Claims

1. A modulator of Kv3.1 and/or Kv3.2 and/or Kv3.3 for use in the prophylaxis or treatment of pain.

2. Use of a modulator of Kv3.1 and/or Kv3.2 and/or Kv3.3 in the manufacture of a medicament for the prophylaxis or treatment of pain.

3. A method of prophylaxis or treatment of pain in a subject by administering a modulator of Kv3.1 and/or Kv3.2 and/or Kv3.3.

4. A pharmaceutical composition comprising a modulator of Kv3.1 and/or Kv3.2 and/or Kv3.3 for use in the prophylaxis or treatment of pain wherein the composition optionally comprises one or more therapeutic agents and/or one or more pharmaceutically acceptable excipients.

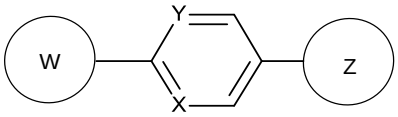
5. The modulator, use, method or composition according to any one of claims 1 to 4, for the prophylaxis of pain.

6. The modulator, use, method or composition according to any one of claims 1 to 4, for the treatment of pain.

7. The modulator, use, method or composition according to any one of claims 1 to 6, wherein the pain is selected from acute pain, chronic pain, nociceptive pain (such as somatic pain or visceral pain), neuropathic pain (such as central neuropathic pain, peripheral neuropathic pain, diabetic neuropathy, post-herpetic neuralgia, spinal cord injury pain, phantom limb (post-amputation) pain or post-stroke central pain, or wherein the neuropathic pain is due to trauma, chemotherapy or heavy metal exposure), inflammatory pain (such as inflammatory pain is caused by appendicitis, rheumatoid arthritis, inflammatory bowel disease or herpes zoster) and miscellaneous pain (such as cancer pain, migraine or other primary headaches, or wide-spread pain of the fibromyalgia type).

8. The modulator, use, method or composition according to any one of claims 1 to 7, wherein a reduction of at least 10% from baseline pain score is achieved, such as a reduction of at least 50% from baseline pain score.

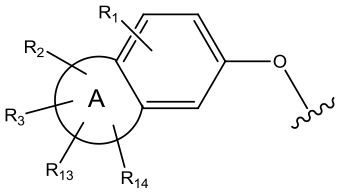
9. The modulator, use, method or composition according to any one of claims 1 to 8, wherein the modulator of Kv3.1 and/or Kv3.2 and/or Kv3.3 is a compound of formula (I):



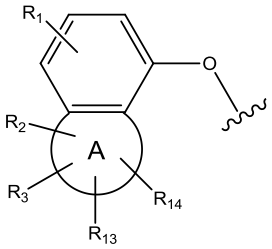
(I)

wherein:

W is group (Wa), group (Wb), group (Wc) or group (Wd):



(Wa);



(Wb);

wherein:

R_1 is H, $C_{1\text{-}4}$alkyl, halo, halo$C_{1\text{-}4}$alkyl, CN, $C_{1\text{-}4}$alkoxy, or halo$C_{1\text{-}4}$alkoxy;

R_2 is H, $C_{1\text{-}4}$alkyl, $C_{3\text{-}5}$ spiro carbocyclyl, halo$C_{1\text{-}4}$alkyl or halo;

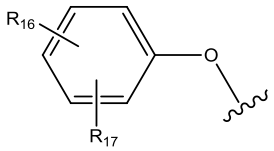
R_3 is H, $C_{1\text{-}4}$alkyl, halo$C_{1\text{-}4}$alkyl, halo; or R_3 is absent;

R_{13} is H, $C_{1\text{-}4}$alkyl, halo$C_{1\text{-}4}$alkyl, halo; or R_{13} is absent;

R_{14} is H, $C_{1\text{-}4}$alkyl, halo$C_{1\text{-}4}$alkyl, halo; or R_{14} is absent;

A is a 5 or 6 membered saturated or unsaturated heterocycle, with at least one O atom; which heterocycle is optionally fused with a cyclopropyl group, or a cyclobutyl group, or a cyclopentyl group to form a tricycle when considered together with the phenyl;

wherein R_2 and R_3 may be attached to the same or a different ring atom; R_2 may be attached to a fused ring atom; and wherein R_{13} and R_{14} may be attached to the same or a different ring atom;

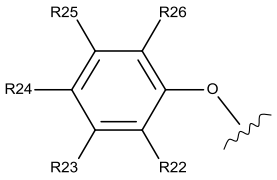


(Wc);

wherein:

R_{16} is halo, $C_{1\text{-}4}$ alkyl, $C_{1\text{-}4}$ alkoxy, halo-$C_{1\text{-}4}$alkyl, halo-$C_{1\text{-}4}$alkoxy, or CN;

R_{17} is H, halo, cyano, $C_{1\text{-}4}$ alkyl or $C_{1\text{-}4}$ alkoxy; with the proviso that when R_{17} is H, R_{16} is not in the para position;



(Wd);

wherein:

R_{22} is H, Cl, F, C_{1-4}alkyl;

R_{23} is H, C_{1-4}alkyl, Cl, CF_3, O-C_{1-4}alkyl, OCF_3 or $N(CH_3)_2$;

R_{24} is H, Cl, F, C_{1-4}alkyl, O-C_{1-4}alkyl, CN, OCF_3 or CF_3;

R_{25} is H, Cl, F, O-C_{1-4}alkyl or C_{1-4}alkyl; and

R_{26} is H or C_{1-4}alkyl;

wherein for R_{22} to R_{26}, C_{1-4}alkyl may be substituted by O-methyl;

with the provisos that:

not all of R_{22} to R_{26} may be H;

when R_4 is H, then R_{23} is methyl or CF_3 and R_{22}, R_{24}, R_{25} and R_{26} are all H;

when one of R_{22}, R_{24}, R_{25} or R_{26} is F, then at least one of R_{22} to R_{26} cannot be H or F; and

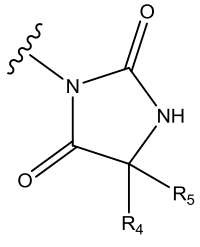
when R_{24} is not H, at least one of R_{22} or R_{23} is not H;

X is CH or N;

Y is CR_{15} or N;

R_{15} is H or C_{1-4}alkyl;

when W is group (Wa), group (Wb) or group (Wc), Z is group (Za):



(Za);

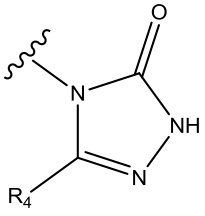
wherein:

R_4 is C_{1-4} alkyl;

R_5 is H or C_{1-4} alkyl;

or R_4 and R_5 can be fused to form C_{3-4} spiro carbocyclyl;

when W is group (Wa), group (Wb) or group (Wd), Z is group (Zb):



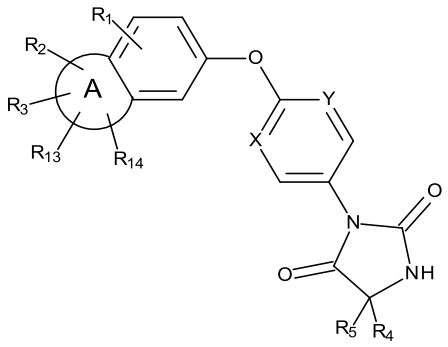
(Zb);

wherein:

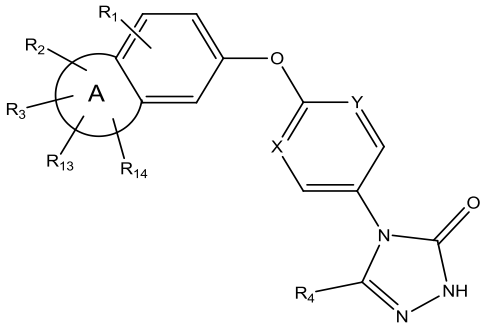
R_4 is H or C_{1-4} alkyl;

or a pharmaceutically acceptable salt and/or solvate thereof and/or derivative thereof.

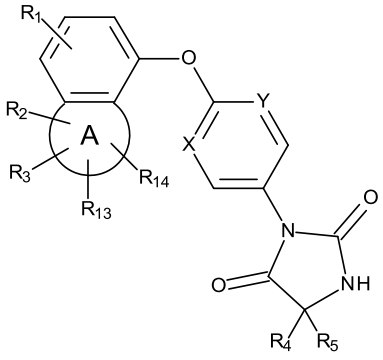
10. The modulator, use, method or composition according to claim 9, wherein the modulator of Kv3.1 and/or Kv3.2 and/or Kv3.3 is selected from a compound of formulae (IA), (IB), (IC), (ID), (IE) and (IF):



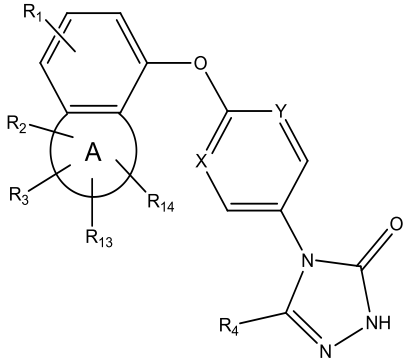
(IA);



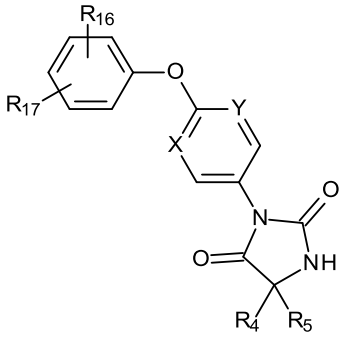
(IB);



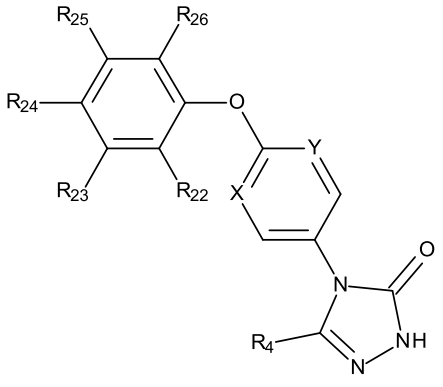
(IC);



(ID);



(IE);



(IF);

wherein

R_1 is H, $C_{1\text{-}4}$alkyl, halo, halo$C_{1\text{-}4}$alkyl;

R_2 is H, $C_{1\text{-}4}$alkyl, $C_{3\text{-}5}$spiro carbocyclyl, or halo$C_{1\text{-}4}$alkyl;

R_3 is H, $C_{1\text{-}4}$alkyl, halo$C_{1\text{-}4}$alkyl or halo; or R_3 is absent

R_{13} is H or is absent;

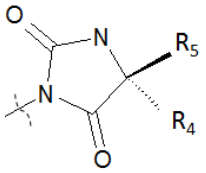
R_{14} is H or is absent;

A is a 5 or 6 membered saturated or unsaturated heterocycle, with at least one O atom;

R_4 is C_{1-4} alkyl;

R_5 is H or C_{1-4}alkyl;

wherein when R_5 is present, R_4 and R_5 have the stereochemical arrangement:



R_{16} is C_{1-4} alkyl, C_{1-4} alkoxy, halo-C_{1-4}alkyl, halo-C_{1-4}alkoxy;

R_{17} is H, cyano or C_{1-4} alkyl; with the proviso that when R_{17} is H, R_{16} is not in the para position;

R_{23} is C_{1-4}alkyl, Cl, CF_3, O-C_{1-4}alkyl, OCF_3 or $N(CH_3)_2$;

R_{24} is H, Cl, F, C_{1-4}alkyl, O-C_{1-4}alkyl, CN, OCF_3;

R_{22}, R_{25} and R_{26} are H;

X is CH or N and

Y is CH or N.

11. The modulator, use, method or composition according to any one of claims 1 to 10 wherein the modulator of Kv3.1 and/or Kv3.2 and/or Kv3.3 is a compound selected from the group consisting of:

5,5-dimethyl-3-[2-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]pyrimidin-5-yl]imidazolidine-2,4-dione (enantiomer 1);

5,5-dimethyl-3-[2-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]pyrimidin-5-yl]imidazolidine-2,4-dione (enantiomer 2) ;

(5R)-3-[6-[(3,3-dimethyl-1H-isobenzofuran-5-yl)oxy]-3-pyridyl]-5-ethyl-5-methyl-imidazolidine-2,4-dione;

3-[6-[(3-tert-butyl-1,3-dihydroisobenzofuran-5-yl)oxy]-3-pyridyl]-5,5-dimethyl-imidazolidine-2,4-dione (enantiomer 1) ;

3-[6-[(3-tert-butyl-1,3-dihydroisobenzofuran-5-yl)oxy]-3-pyridyl]-5,5-dimethyl-imidazolidine-2,4-dione (enantiomer 2);

5,5-dimethyl-3-[6-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]-3-pyridyl]imidazolidine-2,4-dione (enantiomer 1);

5,5-dimethyl-3-[6-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]-3-pyridyl]imidazolidine-2,4-dione (enantiomer 2) ;

5,5-dimethyl-3-(6-spiro[1H-isobenzofuran-3,1'-cyclobutane]-5-yloxy-3-pyridyl)imidazolidine-2,4-dione ;

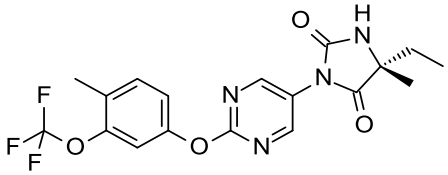
(5R)-3-[6-[(3,3-dimethyl-1H-isobenzofuran-5-yl)oxy]-3-pyridyl]-5-ethyl-imidazolidine-2,4-dione;

(5R)-5-ethyl-3-[6-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]-3-pyridyl]imidazolidine-2,4-dione (diastereoisomer 1) ;

(5R)-5-ethyl-3-[6-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]-3-pyridyl]imidazolidine-2,4-dione (diastereoisomer 2) ;
(5R)-5-ethyl-3-(6-spiro[1H-isobenzofuran-3,1'-cyclobutane]-5-yloxy-3-pyridyl)imidazolidine-2,4-dione;
(5R)-5-ethyl-3-[2-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]pyrimidin-5-yl]imidazolidine-2,4-dione (diastereoisomer 1);
(5R)-5-ethyl-3-[2-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]pyrimidin-5-yl]imidazolidine-2,4-dione (diastereoisomer 2);
(5R)-5-ethyl-3-(2-spiro[1H-isobenzofuran-3,1'-cyclobutane]-5-yloxypyrimidin-5-yl)imidazolidine-2,4-dione ;
(5R)-3-{4-[(3,3-dimethyl-1,3-dihydro-2-benzofuran-5-yl)oxy]phenyl}-5-ethyl-5-methyl-2,4-imidazolidinedione;
(5R)-5-ethyl-5-methyl-3-[2-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrimidin-5-yl]imidazolidine-2,4-dione;
(5R)-5-ethyl-5-methyl-3-{2-[(3,3,7-trimethyl-2,3-dihydro-1-benzofuran-4-yl)oxy]-5-pyrimidinyl}-2,4-imidazolidinedione;
(5R)-3-{2-[(2,2-difluoro-7-methyl-1,3-benzodioxol-4-yl)oxy]-5-pyrimidinyl}-5-ethyl-5-methyl-2,4-imidazolidinedione;
5,5-dimethyl-3-[2-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrimidin-5-yl]imidazolidine-2,4-dione;
(5R)-5-ethyl-3-[2-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrimidin-5-yl]imidazolidine-2,4-dione;
(5R)-5-ethyl-3-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]imidazolidine-2,4-dione;
(5R)-5-ethyl-3-{6-[(3,3,7-trimethyl-2,3-dihydro-1-benzofuran-4-yl)oxy]-3-pyridinyl}-2,4-imidazolidinedione;
(5R)-5-ethyl-3-{2-[(3,3,7-trimethyl-2,3-dihydro-1-benzofuran-4-yl)oxy]-5-pyrimidinyl}-2,4-imidazolidinedione;
(5R)-5-ethyl-5-methyl-3-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]imidazolidine-2,4-dione;
5,5-dimethyl-3-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]imidazolidine-2,4-dione;
(5R)-5-ethyl-5-methyl-3-[2-({4-methyl-3-[(trifluoromethyl)oxy]phenyl}oxy)-5-pyrimidinyl]-2,4-imidazolidinedione;
(5R)-5-ethyl-3-[2-({4-methyl-3-[(trifluoromethyl)oxy]phenyl}oxy)-5-pyrimidinyl]-2,4-imidazolidinedione;
5,5-dimethyl-3-[2-({4-methyl-3-[(trifluoromethyl)oxy]phenyl}oxy)-5-pyrimidinyl]-2,4-imidazolidinedione;
(5R)-5-ethyl-3-[6-({4-methyl-3-[(trifluoromethyl)oxy]phenyl}oxy)-3-pyridinyl]-2,4-imidazolidinedione;
5,5-dimethyl-3-[6-({4-methyl-3-[(trifluoromethyl)oxy]phenyl}oxy)-3-pyridinyl]-2,4-imidazolidinedione;

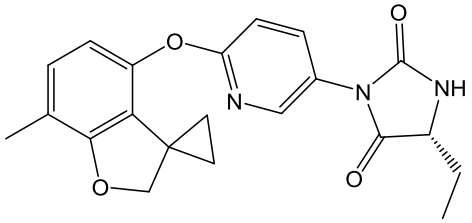
(5R)-5-ethyl-3-(6-{[4-methyl-3-(methyloxy)phenyl]oxy}-3-pyridinyl)-2,4-imidazolidinedione;
5-methyl-4-{6-[(7-methylspiro[1-benzofuran-3,1'-cyclopropan]-4-yl)oxy]pyridin-3-yl}-2,4-dihydro-3H-1,2,4-triazol-3-one; and
5-methyl-4-[6-(spiro[1-benzofuran-3,1'-cyclopropan]-4-yloxy)pyridin-3-yl]-2,4-dihydro-3H-1,2,4-triazol-3-one;
or a pharmaceutically acceptable salt and/or solvate thereof and/or derivative thereof.

12. The modulator, use, method or composition according to claim 11, wherein the modulator of Kv3.1 and/or Kv3.2 and/or Kv3.3 is:



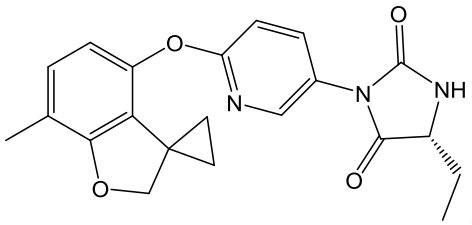
.

13. The modulator, use, method or composition according to claim 11, wherein the modulator of Kv3.1 and/or Kv3.2 and/or Kv3.3 is:



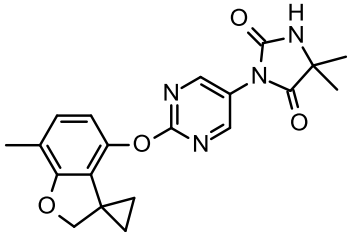
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14. The modulator, use, method or composition according to claim 11, wherein the modulator of Kv3.1 and/or Kv3.2 and/or Kv3.3 is a pharmaceutically acceptable salt of:



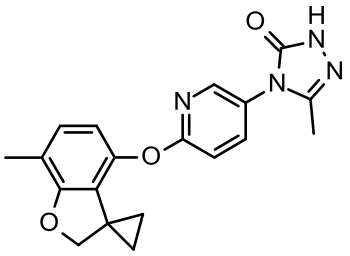
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15. The modulator, use, method or composition according to claim 11, wherein the modulator of Kv3.1 and/or Kv3.2 and/or Kv3.3 is:



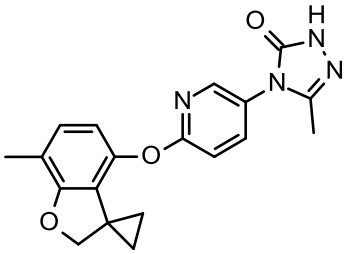
.

16. The modulator, use, method or composition according to claim 11, wherein the modulator of Kv3.1 and/or Kv3.2 and/or Kv3.3 is:



.

17. The modulator, use, method or composition according to claim 11, wherein the modulator of Kv3.1 and/or Kv3.2 and/or Kv3.3 is a pharmaceutically acceptable salt of:



.

18. A method of identifying that a compound is of use in the prophylaxis or treatment of pain, said method comprising the step of determining that the compound is a modulator of Kv3.1 and/or Kv3.2 and/or Kv3.3 channels.

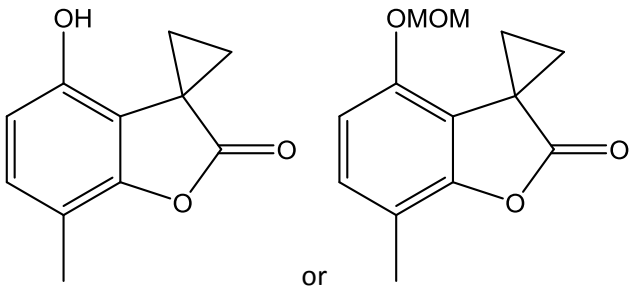
19. A method for the manufacture of a pain medicament, said method comprising the steps:
(i) determining that a compound is a modulator of Kv3.1 and/or Kv3.2 and/or Kv3.3 channels; and
(ii) preparing a medicament comprising the compound.

20. The modulator, use, method or composition according to any one of claims 1 to 17, wherein the modulator of Kv3.1 and/or Kv3.2 and/or Kv3.3 is capable of producing at least 20% potentiation of whole-cell currents mediated by human Kv3.1 and/or Kv3.2 and/or Kv3.3 channels recombinantly expressed in mammalian cells, suitably the pEC_{50} of the modulator is in the range of 4-7.

21. The modulator, use, method or composition according to any one of claims 1 to 20, wherein the modulator of Kv3.1 and/or Kv3.2 and/or Kv3.3 provides an increase of less than 10% in Kv3.4 current at the same concentration, such as 10 uM.

22. The modulator, use, method or composition according to any one of claims 1 to 21, for use in combination with a further therapeutic agent, such as a NSAID, paracetamol, pregabalin, gabapentin or opioid.

23. A compound which is:



or