

Dual acting ATX/CA inhibitors are expected to lower intraocular pressure by facilitating two independent pathways, such as inhibition of aqueous humor (AH) production through CA inhibition at the ciliary body and facilitation of AH outflow by ATX inhibition within the AH drainage system. In conditions of vascular leakage in the eye such as diabetic retinopathy, age related macular disease, or retinal vein occlusion, CA levels have been shown or are expected to increase in the eye and facilitate an increase in pH. This is expected to activate many hydrolytic enzymes that can contribute to disease progression including ATX suggesting additional ATX inhibition by shifting the pH optimum .

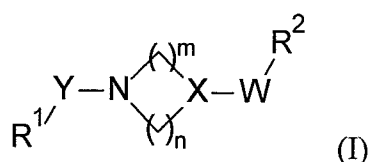
In accordance with the invention, the compounds of formula (I) or their pharmaceutically acceptable salts and esters can be used for the treatment or prophylaxis of diseases, disorders or conditions that are associated with the activity of autotaxin and/or the biological activity of lysophosphatidic acid (LPA).

The compounds of formula (I) or their pharmaceutically acceptable salts and esters herein inhibit autotaxin activity and carbonic anhydrase activity therefore inhibit LPA production and modulate LPA levels and associated signaling. Dual ATX/CA-II inhibitors described herein are useful as agents for the treatment or prevention of diseases or conditions in which ATX activity and/or LPA signaling participates, is involved in the etiology or pathology of the disease, or is otherwise associated with at least one symptom of the disease. The ATX-LPA axis has been implicated for example in angiogenesis, chronic inflammation, autoimmune diseases, fibrotic diseases, cancer and tumor metastasis and progression, ocular conditions, metabolic conditions such as obesity and/or diabetes mellitus, conditions such as cholestatic or other forms of chronic pruritus as well as acute and chronic organ transplant rejection.

Objects of the present disclosure are the compounds of formula (I) and their aforementioned salts and esters and their use as therapeutically active substances, a process for the manufacture of the said compounds, intermediates, pharmaceutical compositions, medicaments containing the said compounds, their pharmaceutically acceptable salts or esters, the use of the said compounds, salts or esters for the treatment or prophylaxis of disorders or conditions that are associated with the activity of ATX and/or the biological activity of lysophosphatidic acid (LPA), particularly in the treatment or prophylaxis of inflammatory conditions, conditions of the nervous system, conditions of the respiratory system, vascular and cardiovascular conditions, fibrotic diseases, cancer, ocular conditions, metabolic conditions, cholestatic and other forms of chronic pruritus and acute and- chronic organ transplant rejection,

and the use of the said compounds, salts or esters for the production of medicaments for the treatment or prophylaxis of inflammatory conditions, conditions of the nervous system, conditions of the respiratory system, vascular and cardiovascular conditions, fibrotic diseases, cancer, ocular conditions, metabolic conditions, cholestatic and other forms of chronic pruritus and acute and chronic organ transplant rejection. More particularly, the compounds of formula (I) and their aforementioned salts and esters and their use as therapeutically active substances, a process for the manufacture of the said compounds, intermediates, pharmaceutical composition, medicaments containing the said compounds, their pharmaceutically acceptable salts or esters, the use of the said compounds, salts or esters for the treatment or prophylaxis of ocular conditions, furthermore particularly glaucoma.

In one aspect, there is provided compounds of formula (I)



wherein

 R^1 is selected from

- 15 i) phenyl substituted by R³, R⁴ and R⁵,
 ii) pyridinyl substituted by R³, R⁴ and R⁵, and
 iii) thiophenyl substituted by R³, R⁴ and R⁵;

X is selected from

- 20 i) CH_3 ;

Y is selected from

- i) $-\text{CH}_2-\text{OC}(\text{O})-$,
- ii) $-(\text{CH}_2)_q\text{C}(\text{O})-$,

iii) $-(\text{CH}=\text{CH})_r-\text{C}(\text{O})-$, and

iv) $-(\text{CH}\equiv\text{CH})_r-\text{C}(\text{O})-$;

W is selected from

i) $-(\text{CR}^9\text{R}^{10})_p-$,

5 ii) $-(\text{CR}^9\text{R}^{10})_p-\text{C}(\text{O})-$,

iii) $-(\text{C R}^9\text{R}^{10})_p-\text{O}-$,

iv) $-(\text{C R}^9\text{R}^{10})_p-\text{S}-$,

v) $-(\text{C R}^9\text{R}^{10})_p-\text{S}(\text{O})-$, and

vi) $-(\text{C R}^9\text{R}^{10})_p-\text{S}(\text{O})_2-$;

10 R^2 is selected from

i) substituted phenyl, wherein the phenyl ring is substituted by R^6 , R^7 and R^8 ,

ii) substituted pyridinyl, wherein the pyridinyl ring is substituted by R^6 , R^7 and R^8 ,

15 iii) substituted thiophenyl, wherein the thiophenyl ring is substituted by R^6 , R^7 and R^8 , and

iv) substituted thiazolyl, wherein the thiazolyl ring is substituted by R^6 , R^7 and R^8 ;

R^3 is selected from

i) halo- C_{1-6} -alkoxy,

20 ii) C_{3-8} -cycloalkyl,

iii) C_{3-8} -cycloalkyl- C_{1-6} -alkyl,

iv) C_{3-8} -cycloalkyl- C_{1-6} -alkoxy,

v) C_{3-8} -cycloalkoxy,

- vi) C₃₋₈-cycloalkoxy-C₁₋₆-alkyl,
- vii) tetrazolylmethyl,
- viii) triazolylmethyl,
- ix) pyrazolylmethyl,
- 5 x) C₁₋₆-alkyltetrazolylmethyl,
- xi) C₁₋₆-alkyltriazolylmethyl,
- xii) C₁₋₆-alkylpyrazolylmethyl,
- xiii) heterocycloalkyl-C₁₋₆-alkoxy;

R⁴ is selected from

- 10 i) halogen,
- ii) hydroxy,
- iii) cyano,
- iv) C₁₋₆-alkyl,
- v) C₁₋₆-alkoxy,
- 15 vi) C₁₋₆-alkoxy-C₁₋₆-alkyl,
- vii) halo-C₁₋₆-alkoxy,
- viii) halo-C₁₋₆-alkyl,
- ix) hydroxy-C₁₋₆-alkyl,
- x) C₃₋₈-cycloalkyl,
- 20 xi) C₃₋₈-cycloalkyl-C₁₋₆-alkyl,
- xii) C₃₋₈-cycloalkyl-C₁₋₆-alkoxy,
- xiii) C₃₋₈-cycloalkoxy,

- xiv) C₃₋₈-cycloalkoxy-C₁₋₆-alkyl,
- xv) C₁₋₆-alkylcarbonylamino,
- xvi) C₃₋₈-cycloalkylcarbonylamino,

R⁵ is selected from

- 5 i) H,
- ii) halogen,
- iii) hydroxy,
- iv) cyano,
- v) C₁₋₆-alkyl,
- 10 vi) C₁₋₆-alkoxy,
- vii) C₁₋₆-alkoxy-C₁₋₆-alkyl,
- viii) halo-C₁₋₆-alkoxy,
- ix) halo-C₁₋₆-alkyl,
- x) hydroxy-C₁₋₆-alkyl,
- 15 xi) C₃₋₈-cycloalkyl,
- xii) C₃₋₈-cycloalkyl-C₁₋₆-alkyl,
- xiii) C₃₋₈-cycloalkyl-C₁₋₆-alkoxy,
- xiv) C₃₋₈-cycloalkoxy,
- xv) C₃₋₈-cycloalkoxy-C₁₋₆-alkyl,
- 20 xvi) C₁₋₆-alkylcarbonylamino,
- xvii) C₃₋₈-cycloalkylcarbonylamino,

R⁶ is aminosulfonyl;

R⁷ and R⁸ are independently selected from

- i) H,
- ii) halogen,
- iii) hydroxy,
- 5 iv) cyano,
- v) C₁₋₆-alkyl,
- vi) C₁₋₆-alkoxy,
- vii) C₁₋₆-alkoxy-C₁₋₆-alkyl,
- viii) halo-C₁₋₆-alkoxy,
- 10 ix) halo-C₁₋₆-alkyl,
- x) hydroxy-C₁₋₆-alkyl,
- xi) C₃₋₈-cycloalkyl,
- xii) C₃₋₈-cycloalkyl-C₁₋₆-alkyl,
- xiii) C₃₋₈-cycloalkyl-C₁₋₆-alkoxy,
- 15 xiv) C₃₋₈-cycloalkoxy, and
- xv) C₃₋₈-cycloalkoxy-C₁₋₆-alkyl;

R⁹ and R¹⁰ are independently selected from

- i) H,
- ii) C₁₋₆-alkyl, and
- 20 iii) C₃₋₈-cycloalkyl;

m and n are independently selected from zero, 1, 2, 3, 4 or 5, with the proviso that the sum of m and n is 2, 3, 4 or 5;

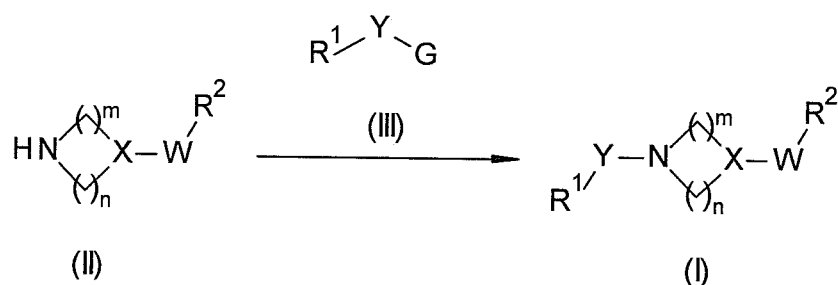
p is selected from zero, 1 or 2;

q is selected from zero or 2;

r is selected from zero and 1;

or pharmaceutically acceptable salts.

- 5 In another aspect, there is provided a process to prepare a compound as defined herein comprising the reaction of a compound of formula (II) in the presence of a compound of formula (III);



- wherein R^1 , R^2 , Y, W, X, m and n are as defined herein and in case Y is $-(\text{CH}_2)_q\text{C}(\text{O})-$, -
 10 $(\text{CH}=\text{CH})_r\text{C}(\text{O})-$ or $-(\text{CH}\equiv\text{CH})_r\text{C}(\text{O})-$, then G is halogen or hydroxy and in case Y is $-\text{OC}(\text{O})-$, then G is chloro.

In another aspect, there is provided a compound as defined herein for use as therapeutically active substance.

- In another aspect, there is provided a pharmaceutical composition comprising a compound
 15 as defined herein and a therapeutically inert carrier.

In another aspect, there is provided a compound as defined herein for use in the treatment or prophylaxis of ocular conditions.

- In another aspect, there is provided use of a compound as defined herein for the preparation of a medicament for the treatment or prophylaxis of ocular conditions selected from
 20 the group consisting of proliferative and non-proliferative diabetic retinopathy, dry and wet age-related macular degeneration (AMD), macular edema, central arterial /venous occlusion, traumatic injury, and glaucoma.

The term “C₁-C₆-alkoxy” denotes a group of the formula -O-R', wherein R' is a C₁-C₆-alkyl group. Examples of C₁-C₆-alkoxy group include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy and tert-butoxy.

5 The term “C₁-C₆-alkoxy-C₁₋₆-alkyl” denotes a C₁-C₆-alkyl group wherein at least one of the hydrogen atoms of the C₁-C₆-alkyl group is replaced by a C₁-C₆-alkoxy group. Particular examples are methoxymethyl, methoxyethyl, ethoxymethyl, ethoxyethyl, iso-propoxymethyl and iso-propoxyethyl.

10 The term “C₁-C₆-alkyl” denotes a monovalent linear or branched saturated hydrocarbon group of 1 to 6 carbon atoms. Examples of C₁-C₆-alkyl include methyl, ethyl, propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, tert-butyl and pentyl. Particular alkyl groups include methyl, isopropyl and tert-butyl.

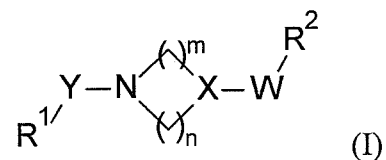
The term “C₁-C₆-alkylcarbonyl” denotes a group of the formula -C(O)-R', wherein R' is a C₁-C₆-alkyl group. Examples of C₁-C₆-alkylcarbonyl group include groups wherein R' is methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy and tert-butoxy.

15 The term “C₁-C₆-alkylcarbonylamino” denotes an amino group wherein the nitrogen atom is substituted by one H atom and by a C₁-C₆-alkylcarbonyl group. Particular example is an amino group wherein the nitrogen atom is substituted by H and tertbutylcarbonyl.

20 The term “C₁-C₆-alkylpyrazolyl” denotes a pyrazolyl group wherein one of the nitrogen atoms is substituted by a C₁-C₆-alkyl group. Particular example is a pyrazolyl group wherein one of the nitrogen atoms is substituted by methyl.

Claims

1. Compounds of formula (I)



wherein

5 R^1 is selected from

- i) phenyl substituted by R³, R⁴ and R⁵,
- ii) pyridinyl substituted by R³, R⁴ and R⁵, and
- iii) thiophenyl substituted by R³, R⁴ and R⁵;

X is selected from

- 10 i) N, and
- i) CH;

Y is selected from

- 15
- i) $-\text{CH}_2-\text{OC}(\text{O})-$,
 - ii) $-(\text{CH}_2)_q\text{C}(\text{O})-$,
 - iii) $-(\text{CH}=\text{CH})_r-\text{C}(\text{O})-$, and
 - iv) $-(\text{CH}\equiv\text{CH})_r-\text{C}(\text{O})-$;

W is selected from

- 20
- i) $-(\text{CR}^9\text{R}^{10})_{\text{p}}-$,
 - ii) $-(\text{CR}^9\text{R}^{10})_{\text{p}}-\text{C}(\text{O})-$,
 - iii) $-(\text{C R}^9\text{R}^{10})_{\text{p}}-\text{O}-$,

- iv) $-(C R^9 R^{10})_p-S-$,
- v) $-(C R^9 R^{10})_p-S(O)-$, and
- vi) $-(C R^9 R^{10})_p-S(O)_2-$;

R^2 is selected from

- 5 i) substituted phenyl, wherein the phenyl ring is substituted by R^6 , R^7 and R^8 ,
- ii) substituted pyridinyl, wherein the pyridinyl ring is substituted by R^6 , R^7 and R^8 ,
- iii) substituted thiophenyl, wherein the thiophenyl ring is substituted by R^6 , R^7 and R^8 , and
- 10 iv) substituted thiazolyl, wherein the thiazolyl ring is substituted by R^6 , R^7 and R^8 ;

R^3 is selected from

- i) halo- C_{1-6} -alkoxy,
- ii) C_{3-8} -cycloalkyl,
- 15 iii) C_{3-8} -cycloalkyl- C_{1-6} -alkyl,
- iv) C_{3-8} -cycloalkyl- C_{1-6} -alkoxy,
- v) C_{3-8} -cycloalkoxy,
- vi) C_{3-8} -cycloalkoxy- C_{1-6} -alkyl,
- vii) tetrazolylmethyl,
- 20 viii) triazolylmethyl,
- ix) pyrazolylmethyl,
- x) C_{1-6} -alkyltetrazolylmethyl,
- xi) C_{1-6} -alkyltriazolylmethyl,

- xii) C₁₋₆-alkylpyrazolylmethyl,
- xiii) heterocycloalkyl-C₁₋₆-alkoxy;

R⁴ is selected from

- i) halogen,
- 5 ii) hydroxy,
- iii) cyano,
- iv) C₁₋₆-alkyl,
- v) C₁₋₆-alkoxy,
- vi) C₁₋₆-alkoxy-C₁₋₆-alkyl,
- 10 vii) halo-C₁₋₆-alkoxy,
- viii) halo-C₁₋₆-alkyl,
- ix) hydroxy-C₁₋₆-alkyl,
- x) C₃₋₈-cycloalkyl,
- xi) C₃₋₈-cycloalkyl-C₁₋₆-alkyl,
- 15 xii) C₃₋₈-cycloalkyl-C₁₋₆-alkoxy,
- xiii) C₃₋₈-cycloalkoxy,
- xiv) C₃₋₈-cycloalkoxy-C₁₋₆-alkyl,
- xv) C₁₋₆-alkylcarbonylamino,
- xvi) C₃₋₈-cycloalkylcarbonylamino,

20 R⁵ is selected from

- i) H,
- ii) halogen,

- iii) hydroxy,
- iv) cyano,
- v) C₁₋₆-alkyl,
- vi) C₁₋₆-alkoxy,
- 5 vii) C₁₋₆-alkoxy-C₁₋₆-alkyl,
- viii) halo-C₁₋₆-alkoxy,
- ix) halo-C₁₋₆-alkyl,
- x) hydroxy-C₁₋₆-alkyl,
- xi) C₃₋₈-cycloalkyl,
- 10 xii) C₃₋₈-cycloalkyl-C₁₋₆-alkyl,
- xiii) C₃₋₈-cycloalkyl-C₁₋₆-alkoxy,
- xiv) C₃₋₈-cycloalkoxy,
- xv) C₃₋₈-cycloalkoxy-C₁₋₆-alkyl,
- xvi) C₁₋₆-alkylcarbonylamino,
- 15 xvii) C₃₋₈-cycloalkylcarbonylamino,

R⁶ is aminosulfonyl;

R⁷ and R⁸ are independently selected from

- i) H,
- ii) halogen,
- 20 iii) hydroxy,
- iv) cyano,
- v) C₁₋₆-alkyl,

- vi) C₁₋₆-alkoxy,
- vii) C₁₋₆-alkoxy-C₁₋₆-alkyl,
- viii) halo-C₁₋₆-alkoxy,
- ix) halo-C₁₋₆-alkyl,
- 5 x) hydroxy-C₁₋₆-alkyl,
- xi) C₃₋₈-cycloalkyl,
- xii) C₃₋₈-cycloalkyl-C₁₋₆-alkyl,
- xiii) C₃₋₈-cycloalkyl-C₁₋₆-alkoxy,
- xiv) C₃₋₈-cycloalkoxy, and
- 10 xv) C₃₋₈-cycloalkoxy-C₁₋₆-alkyl;

R⁹ and R¹⁰ are independently selected from

- i) H,
 - ii) C₁₋₆-alkyl, and
 - iii) C₃₋₈-cycloalkyl;
- 15 m and n are independently selected from zero, 1, 2, 3, 4 or 5, with the proviso that the sum of m and n is 2, 3, 4 or 5;
- p is selected from zero, 1 or 2;
- q is selected from zero or 2;
- r is selected from zero and 1;
- 20 or pharmaceutically acceptable salts.

2. A compound according to claim 1, wherein

R¹ is selected from

- i) phenyl substituted by R^3 , R^4 and R^5 , and
- ii) pyridinyl substituted by R^3 , R^4 and R^5 ;

X is selected from

- i) N, and
- ii) CH;

Y is selected from

- i) $-\text{CH}_2\text{-OC(O)-}$, and
- ii) $-(\text{CH}_2)_q\text{C(O)-}$;

W is selected from

- i) $-(\text{CR}^9\text{R}^{10})_p-$,
- ii) $-(\text{CR}^9\text{R}^{10})_p\text{-C(O)-}$,
- iii) $-(\text{C R}^9\text{R}^{10})_p\text{-O-}$,
- iv) $-(\text{C R}^9\text{R}^{10})_p\text{-S-}$,
- v) $-(\text{C R}^9\text{R}^{10})_p\text{-S(O)-}$, and
- vi) $-(\text{C R}^9\text{R}^{10})_p\text{-S(O)}_2-$;

R^2 is selected from

- i) substituted phenyl, wherein the phenyl ring is substituted by R^6 , R^7 and R^8 ,
- ii) substituted pyridinyl, wherein the pyridinyl ring is substituted by R^6 , R^7 and R^8 ,
- iii) substituted thiophenyl, wherein the thiophenyl ring is substituted by R^6 , R^7 and R^8 , and
- iv) substituted thiazolyl, wherein the thiazolyl ring is substituted by R^6 , R^7 and R^8 ;

R³ is selected from

- i) halo-C₁₋₆-alkoxy,
- ii) cyano,
- iii) C₃₋₈-cycloalkyl-C₁₋₆-alkoxy,
- 5 iv) C₃₋₈-cycloalkoxy,
- v) C₁₋₆-alkyltetrazolylmethyl, and
- vi) tetrahydropyranyl-C₁₋₆-alkoxy;

R⁴ is selected from

- i) halogen,
- 10 ii) cyano,
- iii) halo-C₁₋₆-alkoxy,
- iv) halo-C₁₋₆-alkyl,
- v) C₃₋₈-cycloalkyl, and
- vi) C₁₋₆-alkylcarbonylamino;

15 R⁵ is H;

R⁶ is aminosulfonyl;

R⁷ and R⁸ are independently selected from

- i) H, and
- ii) halogen;

20 R⁹ and R¹⁰ are both H;

m is selected from zero, 1 and 2 and n is selected from 1, 2 and 3, with the proviso that the sum of m and n is 2, 3, 4 or 5;

p is selected from zero, 1 and 2;

q is selected from zero and 2;

or pharmaceutically acceptable salts.

3. A compound according to claim 1 or 2, wherein R^1 is selected from
 - 5 i) phenyl substituted by R^3 , R^4 and R^5 , and
 - ii) pyridinyl substituted by R^3 , R^4 and R^5 .
4. A compound according to claim 1 or 2, wherein R^1 is phenyl substituted by R^3 , R^4 and R^5 .
5. A compound according to claim 1 or 2, wherein Y is selected from
 - i) $-\text{CH}_2\text{-OC(O)-}$, and
 - 10 ii) $-(\text{CH}_2)_q\text{C(O)-}$.
6. A compound according to claim 1 or 2, wherein Y is $-(\text{CH}_2)_q\text{C(O)-}$.
7. A compound according to claim 1 or 2, wherein W is selected from
 - i) $-(\text{C}^9\text{R}^{10})_p-$,
 - ii) $-(\text{C}^9\text{R}^{10})_p\text{-S-}$, and
 - 15 iii) $-(\text{C}^9\text{R}^{10})_p\text{-S(O)}_2-$.
8. A compound according to claim 1 or 2, wherein R^2 is selected from
 - i) substituted phenyl, wherein the phenyl ring is substituted by R^6 , R^7 and R^8 ,
and
 - ii) substituted pyridinyl, wherein the pyridinyl ring is substituted by R^6 , R^7 and
20 R^8 .
9. A compound according to claim 1 or 2, wherein R^3 is selected from
 - i) halo- C_{1-6} -alkoxy,

- ii) cyano,
 - iii) C₃₋₈-cycloalkyl-C₁₋₆-alkoxy,
 - iv) C₃₋₈-cycloalkoxy,
 - v) C₁₋₆-alkyltetrazolylmethyl, and
 - 5 vi) tetrahydropyranyl-C₁₋₆-alkoxy;
10. A compound according to claim 1 or 2, wherein R³ is selected from
- i) C₁₋₆-alkyltetrazolylmethyl, and
 - ii) tetrahydropyranyl-C₁₋₆-alkoxy.
11. A compound according to claim 1 or 2, wherein R⁴ is selected from
- 10 i) halogen,
- ii) cyano,
- iii) halo-C₁₋₆-alkoxy,
- iv) halo-C₁₋₆-alkyl,
- v) C₃₋₈-cycloalkyl, and
- 15 vi) C₁₋₆-alkylcarbonylamino;
12. A compound according to claim 1 or 2, wherein R⁴ is selected from
- i) halo-C₁₋₆-alkyl, and
 - ii) C₃₋₈-cycloalkyl.
13. A compound according to claim 1 or 2, wherein R⁵ is H.
- 20 14. A compound according to claim 1 or 2, wherein R⁷ and R⁸ are independently selected from
- i) H, and
 - ii) halogen.

15. A compound according to claim 1 or 2, wherein R^7 is halogen.
16. A compound according to claim 1 or 2, wherein R^8 is selected from
- i) H, and
 - ii) halogen.
- 5 17. A compound according to claim 1 or 2, wherein R^9 and R^{10} are both H.
18. A compound according to claim 1 or 2, wherein m is selected from zero, 1 and 2 and n is selected from 1, 2 and 3, with the proviso that the sum of m and n is 2, 3, 4 or 5.
19. A compound according to claim 1 or 2, wherein m and n are both 2.
20. A compound according to claim 1 or 2, wherein p is selected from zero and 1.
- 10 21. A compound according to claim 1 or 2, wherein p is zero.
22. A compound according to claim 1 or 2, wherein q is 2.
23. A compound according to claim 1 or 2, wherein
- R^1 is selected from
- i) phenyl substituted by R^3 , R^4 and R^5 , and
 - 15 ii) pyridinyl substituted by R^3 , R^4 and R^5 ;
- X is selected from
- i) N, and
 - ii) CH_3 ;
- Y is selected from
- 20 i) $-CH_2-OC(O)-$, and
 - ii) $-(CH_2)_qC(O)-$;

W is selected from

- i) $-(CR^9R^{10})_p-$,
- ii) $-(CR^9R^{10})_p-C(O)-$,
- iii) $-(CR^9R^{10})_p-O-$,
- iv) $-(CR^9R^{10})_p-S-$,
- 5 v) $-(CR^9R^{10})_p-S(O)-$, and
- vi) $-(CR^9R^{10})_p-S(O)_2-$;

R^2 is selected from

- i) substituted phenyl, wherein the phenyl ring is substituted by R^6 , R^7 and R^8 ,
- 10 ii) substituted pyridinyl, wherein the pyridinyl ring is substituted by R^6 , R^7 and R^8 ,
- iii) substituted thiophenyl, wherein the thiophenyl ring is substituted by R^6 , R^7 and R^8 , and
- iv) substituted thiazolyl, wherein the thiazolyl ring is substituted by R^6 , R^7 and R^8 ;

15 R^3 is selected from

- i) halo- C_{1-6} -alkoxy,
- ii) cyano,
- iii) C_{3-8} -cycloalkyl- C_{1-6} -alkoxy,
- iv) C_{3-8} -cycloalkoxy,
- 20 v) C_{1-6} -alkyltetrazolylmethyl, and
- vi) tetrahydropyranyl- C_{1-6} -alkoxy;

R^4 is selected from

- i) halogen,

- ii) cyano,
- iii) halo-C₁₋₆-alkoxy,
- iv) halo-C₁₋₆-alkyl,
- v) C₃₋₈-cycloalkyl, and
- 5 vi) C₁₋₆-alkylcarbonylamino;

R⁵ is H;

R⁶ is aminosulfonyl;

R⁷ and R⁸ are independently selected from

- i) H, and
- 10 ii) halogen;

R⁹ and R¹⁰ are both H;

m is selected from zero, 1 and 2 and n is selected from 1, 2 and 3, with the proviso that the sum of m and n is 2, 3, 4 or 5;

p is selected from zero, 1 and 2;

- 15 q is selected from zero and 2;

or pharmaceutically acceptable salts.

24. A compound according to any one of claims 1 to 20, selected from

2-((5-methyl-2H-tetrazol-2-yl)methyl)-4-(trifluoromethyl)benzyl 4-(2-fluoro-4-sulfamoylphenyl)piperazine-1-carboxylate;

- 20 [2-cyclopropyl-6-(oxan-4-ylmethoxy)pyridin-4-yl]methyl 4-[(4-sulfamoylphenyl)methyl]piperidine-1-carboxylate;

[5-cyano-3-(2,2-dimethylpropanoylamino)pyridin-2-yl]methyl 4-[(4-sulfamoylphenyl)methyl]piperidine-1-carboxylate ;

[5-chloro-3-[(5-methyltetrazol-2-yl)methyl]pyridin-2-yl]methyl 4-(2-fluoro-4-sulfamoylphenyl)sulfonylpiperidine-1-carboxylate ;

[2-[(5-methyltetrazol-2-yl)methyl]-4-(trifluoromethyl)phenyl]methyl 4-(2-fluoro-4-sulfamoylphenyl)sulfonylpiperidine-1-carboxylate;

5 2-fluoro-4-[[4-[3-[2-[(5-methyltetrazol-2-yl)methyl]-4-(trifluoromethyl)phenyl]propanoyl]piperazin-1-yl]methyl]benzenesulfonamide;

3-fluoro-4-[[4-[3-[2-[(5-methyltetrazol-2-yl)methyl]-4-(trifluoromethyl)phenyl]propanoyl]piperazin-1-yl]methyl]benzenesulfonamide;

10 4-[[4-[2-cyclopropyl-6-(oxan-4-ylmethoxy)pyridine-4-carbonyl]piperazin-1-yl]methyl]-3-fluorobenzenesulfonamide;

3-fluoro-4-[4-[3-[2-[(5-methyltetrazol-2-yl)methyl]-4-(trifluoromethyl)phenyl]propanoyl]piperazine-1-carbonyl]benzenesulfonamide;

2-fluoro-4-[4-[3-[2-[(5-methyltetrazol-2-yl)methyl]-4-(trifluoromethyl)phenyl]propanoyl]piperazine-1-carbonyl]benzenesulfonamide;

15 3,5-difluoro-4-[4-[3-[2-[(5-methyltetrazol-2-yl)methyl]-4-(trifluoromethyl)phenyl]propanoyl]piperazine-1-carbonyl]benzenesulfonamide;

3-fluoro-4-[4-[3-[2-[(5-methyltetrazol-2-yl)methyl]-4-(trifluoromethyl)phenyl]propanoyl]piperazine-1-carbonyl]benzenesulfonamide ;

20 4-(4-(3-(2-((5-methyl-2H-tetrazol-2-yl)methyl)-4-(trifluoromethyl)phenyl)propanoyl)piperazine-1-carbonyl)benzenesulfonamide;

3-[[1-[2-cyclopropyl-6-(oxan-4-ylmethoxy)pyridine-4-carbonyl]piperidin-4-yl]methyl]-4-fluorobenzenesulfonamide;

3-fluoro-4-[1-[3-[2-[(5-methyltetrazol-2-yl)methyl]-4-(trifluoromethyl)phenyl]propanoyl]piperidin-4-yl]sulfanylbenzenesulfonamide;

25 3-fluoro-4-(4-(3-(2-((5-methyl-2H-tetrazol-2-yl)methyl)-4-(trifluoromethyl)phenyl)propanoyl)piperazin-1-yl)benzenesulfonamide;

- 4-[[1-[2-cyclopropyl-6-(oxan-4-ylmethoxy)pyridine-4-carbonyl]piperidin-4-yl]methyl]benzenesulfonamide;
- 4-[[1-[3-[2-[(5-methyltetrazol-2-yl)methyl]-4-(trifluoromethyl)phenyl]propanoyl]piperidin-4-yl]methyl]benzenesulfonamide;
- 5 4-[[1-[3-[2-[(5-methyltetrazol-2-yl)methyl]-4-(trifluoromethyl)phenyl]propanoyl]pyrrolidin-2-yl]methoxy]benzenesulfonamide ;
- 4-[[1-[3-[2-[(5-methyltetrazol-2-yl)methyl]-4-(trifluoromethyl)phenyl]propanoyl]pyrrolidin-3-yl]methoxy]benzenesulfonamide;
- 10 4-(1-(3-(2-((5-methyl-2H-tetrazol-2-yl)methyl)-4-(trifluoromethyl)phenyl)propanoyl)piperidin-4-yl)benzenesulfonamide;
- 4-(4-(3-(2-((5-methyl-2H-tetrazol-2-yl)methyl)-4-(trifluoromethyl)phenyl)propanoyl)piperazin-1-yl)benzenesulfonamide;
- 4-fluoro-3-[[1-[3-[2-[(5-methyltetrazol-2-yl)methyl]-4-(trifluoromethyl)phenyl]propanoyl]piperidin-4-yl]methyl]benzenesulfonamide;
- 15 2,3-difluoro-4-[1-[3-[2-[(5-methyltetrazol-2-yl)methyl]-4-(trifluoromethyl)phenyl]propanoyl]piperidin-4-yl]sulfanylbenzenesulfonamide;
- 2,3-difluoro-4-[1-[3-[2-[(5-methyltetrazol-2-yl)methyl]-4-(trifluoromethyl)phenyl]propanoyl]piperidin-4-yl]sulfinylbenzenesulfonamide;
- 20 2,3-difluoro-4-[1-[3-[2-[(5-methyltetrazol-2-yl)methyl]-4-(trifluoromethyl)phenyl]propanoyl]piperidin-4-yl]sulfonylbenzenesulfonamide;
- 2,3-difluoro-4-[2-[1-[3-[2-[(5-methyltetrazol-2-yl)methyl]-4-(trifluoromethyl)phenyl]propanoyl]piperidin-4-yl]ethylsulfonyl]benzenesulfonamide;
- 2-[1-[3-[2-[(5-methyltetrazol-2-yl)methyl]-4-(trifluoromethyl)phenyl]propanoyl]piperidin-4-yl]sulfanyl-1,3-thiazole-5-sulfonamide;
- 25 2-[1-[3-[2-[(5-methyltetrazol-2-yl)methyl]-4-(trifluoromethyl)phenyl]propanoyl]piperidin-4-yl]sulfonyl-1,3-thiazole-5-sulfonamide;

2-[2-[1-[3-[2-[(5-methyltetrazol-2-yl)methyl]-4-(trifluoromethyl)phenyl]propanoyl]piperidin-4-yl]ethylsulfinyl]-1,3-thiazole-5-sulfonamide;

5 3-fluoro-4-[[1-[3-[2-[(5-methyltetrazol-2-yl)methyl]-4-(trifluoromethyl)phenyl]propanoyl]piperidin-4-yl]methylsulfonyl]benzenesulfonamide;

3-fluoro-4-[[1-[3-[2-[(5-methyltetrazol-2-yl)methyl]-4-(trifluoromethyl)phenyl]propanoyl]piperidin-4-yl]methylsulfinyl]benzenesulfonamide;

3-fluoro-4-[[1-[3-[2-[(5-methyltetrazol-2-yl)methyl]-4-(trifluoromethyl)phenyl]propanoyl]piperidin-4-yl]methylsulfonyl]benzenesulfonamide;

10 3-fluoro-4-[1-[3-[2-[(5-methyltetrazol-2-yl)methyl]-4-(trifluoromethyl)phenyl]propanoyl]azetidin-3-yl]sulfonylbenzenesulfonamide;

3-fluoro-4-[1-[3-[2-[(5-methyltetrazol-2-yl)methyl]-4-(trifluoromethyl)phenyl]propanoyl]azetidin-3-yl]sulfinylbenzenesulfonamide;

15 3-fluoro-4-[1-[3-[2-[(5-methyltetrazol-2-yl)methyl]-4-(trifluoromethyl)phenyl]propanoyl]azetidin-3-yl]sulfonylbenzenesulfonamide;

3-fluoro-4-[1-[3-[2-[(5-methyltetrazol-2-yl)methyl]-4-(trifluoromethyl)phenyl]propanoyl]piperidin-4-yl]sulfinylbenzenesulfonamide;

3-fluoro-4-[1-[3-[2-[(5-methyltetrazol-2-yl)methyl]-4-(trifluoromethyl)phenyl]propanoyl]piperidin-4-yl]sulfonylbenzenesulfonamide;

20 3-fluoro-4-[2-[1-[3-[2-[(5-methyltetrazol-2-yl)methyl]-4-(trifluoromethyl)phenyl]propanoyl]piperidin-4-yl]ethylsulfonyl]benzenesulfonamide;

3-fluoro-4-[2-[1-[3-[2-[(5-methyltetrazol-2-yl)methyl]-4-(trifluoromethyl)phenyl]propanoyl]piperidin-4-yl]ethylsulfinyl]benzenesulfonamide;

25 3-fluoro-4-[2-[1-[3-[2-[(5-methyltetrazol-2-yl)methyl]-4-(trifluoromethyl)phenyl]propanoyl]piperidin-4-yl]ethylsulfonyl]benzenesulfonamide;

3-fluoro-4-[2-[1-[6-(2,2,2-trifluoroethoxy)-5-(trifluoromethyl)pyridine-3-carbonyl]piperidin-4-yl]ethylsulfonyl]benzenesulfonamide;

- 3-fluoro-4-[4-[3-[2-[(5-methyltetrazol-2-yl)methyl]-4-(trifluoromethyl)phenyl]propanoyl]piperazin-1-yl]sulfonylbenzenesulfonamide;
- 4-[[1-[2-cyclopropyl-6-(oxan-4-ylmethoxy)pyridine-4-carbonyl]piperidin-4-yl]methylsulfanyl]-3-fluorobenzenesulfonamide;
- 5 4-[[1-[2-cyclopropyl-6-(oxan-4-ylmethoxy)pyridine-4-carbonyl]piperidin-4-yl]methylsulfinyl]-3-fluorobenzenesulfonamide;
- 4-[[1-[2-cyclopropyl-6-(oxan-4-ylmethoxy)pyridine-4-carbonyl]piperidin-4-yl]methylsulfonyl]-3-fluorobenzenesulfonamide;
- 10 4-[1-(6-cyclobutyloxy-5-cyclopropylpyridine-3-carbonyl)piperidin-4-yl]sulfonyl-3-fluorobenzenesulfonamide;
- 4-[1-[2-cyclopropyl-6-(oxan-4-ylmethoxy)pyridine-4-carbonyl]azetidin-3-yl]sulfanyl-3-fluorobenzenesulfonamide;
- 4-[1-[2-cyclopropyl-6-(oxan-4-ylmethoxy)pyridine-4-carbonyl]azetidin-3-yl]sulfinyl-3-fluorobenzenesulfonamide;
- 15 4-[1-[2-cyclopropyl-6-(oxan-4-ylmethoxy)pyridine-4-carbonyl]azetidin-3-yl]sulfonyl-3-fluorobenzenesulfonamide;
- 4-[1-[2-cyclopropyl-6-(oxan-4-ylmethoxy)pyridine-4-carbonyl]piperidin-4-yl]sulfonyl-2,3-difluorobenzenesulfonamide;
- 20 4-[1-[2-cyclopropyl-6-(oxan-4-ylmethoxy)pyridine-4-carbonyl]piperidin-4-yl]sulfonyl-3-fluorobenzenesulfonamide;
- 4-[1-[3-[4-chloro-2-[(5-methyltetrazol-2-yl)methyl]phenyl]propanoyl]piperidin-4-yl]sulfonyl-3-fluorobenzenesulfonamide;
- 4-[1-[3-[4-cyano-2-[(5-methyltetrazol-2-yl)methyl]phenyl]propanoyl]piperidin-4-yl]sulfonyl-3-fluorobenzenesulfonamide;
- 25 4-[2-[1-[2-cyclopropyl-6-(oxan-4-ylmethoxy)pyridine-4-carbonyl]piperidin-4-yl]ethylsulfanyl]-3-fluorobenzenesulfonamide;

- 4-[2-[1-[2-cyclopropyl-6-(oxan-4-ylmethoxy)pyridine-4-carbonyl]piperidin-4-yl]ethylsulfonyl]-3-fluorobenzenesulfonamide;
- 4-[2-[1-[2-cyclopropyl-6-(oxan-4-ylmethoxy)pyridine-4-carbonyl]piperidin-4-yl]ethylsulfonyl]-3-fluorobenzenesulfonamide;
- 5 4-[2-[1-[5-cyclopropyl-6-(cyclopropylmethoxy)pyridine-3-carbonyl]piperidin-4-yl]ethylsulfonyl]-3-fluorobenzenesulfonamide;
- 4-[4-[2-cyclopropyl-6-(oxan-4-ylmethoxy)pyridine-4-carbonyl]piperazin-1-yl]sulfonyl-3-fluorobenzenesulfonamide;
- 10 4-[4-[3-[2-[(5-methyltetrazol-2-yl)methyl]-4-(trifluoromethyl)phenyl]propanoyl]piperazin-1-yl]sulfonylbenzenesulfonamide ;
- 5-[1-[3-[2-[(5-methyltetrazol-2-yl)methyl]-4-(trifluoromethyl)phenyl]propanoyl]piperidin-4-yl]sulfanylthiophene-2-sulfonamide;
- 5-[2-[1-[3-[2-[(5-methyltetrazol-2-yl)methyl]-4-(trifluoromethyl)phenyl]propanoyl]piperidin-4-yl]ethylsulfonyl]thiophene-2-sulfonamide;
- 15 5-fluoro-6-[1-[3-[2-[(5-methyltetrazol-2-yl)methyl]-4-(trifluoromethyl)phenyl]propanoyl]piperidin-4-yl]sulfanylpyridine-3-sulfonamide;
- 6-[1-[2-cyclopropyl-6-(oxan-4-ylmethoxy)pyridine-4-carbonyl]piperidin-4-yl]sulfanyl-5-fluoropyridine-3-sulfonamide;
- 4-[1-[3-[4-(difluoromethoxy)-2-[(5-methyltetrazol-2-yl)methyl]phenyl]propanoyl]piperidin-4-yl]sulfonyl-3-fluorobenzenesulfonamide;
- 20 4-[2-[1-[3-[4-(difluoromethoxy)-2-[(5-methyltetrazol-2-yl)methyl]phenyl]propanoyl]piperidin-4-yl]ethylsulfinyl]-2,3-difluorobenzenesulfonamide;
- 2,3-difluoro-4-[2-[1-[3-[2-[(5-methyltetrazol-2-yl)methyl]-4-(trifluoromethyl)phenyl]propanoyl]piperidin-4-yl]ethylsulfinyl]benzenesulfonamide;
- 25 2-[2-[1-[3-[4-(difluoromethoxy)-2-[(5-methyltetrazol-2-yl)methyl]phenyl]propanoyl]piperidin-4-yl]ethylsulfinyl]-1,3-thiazole-5-sulfonamide;

2-[2-[1-[3-[2-[(5-methyltetrazol-2-yl)methyl]-4-(trifluoromethyl)phenyl]propanoyl]piperidin-4-yl]ethylsulfonyl]-1,3-thiazole-5-sulfonamide;

5 (+)-3-fluoro-4-[[1-[3-[2-[(5-methyltetrazol-2-yl)methyl]-4-(trifluoromethyl)phenyl]propanoyl]piperidin-4-yl]sulfinyl]benzenesulfonamide;

(+)-4-[[1-[3-[2-[(5-methyltetrazol-2-yl)methyl]-4-(trifluoromethyl)phenyl]propanoyl]pyrrolidin-2-yl]methoxy]benzenesulfonamide;

(+)-4-[[1-[3-[2-[(5-methyltetrazol-2-yl)methyl]-4-(trifluoromethyl)phenyl]propanoyl]pyrrolidin-3-yl]methoxy]benzenesulfonamide;

10 (-)-3-fluoro-4-[[1-[3-[2-[(5-methyltetrazol-2-yl)methyl]-4-(trifluoromethyl)phenyl]propanoyl]piperidin-4-yl]sulfinyl]benzenesulfonamide;

(-)-4-[[1-[3-[2-[(5-methyltetrazol-2-yl)methyl]-4-(trifluoromethyl)phenyl]propanoyl]pyrrolidin-2-yl]methoxy]benzenesulfonamide;

15 (-)-4-[[1-[3-[2-[(5-methyltetrazol-2-yl)methyl]-4-(trifluoromethyl)phenyl]propanoyl]pyrrolidin-3-yl]methoxy]benzenesulfonamide;

4-((4-(3-(2-((5-methyl-2H-tetrazol-2-yl)methyl)-4-(trifluoromethyl)phenyl)propanoyl)piperazin-1-yl)methyl)benzenesulfonamide;

and pharmaceutically acceptable salts thereof.

25. A compound according to any one of claims 1 to 21, selected from

20 3-fluoro-4-[[4-[3-[2-[(5-methyltetrazol-2-yl)methyl]-4-(trifluoromethyl)phenyl]propanoyl]piperazin-1-yl]methyl]benzenesulfonamide;

2,3-difluoro-4-[1-[3-[2-[(5-methyltetrazol-2-yl)methyl]-4-(trifluoromethyl)phenyl]propanoyl]piperidin-4-yl]sulfonylbenzenesulfonamide;

25 3-fluoro-4-[1-[3-[2-[(5-methyltetrazol-2-yl)methyl]-4-(trifluoromethyl)phenyl]propanoyl]piperidin-4-yl]sulfonylbenzenesulfonamide;

3-fluoro-4-[4-[3-[2-[(5-methyltetrazol-2-yl)methyl]-4-(trifluoromethyl)phenyl]propanoyl]piperazin-1-yl]sulfonylbenzenesulfonamide;

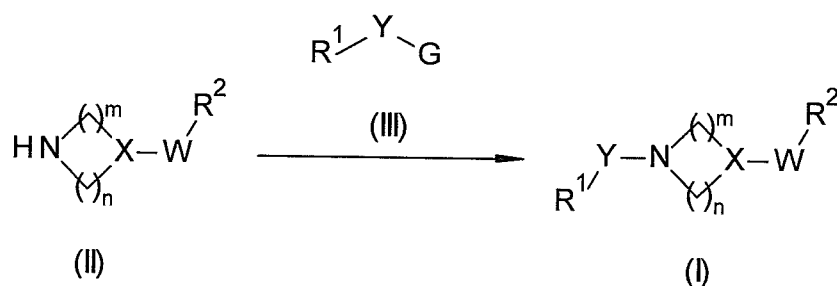
4-[1-[2-cyclopropyl-6-(oxan-4-ylmethoxy)pyridine-4-carbonyl]piperidin-4-yl]sulfonyl-2,3-difluorobenzenesulfonamide;

4-[1-[2-cyclopropyl-6-(oxan-4-ylmethoxy)pyridine-4-carbonyl]piperidin-4-yl]sulfonyl-3-fluorobenzenesulfonamide;

5 5-fluoro-6-[1-[3-[2-[(5-methyltetrazol-2-yl)methyl]-4-(trifluoromethyl)phenyl]propanoyl]piperidin-4-yl]sulfanylpiperidine-3-sulfonamide;

and pharmaceutically acceptable salts thereof.

26. A process to prepare a compound according to any one of claims 1 to 22 comprising the reaction of a compound of formula (II) in the presence of a compound of formula (III);



wherein R¹, R², Y, W, X, m and n are as defined herein and in case Y is -(CH₂)_qC(O)-, -(CH=CH)_r-C(O)- or -(CH≡CH)_r-C(O)-, then G is halogen or hydroxy and in case Y is -OC(O)-, then G is chloro.

15 27. A compound according to any one of claims 1 to 22 for use as therapeutically active substance.

28. A pharmaceutical composition comprising a compound according to any one of claims 1 to 22 and a therapeutically inert carrier.

29. A compound according to any one of claims 1 to 22 for use in the treatment or prophylaxis
20 of ocular conditions.

30. The use of a compound according to any one of claims 1 to 22 for the preparation of a medicament for the treatment or prophylaxis of ocular conditions selected from the group consisting of proliferative and non-proliferative diabetic retinopathy, dry and wet age-

related macular degeneration (AMD), macular edema, central arterial /venous occlusion, traumatic injury, and glaucoma.
