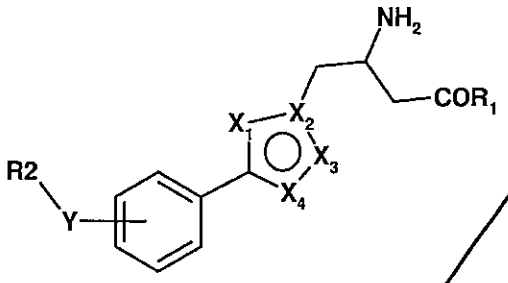
CLAIMS

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof;



(I)

wherein,

R1 is OH or NH_2;

Y is O, S or CH_2;

X1, X2, X3 and X4 are N; or

X1, X2, X3 and X4 are selected from N, NH, C, CH and O with the proviso that at least two of X1, X2, X3 or X4 are N or NH;

R2 is C_1-C_6 alkyl optionally substituted by phenyl; C_3-C_6 cycloalkyl; phenyl optionally being substituted by halogen, cyano, C_1-C_6 alkyl optionally substituted by halogen, C_1-C_6 alkoxy, or a 5 - 6 membered heteroaryl ring containing 1 to 3 heteroatoms selected from N, O and S; or a 5 - 10 membered mono- or bicyclic heteroaryl containing 1 to 4 heteroatoms selected from N, O and S said heteroaryl being optionally substituted by C_1-C_6 alkyl optionally substituted by halogen, cyano or halogen.

2. A compound of claim 1 or a pharmaceutically acceptable salt thereof; wherein R1 is OH or NH_2; Y is O; X1, X2, X3 and X4 are selected from N, NH, C, CH and O with the proviso that at least two of X1, X2, X3 or X4 are N or NH; and

R2 is phenyl optionally being substituted by halogen, cyano, C_1-C_6 alkyl optionally substituted by halogen, C_1-C_6 alkoxy, or a 5 - 6 membered heteroaryl ring containing 1 to 3 heteroatoms selected from N, O and S; or

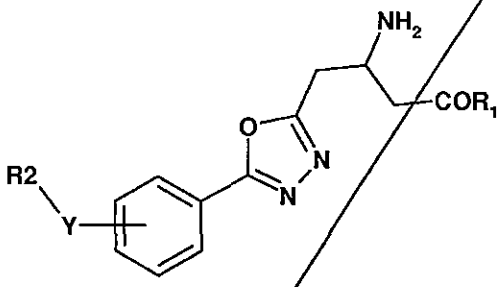
R2 is a 5 - 10 membered mono- or bicyclic heteroaryl containing 1 to 4 heteroatoms selected from N, O and S said heteroaryl being optionally substituted by C_1-C_6 alkyl optionally substituted by halogen, cyano or halogen.

3. A compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein Y is attached in the para-position of the phenyl moiety.

4. A compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein Y is attached in the meta-position of the phenyl moiety.

5. A compound of claim 1 or a pharmaceutically acceptable salt thereof; wherein R1 is OH or NH_2; Y is CH_2; X1, X2, X3 and X4 are N; and
R2 is C_1-C_6 alkyl optionally substituted by phenyl; or C_3-C_6 cycloalkyl.

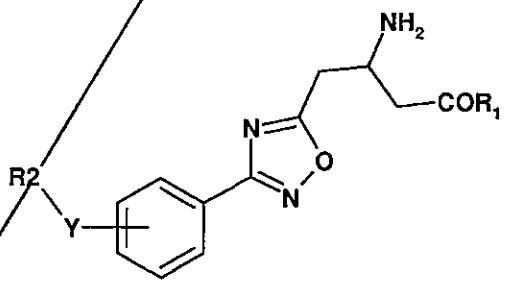
6. A compound of claim 1 which is a compound of formula (II) or a pharmaceutically acceptable salt thereof,



(II)

wherein the variables R1, R2 and Y have the meaning as defined in claim 1.

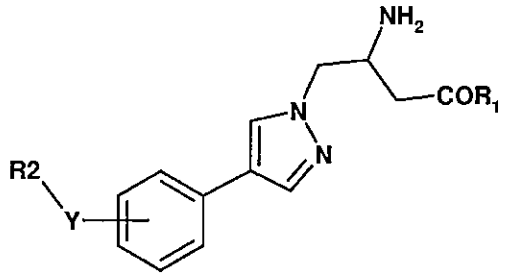
7. A compound of claim 1 which is a compound of formula (III) or a pharmaceutically acceptable salt thereof,



(III)

wherein the variables R1, R2 and Y have the meaning as defined in claim 1.

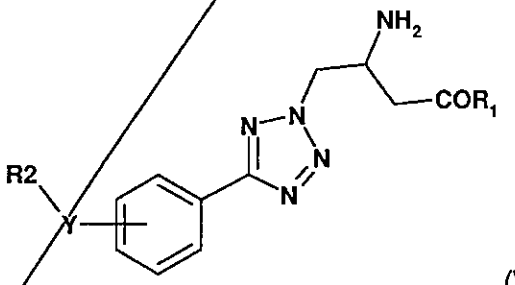
8. A compound of claim 1 which is a compound of formula (IV) or a pharmaceutically acceptable salt thereof,



(IV)

wherein the variables R1, R2 and Y have the meaning as defined in claim 1.

9. A compound in accordance to claim 1, which is a compound of formula (V) or a pharmaceutically acceptable salt thereof;



(V)

wherein the variables R1, R2 and Y have the meaning as defined in claim 1; or wherein is R1 is OH; Y is O; and

R2 is phenyl optionally being substituted by halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy; or R2 is a 5 - 10 membered mono- or bicyclic heteroaryl containing 1 to 4 heteroatoms selected from N, O and S said heteroaryl being optionally substituted by C_1-C_6 alkyl optionally substituted by halogen, cyano or halogen.

10. A compound in accordance to claim 9, or a pharmaceutically acceptable salt thereof; wherein

R1 is OH; Y is O; and R2 is a pyridyl ring being optionally substituted by cyano or halogen.

11. A compound of claim 1 and/or a pharmaceutically acceptable salt thereof, wherein the compound is selected from:

(*R*)-3-amino-4-(5-(4-(benzo[*d*]thiazol-2-yloxy)phenyl)-2*H*-tetrazol-2-yl)butanoic acid;

(*R*)-3-amino-4-(5-(4-((5-chloropyridin-2-yl)oxy)phenyl)-2*H*-tetrazol-2-yl)butanoic acid;

(*R*)-3-amino-4-(5-(4-((5-chloro-3-fluoropyridin-2-yl)oxy)phenyl)-2*H*-tetrazol-2-yl)butanoic acid;

(*R*)-3-amino-4-(5-(4-(4-(oxazol-2-yl)-phenoxy)phenyl)-2*H*-tetrazol-2-yl)-butanoic acid;

(*R*)-3-amino-4-(5-(3-(4-chlorophenoxy)phenyl)-2*H*-tetrazol-2-yl)butanoic acid;

(*R*)-3-amino-4-(5-(4-(4-chlorophenoxy)-phenyl)-2*H*-tetrazol-2-yl)butanoic acid;

(*R*)-3-amino-4-(5-(4-(4-fluorophenoxy)-phenyl)-2*H*-tetrazol-2-yl)butanoic acid;

(*R*)-3-amino-4-(5-(4-(3-chloro-4-fluorophenoxy)phenyl)-2*H*-tetrazol-2-yl)butanoic acid;

(*R*)-3-amino-4-(5-(4-(*p*-tolyloxy)phenyl)-2*H*-tetrazol-2-yl)butanoic acid;

(*S*)-3-amino-4-(5-(3-phenoxyphenyl)-2*H*-tetrazol-2-yl)butanoic acid;

(*S*)-3-amino-4-(5-(4-(benzo[*d*]thiazol-2-yloxy)phenyl)-2*H*-tetrazol-2-yl)butanoic acid;

(*S*)-3-amino-4-(5-(4-(4-chlorophenoxy)-phenyl)-2*H*-tetrazol-2-yl)butanoic acid;

(*R*)-3-amino-4-(5-(3-phenethoxyphenyl)-2*H*-tetrazol-2-yl)butanoic acid;

(*R*)-3-amino-4-(5-(4-phenethoxyphenyl)-2*H*-tetrazol-2-yl)butanoic acid;

(*R*)-3-amino-4-(5-(4-(benzyloxy)phenyl)-2*H*-tetrazol-2-yl)butanoic acid;

(*R*)-3-amino-4-(5-(3-(benzyloxy)phenyl)-2*H*-tetrazol-2-yl)butanoic acid;

(*R*)-3-amino-4-(5-(4-butoxyphenyl)-2*H*-tetrazol-2-yl)butanoic acid;

(*R*)-3-amino-4-(5-(4-(pentyloxy)phenyl)-2*H*-tetrazol-2-yl)butanoic acid;

(*R*)-3-amino-4-(5-(3-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-2*H*-tetrazol-2-yl)butanoic acid;

(*R*)-3-amino-4-(5-(4-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-2*H*-tetrazol-2-yl)butanoic acid;

(*R*)-3-amino-4-(5-(3-(benzo[*d*]thiazol-2-yloxy)phenyl)-2*H*-tetrazol-2-yl)butanoic acid;

(*R*)-3-amino-4-(5-(3-(3,5-difluorophenoxy)phenyl)-2*H*-tetrazol-2-yl)butanoic acid;

(*S*)-3-amino-4-(5-(4-(*p*-tolyloxy)phenyl)-2*H*-tetrazol-2-yl)butanoic acid;

(*R*)-3-amino-4-(5-(4-(4-fluorophenoxy) phenyl)-1,3,4-oxadiazol-2-yl)butanoic acid;

(*R*)-3-amino-4-(5-(4-(4-chlorophenoxy) phenyl)-1,3,4-oxadiazol-2-yl)butanoic acid;

(*R*)-3-amino-4-(3-(4-(4-chlorophenoxy)phenyl)-1,2,4-oxadiazol-5-yl)butanoic acid;

(*R*)-3-amino-4-(3-(4-(4-chlorophenoxy)phenyl)-1,2,4-oxadiazol-5-yl)butanamide;

(*S*)-3-amino-4-(4-(4-(4-chlorophenoxy)phenyl)-1*H*-pyrazol-1-yl)butanoic acid; and

(*S*)-3-amino-4-(5-(4-((5-chloro-3-fluoropyridin-2-yl)oxy)phenyl)-2*H*-tetrazol-2-yl)butanoic acid.

12. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any one of claims 1 to 11 or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable carriers.

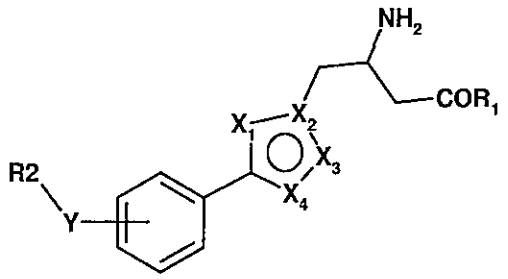
13. A combination comprising a therapeutically effective amount of a compound according to any one of claims 1 to 11 or a pharmaceutically acceptable salt thereof and one or more therapeutically active co-agents.

14. A method of modulating LTA4H activity in a subject, wherein the method comprises administering to the subject a therapeutically effective amount of the compound according to any one of claims 1 to 11 or a pharmaceutically acceptable salt thereof.

15. A compound according to any one of claims 1 to 11 or a pharmaceutically acceptable salt thereof, for use as a medicament, in particular for inhibiting LTA4H activity.

CLAIMS

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof;



(I)

wherein,

R1 is OH or NH_2;

Y is O, S or CH_2;

X1, X2, X3 and X4 are N; or

X1, X2, X3 and X4 are selected from N, NH, C, CH and O with the proviso that at least two of X1, X2, X3 or X4 are N or NH;

R2 is C_1-C_6 alkyl optionally substituted by phenyl; C_3-C_6 cycloalkyl; phenyl optionally being substituted by halogen, cyano, C_1-C_6 alkyl optionally substituted by halogen, C_1-C_6 alkoxy, or a 5 - 6 membered heteroaryl ring containing 1 to 3 heteroatoms selected from N, O and S; or a 5 - 10 membered mono- or bicyclic heteroaryl containing 1 to 4 heteroatoms selected from N, O and S said heteroaryl being optionally substituted by C_1-C_6 alkyl optionally substituted by halogen, cyano or halogen.

2. A compound of claim 1 or a pharmaceutically acceptable salt thereof; wherein R1 is OH or NH_2; Y is O; X1, X2, X3 and X4 are selected from N, NH, C, CH and O with the proviso that at least two of X1, X2, X3 or X4 are N or NH; and

R2 is phenyl optionally being substituted by halogen, cyano, C_1-C_6 alkyl optionally substituted by halogen, C_1-C_6 alkoxy, or a 5 - 6 membered heteroaryl ring containing 1 to 3 heteroatoms selected from N, O and S; or

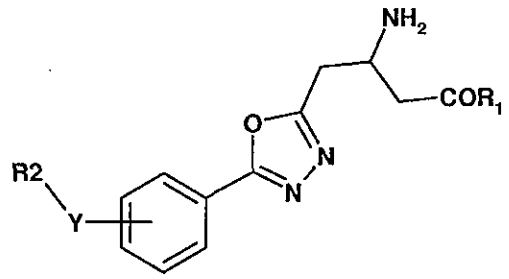
R2 is a 5 - 10 membered mono- or bicyclic heteroaryl containing 1 to 4 heteroatoms selected from N, O and S said heteroaryl being optionally substituted by C_1-C_6 alkyl optionally substituted by halogen, cyano or halogen.

3. A compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein Y is attached in the para-position of the phenyl moiety.

4. A compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein Y is attached in the meta-position of the phenyl moiety.

5. A compound of claim 1 or a pharmaceutically acceptable salt thereof; wherein R1 is OH or NH_2; Y is CH_2; X1, X2, X3 and X4 are N; and
R2 is C_1-C_6 alkyl optionally substituted by phenyl; or C_3-C_6 cycloalkyl.

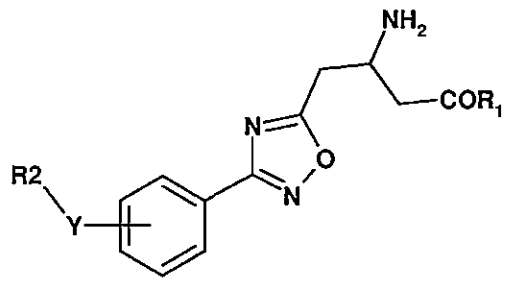
6. A compound of claim 1 which is a compound of formula (II) or a pharmaceutically acceptable salt thereof,



(II)

wherein the variables R1, R2 and Y have the meaning as defined in claim 1.

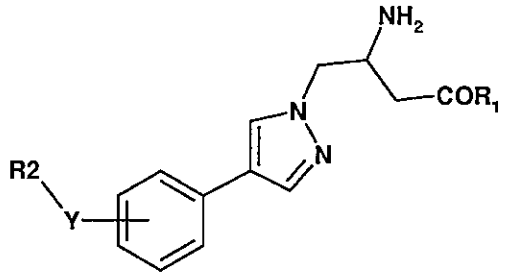
7. A compound of claim 1 which is a compound of formula (III) or a pharmaceutically acceptable salt thereof,



(III)

wherein the variables R1, R2 and Y have the meaning as defined in claim 1.

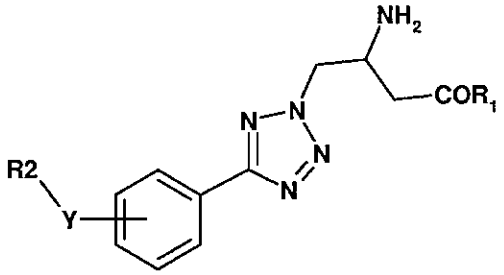
8. A compound of claim 1 which is a compound of formula (IV) or a pharmaceutically acceptable salt thereof,



(IV)

wherein the variables R1, R2 and Y have the meaning as defined in claim 1.

9. A compound in accordance to claim 1, which is a compound of formula (V) or a pharmaceutically acceptable salt thereof;



(V)

wherein the variables R1, R2 and Y have the meaning as defined in claim 1; or wherein is R1 is OH; Y is O; and

R2 is phenyl optionally being substituted by halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy; or R2 is a 5 - 10 membered mono- or bicyclic heteroaryl containing 1 to 4 heteroatoms selected from N, O and S said heteroaryl being optionally substituted by C_1-C_6 alkyl optionally substituted by halogen, cyano or halogen.

10. A compound in accordance to claim 9, or a pharmaceutically acceptable salt thereof; wherein

R1 is OH; Y is O; and R2 is a pyridyl ring being optionally substituted by cyano or halogen.

11. A compound of claim 1 and/or a pharmaceutically acceptable salt thereof, wherein the compound is selected from:

(*R*)-3-amino-4-(5-(4-(benzo[*d*]thiazol-2-yloxy)phenyl)-2*H*-tetrazol-2-yl)butanoic acid;

(*R*)-3-amino-4-(5-(4-((5-chloropyridin-2-yl)oxy)phenyl)-2*H*-tetrazol-2-yl)butanoic acid;

(*R*)-3-amino-4-(5-(4-((5-chloro-3-fluoropyridin-2-yl)oxy)phenyl)-2*H*-tetrazol-2-yl)butanoic acid;

(*R*)-3-amino-4-(5-(4-(4-(oxazol-2-yl)-phenoxy)phenyl)-2*H*-tetrazol-2-yl)-butanoic acid;

(*R*)-3-amino-4-(5-(3-(4-chlorophenoxy)phenyl)-2*H*-tetrazol-2-yl)butanoic acid;

(*R*)-3-amino-4-(5-(4-(4-chlorophenoxy)-phenyl)-2*H*-tetrazol-2-yl)butanoic acid;

(*R*)-3-amino-4-(5-(4-(4-fluorophenoxy)-phenyl)-2*H*-tetrazol-2-yl)butanoic acid;

(*R*)-3-amino-4-(5-(4-(3-chloro-4-fluorophenoxy)phenyl)-2*H*-tetrazol-2-yl)butanoic acid;

(*R*)-3-amino-4-(5-(4-(*p*-tolyloxy)phenyl)-2*H*-tetrazol-2-yl)butanoic acid;

(*S*)-3-amino-4-(5-(3-phenoxyphenyl)-2*H*-tetrazol-2-yl)butanoic acid;

(*S*)-3-amino-4-(5-(4-(benzo[*d*]thiazol-2-yloxy)phenyl)-2*H*-tetrazol-2-yl)butanoic acid;

(*S*)-3-amino-4-(5-(4-(4-chlorophenoxy)-phenyl)-2*H*-tetrazol-2-yl)butanoic acid;

(*R*)-3-amino-4-(5-(3-phenethoxyphenyl)-2*H*-tetrazol-2-yl)butanoic acid;

(*R*)-3-amino-4-(5-(4-phenethoxyphenyl)-2*H*-tetrazol-2-yl)butanoic acid;

(*R*)-3-amino-4-(5-(4-(benzyloxy)phenyl)-2*H*-tetrazol-2-yl)butanoic acid;

(*R*)-3-amino-4-(5-(3-(benzyloxy)phenyl)-2*H*-tetrazol-2-yl)butanoic acid;

(*R*)-3-amino-4-(5-(4-butoxyphenyl)-2*H*-tetrazol-2-yl)butanoic acid;

(*R*)-3-amino-4-(5-(4-(pentyloxy)phenyl)-2*H*-tetrazol-2-yl)butanoic acid;

(*R*)-3-amino-4-(5-(3-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-2*H*-tetrazol-2-yl)butanoic acid;

(*R*)-3-amino-4-(5-(4-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-2*H*-tetrazol-2-yl)butanoic acid;

(*R*)-3-amino-4-(5-(3-(benzo[*d*]thiazol-2-yloxy)phenyl)-2*H*-tetrazol-2-yl)butanoic acid;

(*R*)-3-amino-4-(5-(3-(3,5-difluorophenoxy)phenyl)-2*H*-tetrazol-2-yl)butanoic acid;

(*S*)-3-amino-4-(5-(4-(*p*-tolyloxy)phenyl)-2*H*-tetrazol-2-yl)butanoic acid;

(*R*)-3-amino-4-(5-(4-(4-fluorophenoxy) phenyl)-1,3,4-oxadiazol-2-yl)butanoic acid;

(*R*)-3-amino-4-(5-(4-(4-chlorophenoxy) phenyl)-1,3,4-oxadiazol-2-yl)butanoic acid;

(*R*)-3-amino-4-(3-(4-(4-chlorophenoxy)phenyl)-1,2,4-oxadiazol-5-yl)butanoic acid;

(*R*)-3-amino-4-(3-(4-(4-chlorophenoxy)phenyl)-1,2,4-oxadiazol-5-yl)butanamide;

(*S*)-3-amino-4-(4-(4-(4-chlorophenoxy)phenyl)-1*H*-pyrazol-1-yl)butanoic acid; and

(*S*)-3-amino-4-(5-(4-((5-chloro-3-fluoropyridin-2-yl)oxy)phenyl)-2*H*-tetrazol-2-yl)butanoic acid.

12. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any one of claims 1 to 11 or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable carriers.

13. A combination comprising a therapeutically effective amount of a compound according to any one of claims 1 to 11 or a pharmaceutically acceptable salt thereof and one or more therapeutically active co-agents.

14. A compound according to any one of claims 1 to 11 or a pharmaceutically acceptable salt thereof, for use as a medicament, in particular for inhibiting LTA4H activity.