injury, restenosis, atherosclerosis, acne, type 1 diabetes, type 2 diabetes, sepsis and chronic obstructive pulmonary disorder (COPD).

Throughout this specification and in the claims that follow, unless the context requires otherwise, the word “comprise”, or variations such as “comprises” or “comprising”, should be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

As used herein, the term “pharmaceutically acceptable salts” refers to salts that retain the biological effectiveness and properties of the compounds of this invention and, which typically are not biologically or otherwise undesirable. In many cases, the compounds as defined in the first aspect are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto.

Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids, e.g., acetate, aspartate, benzoate, besylate, bromide/hydrobromide, bicarbonate/carbonate, bisulfate/sulfate, camphorsulfonate, chloride/hydrochloride, chlortheophyllonate, citrate, ethanedisulfonate, fumarate, gluceptate, gluconate, glucuronate, hippurate, hydroiodide/iodide, isethionate, lactate, lactobionate, laurylsulfate, malate, maleate, malonate, mandelate, mesylate, methylsulphate, naphthoate, napsylate, nicotinate, nitrate, octadecanoate, oleate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, polygalacturonate, propionate, stearate, succinate, sulfosalicylate, tartrate, tosylate trifluoroacetate and xinafoate salts.

Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like.

Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, toluenesulfonic acid, 1-hydroxy-2-naphtoic acid and sulfosalicylic acid.

Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases.

Inorganic bases from which salts can be derived include, for example, ammonium salts and metals from columns I to XII of the periodic table. In certain embodiments, the salts are derived from sodium, potassium, ammonium, calcium, magnesium, iron, silver, zinc, and copper; particularly suitable salts include ammonium, potassium, sodium, calcium and magnesium salts.

Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like. Certain organic amines include isopropylamine, benzathine, cholinate, diethanolamine, diethylamine, lysine, meglumine, piperazine and tromethamine.

The pharmaceutically acceptable salts of the present invention can be synthesized from a parent compound, a basic or acidic moiety, by conventional chemical methods. Generally, such salts can be prepared by reacting free acid forms of these compounds with a stoichiometric amount of the appropriate base (such as Na, Ca, Mg, or K hydroxide, carbonate, bicarbonate or the like), or by reacting free base forms of these compounds with a stoichiometric amount of the appropriate acid. Such reactions are typically carried out in water or in an organic solvent, or in a mixture of the two. Generally, use of non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, acetone or acetonitrile is desirable, where practicable. Lists of additional suitable salts can be found, e.g., in "Remington's Pharmaceutical Sciences", 20th ed., Mack Publishing Company, Easton, Pa., (1985); and in "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

Furthermore, the compounds as defined in the first aspect, including their salts, can also be obtained in the form of their hydrates, or include other solvents used for their crystallization.

Compounds as defined in the first aspect that contain groups capable of acting as donors and/or acceptors for hydrogen bonds may be capable of forming co-crystals with suitable co-crystal formers. These co-crystals may be prepared from compounds as defined in the first aspect by known co-crystal forming procedures. Such procedures include grinding, heating, co-subliming, co-melting, or contacting in solution compounds as defined in the first aspect with the co-crystal former under crystallization conditions and isolating co-crystals thereby formed. Suitable co-crystal formers include those described in WO 2004/078163. Hence the invention further provides co-crystals comprising a compound of as defined in the first aspect.

As used herein, the term "an optical isomer" or "a stereoisomer" refers to any of the various stereo isomeric configurations which may exist for a given compound of the present invention and includes geometric isomers. It is understood that a substituent may be attached at a chiral center of a carbon atom. Therefore, the invention includes enantiomers, diastereomers or racemates of the compound. "Enantiomers" are a pair of stereoisomers that are non- superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a "racemic" mixture. The term is used to designate a racemic mixture where appropriate. "Diastereoisomers" are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other. The absolute stereochemistry is specified according to the Cahn- Ingold- Prelog R-S system. When a compound is a pure enantiomer the stereochemistry at each chiral carbon may be specified by either *R* or *S*. Resolved compounds whose absolute

configuration is unknown can be designated (+) or (-) depending on the direction (dextro- or levorotatory) which they rotate plane polarized light at the wavelength of the sodium D line. Certain of the compounds described herein contain one or more asymmetric centers or axes and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)-. The present invention is meant to include all such possible isomers, including racemic mixtures, optically pure forms and intermediate mixtures. Optically active (*R*)- and (*S*)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. If the compound contains a double bond, the substituent may be E or Z configuration. If the compound contains a disubstituted cycloalkyl, the cycloalkyl substituent may have a cis- or trans-configuration. All tautomeric forms are also intended to be included.

Any asymmetric atom (e.g., carbon or the like) of the compound(s) of the present invention can be present in racemic or enantiomerically enriched, for example the (*R*)-, (*S*)- or (*R,S*)- configuration. In certain embodiments, each asymmetric atom has at least 50 % enantiomeric excess, at least 60 % enantiomeric excess, at least 70 % enantiomeric excess, at least 80 % enantiomeric excess, at least 90 % enantiomeric excess, at least 95 % enantiomeric excess, or at least 99 % enantiomeric excess in the (*R*)- or (*S*)- configuration. Substituents at atoms with unsaturated bonds may, if possible, be present in *cis*- (*Z*)- or *trans*- (*E*)- form.

Accordingly, as used herein a compound of the present invention can be in the form of one of the possible isomers, rotamers, atropisomers, tautomers or mixtures thereof, for example, as substantially pure geometric (*cis* or *trans*) isomers, diastereomers, optical isomers (antipodes), racemates or mixtures thereof.

Any resulting mixtures of isomers can be separated on the basis of the physicochemical differences of the constituents, into the pure or substantially pure geometric or optical isomers, diastereomers, racemates, for example, by chromatography and/or fractional crystallization.

Any resulting racemates of final products or intermediates can be resolved into the optical antipodes by known methods, *e.g.*, by separation of the diastereomeric salts thereof, obtained with an optically active acid or base, and liberating the optically active acidic or basic compound. In particular, a basic moiety may thus be employed to resolve the compounds as defined in the first aspect into their optical antipodes, *e.g.*, by fractional crystallization of a salt formed with an optically active acid, *e.g.*, tartaric acid, dibenzoyl tartaric acid, diacetyl tartaric acid, di-*O,O'-p*-toluoyl tartaric acid, mandelic acid, malic acid or camphor-10-sulfonic acid. Racemic products can also be resolved by chiral chromatography, *e.g.*, high pressure liquid chromatography (HPLC) using a chiral adsorbent.

Since the compounds as defined in the first aspect are intended for use in pharmaceutical compositions it will readily be understood that they are each preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions; these less pure preparations of the compounds should contain at least 1 %, more suitably at least 5% and preferably from 10 to 59% of a compound of the invention.

Compounds as defined in the first aspect are either obtained in the free form, as a salt thereof, or as prodrug derivatives thereof.

When both a basic group and an acid group are present in the same molecule, the compounds as defined in the first aspect may also form internal salts, e.g., zwitterionic molecules.

The present invention also provides pro-drugs of the compounds as defined in the first aspect that converts *in vivo* to the compounds as defined in the first aspect. A pro-drug is an active or inactive compound that is modified chemically through *in vivo* physiological action, such as hydrolysis, metabolism and the like, into a compound of this invention following administration of the prodrug to a subject. The suitability and techniques involved in making and using pro-drugs are well known by those skilled in the art. Prodrugs can be conceptually divided into two non-exclusive categories, bioprecursor prodrugs and carrier prodrugs. See *The Practice of Medicinal Chemistry*, Ch. 31-32 (Ed. Wermuth, Academic Press, San Diego, Calif., 2001). Generally, bioprecursor prodrugs are compounds, which are inactive or have low activity compared to the corresponding active drug compound that contain one or more protective groups and are converted to an active form by metabolism or solvolysis. Both the active drug form and any released metabolic products should have acceptably low toxicity.

Carrier prodrugs are drug compounds that contain a transport moiety, *e.g.*, that improve uptake and/or localized delivery to a site(s) of action. Desirably for such a carrier prodrug, the linkage between the drug moiety and the transport moiety is a covalent bond, the prodrug is inactive or less active than the drug compound, and any released transport moiety is acceptably non-toxic. For prodrugs where the transport moiety is intended to enhance uptake, typically the release of the transport moiety should be rapid. In other cases, it is desirable to utilize a moiety that provides slow release, *e.g.*, certain polymers or other moieties, such as cyclodextrins. Carrier prodrugs can, for example, be used to improve one or more of the following properties: increased lipophilicity, increased duration of pharmacological effects, increased site-specificity,

decreased toxicity and adverse reactions, and/or improvement in drug formulation (*e.g.*, stability, water solubility, suppression of an undesirable organoleptic or physiochemical property). For example, lipophilicity can be increased by esterification of (a) hydroxyl groups with lipophilic carboxylic acids (e.g., a carboxylic acid having at least one lipophilic moiety), or (b) carboxylic acid groups with lipophilic alcohols (e.g., an alcohol having at least one lipophilic moiety, for example aliphatic alcohols).

Exemplary prodrugs are, *e.g.*, esters of free carboxylic acids and *S*-acyl derivatives of thiols and *O*-acyl derivatives of alcohols or phenols, wherein acyl has a meaning as defined herein. Suitable prodrugs are often pharmaceutically acceptable ester derivatives convertible by solvolysis under physiological conditions to the parent carboxylic acid, *e.g.*, lower alkyl esters, cycloalkyl esters, lower alkenyl esters, benzyl esters, mono- or di-substituted lower alkyl esters, such as the ω-(amino, mono- or di-lower alkylamino, carboxy, lower alkoxycarbonyl)-lower alkyl esters, the α-(lower alkanoyloxy, lower alkoxycarbonyl or di-lower alkylaminocarbonyl)-lower alkyl esters, such as the pivaloyloxymethyl ester and the like conventionally used in the art. In addition, amines have been masked as arylcarbonyloxymethyl substituted derivatives which are cleaved by esterases *in vivo* releasing the free drug and formaldehyde (Bundgaard, *J. Med. Chem.* 2503 (1989)). Moreover, drugs containing an acidic NH group, such as imidazole, imide, indole and the like, have been masked with N-acyloxymethyl groups (Bundgaard, *Design of Prodrugs*, Elsevier (1985)). Hydroxy groups have been masked as esters and ethers. EP 039,051 (Sloan and Little) discloses Mannich-base hydroxamic acid prodrugs, their preparation and use.

Any formula given herein is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds as defined in the first aspect include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, and chlorine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}F ^{31}P, ^{32}P, ^{35}S, ^{36}Cl, ^{125}I respectively. The invention includes various isotopically labeled compounds as defined herein, for example those into which radioactive isotopes, such as ^{3}H, ^{13}C, and ^{14}C , are present. Such isotopically labeled compounds are useful in metabolic studies (with ^{14}C), reaction kinetic studies (with, for example ^{2}H or ^{3}H), detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an ^{18}F or labeled compound may be particularly desirable for PET or SPECT studies.

Isotopically labeled compounds of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

Further, substitution with heavier isotopes, particularly deuterium (i.e., ^{2}H or D) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements or an improvement in therapeutic index. It is understood that deuterium in this context is regarded as a substituent of a compound of the formula I. The concentration of such a heavier isotope, specifically deuterium, may be defined by the isotopic enrichment factor. The term "isotopic enrichment factor" as used herein means the ratio between the isotopic abundance and the natural abundance of a specified isotope. If a substituent in a compound of this invention is denoted deuterium, such compound has an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5% deuterium incorporation at each designated deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium incorporation), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation).

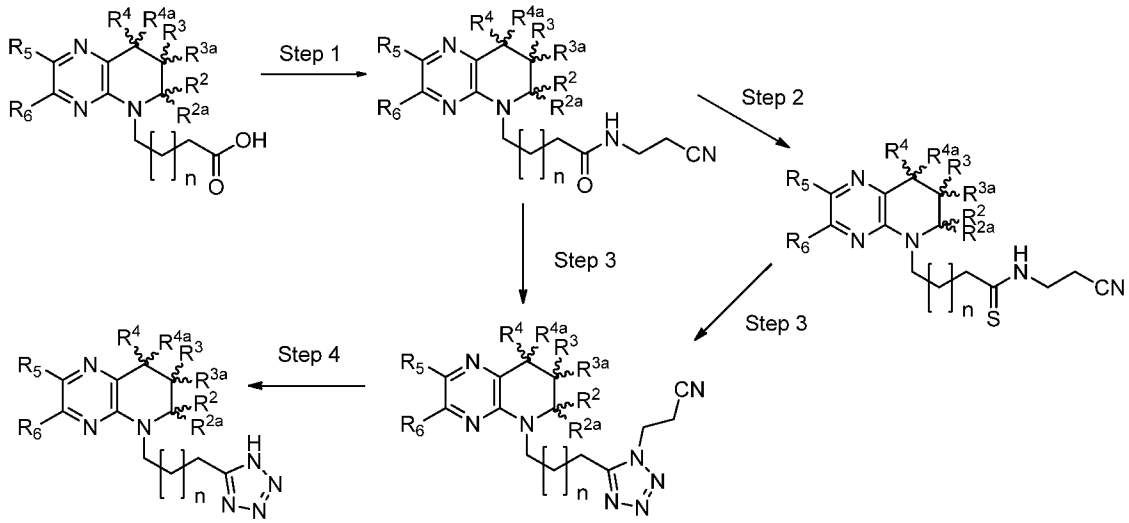
Isotopically-labeled compounds as defined in the first aspect can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagents in place of the non-labeled reagent previously employed.

Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, *e.g.* D_2O, d_6-acetone, d_6-DMSO.

Synthesis

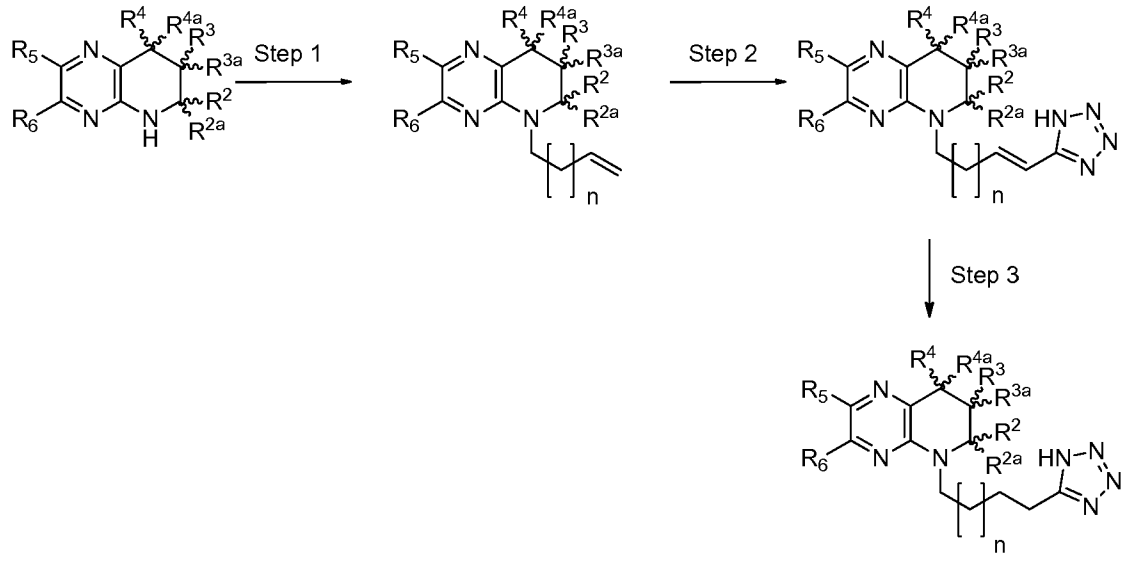
Generally, compounds according to Formula (I), or a pharmaceutically acceptable salt thereof, can be synthesized by the routes described in Schemes 1-9 and the Examples.

Scheme 1:



Scheme 1 begins with a Step 1 reaction taking an appropriately substituted carboxylic acid (see WO 2012/007539 for synthesis) and reacting in an amide coupling step. Step 2 is a conversion to a thioamide. Step 3 is a cyclisation. Step 4 is a deprotection. R^2, R^{2a}, R^3, R^{3a}, R^4, R^{4a}, R^5 and R^6 are as defined in embodiment 1 of the consistory clauses.

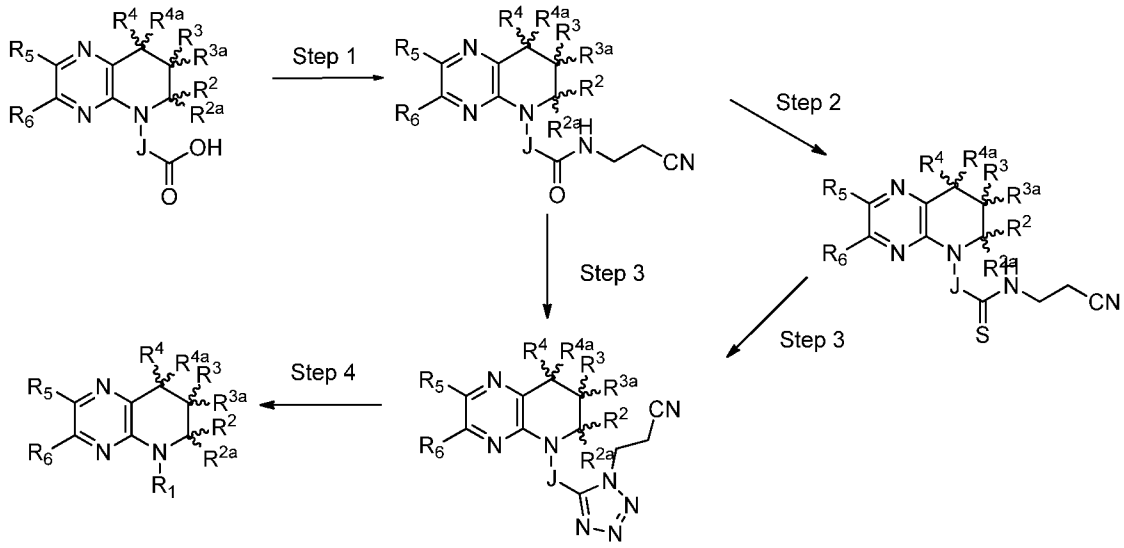
Scheme 2:



Scheme 2 begins with a Step 1 reaction taking an appropriately substituted amine (see WO 2012/007539 for synthesis) and reacting in either an alkylation or reductive amination

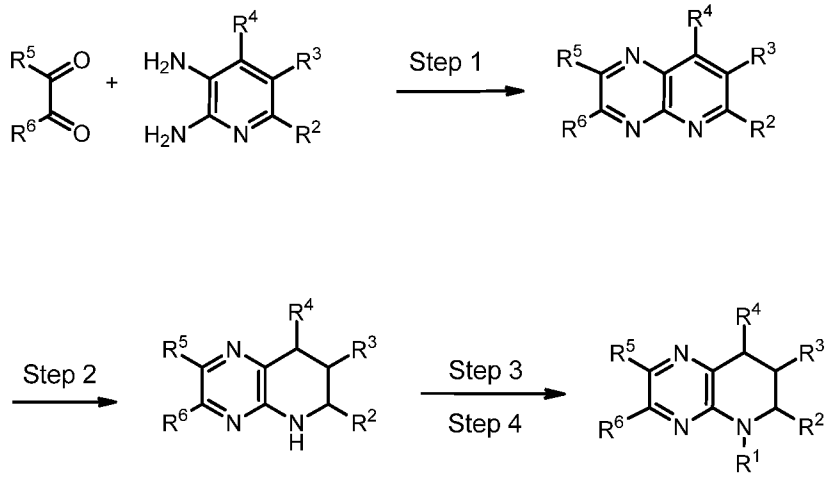
depending on the desired product. Step 2 is an olefin metathesis reaction. Step 3 is a hydrogenation. R^2, R^{2a}, R^3, R^{3a}, R^4, R^{4a}, R^5 and R^6 are as defined in embodiment 1 of the consistory clauses.

Scheme 3:



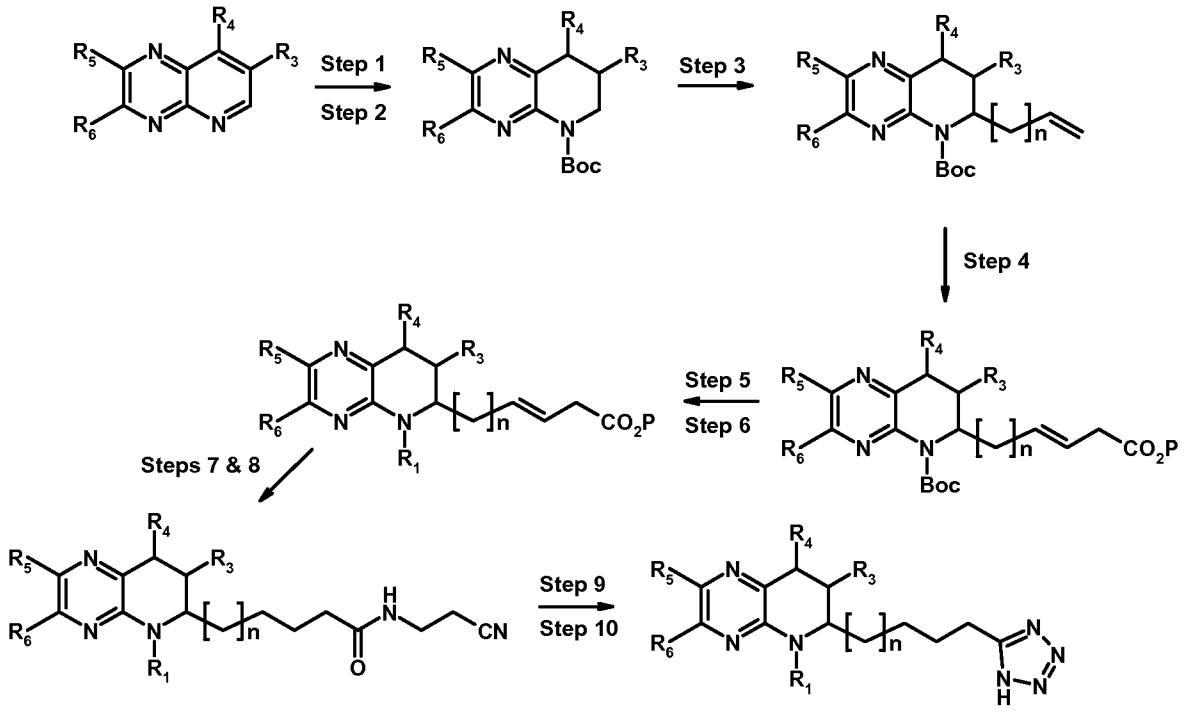
Scheme 3 begins with a Step 1 reaction taking an appropriately substituted carboxylic acid (see WO 2012/007539 for synthesis) and reacting in an amide coupling step. Step 2 is a conversion to a thiomamide. Step 3 is a cyclisation. Step 4 is a deprotection. R^2, R^{2a}, R^3, R^{3a}, R^4, R^{4a}, R^5 and R^6 are as defined in embodiment 1 of the consistory clauses. J is either –X- or –W-R^7-X- as defined in embodiment 1 of the consistory clauses.

Scheme 4:



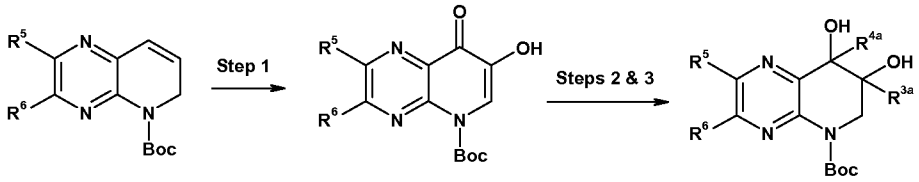
Scheme 4 begins with a Step 1 reaction taking commercially available starting material or starting material that one skilled in the art can synthesize and condensing the material as shown. Step 2 is a hydrogenation. Step 3 is either an alkylation or reductive amination depending on the desired product. Step 4 is a deprotection to form a free tetrazole, if protection is present. R^1, R^2, R^3, R^4, R^5 and R^6 are as defined in embodiment 1 of the consistory clauses.

Scheme 5



Scheme 5 begins with a Step 1 reaction taking an appropriately substituted heterocycle and reducing in hydrogenation reaction. Step 2 is a Boc protection (other suitable protection groups may be used). Step 3 is an alkylation reaction. Step 4 is an olefin metathesis reaction. Step 5 is a deprotection. Step 6 is an alkylation or reductive amination. Step 7 is a hydrogenation. Step 8 is an amide formation. Step 9 is a cyclisation with an azide source. Step 10 is a deprotection. R^1, R^3, R^4, R^5 and R^6 are as defined in embodiment 1 of the consistory clauses.

Scheme 6



Scheme 6 begins with a Step 1 reaction taking 2,3-di-p-tolyl-6H-pyrido[2,3-b]pyrazine-5-carboxylic acid tert-butyl ester (see WO 2012/007539 for synthesis) and doing an oxidation reaction. Steps 2 & 3 are subsequent organometallic additions.

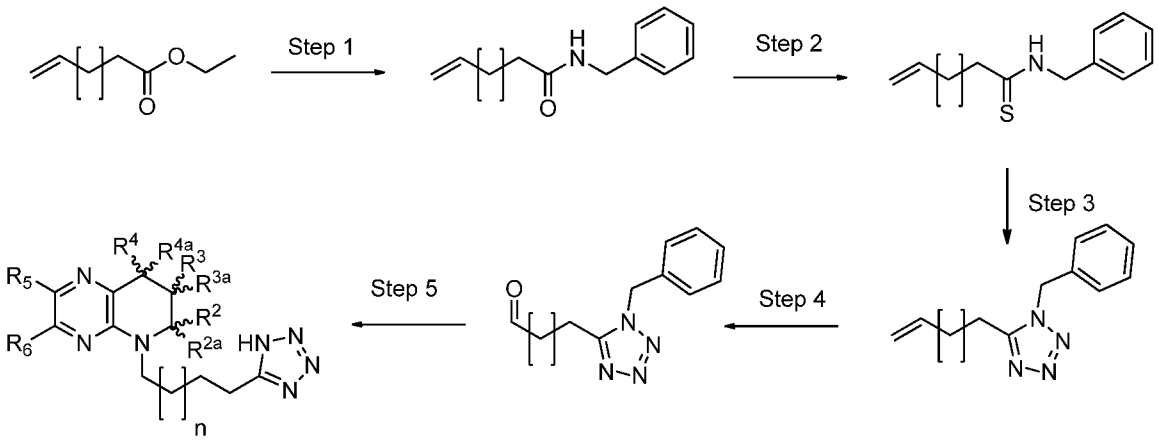
Scheme 7

Scheme 7 begins with a step 1 reaction taking 8-hydroxy-2,3-di-p-tolyl-7,8-dihydro-6H-pyrido[2,3-b]pyrazine-5-carboxylic acid tert-butyl ester (see WO 2012/007539 for synthesis) and doing an oxidation reaction. Step 2 is an organometallic addition.

Scheme 8

Scheme 8 begins with a step 1 reaction taking 7-hydroxy-2,3-di-p-tolyl-7,8-dihydro-6H-pyrido[2,3-b]pyrazine-5-carboxylic acid tert-butyl ester (see WO 2012/007539 for synthesis) and doing an oxidation reaction. Step 2 is an organometallic addition.

Scheme 9



Scheme 9 begins with Step 1, an amide formation using benzylamine; Step 2 is a thioamide formation rection using a sulfonating reagent; Step 3 is the formation of the tetrazole via an azide cyclisation; Step 4 is an oxidation; Step 5 is a reductive amination using the appropratie amine intermediate. R^2, R^{2a}, R^3, R^{3a}, R^4, R^{4a}, R^5 and R^6 are as defined in embodiment 1 of the consistory clauses.

A person skilled in the art appreciates that for Schemes 6-8, R^1 may be installed as disclosed in Schemes 1-5.

The skilled person will appreciate that the general synthetic routes detailed above show common reactions to transform the starting materials as required. The specific reaction conditions are not provided, but these are well known to those skilled in the art and appropriate conditions considered to be within the skilled person's common general knowledge.

The starting materials are either commercially available compounds or are known compounds and can be prepared from procedures described in the organic chemistry art.

Compounds as defined in the first aspect, in free form, may be converted into salt form, and vice versa, in a conventional manner understood by those skilled in the art. The compounds in free or salt form can be obtained in the form of hydrates or solvates containing a solvent used for crystallisation. Compounds as defined in the first aspect can be recovered from reaction mixtures and purified in a conventional manner. Isomers, such as stereoisomers, may be obtained in a conventional manner, e.g., by fractional crystallisation or asymmetric synthesis from correspondingly asymmetrically substituted, e.g., optically active, starting materials.

Compounds as defined in the first aspect or a pharmaceutically acceptable salt thereof can be prepared, e.g., using the reactions and techniques described below and in the Examples. The reactions may be performed in a solvent appropriate to the reagents and materials employed and suitable for the transformations being effected. It will be understood by those skilled in the art of organic synthesis that the functionality present on the molecule should be consistent with the transformations proposed. This will sometimes require a judgment to modify the order of the synthetic steps or to select one particular process scheme over another in order to obtain a desired compound of the invention.

The various substituents on the synthetic intermediates and final products shown in the following reaction schemes can be present in their fully elaborated forms, with suitable protecting groups where required as understood by one skilled in the art, or in precursor forms which can later be elaborated into their final forms by methods familiar to one skilled in the art. The substituents can also be added at various stages throughout the synthetic sequence or after completion of the synthetic sequence. In many cases, commonly used functional group manipulations can be used to transform one intermediate into another intermediate, or one compound as defined in the first aspect into another compound as defined in the first aspect. Examples of such manipulations are conversion of an ester or a ketone to an alcohol; conversion of an ester to a ketone; interconversions of esters, acids and amides; alkylation, acylation and sulfonylation of alcohols and amines; and many others. Substituents can also be added using common reactions, such as alkylation, acylation, halogenation or oxidation. Such manipulations are well-known in the art, and many reference works summarize procedures and methods for such manipulations. Some reference works which gives examples and references to the primary literature of organic synthesis for many functional group manipulations, as well as other transformations commonly used in the art of organic synthesis are *March's Organic Chemistry*, 5th Edition, Wiley and Chichester, Eds. (2001); *Comprehensive Organic Transformations*, Larock, Ed., VCH (1989); *Comprehensive Organic Functional Group Transformations*, Katritzky et al. (series editors), Pergamon (1995); and *Comprehensive Organic Synthesis*, Trost and Fleming (series editors), Pergamon (1991). It will also be recognized that another major consideration in the planning of any synthetic route in this field is the judicious choice of the protecting group used for protection of the reactive functional groups present in the compounds described in this invention. Multiple protecting groups within the same molecule can be chosen such that each of these protecting groups can either be removed without removal of other protecting groups in the same molecule, or several protecting groups can be removed using the same reaction step, depending upon the outcome desired. An

authoritative account describing many alternatives to the trained practitioner is Greene and Wuts, *Protective Groups in Organic Synthesis*, Wiley and Sons, 4th Edition (2006).

Pharmacological Activity

The compounds disclosed herein activate the IP receptor and are useful in the treatment of several diseases and disorders, and in the amelioration of symptoms thereof. Without limitation, these include the following:

Pulmonary arterial hypertension (PAH)

PAH has a multifactorial pathobiology. Vasoconstriction, remodeling of the pulmonary vessel wall, and thrombosis contribute to increased pulmonary vascular resistance in PAH (Humbert et al, J. Am. Coll. Cardiol., 2004, 43:13S-24S.). The compounds as defined in the first aspect disclosed herein are useful in the treatment of pulmonary arterial hypertension (PAH) and symptoms thereof. PAH shall be understood to encompass the following forms of pulmonary arterial hypertension described in the 2003 World Health Organization (WHO) clinical classification of pulmonary arterial hypertension: idiopathic PAH (BPAH); familial PAH (FPAH); PAH associated with other conditions (APAH), such as PAH associated with collagen vascular disease, PAH associated with congenital systemic-to- pulmonary shunts, PAH associated with portal hypertension, PAH associated with HTV infection, PAH associated with drugs or toxins, or PAH associated with Other; and PAH associated with significant venous or capillary involvement. Idiopathic PAH refers to PAH of undetermined cause. Familial PAH refers to PAH for which hereditary transmission is suspected or documented. PAH associated with collagen vascular disease shall be understood to encompass PAH associated with scleroderma, PAH associated with CREST (calcinosis cutis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasias) syndrome, PAH associated with systemic lupus erythematosus (SLE), PAH associated with rheumatoid arthritis, PAH associated with Takayasu's arteritis, PAH associated with polymyositis, and PAH associated with dermatomyositis. PAH associated with congenital systerruc-to-pulmonary shunts shall be understood to encompass PAH associated with atrial septic defect (ASD), PAH associated with ventricular septic defect (VSD) and PAH associated with patent ductus arteriosus.

PAH associated with drugs or toxins shall be understood to encompass PAH associated with ingestion of aminorex, PAH associated with ingestion of a fenfluramine compound (e.g., PAH associated with ingestion of fenfluramine or PAH associated with ingestion of dexfenfluramine), PAH associated with ingestion of certain toxic oils (e g , PAH associated with ingestion of rapeseed oil), PAH associated with ingestion of pyrrolizidine alkaloids (e.g , PAH

associated with ingestion of bush tea) and PAH associated with ingestion of monocrotaline. PAH associated with Other shall be understood to encompass PAH associated with a thyroid disorder, PAH associated with glycogen storage disease, PAH associated with Gaucher disease, PAH associated with hereditary hemorrhagic telangiectasia, PAH associated with a hemoglobinopathy, PAH associated with a myeloproliferative disorder, and PAH associated with splenectomy. PAH associated with significant venous or capillary involvement shall be understood to encompass PAH associated with pulmonary veno-occlusive disease (PVOD) and PAH associated with pulmonary capillary hemangiomatosis (PCH). (See, e.g , Simonneau et al , J. Am. Coll. Cardiol., 2004, 43:5S-12S; McGoon et al., Chest, 2004, 126:14S-34S; Rabinovitch, Annu. Rev. Pathol. Mech. Dis., 2007, 2:369-399; McLaughlin et al , Circulation, 2006, 114:1417-1431; Strauss et al , Clin. Chest. Med., 2007, 28:127-142; Taichman et al., Clin. Chest. Med., 2007, 28:1-22.).

Evidence for the association of PAH with scleroderma and the beneficial effect of an agonist of the IP receptor on PAH is given by Badesch et al (Badesch et al , Ann. Intern. Med., 2000, 132:425-434). Evidence for the association of PAH with the collagen vascular diseases mixed connective tissue disease (MCTD), systemic lupus erythematosus (SLE), Sjogren's syndrome and CREST syndrome and the beneficial effect of an agonist of the IP receptor on PAH is given by Humbert et al. (Eur. Respir. J., 1999, 13:1351-1356). Evidence for the association of PAH with CREST syndrome and the beneficial effect of an agonist of the IP receptor on PAH is given by Miwa et al. (Int. Heart J., 2007, 48:417-422). Evidence for the association of PAH with SLE and the beneficial effect of an agonist of the IP receptor on PAH is given by Robbins et al (Chest, 2000, 117:14-18). Evidence for the association of PAH with HIV infection and the beneficial of an agonist of the IP receptor on PAH is given by Aguilar et al. (Am. J. Respir. Crit. Care Med., 2000, 162:1846-1850). Evidence for the association of PAH with congenital heart defects (including ASD, VSD and patent ductus arteriosus) and the beneficial effect of an agonist of the IP receptor on PAH is given by Rosenzweig et al. (Circulation, 1999, 99:1858-1865).

Evidence for the association of PAH with fenfluramine and with dexfenfluramine, anorexigens, is given by Archer et al. (Am. J. Respir. Crit. Care Med., 1998, 158: 1061-1067). Evidence for the association of PAH with hereditary hemorrhagic telangiectasia is given by McGoon et al. (Chest, 2004, 126:14-34). Evidence for the association of PAH with splenectomy is given by Hoeper et al. (Ann. Intern. Med., 1999, 130:506-509). Evidence for the association of PAH with portal hypertension and the beneficial effect of an agonist of the IP receptor on PAH is given by Hoeper et al. (Eur. Respir. J., 2005, 25:502-508).

Symptoms of PAH include dyspnea, angina, syncope and edema (McLaughlin et al., Circulation, 2006, 114:1417-1431). The compounds as defined in the first aspect disclosed herein are useful in the treatment of symptoms of PAH.

Antiplatelet Therapies (Conditions related to platelet aggregation)

Antiplatelet agents (antiplatelets) are prescribed for a variety of conditions. For example, in coronary artery disease they are used to help prevent myocardial infarction or stroke in patients who are at risk of developing obstructive blood clots (e.g., coronary thrombosis).

In a myocardial infarction, the heart muscle does not receive enough oxygen-rich blood as a result of a blockage in the coronary blood vessels. If taken while an attack is in progress or immediately afterward (preferably within 30 min), antiplatelets can reduce the damage to the heart.

A transient ischemic attack ("TIA" or "mini -stroke") is a brief interruption of oxygen flow to the brain due to decreased blood flow through arteries, usually due to an obstructing blood clot. Antiplatelet drugs have been found to be effective in preventing TIAs. Angina is a temporary and often recurring chest pain, pressure or discomfort caused by inadequate oxygen-rich blood flow (ischemia) to some parts of the heart. In patients with angina, antiplatelet therapy can reduce the effects of angina and the risk of myocardial infarction.

Stroke is an event in which the brain does not receive enough oxygen-rich blood, usually due to blockage of a cerebral blood vessel by a blood clot. In high-risk patients, taking antiplatelets regularly has been found to prevent the formation of blood clots that cause first or second strokes. Angioplasty is a catheter based technique used to open arteries obstructed by a blood clot. Whether or not stenting is performed immediately after this procedure to keep the artery open, antiplatelets can reduce the risk of forming additional blood clots following the procedure(s).

Coronary bypass surgery is a surgical procedure in which an artery or vein is taken from elsewhere in the body and grafted to a blocked coronary artery, rerouting blood around the blockage and through the newly attached vessel. After the procedure, antiplatelets can reduce the risk of secondary blood clots.

Atrial fibrillation is the most common type of sustained irregular heart rhythm (arrhythmia). Atrial fibrillation affects about two million Americans every year. In atrial fibrillation, the atria (the heart's upper chambers) rapidly fire electrical signals that cause them to quiver rather than contract normally. The result is an abnormally fast and highly irregular heartbeat. When given after an episode of atrial fibrillation, antiplatelets can reduce the risk of blood clots forming in the heart and traveling to the brain (embolism).

There is evidence that an IP receptor agonist will inhibit platelet aggregation and thus be a potential treatment as an antiplatelet therapy (see, e.g. , Moncada et al. , Lancet, 1977, 1 : 18-20). It has been shown that genetic deficiency of the IP receptor in mice leads to an increased propensity towards thrombosis (Murata et al, Nature, 1997, 388:678-682).

IP receptor agonists can be used to treat, for example, claudication or peripheral artery disease as well as cardiovascular complications, arterial thrombosis, atherosclerosis, vasoconstriction caused by serotonin, ischemia-reperfusion injury, and restenosis of arteries following angioplasty or stent placement. (See, e.g., Fetalvero et al, Prostaglandins Other Lipid Mediat., 2007, 82:109-118; Arehart et al, Curr. Med. Chem., 2007, 14:2161-2169; Davi et al, N. Engl. J. Med., 2007, 357:2482-2494; Fetalvero et al, Am. J. Physiol. Heart. Circ. Physiol., 2006, 290:H1337-H1346; Murata et al, Nature, 1997, 388:678-682; Wang et al, Proc. Natl. Acad. Sci. USA, 2006, 103:14507-14512; Xiao et al, Circulation, 2001, 104:2210-2215; McCormick et al, Biochem. Soc. Trans., 2007, 35:910-911; Arehart et al, Circ. Res., 2008, Mar 6.).

IP receptor agonists can also be used alone or in combination with thrombolytic therapy, for example, tissue-type plasminogen activator (t-PA), to provide cardioprotection following MI or postischemic myocardial dysfunction or protection from ischemic injury during percutaneous coronary intervention, and the like, including complications resulting therefrom. IP receptor agonists can also be used in antiplatelet therapies in combination with, for example, alpha-tocopherol (vitamin E), echistatin (a disintegrin) or, in states of hypercoagulability, heparin. (See, e.g., Chan., J. Nutr., 1998, 128:1593-1596; Mardla et al, Platelets, 2004, 15:319-324; Bernabei et al, Ann. Thorac. Surg., 1995, 59:149-153; Gainza et al, J. Nephrol., 2006, 19:648-655.)

The IP receptor agonists disclosed herein may provide beneficial improvement in microcirculation to patients in need of antiplatelet therapy by antagonizing the vasoconstrictive products of the aggregating platelets in, for example and not limited to the indications described above.

Accordingly, in some embodiments, the present invention provides methods for reducing platelet aggregation in a patient in need thereof, comprising administering to the patient a composition comprising an IP receptor agonist disclosed herein. In further embodiments, the present invention provides methods for treating coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, atrial fibrillation, or a symptom of any of the foregoing in a patient in need of the treatment, comprising administering to the patient a composition comprising an IP receptor agonist disclosed herein.

In further embodiments, the present invention provides methods for reducing risk of blood clot formation in an angioplasty or coronary bypass surgery patient, or a patient suffering

from atrial fibrillation, comprising administering to the patient a composition comprising an IP receptor agonist disclosed herein at a time where such risk exists.

Atherosclerosis

Atherosclerosis is a complex disease characterized by inflammation, lipid accumulation, cell death and fibrosis. It is the leading cause of mortality in many countries, including the United States. Atherosclerosis, as the term is used herein, shall be understood to encompass disorders of large and medium-sized arteries that result in the progressive accumulation within the intima of smooth muscle cells and lipids.

It has been shown that an agonist of the IP receptor can confer protection from atherosclerosis, such as from atherothrombosis (Arehart et al , Curr. Med. Chem., 2007, 14:2161-2169; Stitham et al , Prostaglandins Other Lipid Mediat., 2007, 82:95-108; Fries et al , Hematology Am. Soc. Hematol. Educ. Program, 2005, :445-451; Egan et al , Science, 2004, 306:1954-1957; Kobayashi et al , J. Clin. Invest , 2004, 114:784-794; Arehart et al , Circ. Res., 2008, Mar 6). It has been shown that defective IP receptor signaling appears to accelerate atherothrombosis in humans, i e that an agonist of the IP receptor can confer protection from atherothrombosis in humans (Arehart et al , Circ. Res., 2008, Mar 6.)

The compounds as defined in the first aspect disclosed herein are useful in the treatment of atherosclerosis, and the treatment of the symptoms thereof. Accordingly, in some embodiments, the present invention provides methods for treating atherosclerosis in a patient in need of the treatment, comprising administering to the patient a composition comprising an IP receptor agonist disclosed herein. In further embodiments, methods are provided for treating a symptom of atherosclerosis in a patient in need of the treatment, comprising administering to the patient a composition comprising an IP receptor agonist disclosed herein.

Asthma

Asthma is a lymphocyte-mediated inflammatory airway disorder characterised by airway eosinophilia, increased mucus production by goblet cells, and structural remodeling of the airway wall. The prevalence of asthma has dramatically increased worldwide in recent decades. It has been shown that genetic deficiency of the IP receptor in mice augments allergic airway inflammation (Takahashi et al , Br J Pharmacol, 2002, 137:315-322). It has been shown that an agonist of the IP receptor can suppress not only the development of asthma when given during the sensitization phase, but also the cardinal features of experimental asthma when given during the challenge phase (Idzko et al , J. Clin. Invest., 2007, 117:464-72, Nagao et al , Am. J. Respir. Cell Mol. Biol., 2003, 29:314-320), at least in part through markedly interfering with the function of antigen-presenting dendnuc cells within the airways (Idzko et al., J. Clin. Invest.,

2007, 117:464-472; Zhou et al , J. Immunol., 2007, 178:702-710; Jaffar et al., J. Immunol., 2007, 179:6193-6203; Jozefowski et al , Int. Immunopharmacol., 2003, 3:865-878). These cells are crucial for both the initiation and the maintenance phases of allergic asthma, as depletion of airway dendritic cells during secondary challenge in sensitized mice abolished all characteristic features of asthma, an effect that could be completely restored by adoptive transfer of wild-type dendritic cells (van Rijt et al., J. Exp. Med., 2005, 201:981-991). It has also been shown that an agonist of the IP receptor can inhibit proinflammatory cytokine secretion by human alveolar macrophages (Raychaudhuri et al. , J. Biol. Chem., 2002, 277:33344-33348). The compounds as defined in the first aspect disclosed herein are useful in the treatment of asthma, and the treatment of the symptoms thereof. Accordingly, in some embodiments, the present invention provides methods for treating asthma in a patient in need of the treatment, comprising administering to the patient a composition comprising IP receptor agonist disclosed herein.

In further embodiments, methods are provided for treating a symptom of asthma in a patient in need of the treatment, comprising administering to the patient a composition comprising IP receptor agonist disclosed herein.

Chronic Obstructive Pulmonary Disease

Activation of the IP-receptor may also be beneficial in chronic obstructive pulmonary disease (COPD). Taprostene, an IP-receptor agonist, suppressed the generation of the $CD8^+$ T cell chemoattractants CXCL9 and CXCL10 from human airway epithelial cells in vitro. (Ayer, L. M., S. M. Wilson, S. L. Traves, D. Proud, M. A. Giembycz. 2008. J. Pharmacol. Exp. Ther. 324: 815-826.) Beraprost, an IP-receptor agonist, protected rats against the development of experimental cigarette smoke-induced emphysema, possibly by means of a concerted inhibitory action on alveolar epithelial cell apoptosis, oxidative burden, matrix metalloproteinase expression, and proinflammatory cytokine generation. (*Chen, Y., M. Hanaoka, P. Chen, Y. Droma, N. F. Voelkel, K. Kubo. 2009. Am. J. Physiol. 296: L648-L656.(*

In further embodiments, methods are provided for treating COPD in a patient in need of the treatment, comprising administering to the patient a composition comprising IP receptor agonist disclosed herein.

Hyperglycemia

Although hyperglycemia is the major cause for the pathogenesis of diabetic complications such as diabetic peripheral neuropathy (DPN), diabetic nephropathy (DN) and diabetic retinopathy (DR), enhanced vasoconstriction and platelet aggregation in diabetic patients has also been implicated to play a role in disease progression (Cameron et al., Naunyn Schmiedebergs Arch. Pharmacol., 2003, 367:607-614). Agonists of the IP receptor promote

vasodilation and inhibit platelet aggregation. Improving microvascular blood flow is able to benefit diabetic complications (Cameron, Diabetologia, 2001, 44:1973-1988).

It has been shown that an agonist of the IP receptor can prevent and reverse motor and sensory peripheral nerve conduction abnormalities in streptozotocin-diabetic rats (Cotter et al., Naunyn Schmiedebergs Arch. Pharmacol., 1993, 347:534-540). Further evidence for the beneficial effect of an agonist of the IP receptor in the treatment of diabetic peripheral neuropathy is given by Hotta et al. (Diabetes, 1996, 45:361-366), Ueno et al. (Jpn. J. Pharmacol., 1996, 70:177-182), Ueno et al. (Life Sci., 1996, 59:PL1O5-PL110), Hotta et al. (Prostaglandins, 1995, 49:339-349), Shindo et al. (Prostaglandins, 1991, 41:85-96), Okuda et al. (Prostaglandins, 1996, 52:375-384), and Koike et al. (FASEB J., 2003, 17:779-781).

Evidence for the beneficial effect of an agonist of the IP receptor in the treatment of diabetic nephropathy is given by Owada et al. (Nephron, 2002, 92:788-796) and Yamashita et al. (Diabetes Res. Clin. Pract., 2002, 57:149-161). Evidence for the beneficial effect of an agonist of the IP receptor in the treatment of diabetic retinopathy is given by Yamagishi et al. (Mol. Med., 2002, 8:546-550), Burnette et al. (Exp. Eye Res., 2006, 83: 1359-1365), and Hotta et al. (Diabetes, 1996, 45:361-366). It has been shown that an agonist of the IP receptor can reduce increased tumor necrosis factor-[alpha] (TNF-[alpha]) levels in diabetic patients, implying that an agonist of the IP receptor may contribute to the prevention of progression in diabetic complications (Fujiwara et al, Exp. Clin. Endocrinol. Diabetes, 2004, 112:390-394).

Evidence that topical administration of an agonist of the IP receptor can result in a decrease in intraocular pressure (IOP) in rabbits and dogs and thereby have beneficial effect in the treatment of glaucoma is given by Hoyng et al (Hoyng et al, Invest. Ophthalmol. Vis. Sci., 1987, 28:470-476).

Agonists of the IP receptor have been shown to have activity for regulation of vascular tone, for vasodilation, and for amelioration of pulmonary hypertension (see, e.g., Strauss et al, Clin Chest Med, 2007, 28:127-142; Driscoll et al, Expert Opin. Pharmacother., 2008, 9:65-81). Evidence for a beneficial effect of an agonist of the IP receptor in the treatment of hypertension is given by Yamada et al. (Peptides, 2008, 29:412-418). Evidence that an agonist of the IP receptor can protect against cerebral ischemia is given by Dogan et al. (Gen. Pharmacol., 1996, 27:1163-1166) and Fang et al (J. Cereb. Blood Flow Metab., 2006, 26:491-501).

Anti-inflammation

Anti-inflammation agents are prescribed for a variety of conditions. For example, in an inflammatory disease they are used to interfere with and thereby reduce an underlying deleterious.

There is evidence that an IP receptor agonist can inhibit inflammation and thus be a potential treatment as an anti-inflammation therapy. It has been shown that an agonist of the IP receptor can inhibit pro-inflammatory cytokine and chemokine (interleukin-12 (IL- 12), tumor necrosis factor-[alpha] (TNF-[alpha]), DL- l[alpha], EL-6, macrophage inflammatory protein- 1 alpha (MIP- l[alpha]), monocyte chemoattractant protein- 1 (MCP-l)) production and T cell stimulatory function of dendritic cells (Jozefowski et al, Int. Immunopharmacol., 2003, 865-878; Zhou et al, J. Immunol., 2007, 178:702-710; Nagao et al, Am. J. Respir. Cell Mol. Biol., 2003, 29:314-320; Idzko et al , J. Clin. Invest., 2007, 117:464-472). It has been shown that an agonist of the IP receptor can inhibit pro-inflammatory cytokine (TNF-[alpha], IL- 1/3, EL-6, granulocyte macrophage stimulating factor (GM-CSF)) production by macrophages (Raychaudhuri et al, J. Biol. Chem., 2002, 277:33344-33348; Czeslick et al, Eur. J. Clin. Invest., 2003, 33:1013-1017; Di Renzo et al, Prostaglandin Leukot. Essent. Fatty Acids, 2005, 73:405-410; Shinomiya et al, Biochem. Pharmacol., 2001, 61:1153-1160). It has been shown that an agonist of the IP receptor can stimulate anti-inflammatory cytokine (DL-IO) production by dendritic cells (Jozefowski et al, Int. Immunopharmacol., 2003, 865-878; Zhou et al, J. Immunol., 2007, 178:702-710). It has been shown that an agonist of the IP receptor can stimulate anti-inflammatory cytokine (DL- 10) production by macrophages (Shinomiya et al , Biochem. Pharmacol., 2001, 61: 1153-1160). It has been shown that an agonist of the IP receptor can inhibit a chemokine (CCL 17)- induced chemotaxis of leukocytes (CD4<+> Th2 T cells) (Jaffar et al, J. Immunol., 2007, 179:6193-6203). It has been shown that an agonist of the IP receptor can confer protection from atherosclerosis, such as from atherothrombosis (Arehart et al, Curr. Med. Chem., 2007, 14:2161-2169; Stitham et al, Prostaglandins Other Lipid Mediat., 2007, 82:95-108; Fries et al, Hematology Am. Soc. Hematol. Educ. Program, 2005, :445-451; Egan et al, Science, 2004, 306:1954-1957; Kobayashi et al, J. Clin. Invest., 2004, 114:784-794; Arehart et al, Circ. Res., 2008, Mar 6). It has been shown that an agonist of the IP receptor can attenuate asthma (Idzko et al, J. Clin. Invest., 2007, 117:464-472; Jaffar et al, J. Immunol., 2007, 179:6193-6203; Nagao et al, Am. J. Respir. Cell. Mol. Biol., 2003, 29:314-320). It has been shown that an agonist of the IP receptor can decrease TNF-[alpha] production in type 2 diabetes patients (Fujiwara et al, Exp. Clin. Endocrinol. Diabetes, 2004, 112:390-394; Goya et al, Metabolism, 2003, 52: 192-198). It has been shown that an agonist of the IP receptor can inhibit ischemia-reperfusion injury (Xiao et al, Circulation, 2001, 104:2210-2215). It has been shown that an agonist of the IP receptor can inhibit restenosis (Cheng et al, Science, 2002, 296:539-541). It has been shown that an agonist of the IP receptor can attenuate pulmonary vascular injury and shock in a rat model of septic shock (Harada et al, Shock, 2008, Feb 21). It

has been shown that an agonist of the IP receptor can reduce the serum levels of TNF-[alpha] in vivo in patients with rheumatoid arthritis, and this is associated with improvement in the clinical course of the disease (Gao et al, Rheumatol. Int., 2002, 22:45-51; Boehme et al, Rheumatol. Int., 2006, 26:340-347).

The compounds as defined in the first aspect disclosed herein provide beneficial reduction of inflammation. The compounds as defined in the first aspect disclosed herein provide beneficial reduction of a deleterious inflammatory response associated with an inflammatory disease. Accordingly, in some embodiments, the present invention provides methods for reducing inflammation in a patient in need thereof, comprising administering to the patient a composition comprising an IP receptor agonist disclosed herein. In some embodiments, the present invention provides methods for decreasing IL-12, TNF-[alpha], IL-l[alpha], IL-ljS, BL-6, MIP-la or MCP-l production in a patient in need thereof, comprising administering to the patient a composition comprising an IP receptor agonist disclosed herein. In some embodiments, the present invention provides methods for decreasing TNF-[alpha] production in a patient in need thereof, comprising administering to the patient a composition comprising an IP receptor agonist disclosed herein. In some embodiments, the present invention provides methods for increasing EL-IO production in a patient in need thereof, comprising administering to the patient a composition comprising an IP receptor agonist disclosed herein. In some embodiments, the present invention provides methods for reducing a deleterious inflammatory response associated with an inflammatory disease in a patient in need thereof, comprising administering to the patient a composition comprising an IP receptor agonist disclosed herein. In some embodiments, the present invention provides methods for treating an inflammatory disease or a symptom thereof in a patient in need of the treatment comprising administering to the patient a composition comprising an IP receptor agonist disclosed herein. In some embodiments, the present invention provides methods for treating an inflammatory disease or a symptom thereof in a patient in need of the treatment comprising administering to the patient a composition comprising an IP receptor agonist disclosed herein. In some embodiments, the present invention provides methods for treating an inflammatory disease or a symptom thereof in a patient in need of the treatment comprising administering to the patient a composition comprising an IP receptor agonist disclosed herein, wherein the inflammatory disease is selected from the group consisting of psoriasis, psoriatic arthritis, rheumatoid arthritis, Crohn's disease, transplant rejection, multiple sclerosis, systemic lupus erythematosus (SLE), ulcerative colitis, ischemia-reperfusion injury, restenosis, atherosclerosis, acne, diabetes

(including type 1 diabetes and type 2 diabetes), sepsis, chronic obstructive pulmonary disease (COPD), and asthma.

Fibrosis

PGI2 signaling has been shown to play a beneficial role in fibrotic diseases of various organs, including kidney, heart, lung, skin, pancreas and liver, as well as in systemic sclerosis and associated pathologies. It has been shown that an agonist of the IP receptor can ameliorate cardiac fibrosis (Chan EC et al (2010) *J Mol Cell Cardiol.* Apr 18; Hirata Y et al (2009) *Biomed Pharmacother.* 63(10):781-6; Kaneshige T et al (2007) *J Vet Med Sci.* 69(12):1271-6). It has been shown that an agonist of the IP receptor can attenuate renal fibrosis (Takenaka M et al (2009) Prostaglandins Leukot Essent Fatty Acids. 80(5-6):263-7). It has been shown that an agonist of the IP receptor can protect against pulmonary fibrosis in a bleomycin model (Zhu Y et al (2010) *Respir Res.* 20;11(1):34). It has been shown that an agonist of the IP receptor can suppress the production of connective tissue growth factor, a key mediator of fibrosis, in scleroderma patients (Stratton R et al (2001) *J Clin Invest.* 108(2):241-50). It has been shown that an agonist of the IP receptor can reduce the incidence of digital ulcerations in patients with systemic sclerosis M. Vayssairat (1999) *J Rheumatol* 26:2173–2178. It has been shown that an agonist of the IP receptor can reduce fingertip necrosis in infants with refractory Renaud's phenomenon (Shouval DS et al (2008) *Clin Exp Rheumatol.* 26(3 Suppl 49):S105-7). It has been shown that an agonist of the IP receptor can reduce markers of endothelial activation in patients with systemic sclerosis (Rehberger P et al (2009) *Acta Derm Venereol.* 89(3):245-9.). It has been shown that an agonist of the IP receptor can reduce severity, frequency, and duration of Raynaud's attacks in patients with systemic sclerosis (Torlay et al (1991) *Ann Rheum Dis* **50**, 800–804). It has been shown that an agonist of the IP receptor can improve portal hemodynamics in patients with systemic sclerosis and Raynaud's phenomenon (Zardi et al (2006) *In Vivo* 20(3):377-80). It has been shown that an agonist of the IP receptor can inhibit the progression of pancreatic fibrosis in obese Zucker rats (Sato et al (2010) *Diabetes* 59(4):1092-100).

The IP receptor agonists disclosed herein may provide beneficial anti-fibrotic effects to patients suffering from fibrosis of the kidney, heart, lung, skin, pancreas and liver which can be idiopathic or secondary to chronic inflammation and systemic sclerosis, for example, and are not limited to the indications described above.

In addition, there is substantial evidence that an agonist of the IP receptor can improve kidney function in acute and chronic renal failure. It has been shown that an agonist of the IP receptor can restore kidney function in endotoxemia-related acute renal failure (Johannes T et

al (2009) *Crit Care Med.* 37(4):1423-32). It has been shown that an agonist of the IP receptor can improve renal function in a model of renal ischemia/reperfusion injury Sahsivar MO et al (2009) *Shock* 32(5):498-502). It has been shown that an agonist of the IP receptor can prevent contrast agent-induced nephropathy in patients with renal dysfunction undergoing cardiac surgery (Spargias K et al (2009) *Circulation* 3;120(18):1793-9.) It has been shown that an agonist of the IP receptor can improve renal function, reduce inflammation and sclerotic changes of the kidney in a model for diabetic nephropathy Watanabe M et al (2009) Am J Nephrol. 2009;30(1):1-11).

The IP receptor agonists disclosed herein may provide beneficial improvement of renal function in patients with acute and chronic kidney injury and nephropathies secondary to dye-contrast agents, ischemia-reperfusion injury, systemic inflammation and diabetes for example, and are not limited to the indications described above.

There is considerable evidence for a causal role of Prostacyclin deficiency in the development of preeclampsia (Mills JL et al (1999) *JAMA* 282: 356–362; Walsh SW (2004) *Prostaglandins Leukot Essent Fatty Acids* 70: 223–232). The administration of an agonist of the IP receptor has been shown to lower blood pressure in a rat model of preeclampsia (Zlatnik MG et al (1999) *Am J Obstet Gynecol.* 180(5):1191-5).

The IP receptor agonists disclosed herein may provide beneficial improvement of hemodynamics in patients with preeclampsia.

The IP receptor agonist disclosed herein may provide beneficial treatment of cystic fibrosis.

The IP receptor agonists disclosed herein may provide chemoprevention. Chemoprevention is the practice of using of drugs, vitamins, or nutritional supplements to reduce the risk of developing, or having a recurrence of cancer. Oral iloprost (*Ventavis*), an analogue of prostacyclin, shows promise as a chemopreventive agent for lung cancer. Data supporting IP receptor agonist chemoprevention was presented by Paul Bunn Jr. MD, who is the executive Director of the International Association for the Study of Lung Cancer at the American Association for Cancer Research 102nd Annual Meeting showed that it significantly improved endobronchial dysplasia in former smokers.

PGI2 and other IP receptor agonists, including the compounds as defined in the first aspect, are also useful as co-therapeutic agents for use in combination with second agents, such as organic nitrates and NO-donors, such as sodium nitroprusside, nitroglycerin, isosorbide mononitrate, isosorbide dinitrate, molsidomine or SIN-1, and inhalational NO; compounds that inhibit the degradation of cyclic guanosine monophosphate (cGMP) and/or cyclic adenosine

monophosphate (cAMP), such as inhibitors of phosphodiesterases (PDE) 1, 2, 3, 4 and/or 5, especially PDE 5 inhibitors such as sildenafil, vardenafil and tadalafil; NO-independent, but haem-dependent stimulators of guanylate cyclase, such as in particular the compounds described in WO 00/06568, WO 00/06569, WO 02/42301 and WO 03/095451; NO- and haem-independent activators of guanylate cyclase, such as in particular the compounds described in WO 01/19355, WO 01/19776, WO 01/19778, WO 01/19780, WO 02/070462 and WO 02/070510; compounds which inhibit human neutrophilic elastase, such as sivelestat or DX-890 (Reltran); compounds inhibiting the signal transduction cascade, such as tyrosine kinase and/or serine/threonine kinase inhibitors, in particular imatinib, gefitinib, erlotinib, sorafenib and sunitinib; compounds influencing the energy metabolism of the heart, for example and preferably etomoxir, dichloroacetate, ranolazine or trimetazidine; antithrombotic agents, for example and preferably from the group comprising platelet aggregation inhibitors, anticoagulants or profibrinolytic substances; active substances for lowering blood pressure, for example and preferably from the group comprising calcium antagonists, angiotensin II antagonists, ACE inhibitors, endothelin antagonists, renin inhibitors, aldosterone synthase inhibitors, alpha receptor blockers, beta receptor blockers, mineralocorticoid receptor antagonists, Rho-kinase inhibitors and diuretics; and/or active substances that modify lipid metabolism, for example and preferably from the group comprising thyroid receptor agonists, inhibitors of cholesterol synthesis, for example and preferably HMG-CoA-reductase inhibitors or inhibitors of squalene synthesis, 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, particularly in the treatment of PAH or diseases and disorders such as those mentioned hereinbefore, e.g., as potentiators of therapeutic activity of such drugs or as a means of reducing required dosaging or potential side effects of such drugs.

In particular, an embodiment of this invention is a pharmaceutical combination comprising the compounds as defined in the first aspect, or a pharmaceutically acceptable salt thereof, and a second agent wherein the second agent is a PDEV inhibitor or neutral endopeptidase inhibitor.

The compounds as defined in the first aspect, or a pharmaceutically acceptable salt thereof, may be mixed with a second agent in a fixed pharmaceutical composition or it may be administered separately, before, simultaneously with or after the other drug substance.

Accordingly, the invention includes as a further aspect a combination of an IP receptor activity with osmotic agents (hypertonic saline, dextran, mannitol, Xylitol), ENaC blockers, an

anti-inflammatory, bronchodilatory, antihistamine, anti-tussive, antibiotic and/or DNase drug substance, wherein the IP receptor agonist and the further drug substance may be in the same or different pharmaceutical composition.

Suitable antibiotics include macrolide antibiotics, e.g., tobramycin (TOBI™).

Suitable DNase drug substances include dornase alfa (Pulmozyme™), a highly-purified solution of recombinant human deoxyribonuclease I (rhDNase), which selectively cleaves DNA. Dornase alfa is used to treat cystic fibrosis.

Other useful combinations of IP receptor agonist with anti-inflammatory drugs are those with antagonists of chemokine receptors, e.g., CCR-1, CCR-2, CCR-3, CCR-4, CCR-5, CCR-6, CCR-7, CCR-8, CCR-9 and CCR10, CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, particularly CCR-5 antagonists, such as Schering-Plough antagonists SC-351125, SCH-55700 and SCH-D; Takeda antagonists, such as *N*-[[4-[[[6,7-dihydro-2-(4-methyl-phenyl)-5*H*-benzo-cyclohepten-8-yl]carbonyl]amino]phenyl]-methyl]tetrahydro-*N,N*-dimethyl-2*H*-pyran-4-amin-ium chloride (TAK-770); and CCR-5 antagonists described in USP 6,166,037 (particularly claims 18 and 19), WO 00/66558 (particularly claim 8), WO 00/66559 (particularly claim 9), WO 04/018425 and WO 04/026873.

Suitable anti-inflammatory drugs include steroids, for example corticosteroids. Suitable steroids include budesonide, beclamethasone (e.g. dipropionate), butixocort (e.g. propionate), CHF5188, ciclesonide, dexamethasone, flunisolide, fluticasone (e.g. propionate or furoate), GSK-685698, GSK-870086, LAS40369, methyl prednisolone, mometasone (e.g. furoate), prednisolone, rofleponide, and triamcinolone (e.g. acetonide). In certain preferred embodiments the steroid is long-acting corticosteroids such as budesonide, ciclesonide, fluticasone or mometasone.

Suitable second active ingredients include β_2-agonists. Suitable β_2-agonists include arformoterol (e.g. tartrate), albuterol/salbutamol (e.g. racemate or single enantiomer such as the R-enantiomer, or salt thereof especially sulfate), AZD3199, bambuterol, BI-171800, bitolterol (e.g. mesylate), carmoterol, clenbuterol, etanterol, fenoterol (e.g. racemate or single enantiomer such as the R-enantiomer, or salt thereof especially hydrobromide), flerbuterol, formoterol (e.g. racemate or single diastereomer such as the R,R-diastereomer, or salt thereof especially fumarate or fumarate dihydrate), GSK-159802, GSK-597901, GSK-678007, indacaterol (e.g. racemate or single enantiomer such as the R-enantiomer, or salt thereof especially maleate, acetate or xinafoate), LAS100977, metaproterenol, milveterol (e.g. hydrochloride), naminterol, olodaterol (e.g. racemate or single enantiomer such as the R-enantiomer, or salt thereof especially hydrochloride), PF-610355, pirbuterol (e.g. acetate), procaterol, reproterol,

salmefamol, salmeterol (e.g. racemate or single enantiomer such as the R-enantiomer, or salt thereof especially xinafoate), terbutaline (e.g. sulphate) and vilanterol (or a salt thereof especially trifenatate. In certain preferred embodiments the β_2-agonist is an ultra-long-acting β_2-agonist such as indacaterol, or potentially carmoterol, LAS-100977, milveterol, olodaterol, PF-610355 or vilanterol. A preferred embodiment one of the second active ingredients is indacaterol (i.e. (R)-5-[2-(5,6-diethyl-indan-2-ylamino)-1-hydroxyethyl]-8-hydroxy-1H-quinolin-2-one) or a salt thereof. This is a β_2-adrenoceptor agonist that has an especially long duration of action (i.e. over 24 hours) and a short onset of action (i.e. about 10 minutes). This compound is prepared by the processes described in international patent applications WO 2000/75114 and WO 2005/123684. It is capable of forming acid addition salts, particularly pharmaceutically acceptable acid addition salts. A preferred salt of (R)-5-[2-(5,6-diethyl-indan-2-ylamino)-1-hydroxyethyl]-8-hydroxy-1H-quinolin-2-one is the maleate salt. Another preferred salt is (R)-5-[2-(5,6-diethyl-indan-2-ylamino)-1-hydroxyethyl]-8-hydroxy-1H-quinolin-2-one acetate. Another preferred salt is (R)-5-[2-(5,6-diethyl-indan-2-ylamino)-1-hydroxyethyl]-8-hydroxy-1H-quinolin-2-one xinafoate.

Suitable bronchodilatory drugs include anticholinergic or antimuscarinic agents, such as aclidinium (e.g. bromide), BEA-2108 (e.g. bromide), BEA-2180 (e.g. bromide), CHF-5407, darifenacin (e.g. bromide), darotropium (e.g. bromide), glycopyrrolate (e.g. racemate or single enantiomer, or salt thereof especially bromide), dexpirronium (e.g. bromide), iGSK-202405, GSK-203423, GSK-573719, GSK-656398, ipratropium (e.g. bromide), LAS35201, LAS186368, otilonium (e.g. bromide), oxitropium (e.g. bromide), oxybutynin, PF-3715455, PF-3635659, pirenzepine, revatropate (e.g. hydrobromide), solifenacin (e.g. succinate), SVT-40776, TD-4208, terodiline, tiotropium (e.g. bromide), tolterodine (e.g. tartrate), and trospium (e.g. chloride). In certain preferred embodiments the muscarinic antagonists is long-acting muscarinic antagonist such as darotropium bromide, glycopyrrolate or tiotropium bromide.

Suitable dual anti-inflammatory and bronchodilatory drugs include dual beta-2 adrenoceptor agonist/muscarinic antagonists such as GSK-961081 (e.g. succinate). and those disclosed in USP 2004/0167167, WO 04/74246 and WO 04/74812.

Suitable antihistamine drug substances include cetirizine hydrochloride, acetaminophen, clemastine fumarate, promethazine, loratidine, desloratidine, diphenhydramine and fexofenadine hydrochloride, activastine, astemizole, azelastine, ebastine, epinastine, mizolastine and tefenadine, as well as those disclosed in JP 2004107299, WO 03/099807 and WO 04/026841.

Accordingly, the invention includes as a further aspect a combination of IP receptor agonist with agents that inhibit ALK5 and/or ALK4 phosphorylation of Smad2 and Smad3.

Accordingly, the invention includes as a further aspect a combination of IP receptor agonist with second agents that are Rho-kinase inhibitors.

Accordingly, the invention includes as a further aspect a combination of IP receptor agonist with second agents that are tryptophan hydroylase 1 (TPH1) inhibitors.

Accordingly, the invention includes as a further aspect a combination of IP receptor agonist with second agents that are multi-kinase inhibitors, such as imatinib mysilate, Gleevec. Imatinib functions as a specific inhibitor of a number of tyrosine kinase enzymes. It occupies the *TK* active site, leading to a decrease in activity. *TK* enzymes in the body include the insulin receptor. Imatinib is specific for the *TK* domain in the Abelson proto-oncogene, c-kit and PDGF-R (platelet-derived growth factor receptor).

In an embodiment of this invention, the IP receptor agonist of this invention are dosed in combination with a second active agent selected from phosphodiesterase V inhibitors, neutral endopeptidase 1 inhibitors, THP1 inhibitors, multi-kinase inhibitors, endothelin antagonist, diuretic, aldosteron receptor blocker, and endothelin receptor blocker.

In an embodiment of this invention, the IP receptor agonist of this invention are dosed in combination with a second active agent selected from phosphodiesterase V inhibitors, neutral endopeptidase 1 inhibitors, THP1 inhibitors, and multi-kinase inhibitors, such as PDGFR or c-Kit.

In another aspect the invention provides a compound as defined in the first aspect, or a pharmaceutically acceptable salt thereof, for use in the manufacture of a medicament for the treatment of a condition responsive to IP receptor agonist activity, particularly in PAH.

The agents of the invention may be administered by any appropriate route, e.g. orally, e.g., in the form of a tablet or capsule; parenterally, e.g., intravenously; by inhalation, e.g., in the treatment of an obstructive airways disease; intranasally, e.g., in the treatment of allergic rhinitis; topically to the skin; or rectally. In a further aspect, the invention also provides a pharmaceutical composition comprising a compound as defined in the first aspect, in free form or in the form of a pharmaceutically acceptable salt, optionally together with a pharmaceutically acceptable diluent or carrier therefor. The composition may contain a co-therapeutic agent, such as an anti-inflammatory, broncho-dilatory, antihistamine or anti-tussive drug as hereinbefore described. Such compositions may be prepared using conventional diluents or excipients and techniques known in the galenic art. Thus oral dosage forms may include tablets

and capsules. Formulations for topical administration may take the form of creams, ointments, gels or transdermal delivery systems, e.g., patches. Compositions for inhalation may comprise aerosol or other atomizable formulations or dry powder formulations.

When the composition comprises an aerosol formulation, it preferably contains, e.g., a hydro-fluoro-alkane (HFA) propellant, such as HFA134a or HFA227 or a mixture of these, and may contain one or more co-solvents known in the art, such as ethanol (up to 20% by weight), and/or one or more surfactants, such as oleic acid or sorbitan trioleate, and/or one or more bulking agents, such as lactose. When the composition comprises a dry powder formulation, it preferably contains, e.g., the compound as defined in the first aspect or a pharmaceutically acceptable salt thereof having a particle diameter up to 10 microns, optionally together with a diluent or carrier, such as lactose, of the desired particle size distribution and a compound that helps to protect against product performance deterioration due to moisture, e.g., magnesium stearate. When the composition comprises a nebulised formulation, it preferably contains, e.g., the compound as defined in the first aspect or a pharmaceutically acceptable salt thereof either dissolved, or suspended, in a vehicle containing water, a co-solvent, such as ethanol or propylene glycol and a stabilizer, which may be a surfactant.

Further aspects of the invention include:

(a) a compound as defined in the first aspect or a pharmaceutically acceptable salt thereof in inhalable form, e.g., in an aerosol or other atomisable composition or in inhalable particulate, e.g., micronised form;

(b) an inhalable medicament comprising a compound as defined in the first aspect or a pharmaceutically acceptable salt thereof in inhalable form;

(c) a pharmaceutical product comprising a compound of formula (I) in inhalable form in association with an inhalation device; and

(d) an inhalation device containing a compound as defined in the first aspect or a pharmaceutically acceptable salt thereof in inhalable form.

Dosages of compounds as defined in the first aspect or a pharmaceutically acceptable salt thereof employed in practicing the present invention will of course vary depending, e.g., on the particular condition to be treated, the effect desired and the mode of administration. In general, suitable daily dosages for administration by inhalation are of the order of 0.005-10 mg, while for oral administration suitable daily doses are of the order of 0.05-100 mg.

Pharmaceutical Use and Assay

Compounds of and their pharmaceutically acceptable salts, hereinafter referred to alternatively as "agents of the invention", are useful as pharmaceuticals. In particular, the compounds are suitable IP receptor agonist and may be tested in the following assays.

Activity of compounds at the IP receptor (IP receptor) is assessed by measuring cAMP accumulation in CHO cells stably expressing the IP receptor (CHO-IP) using the PerkinElmer AlphaScreen assay. This technology measures the endogenous production of cAMP, in a non-radioactive luminescence proximity homogenous assay. A biological reaction occurs between streptavidin coated donor beads, biotinylated cAMP and anti-cAMP acceptor beads, bringing the donor and acceptor beads close enough together so that upon excitation a fluorescence signal is produced. On production of endogenous cAMP, competition between the biotinylated cAMP and cellular-derived cAMP causes a reduction in the fluorescent signal. The reduction in signal is proportional to the amount of cAMP being produced, thus it is possible to quantify the amount of cAMP being produced on stimulation with agonist.

Test and reference compounds are prepared at 100x [final] in 100 % DMSO, and diluted 1:3 using a Biomek Fx (Beckman Coulter). This is followed by an intermediate dilution to give 5x [final] in assay buffer (HBSS containing 5 mM HEPES, 0.1 % (w/v) BSA). 5 µL of 5x [final] test compounds, reference compounds and buffer/DMSO control are then transferred to a 384-well white OptiPlate, containing 20 µL CHO-IP cell suspension (15,000 cells/well, prepared from frozen), and plate is incubated at room temperature for 1 hour. A cAMP standard curve is constructed for each experiment (concentration range of 10000 nM to 0.001 nM, in assay buffer) and 25 µL of each concentration added to the last two columns of the assay plate. The incubation is terminated by the addition of lysis buffer (dH_2O; 0.3 % (v v^{-1}) Tween-20) containing 20 units mL^{-1} streptavidin coated donor beads and biotinylated cAMP (pre-incubated for 30 minutes) and 20 units mL^{-1} anti-cAMP acceptor beads, which are added to the lysis buffer just before addition to the assay plate. The assay plate is then incubated at room temperature in the dark, for 60 minutes with gentle shaking, and read on the Envision plate reader (Perkin Elmer).

The raw data of the reference compounds, test compounds and controls are converted into cAMP concentrations, using the cAMP standard curve, in GraphPadPrism (GraphPad Software Inc). EC_{50} as well as maximal values of the agonist curves are determined using a 4-parameter logistic equation. The % maximum response values of all test compounds are determined using the top of the treprostinil concentration-response curve.

Compounds of the Examples, herein below, generally have EC_{50} values in the data measurements described above below 5 µM. Table 1 provides a list of representative compounds with their EC_{50} value.

Table 1.

Example	EC_{50} /μM
1	0.00011
2	0.00007
3	0.00004
3a	0.00206
3b	0.00171
4	0.00563
4a	0.00062
4b	0.00086

The invention is illustrated by the following Examples.

Examples

General Conditions:

Mass spectra were run on LCMS systems using electrospray ionization. These were either Agilent 1100 HPLC/Micromass Platform Mass Spectrometer combinations or Waters Acquity UPLC with SQD Mass Spectrometer. $[M+H]^+$ refers to mono-isotopic molecular weights.

NMR spectra were run on open access Bruker AVANCE 400 NMR spectrometers using ICON-NMR. Spectra were measured at 298K and were referenced using the solvent peak.

The following examples are intended to illustrate the invention and are not to be construed as being limitations thereon. Temperatures are given in degrees centigrade. If not mentioned otherwise, all evaporations are performed under reduced pressure, preferably between about 15 mm Hg and 100 mm Hg (= 20-133 mbar). The structure of final products, intermediates and starting materials is confirmed by standard analytical methods, *e.g.*, microanalysis and spectroscopic characteristics, *e.g.*, MS, IR, NMR. Abbreviations used are those conventional in the art. If not defined, the terms have their generally accepted meanings.

Abbreviations:

AcOH	acetic acid
br	broad
d	doublet
DCM	dichloromethane
DCE	1,2-dichloroethane
DEAD	Diethyl azodicarboxylate

DIPEA	Diisopropylethylamine
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
EDCI	1-ethyl-3-(3'-dimethylaminopropyl) carbodiimide
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
h	hour(s)
HPLC	high pressure liquid chromatography
LCMS	liquid chromatography and mass spectrometry
MeOH	methanol
MeCN	acetonitrile
MS	mass spectrometry
m	multiplet
min	minutes
ml	milliliter(s)
m/z	mass to charge ratio
NMR	nuclear magnetic resonance
ppm	parts per million
PS	polymer supported
Rt	retention time
RT	room temperature
s	singlet
sat.	saturated
SCX-2	strong cation exchange (e.g. Isolute® SCX-2 columns from Biotage)
t	triplet
TBME	methyl-tert-butyl ether
THF	tetrahydrofuran

Referring to the examples that follow, compounds of the preferred embodiments were synthesized using the methods described herein, or other methods, which are known in the art. The various starting materials, intermediates, and compounds of the preferred embodiments may be isolated and purified, where appropriate, using conventional techniques such as

precipitation, filtration, crystallization, evaporation, distillation, and chromatography. Unless otherwise stated, all starting materials are obtained from commercial suppliers and used without further purification. Salts may be prepared from compounds by known salt-forming procedures.

It should be understood that the organic compounds according to the preferred embodiments may exhibit the phenomenon of tautomerism. As the chemical structures within this specification can only represent one of the possible tautomeric forms, it should be understood that the preferred embodiments encompasses any tautomeric form of the drawn structure.

If not indicated otherwise, the analytical LCMS conditions are as follows:

2minLC_v003

Column	Waters BEH C18 50 x 2.1 mm, 1.7 m
Column Temperature	50 °C
Eluents	A: H_2O, B: acetonitrile, both containing 0.1% TFA
Flow Rate	0.8 ml/min
Gradient	0.20 min 5% B; 5% to 95% B in 1.30 min, 0.25 min 95% B

2minLowpH

Column:	Waters Acquity CSH 1.7µm, 2.1 x 50mm
Temperature:	50 °C
Mobile Phase:	A: Water +0.1% Formic Acid B: Acetonitrile +0.1% Formic Acid
Flow rate:	1.0mL/min
Gradient:	0.0min 5%B, 0.2-1.3min 5-98%B, 1.3-1.55min 98%B, 1.55-1.6min 98-5%B

2minLowpHv01:

Column:	Waters Acquity CSH 1.7µm, 2.1 x 50mm
Temperature:	50 ° C
Mobile Phase:	A: Water +0.1% Formic Acid B: Acetonitrile +0.1% Formic Acid
Flow rate:	1.0mL/min
Gradient:	0.0min 5%B, 0.2-1.55min 5-98%B, 1.55-1.75min 98%B, 1.75-1.8min 98-5%B

10minLC_v003

Column	Waters BEH C18 50x2.1 mm, 1.7 m
Column Temperature	50 °C
Eluents	A: H_2O, B: acetonitrile, both containing 0.1% TFA
Flow Rate	0.8 ml/min
Gradient	0.20 min 5% B; 5% to 95% B in 7.80 min, 1.00 min 95% B

10minLowpH

Column:	Waters Acquity CSH 1.7µm, 2.1 x 100mm
Temperature:	50 °C
Mobile Phase:	A: Water +0.1% Formic Acid B: Acetonitrile +0.1% Formic Acid
Flow rate:	0.7mL/min
Gradient:	0.0min 2%B, 0.5-8.0min 2-98%B, 8.0-9.0min 98%B, 9.0-9.1min 98-2%B

A

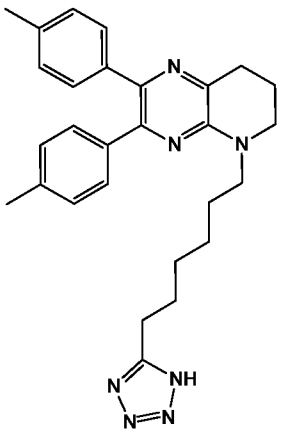
Column	Zorbax Eclipse XDB-C18 4.6x 50 mm, 1.8 µm
Column Temperature	35 °C
Eluents	A: H_2O + 0.1% TFA, B: acetonitrile + 0.1% TFA
Flow Rate	1 ml/min
Gradient	5-100% MeCN (6 min), 100 MeCN (1.5 min), 100-5% MeCN (0.5 min)

Example compounds of the present invention include:

Preparation of Final Compounds

Example 1:

5-(6-(1H-Tetrazol-5-yl)hexyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazine



Step 1: N-(2-Cyanoethyl)-7-(2,3-di-p-tolyl-7,8-dihydropyrido[2,3-b]pyrazin-5(6H)-yl)heptanamide
A solution comprising 7-(2,3-di-p-tolyl-7,8-dihydropyrido[2,3-b]pyrazin-5(6H)-yl)heptanoic acid (Intermediate D) (400 mg, 0.902 mmol), HATU (411 mg, 1.082 mmol) and DIPEA (0.189 ml, 1.082 mmol) in DCM (10 ml) was treated with 3-aminopropanenitrile (0.079 ml, 1.082 mmol) and stirred at RT overnight. The mixture was washed with brine and passed through a phase separating column. The solvent was removed under reduced pressure to afford the titled compound;
LCMS; Rt 1.28 mins MS m/z 496 $[M+H]^+$; Method 2minLowpH.

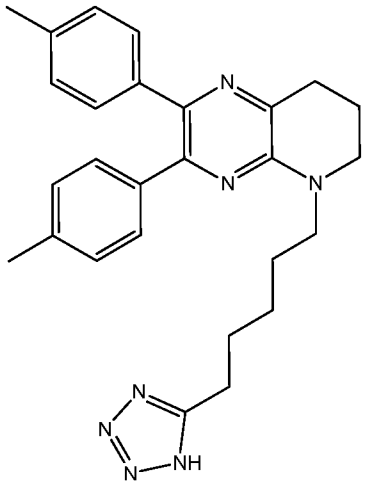
Step 2: 3-(5-(6-(2,3-Di-p-tolyl-7,8-dihydropyrido[2,3-b]pyrazin-5(6H)-yl)hexyl)-1H-tetrazol-1-yl)propanenitrile
A mixture comprising N-(2-cyanoethyl)-7-(2,3-di-p-tolyl-7,8-dihydropyrido[2,3-b]pyrazin-5(6H)-yl)heptanamide (step 1) (250 mg, 0.504 mmol), triphenylphosphine (265 mg, 1.009 mmol), trimethylsilyl azide (0.134 ml, 1.009 mmol) and DEAD (0.160 ml, 1.009 mmol) in THF (10 ml) was stirred at RT overnight. The solvent was removed under reduced pressure and the resulting crude was dissolved in DCM and washed with brine. The organic portion was passed through a phase separating column and loaded onto a silica cartridge. Purification by chromatography eluting with 0-100% EtOAc in iso-hexane afforded the titled compound as a yellow oil;
LCMS; Rt 1.31 mins MS m/z 521 $[M+H]^+$; Method 2minLowpH.

Step 3: 5-(6-(1H-Tetrazol-5-yl)hexyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazine
3-(5-(6-(2,3-Di-p-tolyl-7,8-dihydropyrido[2,3-b]pyrazin-5(6H)-yl)hexyl)-1H-tetrazol-1-yl)propanenitrile (step 2)(100 mg, 0.192 mmol) in MeOH (5 ml) was treated with 1M NaOH

(0.576 ml, 0.576 mmol) and stirred at RT overnight. The reaction mixture was acidified with 1M HCl and concentrated under reduced pressure. The resulting yellow solution was extracted with DCM and the organic extracts were passed through a phase separating column. The solvent was removed under reduced pressure and the crude product was purified by mass directly LCMS. The appropriate fractions were concentrated under reduced pressure and extracted with DCM. The organic extracts were passed through a phase separating column and concentrated under reduced pressure. Further purification by chromatography on silica eluting with 0-100% EtOAc in iso-hexane followed by 0-30% MeOH in DCM afforded the titled compound;
1H NMR (400MHz, DMSO-d6) δ 15.9 (1H,s), 7.22 (2H,d) 7.14 (2H,d), 7.05 (4H,m), 3.58 (2H,m), 3.45 (2H,m), 2.89 (2H,m), 2.82 (2H,m), 2.27 (6H,s), 2.01 (2H,m) 1.65 (4H, m), 1.35 (4H,m)
LCMS; Rt 1.27 mins MS m/z 468 $[M+H]^+$; Method 2minLowpH.

Example 2:

5-(5-(1H-tetrazol-5-yl)pentyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazine



Step 1: N-(2-Cyanoethyl)-6-(2,3-di-p-tolyl-7,8-dihydropyrido[2,3-b]pyrazin-5(6H)-yl)hexanamide
A solution of 6-(2,3-di-p-tolyl-7,8-dihydropyrido[2,3-b]pyrazin-5(6H)-yl)hexanoic acid (Intermediate C) (430 mg, 1.001 mmol), HATU (457 mg, 1.201 mmol) and DIPEA (0.210 ml, 1.201 mmol) in DCM (5 ml) was treated with 3-aminopropanenitrile (0.088 ml, 1.201 mmol) and stirred at RT overnight. The resulting mixture was diluted with water and extracted with DCM (3x). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to afford a dark oil. The oil was purified by chromatography on silica eluting with 50-100% EtOAc in iso-hexane. The material was further purified by loading onto an

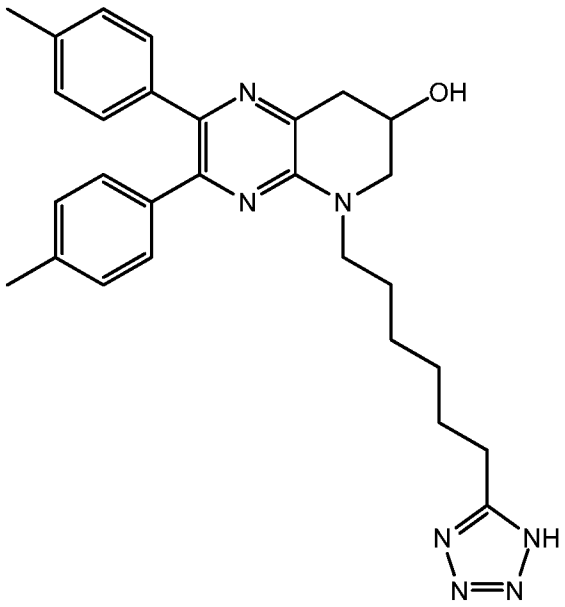
Isolute™ SCX-2 cartridge and eluting with MeOH followed by 2M NH_3 in MeOH. The methanolic ammonia fractions were concentrated under reduced pressure to afford the titled compound;
LCMS; Rt 1.23 mins MS m/z 482.6 $[M+H]^+$; Method 2minLowpH.

Step 2: 3-{5-[5-(2,3-Di-p-tolyl-7,8-dihydro-6H-pyrido[2,3-b]pyrazin-5-yl)-pentyl]-tetrazol-1-yl}-propionitrile
A suspension of N-(2-cyanoethyl)-6-(2,3-di-p-tolyl-7,8-dihydropyrido[2,3-b]pyrazin-5(6H)-yl) hexanamide (step 1) (200 mg, 0.415 mmol) in acetonitrile (6 ml) was treated with sodium azide (29.7 mg, 0.457 mmol) followed by triflic anhydride (0.281 ml, 1.661 mmol) and the resulting yellow solution was stirred at room temperature for 2 days. The mixture was diluted with sat.$NaHCO_3$ (20 ml) and extracted with EtOAc (x2). The organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by chromatography on silica eluting with 20-100% EtOAc in iso-hexane afforded the titled compound;
LCMS; Rt 6.07 mins MS m/z 507 $[M+H]^+$; Method 10minLowpH.

Step 3: 5-(5-(1H-Tetrazol-5-yl)pentyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazine
A solution of 3-{5-[5-(2,3-di-p-tolyl-7,8-dihydro-6H-pyrido[2,3-b]pyrazin-5-yl)-pentyl]-tetrazol-1-yl}-propionitrile (step 2)(50 mg, 0.099 mmol) in MeOH (3 ml) was treated with 1M NaOH (0.296 ml, 0.296 mmol) and the resulting solution was stirred at room temperature for 16 hours. The reaction mixture was concentrated under vacuum. The residue was diluted with water, acidified (pH 4, 2N HCl) and extracted with EtOAc (x2). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to afford the titled compound as a solid;
LCMS; Rt 1.22 mins MS m/z 454.6 $[M+H]^+$; Method 2minLowpH.
^{1}H NMR (400 MHz, CHLOROFORM-*d*) d 7.33 (2 H, d) 7.21 (2 H, d) 7.09 (2 H, d) 7.04 (2 H, d) 3.73 - 3.68 (2 H, m) 3.47 - 3.43 (2 H, m) 3.06 (2 H, t) 2.75 (2 H, t) 2.37 (3 H, s) 2.31 (3 H, s) 2.10 (2 H, m) 1.82 (2 H, m) 1.72 - 1.68 (2 H, m) 1.37 (2 H, m)

Example 3:

***rac*-5-(6-(1H-Tetrazol-5-yl)hexyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol**



Step 1: *rac*-2,3-Di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol

rac-Tert-butyl 7-hydroxy-2,3-di-p-tolyl-7,8-dihydropyrido[2,3-b]pyrazine-5(6H)-carboxylate (Intermediate E) (6.9 g, 15.99 mmol) in MeCN (300 ml) was treated with 10% citric acid (aq) (92 g, 48.0 mmol) and heated at 40 °C for 48 h. . After cooling to RT, the MeCN was removed by distillation and the resulting suspension was collected by filtration and washed with water. The solid was dried under vacuum at 40 °C and suspended in EtOAc (25 ml). The suspension was collected by filtration to afford the titled compound;

LC-MS: Rt 1.03 mins; MS m/z 332.6 [M+H]+; Method 2minLowpH.

Step 2: *rac*-5-(Hex-5-enyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol

To a solution of *rac*-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol (step 1) (500 mg, 1.509 mmol) in DCE (15 ml) was added 5-hexenal (444 mg, 4.53 mmol) followed by sodium triacetoxyborohydride (959 mg, 4.53 mmol). After stirring at RT under an atmosphere of nitrogen overnight, the mixture was diluted with water (30 ml) and extracted with EtOAc (30 ml). The organic layer was separated, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a brown oil. Purification by chromatography on silica eluting with 0-60% EtOAc in iso-hexane afforded the title compound;

LC-MS: Rt 1.38 mins; MS m/z 414.1 [M+H]+; Method 2minLowpH.

Step 3: *rac*-(E)-5-(6-(1H-Tetrazol-5-yl)hex-5-enyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol

A mixture comprising *rac*-5-(hex-5-enyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,2-3]pyrazin-7-ol (step 2) (593 mg, 1.434 mmol) in THF (7.170 ml) at RT under nitrogen was treated with 5-vinyl-1H-tetrazole (Intermediate F) (438 mg, 4.56 mmol) and CuI (82 mg, 0.430 mmol). Grubbs II catalyst (243 mg, 0.287 mmol) was added portionwise over 20 minutes to the stirred mixture and stirring continued at RT for 2 hours. The mixture was heated to 40°C overnight and allowed to cool to RT. The solvent was removed under reduced pressure and purification by reverse phase C18 column chromatography eluting with MeCN in water afforded the titled compound; LC-MS: Rt 1.15 mins; MS m/z 482.4 [M+H]+; Method 2minLowpH.

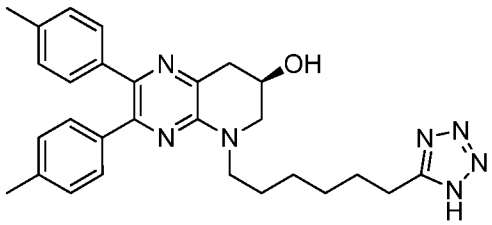
Step 4: *rac*-5-(6-(1H-Tetrazol-5-yl)hexyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol

To a solution of *rac-(*E)-5-(6-(1H-tetrazol-5-yl)hex-5-enyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol (step 3) (65 mg, 0.135 mmol) in EtOH (5 ml) was added 5% Pd/C (50% wet) (287 mg, 0.067 mmol) and the resulting mixture was placed under a positive pressure (0.35 bar) of hydrogen at RT for 2 hours. The mixture was filtered through Celite® (filter material) and washed with MeOH (~30 ml). The filtrate was concentrated under reduced pressure and purification of the crude product by chromatography on silica eluting with DCM/MeOH afforded the titled compound;

LC-MS: Rt 1.14 mins; MS m/z 484.4[M+H]+; Method 2minLowpH.

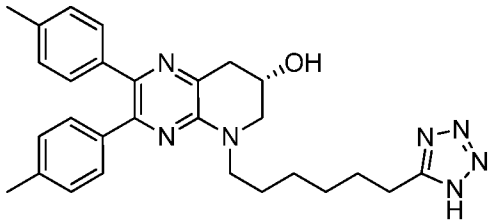
1H NMR dpx47914 (400MHz, CDCl3) δ 7.15 (2H,d) 7.10 (2H,d), 6.94 (4H,m), 4.24 (1H,m), 3.71 (1H,m), 3.35 (1H,d), 3.23 (2H,m), 3.04 (2H,m), 2.65 (2H,t), 2.22 (6H, s), 1.59 (2H,m), 1.48 (2H,m), 1.23 (4H,m)

Example 3a: *(R)*- or *(S)*-5-(6-(1H-tetrazol-5-yl)hexyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol] and Example 3b: *(R)*- or *(S)*-5-(6-(1H-tetrazol-5-yl)hexyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol]



(R) Stereoisomer

and



(S) Stereoisomer

Chiral separation of 5-(6-(1H-tetrazol-5-yl)hexyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol] (Racemate Example 3) using Supercritical Fluid Chromatography afforded the individual enantiomers:

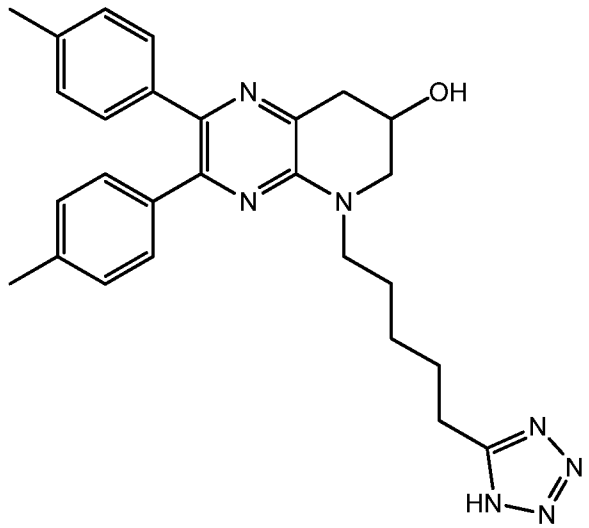
METHOD DETAILS:

Column:	2 x Phenomenex LUX C2 Coupled 250 x 10 mm, 5 um @ 35degC
Mobile phase:	50% Methanol / 50% CO_2
Flow:	10 ml/min
Detection:	UV @ 220 nm
Instrument:	Berger Minigram SFC2

Example 3a: First eluted peak: *(R)*-5-(6-(1H-Tetrazol-5-yl)hexyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol] or *(S)*-5-(6-(1H-Tetrazol-5-yl)hexyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol]
SFC Retention Time = 6.775 min
LCMS: Rt 1.12 mins MS m/z 484.6 [M+H]+; Method 2minLowpH

Example 3b: Second eluted peak: *(R)*-5-(6-(1H-Tetrazol-5-yl)hexyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol] or *(S)*-5-(6-(1H-Tetrazol-5-yl)hexyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol]
SFC Retention Time = 8.568 min
LCMS: Rt 1.13 mins MS m/z 484.2 [M+H]+; Method 2minLowpH

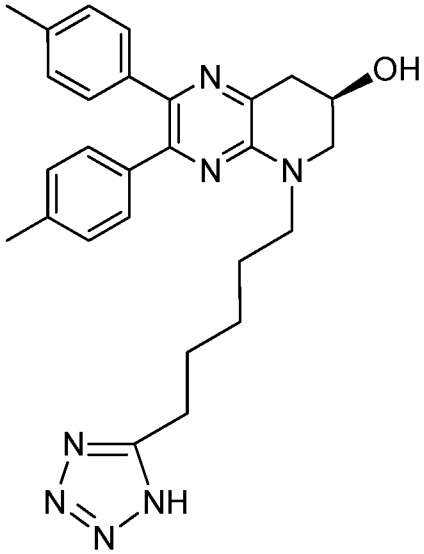
Example 4:
***rac*-5-(5-(1H-Tetrazol-5-yl)pentyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[3,2-b]pyrazin-7-ol**



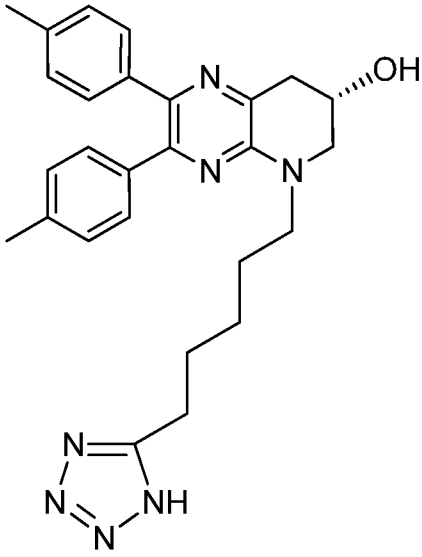
The title compound was prepared analogously *rac*-5-(6-(1H-tetrazol-5-yl)hexyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol (Example 3) by replacing 5-hexenal (step 2) with 4-pentenal;

LC-MS Rt =1.10 mins; [M+H]+ 470.4, Method 2minLowpH

Example 4a: *(R)*- or *(S)*-5-(5-(1H-Tetrazol-5-yl)pentyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol] and Example 4b: *(R)*- or *(S)*-5-(5-(1H-Tetrazol-5-yl)pentyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol]



and



(R)-stereoisomer

(S)-stereoisomer

Step 1: N-benzylhept-6-enamide

A solution of ethyl hept-6-enoate (5 g, 32.0 mmol), benzylamine (4.12 g, 38.4 mmol) and 1,5,7-Triazabicyclo[4,4,0]dec-5-ene (1.337 g, 9.60 mmol) was heated to 75°C for 3 hours. The mixture was cooled to RT and then diluted with diethyl ether (30 ml) and washed with 2M aqueous HCl. The organics were dried over MgSO4, filtered and the solvent removed under reduced pressue to afford the title compound:

Step 2: N-benzylhept-6-enethioamide

A solution of N-benzylhept-6-enamide (7.4 g, 34.1 mmol) in Tetrahydrofuran (50 ml) was treated with Lawesson's Reagent (3.58 g, 8.85 mmol). The reaction mixture was stirred at room temperature overnight. Further Lawesson's Reagent (3.58 g, 8.85 mmol) was added and stirring continued for 3 hours. The reaction mixture was then treated with Silica and the solvent removed under reduced pressure. Purification by chromatography eluting with 0-40% Ethyl Acetate in Iso-hexane afforded the title compound:

Step 3: 1-benzyl-5-(hex-5-enyl)-1H-tetrazole

A solution of N-benzylhept-6-enethioamide in THF (50 ml) was treated with SMOPEX-301 (103 g, 103 mmol) and then Di-tert-butyl azodicarboxylate (23.68 g, 103 mmol). Reaction mixture

was stirred at room temperature for 15 minutes then treated with Trimethylsilyl azide (13.65 ml, 103 mmol). The reaction mixture was stirred at room temperature for two days. The reaction mixture was then filtered, rinsing the SMOPEX with Ethyl Acetate. The filtrate was then evaporated to dryness under reduced pressure. Purification by chromatography eluting with 0-60% Ethyl Acetate in Iso-hexane afforded the title compound:

Step 3: 5-(1-benzyl-1H-tetrazol-5-yl)pentanal
A solution of 1-benzyl-5-(hex-5-en-1-yl)-1H-tetrazole (1.0g, 4.13 mmol) in THF (10 ml) and water (10 ml) was treated with Sodium periodate (2.65 g, 12.38 mmol), followed by the addition of Os EnCat (Reaxa) (206 mg, 0.041 mmol). The reaction mixture was stirred at room temperature over night. The reaction mixture was then treated with Ethyl Acetate (20 ml) and water (50 ml) and then filtered, rinsing the solid with water and Ethyl Acetate. The filtrate was separated and the organic layer washed with brine. The organics were dried over MgSO4 and the solvent removed under reduced pressure to afford the title compound.

Step 4: 5-(5-(1-benzyl-1H-tetrazol-5-yl)pentyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol
A suspension of *rac*-2,3-Di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol 1 (391 mg, 1.180 mmol) and 5-(1-benzyl-1H-tetrazol-5-yl)pentanal (576 mg, 2.359 mmol) in DCE was stirred at RT for 10 minutes and then treated wit Sodium triacetoxy borohydride (500mg, 2.35 mmol). Suspension was stirred at RT overnight. Reaction mixture ws then treated with water and stirred vigorously for 20 minutues and then diluted with Ethyl Acetate and brine. Organic layer was separated, dried over MgSO4 and filtered. Filtrate was treated with Silica gel and the suspension evaporated to dryness under reduced pressure. Purification by chromatography eluting with 0-15% tert-butyl-methylether followed by trituration using ether afforded the title compound:
LCMS; Rt 1.42 mins MS m/z 560.4 [M+H]+; Method 2minLowpHv01

Step 5: Example 4a: *(R)*- or *(S)*-5-(5-(1H-Tetrazol-5-yl)pentyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol] and Example 4b: *(R)*- or *(S)*-5-(5-(1H-Tetrazol-5-yl)pentyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol]
A solution of BAETTUR1-004-EXP038 (340 mg, 0.607 mmol) in EtOH (10ml), under nitrogen, was treated with AMMONIUM FORMATE (192 mg, 3.04 mmol) and 10% PALLADIUM ON CARBON (64.6 mg, 0.061 mmol). Black suspension was then heated at reflux for 6 hours, then

cooled to RT and stirred at RT for 16 hours, overnight. Reaction mixture waas then loaded onto a pre-packed 10g celite column. Column was eluted with a 1:1 ratio of EtOH : DCM. Solvent was collected and evaporated to dryness under reduced pressure. Resultant residue was dissolved in DCM (50ml) and washed with water (x2), passing the organics through a phase separating column. Organic solvent was reduced to dryness under reduced pressure to afford the titled compounds as a mix of enantiomers.

Chiral separation *rac*-5-(5-(1H-Tetrazol-5-yl)pentyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[3,2-b]pyrazin-7-ol (Racemate Example 4) using Supercritical Fluid Chromatography afforded the individual enantiomers:

METHOD DETAILS:

Column:	2 x Phenomenex LUX C2 250 x 10 mm, 5 um @ 35degC
Mobile phase:	35% Methanol+ 0.1% DEA / 65% CO_2
Flow:	10 ml/min
Detection:	UV @ 220 nm
Instrument:	Berger Minigram SFC2

Example 4a: First eluted peak: *(R)*-5-(5-(1H-Tetrazol-5-yl)pentyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol] or *(S)*-5-(5-(1H-Tetrazol-5-yl)pentyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol]
SFC Retention Time= 3.732 mins
LCMS: Rt 1.20mins MS m/z 470.5 [M+H]+ Method 2minLowpHv01
This compound was further purified by chromatography on silica eluting with 0-10% MeOH in DCM to afford *(R)*-5-(5-(1H-Tetrazol-5-yl)pentyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol] or *(S)*-5-(5-(1H-Tetrazol-5-yl)pentyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol];
LCMS: Rt 1.20mins MS m/z 470.6 [M+H]+ Method 2minLowpHv01

Example 4b: Second eluted Peak: *(R)*-5-(5-(1H-Tetrazol-5-yl)pentyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol] or *(S)*-5-(5-(1H-Tetrazol-5-yl)pentyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol]
SFC Retention Time= 4.655 mins
LCMS: Rt 1.20mins MS m/z 470.3/471.6 [M+H]+ Method 2minLowpHv01

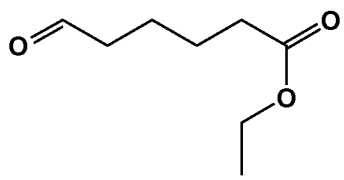
This compound was further purified by chromatography on silica eluting with 0-10% MeOH in DCM to afford *(R)*-5-(5-(1H-Tetrazol-5-yl)pentyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol] or *(S)*-5-(5-(1H-Tetrazol-5-yl)pentyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol];

LCMS:Rt 1.20mins MS m/z 470.7 [M+H]+ Method 2minLowpHv01

Preparation of Intermediates

Intermediate A

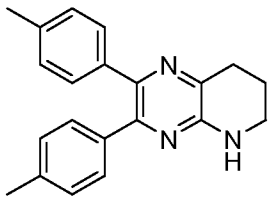
Ethyl 6-oxohexanoate



KBr (0.111 g, 0.936 mmol) in water (30 ml) was treated with sodium bicarbonate (4.72 g, 56.2 mmol). The solution was cooled (ice-bath) and treated with a solution of (2,2,6,6-tetramethyl piperidin-1-yl)oxidanyl (0.029 g, 0.187 mmol) in DCM (30 ml) followed by sodium hypochlorite (1.387 ml, 22.47 mmol) and ethyl 6-hydroxyhexaonate (3 g, 18.73 mmol). The reaction mixture was partitioned between EtOAc and water and the organic portion was separated, dried ($MgSO_4$) and concentrated under reduced pressure to afford the titled compound

Intermediate B

2,3-Di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazine



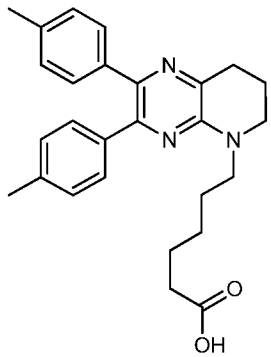
Step 1: 2,3-Di-p-tolylpyrido[2,3-b]pyrazine

A solution of 1,2-di-p-tolylethane-1,2-dione (commercially available)(175 g, 733 mmol) and pyridine-2,3-diamine (80 g, 733 mmol) in EtOH (1609 ml) and AcOH (179 ml) was heated to reflux (bath at 85 °C) for 1.5 h. The mixture was allowed to cool and concentrated *in vacuo*.

The crude material was dissolved in DCM (500 ml) and filtered through silica to remove baseline impurities. The silica was washed with EtOAc (2 L). The combined filtrate layers were concentrated *in vacuo* to give a brown solid. The material was triturated in 1:1 TBME/heptane (300 ml). The solid was removed by filtration and washed with 1:1 TBME/heptane (200 ml) before drying at RT over 2 days to afford the titled compound as an AcOH salt (1 eq).
HPLC (Agilent 1200), Rt 5.37 min, Method A.

Step 2: 2,3-Di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazine
A solution of 2,3-di-p-tolylpyrido[2,3-b]pyrazine (step 1)(181 g, 487 mmol) in EtOH/THF (1:2, 2100 ml) was treated with 10% palladium on carbon (30 g, 28.8 mmol) and the reaction mixture was placed under 0.1 bar of hydrogen at RT. After 2 days and 4 days respectively, additional batches of 10% palladium on carbon (10 g, 9.6 mmol, twice) were added along with Et_3N (85 ml, 706 mmol, twice). After 7 days in total, the reaction mixture was filtered through Hyflo (filter material) and washed through with THF (2.5 L in portions). The filtrate was concentrated *in vacuo* to give a green/yellow solid. The solid was triturated with 1:1 TBME/heptane (500 ml) and filtered. The solid was washed with 1:1 TBME/heptane (200 ml) to give a pale yellow solid which was dried overnight to afford the titled compound;
HPLC (Agilent 1200), Rt 4.73 min, Method A.

Intermediate C
6-(2,3-Di-p-tolyl-7,8-dihydropyrido[2,3-b]pyrazin-5(6H)-yl)hexanoic acid



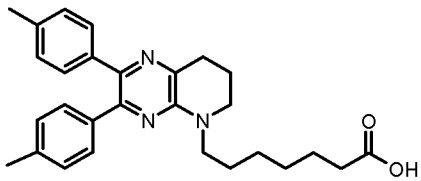
Step 1: Ethyl 6-(2,3-di-p-tolyl-7,8-dihydropyrido[2,3-b]pyrazin-5(6H)-yl)hexanoate
A solution of 2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazine (Intermediate B) (2.0 g, 6.34 mmol) and ethyl 6-oxohexanoate (Intermediate A) (2.508 g, 12.68 mmol) in 1,2-dichloroethane (50 ml) was treated with sodium triacetoxyborohydride (3.36 g, 15.85 mmol) and the resultant

suspension was stirred at room temperature overnight. The resulting solution was treated with sat.$NaHCO_3$ and extracted with DCM (x3). The organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was loaded onto an Isolute® SCX-2 cartridge and eluted with MeOH followed by 2M NH_3 in MeOH. The methanolic ammonia fractions were concentrated under reduced pressure and further purified by chromatography on silica eluting with 10-50% EtOAc in iso-hexane to afford the titled compound;
LCMS; Rt 1.44 mins MS m/z 458.4 $[M+H]^+$; Method 2minLowpH.

Step 2: 6-(2,3-Di-p-tolyl-7,8-dihydropyrido[2,3-b]pyrazin-5(6H)-yl)hexanoic acid
A solution of 6-ethoxy-6-oxohexyl 6-(2,3-di-p-tolyl-7,8-dihydropyrido[2,3-b]pyrazin-5(6H)-yl)hexanoate (step 1)(2.8 g, 6.12 mmol) in MeOH (50 ml) was treated with 1M sodium hydroxide (9.18 ml, 18.36 mmol) and the resulting white suspension was heated at 50 °C for 2 hours. The mixture was allowed to cool to room temperature and concentrated under reduced pressure. The residue was diluted with water, acidified (pH 4, 2N HCl) and extracted with DCM (x3). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to afford an oil which crystallized to yield the titled compound as an off-while solid;
^{1}H NMR (400 MHz, $CDCl_3$-d) δ 7.30 - 7.35 (2 H, m) 7.21 - 7.28 (2 H, m) 7.02 - 7.08 (4 H, m) 3.57 - 3.75 (2 H, m) 3.42 - 3.48 (2 H, m) 2.98 - 3.04 (2 H, m) 2.30 - 2.38 (8 H, m) 2.05 - 2.13 (2 H, m) 1.65 - 1.77 (4 H, m) 1.38 - 1.47 (2 H, m)
LCMS; Rt 6.24 mins MS m/z 430 $[M+H]^+$; Method 10minLowpH.

Intermediate D

7-(2,3-Di-p-tolyl-7,8-dihydropyrido[2,3-b]pyrazin-5(6H)-yl)heptanoic acid



Step 1: Ethyl 7-(2,3-di-p-tolyl-7,8-dihydropyrido[2,3-b]pyrazin-5(6H)-yl)heptanoate
To a solution of 2,3-Di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazine (Intermediate B) (10 g, 31.7 mmol) in DCE (300 ml) was added DIPEA (6.09 ml, 34.9 mmol) followed by ethyl 7-oxoheptanoate (10.92 g, 63.4 mmol). The mixture was stirred at RT for 10 minutes and sodium triacetoxyborohydride (16.80 g, 79 mmol) was added portionwise. The reaction mixture was heated at 40 °C overnight and then added slowly to water (500 ml) and stirred at RT for 10 minutes. The organic layer was separated and the aqueous layer extracted with

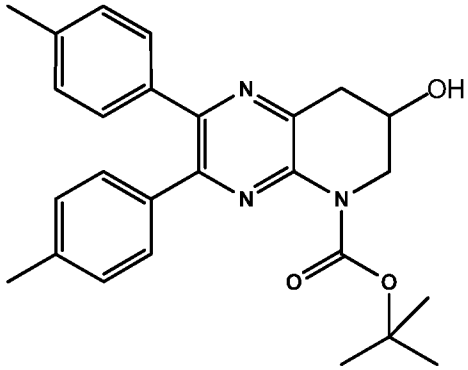
dichloromethane (2 x 200 ml). The combined organics were washed with brine (200 ml), dried over anhydrous sodium sulfate and concentrated *in vacuo* to give a pale yellow oil. Isolute Separtis SCX-2 (capture/ release super cation exchange resin) (222 g, 127 mmol) was added to a column and the product was loaded with MeOH (50 ml). The column was flushed with MeOH (750 L) followed by 2 N NH_3/MeOH (1000 ml, prepared from 280 ml 7 N + 720 ml MeOH) to afford the titled compound. No further purification was carried out;
HPLC (Agilent 1200) Rt 6.38 min, Method A

Step 2: 7-(2,3-Di-p-tolyl-7,8-dihydropyrido[2,3-b]pyrazin-5(6H)-yl)heptanoic acid

Ethyl 7-(2,3-di-p-tolyl-7,8-dihydropyrido[2,3-b]pyrazin-5(6H)-yl)heptanoate (step 1) was dissolved in THF (94 ml) and lithum hydroxide monohydrate (7.79 g, 186 mmol) in water (94 ml) was added dropwise. The reaction mixture was warmed to 50 °C and stirred for 7.5 hours.
The reaction mixture was concentrated *in vacuo* to remove the THF and diluted with water (500 ml). The pH of the aqueous layer was adjusted to pH 2 with 1 N HCl (100 ml) and extracted with EtOAc (3 x 500 ml). The combined organic layers were washed with brine (200 ml), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude solid was suspended in TBME/hexane (1:1, 100 ml) and rotated on the rotary evaporator (no vacuum) at RT until crystals formed. The solid was removed by filtration, washed with heptanes (50 ml) and dried at RT overnight. The solid was re-crystallized from a hot mixture of EtOH (211 ml) and water (159 ml). After seeding and stirring for 1 h at 5°C, the crystals were filtered off and the product dried overnight at 40°C in a vacuum oven to afford the title compound;
LCMS; Rt 4.54 mins MS m/z 444.4 $[M+H]^+$; Method 10minLC_v003
^{1}H NMR (400 MHz, DMSO-d6) δ 11.95 (1H, br s), 7.21(2H, d), 7.13 (2H, d), 7.07 (2H, d), 7.03 (2H, d), 3.57 (2H, m), 3.44 (2H, m), 2.88 (2H, t), 2.27 (3H, s), 2.26 (3H, s), 2.15 (2H, t), 2.00 (2H, m), 1.59 (2H, m), 1.47 (2H, m), 1.36-1.25 (4H, m).

Intermediate E

***rac*-Tert-butyl 7-hydroxy-2,3-di-p-tolyl-7,8-dihydropyrido[2,3-b]pyrazine-5(6H)-carboxylate**



Step 1: Tert-butyl 2,3-di-p-tolylpyrido[2,3-b]pyrazine-5(6H)-carboxylate

2,3-Di-p-tolylpyrido[2,3-bpyrazine (Intermediate B step 1) (2 g, 6.42 mmol) was dissolved in THF (15 ml). The mixture was degassed by bubbling through with nitrogen for 5 mins and 1M $LiAlH_4$ in THF (3.21 ml, 3.21 mmol) was added dropwise over ~ 3 minutes at 5°C (ice-bath). Di-t-butyl dicarbonate (2.80 g, 12.85 mmol) was added in DCM (15.00 ml) in a single portion and the resulting mixture was stirred at RT overnight. A further portion of di-t-butyl dicarbonate (1.4 g) was added and the mixture was warmed to 40 °C for 3h. Aqueous potassium sodium tartrate tetrahydrate "Rochelle's salt" (~ 10 ml; 10 % by wt) was added followed by DCM (20 ml) and the mixture was stirred vigorously for 10 min. The biphasic mixture was transferred to a separating funnel and the phases were separated. The organic portion was washed with Rochelles salt (30 ml), $NaHCO_3$ dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the crude product by chromatography on silica eluting with 0-40% TBME in iso-hexane afforded the titled compound;

LC-MS: Rt 1.35 mins; MS m/z 414.3 [M+H]+; Method 2minLowpH30.

Step 2: *rac*-Tert-butyl 7,8-dihydroxy-2,3-di-p-tolyl-7,8-dihydropyrido[2,3-b]pyrazine-5(6H)-carboxylate

N-Methylmorpholine oxide (17.00 g, 145 mmol) was charged to a 1L flask and treated with tert-butyl 2,3-di-p-tolylpyrido[2,3-b]pyrazine-5(6H)-carboxylate (step 1) (40 g, 97 mmol) followed by acetone (450 ml) and water (50.0 ml). The mixture was stirred at RT under N_2 to obtain a solution. To the flask was added the OsO_4 EnCat (encapsulated osmium tetroxide catalyst)(0.2 mmol/g) (4.84 g, 0.967 mmol) and the mixture was stirred at RT for 10 minutes then warmed to 40 °C. The mixture was stirred at 40 °C for 6 hours and then overnight. After heating for a further 6 hours, additional Os ENCat (250 mg) was added followed by N-methylmorpholine oxide (2 g, 0.17 eq). Stirring continued and after 2 hours, the reaction mixture was allowed to

cool to RT and filtered under vacuum, washing with acetone. The resulting filtrate was left to stand at RT over 2 days. MP-TMT (macroporous polystyrene-bound trimercaptotriazine- metal scavenger, 5 g) was added and after stirring for 5 minutes, the mixture was filtered. The filtrate was concentrated under reduced pressure. The crude product was suspended in EtOAc (~ 500 mL) and heated to reflux, producing a clear solution. After cooling to RT, water (300 ml) and MeOH (30 ml) were added. The resultant biphasic mixture was separated and the organic portion was washed with sat. ammonium hydrochloride solution (200 ml), dried over $MgSO_4$ and concentrated under reduced pressure to afford a yellow solid. The solid was suspended in acetone (450 mL) and heated to 57°C and stirred overnight. The mixture was allowed to cool to RT and placed in fridge for 2-3 hours.. The resultant solid was filtered under suction, washing with minimum quantity of EtOAc to give an off- white solid, which was dried in vacuum oven @ 40 °C to afford the titled compound;
LC-MS: Rt 1.22 mins; MS m/z 448.4 [M+H]+; Method 2minLowpH.

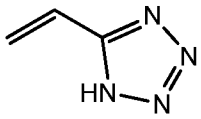
Step 3: *rac*-tert-Butyl 2-thioxo-7,8-di-p-tolyl-3a,4-dihydro-[1,3]dioxolo[4',5':4,5]pyrido[2,3-b]pyrazine-5(9bH)-carboxylate
rac-Tert-butyl 7,8-dihydroxy-2,3-di-p-tolyl-7,8-dihydropyrido[2,3-b]pyrazine-5(6H)-carboxylate (step 2)(1.28 g, 2.86 mmol) in THF (50 ml) was treated with 1,1'-thiocarbonyldiimidazole (1.019 g, 5.72 mmol) and the resulting solution was heated at reflux for 3 hours. After cooling to RT, the solvent was removed under reduced pressure and the crude residue was partitioned between DCM (300 ml) and water. The organic layer was separated and evaporated under reduced pressure. EtOAc was added to the residue and the mixture was filtered. The solid was washed with EtOAc (2 x 5 ml) to afford the titled compound;
LC-MS: Rt 1.35 mins; MS m/z 434.2 [M+H]+; Method 2minLowpH

Step 4: *rac*-tert-Butyl 7-hydroxy-2,3-di-p-tolyl-7,8-dihydropyrido[2,3-b]pyrazine-5(6H)-carboxylate
A suspension of *rac*-tert-butyl 2-thioxo-7,8-di-p-tolyl-3a,4-dihydro-[1,3]dioxolo[4',5':4,5] pyrido[2,3-b]pyrazine-5(9bH)-carboxylate (step 3) (14 g, 28.6 mmol) in toluene (400 ml) was treated with tributyltin hydride (16.65 g, 57.2 mmol) and heated at reflux for 2 hours. A further portion of tributyltin hydride (10 g) was added and refluxing continued for 6 hours and the mixture was stirred at RT overnight. The solvent was removed under reduced pressure and the residue was suspended in iso-hexane (250 ml) and stirred for 30 mins. The suspension was collected by filtration was washed with iso-hexane (3 x 50 ml). The solid was stirred in tert-butyl

methyl ether (250 ml) for 30 minutes and collected by filtration and washed with further tert-butyl methyl ether to afford the title compound;
LC-MS: Rt 1.25 mins; MS m/z 432.5 [M+H]+; Method 2minLowpH

Intermediate F

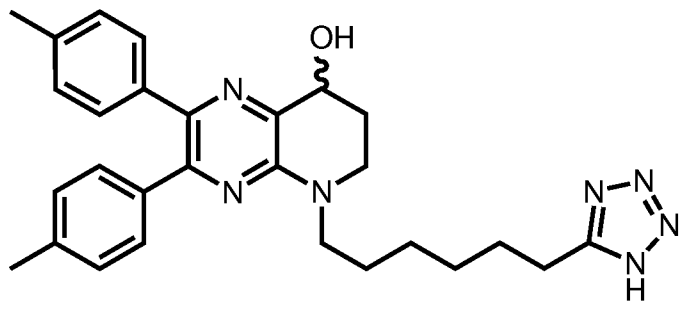
5-Vinyl-1H-tetrazole

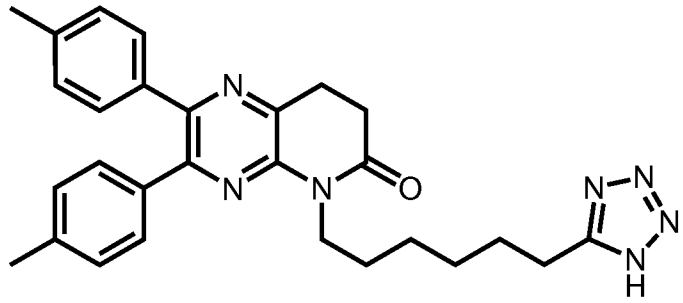
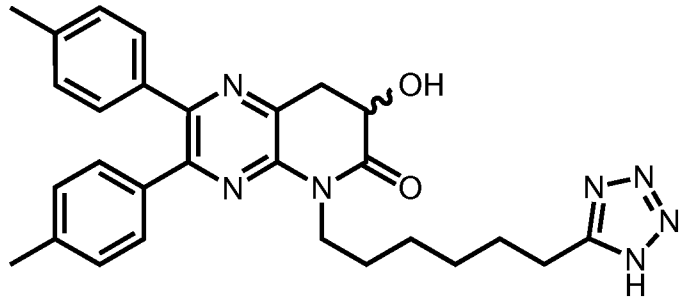
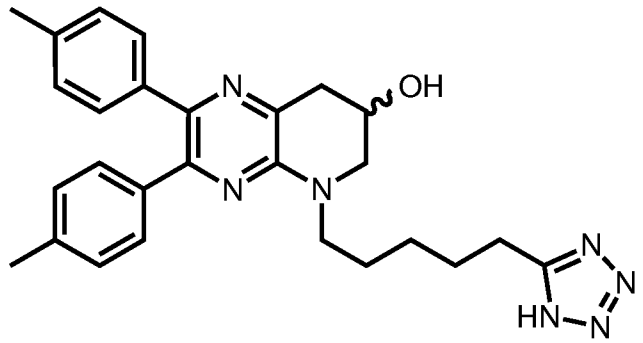
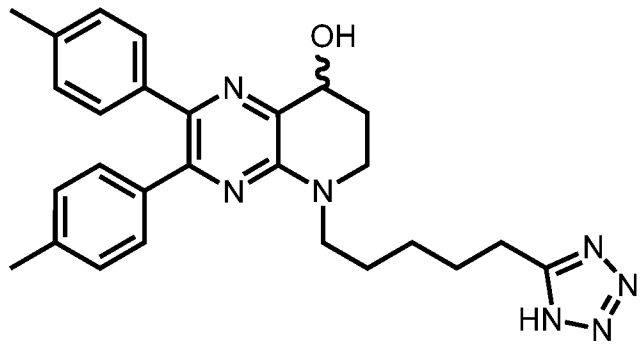


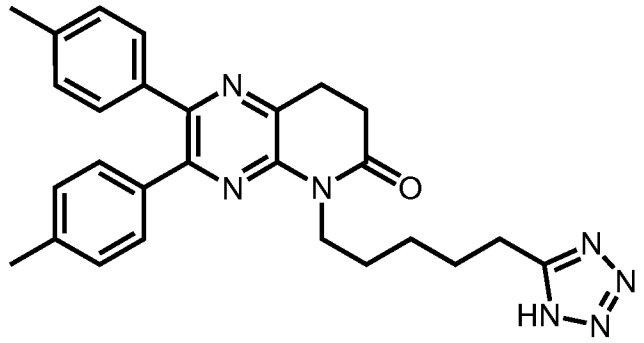
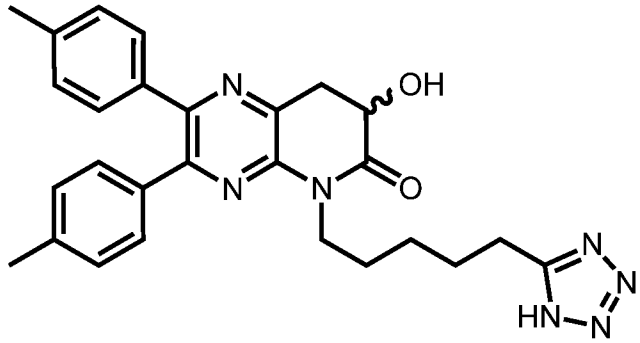
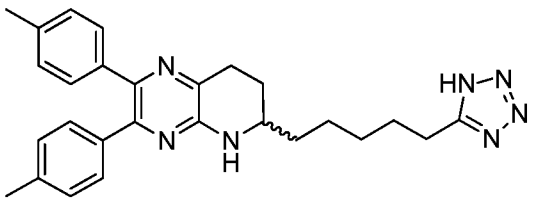
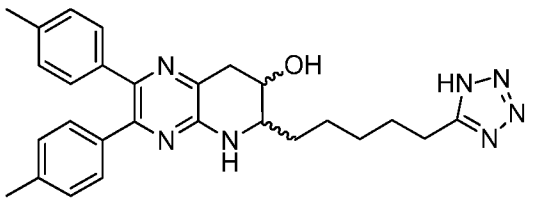
To a flask of $AlCl_3$ (2.51 g, 18.85 mmol) was added dropwise THF (40 ml) followed by portionwise addition of sodium azide (4.90 g, 75 mmol) and acrylonitrile (1 g, 18.85 mmol). The resulting mixture was placed under an atmosphere of nitrogen and stirred at reflux overnight. After cooling to RT, 15% HCl(aq) was added dropwise and the mixture was purged with nitrogen. The reaction mixture was partitioned between EtOAc (60 ml) and water (60 ml). The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a solid. Recrystallisation of the solid from chloroform afforded the titled compound.

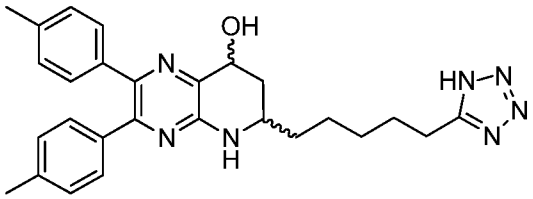
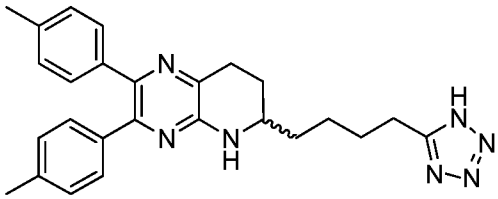
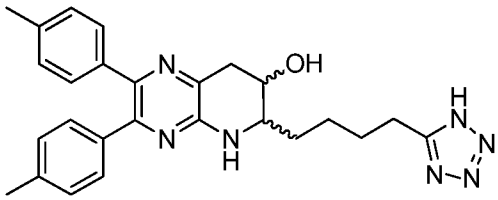
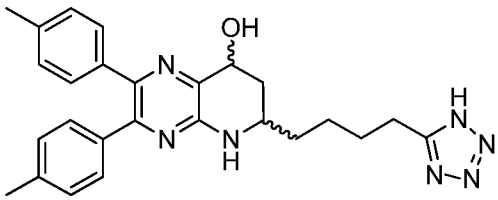
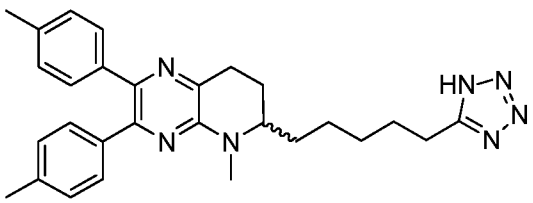
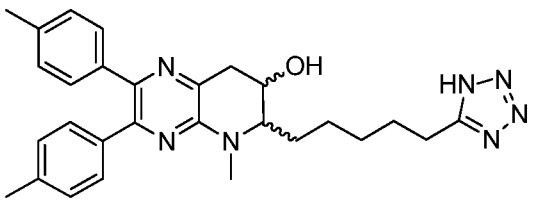
Prophetic compounds

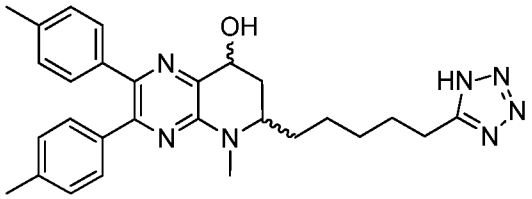
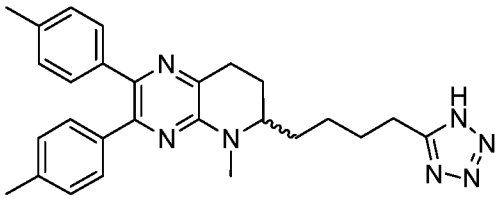
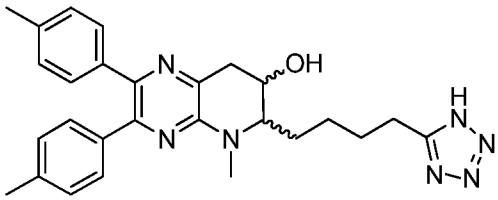
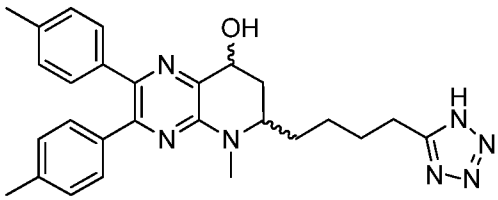
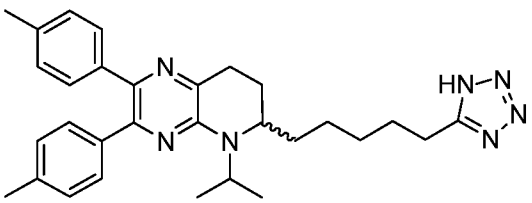
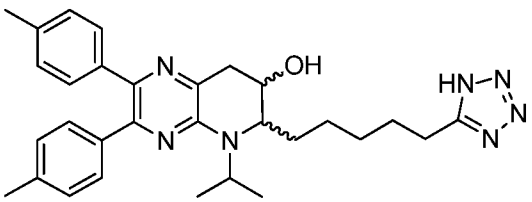
The following compounds may be prepared according to methods as described herein or as disclosed in PCT patent application PCT/EP2011/062028 (WO 2012/007539).

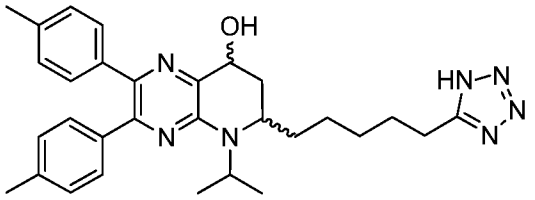
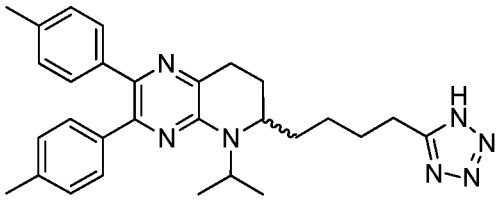
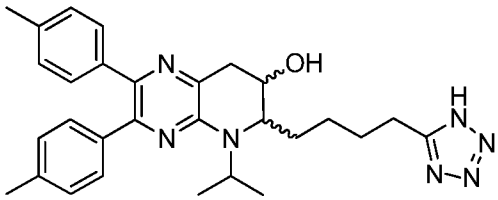
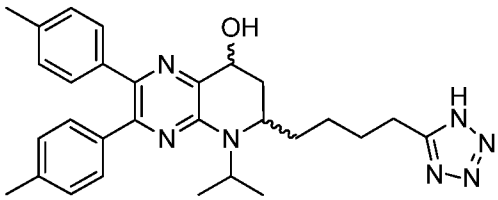
Structure	Name
	(rac or R or S)-5-(6-(1H-tetrazol-5-yl)hexyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-8-ol

	5-(6-(1H-tetrazol-5-yl)hexyl)-2,3-di-p-tolyl-7,8-dihydropyrido[2,3-b]pyrazin-6(5H)-one
	(rac or R or S)-5-(6-(1H-tetrazol-5-yl)hexyl)-7-hydroxy-2,3-di-p-tolyl-7,8-dihydropyrido[2,3-b]pyrazin-6(5H)-one
	(rac or R or S)- 5-(5-(1H-tetrazol-5-yl)pentyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol
	(rac or R or S)5-(5-(1H-tetrazol-5-yl)pentyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-8-ol

	5-(5-(1H-tetrazol-5-yl)pentyl)-2,3-di-p-tolyl-7,8-dihydropyrido[2,3-b]pyrazin-6(5H)-one
	(rac or R or S)-5-(5-(1H-tetrazol-5-yl)pentyl)-7-hydroxy-2,3-di-p-tolyl-7,8-dihydropyrido[2,3-b]pyrazin-6(5H)-one
	6-(5-(1H-Tetrazol-5-yl)pentyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazine
	6-(5-(1H-Tetrazol-5-yl)pentyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol

	6-(5-(1H-Tetrazol-5-yl)pentyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-8-ol
	6-(4-(1H-Tetrazol-5-yl)butyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazine
	6-(4-(1H-Tetrazol-5-yl)butyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol
	6-(4-(1H-Tetrazol-5-yl)butyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-8-ol
	6-(5-(1H-Tetrazol-5-yl)pentyl)-5-methyl-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazine
	6-(5-(1H-Tetrazol-5-yl)pentyl)-5-methyl-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol

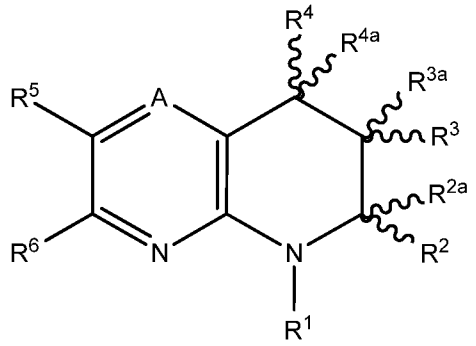
	6-(5-(1H-Tetrazol-5-yl)pentyl)-5-methyl-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-8-ol
	6-(4-(1H-Tetrazol-5-yl)butyl)-5-methyl-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazine
	6-(4-(1H-Tetrazol-5-yl)butyl)-5-methyl-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol
	6-(4-(1H-Tetrazol-5-yl)butyl)-5-methyl-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-8-ol
	6-(5-(1H-Tetrazol-5-yl)pentyl)-5-isopropyl-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazine
	6-(5-(1H-Tetrazol-5-yl)pentyl)-5-isopropyl-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol

	6-(5-(1H-Tetrazol-5-yl)pentyl)-5-isopropyl-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-8-ol
	6-(4-(1H-Tetrazol-5-yl)butyl)-5-isopropyl-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazine
	6-(4-(1H-Tetrazol-5-yl)butyl)-5-isopropyl-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol
	6-(4-(1H-Tetrazol-5-yl)butyl)-5-isopropyl-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-8-ol

From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

Consistory Clauses

Embodiment 1. A compound represented by Formula I



(I)

or a pharmaceutically acceptable salt thereof, wherein

A is N or CR';

R' is H, C_1-C_8 alkyl optionally substituted by one or more halogen atoms;

R^1 is selected from H; C_1-C_8 alkyl optionally substituted by one or more halogen atoms, OH, C_1-C_4 alkoxy, C_3-C_7 cycloalkyl or C_3-C_7 cycloalkyloxy; -(C_2-C_4 alkyl)-$NR^{19}R^{21}$ and C_3-C_7 cycloalkyl; or

R^1 is -X-Y; or

R^1 is -W-R^7-X-Y; or

R^1 is –$S(O)_2$-X-Y; or

R^1 is –$S(O)_2$-W-R^7-X-Y;

R^2 is selected from H; C_1-C_8 alkyl optionally substituted by one or more halogen atoms, OH, C_1-C_4 alkoxy, C_3-C_7 cycloalkyl or C_3-C_7 cycloalkyloxy; -(C_1-C_4 alkyl)-$NR^{19}R^{21}$ and C_3-C_7 cycloalkyl; or

R^2 is -X-Y; or

R^2 is -W-R^7-X-Y; or

R^2 is –$S(O)_2$- X-Y; or

R^2 is –$S(O)_2$-W-R^7-X-Y;

R^{2a} is selected from H; C_1-C_8 alkyl optionally substituted by one or more halogen atoms, OH, C_1-C_4 alkoxy, C_3-C_7 cycloalkyl or C_3-C_7 cycloalkyloxy; and C_3-C_7 cycloalkyl; or

R^2 and R^{2a} taken together are oxo;

wherein either R^1 or R^2 is -X-Y, -W-R^7-X-Y, –$S(O)_2$- X-Y; or –$S(O)_2$-W-R^7-X-Y;

R^3 is selected from H; OH; C_1-C_8 alkyl optionally substituted by one or more halogen atoms, OH, C_1-C_4 alkoxy, C_3-C_7 cycloalkyl or C_3-C_7 cycloalkyloxy; C_1-C_4 alkoxy; OR'; -(C_0-C_4alkyl)-$NR^{19}R^{21}$; CN; halogen and C_3-C_7 cycloalkyl;

R^{3a} is selected from H; C_1-C_8 alkyl optionally substituted by one or more halogen atoms, OH, C_1-C_4 alkoxy, C_3-C_7 cycloalkyl or C_3-C_7 cycloalkyloxy; and C_3-C_7 cycloalkyl; or

R^3 and R^{3a} taken together are oxo;

R^4 is selected from H; OH; C_1-C_8 alkyl optionally substituted by one or more halogen atoms, OH, C_1-C_4 alkoxy, C_3-C_7 cycloalkyl or C_3-C_7 cycloalkyloxy; C_1-C_4 alkoxy; OR'; -(C_0-C_4alkyl)-$NR^{19}R^{21}$; CN; halogen and C_3-C_7 cycloalkyl;

R^{4a} is selected from H; C_1-C_8 alkyl optionally substituted by one or more halogen atoms, OH, C_1-C_4 alkoxy, C_3-C_7 cycloalkyl or C_3-C_7 cycloalkyloxy; and C_3-C_7 cycloalkyl; or

R^4 and R^{4a} taken together are oxo;

R^5 and R^6 are independently selected from -(C_0-C_4 alkyl)-C_6-C_{14} aryl and -(C_0-C_4 alkyl)-4 to 14 membered heteroaryl, wherein the aryl and heteroaryl are each optionally substituted by one or more Z substituents;

W is C_1-C_8 alkylene optionally substituted by hydroxy, halogens or C_1-C_4 alkyl;

X is C_1-C_8 alkylene optionally substituted by hydroxy, halogens or C_1-C_4 alkyl;

Y is tetrazolyl;

R^7 is a divalent moiety represented by -O-, -S-, -NHC(O)-, -CH_2=CH_2-, -C_6-C_{14} aryl-D-; -3 to 14 membered heterocyclyl-D-, wherein the heterocyclyl contains at least one heteroatom selected from N, O and S, wherein D is O, S, NH or not present;

Z is independently OH, aryl, O-aryl, benzyl, O-benzyl, C_1-C_6 alkyl optionally substituted by one or more OH groups or NH_2 groups, C_1-C_6 alkyl optionally substituted by one or more halogen atoms, C_1-C_6 alkoxy optionally substituted by one or more OH groups, C_1-C_6 alkoxy optionally substituted by one or more halogen, C_1-C_6 alkoxy optionally substituted by C_1-C_4 alkoxy, $NR^{18}(SO_2)R^{21}$, $(SO_2)NR^{19}R^{21}$, $(SO_2)R^{21}$, $NR^{18}C(O)R^{21}$, $C(O)NR^{19}R^{21}$, $NR^{18}C(O)NR^{19}R^{21}$, $NR^{18}C(O)OR^{19}$, $NR^{19}R^{21}$, $C(O)OR^{19}$, $C(O)R^{19}$, SR^{19}, OR^{19}, oxo, CN, NO_2, halogen or a 3 to 14 membered heterocyclyl, wherein the heterocyclyl contains at least one heteroatom selected from N, O and S;

R^{18} is independently H or C_1-C_6 alkyl;

R^{19} and R^{21} are each independently H; C_1-C_8 alkyl; C_3-C_8 cycloalkyl; C_1-C_4 alkoxy-C_1-C_4 alkyl; (C_0-C_4 alkyl)-aryl optionally substituted by one or more groups selected from C_1-C_6 alkyl, C_1-C_6 alkoxy and halogen; (C_0-C_4 alkyl)- 3- to 14-membered heterocyclyl, the heterocyclyl including one or more heteroatoms selected from N, O and S, optionally substituted by one or more groups selected from halogen, oxo, C_1-C_6 alkyl and C(O)C_1-C_6 alkyl; (C_0-C_4 alkyl)-O-aryl optionally substituted by one or more groups selected from C_1-C_6 alkyl, C_1-C_6 alkoxy and halogen; and (C_0-C_4 alkyl)- O-3- to 14-membered heterocyclyl, the heterocyclyl including one or

more heteroatoms selected from N, O and S, optionally substituted by one or more groups selected from halogen, C_1-C_6 alkyl or C(O)C_1-C_6 alkyl; wherein the alkyl groups are optionally substituted by one or more halogen atoms, C_1-C_4 alkoxy, $C(O)NH_2$, C(O)NHC_1-C_6 alkyl or C(O)N(C_1-C_6 alkyl)$_2$; or

R^{19} and R^{21} together with the nitrogen atom to which they attached form a 5- to 10-membered heterocyclyl, the heterocyclyl including one or more further heteroatoms selected from N, O and S, the heterocyclyl being optionally substituted by one or more substituents selected from OH; halogen; aryl; 5- to 10-membered heterocyclyl including one or more heteroatoms selected from N, O and S; $S(O)_2$-aryl; $S(O)_2$-C_1-C_6 alkyl; C_1-C_6 alkyl optionally substituted by one or more halogen atoms; C_1-C_6 alkoxy optionally substituted by one or more OH groups or C_1-C_4 alkoxy; and C(O)OC_1-C_6 alkyl, wherein the aryl and heterocyclyl substituent groups are themselves optionally substituted by C_1-C_6 alkyl, C_1-C_6 haloalkyl or C_1-C_6 alkoxy.

Embodiment 2. The compound according to embodiment 1, wherein

either R^1 or R^2 is -X-Y or -W-R^7-X-Y;

W is C_1-C_6 alkylene optionally substituted by hydroxy, halogens or C_1-C_4 alkyl;

X is C_1-C_6 alkylene optionally substituted by hydroxy, halogens or C_1-C_4 alkyl;

R' is H, C_1-C_4 alkyl optionally substituted by one or more halogen atoms;

R^7 is a divalent moiety represented by -C_6-C_{14} aryl-D-; -3 to 14 membered heterocyclyl-D-, wherein the heterocyclyl contains at least one heteroatom selected from N, O and S, wherein D is O.

Embodiment 3: The compound according to embodiment 1 or 2, wherein

either R^1 or R^2 is -X-Y;

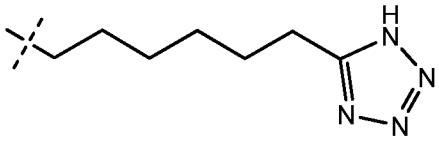
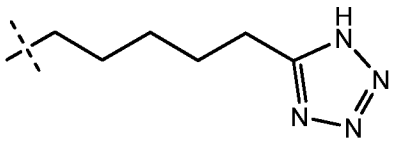
X is C_1-C_6 alkylene optionally substituted by hydroxy, halogens or C_1-C_4 alkyl.

Embodiment 4: The compound according to any one of embodiments 1 to 3, wherein

either R^1 or R^2 is -$(CH_2)_m$-tetrazolyl;

m is 1, 2, 3, 4, 5, 6, 7 or 8.

Embodiment 5: The compound according to an one of embodiments 1 to 4, wherein

either R^1 or R^2 is  or  .

Embodiment 6: The compound according to any one of embodiments 1 to 5, wherein

R^2 and R^{2a} are independently selected from H and C_1-C_4 alkyl optionally substituted by one or more halogen atoms or OH; or R^2 and R^{2a} taken together are oxo;

R^3 and R^{3a} are independently selected from H; C_1-C_4 alkyl optionally substituted by one or more halogen atoms or OH; and OH; or R^3 and R^{3a} taken together are oxo;

R^4 and R^{4a} are independently selected from H; C_1-C_4 alkyl optionally substituted by one or more halogen atoms or OH; and OH; or R^4 and R^{4a} taken together are oxo.

Embodiment 7: The compound according to any one of embodiments 1 to 6, wherein

R^2 and R^{2a} are H; or

R^2 and R^{2a} taken together are oxo;

R^3 and R^{3a} are independently selected from H and OH;

R^4 and R^{4a} are independently selected from H and OH.

Embodiment 8: The compound according to any one of the preceding embodiments, wherein

R^5 and R^6 are independently selected from C_6-C_{14} aryl and 5 to 6 membered heteroaryl, wherein the heteroaryl contains at least one heteroatom selected from N, O and S, wherein the aryl and heteroaryl are each optionally substituted by one or more Z substituents.

Embodiment 9: The compound according to any one of embodiments 1 to 8, wherein

R^5 and R^6 are independently selected from phenyl; 2-pyridyl, 3-pyridyl, or 4-pyridyl, wherein the phenyl, 2-pyridyl, 3-pyridyl, and 4-pyridyl are each optionally substituted by one or more Z substituents.

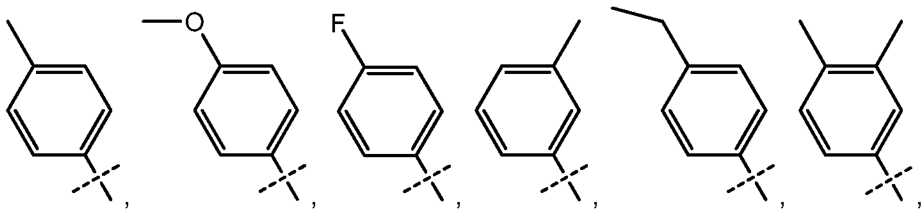
Embodiment 10: The compound according to any one of the embodiments 1 to 9, wherein R^5 and R^6 are independently selected from phenyl optionally substitued by OH, C_1-C_4 alkyl optionally substituted by one or more OH groups or NH_2 groups; C_1-C_4 alkyl optionally substituted by one or more halogen atoms; C_1-C_4 alkoxy optionally substituted by one or more OH groups or C_1-C_4 alkoxy; $NR^{19}R^{21}$; $C(O)OR^{19}$; $C(O)R^{19}$; SR^{19}; OR^{19}; CN; NO_2; and halogen.

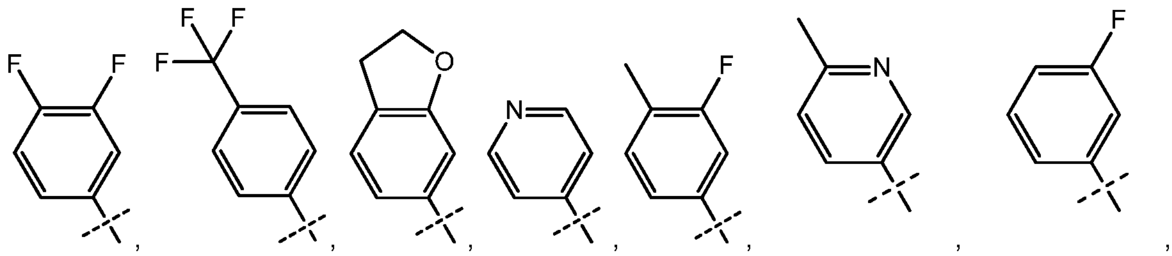
Embodiment 11: The compound according to any one of embodiments 1 to 10, wherein R^5 and R^6 are independently selected from phenyl optionally substituted by C_1-C_4 alkyl optionally substituted by one or more OH groups or NH_2 groups; C_1-C_4 alkyl optionally substituted by one or more halogen atoms; C_1-C_4 alkoxy optionally substituted by one or more OH groups or C_1-C_4 alkoxy; and halogen.

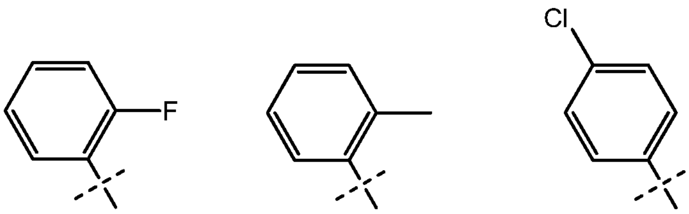
Embodiment 12: The compound according to any one of embodiments 1 to 11, wherein R^5 and R^6 are independently selected from phenyl optionally substituted by C_1-C_4 alkoxy or halogen, and C_1-C_4 alkyl optionally substituted by one or more halogen atoms.

Embodiment 13: The compound according to any one of embodiments 1 to 12, wherein R^5 and R^6 are independently selected from phenyl optionally substituted by methyl, ethyl, trifluoromethyl, methoxy or halogen.

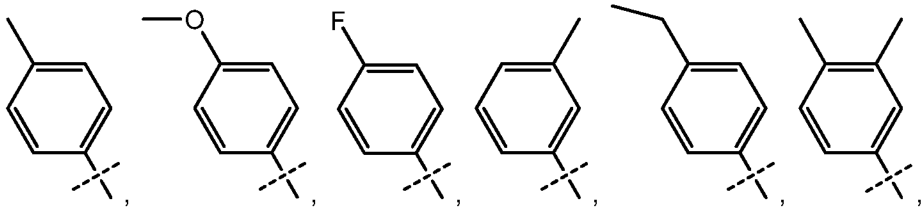
Embodiment 14: The compound according to any one of embodiments 1 to 13, wherein

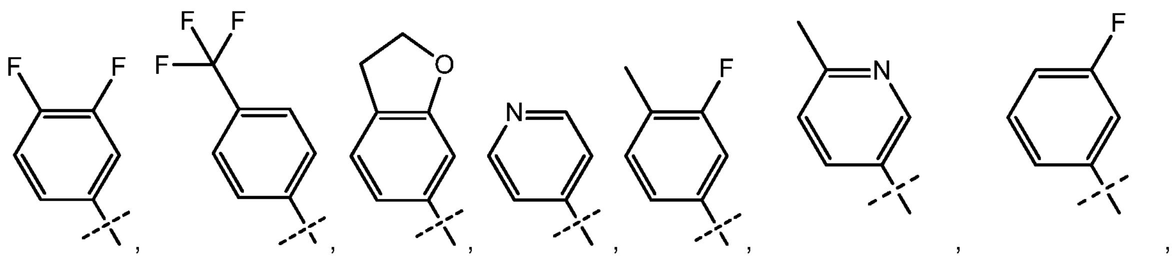
R^5 is 

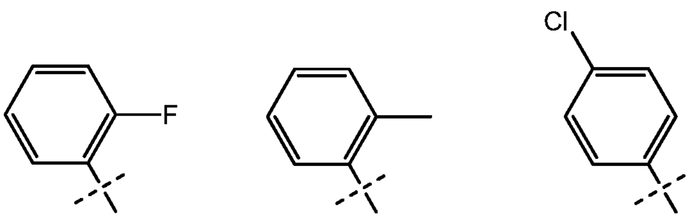




, or ; and

R^6 is 





, or .

Embodiment 15: The compound according to any one of embodiments 1 to 14, wherein

R^3, R^{3a}, R^4 and R^{4a} are independently selected from H, OH, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_3-C_6 cycloalkyl, CN and halogen.

Embodiment 16: The compound according to any one of embodiments 1 to 15, wherein

R^3, R^{3a}, R^4 and R^{4a} are independently H, OH, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_3-C_5 cycloalkyl and halogen.

Embodiment 17: The compound according to any one of embodiments 1 to 16, wherein

R^3, R^{3a}, R^4 and R^{4a} are independently selected from H, OH, methyl, ethyl, isopropyl, tert-butyl, methoxy, ethoxy, propoxy, butoxy, cyclopropyl, fluorine, bromine and chlorine.

Embodiment 18: The compound according to any one of embodiments 1 to 9, wherein

Z is independently selected from OH, C_6-aryl, O-C_6-aryl, benzyl, O-benzyl, C_1-C_4 alkyl optionally substituted by one or more OH groups or NH_2 groups, C_1-C_4 alkyl optionally substituted by one or more halogen atoms, C_1-C_4 alkoxy optionally substituted by one or more OH groups or C_1-C_4 alkoxy, $NR^{18}(SO_2)R^{21}$, $(SO_2)NR^{19}R^{21}$, $(SO_2)R^{21}$, $NR^{18}C(O)R^{21}$, $C(O)NR^{19}R^{21}$, $NR^{18}C(O)NR^{19}R^{21}$, $NR^{18}C(O)OR^{19}$, $NR^{19}R^{21}$, $C(O)OR^{19}$, $C(O)R^{19}$, SR^{19}, OR^{19}, oxo, CN, NO_2, halogen and a 4 to 6 membered heterocyclyl, wherein the heterocyclyl contains at least one heteroatom selected from N, O and S;

R^{18} is H or C_1-C_4 alkyl;

R^{19} and R^{21} are each independently selected from H; C_1-C_4 alkyl; C_3-C_6 cycloalkyl; C_1-C_4 alkoxy-C_1-C_4 alkyl; (C_0-C_4 alkyl)-aryl optionally substituted by one or more groups selected from C_1-C_4 alkyl, C_1-C_4 alkoxy and halogen; (C_0-C_4 alkyl)- 4- to 6-membered heterocyclyl, the heterocyclyl including one or more heteroatoms selected from N, O and S, optionally substituted by one or more groups selected from halogen, oxo, C_1-C_4 alkyl and $C(O)C_1$-C_4 alkyl; (C_0-C_4 alkyl)-O-aryl optionally substituted by one or more groups selected from C_1-C_6 alkyl, C_1-C_6 alkoxy and halogen; and (C_0-C_4 alkyl)- O-3- to 14-membered heterocyclyl, the heterocyclyl including one or more heteroatoms selected from N, O and S, optionally substituted by one or more groups selected from halogen, C_1-C_6 alkyl or $C(O)C_1$-C_6 alkyl; wherein the alkyl groups are optionally substituted by one or more halogen atoms, C_1-C_4 alkoxy, $C(O)NH_2$, $C(O)NHC_1$-C_6 alkyl or $C(O)N(C_1$-C_6 alkyl$)_2$; or

R^{19} and R^{21} together with the nitrogen atom to which they are attached form a 5- to 6-membered heterocyclyl, the heterocyclyl including one or more further heteroatoms selected from N, O and S, the heterocyclyl being optionally substituted by one or more substituents selected from OH; halogen; aryl; 5- to 6-membered heterocyclyl including one or more heteroatoms selected from N, O and S; $S(O)_2$-aryl; $S(O)_2$-C_1-C_6 alkyl; C_1-C_6 alkyl optionally substituted by one or more halogen atoms; C_1-C_4 alkoxy optionally substituted by one or more OH groups or C_1-C_4 alkoxy; and C(O)OC_1-C_6 alkyl, wherein the aryl and heterocyclyl substituent groups are themselves optionally substituted by C_1-C_6 alkyl, C_1-C_6 haloalkyl or C_1-C_6 alkoxy.

Embodiment 19: The compound according to any one of embodiments 1 to 9, wherein

Z is independently OH, C_1-C_4 alkyl optionally substituted by one or more OH groups or NH_2 groups, C_1-C_4 alkyl optionally substituted by one or more halogen atoms, C_1-C_4 alkoxy optionally substituted by one or more OH groups or C_1-C_4 alkoxy, $NR^{19}R^{21}$, $C(O)OR^{19}$, $C(O)R^{19}$, SR^{19}, OR^{19}, CN, NO_2, or halogen;

R^{19} and R^{21} are each independently H; C_1-C_4 alkyl; C_3-C_6 cycloalkyl; or C_1-C_4 alkoxy-C_1-C_4 alkyl, wherein all alkyls are optionally substituted with halogens.

Embodiment 20: The compound according to any one of embodiments 1 to 9, wherein

Z is independently OH, C_1-C_4 alkyl optionally substituted by one or more OH groups or NH_2 groups, C_1-C_4 alkyl optionally substituted by one or more halogen atoms, C_1-C_4 alkoxy optionally substituted by one or more OH groups or C_1-C_4 alkoxy, $C(O)OR^{19}$, $C(O)R^{19}$, OR^{19}, CN, or halogen;

R^{19} is H; C_1-C_4 alkyl; C_3-C_6 cycloalkyl; or C_1-C_4 alkoxy-C_1-C_4 alkyl, wherein all alkyl are optionally substituted with halogens.

Embodiment 21: The compound according to any one of embodiments 1 to 9, wherein

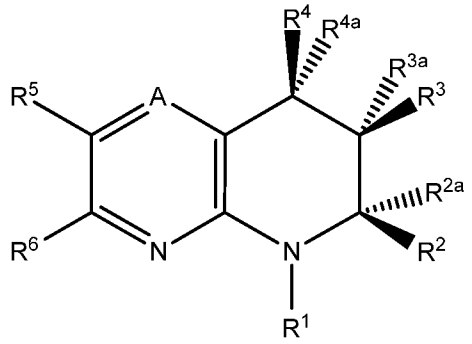
Z is independently, C_1-C_4 alkyl optionally substituted by one or more halogen atoms, C_1-C_4 alkoxy or halogen;

Embodiment 22: The compound according to any one of embodiments 1 to 21, wherein A is N.

Embodiment 23: The compound according to any one of embodiments 1 to 22, wherein A is CR'.

Embodiment 24: The compound according to embodiment 23, wherein R' is H.

Embodiment 25: The compound according to embodiment 1 to 24, wherein formula (I) has the following stereochemistry:



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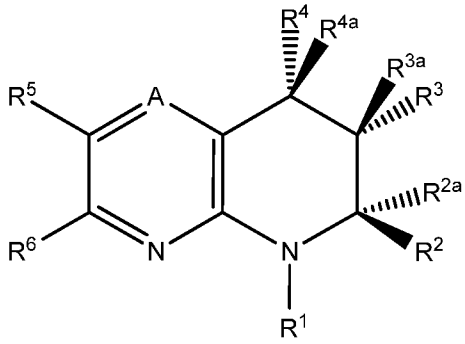

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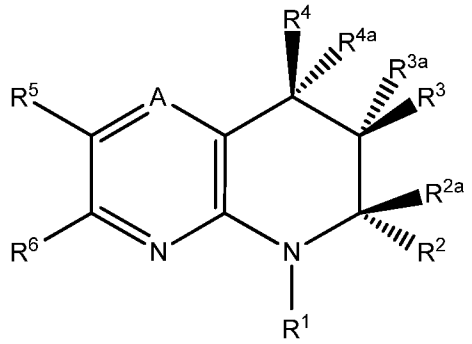

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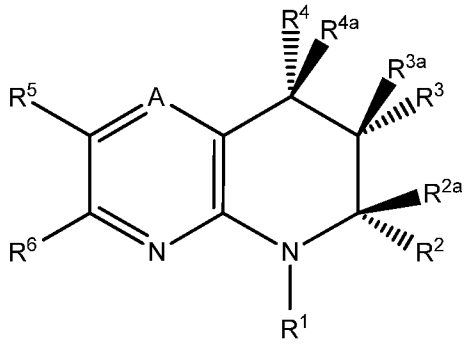


(I)''''.

Embodiment 26: The compound according to embodiment 1, wherein the compound is selected from

5-(6-(1H-Tetrazol-5-yl)hexyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazine;

5-(5-(2H-Tetrazol-5-yl)pentyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazine;

5-(6-(1H-Tetrazol-5-yl)hexyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[3,2-b]pyrazin-7-ol;

(rac or R or S)-5-(6-(1H-tetrazol-5-yl)hexyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-8-ol;

5-(6-(1H-tetrazol-5-yl)hexyl)-2,3-di-p-tolyl-7,8-dihydropyrido[2,3-b]pyrazin-6(5H)-one;

(rac or R or S)-5-(6-(1H-tetrazol-5-yl)hexyl)-7-hydroxy-2,3-di-p-tolyl-7,8-dihydropyrido[2,3-b]pyrazin-6(5H)-one;

(rac or R or S)- 5-(5-(1H-tetrazol-5-yl)pentyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol;
(rac or R or S)5-(5-(1H-tetrazol-5-yl)pentyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-8-ol;
5-(5-(1H-tetrazol-5-yl)pentyl)-2,3-di-p-tolyl-7,8-dihydropyrido[2,3-b]pyrazin-6(5H)-one;
(rac or R or S)-5-(5-(1H-tetrazol-5-yl)pentyl)-7-hydroxy-2,3-di-p-tolyl-7,8-dihydropyrido[2,3-b]pyrazin-6(5H)-one;
6-(5-(1H-Tetrazol-5-yl)pentyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazine;
6-(5-(1H-Tetrazol-5-yl)pentyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol;
6-(5-(1H-Tetrazol-5-yl)pentyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-8-ol;
6-(4-(1H-Tetrazol-5-yl)butyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazine;
6-(4-(1H-Tetrazol-5-yl)butyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol;
6-(4-(1H-Tetrazol-5-yl)butyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-8-ol;
6-(5-(1H-Tetrazol-5-yl)pentyl)-5-methyl-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazine;
6-(5-(1H-Tetrazol-5-yl)pentyl)-5-methyl-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol;
6-(5-(1H-Tetrazol-5-yl)pentyl)-5-methyl-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-8-ol;
6-(4-(1H-Tetrazol-5-yl)butyl)-5-methyl-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazine;
6-(4-(1H-Tetrazol-5-yl)butyl)-5-methyl-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol;
6-(4-(1H-Tetrazol-5-yl)butyl)-5-methyl-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-8-ol;
6-(5-(1H-Tetrazol-5-yl)pentyl)-5-isopropyl-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazine;
6-(5-(1H-Tetrazol-5-yl)pentyl)-5-isopropyl-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol;
6-(5-(1H-Tetrazol-5-yl)pentyl)-5-isopropyl-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-8-ol;
6-(4-(1H-Tetrazol-5-yl)butyl)-5-isopropyl-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazine;
6-(4-(1H-Tetrazol-5-yl)butyl)-5-isopropyl-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol;
6-(4-(1H-Tetrazol-5-yl)butyl)-5-isopropyl-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-8-ol;
or a pharmaceutically acceptable salt thereof.

Embodiment 26.1: The compound according to embodiment 1, wherein the compound is selected from
5-(6-(1H-Tetrazol-5-yl)hexyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazine;

5-(5-(1H-Tetrazol-5-yl)pentyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazine;
5-(6-(1H-Tetrazol-5-yl)hexyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol;
(R)-5-(6-(1H-tetrazol-5-yl)hexyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol;
(S)-5-(6-(1H-tetrazol-5-yl)hexyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol;
rac-5-(5-(1H-Tetrazol-5-yl)pentyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[3,2-b]pyrazin-7-ol;
(R)-5-(5-(1H-Tetrazol-5-yl)pentyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol; and
(S)-5-(5-(1H-Tetrazol-5-yl)pentyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol;
or a pharmaceutically acceptable salt thereof.

Embodiment 27: The compound according to embodiment 1, wherein the compound is selected from
5-(6-(1H-Tetrazol-5-yl)hexyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazine;
5-(5-(1H-Tetrazol-5-yl)pentyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazine;
5-(6-(1H-Tetrazol-5-yl)hexyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol;
or a pharmaceutically acceptable salt thereof.

Embodiment 28: The compound according to any one of embodiments 1 to 27, or a pharmaceutically acceptable salt thereof, for use as a medicament.

Embodiment 29: The compound according to any one of embodiments 1 to 27, or a pharmaceutically acceptable salt thereof, for use in the treatment of a disorder or disease mediated by the IP receptor.

Embodiment 30: The compound according to any one of embodiments 1 to 27, or a pharmaceutically acceptable salt thereof, for use in the treatment of a disorder or disease selected from PAH, disorders in need of antiplatelet therapy, atherosclerosis, asthma, COPD, hyperglycemia, inflammatory disease and fibrotic diseases.

Embodiment 31: The compound according to any one of embodiments 1 to 27, or a pharmaceutically acceptable salt thereof, for use in the treatment of a disorder or disease selected from PAH, atherosclerosis, asthma, COPD, hyperglycemia and fibrotic diseases.

Embodiment 32: The compound according to any one of embodiments 1 to 27, or a pharmaceutically acceptable salt thereof, for use in the treatment of a disorder or disease selected from PAH, asthma, COPD and cystic fibrosis.

Embodiment 33: The compound according to any one of embodiments 1 to 27, or a pharmaceutically acceptable salt thereof, for use in the treatment of a disorder or disease selected from PAH and COPD.

Embodiment 34: The compound according to any one of embodiments 1 to 27, or a pharmaceutically acceptable salt thereof, for use in the treatment of PAH.

Embodiment 35: A pharmaceutical composition, comprising:
a therapeutically effective amount of the compound according to any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof, and
one or more pharmaceutically acceptable carriers.

Embodiment 36: A pharmaceutical combination, comprising:
a therapeutically effective amount of the compound according to any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof, and
a second active agent.

Embodiment 37: A method of treating pulmonary arterial hypertension in a patient in need thereof, comprising:
administering to the subject in need thereof a therapeutically effective amount of the compound according to any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof.

Embodiment 38: Use of a compound according to any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disorder or disease mediated by the IP receptor.

Embodiment 39: Use of a compound according to any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disorder or disease selected from PAH, atherosclerosis, asthma, COPD, hyperglycemia and fibrotic diseases.

Embodiment 40: Use of a compound according to any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disorder or disease selected from PAH, asthma, COPD and cystic fibrosis.

Embodiment 41: Use of a compound according to any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disorder or disease selected from PAH or COPD.

Embodiment 42: Use of a compound according to any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of PAH.

Embodiment 43: Use of a compound according to any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof, for the treatment of pulmonary arterial hypertension.

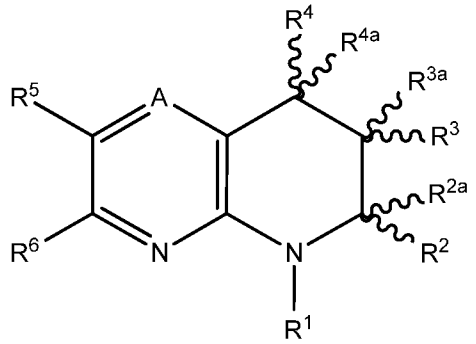
Embodiment 44: A method for the prevention or treatment of a condition affected by activation of the IP receptor, comprising:
administering an effective amount to activate the IP receptor of at least one compound according to any of claims 1 to 27 to a subject in need of such treatment.

Embodiment 45: A method for the prevention or treatment of a disorder or disease selected from PAH, atherosclerosis, asthma, COPD, hyperglycemia and fibrotic diseases, comprising:
administering an effective amount to activate the IP receptor of at least one compound according to any of claims 1 to 27 to a subject in need of such treatment.

Embodiment 46: A method for the prevention or treatment of a disorder or disease selected from PAH, asthma, COPD and cystic fibrosis, comprising:
administering an effective amount to activate the IP receptor of at least one compound according to any of claims 1 to 27 to a subject in need of such treatment.

Claims

1. A compound represented by Formula I



(I)

or a pharmaceutically acceptable salt thereof, wherein

A is N or CR';

R' is H, C_1-C_8 alkyl optionally substituted by one or more halogen atoms;

R^1 is selected from H; C_1-C_8 alkyl optionally substituted by one or more halogen atoms, OH, C_1-C_4 alkoxy, C_3-C_7 cycloalkyl or C_3-C_7 cycloalkyloxy; -(C_2-C_4 alkyl)-$NR^{19}R^{21}$ and C_3-C_7 cycloalkyl;

or

R^1 is -X-Y; or

R^1 is -W-R^7-X-Y; or

R^1 is –$S(O)_2$-X-Y; or

R^1 is –$S(O)_2$-W-R^7-X-Y;

R^2 is selected from H; C_1-C_8 alkyl optionally substituted by one or more halogen atoms, OH, C_1-C_4 alkoxy, C_3-C_7 cycloalkyl or C_3-C_7 cycloalkyloxy; -(C_1-C_4 alkyl)-$NR^{19}R^{21}$ and C_3-C_7 cycloalkyl;

or

R^2 is -X-Y; or

R^2 is -W-R^7-X-Y; or

R^2 is –$S(O)_2$- X-Y; or

R^2 is –$S(O)_2$-W-R^7-X-Y;

R^{2a} is selected from H; C_1-C_8 alkyl optionally substituted by one or more halogen atoms, OH, C_1-C_4 alkoxy, C_3-C_7 cycloalkyl or C_3-C_7 cycloalkyloxy; and C_3-C_7 cycloalkyl; or

R^2 and R^{2a} taken together are oxo;

wherein either R^1 or R^2 is -X-Y, -W-R^7-X-Y, –$S(O)_2$- X-Y; or –$S(O)_2$-W-R^7-X-Y;

R^3 is selected from H; OH; C_1-C_8 alkyl optionally substituted by one or more halogen atoms, OH, C_1-C_4 alkoxy, C_3-C_7 cycloalkyl or C_3-C_7 cycloalkyloxy; C_1-C_4 alkoxy; OR'; -(C_0-C_4alkyl)-$NR^{19}R^{21}$; CN; halogen and C_3-C_7 cycloalkyl;

R^{3a} is selected from H; C_1-C_8 alkyl optionally substituted by one or more halogen atoms, OH, C_1-C_4 alkoxy, C_3-C_7 cycloalkyl or C_3-C_7 cycloalkyloxy; and C_3-C_7 cycloalkyl; or

R^3 and R^{3a} taken together are oxo;

R^4 is selected from H; OH; C_1-C_8 alkyl optionally substituted by one or more halogen atoms, OH, C_1-C_4 alkoxy, C_3-C_7 cycloalkyl or C_3-C_7 cycloalkyloxy; C_1-C_4 alkoxy; OR'; -(C_0-C_4alkyl)-$NR^{19}R^{21}$; CN; halogen and C_3-C_7 cycloalkyl;

R^{4a} is selected from H; C_1-C_8 alkyl optionally substituted by one or more halogen atoms, OH, C_1-C_4 alkoxy, C_3-C_7 cycloalkyl or C_3-C_7 cycloalkyloxy; and C_3-C_7 cycloalkyl; or

R^4 and R^{4a} taken together are oxo;

R^5 and R^6 are independently selected from -(C_0-C_4 alkyl)-C_6-C_{14} aryl and -(C_0-C_4 alkyl)-4 to 14 membered heteroaryl, wherein the aryl and heteroaryl are each optionally substituted by one or more Z substituents;

W is C_1-C_8 alkylene optionally substituted by hydroxy, halogens or C_1-C_4 alkyl;

X is C_1-C_8 alkylene optionally substituted by hydroxy, halogens or C_1-C_4 alkyl;

Y is tetrazolyl;

R^7 is a divalent moiety represented by -O-, -S-, -NHC(O)-, -CH_2=CH_2-, -C_6-C_{14} aryl-D-; -3 to 14 membered heterocyclyl-D-, wherein the heterocyclyl contains at least one heteroatom selected from N, O and S, wherein D is O, S, NH or not present;

Z is independently OH, aryl, O-aryl, benzyl, O-benzyl, C_1-C_6 alkyl optionally substituted by one or more OH groups or NH_2 groups, C_1-C_6 alkyl optionally substituted by one or more halogen atoms, C_1-C_6 alkoxy optionally substituted by one or more OH groups, C_1-C_6 alkoxy optionally substituted by one or more halogen, C_1-C_6 alkoxy optionally substituted by C_1-C_4 alkoxy, $NR^{18}(SO_2)R^{21}$, $(SO_2)NR^{19}R^{21}$, $(SO_2)R^{21}$, $NR^{18}C(O)R^{21}$, $C(O)NR^{19}R^{21}$, $NR^{18}C(O)NR^{19}R^{21}$, $NR^{18}C(O)OR^{19}$, $NR^{19}R^{21}$, $C(O)OR^{19}$, $C(O)R^{19}$, SR^{19}, OR^{19}, oxo, CN, NO_2, halogen or a 3 to 14 membered heterocyclyl, wherein the heterocyclyl contains at least one heteroatom selected from N, O and S;

R^{18} is independently H or C_1-C_6 alkyl;

R^{19} and R^{21} are each independently H; C_1-C_8 alkyl; C_3-C_8 cycloalkyl; C_1-C_4 alkoxy-C_1-C_4 alkyl; (C_0-C_4 alkyl)-aryl optionally substituted by one or more groups selected from C_1-C_6 alkyl, C_1-C_6 alkoxy and halogen; (C_0-C_4 alkyl)- 3- to 14-membered heterocyclyl, the heterocyclyl including one or more heteroatoms selected from N, O and S, optionally substituted by one or more

groups selected from halogen, oxo, C_1-C_6 alkyl and C(O)C_1-C_6 alkyl; (C_0-C_4 alkyl)-O-aryl optionally substituted by one or more groups selected from C_1-C_6 alkyl, C_1-C_6 alkoxy and halogen; and (C_0-C_4 alkyl)- O-3- to 14-membered heterocyclyl, the heterocyclyl including one or more heteroatoms selected from N, O and S, optionally substituted by one or more groups selected from halogen, C_1-C_6 alkyl or C(O)C_1-C_6 alkyl; wherein the alkyl groups are optionally substituted by one or more halogen atoms, C_1-C_4 alkoxy, C(O)NH_2, C(O)NHC_1-C_6 alkyl or C(O)N(C_1-C_6 alkyl)$_2$; or

R^{19} and R^{21} together with the nitrogen atom to which they attached form a 5- to 10-membered heterocyclyl, the heterocyclyl including one or more further heteroatoms selected from N, O and S, the heterocyclyl being optionally substituted by one or more substituents selected from OH; halogen; aryl; 5- to 10-membered heterocyclyl including one or more heteroatoms selected from N, O and S; S(O)$_2$-aryl; S(O)$_2$-C_1-C_6 alkyl; C_1-C_6 alkyl optionally substituted by one or more halogen atoms; C_1-C_6 alkoxy optionally substituted by one or more OH groups or C_1-C_4 alkoxy; and C(O)OC_1-C_6 alkyl, wherein the aryl and heterocyclyl substituent groups are themselves optionally substituted by C_1-C_6 alkyl, C_1-C_6 haloalkyl or C_1-C_6 alkoxy.

2. The compound according to claim 1, wherein

either R^1 or R^2 is -X-Y; or -W-R^7-X-Y;

W is C_1-C_6 alkylene optionally substituted by hydroxy, halogens or C_1-C_4 alkyl;

X is C_1-C_6 alkylene optionally substituted by hydroxy, halogens or C_1-C_4 alkyl;

R' is H, C_1-C_4 alkyl optionally substituted by one or more halogen atoms;

R^7 is a divalent moiety represented by -C_6-C_{14} aryl-D-; -3 to 14 membered heterocyclyl-D-, wherein the heterocyclyl contains at least one heteroatom selected from N, O and S, wherein D is O.

3. The compound according to any of the preceding claims, wherein

either R^1 or R^2 is -X-Y;

X is C_1-C_6 alkylene optionally substituted by hydroxy, halogens or C_1-C_4 alkyl.

4. The compound according to any of the preceding claims, wherein

R^2 and R^{2a} are independently selected from H and C_1-C_4 alkyl optionally substituted by one or more halogen atoms or OH; or R^2 and R^{2a} taken together are oxo;

R^3 and R^{3a} are independently selected from H; C_1-C_4 alkyl optionally substituted by one or more halogen atoms or OH; and OH; or R^3 and R^{3a} taken together are oxo;

R^4 and R^{4a} are independently selected from H; C_1-C_4 alkyl optionally substituted by one or more halogen atoms or OH; and OH; or R^4 and R^{4a} taken together are oxo.

5. The compound according to any of the preceding claims, wherein

R^5 is phenyl optionally substitued by OH, C_1-C_4 alkyl optionally substituted by one or more OH groups or NH_2 groups; C_1-C_4 alkyl optionally substituted by one or more halogen atoms; C_1-C_4 alkoxy optionally substituted by one or more OH groups or C_1-C_4 alkoxy; $NR^{19}R^{21}$; $C(O)OR^{19}$; $C(O)R^{19}$; SR^{19}; OR^{19}; CN; NO_2; or halogen; and

R^6 is phenyl optionally substituted by OH, C_1-C_4 alkyl optionally substituted by one or more OH groups or NH_2 groups; C_1-C_4 alkyl optionally substituted by one or more halogen atoms; C_1-C_4 alkoxy optionally substituted by one or more OH groups or C_1-C_4 alkoxy; $NR^{19}R^{21}$, $C(O)OR^{19}$, $C(O)R^{19}$, SR^{19}, OR^{19}, CN, NO_2, or halogen.

6. The compound according to any of the preceding claims wherein

R^5 is phenyl optionally substituted by C_1-C_4 alkoxy, halogen or C_1-C_4 alkyl optionally substituted by one or more halogen atoms; and

R^6 is phenyl optionally substituted by C_1-C_4 alkoxy, halogen or C_1-C_4 alkyl optionally substituted by one or more halogen atoms.

7. The compound according to claim 1, wherein the compound is selected from
5-(6-(1H-Tetrazol-5-yl)hexyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazine;
5-(5-(1H-Tetrazol-5-yl)pentyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazine;
5-(6-(1H-Tetrazol-5-yl)hexyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol;
(R)-5-(6-(1H-tetrazol-5-yl)hexyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol;
(S)-5-(6-(1H-tetrazol-5-yl)hexyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol;
rac-5-(5-(1H-Tetrazol-5-yl)pentyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[3,2-b]pyrazin-7-ol;
(R)-5-(5-(1H-Tetrazol-5-yl)pentyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol; and
(S)-5-(5-(1H-Tetrazol-5-yl)pentyl)-2,3-di-p-tolyl-5,6,7,8-tetrahydropyrido[2,3-b]pyrazin-7-ol;
or a pharmaceutically acceptable salt thereof.

8. A pharmaceutical composition, comprising:
a therapeutically effective amount of the compound according to any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, and
one or more pharmaceutically acceptable carriers.

9. A pharmaceutical combination, comprising:
a therapeutically effective amount of the compound according to any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, and
a second active agent.

10. The compound according to any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, for use as a medicament.

11. The compound according to any one of embodiments 1 to 7, or a pharmaceutically acceptable salt thereof, for use in the treatment of a disorder or disease mediated by the IP receptor.

12. The compound according to any one of embodiments 1 to 7, or a pharmaceutically acceptable salt thereof, for use in the treatment of a disorder or disease selected from PAH, disorders in need of antiplatelet therapy, atherosclerosis, asthma, COPD, hyperglycemia, inflammatory disease and fibrotic diseases.

13. Use of a compound according to any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a disorder or disease mediated by the IP receptor.

14. Use of a compound according to any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, for the treatment of a disease selected from PAH, disorders in need of antiplatelet therapy, atherosclerosis, asthma, COPD, hyperglycemia, inflammatory disease and fibrotic diseases.

15. A method for the prevention or treatment of a condition affected by activation of the IP receptor, comprising:
administering an effective amount to activate the IP receptor of at least one compound according to any of claims 1 to 7 to a subject in need of such treatment.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2013/050280

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 A61K31/4985 A61P9/00 A61P11/00
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)
C07D A61K A61P

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2007/017096 A1 (ALMIRALL PRODESFARMA SA [ES]; VIDAL JUAN BERNAT [ES]; ESTEVE TRIAS CRI) 15 February 2007 (2007-02-15) the whole document	1-15
A	WO 2010/008864 A2 (AMIRA PHARMACEUTICALS INC [US]; HUTCHINSON JOHN HOWARD [US]; STEARNS B) 21 January 2010 (2010-01-21) the whole document	1-15
A	US 2010/280041 A1 (CHEN ING-JUN [TW]) 4 November 2010 (2010-11-04) the whole document	1-15

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 March 2013	11/04/2013

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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