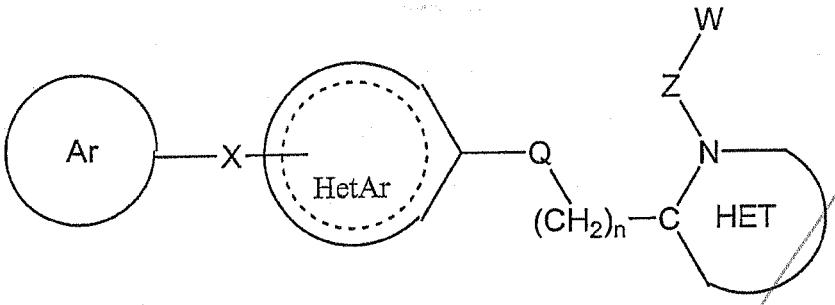
CLAIMS

We claim:

1. A compound of formula:



wherein

Ar is selected from the group consisting of

aryl;

heteroaryl;

aryl substituted with from one to three substituents independently selected from the group consisting of halogen, loweralkyl, loweracyl, loweralkoxy, fluoroloweralkyl, fluoroloweralkoxy, hydroxy, hydroxy(C_1-C_4) alkyl, formyl, formyl(C_1-C_4) alkyl, cyano, cyano(C_1-C_4) alkyl, benzyl, benzyloxy, phenyl, substituted phenyl, heteroaryl, heterocyclylalkyl, substituted heteroaryl, and nitro; and

heteroaryl substituted with from one to three substituents independently selected from the group consisting of halogen, loweralkyl, loweracyl, loweralkoxy, fluoroloweralkyl, fluoroloweralkoxy, formyl, cyano, benzyl, benzyloxy, phenyl, heteroaryl, heterocyclylalkyl and nitro;

X is selected from the group consisting of direct bond, O, SO, $S(O_2)$, NR^1, CH_2, CF_2, CH_2CH_2, CH_2NR^1, NR^1CH_2, CH=CH, C=O, CH_2C=O, $CR^{1a}R^{1b}$, $OCR^{1a}R^{1b}$, $CR^{1a}R^{1b}O$; SO_2NR^1, NR^1SO_2, $C(=O)NR^1$ and $NR^1C(=O)$;

R^1 is selected separately in each occurrence from the group consisting of H and lower alkyl;

R^{1a} is selected from the group consisting of H, OH and lower alkyl;

R^{1b} is selected from the group consisting of H and lower alkyl, or R^{1a} and R^{1b} taken together may form a 3-6 membered ring, which may optionally contain a heteroatom chosen from O, S, and N;

HetAr is an aryl or heteroaryl ring attached via a ring carbon to Q, further characterized in that Q and X cannot be on adjacent positions in said aryl or heteroaryl ring;

Q is chosen from -O-, $-NR^1-$ and $S(O)_p$;

Q and X cannot be on adjacent positions in said benzene or pyridine ring;

p is zero, 1 or 2;

n is an integer selected from 1-5;

HET is selected from the group consisting of

4-7-membered saturated nitrogenous heterocycle and

4-7-membered saturated nitrogenous heterocycle substituted with one or two substituents independently selected from the group consisting of halogen, hydroxyl, amino, carboxy, loweralkyl, loweracyl, loweralkoxy, N-oxide, fluoroloweralkyl, fluoroloweralkoxy, formyl, cyano, benzyl, benzyloxy, phenyl, heteroaryl and nitro; and

taken together ZW is H or

Z is $(CH_2)_{1-10}$, in which one or two (CH_2) may optionally be replaced by -O-, $-NR^1-$, -SO-, $-S(O)_2-$, -C(=O)- or -C=O(NH)-, provided that said -O-, $-NR^1-$, -SO-, $-S(O)_2-$, -C(=O)- or -C=O(NH)- are not at the point of attachment to HET and are separated by at least one $-(CH_2)-$;

W is selected from the group consisting of acyl, hydroxyl, carboxyl, amino, $-C(O)NHR^4$, aminoacyl, -COOalkyl, -CHO, heterocyclyl, substituted aryl, substituted heterocyclyl, sulfonamide, -C(O)fluoroalkyl, $-C(O)CH_2C(O)Oalkyl$, $-C(O)CH_2C(O)Ofluoroalkyl$, -SH, -C(O)NH(OH), $-C(O)N(OH)R^4$, -N(OH)C(O)OH, $-N(OH)C(O)R^4$; and

R^4 is selected from the group consisting of H, (C_1-C_4) alkyl, and phenyl(C_1-C_4) alkyl;

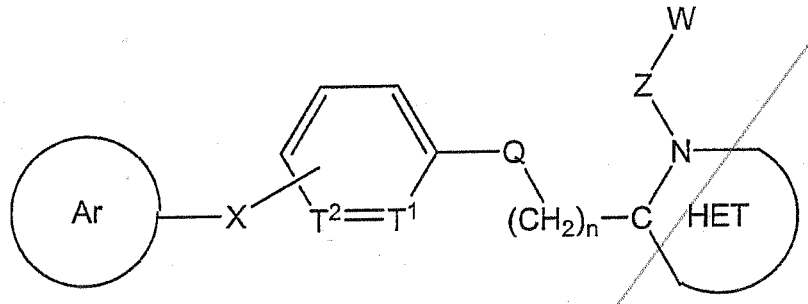
with the provisos that;

(a) when Q is -O-, HET is (*S*)-pyrrolidine, *rac*-pyrrolidine or piperidine, Ar is phenyl or halo-substituted phenyl, and HetAr is *p*-phenylene, then the Z-W combination is other than H;

(b) when Q is NR^1, HET is thiazolidine, Ar is phenyl or substituted phenyl and HetAr is meta-phenylene, then the ZW combination is other than H; and

(c) when Q is -O-, HET is azetidine, Ar is phenyl, n is 1 and HetAr is a 2,5-substituted pyridine, then the Z-W combination is other than H.

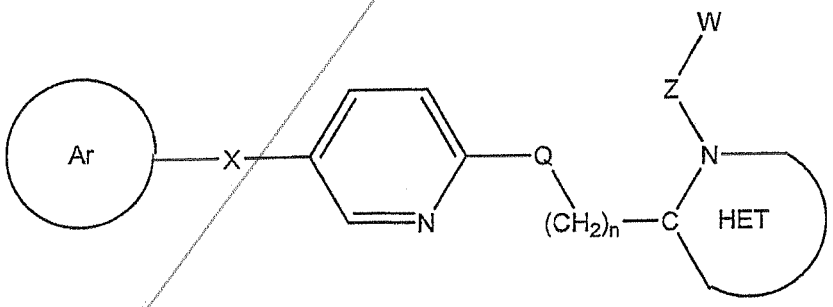
2. A compound according to claim 1 of formula:



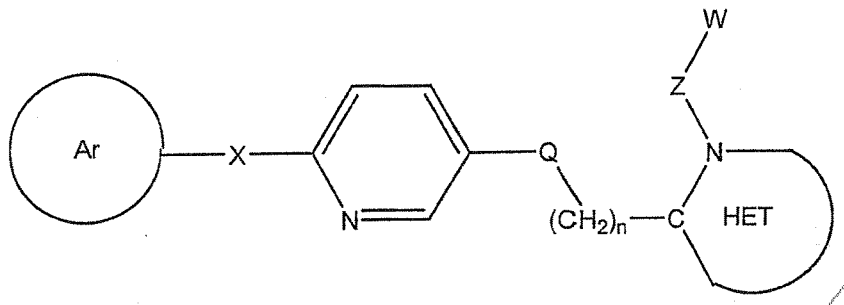
wherein

T^1 and T^2 are carbon, forming a benzene ring, or, when X is at the *para* position relative to Q, one of T^1 and T^2 may be nitrogen, forming a pyridine ring.

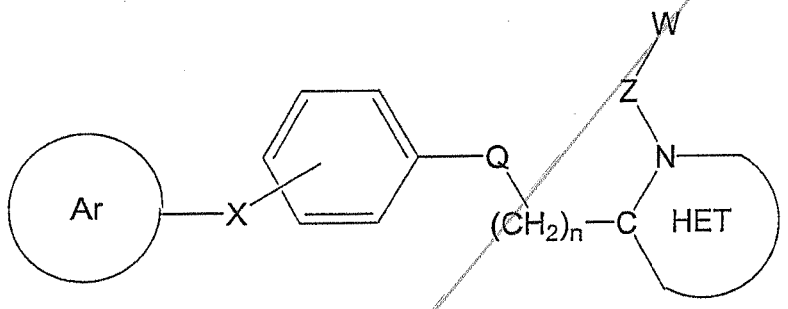
3. A compound according to claim 2 wherein the T^1/T^2 ring is pyridinyl of formula:



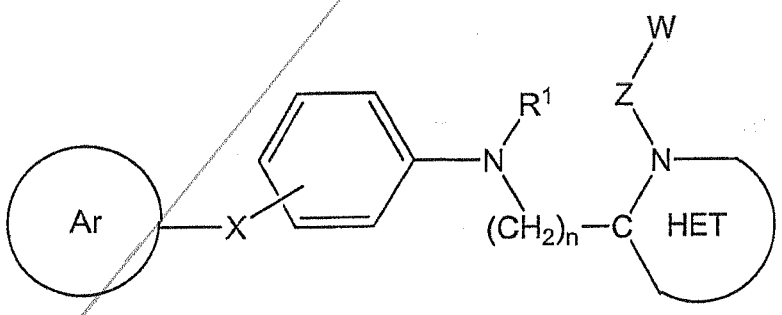
4. A compound according to claim 2 wherein the T^1/T^2 ring is pyridinyl of formula:



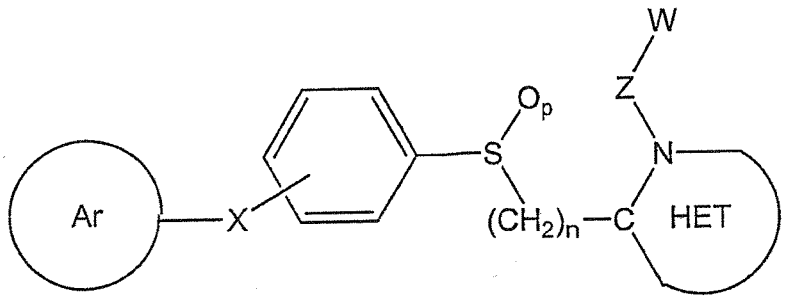
5. A compound according to claim 2 wherein the T^1/T^2 ring is para or meta phenylene of formula:



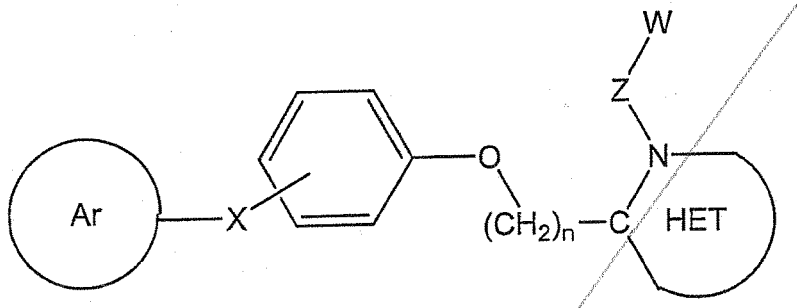
6. A compound according to claim 5 wherein Q is $-NR^1-$ of formula:



7. A compound according to claim 5 wherein Q is -S(O)$_p$- of formula:



8. A compound according to claim 5 wherein Q is -O- of formula:



wherein

Ar is selected from the group consisting of

aryl;

heteroaryl;

aryl substituted with from one to three substituents independently selected from the group consisting of halogen, loweralkyl, loweracyl, loweralkoxy, fluoroloweralkyl, fluoroloweralkoxy, formyl, cyano, benzyl, benzyloxy, phenyl, heteroaryl and nitro; and

heteroaryl substituted with from one to three substituents independently selected from the group consisting of halogen, loweralkyl, loweracyl, loweralkoxy, fluoroloweralkyl, fluoroloweralkoxy, formyl, cyano, phenyl, heteroaryl and nitro;

X is selected from the group consisting of direct bond, O, SO, S(O_2), NR^1, CH_2, CF_2, CH_2O, C=O and CH_2C=O;

R^1 is selected independently in each occurrence from the group consisting of H and lower alkyl;

n is an integer selected from 1-5;

HET is selected from the group consisting of

4-7-membered saturated nitrogenous heterocycle and

4-7-membered saturated nitrogenous heterocycle substituted with one or two substituents independently selected from the group consisting of halogen, loweralkyl, loweracyl, loweralkoxy, fluoroloweralkyl, fluoroloweralkoxy, formyl, cyano, benzyl, benzyloxy, phenyl, heteroaryl and nitro;

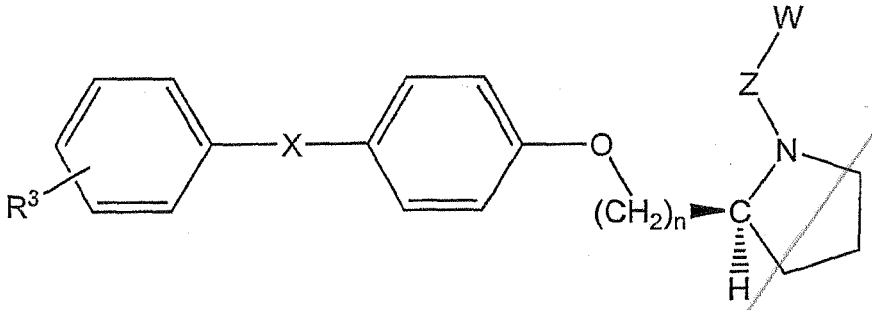
Z is $(CH_2)_{1-10}$; in which one or two (CH_2) may optionally be replaced by -O-, $-NR^1-$, -SO, $-S(O)_2-$, -C(=O)- or -C=O(NH)-, provided that said -O-, -NR-, -SO-, $-S(O)_2-$, -C(=O)- or -C=O(NH)- are not at the point of attachment to HET and are separated by at least two $-(CH_2)-$;

W is selected from acyl, hydroxyl, carboxyl, amino, carboxamido, aminoacyl, -COOalkyl, -CHO, heterocyclyl, substituted aryl, and substituted heterocyclyl.

9. A compound according to claim 8 wherein X is selected from CH_2, O and NR^1.

10. A compound according to claim 8 wherein HET is selected from the group consisting of pyrrolidinone, pyrrolidine, piperidine, piperidinone, piperazine, morpholine, thiomorpholine, thiazolidine, thiazolidinone, oxazolidine and oxazolidinone and substituted pyrrolidinone, substituted pyrrolidine, substituted piperidine, substituted piperidinone, substituted piperazine, substituted morpholine, substituted thiomorpholine, substituted thiazolidine, substituted thiazolidinone, substituted oxazolidine and substituted oxazolidinone.

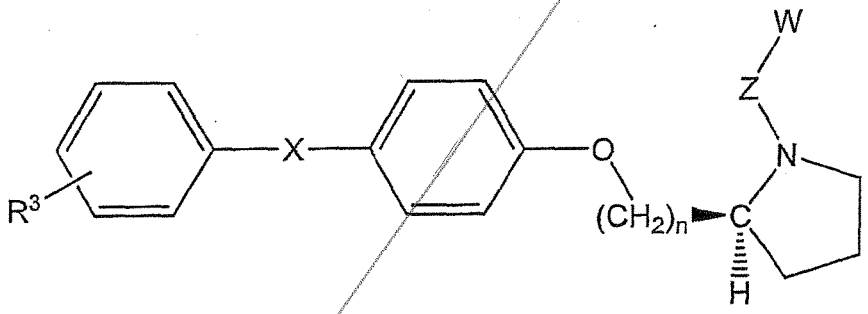
11. A compound according to claim 8 wherein HET is (*S*) pyrrolidine, of the formula



wherein

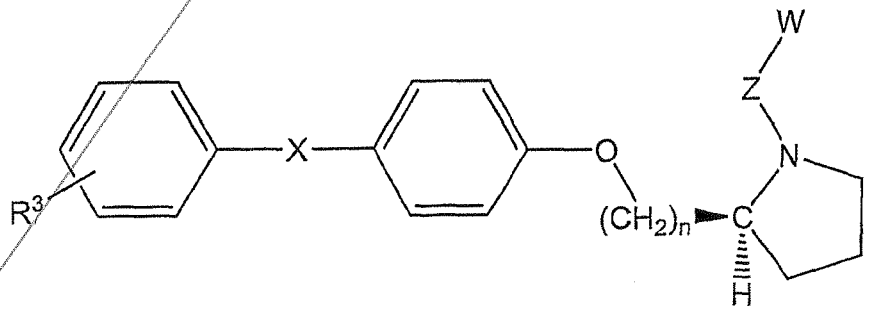
R^3 is chosen from halogen, CF_3, methyl, methoxy and CF_3O.

12. A compound according to claim 8 wherein HET is (*S*) pyrrolidine, of the formula



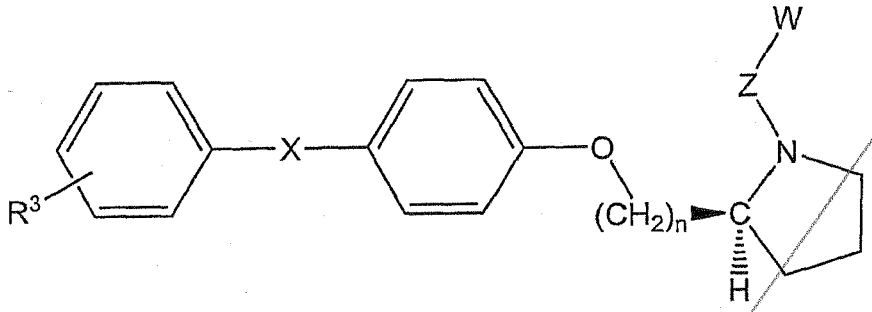
wherein X is O or CH_2.

13. A compound according to claim 8 wherein HET is (*S*) pyrrolidine, of the formula



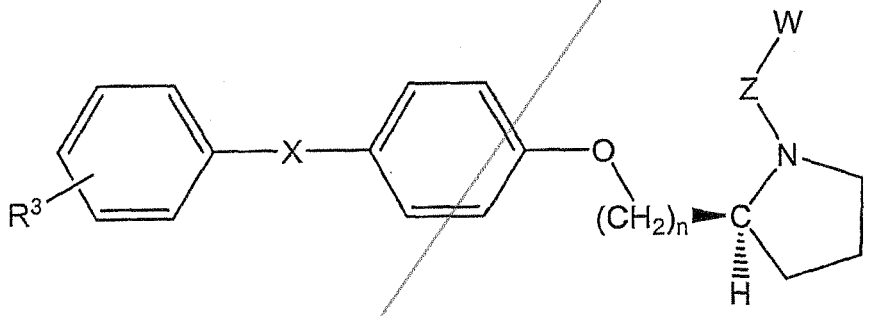
wherein n is 1 or 2.

14. A compound according to claim 8 wherein HET is (*S*) pyrrolidine, of the formula



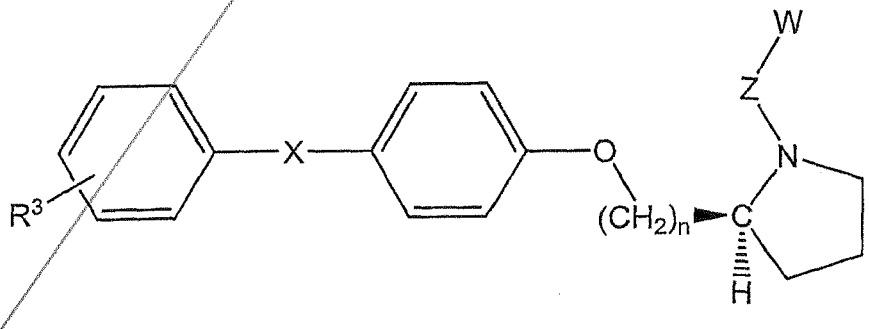
wherein Z is C_1-C_4 alkylene.

15. A compound according to claim 8 wherein HET is (*S*) pyrrolidine, of the formula



wherein W is COOH.

16. A compound according to claim 8 wherein HET is (*S*) pyrrolidine, of the formula



wherein

R^3 is chosen from halogen, CF_3, methyl, methoxy, CF_3O;

X is O or CH_2;

n is 1 or 2;

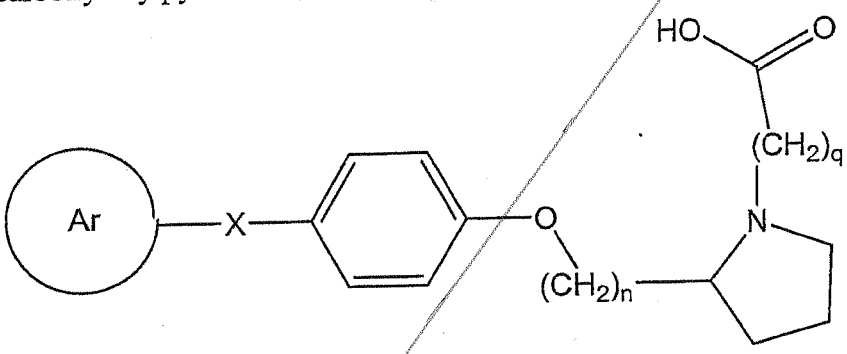
Z is C_1-C_4 alkylene and;

W is COOH.

17. A compound according to claim 10 wherein HET is pyrrolidine and the Z-W combination is other than H.

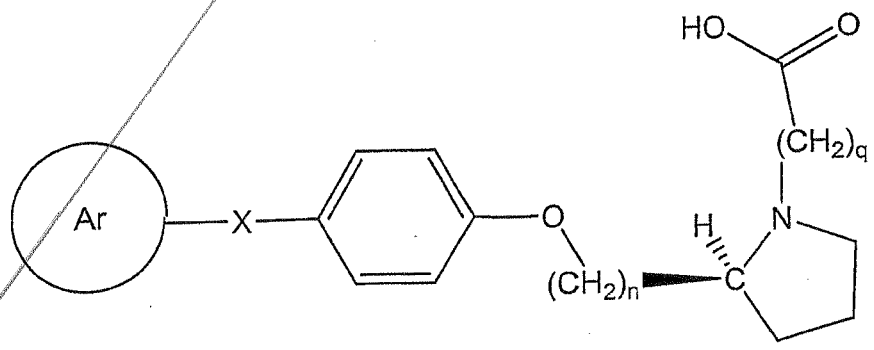
18. A compound according to claim 17 wherein HET-Z-W is selected from the group consisting of pyridinylmethylpyrrolidine, oxadiazolylmethylpyrrolidine, carboxyalkylpyrrolidine, and alkoxycarbonylalkylpyrrolidine.

19. A compound according to claim 18 wherein HET-Z-W is carboxyalkylpyrrolidine, of the formula:



wherein q is an integer selected from 2-6.

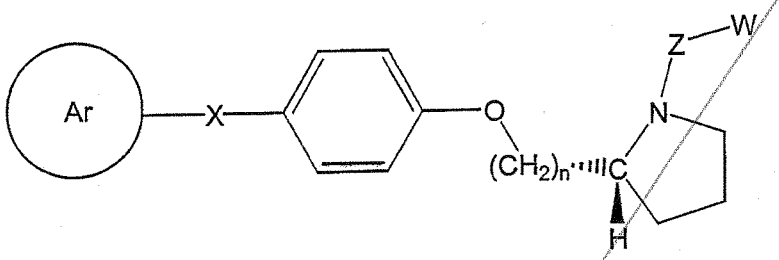
20. A compound according to claim 18 wherein HET-Z-W is carboxyalkyl (*S*) pyrrolidine, of formula:



wherein q is an integer selected from 2-6.

21. A compound according to claim 17 wherein HET is selected from the group consisting of pyrrolidine, pyrrolidinone, piperidine and piperidinone.

22. A compound according to claim 8 in which HET is (*R*) pyrrolidine of the formula:



wherein

Ar is selected from the group consisting of

aryl;

heteroaryl;

aryl substituted with from one to three substituents independently selected from the group consisting of halogen, loweralkyl, loweracyl, loweralkoxy, fluoroloweralkyl, fluoroloweralkoxy, hydroxy, hydroxy(C_1-C_4) alkyl, formyl, formyl(C_1-C_4) alkyl, cyano, cyano(C_1-C_4) alkyl, benzyl, benzyloxy, phenyl, substituted phenyl, heteroaryl, heterocyclylalkyl, substituted heteroaryl, and nitro; and

heteroaryl substituted with from one to three substituents independently selected from the group consisting of halogen, (C_1-C_4) alkyl, (C_1-C_4) alkoxy, benzyl, benzyloxy, phenyl;

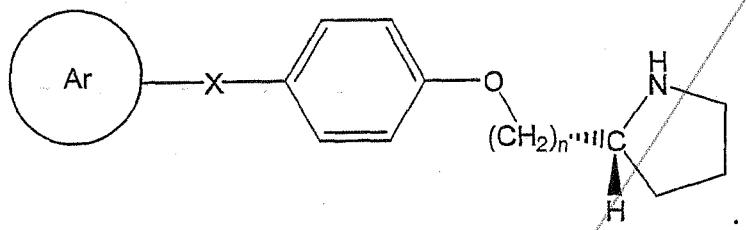
X is selected from the group consisting of direct bond, O, SO, $S(O_2)$, NR^1, CH_2, CF_2, CH_2CH_2, CH_2NH, $NHCH_2$, CH=CH, C=O and CH_2C=O;

taken together ZW is H or

Z is $(CH_2)_{1-10}$; in which one or two (CH_2) may optionally be replaced by -O-, -NR^1-, -SO-, -$S(O)_2$-, -C(=O)- or -C=O(NH)-, provided that said -O-, -NR^1-, -SO-, -$S(O)_2$-, -C(=O)- or -C=O(NH)- are not at the point of attachment to HET and are separated by at least one -(CH_2)-; and

W is selected from the group consisting of acyl, hydroxyl, carboxyl, amino, carboxamido, aminoacyl, -COOalkyl, -CHO, heterocyclyl, substituted aryl, substituted heterocyclyl.

23. A compound according to claim 22 wherein ZW is H, of the formula:

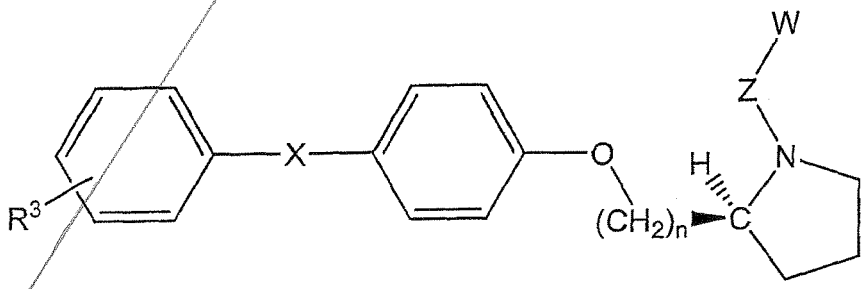


24. A compound according to claim 23 wherein X is selected from CH_2, O and NR^1.

25. A compound according to claim 24 wherein X is CH_2 or O, n is 1, and Ar is para-substituted phenyl.

26. A compound according to claim 25 wherein Ar is heteroarylphenyl.

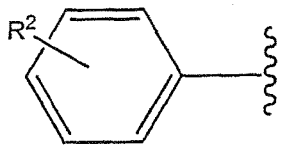
27. A compound according to claim 8 wherein HET is (*S*) pyrrolidine, of the formula:



wherein

R^3 represents one to three residues independently selected from the group consisting of benzyl, benzyloxy, phenyl, heteroaryl and heteroaryl substituted with halogen, methyl, methoxy or trifluoromethoxy.

28. A compound according to any of claims 1-10 or 17-26 wherein Ar is

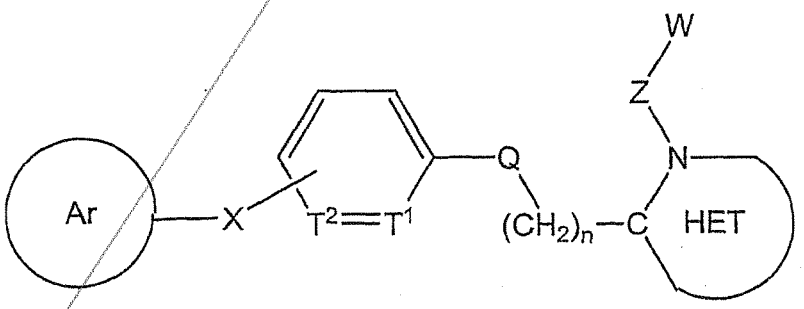


wherein the wavy line indicates the point of attachment to X and R^2 is chosen from hydrogen, halogen, trifluoromethyl, methyl, methoxy, thienyl, furanyl, and thienyl or furanyl substituted with halogen, trifluoromethyl, methyl or methoxy.

29. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one compound according to any of claims 1-27.

30. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one compound according to claim 28.

31. A method for inhibiting leukotriene A4 hydrolase comprising contacting the LTA4H enzyme with a therapeutically effective amount of a compound of formula:



wherein

Ar is selected from the group consisting of

aryl;

heteroaryl;

aryl substituted with from one to three substituents independently selected from the group consisting of halogen, loweralkyl, loweracyl, loweralkoxy, fluoroloweralkyl, fluoroloweralkoxy, hydroxy, hydroxy(C_1-C_4) alkyl, formyl, formyl(C_1-C_4) alkyl, cyano, cyano(C_1-C_4) alkyl, benzyl, benzyloxy, phenyl, substituted phenyl, heteroaryl, heterocyclylalkyl, substituted heteroaryl, and nitro; and

heteroaryl substituted with from one to three substituents independently selected from the group consisting of halogen, loweralkyl, loweracyl, loweralkoxy, fluoroloweralkyl, fluoroloweralkoxy, formyl, cyano, benzyl, benzyloxy, phenyl, heteroaryl, heterocyclylalkyl and nitro;

X is selected from the group consisting of direct bond, O, SO, $S(O_2)$, NR^1, CH_2, CF_2, CH_2CH_2, CH_2NR^1, NR^1CH_2, CH=CH, C=O, CH_2C=O, $CR^{1a}R^{1b}$, $OCR^{1a}R^{1b}$, $CR^{1a}R^{1b}O$; SO_2NR^1, NR^1SO_2, $C(=O)NR^1$ and $NR^1C(=O)$;

R^1 is selected separately in each occurrence from the group consisting of H and lower alkyl;

R^{1a} is selected from the group consisting of H, OH and lower alkyl;

R^{1b} is selected from the group consisting of H and lower alkyl, or R^{1a} and R^{1b} taken together may form a 3-6 membered ring, which may optionally contain a heteroatom chosen from O, S, and N;

T^1 and T^2 are carbon, forming a benzene ring, or, when X is at the *para* position relative to Q, one of T^1 and T^2 may be nitrogen, forming a pyridine ring;

Q is chosen from -O-, $-NR^1-$ and $S(O)_p$;

Q and X cannot be on adjacent positions in said benzene or pyridine ring;

p is zero, 1 or 2;

n is an integer selected from 1-5;

HET is selected from the group consisting of

4-7-membered saturated nitrogenous heterocycle and

4-7-membered saturated nitrogenous heterocycle substituted with one or two substituents independently selected from the group consisting of

halogen, hydroxyl, amino, carboxy, loweralkyl, loweracyl, loweralkoxy, N-oxide, fluoroloweralkyl, fluoroloweralkoxy, formyl, cyano, benzyl, benzyloxy, phenyl, heteroaryl and nitro; and

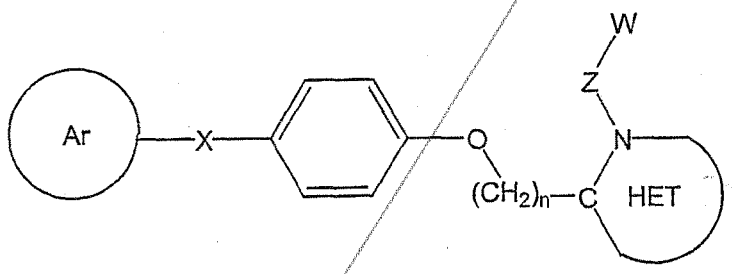
taken together ZW is H or

Z is $(CH_2)_{1-10}$, in which one or two (CH_2) may optionally be replaced by -O-, $-NR^1-$, -SO-, $-S(O)_2-$, -C(=O)- or -C=O(NH)-, provided that said -O-, $-NR^1-$, -SO-, $-S(O)_2-$, -C(=O)- or -C=O(NH)- are not at the point of attachment to HET and are separated by at least one $-(CH_2)-$;

W is selected from the group consisting of acyl, hydroxyl, carboxyl, amino, $-C(O)NHR^4$, aminoacyl, -COOalkyl, -CHO, heterocyclyl, substituted aryl, substituted heterocyclyl, sulfonamide, -C(O)fluoroalkyl, $-C(O)CH_2C(O)Oalkyl$, $-C(O)CH_2C(O)Ofluoroalkyl$, -SH, -C(O)NH(OH), $-C(O)N(OH)R^4$, -N(OH)C(O)OH, $-N(OH)C(O)R^4$; and

R^4 is selected from the group consisting of H, (C_1-C_4) alkyl, and phenyl(C_1-C_4) alkyl.

32. A method for inhibiting leukotriene A4 hydrolase comprising contacting the LTA4H enzyme with a therapeutically effective amount of a compound of formula:



wherein

Ar is selected from the group consisting of

aryl;

heteroaryl;

aryl substituted with from one to three substituents independently selected from the group consisting of halogen, loweralkyl, loweracyl, loweralkoxy, fluoroloweralkyl, fluoroloweralkoxy, formyl, cyano, benzyl, benzyloxy, phenyl, heteroaryl and nitro; and

heteroaryl substituted with from one to three substituents independently selected from the group consisting of halogen, loweralkyl, loweracyl, loweralkoxy, fluoroloweralkyl, fluoroloweralkoxy, formyl, cyano, phenyl, heteroaryl and nitro;

X is selected from the group consisting of direct bond, O, SO, $S(O_2)$, NR^1, CH_2, CF_2, CH_2O, C=O and CH_2C=O;

R^1 is selected independently in each occurrence from the group consisting of H and lower alkyl;

n is an integer selected from 1-5;

HET is selected from the group consisting of

4-7-membered saturated nitrogenous heterocycle and

4-7-membered saturated nitrogenous heterocycle substituted with one or two substituents independently selected from the group consisting of halogen, loweralkyl, loweracyl, loweralkoxy, fluoroloweralkyl, fluoroloweralkoxy, formyl, cyano, benzyl, benzyloxy, phenyl, heteroaryl and nitro;

taken together ZW is H or

Z is $(CH_2)_{1-10}$; in which one or two (CH_2) may optionally be replaced by -O-, -NR-, -SO-, $-S(O)_2-$, -C(=O)- or -C=O(NH)-, provided that said -O-, -NR-, -SO-, $-S(O)_2-$, -C(=O)- or -C=O(NH)- are not at the point of attachment to HET and are separated by at least two $-(CH_2)-$; and

W is selected from acyl, hydroxyl, carboxyl, amino, carboxamido, aminoacyl, -COOalkyl, -CHO, heterocyclyl, substituted aryl, and substituted heterocyclyl.

33. A method for treating a disorder associated with leukotriene A4 hydrolase comprising administering to a mammal a therapeutically effective amount of a compound according to any of claims 1-27.

34. A method according to claim 33 wherein said disorder associated with leukotriene A4 hydrolase is inflammation.

35. A method according to claim 33 wherein said disorder is selected from allergic inflammation, acute inflammation and chronic inflammation.

36. A method according to claim 33 wherein said disorder is chosen from asthma, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, multiple sclerosis, inflammatory bowel diseases (IBD) and psoriasis.

37. A method according to claim 33 wherein said disorder is chosen from atherosclerosis, thrombosis, stroke, acute coronary syndrome, stable angina, peripheral vascular disease, critical leg ischemia, intermittent claudication, abdominal aortic aneurysm and myocardial infarction.

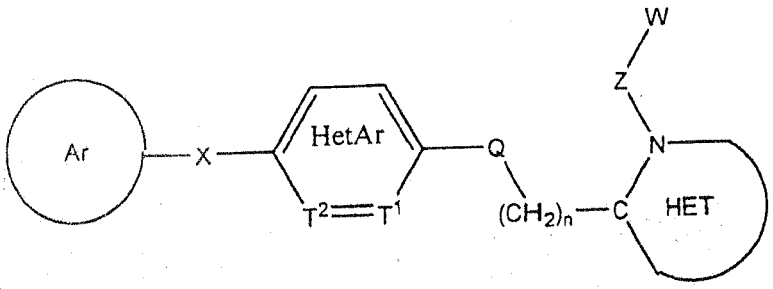
38. A method for treating a disorder associated with leukotriene A4 hydrolase comprising administering to a mammal a therapeutically effective amount of a compound according to claim 28.

39. A method for treating inflammation comprising administering to a mammal a therapeutically effective amount of a compound according to any of claims 1-27 and an inhibitor of 5-lipoxygenase activating protein (FLAP).

40. A method for treating inflammation comprising administering to a mammal a therapeutically effective amount of a compound according to any of claims 1-27 and a leukotriene B4 (LTB4) antagonist.

Claims:

1. A compound of formula:



wherein

Ar is selected from the group consisting of

aryl;

heteroaryl;

aryl substituted with from one to three substituents independently selected from the group consisting of halogen, loweralkyl, loweralkoxy, fluoroloweralkyl, fluoroloweralkoxy, hydroxy, hydroxy(C_1-C_4) alkyl, formyl, formyl(C_1-C_4) alkyl, cyano, cyano(C_1-C_4) alkyl, benzyl, benzyloxy, phenyl, heteroaryl, heterocyclylalkyl, substituted heteroaryl, and nitro; and

heteroaryl substituted with from one to three substituents independently selected from the group consisting of halogen, loweralkyl, loweracyl, loweralkoxy, fluoroloweralkyl, fluoroloweralkoxy, formyl, cyano, benzyl, benzyloxy, and nitro;

X is selected from the group consisting of O, SO, $S(O_2)$, NR^1, CH_2, CF_2, CH_2CH_2, CH_2NR^1, NR^1CH_2, CH=CH, C=O, CH_2C=O, $CR^{1a}R^{1b}$, $OCR^{1a}R^{1b}$, $CR^{1a}R^{1b}O$; C(=O)NR^1 and NR^1C(=O);

R^1 is selected separately in each occurrence from the group consisting of H and lower alkyl;

R^{1a} is selected from the group consisting of H, OH and lower alkyl;

R^{1b} is selected from the group consisting of H and lower alkyl, or R^{1a} and R^{1b} taken together may form a 3-6 membered ring, which may optionally contain a heteroatom chosen from O, S, and N;

T^1 and T^2 are carbon, forming a benzene ring, or one of T^1 and T^2 may be nitrogen, forming a pyridine ring;

Q is chosen from -O-, $-NR^1-$ and $S(O)_p$;

p is zero, 1 or 2;

n is an integer selected from 1-5;

HET is selected from the group consisting of

4-7-membered saturated nitrogenous heterocycle and

4-7-membered saturated nitrogenous heterocycle substituted with one or two substituents independently selected from the group consisting of halogen, hydroxyl, amino, carboxy, loweralkyl, loweracyl, loweralkoxy, N-oxide, fluoroloweralkyl, fluoroloweralkoxy, formyl, cyano, benzyl, benzyloxy, phenyl, heteroaryl and nitro; and

taken together ZW is H or

Z is $(CH_2)_{1-10}$, in which one or two (CH_2) may optionally be replaced by -O-, $-NR^1-$, -SO-, $-S(O)_2-$, -C(=O)- or -C=O(NH)-, provided that said -O-, $-NR^1-$, -SO-, $-S(O)_2-$, -C(=O)- or -C=O(NH)- are not at the point of attachment to HET and are separated by at least one $-(CH_2)-$;

W is selected from the group consisting of acyl, hydroxyl, carboxyl, amino, $-C(O)NHR^4$, aminoacyl, -COOalkyl, -CHO, heterocyclyl, substituted aryl, substituted heterocyclyl, sulfonamide, -C(O)fluoroalkyl, $-C(O)CH_2C(O)Oalkyl$, $-C(O)CH_2C(O)Ofluoroalkyl$, -SH, -C(O)NH(OH), $-C(O)N(OH)R^4$, $-N(OH)C(O)OH$, $-N(OH)C(O)R^4$; and

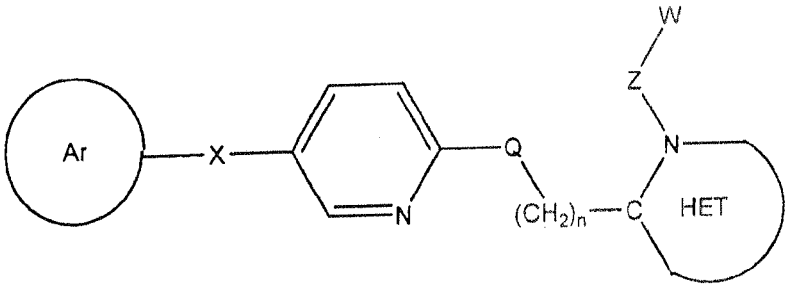
R^4 is selected from the group consisting of H, (C_1-C_4) alkyl, and phenyl(C_1-C_4) alkyl;

with the provisos that;

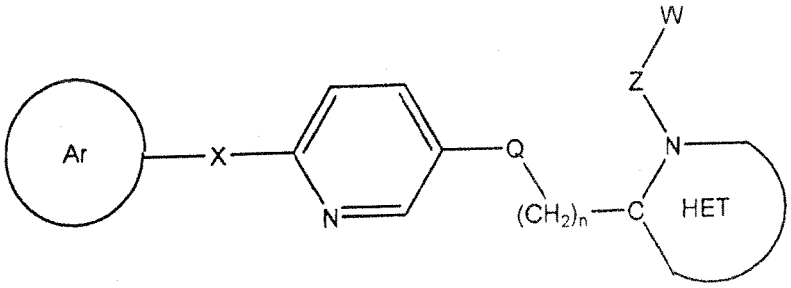
(a) when Q is -O-, HET is (*S*)-pyrrolidine, *rac*-pyrrolidine or piperidine, Ar is phenyl or halo-substituted phenyl, and HetAr is *p*-phenylene, then the Z-W combination is other than H; and

(b) when Q is -O-, HET is azetidine, Ar is phenyl, n is 1 and HetAr is a 2,5-substituted pyridine, then the Z-W combination is other than H.

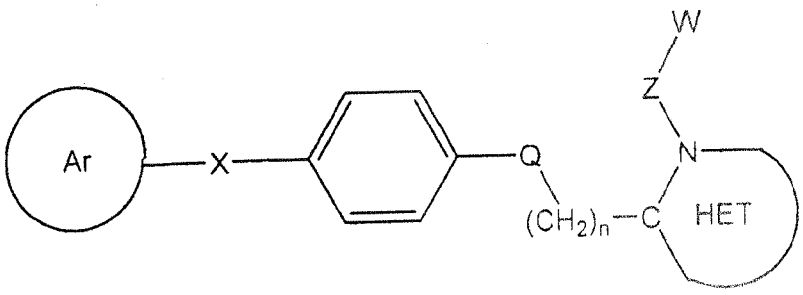
2. A compound according to claim 1 wherein HetAr is pyridinyl of formula:



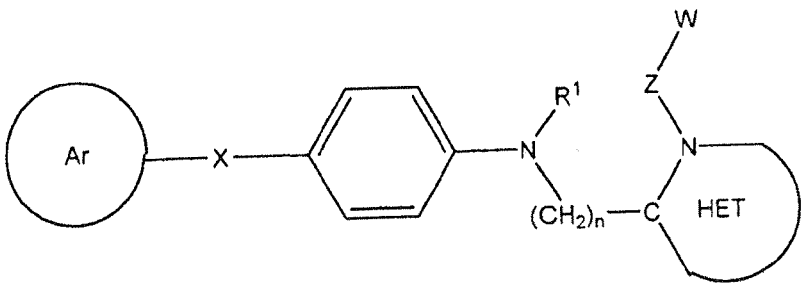
3. A compound according to claim 1 wherein HetAr is pyridinyl of formula:



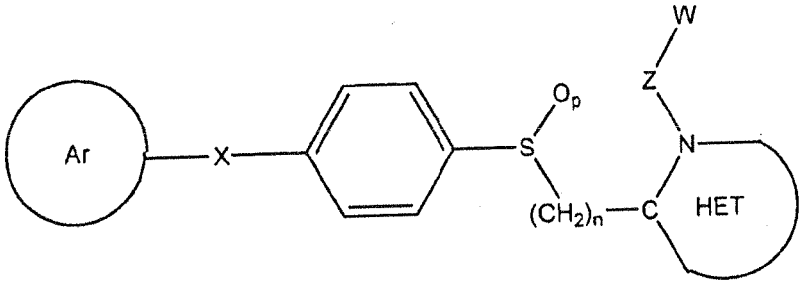
4. A compound according to claim 1 wherein HetAr is para phenylene of formula:



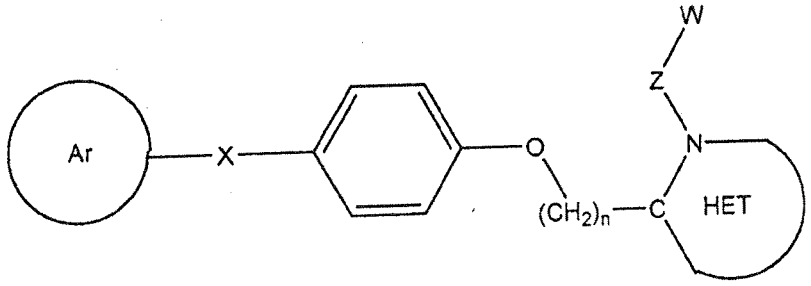
5. A compound according to claim 4 wherein Q is -NR^1- of formula:



6. A compound according to claim 4 wherein Q is -$S(O)_p$- of formula:



7. A compound according to claim 4 wherein Q is -O- of formula:



wherein

Ar is selected from the group consisting of

aryl;

heteroaryl;

aryl substituted with from one to three substituents independently selected from the group consisting of halogen, loweralkyl, loweralkoxy, fluoroloweralkyl, fluoroloweralkoxy, formyl, cyano, benzyl, benzyloxy, phenyl, heteroaryl and nitro; and

heteroaryl substituted with from one to three substituents independently selected from the group consisting of halogen, loweralkyl, loweracyl, loweralkoxy, fluoroloweralkyl, fluoroloweralkoxy, formyl, cyano, and nitro;

X is selected from the group consisting of O, SO, $S(O_2)$, NR^1, CH_2, CF_2, CH_2O, C=O and $CH_2C=O$;

R^1 is selected independently in each occurrence from the group consisting of H and lower alkyl;

n is an integer selected from 1-5;

HET is selected from the group consisting of

4-7-membered saturated nitrogenous heterocycle and

4-7-membered saturated nitrogenous heterocycle substituted with one or two substituents independently selected from the group consisting of halogen, loweralkyl, loweracyl, loweralkoxy, fluoroloweralkyl, fluoroloweralkoxy, formyl, cyano, benzyl, benzyloxy, phenyl, heteroaryl and nitro;

Z is $(CH_2)_{1-10}$; in which one or two (CH_2) may optionally be replaced by -O-, $-NR^1-$, -SO, $-S(O)_2-$, -C(=O)- or -C=O(NH)-, provided that said -O-, -NR-, -SO-, $-S(O)_2-$, -C(=O)- or -C=O(NH)- are not at the point of attachment to HET and are separated by at least two $-(CH_2)-$;

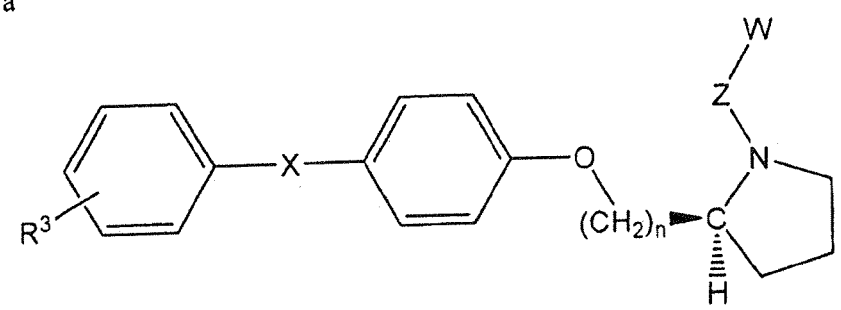
W is selected from acyl, hydroxyl, carboxyl, amino, carboxamido, aminoacyl, -COOalkyl, -CHO, heterocyclyl, substituted aryl, and substituted heterocyclyl.

8. A compound according to claim 7 wherein X is selected from CH_2, O and NR^1.

9. A compound according to claim 7 wherein HET is selected from the group consisting of pyrrolidinone, pyrrolidine, piperidine, piperidinone, piperazine, morpholine, thiomorpholine, thiazolidine, thiazolidinone, oxazolidine and oxazolidinone and

substituted pyrrolidinone, substituted pyrrolidine, substituted piperidine, substituted piperidinone, substituted piperazine, substituted morpholine, substituted thiomorpholine, substituted thiazolidine, substituted thiazolidinone, substituted oxazolidine and substituted oxazolidinone.

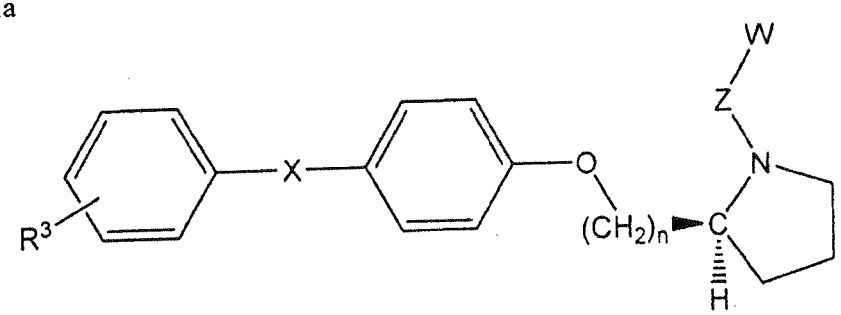
10. A compound according to claim 7 wherein HET is (*S*) pyrrolidine, of the formula



wherein

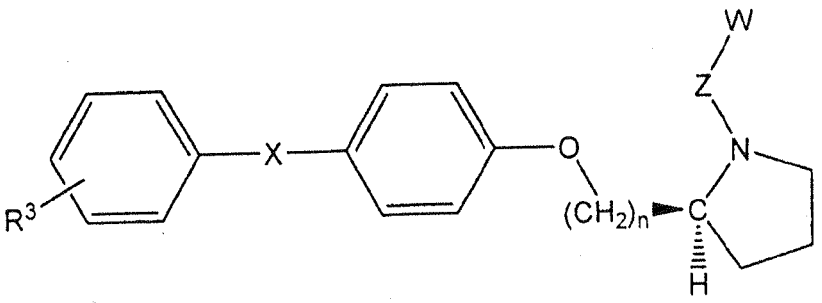
R^3 is chosen from halogen, CF_3, methyl, methoxy and CF_3O.

11. A compound according to claim 10 wherein HET is (*S*) pyrrolidine, of the formula



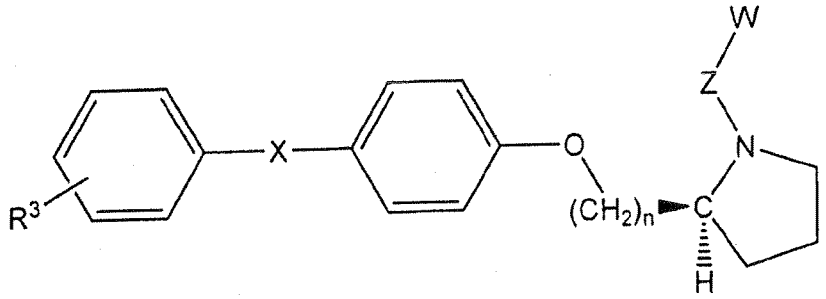
wherein X is O or CH_2.

12. A compound according to claim 10 wherein HET is (*S*) pyrrolidine, of the formula



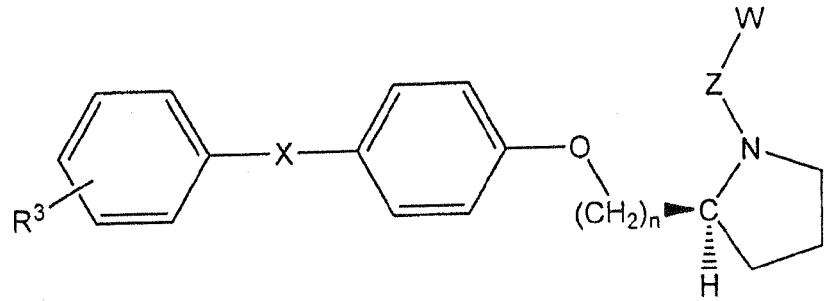
wherein n is 1 or 2.

13. A compound according to claim 10 wherein HET is (*S*) pyrrolidine, of the formula



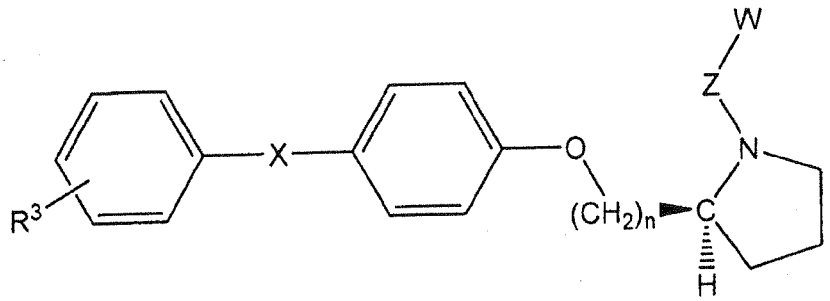
wherein Z is C_1-C_4 alkylene.

14. A compound according to claim 10 wherein HET is (*S*) pyrrolidine, of the formula



wherein W is COOH.

15. A compound according to claim 7 wherein HET is (*S*) pyrrolidine, of the formula



wherein

R^3 is chosen from halogen, CF_3, methyl, methoxy, CF_3O;

X is O or CH_2;

n is 1 or 2;

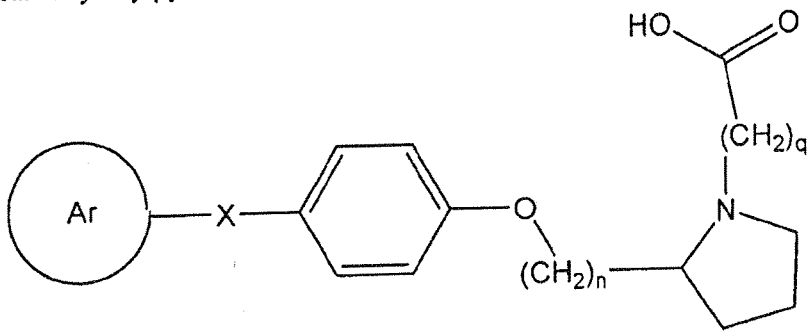
Z is C_1-C_4 alkylene and;

W is COOH.

16. A compound according to claim 9 wherein HET is pyrrolidine.

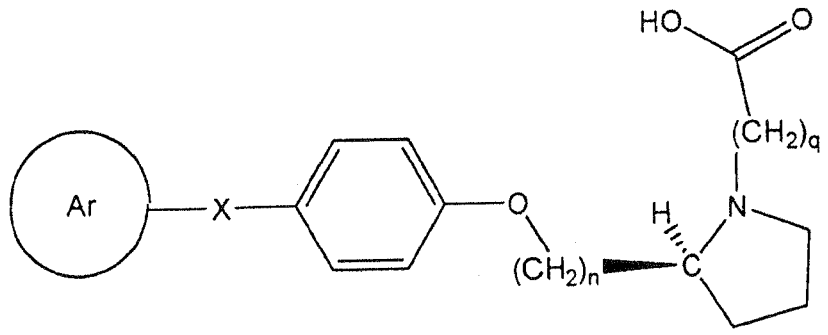
17. A compound according to claim 16 wherein HET-Z-W is selected from the group consisting of pyridinylmethylpyrrolidine, oxadiazolylmethylpyrrolidine, carboxyalkylpyrrolidine, and alkoxycarbonylalkylpyrrolidine.

18. A compound according to claim 17 wherein HET-Z-W is carboxyalkylpyrrolidine, of the formula:



wherein q is an integer selected from 2-6.

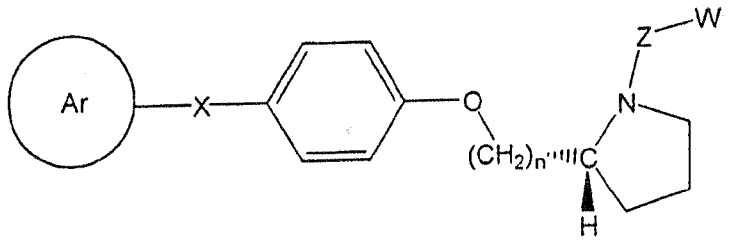
19. A compound according to claim 17 wherein HET-Z-W is carboxyalkyl (*S*) pyrrolidine, of formula:



wherein q is an integer selected from 2-6.

20. A compound according to claim 9 wherein HET is selected from the group consisting of pyrrolidine, pyrrolidinone, piperidine and piperidinone.

21. A compound according to claim 1 in which HET is (*R*) pyrrolidine of the formula:



wherein

Ar is selected from the group consisting of

aryl;

heteroaryl;

aryl substituted with from one to three substituents independently selected from the group consisting of halogen, loweralkyl, loweralkoxy, fluoroloweralkyl, fluoroloweralkoxy, hydroxy, hydroxy(C_1-C_4) alkyl, formyl, formyl(C_1-C_4) alkyl, cyano, cyano(C_1-C_4) alkyl, benzyl, benzyloxy, phenyl, heteroaryl, heterocyclylalkyl, substituted heteroaryl, and nitro; and

heteroaryl substituted with from one to three substituents independently selected from the group consisting of halogen, (C_1-C_4) alkyl, (C_1-C_4) alkoxy, benzyl, and benzyloxy;

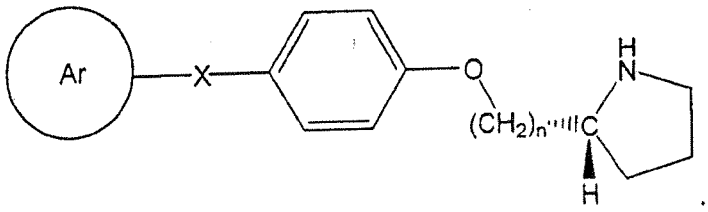
X is selected from the group consisting of O, SO, $S(O_2)$, NR^1, CH_2, CF_2, CH_2CH_2, CH_2NH, $NHCH_2$, CH=CH, C=O and CH_2C=O;

taken together ZW is H or

Z is $(CH_2)_{1-10}$; in which one or two (CH_2) may optionally be replaced by -O-, $-NR^1$-, -SO-, $-S(O)_2$-, -C(=O)- or -C=O(NH)-, provided that said -O-, $-NR^1$-, -SO-, $-S(O)_2$-, -C(=O)- or -C=O(NH)- are not at the point of attachment to HET and are separated by at least one $-(CH_2)$-; and

W is selected from the group consisting of acyl, hydroxyl, carboxyl, amino, carboxamido, aminoacyl, -COOalkyl, -CHO, heterocyclyl, substituted aryl, and substituted heterocyclyl.

22. A compound according to claim 21 wherein ZW is H, of the formula:

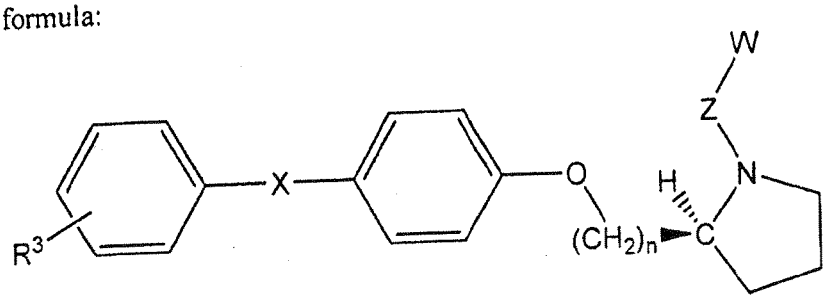


23. A compound according to claim 22 wherein X is selected from CH_2, O and NR^1.

24. A compound according to claim 23 wherein X is CH_2 or O, n is 1, and Ar is para-substituted phenyl.

25. A compound according to claim 24 wherein Ar is heteroarylphenyl.

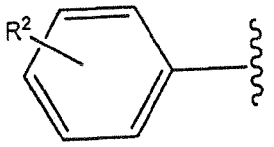
26. A compound according to claim 1 wherein HET is (*S*) pyrrolidine, of the formula:



wherein

R^3 represents one to three residues independently selected from the group consisting of benzyl, benzyloxy, phenyl, heteroaryl and heteroaryl substituted with halogen, methyl, methoxy or trifluoromethoxy.

27. A compound according to any one of claims 1-9 or 16-25 wherein Ar is

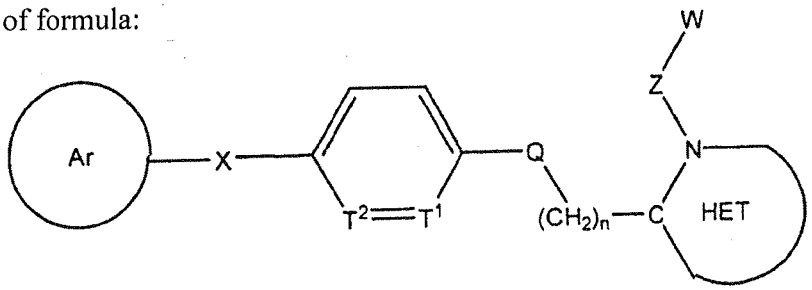


wherein the wavy line indicates the point of attachment to X and R^2 is chosen from hydrogen, halogen, trifluoromethyl, methyl, methoxy, thienyl, furanyl, and thienyl or furanyl substituted with halogen, trifluoromethyl, methyl or methoxy.

28. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one compound according to any one of claims 1-26.

29. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one compound according to claim 27.

30. A method for in vitro inhibiting leukotriene A4 hydrolase comprising contacting the LTA4H enzyme with a therapeutically effective amount of a compound of formula:



wherein

Ar is selected from the group consisting of

aryl;

heteroaryl;

aryl substituted with from one to three substituents independently selected from the group consisting of halogen, loweralkyl, loweralkoxy, fluoroloweralkyl, fluoroloweralkoxy, hydroxy, hydroxy(C_1-C_4) alkyl, formyl, formyl(C_1-C_4) alkyl, cyano, cyano(C_1-C_4) alkyl, benzyl, benzyloxy, phenyl, heteroaryl, heterocyclylalkyl, substituted heteroaryl, and nitro; and

heteroaryl substituted with from one to three substituents independently selected from the group consisting of halogen, loweralkyl, loweracyl, loweralkoxy, fluoroloweralkyl, fluoroloweralkoxy, formyl, cyano, benzyl, benzyloxy, and nitro;

X is selected from the group consisting of O, SO, $S(O_2)$, NR^1, CH_2, CF_2, CH_2CH_2, CH_2NR^1, NR^1CH_2, CH=CH, C=O, CH_2C=O, $CR^{1a}R^{1b}$, $OCR^{1a}R^{1b}$, $CR^{1a}R^{1b}O$; $C(=O)NR^1$ and $NR^1C(=O)$;

R^1 is selected separately in each occurrence from the group consisting of H and lower alkyl;

R^{1a} is selected from the group consisting of H, OH and lower alkyl;

R^{1b} is selected from the group consisting of H and lower alkyl, or R^{1a} and R^{1b} taken together may form a 3-6 membered ring, which may optionally contain a heteroatom chosen from O, S, and N;

T^1 and T^2 are carbon, forming a benzene ring, orone of T^1 and T^2 may be nitrogen, forming a pyridine ring;

Q is chosen from -O-, $-NR^1-$ and $S(O)_p$;

p is zero, 1 or 2;

n is an integer selected from 1-5;

HET is selected from the group consisting of

4-7-membered saturated nitrogenous heterocycle and

4-7-membered saturated nitrogenous heterocycle substituted with one or two substituents independently selected from the group consisting of halogen, hydroxyl, amino, carboxy, loweralkyl, loweracyl, loweralkoxy, N-oxide, fluoroloweralkyl, fluoroloweralkoxy, formyl, cyano, benzyl, benzyloxy, phenyl, heteroaryl and nitro; and

taken together ZW is H or

Z is $(CH_2)_{1-10}$, in which one or two (CH_2) may optionally be replaced by -O-, $-NR^1-$, -SO-, $-S(O)_2-$, -C(=O)- or -C=O(NH)-, provided that said -O-, $-NR^1-$, -SO-, $-S(O)_2-$, -C(=O)- or -C=O(NH)- are not at the point of attachment to HET and are separated by at least one $-(CH_2)-$;

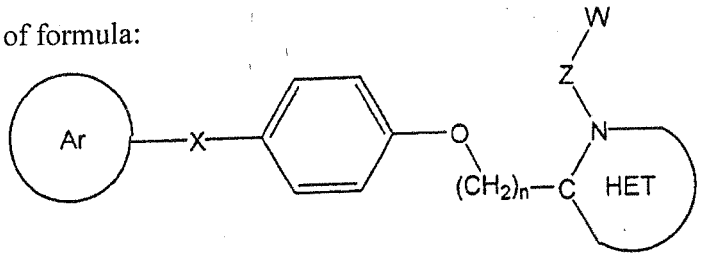
W is selected from the group consisting of acyl, hydroxyl, carboxyl, amino, $-C(O)NHR^4$, aminoacyl, -COOalkyl, -CHO, heterocyclyl, substituted aryl, substituted heterocyclyl, sulfonamide, -C(O)fluoroalkyl, $-C(O)CH_2C(O)$Oalkyl,

-C(O)CH_2C(O)Ofluoroalkyl, -SH, -C(O)NH(OH), -C(O)N(OH)R^4,

-N(OH)C(O)OH, -N(OH)C(O)R^4; and

R^4 is selected from the group consisting of H, (C_1-C_4) alkyl, and phenyl(C_1-C_4) alkyl.

31. A method for in vitro inhibiting leukotriene A4 hydrolase comprising contacting the LTA4H enzyme with a therapeutically effective amount of a compound of formula:



wherein

Ar is selected from the group consisting of

aryl;

heteroaryl;

aryl substituted with from one to three substituents independently selected from the group consisting of halogen, loweralkyl, loweralkoxy, fluoroloweralkyl, fluoroloweralkoxy, formyl, cyano, benzyl, benzyloxy, phenyl, heteroaryl and nitro; and

heteroaryl substituted with from one to three substituents independently selected from the group consisting of halogen, loweralkyl, loweracyl, loweralkoxy, fluoroloweralkyl, fluoroloweralkoxy, formyl, cyano, and nitro;

X is selected from the group consisting of O, SO, $S(O_2)$, NR^1, CH_2, CF_2, CH_2O, C=O and CH_2C=O;

R^1 is selected independently in each occurrence from the group consisting of H and lower alkyl;

n is an integer selected from 1-5;

HET is selected from the group consisting of

4-7-membered saturated nitrogenous heterocycle and

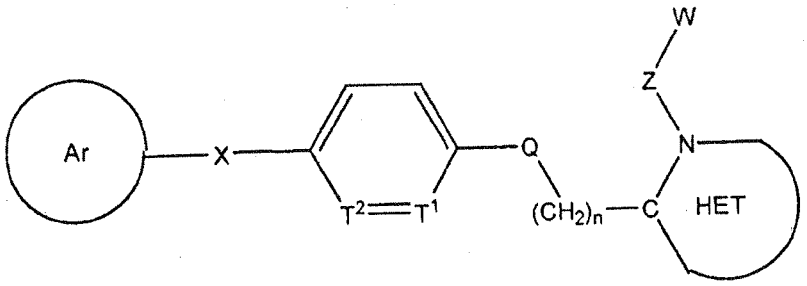
4-7-membered saturated nitrogenous heterocycle substituted with one or two substituents independently selected from the group consisting of halogen, loweralkyl, loweracyl, loweralkoxy, fluoroloweralkyl, fluoroloweralkoxy, formyl, cyano, benzyl, benzyloxy, phenyl, heteroaryl and nitro;

taken together ZW is H or

Z is $(CH_2)_{1-10}$; in which one or two (CH_2) may optionally be replaced by -O-, -NR-, -SO-, $-S(O)_2-$, -C(=O)- or -C=O(NH)-, provided that said -O-, -NR-, -SO-, $-S(O)_2-$, -C(=O)- or -C=O(NH)- are not at the point of attachment to HET and are separated by at least two $-(CH_2)-$; and

W is selected from acyl, hydroxyl, carboxyl, amino, carboxamido, aminoacyl, -COOalkyl, -CHO, heterocyclyl, substituted aryl, and substituted heterocyclyl.

32. Use of a compound of formula



wherein

Ar is selected from the group consisting of

aryl;

heteroaryl;

aryl substituted with from one to three substituents independently selected from the group consisting of halogen, loweralkyl, loweralkoxy, fluoroloweralkyl, fluoroloweralkoxy, hydroxy, hydroxy(C_1-C_4) alkyl, formyl, formyl(C_1-C_4) alkyl, cyano, cyano(C_1-C_4) alkyl, benzyl,

benzyloxy, phenyl, heteroaryl, heterocyclylalkyl, substituted heteroaryl, and nitro; and

heteroaryl substituted with from one to three substituents independently selected from the group consisting of halogen, loweralkyl, loweracyl, loweralkoxy, fluoroloweralkyl, fluoroloweralkoxy, formyl, cyano, benzyl, benzyloxy, and nitro;

X is selected from the group consisting of O, SO, $S(O_2)$, NR^1, CH_2, CF_2, CH_2CH_2, CH_2NR^1, NR^1CH_2, CH=CH, C=O, CH_2C=O, $CR^{1a}R^{1b}$, $OCR^{1a}R^{1b}$, $CR^{1a}R^{1b}O$; $C(=O)NR^1$ and $NR^1C(=O)$;

R^1 is selected separately in each occurrence from the group consisting of H and lower alkyl;

R^{1a} is selected from the group consisting of H, OH and lower alkyl;

R^{1b} is selected from the group consisting of H and lower alkyl, or R^{1a} and R^{1b} taken together may form a 3-6 membered ring, which may optionally contain a heteroatom chosen from O, S, and N;

T^1 and T^2 are carbon, forming a benzene ring, orone of T^1 and T^2 may be nitrogen, forming a pyridine ring;

Q is chosen from -O-, $-NR^1$- and $S(O)_p$;

p is zero, 1 or 2;

n is an integer selected from 1-5;

HET is selected from the group consisting of

4-7-membered saturated nitrogenous heterocycle and

4-7-membered saturated nitrogenous heterocycle substituted with one or two substituents independently selected from the group consisting of halogen, hydroxyl, amino, carboxy, loweralkyl, loweracyl, loweralkoxy, N-oxide, fluoroloweralkyl, fluoroloweralkoxy, formyl, cyano, benzyl, benzyloxy, phenyl, heteroaryl and nitro; and

taken together ZW is H or

Z is $(CH_2)_{1-10}$, in which one or two (CH_2) may optionally be replaced by -O-, $-NR^1$-, -SO-, $-S(O)_2$-, -C(=O)- or -C=O(NH)-, provided that said -O-, $-NR^1$-, -SO-,

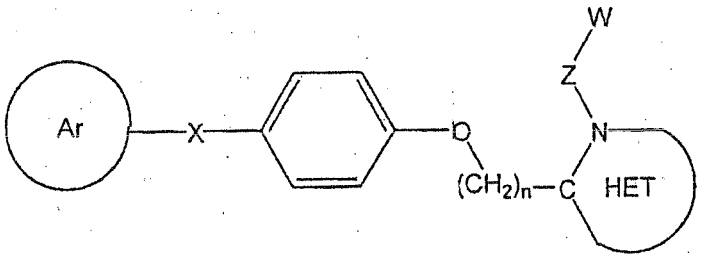
$-S(O)_2-$, -C(=O)- or -C=O(NH)- are not at the point of attachment to HET and are separated by at least one $-(CH_2)-$;

W is selected from the group consisting of acyl, hydroxyl, carboxyl, amino, $-C(O)NHR^4$, aminoacyl, -COOalkyl, -CHO, heterocyclyl, substituted aryl, substituted heterocyclyl, sulfonamide, -C(O)fluoroalkyl, $-C(O)CH_2C(O)Oalkyl$, $-C(O)CH_2C(O)Ofluoroalkyl$, -SH, -C(O)NH(OH), $-C(O)N(OH)R^4$, $-N(OH)C(O)OH$, $-N(OH)C(O)R^4$; and

R^4 is selected from the group consisting of H, (C_1-C_4) alkyl, and phenyl(C_1-C_4) alkyl;

in the preparation of a medicament for treating a disorder associated with leukotriene A4 hydrolase.

33. Use of a compound of formula



wherein

Ar is selected from the group consisting of

aryl;

heteroaryl;

aryl substituted with from one to three substituents independently selected from the group consisting of halogen, loweralkyl, loweralkoxy, fluoroloweralkyl, fluoroloweralkoxy, formyl, cyano, benzyl, benzyloxy, phenyl, heteroaryl and nitro; and

heteroaryl substituted with from one to three substituents independently selected from the group consisting of halogen, loweralkyl, loweracyl, loweralkoxy, fluoroloweralkyl, fluoroloweralkoxy, formyl, cyano, and nitro;

X is selected from the group consisting of O, SO, $S(O_2)$, NR^1, CH_2, CF_2, CH_2O, C=O and $CH_2C=O$;

R^1 is selected independently in each occurrence from the group consisting of H and lower alkyl;

n is an integer selected from 1-5;

HET is selected from the group consisting of

4-7-membered saturated nitrogenous heterocycle and

4-7-membered saturated nitrogenous heterocycle substituted with one or two substituents independently selected from the group consisting of halogen, loweralkyl, loweracyl, loweralkoxy, fluoroloweralkyl, fluoroloweralkoxy, formyl, cyano, benzyl, benzyloxy, phenyl, heteroaryl and nitro;

taken together ZW is H or

Z is $(CH_2)_{1-10}$; in which one or two (CH_2) may optionally be replaced by -O-, -NR-, -SO-, $-S(O)_2-$, -C(=O)- or -C=O(NH)-, provided that said -O-, -NR-, -SO-, $-S(O)_2-$, -C(=O)- or -C=O(NH)- are not at the point of attachment to HET and are separated by at least two $-(CH_2)-$; and

W is selected from acyl, hydroxyl, carboxyl, amino, carboxamido, aminoacyl, -COOalkyl, -CHO, heterocyclyl, substituted aryl, and substituted heterocyclyl;

in the preparation of a medicament for treating a disorder associated with leukotriene A4 hydrolase.

34. Use of a compound according to any one of claims 1-27 in the preparation of a medicament for treating a disorder associated with leukotriene A4 hydrolase.

35. Use of a compound according to any one of claims 1-26 in the preparation of a medicament for treating inflammation in a mammal being treated with an inhibitor of 5-lipoxygenase activating protein (FLAP) or a leukotriene B4 (LTB4) antagonist.