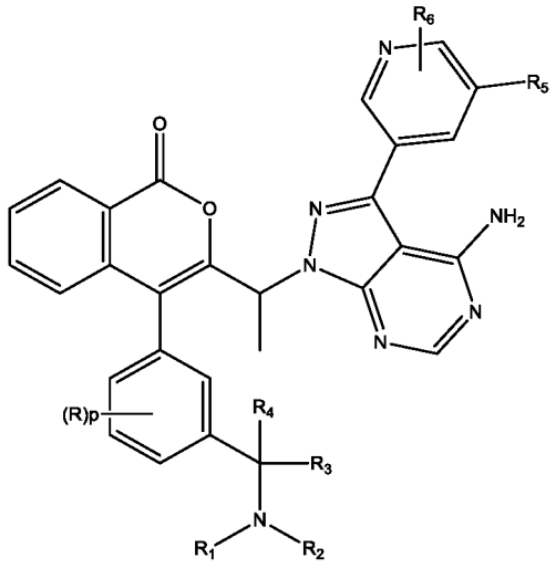
CLAIMS

1. A compound of formula (I):



(I)

wherein:

each R, when present, is independently selected from the group consisting of: OR_7, halogen, (C_1-C_6) alkyl;

R_1 and R_2 the same or different, are at each occurrence independently (C_1-C_6) alkyl, R_3 and R_4, the same or different, in each occurrence are independently H or (C_1-C_6) alkyl;

or

R_1 and R_2 taken together with the nitrogen atom they are linked to, form a 5 or 6 membered heterocyclic radical, wherein at least one further ring carbon atom in the said heterocyclic radical is optionally replaced by at least one heteroatom selected from N, NH, S or O and optionally bears at least one - oxo (=O) substituent group; the said

heterocyclic radical is further optionally substituted by an (C_1-C_6) alkyl group, and R_3 and R_4 are H;

or

R_3 and R_2 taken together, form a 5 or 6 membered heterocyclic radical comprising the N atom; the said heterocyclic radical is further optionally substituted by an (C_1-C_6) alkyl group, R_1 is an (C_1-C_6) alkyl group and R_4 is H;

R_5 is OR_7;

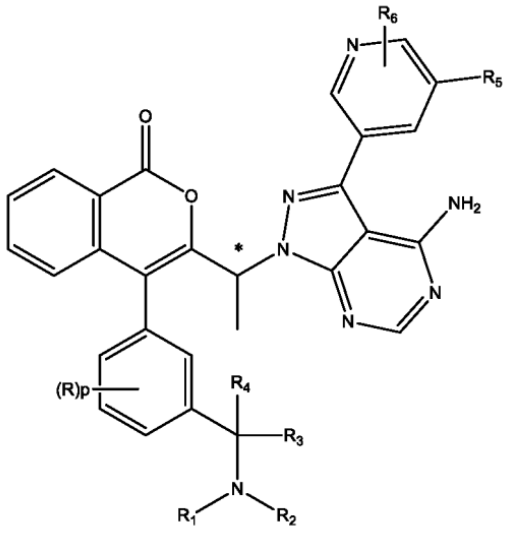
R_6 is selected from the group consisting of: H, OR_7, (C_1-C_6) alkyl, (C_1-C_6) haloalkyl, (C_1-C_6) hydroxyalkyl;

R_7 is H;

p is zero or an integer ranging from 1 to 4;

and pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein the absolute configuration at carbon (*) is (S) or (R) with reference to the stereogenic center represented in formula (Ia) by the carbon atom labelled with an asterisk (*):



3. A compound according to anyone of claim 1 or 2

wherein:

R_1 and R_2 taken together with the nitrogen atom they are linked to, form a 4-methylpiperazine-1-yl group;

R_3 and R_4 are H;

R, R_5, R_6 and p are as defined in claim 1;

or pharmaceutically acceptable salts thereof.

4. A compound according to anyone of claim 1 or 2

wherein:

R_3 and R_2 taken together, form a 5 membered heterocyclic radical comprising the N atom; the said heterocyclic radical is further substituted by an (C_1-C_6) alkyl group which is methyl; R_1 is an (C_1-C_6) alkyl group which is methyl and R_4 is H; and

R, R_5, R_6 and p are as defined above;

or pharmaceutically acceptable salts thereof.

5. A compound according to anyone of claim 1 or 2

wherein:

R_1 and R_2 are (C_1-C_6) alkyl which is methyl,

R_3 and R_4 are independently H or (C_1-C_6) alkyl which is methyl; and

R, R_5, R_6 and p are as defined in claim 1;

or pharmaceutically acceptable salts thereof.

6. A compound according to anyone of claim 1 to 5 wherein:

R is -H;

R_5 is - OH;

R_6 is H;

or pharmaceutically acceptable salts thereof.

7. A compound according to anyone of claim 1 or 2 which is selected in the list consisting of:

3-{1-[4-Amino-3-(5-hydroxypyridin-3-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]ethyl}-4-{3-[(4-methylpiperazin-1-yl)methyl]phenyl}-1*H*- isochromen-1-one;

3-(1-(4-Amino-3-(5-hydroxypyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-4-(3-((dimethylamino)methyl)phenyl)-1H- isochromen-1-one;

3-{1-[4-Amino-3-(5-hydroxypyridin-3-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]ethyl}-4-{4-chloro-3-[(dimethylamino)methyl]phenyl}-1*H*-isochromen-1-one;

3-{1-[4-Amino-3-(5-hydroxypyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}-4-{3-[(2R)-1-methylpyrrolidin-2-yl]phenyl}-1H- isochromen-1-one;

3-{1-[4-Amino-3-(5-hydroxypyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}-4-{4-fluoro-3-[(4-methylpiperazin-1-yl)methyl]phenyl}-1H-isochromen-1-one;

3-(1-(4-Amino-3-(5-hydroxypyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-4-(3-fluoro-5-((4-methylpiperazin-1-yl)methyl)phenyl)-1H-isochromen-1-one;

3-(1-(4-Amino-3-(5-hydroxypyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-4-(3-(1-(dimethylamino)ethyl)phenyl)-1H- isochromen-1-one;

or pharmaceutical acceptable salts thereof.

8. A compound according to claim 1 which is selected in the list consisting of:

(R) and/or (S)-3-(1-(4-amino-3-(5-hydroxypyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-4-(3-((4-methylpiperazin-1-yl)methyl)phenyl)-1H-isochromen-1-one Hydrobromide;

(R) and/or (S)-3-(1-(4-amino-3-(5-hydroxypyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-4-(3-((4-methylpiperazin-1-yl)methyl)phenyl)-1H-isochromen-1-one Hydrochloride;

(R) and/or (S)-3-(1-(4-amino-3-(5-hydroxypyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-4-(3-((4-methylpiperazin-1-yl)methyl)phenyl)-1H-isochromen-1-one Hemi 1,5-Naphthalenedisulfonate;

(R) and/or (S)-3-(1-(4-amino-3-(5-hydroxypyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-4-(3-((4-methylpiperazin-1-yl)methyl)phenyl)-1H-isochromen-1-one Hemisulfate;

(R) and/or (S)-3-(1-(4-amino-3-(5-hydroxypyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-4-(3-((4-methylpiperazin-1-yl)methyl)phenyl)-1H-isochromen-1-one Tosylate;

(R) and/or (S)-3-(1-(4-amino-3-(5-hydroxypyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-4-(3-((4-methylpiperazin-1-yl)methyl)phenyl)-1H-isochromen-1-one Mesylate;

(R) and/or (S)-3-(1-(4-amino-3-(5-hydroxypyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-4-(3-((4-methylpiperazin-1-yl)methyl)phenyl)-1H-isochromen-1-one 2-Naphthalene sulfonate;

(R) and/or (S)-3-(1-(4-amino-3-(5-hydroxypyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-4-(3-((4-methylpiperazin-1-yl)methyl)phenyl)-1H-isochromen-1-one Isethionate;

(R) and/or (S)-3-(1-(4-amino-3-(5-hydroxypyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-4-(3-((4-methylpiperazin-1-yl)methyl)phenyl)-1H-isochromen-1-one Maleate;

(R) and/or (S)-3-(1-(4-amino-3-(5-hydroxypyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-4-(3-((4-methylpiperazin-1-yl)methyl)phenyl)-1H-isochromen-1-one Esylate;

(R) and/or (S)-3-(1-(4-amino-3-(5-hydroxypyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-4-(3-((4-methylpiperazin-1-yl)methyl)phenyl)-1H-isochromen-1-one Hemipamoate;

(R) and/or (S)-3-(1-(4-amino-3-(5-hydroxypyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-4-(3-((4-methylpiperazin-1-yl)methyl)phenyl)-1H-isochromen-1-one Xinafoate;

(R) and/or (S)-3-(1-(4-amino-3-(5-hydroxypyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-4-(3-((4-methylpiperazin-1-yl)methyl)phenyl)-1H-isochromen-1-one Salycilate;

(R) and/or (S)-3-(1-(4-amino-3-(5-hydroxypyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-4-(3-((4-methylpiperazin-1-yl)methyl)phenyl)-1H-isochromen-1-one Benzoate.

9. A compound according to claim 1 which is selected in the list consisting of:

(R) and/or (S)-3-(1-(4-amino-3-(5-hydroxypyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-4-(3-((dimethylamino)methyl)phenyl)-1H-isochromen-1-one Hydrobromide;

(R) and/or (S)-3-(1-(4-amino-3-(5-hydroxypyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-4-(3-((dimethylamino)methyl)phenyl)-1H-isochromen-1-one Hydrochloride;

(R) and/or (S)-3-(1-(4-amino-3-(5-hydroxypyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-4-(3-((dimethylamino)methyl)phenyl)-1H-isochromen-1-one Mesylate;

(R) and/or (S)-3-(1-(4-amino-3-(5-hydroxypyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-4-(3-((dimethylamino)methyl)phenyl)-1H-isochromen-1-one 2-Naphthalene sulfonate;

(R) and/or (S)-3-(1-(4-amino-3-(5-hydroxypyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-4-(3-((dimethylamino)methyl)phenyl)-1H-isochromen-1-one Maleate;

(R) and/or (S)-3-(1-(4-amino-3-(5-hydroxypyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-4-(3-((dimethylamino)methyl)phenyl)-1H-isochromen-1-one Esylates.

10. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 9, in admixture with one or more pharmaceutically acceptable carrier or excipient.

11. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 9, in combination with one or more active ingredients.

12. A compound according to any one of claims 1 to 9, for use as a medicament.

13. A compound as defined in any one of claims 1 to 9, for use in the treatment of a respiratory disorder associated by PI3K enzymes mechanisms selected from idiopathic chronic cough, cough-variant asthma, cough associated with thoracic tumour or lung cancer, viral or post-viral cough, upper airways cough syndrome (UACS), post nasal drip cough, cough associated gastro- oesophageal reflux disease (both acid and non acid reflux), asthma, chronic bronchitis, chronic obstructive pulmonary disease (COPD) and interstitial lung disease.

14. A compound for use according to claim 13 wherein the disorder associated by PI3K enzymes mechanisms is asthma or chronic obstructive pulmonary disease COPD.

15. A compound for use according to claim 13 wherein the disorder associated by PI3K enzymes mechanisms is idiopathic pulmonary fibrosis (IPF), cough and chronic cough.

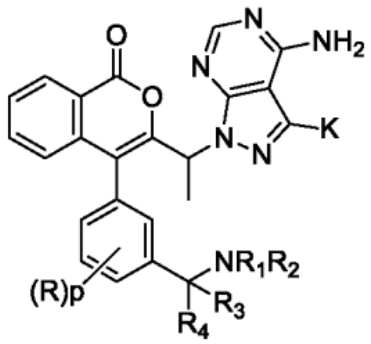
16. Use of a compound as defined in any one of claims 1 to 9 in the manufacture of a medicament for the treatment of a respiratory disorder associated by PI3K enzymes mechanisms selected from idiopathic chronic cough, cough-variant asthma, cough associated with thoracic tumour or lung cancer, viral or post-viral cough, upper airways

cough syndrome (UACS), post nasal drip cough, cough associated gastro- oesophageal reflux disease (both acid and non acid reflux), asthma, chronic bronchitis, chronic obstructive pulmonary disease (COPD) and interstitial lung disease.

17. The use according to claim 16, wherein the disorder associated by PI3K enzymes mechanisms is asthma or chronic obstructive pulmonary disease COPD.

18. The use according to claim 16, wherein the disorder associated by PI3K enzymes mechanisms is idiopathic pulmonary fibrosis (IPF), cough and chronic cough.

19. Compounds of formula (II)

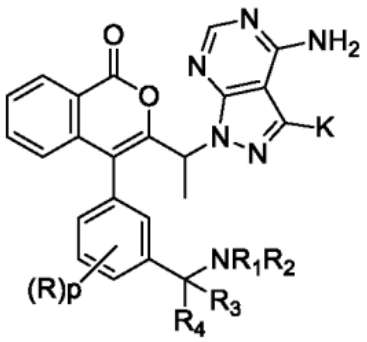


II

wherein

when R absent, p=0, R_3 and R_4 are H, K= R" is metoxypyridine; and R_1 and R_2 are as defined in claim 1.

20. Use of compounds of formula (II)



II

wherein

when R absent, p=0, R_3 and R_4 are H, K= R" is metoxypyridine; and R_1 and R_2 are as defined in claim 1

or

when K = I; p, R, R_1, R_2, R_3, R_4 are as in claim 1;

as intermediate in the preparation of compounds of formula (I) as described in claim 1.

21. Process wherein compounds of formula (II) used according to claim 20, undergo subsequent steps of deprotection or coupling; optionally followed by a final step of chiral separation to arrive at the compounds according to claim 1.

22. A pharmaceutical formulation for inhalation according to claim 10 in the form of a dry powder, wherein a carrier is present comprising coarse particles of one or more pharmaceutically acceptable excipient, and further optionally an additive is present with lubricant or anti-adherent properties.

23. The pharmaceutical formulation according to claim 22, wherein the coarse particles have a mass diameter comprised between 30 and 500 micron.

24. A dry powder inhaler device filled with a pharmaceutical formulation as defined in claim 22 or 23.

25. A kit comprising a pharmaceutical formulation as defined in claim 22 or 23 and a dry powder inhaler device.

26. A pharmaceutical formulation for inhalation according to claim 10 in the form of a propellant-free pharmaceutical formulation wherein the said compound or salt thereof is dissolved or suspended in an aqueous vehicle, optionally comprising further pharmaceutically acceptable excipients.

27. A kit comprising a pharmaceutical formulation as defined in claim 26 and a nebulizer.