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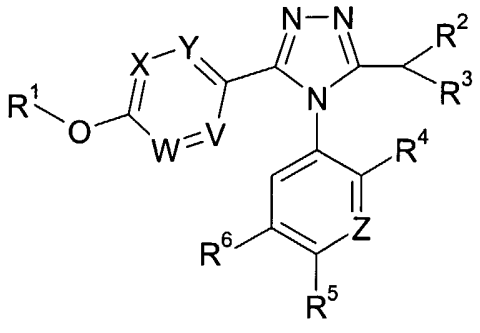
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(54) Title: SUBSTITUTED TRIAZOLE DERIVATIVES AS OXYTOCIN ANTAGONISTS



(I)

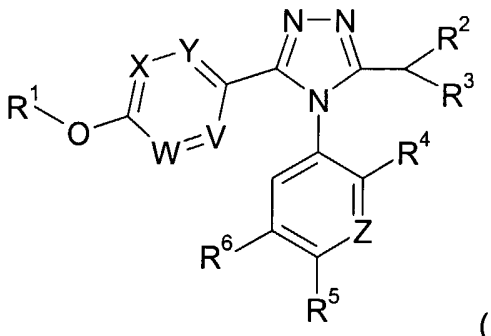
(57) Abstract: The present invention relates to a class of substituted triazoles of formula (I) with activity as oxytocin antagonists, uses thereof, processes for the preparation thereof and compositions containing said inhibitors. These inhibitors have utility in a variety of therapeutic areas including sexual dysfunction, particularly premature ejaculation (P.E.).

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Substituted Triazole Derivatives as Oxytocin Antagonists

The present invention relates to a class of substituted triazoles with activity as oxytocin antagonists, uses thereof, processes for the preparation thereof and compositions containing said inhibitors. These inhibitors have utility in a variety of therapeutic areas including sexual dysfunction, particularly premature ejaculation (P.E.).

The present invention provides for compounds of formula (I)



(I)

wherein:

V, W, X and Y, which may be the same or different, represent CH, C-(C_1-C_6)alkyl, C-halo, C-CF_3, C-CN, C-NH(C_1-C_6)alkyl, C-N((C_1-C_6)alkyl)$_2$, C-C(O)(C_1-C_6)alkyl, C-C(O)O(C_1-C_6)alkyl, C-C(O)NH(C_1-C_6)alkyl, C-C(O)N((C_1-C_6)alkyl)$_2$, C-C(O)OH, C-O(C_1-C_6)alkyl, C-C(O)NH_2 or N;

Z is CH or N;

R^1 is selected from:

i) (C_1-C_6)alkyl, which is optionally substituted by one or more substituents each independently selected from O(C_1-C_6)alkyl, CF_3 and phenyl; and

ii) a 5-8 membered saturated or partially saturated heterocycle containing 1-3 heteroatoms each independently selected from N, O and S; said ring being optionally substituted with one or more groups selected from CN, halo, (C_1-C_6)alkyl, O(C_1-C_6)alkyl, NH(C_1-C_6)alkyl,

$N((C_1\text{-}C_6)alkyl)_2$, $CO(C_1\text{-}C_6)alkyl$, $C(O)O(C_1\text{-}C_6)alkyl$, $C(O)NH(C_1\text{-}C_6)alkyl$, $C(O)N((C_1\text{-}C_6)alkyl)_2$, C(O)OH and $C(O)NH_2$;

R^2 is selected from:

(i) H;

(ii) $(C_1\text{-}C_6)alkyl$, which is optionally substituted by $O(C_1\text{-}C_6)alkyl$ or phenyl;

(iii) $O(C_1\text{-}C_6)alkyl$, which is optionally substituted by $O(C_1\text{-}C_6)alkyl$;

(iv) $NH(C_1\text{-}C_6)alkyl$, said alkyl group being optionally substituted by $O(C_1\text{-}C_6)alkyl$;

(v) $N((C_1\text{-}C_6)alkyl)_2$, wherein one or both of said alkyl groups may be optionally substituted by $O(C_1\text{-}C_6)alkyl$;

(vi) $N(CH_2CH=CH_2)_2$;

(vii) a 5-8 membered N-linked saturated or partially saturated heterocycle containing 1-3 heteroatoms, each independently selected from N, O and S, wherein at least one heteroatom is N and said ring may optionally incorporate one or two carbonyl groups; said ring being optionally substituted with one or more groups selected from CN, halo, $(C_1\text{-}C_6)alkyl$, $O(C_1\text{-}C_6)alkyl$, $NH(C_1\text{-}C_6)alkyl$, $N((C_1\text{-}C_6)alkyl)_2$, $C(O)(C_1\text{-}C_6)alkyl$, $C(O)O(C_1\text{-}C_6)alkyl$, $C(O)NH(C_1\text{-}C_6)alkyl$, $C(O)N((C_1\text{-}C_6)alkyl)_2$, C(O)OH, $C(O)NH_2$ and $C(O)OCH_2Ph$; and

(viii) a 5-7 membered N-linked aromatic heterocycle containing 1-3 heteroatoms each independently selected from N, O and S, wherein at least one heteroatom is N; said ring being optionally substituted with one or more groups selected from CN, halo, $(C_1\text{-}C_6)alkyl$, $O(C_1\text{-}C_6)alkyl$, $NH(C_1\text{-}C_6)alkyl$, $N((C_1\text{-}C_6)alkyl)_2$, $C(O)(C_1\text{-}C_6)alkyl$, $C(O)O(C_1\text{-}C_6)alkyl$, $C(O)NH(C_1\text{-}C_6)alkyl$, $C(O)N((C_1\text{-}C_6)alkyl)_2$, C(O)OH, $C(O)NH_2$ and $C(O)OCH_2Ph$;

R^3 is selected from H, $(C_1\text{-}C_6)alkyl$ and $O(C_1\text{-}C_6)alkyl$;

R^4 is selected from H, $(C_1\text{-}C_6)alkyl$ and $O(C_1\text{-}C_6)alkyl$, wherein said alkoxy group may be optionally substituted with a 5-8 membered N-linked saturated or partially

saturated heterocycle containing 1-3 heteroatoms each independently selected from N, O and S, wherein at least one heteroatom is N; said ring being optionally substituted with one or more $C(O)(C_1\text{-}C_6)$alkyl groups;

R^5 is selected from H, halo, $(C_1\text{-}C_6)$alkyl, $O(C_1\text{-}C_6)$alkyl, $NH(C_1\text{-}C_6)$alkyl and $N((C_1\text{-}C_6)alkyl)_2$; and

R^6 is H, $(C_1\text{-}C_6)$alkyl, $O(C_1\text{-}C_6)$alkyl or halo; or

R^5 and R^6 may be joined to form a $(C_1\text{-}C_4)$alkylene link, said link optionally incorporating 1-2 heteroatoms each independently selected from N, O and S;

a tautomer thereof or a pharmaceutically acceptable salt, solvate or polymorph of said compound or tautomer;

with the proviso that when:

(a) any three of V, W, X and Y represent CH and the other represents CH, $C\text{-}(C_1\text{-}C_6)$alkyl, C-halo, $C\text{-}NH(C_1\text{-}C_6)$alkyl or $C\text{-}N((C_1\text{-}C_6)alkyl)_2$; and
R^2 is H or $(C_1\text{-}C_6)$alkyl; and
R^3 is H or $(C_1\text{-}C_6)$alkyl; and
R^4 is other than H, then
R^1 is selected from:
i) $(C_1\text{-}C_6)$alkyl, which is optionally substituted by one or more substituents each independently selected from $O(C_1\text{-}C_6)$alkyl and CF_3; and
ii) a 5-6 membered saturated heterocycle containing 1-2 oxygen atoms;
said ring being optionally substituted with one or more groups selected from CN, halo, $(C_1\text{-}C_6)$alkyl, $O(C_1\text{-}C_6)$alkyl, $NH(C_1\text{-}C_6)$alkyl, $N((C_1\text{-}C_6)alkyl)_2$, $CO(C_1\text{-}C_6)$alkyl, $C(O)O(C_1\text{-}C_6)$alkyl, $C(O)NH(C_1\text{-}C_6)$alkyl, $C(O)N((C_1\text{-}C_6)alkyl)_2$, C(O)OH and $C(O)NH_2$; or

(b) any two of V, W, X and Y represent CH and the other two represent CH, $C\text{-}(C_1\text{-}C_4)$alkyl, C-halo, $C\text{-}CF_3$, $C\text{-}NH(C_1\text{-}C_4)$alkyl, $C\text{-}N((C_1\text{-}C_4)alkyl)_2$ or $C\text{-}O(C_1\text{-}C_4)$alkyl; and

R^1 is (C_1-C_4)alkyl; and
R^2 is H or (C_1-C_3)alkyl; and
R^3 is H or (C_1-C_3)alkyl; and
R^4 is H, (C_1-C_4)alkyl or (C_1-C_4)alkoxy; then
Z is N.

Unless otherwise indicated, alkyl and alkoxy groups may be straight or branched and contain 1 to 6 carbon atoms and preferably 1 to 4 carbon atoms. Examples of alkyl include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, pentyl and hexyl. Examples of alkoxy include methoxy, ethoxy, isopropoxy and n-butoxy.

Halo means fluoro, chloro, bromo or iodo and is preferably fluoro.

A heterocycle may be saturated, partially saturated or aromatic. Examples of heterocyclic groups are tetrahydrofuranyl, thiolanyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, sulfolanyl, dioxolanyl, dihydropyranyl, tetrahydropyranyl, piperidinyl, pyrazolinyl, pyrazolidinyl, dioxanyl, morpholinyl, dithianyl, thiomorpholinyl, piperazinyl, azepinyl, oxazepinyl, thiazepinyl, thiazolinyl and diazapanyl. Examples of aromatic heterocyclic groups are furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, 1,2,4-triazolyl, 1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl, thiadiazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl.

Unless otherwise indicated, the term substituted means substituted by one or more defined groups. In the case where groups may be selected from a number of alternative groups, the selected groups may be the same or different.

In a preferred aspect, the present invention comprises compounds of formula (I) wherein
X and W are each independently selected from CH, C-(C_1-C_3)alkyl, C-halo, C-CF_3 and N;
V and Y are each independently selected from CH, C-O(C_1-C_3)alkyl and N;
Z is CH or N;

R^1 is selected from:

i) $(C_1$-$C_4)$alkyl, which is optionally substituted by one or more substituents each independently selected from $O(C_1$-$C_3)$alkyl and CF_3; and

ii) a 5-6 membered saturated heterocycle containing 1-2 oxygen atoms; said ring being optionally substituted with one or more groups selected from CN, halo, $(C_1$-$C_6)$alkyl, $O(C_1$-$C_6)$alkyl, $NH(C_1$-$C_6)$alkyl, $N((C_1$-$C_6)alkyl)_2$, $CO(C_1$-$C_6)$alkyl, $C(O)O(C_1$-$C_6)$alkyl, $C(O)NH(C_1$-$C_6)$alkyl, $C(O)N((C_1$-$C_6)alkyl)_2$, C(O)OH and $C(O)NH_2$;

R^2 is selected from:

i) H;

ii) $(C_1$-$C_3)$alkyl, which is optionally substituted by OCH_3;

iii) $O(C_1$-$C_3)$alkyl, which is optionally substituted by OCH_3;

iv) $NH(C_1$-$C_3)$alkyl, which is optionally substituted by OCH_3;

v) $N(CH_3)(C_1$-$C_3)$alkyl, wherein said alkyl group may be optionally substituted by OCH_3;

vi) $N(CH_2CH=CH_2)_2$;

vii) a 5-6 membered N-linked saturated heterocycle containing 1-2 nitrogen atoms; said ring may optionally incorporate one or two carbonyl groups; said ring being optionally substituted by $C(O)NH_2$ or $C(O)OCH_2Ph$; and

viii) 1,2,3-triazol-2-yl and 1,2,3-triazol-1-yl;

R^3 is H or $(C_1$-$C_3)$alkyl;

R^4 is selected from H and $O(C_1$-$C_3)$alkyl, wherein said alkoxy group may be optionally substituted with a 5-6 membered N-linked saturated or partially saturated heterocycle containing 1-2 heteroatoms each independently selected from N and O, wherein at least one heteroatom is N; said ring being optionally substituted with one or more $C(O)(C_1$-$C_3)$alkyl groups;

R^5 is H, chloro, $(C_1$-$C_3)$alkyl or $O(C_1$-$C_3)$alkyl; and

R^6 is H or chloro; or

R^5 and R^6 may be joined to form a link, said link being $(C_1$-$C_2)$alkylene, said alkylene link optionally incorporating 1-2 O atoms.

In another preferred aspect, the present invention comprises compounds of formula (I) wherein

X and W are each independently selected from CH, C-CH_3, C-CH_2CH_3, C-F, C-Cl, C-CF_3 and N;

V and Y are each independently selected from CH, C-OCH_3 and N;

Z is CH or N;

R^1 is selected from:

i) (C_1-C_3)alkyl, which is optionally substituted by OCH_3 and CF_3; and

ii) tetrahydrafuranyl;

R^2 is selected from H, CH_3, OCH_3, OCH_2CH_3, $OCH(CH_3)_2$, $OCH_2CH_2OCH_3$, $NHCH_3$, $N(CH_3)_2$, $NHCH_2CH_2OCH_3$, $N(CH_3)CH_2CH_2OCH_3$, $N(CH_2CH{=}CH_2)_2$, pyrrolidin-1-yl, pyrrolidin-1-yl-2-carboxylic acid amide, 2,5-dioxopiperazin-4-yl-1-carboxylic acid benzyl ester, piperazin-1-yl-2-one and piperazin-4-yl-2-one;

R^3 is H or CH_3;

R^4 is selected from H, methoxy, 2-(morpholin-4-yl)ethoxy and 2-(1-acetyl-piperazin-4-yl)ethoxy;

R^5 is H, chloro, methyl or methoxy; and

R^6 is H or chloro; or

R^5 and R^6 may be joined to form a link, said link being ethoxy.

In one preferred aspect, the present invention comprises compounds of formula (I) according to the above preferred aspects wherein Z is CH.

In another preferred aspect, the present invention comprises compounds of formula (I) according to the above preferred aspects wherein Z is N.

Preferred embodiments of the compounds of formula (I) according to the above aspects are those that incorporate one or more of the following preferences.

Preferably, X and W are each independently selected from CH, C-(C_1-C_6)alkyl, C-halo, C-CF_3 and N.

More preferably, X and W are each independently selected from CH, C-(C_1-C_3)alkyl, C-halo, C-CF_3 and N.

Yet more preferably, X and W are each independently selected from CH, C-CH_3, C-CH_2CH_3, C-F, C-Cl, C-CF_3 and N.

Most preferably W is selected from CH, C-F and N; and X is selected from CH, CCH_3, C-F, C-Cl and N.

Preferably, V and Y are each independently selected from CH, C-O(C_1-C_6)alkyl and N.

More preferably, V and Y are each independently selected from CH, C-O(C_1-C_3)alkyl and N.

Yet more preferably, V and Y are each independently selected from CH, C-OCH_3 and N.

Most preferably, V is selected from CH and N; and Y is selected from CH, C-OCH_3 and N.

Preferably, R^1 is selected from:

i) (C_1-C_6)alkyl, which is optionally substituted by one or more substituents each independently selected from O(C_1-C_6)alkyl and CF_3; and

ii) a 5-6 membered saturated or partially saturated heterocycle containing 1-2 heteroatoms each independently selected from N and O; said ring being optionally substituted with one or more groups selected from CN, halo, (C_1-C_6)alkyl, O(C_1-C_6)alkyl, NH(C_1-C_6)alkyl, N((C_1-C_6)alkyl)$_2$, CO(C_1-C_6)alkyl, C(O)O(C_1-C_6)alkyl, C(O)NH(C_1-C_6)alkyl, C(O)N((C_1-C_6)alkyl)$_2$, C(O)OH and $C(O)NH_2$.

More preferably, R^1 is selected from:

i) (C_1-C_4)alkyl, which is optionally substituted by one or more substituents each independently selected from O(C_1-C_3)alkyl and CF_3; and

ii) a 5-6 membered saturated heterocycle containing 1-2 oxygen atoms; said ring being optionally substituted with one or more groups selected from CN, halo, (C_1-C_6)alkyl, O(C_1-C_6)alkyl, NH(C_1-C_6)alkyl, N((C_1-C_6)alkyl)$_2$, CO(C_1-C_6)alkyl, C(O)O(C_1-C_6)alkyl, C(O)NH(C_1-C_6)alkyl, C(O)N((C_1-C_6)alkyl)$_2$, C(O)OH and $C(O)NH_2$.

Yet more preferably, R^1 is selected from:

i) (C_1-C_4)alkyl, which is optionally substituted by one or more substituents each independently selected from O(C_1-C_3)alkyl and CF_3; and

ii) a 5-6 membered saturated heterocycle containing 1-2 oxygen atoms.

Even more preferably, R^1 is selected from:

i) $(C_1\text{-}C_3)$alkyl, which is optionally substituted by OCH_3 and CF_3; and

iii) tetrahydrafuranyl.

Most preferably, R^1 is selected from methyl, ethyl, n-propyl, isopropyl, 2,2,2-trifluoroethyl, 2-methoxyethyl, 2-methoxyprop-1-yl, 1-methoxyprop-2-yl and tetrahydrafuran-3-yl.

Preferably, R^2 is selected from:

i) H;

ii) $(C_1\text{-}C_3)$alkyl, which is optionally substituted by $O(C_1\text{-}C_3)$alkyl;

iii) $O(C_1\text{-}C_3)$alkyl, which is optionally substituted by $O(C_1\text{-}C_3)$alkyl;

iv) $NH(C_1\text{-}C_3)$alkyl, said alkyl group being optionally substituted by $O(C_1\text{-}C_3)$alkyl;

v) $N((C_1\text{-}C_3)alkyl)_2$, wherein one or both of said alkyl groups may be optionally substituted by $O(C_1\text{-}C_3)$alkyl;

vi) $N(CH_2CH{=}CH_2)_2$;

vii) a 5-6 membered N-linked saturated heterocycle containing 1-2 nitrogen atoms; said ring may optionally incorporate one or two carbonyl groups; said ring being optionally substituted by $C(O)NH_2$ or $C(O)OCH_2Ph$; and

viii) a 5-6 membered N-linked aromatic heterocycle containing 1-3 heteroatoms each independently selected from N, O and S, wherein at least two heteroatoms are N.

More preferably, R^2 is selected from:

i) H;

ii) $(C_1\text{-}C_3)$alkyl, which is optionally substituted by OCH_3;

iii) $O(C_1\text{-}C_3)$alkyl, which is optionally substituted by OCH_3;

iv) $NH(C_1\text{-}C_3)$alkyl, which is optionally substituted by OCH_3;

v) $N(CH_3)(C_1\text{-}C_3)$alkyl, wherein said alkyl group may be optionally substituted by OCH_3;

vi) $N(CH_2CH{=}CH_2)_2$;

vii) a 5-6 membered N-linked saturated heterocycle containing 1-2 nitrogen atoms; said ring may optionally incorporate one or two carbonyl groups; said ring being optionally substituted by $C(O)NH_2$ or $C(O)OCH_2Ph$; and

viii) 1,2,3-triazol-2-yl and 1,2,3-triazol-1-yl.

Most preferably, R^2 is selected from H, CH_3, OCH_3, OCH_2CH_3, $OCH(CH_3)_2$, $OCH_2CH_2OCH_3$, $NHCH_3$, $N(CH_3)_2$, $NHCH_2CH_2OCH_3$, $N(CH_3)CH_2CH_2OCH_3$, $N(CH_2CH{=}CH_2)_2$, pyrrolidin-1-yl, pyrrolidin-1-yl-2-carboxylic acid amide, 2,5-dioxopiperazin-4-yl-1-carboxylic acid benzyl ester, piperazin-1-yl-2-one and piperazin-4-yl-2-one.

Preferably, R^3 is H or $(C_1\text{-}C_6)$alkyl.
More preferably, R^3 is H or $(C_1\text{-}C_3)$alkyl.
Yet more preferably, R^3 is H or CH_3.
Most Preferably, R^3 is H.

Preferably, R^4 is selected from H and $O(C_1\text{-}C_6)$alkyl, wherein said alkoxy group may be optionally substituted with a 5-8 membered N-linked saturated or partially saturated heterocycle containing 1-3 heteroatoms each independently selected from N, O and S, wherein at least one heteroatom is N; said ring being optionally substituted with one or more $C(O)(C_1\text{-}C_6)$alkyl groups.

More preferably, R^4 is selected from H and $O(C_1\text{-}C_3)$alkyl, wherein said alkoxy group may be optionally substituted with a 5-6 membered N-linked saturated or partially saturated heterocycle containing 1-2 heteroatoms each independently selected from N and O, wherein at least one heteroatom is N; said ring being optionally substituted with one or more $C(O)(C_1\text{-}C_3)$alkyl groups.

Most preferably, R^4 is selected from H, methoxy, 2-(morpholin-4-yl)ethoxy, 2-(1-acetyl-piperazin-4-yl)ethoxy.

Preferably, R^5 is H, chloro, fluoro, $(C_1$-$C_3)$alkyl or $O(C_1$-$C_3)$alkyl; or R^5 and R^6 may be joined to form a link, said link being $(C_1$-$C_3)$alkylene, said alkylene link optionally incorporating 1-2 heteroatoms each independently selected from N and O.

More preferably, R^5 is H, chloro, $(C_1$-$C_3)$alkyl or $O(C_1$-$C_3)$alkyl; or R^5 and R^6 may be joined to form a link, said link being $(C_1$-$C_2)$alkylene, said alkylene link optionally incorporating 1-2 O atoms.

Most preferably, R^5 is H, chloro, methyl or methoxy; or R^5 and R^6 may be joined to form a link, said link being ethoxy.

Preferably, R^6 is H, chloro or fluoro; or R^5 and R^6 may be joined to form a link, said link being $(C_1$-$C_3)$alkylene, said alkylene link optionally incorporating 1-2 heteroatoms each independently selected from N and O.

More preferably, R^6 is H or chloro; or R^5 and R^6 may be joined to form a link, said link being $(C_1$-$C_2)$alkylene, said alkylene link optionally incorporating 1-2 O atoms.

Most preferably, R^6 is H or chloro; or R^5 and R^6 may be joined to form a link, said link being ethoxy.

Preferred compounds of formula (I) are:

5-[3-(3-chloro-4-ethoxy-phenyl)-5-ethoxymethyl-[1,2,4]triazol-4-yl]-2-methoxy-pyridine;

2-methoxy-5-{3-[2-methoxy-4-(2-methoxy-1-methyl-ethoxy)-phenyl]-5-[1,2,3]triazol-2-ylmethyl-[1,2,4]triazol-4-yl}-pyridine;

2-methoxy-5-{3-[2-methoxy-4-(2-methoxy-1-methyl-ethoxy)-phenyl]-5-[1,2,3]triazol-2-ylmethyl-[1,2,4]triazol-4-yl}-pyridine;

5-[3-(4-ethoxy-3-methyl-phenyl)-5-(2-methoxy-ethoxymethyl)-[1,2,4]triazol-4-yl]-2-methoxy-pyridine;

3-ethoxy-6-[5-methoxymethyl-4-(6-methoxy-pyridin-3-yl)-4H-[1,2,4]triazol-3-yl]-2-methyl-pyridine;

3-ethoxy-6-[5-methoxymethyl-4-(6-methoxy-pyridin-3-yl)-4H-[1,2,4]triazol-3-yl]-2-trifluoromethyl-pyridine;

6-[5-isopropoxymethyl-4-(6-methoxy-pyridin-3-yl)-4H-[1,2,4]triazol-3-yl]-3-methoxy-2-methyl-pyridine; and
3-ethoxy-6-[5-ethyl-4-(6-methoxy-pyridin-3-yl)-4H-[1,2,4]triazol-3-yl]-2-methyl-pyridine;
and tautomers thereof and pharmaceutically acceptable salts, solvates and polymorphs of said compound or tautomer.

Pharmaceutically acceptable salts of the compounds of formula (I) comprise the acid addition and base salts thereof.

Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include the acetate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, saccharate, stearate, succinate, tartrate, tosylate and trifluoroacetate salts.

Suitable base salts are formed from bases which form non-toxic salts. Examples include the aluminium, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts.

Hemisalts of acids and bases may also be formed, for example, hemisulphate and hemicalcium salts.

For a review on suitable salts, see Handbook of Pharmaceutical Salts: Properties, Selection, and Use by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

Pharmaceutically acceptable salts of compounds of formula (I) may be prepared by one or more of three methods:

(i) by reacting the compound of formula (I) with the desired acid or base;

(ii) by removing an acid- or base-labile protecting group from a suitable precursor of the compound of formula (I) using the desired acid or base; or

(iii) by converting one salt of the compound of formula (I) to another by reaction with an appropriate acid or base or by means of a suitable ion exchange column.

All three reactions are typically carried out in solution. The resulting salt may precipitate out and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionisation in the resulting salt may vary from completely ionised to almost non-ionised.

The compounds of the invention may exist in both unsolvated and solvated forms. The term 'solvate' is used herein to describe a molecular complex comprising the compound of the invention and a stoichiometric or non-stoichiometric amount of one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is water.

Included within the scope of the invention are complexes such as clathrates, drug-host inclusion complexes wherein the drug and host are present in stoichiometric or non-stoichiometric amounts. Also included are complexes of the drug containing two or more organic and/or inorganic components which may be in stoichiometric or non-stoichiometric amounts. The resulting complexes may be ionised, partially ionised, or non-ionised. For a review of such complexes, see J Pharm Sci, 64 (8), 1269-1288, by Haleblian (August 1975).

Hereinafter all references to compounds of formula (I) include references to salts, solvates and complexes thereof and to solvates and complexes of salts thereof.

The compounds of the invention include compounds of formula (I) as hereinbefore defined, including all polymorphs and crystal habits thereof, prodrugs and isomers thereof (including optical, geometric and tautomeric isomers) as hereinafter defined and isotopically-labeled compounds of formula (I).

As indicated, so-called 'pro-drugs' of the compounds of formula (I) are also within the scope of the invention. Thus certain derivatives of compounds of formula (I) which may have little or no pharmacological activity themselves can, when administered into or onto the body, be converted into compounds of formula (I) having the desired activity, for example, by hydrolytic cleavage. Such derivatives are referred to as 'prodrugs'. Further information on the use of prodrugs may be found in Pro-drugs as Novel Delivery Systems, Vol. 14, ACS Symposium Series (T. Higuchi and W. Stella) and Bioreversible Carriers in Drug Design, Pergamon Press, 1987 (ed. E. B. Roche, American Pharmaceutical Association).

Prodrugs in accordance with the invention can, for example, be produced by replacing appropriate functionalities present in the compounds of formula (I) with certain moieties known to those skilled in the art as 'pro-moieties' as described, for example, in Design of Prodrugs by H. Bundgaard (Elsevier, 1985).

Some examples of prodrugs in accordance with the invention include

(i) where the compound of formula I contains a carboxylic acid functionality, an ester thereof, for example, a compound wherein the hydrogen of the carboxylic acid functionality of the compound of formula (I) is replaced by $(C_1\text{-}C_8)$alkyl; and

(ii) where the compound of formula (I) contains a primary or secondary amino functionality, an amide thereof, for example, a compound wherein, as the case may be, one or both hydrogens of the amino functionality of the compound of formula (I) is/are replaced by $(C_1\text{-}C_{10})$alkanoyl.

Further examples of replacement groups in accordance with the foregoing examples and examples of other prodrug types may be found in the aforementioned references. Moreover, certain compounds of formula (I) may themselves act as prodrugs of other compounds of formula (I).

Also included within the scope of the invention are metabolites of compounds of formula (I), that is, compounds formed *in vivo* upon administration of the drug. Some examples of metabolites in accordance with the invention include

(i) where the compound of formula (I) contains a methyl group, an hydroxymethyl derivative thereof ($-CH_3$ -> $-CH_2OH$):

(ii) where the compound of formula (I) contains an alkoxy group, an hydroxy derivative thereof (-OR -> -OH);

(iii) where the compound of formula (I) contains a tertiary amino group, a secondary amino derivative thereof ($-NR^1R^2$ -> $-NHR^1$ or $-NHR^2$);

(iv) where the compound of formula (I) contains a secondary amino group, a primary derivative thereof ($-NHR^1$ -> $-NH_2$);

(v) where the compound of formula (I) contains a phenyl moiety, a phenol derivative thereof (-Ph -> -PhOH); and

(vi) where the compound of formula (I) contains an amide group, a carboxylic acid derivative thereof ($-CONH_2$ -> COOH).

Compounds of formula (I) containing one or more asymmetric carbon atoms can exist as two or more stereoisomers. Where a compound of formula (I) contains an alkenyl or alkenylene group, geometric *cis*/*trans* (or Z/E) isomers are possible. Where structural isomers are interconvertible *via* a low energy barrier, tautomeric isomerism ('tautomerism') can occur. This can take the form of proton tautomerism in compounds of formula (I) containing, for example, a keto group, or so-called valence tautomerism in compounds which contain an aromatic moiety. It follows that a single compound may exhibit more than one type of isomerism.

Included within the scope of the present invention are all stereoisomers, geometric isomers and tautomeric forms of the compounds of formula (I), including compounds exhibiting more than one type of isomerism, and mixtures of one or more thereof. Also included are acid addition salts wherein the counterion is optically active, for example, *d*-lactate or *l*-lysine, or racemic, for example, *dl*-tartrate or *dl*-arginine.

Cis/*trans* isomers may be separated by conventional techniques well known to those skilled in the art, for example, chromatography and fractional crystallisation.

Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC).

Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, an alcohol, or, in the case where the compound of formula (I) contains an acidic or basic moiety, a base or acid such as 1-phenylethylamine or tartaric acid. The resulting diastereomeric mixture may be separated by chromatography and/or fractional crystallization and one or both of the diastereoisomers converted to the corresponding pure enantiomer(s) by means well known to a skilled person.

Chiral compounds of the invention (and chiral precursors thereof) may be obtained in enantiomerically-enriched form using chromatography, typically HPLC, on an asymmetric resin with a mobile phase consisting of a hydrocarbon, typically heptane or hexane, containing from 0 to 50% by volume of isopropanol, typically from 2% to 20%, and from 0 to 5% by volume of an alkylamine, typically 0.1% diethylamine. Concentration of the eluate affords the enriched mixture.

Stereoisomeric conglomerates may be separated by conventional techniques known to those skilled in the art - see, for example, Stereochemistry of Organic Compounds by E. L. Eliel and S. H. Wilen (Wiley, New York, 1994).

The present invention includes all pharmaceutically acceptable isotopically-labelled compounds of formula (I) wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number which predominates in nature.

Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as ^{2}H and ^{3}H, carbon, such as ^{11}C, ^{13}C and ^{14}C, chlorine, such as ^{36}Cl, fluorine, such as ^{18}F, iodine, such as ^{123}I and ^{125}I, nitrogen, such as ^{13}N and ^{15}N, oxygen, such as ^{15}O, ^{17}O and ^{18}O, phosphorus, such as ^{32}P, and sulphur, such as ^{35}S.

Certain isotopically-labelled compounds of formula (I), for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, *i.e.* ^{3}H, and carbon-14, *i.e.* ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

Substitution with heavier isotopes such as deuterium, *i.e.* ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances. Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

Isotopically-labeled compounds of formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, *e.g.* D_2O, d_6-acetone, d_6-DMSO.

Also within the scope of the invention are intermediate compounds as hereinafter defined, all salts, solvates and complexes thereof and all solvates and complexes of salts thereof as defined hereinbefore for compounds of formula (I). The invention includes all polymorphs of the aforementioned species and crystal habits thereof.

When preparing compounds of formula (I) in accordance with the invention, it is open to a person skilled in the art to routinely select the form of intermediate which provides the best combination of features for this purpose. Such features include the melting point, solubility, processability and yield of the intermediate form and the resulting ease with which the product may be purified on isolation.

Compounds of the invention intended for pharmaceutical use may be administered as crystalline or amorphous products. They may be obtained, for example, as solid plugs, powders, or films by methods such as precipitation, crystallization, freeze drying, spray drying, or evaporative drying. Microwave or radio frequency drying may be used for this purpose.

They may be administered alone or in combination with one or more other compounds of the invention or in combination with one or more other drugs (or as any combination thereof). Generally, they will be administered as a formulation in association with one or more pharmaceutically acceptable excipients. The term 'excipient' is used herein to describe any ingredient other than the compound(s) of the invention. The choice of excipient will to a large extent depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form.

Pharmaceutical compositions suitable for the delivery of compounds of the present invention and methods for their preparation will be readily apparent to those skilled in the art. Such compositions and methods for their preparation may be found, for example, in Remington's Pharmaceutical Sciences, 19th Edition (Mack Publishing Company, 1995).

The compounds of the invention may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the blood stream directly from the mouth. Formulations suitable for oral administration include solid formulations such as tablets, capsules containing particulates, liquids, or powders, lozenges (including liquid-filled), chews, multi- and nano-particulates, gels, solid solution, liposome, films, ovules, sprays and liquid formulations.

Liquid formulations include suspensions, solutions, syrups and elixirs. Such formulations may be employed as fillers in soft or hard capsules and typically comprise a carrier, for example, water, ethanol, polyethylene glycol, propylene

glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet.

The compounds of the invention may also be used in fast-dissolving, fast-disintegrating dosage forms such as those described in Expert Opinion in Therapeutic Patents, 11 (6), 981-986, by Liang and Chen (2001).

For tablet dosage forms, depending on dose, the drug may make up from 1 weight % to 80 weight % of the dosage form, more typically from 5 weight % to 60 weight % of the dosage form. In addition to the drug, tablets generally contain a disintegrant. Examples of disintegrants include sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, crospovidone, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, lower alkyl-substituted hydroxypropyl cellulose, starch, pregelatinised starch and sodium alginate. Generally, the disintegrant will comprise from 1 weight % to 25 weight %, preferably from 5 weight % to 20 weight % of the dosage form.

Binders are generally used to impart cohesive qualities to a tablet formulation. Suitable binders include microcrystalline cellulose, gelatin, sugars, polyethylene glycol, natural and synthetic gums, polyvinylpyrrolidone, pregelatinised starch, hydroxypropyl cellulose and hydroxypropyl methylcellulose. Tablets may also contain diluents, such as lactose (monohydrate, spray-dried monohydrate, anhydrous and the like), mannitol, xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch and dibasic calcium phosphate dihydrate.

Tablets may also optionally comprise surface active agents, such as sodium lauryl sulfate and polysorbate 80, and glidants such as silicon dioxide and talc. When present, surface active agents may comprise from 0.2 weight % to 5 weight % of the tablet, and glidants may comprise from 0.2 weight % to 1 weight % of the tablet.

Tablets also generally contain lubricants such as magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, and mixtures of magnesium stearate with sodium lauryl sulphate. Lubricants generally comprise from 0.25 weight % to 10 weight %, preferably from 0.5 weight % to 3 weight % of the tablet. Other possible ingredients include anti-oxidants, colourants, flavouring agents, preservatives and taste-masking agents.

Exemplary tablets contain up to about 80% drug, from about 10 weight % to about 90 weight % binder, from about 0 weight % to about 85 weight % diluent, from about 2 weight % to about 10 weight % disintegrant, and from about 0.25 weight % to about 10 weight % lubricant. Tablet blends may be compressed directly or by roller to form tablets. Tablet blends or portions of blends may alternatively be wet-, dry-, or melt-granulated, melt congealed, or extruded before tabletting. The final formulation may comprise one or more layers and may be coated or uncoated; it may even be encapsulated. The formulation of tablets is discussed in Pharmaceutical Dosage Forms: Tablets, Vol. 1, by H. Lieberman and L. Lachman (Marcel Dekker, New York, 1980).

Consumable oral films for human or veterinary use are typically pliable water-soluble or water-swellable thin film dosage forms which may be rapidly dissolving or mucoadhesive and typically comprise a compound of formula (I), a film-forming polymer, a binder, a solvent, a humectant, a plasticiser, a stabiliser or emulsifier, a viscosity-modifying agent and a solvent. Some components of the formulation may perform more than one function.

The compound of formula (I) may be water-soluble or insoluble. A water-soluble compound typically comprises from 1 weight % to 80 weight %, more typically from 20 weight % to 50 weight %, of the solutes. Less soluble compounds may comprise a greater proportion of the composition, typically up to 88 weight % of the solutes. Alternatively, the compound of formula (I) may be in the form of multiparticulate beads.

The film-forming polymer may be selected from natural polysaccharides, proteins, or synthetic hydrocolloids and is typically present in the range 0.01 to 99 weight %, more typically in the range 30 to 80 weight %.

Other possible ingredients include anti-oxidants, colorants, flavourings and flavour enhancers, preservatives, salivary stimulating agents, cooling agents, co-solvents (including oils), emollients, bulking agents, anti-foaming agents, surfactants and taste-masking agents.

Films in accordance with the invention are typically prepared by evaporative drying of thin aqueous films coated onto a peelable backing support or paper. This may be done in a drying oven or tunnel, typically a combined coater dryer, or by freeze-drying or vacuuming.

Solid formulations for oral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

Suitable modified release formulations for the purposes of the invention are described in US Patent No. 6,106,864. Details of other suitable release technologies such as high energy dispersions and osmotic and coated particles are to be found in Pharmaceutical Technology On-line, 25(2), 1-14, by Verma *et al* (2001). The use of chewing gum to achieve controlled release is described in WO 00/35298.

The compounds of the invention may also be administered directly into the blood stream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques. Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water. The preparation of parenteral formulations under sterile conditions, for example, by lyophilisation,

may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.

The solubility of compounds of formula (I) used in the preparation of parenteral solutions may be increased by the use of appropriate formulation techniques, such as the incorporation of solubility-enhancing agents. Formulations for parenteral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release. Thus compounds of the invention may be formulated as a solid, semi-solid, or thixotropic liquid for administration as an implanted depot providing modified release of the active compound. Examples of such formulations include drug-coated stents and poly(*dl*-lactic-coglycolic)acid (PGLA) microspheres.

The compounds of the invention may also be administered topically to the skin or mucosa, that is, dermally or transdermally. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibres, bandages and microemulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol. Penetration enhancers may be incorporated - see, for example, J Pharm Sci, 88 (10), 955-958, by Finnin and Morgan (October 1999). Other means of topical administration include delivery by electroporation, iontophoresis, phonophoresis, sonophoresis and microneedle or needle-free (*e.g.* Powderject™, Bioject™, *etc.*) injection. Formulations for topical administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

The compounds of the invention can also be administered intranasally or by inhalation, typically in the form of a dry powder (either alone, as a mixture, for example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with phospholipids, such as phosphatidylcholine) from a dry powder inhaler or as an aerosol spray from a pressurised container, pump, spray,

atomiser (preferably an atomiser using electrohydrodynamics to produce a fine mist), or nebuliser, with or without the use of a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. For intranasal use, the powder may comprise a bioadhesive agent, for example, chitosan or cyclodextrin.

The pressurised container, pump, spray, atomizer, or nebuliser contains a solution or suspension of the compound(s) of the invention comprising, for example, ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilising, or extending release of the active, a propellant(s) as solvent and an optional surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

Prior to use in a dry powder or suspension formulation, the drug product is micronised to a size suitable for delivery by inhalation (typically less than 5 microns). This may be achieved by any appropriate comminuting method, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing to form nanoparticles, high pressure homogenisation, or spray drying.

Capsules (made, for example, from gelatin or hydroxypropylmethylcellulose), blisters and cartridges for use in an inhaler or insufflator may be formulated to contain a powder mix of the compound of the invention, a suitable powder base such as lactose or starch and a performance modifier such as *l*-leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of the monohydrate, preferably the latter. Other suitable excipients include dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose and trehalose.

A suitable solution formulation for use in an atomiser using electrohydrodynamics to produce a fine mist may contain from 1μg to 20mg of the compound of the invention per actuation and the actuation volume may vary from 1μl to 100μl. A typical formulation may comprise a compound of formula (I), propylene glycol, sterile water, ethanol and sodium chloride. Alternative solvents which may be used instead of propylene glycol include glycerol and polyethylene glycol.

Suitable flavours, such as menthol and levomenthol, or sweeteners, such as saccharin or saccharin sodium, may be added to those formulations of the invention intended for inhaled/intranasal administration.

Formulations for inhaled/intranasal administration may be formulated to be immediate and/or modified release using, for example, PGLA. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

In the case of dry powder inhalers and aerosols, the dosage unit is determined by means of a valve which delivers a metered amount. Units in accordance with the invention are typically arranged to administer a metered dose or "puff" containing from 2 to 30mg of the compound of formula (I). The overall daily dose will typically be in the range 50 to 100mg which may be administered in a single dose or, more usually, as divided doses throughout the day.

The compounds of the invention may be administered rectally or vaginally, for example, in the form of a suppository, pessary, or enema. Cocoa butter is a traditional suppository base, but various alternatives may be used as appropriate. Formulations for rectal/vaginal administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

The compounds of the invention may also be administered directly to the eye or ear, typically in the form of drops of a micronised suspension or solution in isotonic, pH-adjusted, sterile saline. Other formulations suitable for ocular and aural administration include ointments, biodegradable (*e.g.* absorbable gel sponges, collagen) and non-biodegradable (*e.g.* silicone) implants, wafers, lenses and particulate or vesicular systems, such as niosomes or liposomes. A polymer such as crossed-linked polyacrylic acid, polyvinylalcohol, hyaluronic acid, a cellulosic polymer, for example, hydroxypropylmethylcellulose, hydroxyethylcellulose, or methyl cellulose, or a heteropolysaccharide polymer, for example, gelan gum, may be incorporated together with a preservative, such as benzalkonium chloride. Such formulations may also be delivered by

iontophoresis. Formulations for ocular/aural administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted, or programmed release.

The compounds of the invention may be combined with soluble macromolecular entities, such as cyclodextrin and suitable derivatives thereof or polyethylene glycol-containing polymers, in order to improve their solubility, dissolution rate, taste-masking, bioavailability and/or stability for use in any of the aforementioned modes of administration. Drug-cyclodextrin complexes, for example, are found to be generally useful for most dosage forms and administration routes. Both inclusion and non-inclusion complexes may be used. As an alternative to direct complexation with the drug, the cyclodextrin may be used as an auxiliary additive, *i.e.* as a carrier, diluent, or solubiliser. Most commonly used for these purposes are alpha-, beta- and gamma-cyclodextrins, examples of which may be found in International Patent Applications Nos. WO 91/11172, WO 94/02518 and WO 98/55148.

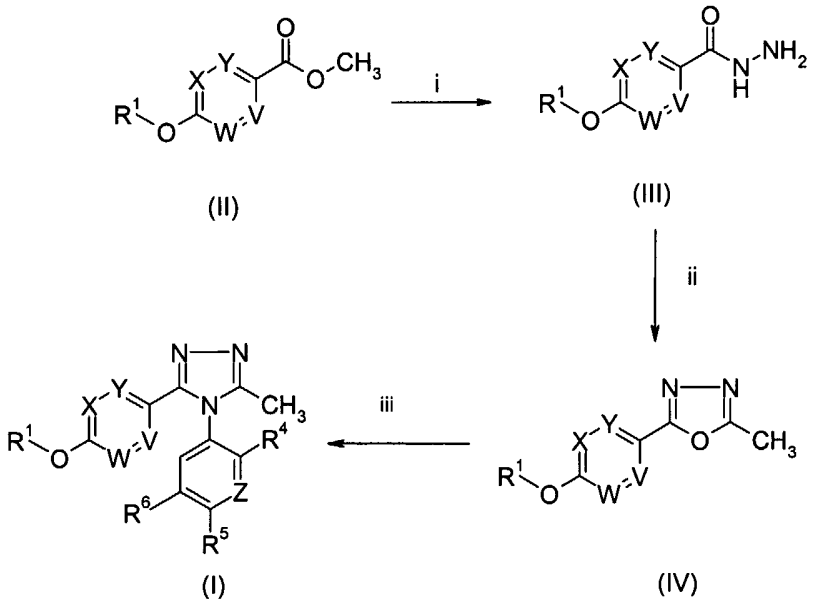
Inasmuch as it may desirable to administer a combination of active compounds, for example, for the purpose of treating a particular disease or condition, it is within the scope of the present invention that two or more pharmaceutical compositions, at least one of which contains a compound in accordance with the invention, may conveniently be combined in the form of a kit suitable for coadministration of the compositions. Thus the kit of the invention comprises two or more separate pharmaceutical compositions, at least one of which contains a compound of formula (I) in accordance with the invention, and means for separately retaining said compositions, such as a container, divided bottle, or divided foil packet. An example of such a kit is the familiar blister pack used for the packaging of tablets, capsules and the like. The kit of the invention is particularly suitable for administering different dosage forms, for example, oral and parenteral, for administering the separate compositions at different dosage intervals, or for titrating the separate compositions against one another. To assist compliance, the kit typically comprises directions for administration and may be provided with a so-called memory aid.

For administration to human patients, the total daily dose of the compounds of the invention is typically in the range 50mg to 100mg depending, of course, on the mode of administration and efficacy. For example, oral administration may require a total daily dose of from 50mg to 100mg. The total daily dose may be administered in single or divided doses and may, at the physician's discretion, fall outside of the typical range given herein. These dosages are based on an average human subject having a weight of about 60kg to 70kg. The physician will readily be able to determine doses for subjects whose weight falls outside this range, such as infants and the elderly.

For the avoidance of doubt, references herein to "treatment" include references to curative, palliative and prophylactic treatment.

Processes

Compounds of general formula (I) where X is selected from CH, C-(C_1-C_6)alkyl, C-halo and C-O(C_1-C_6)alkyl; R^2 is H; R^3 is H; and where R^1, R^4, R^5, R^6, V, W, Y and Z are as described herein may be prepared according to reaction scheme 1.



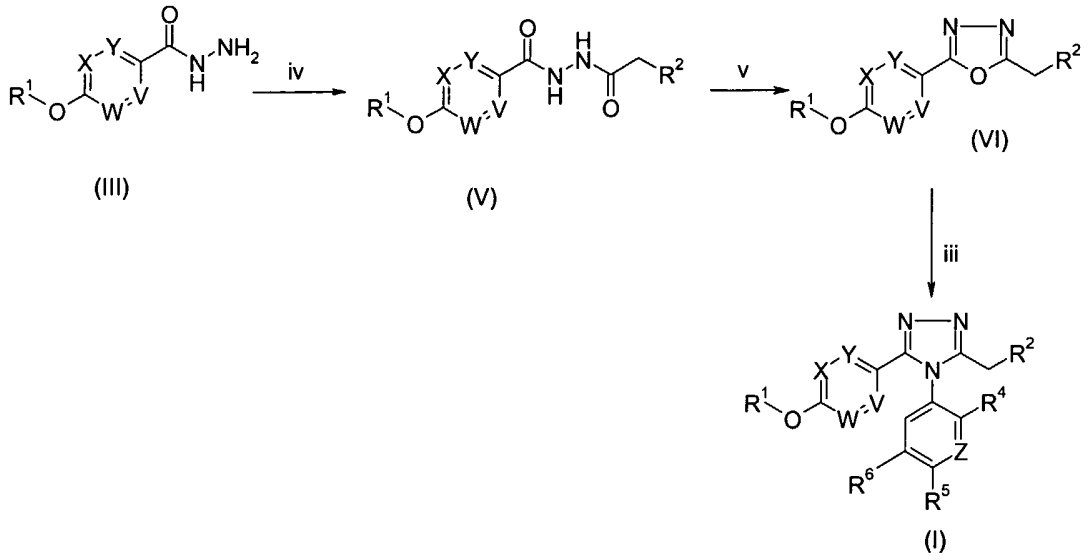
Scheme 1

Compounds of formula (III) are either commercially available or can be prepared from compounds of formula (II) by process step (i), which comprises reaction with hydrazine monohydrate in a suitable solvent such as methanol or ethanol heated to reflux. Typical conditions comprise heating 1 equivalent of aryl ester (II) and 3 equivalents of hydrazine monohydrate in methanol at 75°C for 48 hours.

Compounds of formula (IV) may be prepared from compounds of formula (III) by process step (ii), which comprises reaction with N,N-dimethylacetamide dimethyl acetal (*ex* Aldrich) in a suitable solvent such as N,N-dimethylformamide, N-methyl pyrrollidine or toluene followed by the addition of a suitable acid catalyst such as trifluoroacetic acid, *para*-toluenesulfonic acid, camphor sulfonic acid or hydrochloric acid. Typical conditions comprise heating 1 equivalent of aryl hydrazine (III) and 1.3 equivalents of N,N-dimethylacetamide dimethyl acetal in N,N-dimethylformamide at 60°C for 2 hours, followed by concentration *in vacuo*, addition of toluene and 0.025 equivalents of *para*-toluenesulfonic acid and heating at reflux for 2 hours.

Compounds of formula (I) may be prepared from compounds of formula (IV) by process of step (iii), which comprises reaction with a suitable aniline or aminopyridine in the presence of a suitable acid, such as trifluoroacetic acid, *para*-toluenesulfonic acid, camphor sulfonic acid or hydrochloric acid in a suitable solvent, such as xylene or toluene by heating at elevated temperature. Typical conditions comprise heating 1 equivalent of 1,2,4-oxidiazole (IV), 3 equivalents of aniline or aminopyridine and 0.04 equivalents of *para*-toluenesulfonic acid in xylene at 150°C for 22 hours.

Compounds of general formula (I) where R^3 is H; X is selected from CH, C-(C_1-C_6)alkyl, C-halo and C-O(C_1-C_6)alkyl; Y is selected from CH, C-(C_1-C_6)alkyl, C-halo and C-O(C_1-C_6)alkyl; and where R^1, R^2, R^4, R^5, R^6, V, W and Z are as described herein may alternatively be prepared according to reaction scheme 2.



Scheme 2

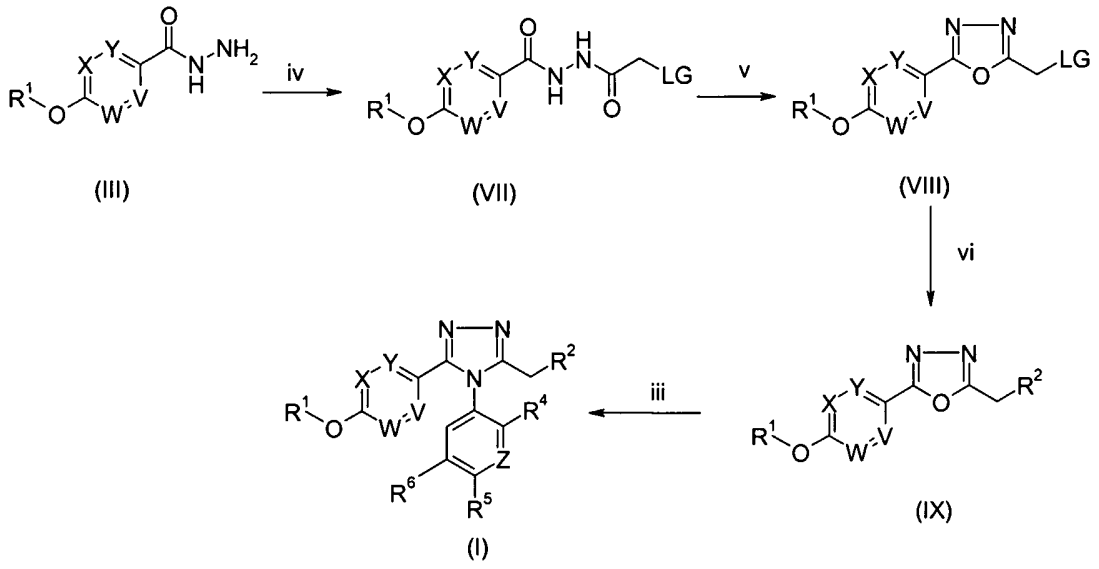
Compounds of formula (V) can be prepared from the aryl hydrazides of formula (III) by process step (iv), which comprises reaction with an acid chloride, such as $R^2CH_2C(O)Cl$, in the presence of base such as triethylamine, N-methylmorpholine, sodium carbonate or potassium hydroxide. Typical conditions comprise reacting 1.0 equivalents of aryl hydrazide (III), 1.0-1.3 equivalents of acid chloride ($R^2CH_2C(O)Cl$) and 1.2-2.0 equivalents of N-methyl morpholine in dichloromethane at 25°C.

Compounds of formula (VI) can be prepared from diacylhydrazines of formula (V) by process step (v), which comprises reaction with a suitable dehydrating agent such as phosphorous oxychloride, trifluoromethanesulfonic anhydride or phosphorous pentachloride at a temperature of 25° to 110°C. Typical conditions comprise heating 1.0 equivalents of diacylhydrazine (V) in phosphorous oxychloride at 110°C for 4 hours.

Compounds of formula (I) may be prepared from compounds of formula (VI) by process step (iii), which comprises reaction with a suitable aniline or aminopyridine in the presence of a suitable acid such as trifluoroacetic acid, *para*-toluenesulfonic acid, camphor sulfonic acid or hydrochloric acid, in a suitable solvent such as xylene or toluene, by heating at elevated temperature. Typical conditions comprise heating 1 equivalent of 1,2,4-oxidiazole (V), 3

equivalents of aniline or aminopyridine and 0.04 equivalents of *para*-toluenesulfonic acid in xylene at 150°C for 22 hours.

Compounds of general formula (I) where R^2 is NR^7R^8 or OR^9 and wherein R^7, R^8 and R^9 are the substituents on the N-linked and O-linked R^2 groups as described herein; R^3 is H; and where R^1, R^4, R^5, R^6, W, V, X, Y and Z are described herein may alternatively be prepared according to reaction scheme 3.



Scheme 3

Compounds of formula (VII) can be prepared from aryl hydrazides of formula (III) by process step (iv), which comprises reaction with an acid chloride LG-$CH_2C(O)Cl$ as described in scheme 2, where LG is a leaving group such as halo or mesylate.

Compounds of formula (VIII) can be prepared from compounds of formula (VII) by process step (v) as described previously in scheme 2.

Compounds of formula (IX) can be prepared from alkyl chlorides of formula (VIII) by process step (vi), which;

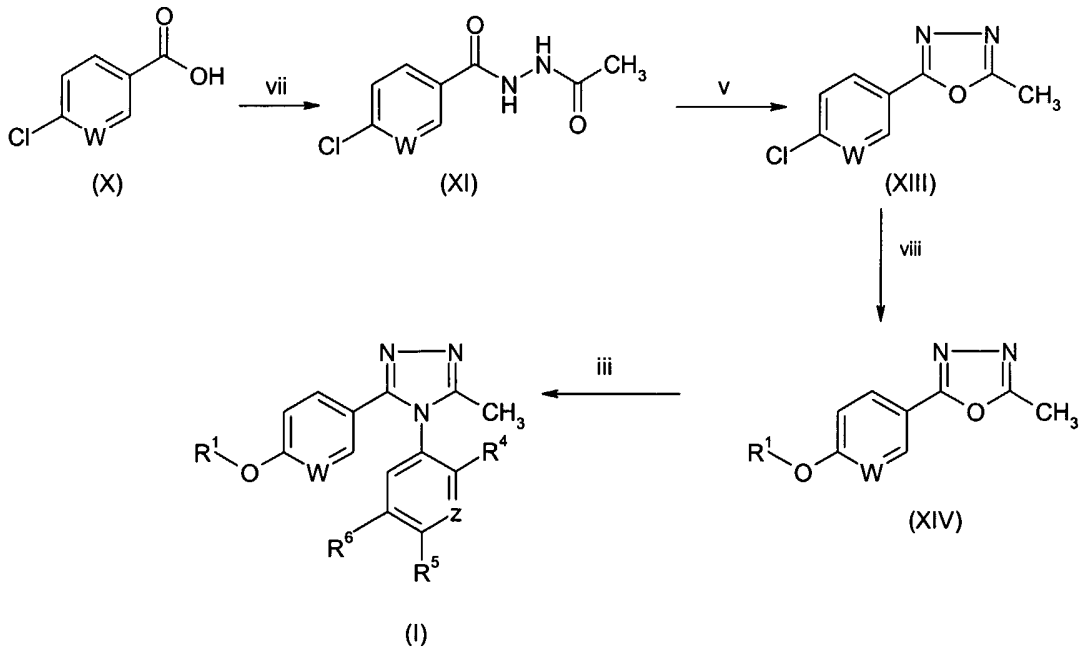
(a) when R^2 is NR^7R^8, comprises reaction with a suitable primary or secondary amine (HNR^7R^8), optionally in the presence of a base such as potassium carbonate, sodium carbonate or cesium carbonate, in a suitable solvent such as acetonitrile or N,N-dimethylformamide by heating at 25°C-50°C

for 2-18 hours. Typical conditions comprise heating 1 equivalent of alkyl halide (VIII), 1.5 equivalents of amine and 2 equivalents of potassium carbonate in acetonitrile for 18 hours at 25°C; or

(b) when R^2 is OR^9, compounds of formula (IX) can be prepared by the reaction of alkyl halide (VIII) with a suitable alkoxide salt such as R^9ONa, optionally generated *in situ*, in a suitable solvent such as tetrahydrofuran or R^9OH, by stirring at room temperature for 2-18 hours. Typical conditions comprise stirring 1 equivalent of alkyl halide (VIII), 1.5 equivalents of alcohol (R^9OH) and 2 equivalents of sodium hydride in tetrahydrofuran at room temperature for 2 hours.

Compounds of formula (I) can be prepared from compounds of formula (IX) by process step (iii) as described previously in scheme 1.

Compounds of general formula (I) where R^2 is H; R^3 is H; W is N; V, X and Y are CH; and where R^1, R^4, R^5, R^6 and Z are described herein may alternatively be prepared according to reaction scheme 4.



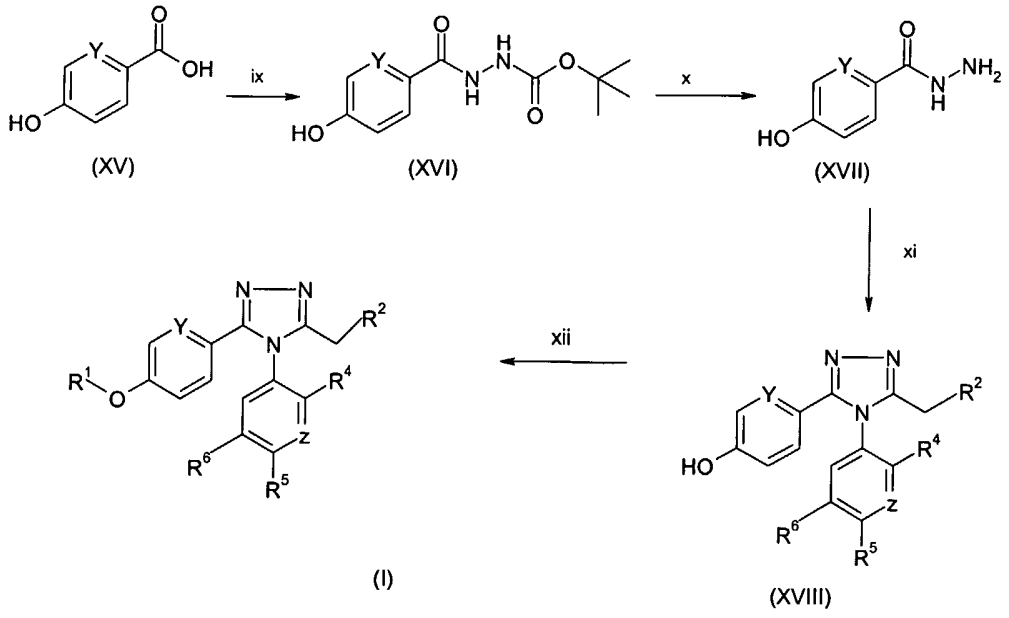
Scheme 4

Compounds of formula (X) are commercially available.

Compounds of formula (XI) may be prepared from compounds of formula (X) by process step (vii), which comprises reaction with acetyl hydrazine in the presence of a suitable coupling reagent such as O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU) and a suitable base such as triethylamine, in a suitable solvent such as N,N-dimethylformamide. Typical conditions comprise stirring 1.0 equivalent of chloronicotinic acid (X), one equivalent of acetyl hydrazine, one equivalent of HBTU and one equivalent of triethylamine in N,N-dimethylformamide at 25°C for 48 hours.

Compounds of formula (XIII) can be prepared from compounds of formula (XI) by process step (v) as described previously in scheme 2. Compounds of formula (XIV) can be prepared from compounds of formula (XIII) by process step (viii), which comprises reaction with alkoxide salt, R^1OM, in a suitable solvent such as 1-methyl-2-pyrrolidinone (NMP) or propan-1-ol by heating at 110°C. Typical conditions comprise heating 1.0 equivalent of oxidiazole (XIII) and 1.2 equivalents of sodium alkoxide in propan-1-ol at 110°C in a microwave for 5 minutes.

Compounds of general formula (I) where R^3 is H; Y is N; V, W and X are CH and where R^1, R^2, R^4, R^5, R^6 and Z are as described herein may alternatively be prepared according to reaction scheme 5.



Scheme 5

Compounds of formula (XV) are commercially available.

Compounds of formula (XVI) may be prepared from compounds of formula (XV) by process step (ix), which comprises reaction with a suitable chlorinating agent such as oxalyl chloride or thionyl chloride in a suitable solvent such as N,N-dimethylformamide followed by the addition of *tert*-butyl carbazate and a suitable base such as triethylamine. Typical conditions comprise adding 1.6 equivalents of oxalyl chloride to a solution of 1.0 equivalent of pyridine acid (XV), and a catalytic quantity of N,N-dimethylformamide in dichlormethane at 0°C, allowing the mixture to warm to room temperature and stirring for three hours. 1.6 Equivalents of N-ethyldiisopropylamine are then added followed by 2.7 equivalents of *tert*-butyl carbazate and the reaction stirred at room temperature for 18 hours.

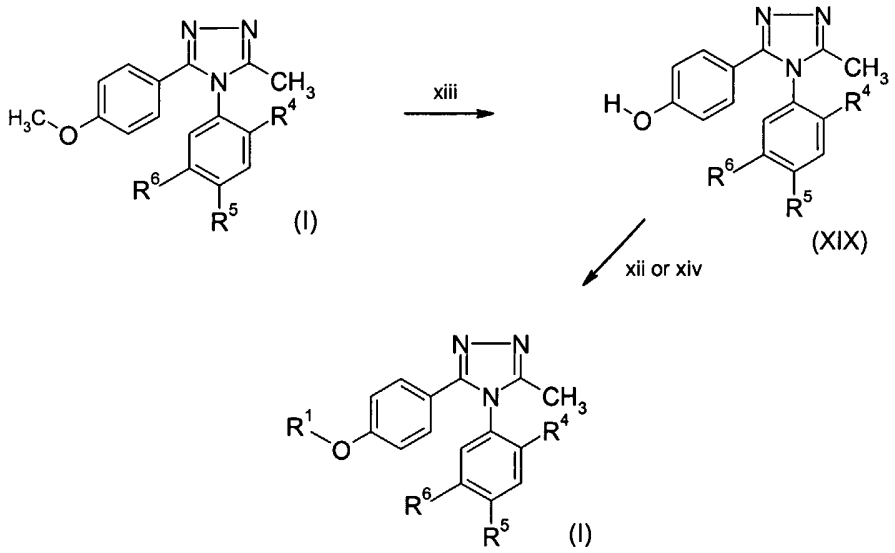
Compounds of formula (XVII) may be prepared from compounds of formula (XVI) by process step (x), which comprises reaction with a suitable acid such as trifluoroacetic acid or hydrochloric acid in a suitable solvent such as dichloromethane. Typical conditions comprise adding a mixture of trifluoroacetic acid and dichloromethane in a 1:4 ratio to the *tert*-butyl carbamate at 0°C.

Compounds of formula (XVIII) may be prepared from compounds of formula (XVII) by process step (xi), which comprises reaction with a suitable imidate in a suitable solvent such as N,N-dimethylformamide at 120°C. Typical conditions comprise heating 1.0 equivalents of hydrazide and 2.0 equivalents of imidate from preparation 2 in N,N-dimethylformamide at 120°C for 8 hours.

Compounds of formula (I) may be prepared from compounds of formula (XVIII) by process step (xii), which comprises reaction with a suitable phosphine such as triphenyl phosphine, a suitable azodicarboxylate such as diethyl azodicarboxylate and the required alcohol in a suitable solvent such as tetrahyrofuran or dichloromethane between 0°C and reflux for between 1 and 18 hours. Typical conditions comprise of the addition of 2 equivalents of di-*tert*-butyl azodicarboxylate to a solution of 1 equivalent of phenol (XVIII), 2 equivalents of

triphenyl phosphine and 1.4 equivalents of the required alkyl alcohol in tetrahydrofuran and stirring at room temperature for 18 hours.

Compounds of general formula (I) where R^2 and R^3 are H; V, W, X, Y and Z are CH; and where R^1, R^4, R^5 and R^6 are as described herein may alternatively be prepared according to reaction scheme 6.



Scheme 6

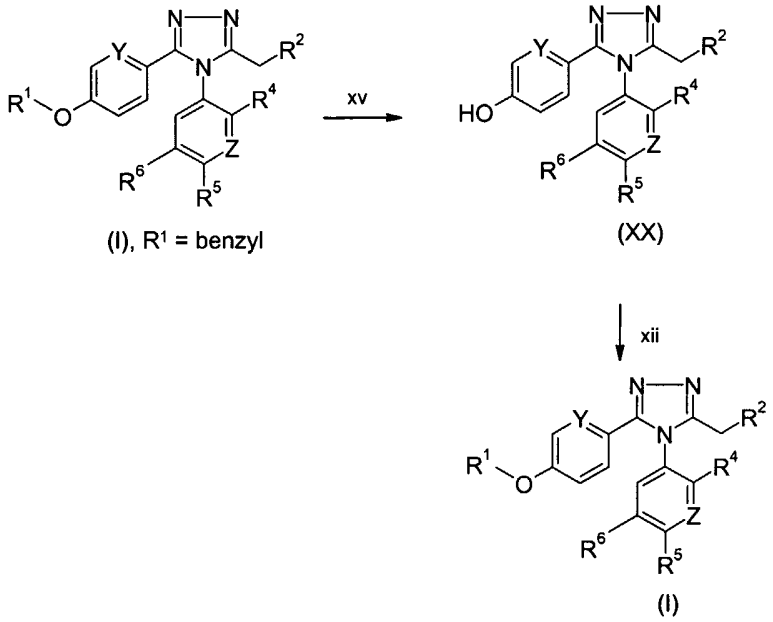
Compounds of formula (I) where R^1 is methyl can be prepared from compounds of formula (II) by process steps (i), (ii) and (iii) as described previously in scheme 1.

Compounds of formula (XIX) can be prepared from compounds of formula (I) where R^1 is CH_3 by process step (xiii), which comprises reaction with 1.0-4.0 equivalents of boron tribromide in a suitable solvent such as dichloromethane between 25°C and reflux for between 4 and 18 hours. Typical conditions comprise heating 1 equivalent of methoxy ether (I) and 3.4 equivalents of boron tribromide in dichloromethane at reflux for 4 hours and then allowing to stand at 25°C for 18 hours.

Compounds of formula (I) can be prepared from compounds of formula (XIX) by either process step (xii) or process step (xiv). Process step (xii) is as previously

described in scheme 5. Alternatively, process step (xiv) comprises reaction with 1.1-1.5 equivalents of sodium hydride in a suitable solvent such as tetrahydofuran or N,N-dimethylformamide followed by the addition of a suitable alkyl halide, R^1Hal. Typical conditions comprise stirring 1.2 equivalents of sodium hydride in mineral oil (60%) and compounds of formula (XIX) in a 1:1 mixture of tetrahyrofuran and N,N-dimethylformamide at room temperature for 1 hour followed by the addition of 1 equivalent of 2-bromopropane at room temperature.

Compounds of general formula (I) where R^3 is H; V, W and X are CH; and where R^1, R^2, R^4, R^5, R^6, Y and Z are as described herein may alternatively be prepared according to reaction scheme 7.



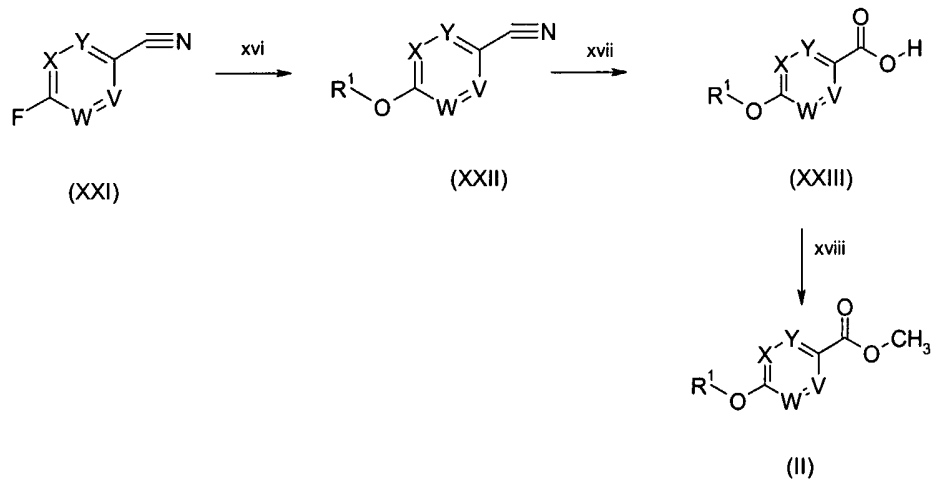
Scheme 7

Compounds of formula (I) where R^1 is benzyl and R^2 is H can be prepared from compounds of formula (II) by process steps (i), (ii) and (iii) as described in scheme 1. Alternatively, benzyl ether compounds of formula (I) where R^2 is as described herein can be prepared from compounds of formula (III) where R^1 is benzyl by process steps (iv), (v) and (iii) as described in scheme 2 or by process steps (iv), (v), (vi) and (iii) as described in scheme 3.

Compounds of formula (XX) can be prepared from compounds of formula (I) where R^1 is benzyl by process step (xv), which comprises reaction with hydrogen gas and a suitable palladium catalyst in a suitable solvent as described in "Protecting Groups" by Philip Kocienski, 1994, Thieme and references therein.

Compounds of formula (I) can be prepared from compounds of formula (XX) using process step (XII) described in scheme 5.

Compounds of general formula (II) where R^1, V, W, X, and Y are described herein may be prepared according to reaction scheme 8.



Scheme 8

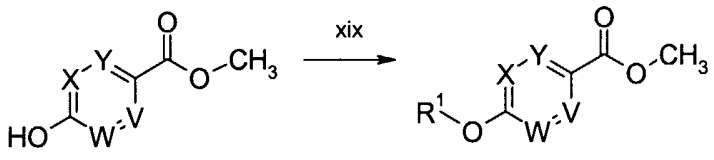
Compounds of formula (XXI) are commercially available.

Compounds of general formula (XXII) can be prepared from compounds of formula (XXI) by process step (xvi), which comprises reaction with an alcohol HOR^1 in the presence of a suitable base such as sodium hydride, in a suitable solvent such as tetrahydrofuran or N,N-dimethylformamide. Typical conditions comprise stirring 1 equivalent of halo aryl nitrile (XXI), 1 equivalent of alcohol HOR^1 and 1.0-1.5 equivalents of sodium hydride in tetrahydrofuran for 18 hours at 25°C.

Compounds of general formula (XXIII) can be prepared from compounds of formula (XXII) by process step (xvii) as described in Bioorg Med. Chem.; **10** (3), 557-560; 2002.

Compounds of general formula (II) are prepared from compounds of formula (XXIII) by process step (xviii), which comprises reaction with methanol in the presence of an acid catalyst such as sulphuric acid. Typical conditions comprise heating 1.0 equivalent of aryl carboxylic acid (XXIII), excess methanol and 0.04 equivalents of sulphuric acid at reflux for 48 hours.

Compounds of general formula (II) where R^1, V, W, X, and Y are as described herein may alternatively be prepared according to reaction scheme 9.



(XXIV) (II)

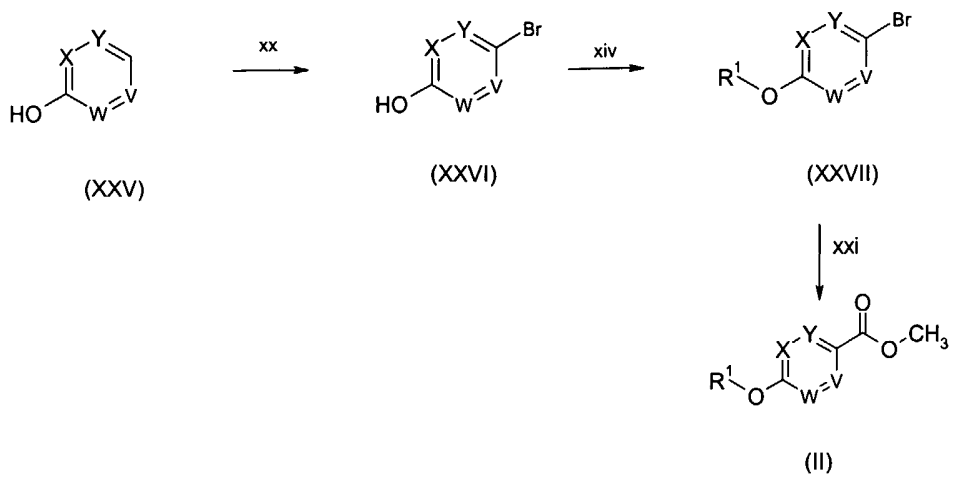
Scheme 9

Compounds of formula (XXIV) are commercially available.

Compounds of general formula (II) can be prepared from compounds of formula (XXIV) by process step (xix), which comprises reaction with a suitable alkyl halide, R^1Hal, in the presence of a suitable base such as potassium hydroxide in a suitable solvent such as N,N-dimethylformamide. Typical conditions comprise stirring 1 equivalent of aryl ester (XXIV), 1.0-1.5 equivalents of alkyl halide and 1.5-2.0 equivalents of potassium carbonate in N,N-dimethylformamide at room temperature for 2 hours.

Alternatively, compounds of general formula (II) can be prepared from compounds of general formula (XXIV) by process step (xii) described in scheme 5.

Compounds of general formula (II) where R^1, V, W, X, and Y are as described herein may alternatively be prepared according to reaction scheme 10.



(XXV) (XXVI) (XXVII) (II)

Scheme 10

Compounds of formula (XXV) are commercially available.

Compounds of general formula (XXVI) can be prepared from compounds of formula (XXV) by process step (xx), which comprises reaction with bromine in aqueous sodium hydroxide solution. Typical conditions comprise stirring 0.5 equivalents of bromine and 1 equivalent of (XXV) in a 0.5M aqueous solution of sodium hydroxide for 24 hours.

Compounds of formula (XXVII) can be prepared from compounds of formula (XXVI) by process step (xiv) as previously described in scheme 6.

Compounds of formula (II) can alternatively be prepared from compounds of formula (XXVII) by process step (xxi), which comprises reaction with carbon monoxide, 0.05-0.30 equivalents of a suitable palladium catalyst such as dichloro-bis(triphenylphosphine)palladium and a suitable base such as triethylamine in a suitable solvent such as acetonitrile. Typical conditions comprise stirring 1 equivalent of aryl bromide (XXVII), 1.5 equivalents of triethylamine, 0.03 equivalents of dichloro-bis(triphenylphoshine)palladium in a 1:4 mixture of methanol:aceonitrile at 60°C and 60psi for 18 hours.

All of the above reactions and the preparations of novel starting materials disclosed in the preceding methods are conventional and appropriate reagents and reaction conditions for their performance or preparation as well as procedures for isolating the desired products will be well known to those skilled in the art with reference to literature precedents and the examples and preparations hereto.

The compounds of the invention are useful because they have pharmacological activity in mammals, including humans. More particularly, they are useful in the treatment or prevention of a disorder in which modulation of the levels of oxytocin could provide a beneficial effect. Disease states that may be mentioned include sexual dysfunction, particularly premature ejaculation, preterm labour, complications in labour, appetite and feeding disorders, benign prostatic hyperplasia, premature birth, dysmenorrhoea, congestive heart failure, arterial hypertension, liver cirrhosis, nephrotic hypertension, occular hypertension, obsessive compulsive disorder and neuropsychiatric disorders.

Sexual dysfunction (SD) is a significant clinical problem which can affect both males and females. The causes of SD may be both organic as well as psychological. Organic aspects of SD are typically caused by underlying vascular diseases, such as those associated with hypertension or diabetes mellitus, by prescription medication and/or by psychiatric disease such as depression. Physiological factors include fear, performance anxiety and interpersonal conflict. SD impairs sexual performance, diminishes self-esteem and disrupts personal relationships thereby inducing personal distress. In the clinic, SD disorders have been divided into female sexual dysfunction (FSD) disorders and male sexual dysfunction (MSD) disorders (Melman *et al, J. Urology*, 1999, 161, 5-11).

FSD can be defined as the difficulty or inability of a woman to find satisfaction in sexual expression. FSD is a collective term for several diverse female sexual disorders (Leiblum, S.R. (1998). Definition and classification of female sexual disorders. *Int. J. Impotence Res.*, 10, S104-S106; Berman, J.R., Berman, L. & Goldstein, I. (1999). Female sexual dysfunction: Incidence, pathophysiology,

evaluations and treatment options. *Urology*, 54, 385-391). The woman may have lack of desire, difficulty with arousal or orgasm, pain with intercourse or a combination of these problems. Several types of disease, medications, injuries or psychological problems can cause FSD. Treatments in development are targeted to treat specific subtypes of FSD, predominantly desire and arousal disorders.

The categories of FSD are best defined by contrasting them to the phases of normal female sexual response: desire, arousal and orgasm (Leiblum, S.R. (1998). Definition and classification of female sexual disorders, *Int. J. Impotence Res.*, 10, S104-S106). Desire or libido is the drive for sexual expression. Its manifestations often include sexual thoughts either when in the company of an interested partner or when exposed to other erotic stimuli. Arousal is the vascular response to sexual stimulation, an important component of which is genital engorgement and includes increased vaginal lubrication, elongation of the vagina and increased genital sensation/sensitivity. Orgasm is the release of sexual tension that has culminated during arousal.

Hence, FSD occurs when a woman has an inadequate or unsatisfactory response in any of these phases, usually desire, arousal or orgasm. FSD categories include hypoactive sexual desire disorder, sexual arousal disorder, orgasmic disorders and sexual pain disorders. Although the compounds of the invention will improve the genital response to sexual stimulation (as in female sexual arousal disorder), in doing so it may also improve the associated pain, distress and discomfort associated with intercourse and so treat other female sexual disorders.

Thus, in accordance with a further aspect of the invention, there is provided the use of a compound of the invention in the preparation of a medicament for the treatment or prophylaxis of hypoactive sexual desire disorder, sexual arousal disorder, orgasmic disorder and sexual pain disorder, more preferably for the treatment or prophylaxis of sexual arousal disorder, orgasmic disorder, and sexual pain disorder, and most preferably in the treatment or prophylaxis of sexual arousal disorder.

Hypoactive sexual desire disorder is present if a woman has no or little desire to be sexual, and has no or few sexual thoughts or fantasies. This type of FSD can be caused by low testosterone levels, due either to natural menopause or to surgical menopause. Other causes include illness, medications, fatigue, depression and anxiety.

Female sexual arousal disorder (FSAD) is characterised by inadequate genital response to sexual stimulation. The genitalia do not undergo the engorgement that characterises normal sexual arousal. The vaginal walls are poorly lubricated, so that intercourse is painful. Orgasms may be impeded. Arousal disorder can be caused by reduced oestrogen at menopause or after childbirth and during lactation, as well as by illnesses, with vascular components such as diabetes and atherosclerosis. Other causes result from treatment with diuretics, antihistamines, antidepressants eg SSRIs or antihypertensive agents.

Sexual pain disorders (includes dyspareunia and vaginismus) is characterised by pain resulting from penetration and may be caused by medications which reduce lubrication, endometriosis, pelvic inflammatory disease, inflammatory bowel disease or urinary tract problems.

The prevalence of FSD is difficult to gauge because the term covers several types of problem, some of which are difficult to measure, and because the interest in treating FSD is relatively recent. Many women's sexual problems are associated either directly with the female ageing process or with chronic illnesses such as diabetes and hypertension.

Because FSD consists of several subtypes that express symptoms in separate phases of the sexual response cycle, there is not a single therapy. Current treatment of FSD focuses principally on psychological or relationship issues. Treatment of FSD is gradually evolving as more clinical and basic science studies are dedicated to the investigation of this medical problem. Female sexual complaints are not all psychological in pathophysiology, especially for those individuals who may have a component of vasculogenic dysfunction (eg FSAD) contributing to the overall female sexual complaint. There are at present

no drugs licensed for the treatment of FSD. Empirical drug therapy includes oestrogen administration (topically or as hormone replacement therapy), androgens or mood-altering drugs such as buspirone or trazodone. These treatment options are often unsatisfactory due to low efficacy or unacceptable side effects.

The Diagnostic and Statistical Manual (DSM) IV of the American Psychiatric Association defines Female Sexual Arousal Disorder (FSAD) as being:

> "a persistent or recurrent inability to attain or to maintain until completion of the sexual activity adequate lubrication-swelling response of sexual excitement. The disturbance must cause marked distress or interpersonal difficulty."

The arousal response consists of vasocongestion in the pelvis, vaginal lubrication and expansion and swelling of the external genitalia. The disturbance causes marked distress and/or interpersonal difficulty.

FSAD is a highly prevalent sexual disorder affecting pre-, peri- and post menopausal (±HRT) women. It is associated with concomitant disorders such as depression, cardiovascular diseases, diabetes and UG disorders.

The primary consequences of FSAD are lack of engorgement/swelling, lack of lubrication and lack of pleasurable genital sensation. The secondary consequences of FSAD are reduced sexual desire, pain during intercourse and difficulty in achieving an orgasm.

Male sexual dysfunction (MSD) is generally associated with either erectile dysfunction, also known as male erectile dysfunction (MED) and/or ejaculatory disorders such as premature ejaculation, anorgasmia (unable to achieve orgasm) or desire disorders such as hypoactive sexual desire disorder (lack of interest in sex).

PE is a relatively common sexual dysfunction in men. It has been defined in several different ways but the most widely accepted is the Diagnostic and Statistical Manual of Mental Disorders IV one which states:

> "PE is a lifelong persistent or recurrent ejaculation with minimal sexual stimulation before, upon or shortly after penetration and before the patient wishes it. The clinician must take into account factors that affect duration of the excitement phase, such as age, novelty of the sexual partner or stimulation, and frequency of sexual activity. The disturbance causes marked distress of interpersonal difficulty."

The International Classification of Diseases 10 definition states:

> "There is an inability to delay ejaculation sufficiently to enjoy lovemaking, manifest as either of the following: (1) occurrence of ejaculation before or very soon after the beginning of intercourse (if a time limit is required: before or within 15 seconds of the beginning of intercourse); (2) ejaculation occurs in the absence of sufficient erection to make intercourse possible. The problem is not the result of prolonged abstinence from sexual activity"

Other definitions which have been used include classification on the following criteria:

- Related to partner's orgasm
- Duration between penetration and ejaculation
- Number of thrust and capacity for voluntary control

Psychological factors may be involved in PE, with relationship problems, anxiety, depression, prior sexual failure all playing a role.

Ejaculation is dependent on the sympathetic and parasympathetic nervous systems. Efferent impulses via the sympathetic nervous system to the vas deferens and the epididymis produce smooth muscle contraction, moving sperm

into the posterior urethra. Similar contractions of the seminal vesicles, prostatic glands and the bulbouretheral glands increase the volume and fluid content of semen. Expulsion of semen is mediated by efferent impulses originating from a population of lumber spinothalamic cells in the lumbosacral spinal cord (Coolen & Truitt, *Science*, 2002, 297, 1566) which pass via the parasympathetic nervous system and cause rhythmic contractions of the bulbocavernous, ischiocavernous and pelvic floor muscles. Cortical control of ejaculation is still under debate in humans. In the rat the medial pre-optic area and the paraventricular nucleus of the hypothalamus seem to be involved in ejaculation.

Ejaculation comprises two separate components – emission and ejaculation. Emission is the deposition of seminal fluid and sperm from the distal epididymis, vas deferens, seminal vesicles and prostrate into the prostatic urethra. Subsequent to this deposition is the forcible expulsion of the seminal contents from the urethral meatus. Ejaculation is distinct from orgasm, which is purely a cerebral event. Often the two processes are coincidental.

A pulse of oxytocin in peripheral serum accompanies ejaculation in mammals. In man oxytocin but not vasopressin plasma concentrations are significantly raised at or around ejaculation. Oxytocin does not induce ejaculation itself; this process is 100% under nervous control via α1-adrenoceptor/sympathetic nerves originating from the lumbar region of the spinal cord. The systemic pulse of oxytocin may have a role in the peripheral ejaculatory response. It could serve to modulate the contraction of ducts and glandular lobules throughout the male genital tract, thus influencing the fluid volume of different ejaculate components for example. Oxytocin released centrally into the brain could influence sexual behaviour, subjective appreciation of arousal (orgasm) and latency to subsequent ejaculation.

Accordingly, one aspect of the invention provides for the use of a compound of formula (I), without the proviso, in the preparation of a medicament for the prevention or treatment of sexual dysfunction, preferably male sexual dysfunction, most preferably premature ejaculation.

It has been demonstrated in the scientific literature that the number of oxytocin receptors in the uterus increases during pregnancy, most markedly before the onset of labour (Gimpl & Fahrenholz, 2001, *Physiological Reviews*, 81 (2), 629-683.). Without being bound by any theory it is known that the inhibition of oxytocin can assist in preventing preterm labour and in resolving complications in labour.

Accordingly, another aspect of the invention provides for the use of a compound of formula (I), without the proviso, in the preparation of a medicament for the prevention or treatment of preterm labour and complications in labour.

Oxytocin has a role in feeding; it reduces the desire to eat (Arletti *et al.*, *Peptides*, 1989, 10, 89). By inhibiting oxytocin it is possible to increase the desire to eat. Accordingly oxytocin inhibitors are useful in treating appetite and feeding disorders.

Accordingly, a further aspect of the invention provides for the use of a compound of formula (I), without the proviso, in the preparation of a medicament for the prevention or treatment of appetite and feeding disorders.

Oxytocin is implicated as one of the causes of benign prostatic hyperplasia (BPH). Analysis of prostate tissue have shown that patients with BPH have increased levels of oxytocin (Nicholson & Jenkin, *Adv. Exp. Med. & Biol.*, 1995, 395, 529). Oxytocin antagonists can help treat this condition.

Accordingly, another aspect of the invention provides for the use of a compound of formula (I), wihout the proviso, in the preparation of a medicament for the prevention or treatment of benign prostatic hyperplasia.

Oxytocin has a role in the causes of dysmenorrhoea due to its activity as a uterine vasoconstrictor (Akerlund, *Ann. NY Acad. Sci.*, 1994, 734, 47). Oxytocin antagonists can have a therapeutic effect on this condition.

Accordingly, a further aspect of the invention provides for the use of a compound of formula (I), without the proviso, in the preparation of a medicament for the prevention of treatment of dysmenorrhoea.

It is to be appreciated that all references herein to treatment include curative, palliative and prophylactic treatment.

The compounds of the present invention may be coadministered with one or more agents selected from:

1) One or more selective serotonin reuptake inhibitors (SSRIs) such as dapoxetine, paroxetine, 3-[(dimethylamino)methyl]-4-[4-(methylsulfanyl)phenoxy]benzenesulfonamide (Example 28, WO 0172687), 3-[(dimethylamino)methyl]-4-[3-methyl-4-(methylsulfanyl)phenoxy]benzenesulfonamide (Example 12, WO 0218333), *N*-methyl-*N*-({3-[3-methyl-4-(methylsulfanyl)phenoxy]-4-pyridinyl}methyl)amine (Example 38, PCT Application no PCT/IB02/01032).
2) One or more local anaesthetics;
3) one or more α-adrenergic receptor antagonists (also known as α-adrenoceptor blockers, α-receptor blockers or α-blockers); suitable α_1-adrenergic receptor antagonists include: phentolamine, prazosin, phentolamine mesylate, trazodone, alfuzosin, indoramin, naftopidil, tamsulosin, phenoxybenzamine, rauwolfa alkaloids, Recordati 15/2739, SNAP 1069, SNAP 5089, RS17053, SL 89.0591, doxazosin, Example 19 of WO9830560, terazosin and abanoquil; suitable α_2- adrenergic receptor antagonists include dibenarnine, tolazoline, trimazosin, efaroxan, yohimbine, idazoxan clonidine and dibenarnine; suitable non-selective α-adrenergic receptor antagonists include dapiprazole; further α- adrenergic receptor antagonists are described in PCT application WO99/30697 published on 14th June 1998 and US patents: 4,188,390; 4,026,894; 3,511,836; 4,315,007; 3,527,761; 3,997,666; 2,503,059; 4,703,063;

3,381,009; 4,252,721 and 2,599,000 each of which is incorporated herein by reference;

4) one or more cholesterol lowering agents such as statins (e.g. atorvastatin/Lipitor- trade mark) and fibrates;

5) one or more of a serotonin receptor agonist, antagonist or modulator, more particularly agonists, antagonists or modulators for example 5HT1A, 5HT2A, 5HT2C, 5HT3, 5HT6 and/or 5HT7 receptors, including those described in WO-09902159, WO-00002550 and/or WO-00028993;

6) one or more NEP inhibitors, preferably wherein said NEP is EC 3.4.24.11 and more preferably wherein said NEP inhibitor is a selective inhibitor for EC 3.4.24.11, more preferably a selective NEP inhibitor is a selective inhibitor for EC 3.4.24.11, which has an IC_{50} of less than 100nM (e.g. ompatrilat, sampatrilat) suitable NEP inhibitor compounds are described in EP-A-1097719, WO 02/079143 and WO 04/080985; IC50 values against NEP and ACE may be determined using methods described in published patent application EP1097719-A1, paragraphs [0368] to [0376];

7) one or more of an antagonist or modulator for vasopressin receptors, such as relcovaptan (SR 49059), conivaptan, atosiban, VPA-985, CL-385004, Vasotocin.

8) Apomorphine - teachings on the use of apomorphine as a pharmaceutical may be found in US-A-5945117;

9) Dopamine agonists (in particular selective D2, selective D3, selective D4 and selective D2-like agents) such as Pramipexole (Pharmacia Upjohn compound number PNU95666), ropinirole, apomorphine, surmanirole, quinelorane, PNU-142774, bromocriptine, carbergoline, Lisuride;

10) Melanocortin receptor agonists (e.g. Melanotan II and PT141) and selective MC3 and MC4 agonists (e.g.THIQ);

11) Mono amine transport inhibitors, particularly Noradrenaline Re-uptake Inhibitors (NRIs) (e.g. Reboxetine), other Serotonin Re-uptake Inhibitors (SRIs) (e.g. paroxetine, dapoxetine) or Dopamine Re-uptake Inhibitors (DRIs);

12) $5\text{-}HT_{1A}$ antagonists (e.g. robalzotan); and

13) PDE inhibitors such as PDE2 (e.g. erythro-9-(2-hydroxyl-3-nonyl)-adenine) and Example 100 of EP 0771799-incorporated herein by reference) and in

particular a PDE5 inhibitor such as the pyrazolo [4,3-d]pyrimidin-7-ones disclosed in EP-A-0463756; the pyrazolo [4,3-d]pyrimidin-7-ones disclosed in EP-A-0526004; the pyrazolo [4,3-d]pyrimidin-7-ones disclosed in published international patent application WO 93/06104; the isomeric pyrazolo [3,4-d]pyrimidin-4-ones disclosed in published international patent application WO 93/07149; the quinazolin-4-ones disclosed in published international patent application WO 93/12095; the pyrido [3,2-d]pyrimidin-4-ones disclosed in published international patent application WO 94/05661; the purin-6-ones disclosed in published international patent application WO 94/00453; the pyrazolo [4,3-d]pyrimidin-7-ones disclosed in published international patent application WO 98/49166; the pyrazolo [4,3-d]pyrimidin-7-ones disclosed in published international patent application WO 99/54333; the pyrazolo [4,3-d]pyrimidin-4-ones disclosed in EP-A-0995751; the pyrazolo [4,3-d]pyrimidin-7-ones disclosed in published international patent application WO 00/24745; the pyrazolo [4,3-d]pyrimidin-4-ones disclosed in EP-A-0995750; the compounds disclosed in published international application WO95/19978; the compounds disclosed in published international application WO 99/24433 and the compounds disclosed in published international application WO 93/07124; the pyrazolo [4,3-d]pyrimidin-7-ones disclosed in published international application WO 01/27112; the pyrazolo [4,3-d]pyrimidin-7-ones disclosed in published international application WO 01/27113; the compounds disclosed in EP-A-1092718 and the compounds disclosed in EP-A-1092719.

Preferred PDE5 inhibitors for use with the invention:

5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (sildenafil) also known as 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulphonyl]-4-methylpiperazine (see EP-A-0463756);

5-(2-ethoxy-5-morpholinoacetylphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (see EP-A-0526004);

3-ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-n-propoxyphenyl]-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (see WO98/49166);

3-ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(2-methoxyethoxy)pyridin-3-yl]-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (see WO99/54333);

(+)-3-ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-(2-methoxy-1(R)-methylethoxy)pyridin-3-yl]-2-methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, also known as 3-ethyl-5-{5-[4-ethylpiperazin-1-ylsulphonyl]-2-([(1R)-2-methoxy-1-methylethyl]oxy)pyridin-3-yl}-2-methyl-2,6-dihydro-7H-pyrazolo[4,3-d] pyrimidin-7-one (see WO99/54333);

5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-[2-methoxyethyl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, also known as 1-{6-ethoxy-5-[3-ethyl-6,7-dihydro-2-(2-methoxyethyl)-7-oxo-2H-pyrazolo[4,3-d]pyrimidin-5-yl]-3-pyridylsulphonyl}-4-ethylpiperazine (see WO 01/27113, Example 8);

5-[2-*iso*-Butoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-(1-methylpiperidin-4-yl)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (see WO 01/27113, Example 15);

5-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-phenyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (see WO 01/27113, Example 66);

5-(5-Acetyl-2-propoxy-3-pyridinyl)-3-ethyl-2-(1-isopropyl-3-azetidinyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (see WO 01/27112, Example 124);

5-(5-Acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidinyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (see WO 01/27112, Example 132);

(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl) -pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione (IC-351), i.e. the compound of examples 78 and 95 of published international application WO95/19978, as well as the compound of examples 1, 3, 7 and 8;

2-[2-ethoxy-5-(4-ethyl-piperazin-1-yl-1-sulphonyl)-phenyl]-5-methyl-7-propyl-3H-imidazo[5,1-f][1,2,4]triazin-4-one (vardenafil) also known as 1-[[3-(3,4-dihydro-5-methyl-4-oxo-7-propylimidazo[5,1-f]-as-triazin-2-yl)-4-ethoxyphenyl]sulphonyl]-4-ethylpiperazine, i.e. the compound of examples 20, 19, 337 and 336 of published international application WO99/24433; and

the compound of example 11 of published international application WO93/07124 (EISAI); and

compounds 3 and 14 from Rotella D P, *J. Med. Chem.,* 2000, 43, 1257.

Still further PDE5 inhibitors for use with the invention include:

4-bromo-5-(pyridylmethylamino)-6-[3-(4-chlorophenyl)-propoxy]-3(2H)pyridazinone; 1-[4-[(1,3-benzodioxol-5- ylmethyl)amiono]-6-chloro-2-quinozolinyl]-4-piperidine-carboxylic acid, monosodium salt; (+)-cis-5,6a,7,9,9,9a-hexahydro-2-[4-(trifluoromethyl)-phenylmethyl-5-methyl-cyclopent-4,5]imidazo[2,1-b]purin-4(3H)one; furazlocillin; cis-2-hexyl-5-methyl-3,4,5,6a,7,8,9,9a- octahydrocyclopent[4,5]-imidazo[2,1-b]purin-4-one; 3-acetyl-1-(2-chlorobenzyl)-2-propylindole-6- carboxylate; 3-acetyl-1-(2-chlorobenzyl)-2-propylindole-6-carboxylate; 4-bromo-5-(3-pyridylmethylamino)-6-(3-(4-chlorophenyl) propoxy)-3- (2H)pyridazinone; l-methyl-5(5-morpholinoacetyl-2-n-propoxyphenyl)-3-n-propyl-1,6-dihydro-7H-pyrazolo(4,3-d)pyrimidin-7-one; 1-[4-[(1,3-benzodioxol-5-ylmethyl)arnino]-6-chloro-2- quinazolinyl]-4-piperidinecarboxylic acid, monosodium salt; Pharmaprojects No. 4516 (Glaxo Wellcome); Pharmaprojects No. 5051 (Bayer); Pharmaprojects No. 5064 (Kyowa Hakko; see WO 96/26940); Pharmaprojects No. 5069 (Schering Plough); GF-196960 (Glaxo Wellcome); E-8010 and E-4010 (Eisai); Bay-38-3045 & 38-9456 (Bayer) and Sch-51866.

The contents of the published patent applications and journal articles and in particular the general formulae of the therapeutically active compounds of the claims and exemplified compounds therein are incorporated herein in their entirety by reference thereto.

More preferred PDE5 inhibitors for use with the invention are selected from the group:

5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (sildenafil);

(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl) -pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione (IC-351);

2-[2-ethoxy-5-(4-ethyl-piperazin-1-yl-1-sulphonyl)-phenyl]-5-methyl-7-propyl-3H-imidazo[5,1-f][1,2,4]triazin-4-one (vardenafil); and

5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-[2-methoxyethyl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one or 5-(5-Acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidinyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one and pharmaceutically acceptable salts thereof.

A particularly preferred PDE5 inhibitor is 5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (sildenafil) (also known as 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulphonyl]-4-methylpiperazine) and pharmaceutically acceptable salts thereof. Sildenafil citrate is a preferred salt.

Preferred agents for coadministration with the compounds of the present invention are PDE5 inhibitors, selective serotonin reuptake inhibitors (SSRIs), vasopressin V_{1A} antagonists, α-adrenergic receptor antagonists, NEP inhibitors, dopamine agonists and melanocortin receptor agonists as described above. Particularly preferred agents for coadministration are PDE5 inhibitors, SSRIs, and V_{1A} antagonists as described herein.

The compounds of the formula (I) can be administered alone but will generally be administered in admixture with a suitable pharmaceutical excipient, diluent or carrier selected with regard to the intended route of administration and standard pharmaceutical practice.

The present invention provides for a composition comprising a compound of formula (I) and a pharmaceutically acceptable diluent or carrier.

A suitable assay for determining the oxytocin antagonist activity of a compound is detailed herein below.

Oxytocin Receptor Beta-lactamase Assay:

Materials:

Cell culture/Reagents

A: cell culture
Nutrient Mixture
F12 Ham's
Foetal Bovine Serum (FBS)
Geneticin
Zeocin
Trypsin/EDTA
PBS (phosphate buffered saline)
HEPES

B: reagents
Oxytocin
OT receptor-specific antagonist
Molecular grade Dimethyl Sulphoxide (DMSO)
Trypan Blue Solution 0.4%
CCF4-AM (Solution A)
Pluronic F127s (Solution B)
24%PEG, 18%TR40 (Solution C)
Probenecid (Dissolved at 200mM in 200mM NaOH, Solution D)

Methods:

Cell Culture: Cells used are CHO-OTR/NFAT-β-Lactamase. The NFAT-β-lactamase expression construct was transfected into the CHO-OTR cell line and clonal populations were isolated via fluorescence activated cell sorting (FACS). An appropriate clone was selected to develop the assay.

Growth Medium
90% F12 Nutrient Mix, 15mM HEPES
10% FBS
400μg/ml Geneticin
200 μg/ml Zeocin
2mM L-Glutamine

Assay media
99.5% F12 Nutrient Mix, 15mM HEPES
0.5% FBS

Recovery of cells- A vial of frozen cells is thawed rapidly in 37°C water bath and the cell suspension transferred into a T225 flask with 50ml of fresh growth medium and then incubated at 37°C, 5% CO_2 in an incubator until the cells adhered to the flask Replace media with 50ml of fresh growth media the following day.

Culturing cells- CHO-OTR-NFAT-βLactamase cells were grown in growth medium. Cells were harvested when they reached 80-90% confluence removing the medium and washing with pre-warmed PBS. PBS was then removed and Trypsin/EDTA added (3mls for T225cm^2 flask) before incubating for 5 min in 37°C/5%CO_2 incubator. When cells were detached, pre-warmed growth media was added (7mls for T225cm^2 flask) and the cells re-suspended and mixed gently by pipetting to achieve single cell suspension. The cells were split into T225 flask at 1:10 (for 3days growth) and 1:30 (for 5 days growth) ratio in 35ml growth medium.

β-Lactamase assay Method:

DAY 1 Cell plate preparation

Cells grown at 80-90% confluence were harvested and counted. Suspensions of cells at 2x105 cells/ml in growth medium were prepared and 30µl of cells suspension added in 384-well, black clear-bottom plates. A blank plate containing diluents from each reagent was used for background subtraction. Plates were incubated at 37°C, 5% CO_2 overnight.

DAY 2 Cells stimulation

- 10µl antagonist/compound (diluted in assay media containing 1.25% DMSO = antagonist diluent) was added to appropriate wells and incubated for 15 minutes at 37°C, 5% CO_2.
- 10µl oxytocin, made up in assay media, was added to all wells and incubated for 4 hours at 37°C, 5% CO_2.
- A separate 384-well cell plate was used to generate an oxytocin dose response curve. (10 µl antagonist diluent was added to every well.10µl of oxytocin was then added. The cells are then treated as per antagonist/compound cell plates).

Preparation of 1ml of 6x Loading Buffer with Enhanced Loading Protocol (this requires scale-up according to number of plates to be screened)

- 12µl of solution A (1mM CCF4-AM in Dry DMSO) was added to 60µl of solution B (100mg/ml Pluronic-F127 in DMSO + 0.1% Acetic Acid) and vortexed.
- The resulting solution was added to 925µl of solution C (24% w/w PEG400, 18% TR40 v/v in water).
- 75µl of solution D was added (200mM probenecid in 200mM NaOH).
- 10µl of 6x Loading Buffer was added to all wells and incubated for 1.5hrs – 2hrs at room temperature in the dark.

- The plates were read using an LJL Analyst, Excitation 405nm, Emission 450nm and 530nm, gain optimal, lagtime 0.40μs integration, 4 flashes, bottom reading.

Using the assay described above, the compounds of the present invention all exhibit oxytocin antagonist activity, expressed as a Ki value, of less than 500nM. Preferred examples have Ki values of less than 200nM and particularly preferred examples have Ki values of less than 50nM.

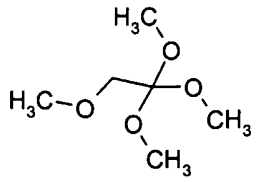
The compound of example 29 has a Ki value of 21nM.

The invention is illustrated by the following non-limiting examples in which the following abbreviations and definitions are used:

Arbocel®	Filtration agent, from J. Rettenmaier & Sohne, Germany
APCI+	Atmospheric Pressure Chemical Ionisation (positive scan)
$CDCl_3$	Chloroform-d1
d	Doublet
dd	Doublet of doublets
DMSO	Dimethylsulfoxide
ES+	Electrospray ionisation positive scan.
eq	Equivalent
^1H NMR	Proton Nuclear Magnetic Resonance Spectroscopy
MS	(Low Resolution) Mass Spectroscopy
m	Multiplet
m/z	Mass spectrum peak
q	Quartet
s	Singlet
t	Triplet
δ	Chemical shift

Preparation 1

1,1,1,2-Tetramethoxy-ethane

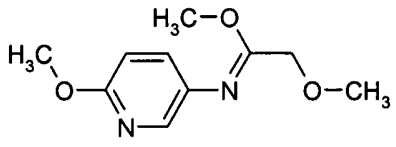


Methoxyacetonitrile (50.0g, 704mmol) was dissolved in a mixture of methanol (34mL) and diethyl ether (210mL) and the mixture cooled to 0°C. Hydrogen chloride gas was bubbled through the solution for 20 minutes and the reaction mixture was stirred at room temperature for 2 hours. Hydrogen chloride gas was bubbled through the mixture for a second time and it was then allowed to stand at -15°C for 18 hours. The mixture was filtered and the resulting white residue was washed with diethyl ether, dissolved in methanol (340mL) and stirred for 90 minutes. The solution was diluted with ether (370mL), heated under reflux for 6 hours and then left to stand at room temperature for 18 hours. Additional ether (200mL) was added and the mixture was filtered off. The filtrate was washed with 10% sodium carbonate solution, dried over magnesium sulfate and concentrated *in vacuo* to yield the title product, 34.5g.

^{1}H NMR($CDCl_3$, 400MHz) δ: 3.29(s, 9H), 3.39(s, 3H), 3.50(s, 2H)

Preparation 2

2-Methoxy-N-(6-methoxy-pyridin-3-yl)-acetimidic acid methyl ester

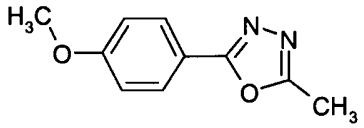


The product of preparation 1 (7.0g, 46.7mmol) and 6-methoxy-pyridin-3-ylamine (4.0g, 32.0mmol) were dissolved in dimethyl sulfoxide (100mL) and heated at 120°C for 4 hours. The reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel, eluting with dichloromethane:methanol 100:0 to 95:5, to yield the title product, 861mg.

^{1}H NMR($CDCl_3$, 400MHz) δ: 3.29(s, 3H), 3.84(s, 3H), 3.89(s, 3H), 3.92(s, 2H), 6.68(d, 1H), 7.10(dd, 1H), 7.63(d, 1H). MS APCI+ m/z 211 $[MH]^+$

Preparation 3

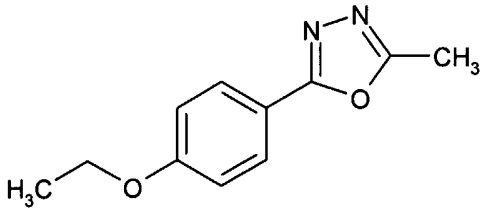
2-(4-Methoxy-phenyl)-5-methyl-[1,3,4]oxadiazole



(4-Methoxyphenyl)-acyl hydrazine (10.0g, 60.2mmol) and N,N-dimethylacetamide dimethyl acetal (12mL, 82.0mmol) were dissolved in N,N-dimethylformamide (100mL) and the solution was heated to 60°C for 2 hours. The solvent was evaporated under reduced pressure and the residue was taken up in toluene (80mL) and treated with *para*-toluenesulfonic acid (300mg, 1.50mmol). The mixture was heated under reflux for 2 hours, allowed to cool, and the precipitate was collected by filtration. The crude product was washed with ether and dried *in vacuo* to yield a white solid. The filtrate was concentrated *in vacuo* and the residue was combined with the white solid, dissolved in toluene (50mL) and treated with *para*-toluenesulfonic acid (100mg, 0.75mmol). The mixture was heated under reflux for 3 hours, allowed to cool and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with pentane:ethyl acetate 80:20 to 40:60, to yield the title product, 11.30g. ^{1}H NMR($CDCl_3$, 400MHz) δ: 2.59(s, 3H), 3.87(s, 3H), 6.98(d, 2H), 7.94(m, 2H). MS APCI+ m/z 191 $[MH]^+$

Preparation 4

2-(4-Ethoxy-phenyl)-5-methyl-[1,3,4]oxadiazole



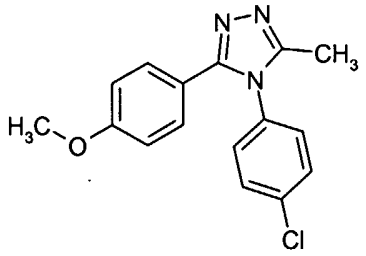
To a suspension of N,N-dimethylacetamide dimethyl acetal (2.4mL, 16.7mmol) in N,N-dimethylformamide (20mL) was added (4-ethoxyphenyl)-acyl hydrazine (2g, 11.1mmol) and the mixture was heated at 60°C for 3.5 hours. The solvent was removed *in vacuo* to give a yellow oil that was twice azeotroped with toluene to produce a pale yellow solid. Toluene (30mL) and *para*-toluenesulfonic acid (150mg, cat) were added to the reaction vessel and the mixture was heated

under reflux for 2 hours. The solvent was then evaporated under reduced pressure and the residue was dissolved in ethyl acetate and washed with sodium hydrogen carbonate solution. The organic phase was dried over sodium sulfate and concentrated *in vacuo* to give an orange coloured solid. Purification by column chromatography on silica gel, eluting with ethyl acetate: pentane, 50:50, gave the title product in 92% yield (2.08g).

^{1}H NMR ($CDCl_3$ 400MHz) δ: 1.44(t, 3H), 2.58(s, 3H), 4.10(q, 2H), 6.98(m, 2H) 7.94 (m, 2H). MS APCI+ m/z 205 $[MH]^+$

Preparation 5

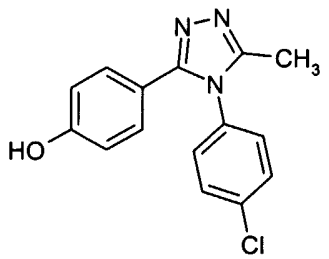
4-(4-Chloro-phenyl)-3-(4-methoxy-phenyl)-5-methyl-4H-[1,2,4]triazole



The product of preparation 3 (5.00g, 26.3mmol) was added to a solution of *para*-toluenesulfonic acid (100mg, 0.75mmol) and 4-chloroaniline (10.0g, 62.5mmol) in xylene (150mL) and the reaction mixture heated to 150°C for 22 hours. The reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel, eluting with dichloromethane:methanol:0.88 ammonia, 100:0:0 to 97:3:0.3, to yield the title product, 4.90g. ^{1}H NMR($CDCl_3$, 400MHz) *δ*: 2.33(s, 3H), 3.77(s, 3H), 6.80(m, 2H), 7.14(m, 2H), 7.31(m, 2H), 7.47(m, 2H). MS ES+ m/z 300 $[MH]^+$

Preparation 6

4-[4-(4-Chloro-phenyl)-5-methyl-4H-[1,2,4]triazol-3-yl]-phenol

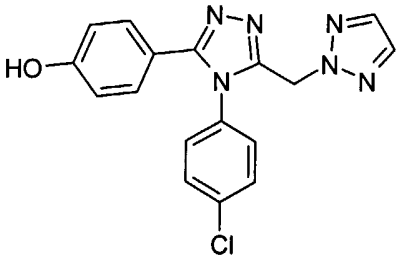


The ether of preparation 5 (4.9g, 16.3mmol) was dissolved in dichloromethane (55mL) and a 1M solution of boron tribromide in dichloromethane (33mL, 33.0mmol) was added. The reaction mixture was heated under reflux for 4 hours and then allowed to stand at room temperature for 18 hours. The reaction mixture was poured into iced water, the phases separated, and the aqueous layer was extracted with dichloromethane (50mL). The combined organic layers were dried over magnesium sulfate and concentrated *in vacuo* to yield some title product. The aqueous phase was basified with 2M sodium hydroxide solution and extracted with dichloromethane (3x50mL). The aqueous was then acidified with 2M hydrochloric acid and was extracted with additional dichloromethane (3x50mL). The combined organics were dried over magnesium sulfate and concentrated *in vacuo* to yield further product. Purification of the combined crude product by column chromatography on silica gel, eluting with dichloromethane: methanol:0.88 ammonia 100:0:0 to 97:3:0.3, yielded the title product, 2.10g.

^{1}H NMR(DMSO-D_6, 400MHz) δ: 2.20(s, 3H), 6.70(m, 2H), 7.13(m, 2H), 7.42(m, 2H), 7.60(m, 2H), 9.79(s, 1H). MS ES+ m/z 286 $[MH]^+$

Preparation 7

4-[4-(4-Chloro-phenyl)-5-[1,2,3]triazol-2-ylmethyl-4H-[1,2,4]triazol-3-yl]-phenol

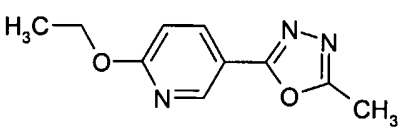


The title compound was prepared from the ether product of example 46, using the method described for preparation 6, as a white solid in 97% yield.

^{1}H NMR(CD_3OD, 400MHz) δ: 5.78(s, 2H), 6.72(d, 2H), 7.17(d, 2H), 7.21(d, 2H), 7.45(d, 2H), 7.59(s, 2H). MS ES^- m/z 351 $[M-H]^-$

Preparation 8

2-Ethoxy-5-(5-methyl-[1,3,4]oxadiazol-2-yl)-pyridine

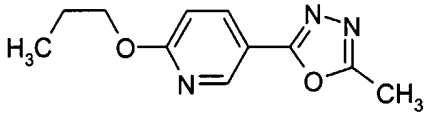


2-Chloro-5-(5-methyl-[1,3,4]-oxadiazol-2-yl)pyridine (J. Het. Chem., 1980, 17(3), 425-427, pg. 426, compound 3) (400mg, 2.04mmol) and sodium ethoxide (170mg, 2.46mmol) were dissolved in 1-methyl-2-pyrrolidinone (5mL) and the reaction mixture heated in a microwave at 110°C for 240 seconds. The reaction mixture was adsorbed onto silica and purified by column chromatography, eluting with pentane:ethyl acetate 50:50, to yield the title product, 215mg (27%)

^{1}H NMR($CDCl_3$, 400MHz) δ: 1.41(t, 3H), 2.61(s, 3H), 4.43(q, 2H), 6.83(m, 1H), 8.18(m, 1H), 8.77(m, 1H). MS APCI+ m/z 206 $[MH]^+$

Preparation 9

5-(5-Methyl-[1,3,4]oxadiazol-2-yl)-2-propoxy-pyridine

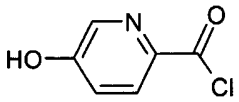


The title compound was prepared by the method described for preparation 8 using sodium propoxide, as a white solid in 69% yield.

^{1}H NMR($CDCl_3$, 400MHz) δ: 1.40(t, 3H), 2.20(m, 2H), 2.59(s, 3H), 4.43(q, 2H), 6.83(m, 1H), 8.18(m, 1H), 8.77(m, 1H). MS ES^+ m/z 242 $[MNa]^+$

Preparation 10

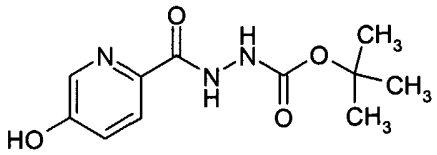
5-Hydroxy-pyridine-2-carbonyl chloride



5-Hydroxy-pyridine-2-carboxylic acid (1.00g, 7.19mmol) was dissolved in a mixture of dichloromethane (25mL) and N,N-dimethylformamide (20μL) The solution was cooled to 0°C, treated dropwise with oxalyl chloride (1mL, 11.46mmol) and stirred at room temperature for 3 hours. The mixture was then concentrated *in vacuo* and the residue was azeotroped with dichloromethane to yield the title product, 1.13g. MS ES+ m/z 158 $[MH]^+$

Preparation 11

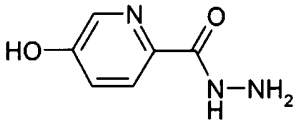
N'-(5-Hydroxy-pyridine-2-carbonyl)-hydrazinecarboxylic acid *tert*-butyl ester



The acid chloride of preparation 10 (1.13g, 7.19mmol) was dissolved in dichloromethane (12.5mL) and treated with a solution of *tert*-butyl carbazate (2.60g, 19.67mmol) and N-ethyldiisopropylamine (2mL, 11.48mmol) in dichloromethane (12.5mL). The reaction mixture was stirred at room temperature for 18 hours and was then diluted with dichloromethane (50mL) and washed with water (20mL) and brine (20mL). The dichloromethane phase was dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with dichloromethane:methanol:0.88 ammonia 90:10:1 to 85:15:1.5, to yield the title product, 774mg. ^{1}H NMR(DMSO-D_6, 400MHz) δ: 1.41(s, 9H), 7.27(d, 1H), 7.85(d, 1H), 8.11(d, 1H) MS APCI+ m/z 252 $[M-H]^-$

Preparation 12

5-Hydroxy-pyridine-2-carboxylic acid hydrazide

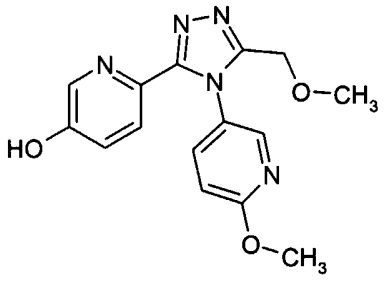


The BOC protected product of preparation 11 (770mg, 3.04mmol) was dissolved in dichloromethane (20mL), cooled to 0°C and treated with trifluoroacetic acid (5mL). The reaction mixture was stirred at room temperature for 5 hours and was then concentrated *in vacuo*. The residue was taken up into 10% sodium carbonate solution, yielding a pink precipitate that was filtered off and dried *in vacuo* to yield the title product, 322mg.

^{1}H NMR(DMSO-D_6, 400MHz) δ: 4.41(m, 2H), 7.26(m, 1H), 7.83(d, 1H), 8.09(d, 1H), 9.47(m, 1H). MS APCI+ m/z 154 $[MH]^+$

Preparation 13

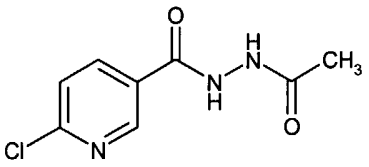
6-[5-Methoxymethyl-4-(6-methoxy-pyridin-3-yl)-4H-[1,2,4]triazol-3-yl]-pyridin-3-ol



The hydrazide of preparation 12 (300mg, 2.0mmol) and the product of preparation 2 (861mg, 4.1mmol), were dissolved in N,N-dimethylformamide (5mL) and stirred at 120°C for 8 hours. The reaction mixture was concentrated *in vacuo* and the residue was taken up in dichloromethane (2mL) and treated with ethyl acetate (2mL). The mixture was allowed to stand for 18 hours and a precipitate formed that was filtered off and dried *in vacuo* to yield the title product, 65mg. ^{1}H NMR(DMSO-D_6, 400MHz) δ: 3.14(s, 3H), 3.88(s, 3H), 4.38(s, 2H), 6.90(d, 1H), 7.25(m, 1H), 7.71(m, 1H), 7.85(d, 1H), 7.86(d, 1H), 8.14(d, 1H), 10.33(d, 1H). MS APCI+ m/z 314 $[MH]^+$

Preparation 14

6-Chloro-nicotinic acid N'-acetyl-hydrazide

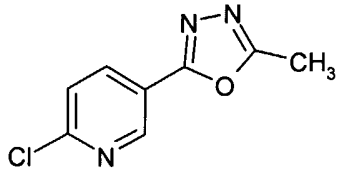


Triethylamine (10mL) was added to a solution of 6-Chloro-nicotinic acid (7.8g, 50mmol), acetic hydrazide (3.7g, 50mmol) and HBTU (20g, 52.8mmol) in N,N-dimethylformamide (400mL). The mixture was stirred at room temperature for 48 hours before the solvent was evaporated under reduced pressure. The residue was then partitioned between ethyl acetate and water and the phases were separated. Upon standing for 18 hours, a precipitate was formed in both organic and aqueous layers. The precipitates were collected by filtration, combined and dried to give the title compound in 47% yield (5.04g).

^{1}H NMR(CD_3OD, 400MHz) δ: 2.06(s, 3H), 3.30(m, 2H), 7.58(d, 1H), 8.23(m, 1H), 8.83(d, 1H). MS APCI+ m/z 214 $[MH]^+$

Preparation 15

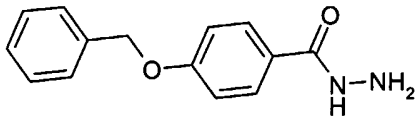
2-Chloro-5-(5-methyl-[1,3,4]oxadiazol-2-yl)-pyridine



The product of preparation 14 (3.45g, 16.1mmol) was added to phosphorous oxychloride (20mL) and heated under reflux for 6 hours. The reaction mixture was then allowed to cool to room temperature and was concentrated *in vacuo*. The residue was taken up in ethyl acetate and water (500mL) and treated with a saturated sodium hydrogen carbonate solution. The phases were separated and the aqueous layer was extracted with ethyl acetate (x4). The organics were combined, dried over sodium sulfate and concentrated *in vacuo*. Purification by column chromatography on silica gel, eluting with pentane:ethyl acetate, 100:0 to 50:50, provided 1.93 g of the title product (98%). ^{1}H NMR($CDCl_3$, 400MHz) δ: 2.64(s, 3H), 7.49(m, 1H), 8.29(m, 1H), 9.01(m, 1H). MS APCI+ m/z 196 $[MH]^+$

Preparation 16

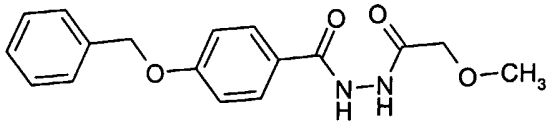
4-Benzyloxy-benzoic acid hydrazide



4-Benzyloxy-benzoic acid methyl ester (30.9g, 127.5mmol) and hydrazine hydrate (18.6mL, 381mmol) were dissolved in methanol (600mL) and heated under reflux for 72 hours. The solvent was concentrated to low volume under reduced pressure and was then cooled. The precipitate that formed was filtered off, washed with methanol and dried *in vacuo* to yield the title product. ^{1}H NMR(DMSO-D_6, 400MHz) δ: 4.40(m, 2H), 5.14(s, 2H), 7.03(d, 2H), 7.34(dd, 1H), 7.38(t, 2H), 7.43(m, 2H), 7.77(d, 2H), 9.56(s, 1H). MS APCI+ m/z 243 $[MH]^+$

Preparation 17

4-Benzyloxy-benzoic acid N'-(2-methoxy-acetyl)-hydrazide

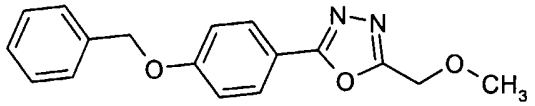


The product of preparation 16 (20g, 83mmol), methoxyacetyl chloride (8.2mL, 90mmol) and 4-methylmorpholine (16.4mL, 150mmol) were dissolved in dichloromethane (250mL) and stirred at room temperature for 18 hours. The mixture was then diluted with dichloromethane/methanol (500mL, 90:10) and washed with water. The organic phase was separated, dried over sodium sulfate and concentrated *in vacuo* to yield the title product, 17.5g.

MS APCI+ m/z 315 $[MH]^+$

Preparation 18

2-(4-Benzyloxy-phenyl)-5-methoxymethyl-[1,3,4]oxadiazole

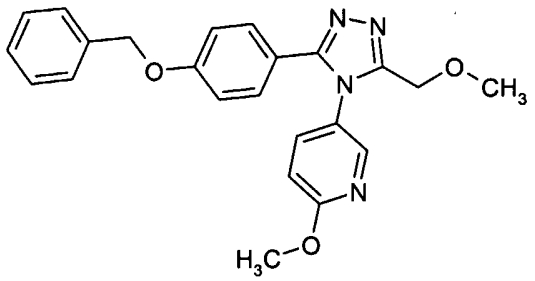


The product of preparation 17 (17.5g, 56mmol) was added to phosphorous oxychloride (50mL) and the reaction mixture was heated to 110°C for 4 hours. The mixture was then cooled to room temperature and concentrated *in vacuo*. The residue was taken up in ethyl acetate and water and was treated with a saturated sodium hydrogen carbonate solution. The phases were separated and the aqueous layer was extracted with ethyl acetate (2x200mL). The organics were combined, dried over magnesium sulfate and concentrated *in vacuo* to yield the title product as a light brown solid in 30% yield, 5.0g.

^1H NMR($CDCl_3$, 400MHz) δ: 3.46(s, 3H), 4.67(s, 2H), 5.11(s, 2H), 7.06(d, 2H), 7.31-7.45 (m, 5H), 7.99(d, 2H). MS APCI+ m/z 297 $[MH]^+$

Preparation 19

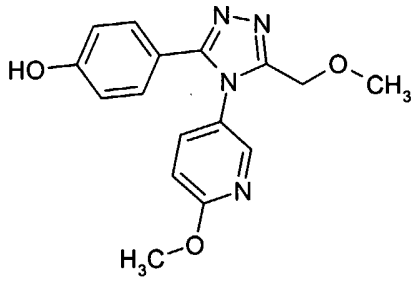
5-[3-(4-Benzyloxy-phenyl)-5-methoxymethyl-[1,2,4]triazol-4-yl]-2-methoxy-pyridine



The product of preparation 18 (5.0g, 16.9mmol), 2-methoxy-5-aminopyridine (6.5g, 52.4mmol) and *para*-toluenesulfonic acid (400mg) were dissolved in xylene (200mL) and heated under reflux for 18 hours. The solvent was then evaporated under reduced pressure and the residue was taken up in dichloromethane (300mL) and washed with water (300mL). The organic phase was dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with dichloromethane:methanol 100:0 to 97:3, to yield the title product, 2.16g. ^{1}H NMR($CDCl_3$, 400MHz) δ: 3.35(s, 3H), 4.00(s, 3H), 4.47(s, 2H), 5.05(m, 2H), 6.84(d, 1H), 6.92(q, 2H), 7.33-7.43(m, 7H), 7.50(dd, 1H), 8.12(d, 1H). MS APCI+ m/z 403 $[MH]^+$

Preparation 20

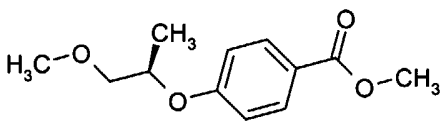
4-[5-Methoxymethyl-4-(6-methoxy-pyridin-3-yl)-4H-[1,2,4]triazol-3-yl]-phenol



The benzyl-protected alcohol of preparation 19 (2.0g, 5.0mmol) and 10% Pd/C (250mg) was added to ethanol (30mL) and the mixture was stirred under 60psi of hydrogen gas for 18 hours. The reaction mixture was then filtered through Arbocel®, washing through with dichloromethane:methanol 95:5. The filtrate was concentrated *in vacuo* and trituration of the residue with dichloromethane gave the title product, 1.20g. ^{1}H NMR(DMSO-D_6, 400MHz) δ: 3.14(s, 3H), 3.88(s, 3H), 4.37(s, 2H), 6.72(m, 2H), 6.94(d, 1H), 7.19(d, 2H), 7.75(m, 1H), 8.19(d, 1H), 9.89(m, 1H). MS APCI+ m/z 313 $[MH]^+$

Preparation 21

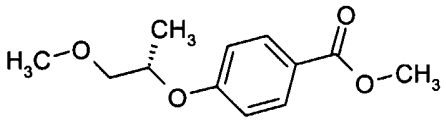
4-(2-methoxy-(1*R*)-1-methyl-ethoxy)-benzoic acid methyl ester



4-Hydroxy-benzoic acid methyl ester (25.0g, 164mmol), (2*S*)-1-Methoxy-propan-2-ol (12.8g, 142mmol) and triphenylphosphine (55.9g, 213mmol) were dissolved in tetrahydrofuran (200mL) and the mixture was cooled to 0°C. Dibenzyl azodicarboxylate (37.0g, 160mmol) was added dropwise and the reaction mixture was stirred at room temperature for 18 hours. The solvent was then concentrated to low volume *in vacuo*, treated with triethyl silane (50mL) and cooled again to 0°C. Trifluoroacetic acid (247mL, 2.85mol) was added dropwise and the solution was stirred at room temperature for 18 hours. The solution was then concentrated *in vacuo* and the residue was triturated with both diethyl ether and diethyl ether:pentane, 50:50. Purification of the resulting solid by column chromatography on silica gel, eluting with pentane:ethyl acetate 90:10 to 75:25, yielded the title product, 55.7g. ^{1}H NMR($CDCl_3$, 400MHz) δ: 1.33(d, 3H), 3.40(s, 3H), 3.50(m, 1H), 3.59(m, 1H), 3.87(s, 3H), 4.64(m, 1H), 6.94(d, 2H), 7.97(d, 2H). MS APCI+ m/z 225 $[MH]^+$

Preparation 22

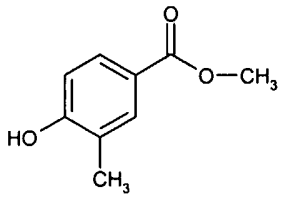
4-(2-methoxy-(1*S*)-1-methyl-ethoxy)-benzoic acid methyl ester



The title product was prepared by the method described for preparation 21 using (2*R*)-1-methoxy-propan-2-ol. ^{1}H NMR($CDCl_3$, 400MHz) δ: 1.33(d, 3H), 3.39(s, 3H), 3.51(m, 1H), 3.61(m, 1H), 3.88(s, 3H), 4.64(m, 1H), 6.91(d, 2H), 7.97(d, 2H) MS APCI+ m/z 225 $[MH]^+$

Preparation 23

4-Hydroxy-3-methyl-benzoic acid methyl ester

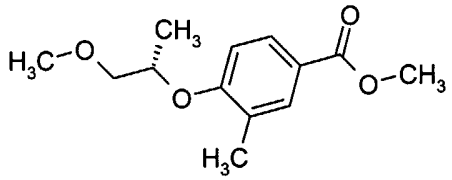


Concentrated sulfuric acid (0.5mL) was added to a solution of 4-hydroxy-3-methylbenzoic acid (25g, 164mmol) in methanol (200mL) and the resulting mixture was heated under reflux for 48 hours. The solvent was then evaporated under reduced pressure and the residue was dissolved in ethyl acetate (150mL)

and washed with sodium hydrogen carbonate solution and brine. The organic phase was dried over magnesium sulfate and concentrated *in vacuo* to give a crystalline solid. The solid was broken up, washed with diethyl ether and dried to afford the title compound as a white solid in 88% yield (24g). ^{1}H NMR(DMSO-D_6, 400MHz) δ: 2.18(s, 3H), 3.88(s, 3H), 6.94(d, 1H), 7.61(d, 1H), 7.75(s, 1H), 10.19(s, 1H). MS APCI+ m/z 167 $[MH]^+$

Preparation 24-a

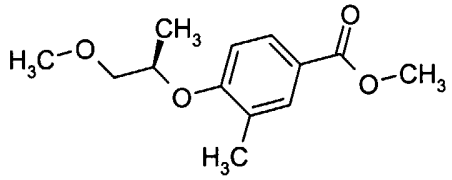
4-(2-methoxy-(1*S*)-methyl-ethoxy)-3-methyl-benzoic acid methyl ester



The title compound was prepared by the method described for preparation 21 using the product of preparation 23 and (2*R*)-1-methoxy-propan-2-ol. 11.2g of the desired product were produced in 91% yield. ^{1}H NMR($CDCl_3$, 400MHz) δ: 1.40(d, 3H), 2.20(s, 3H), 3.40(s, 3H), 3.50(m, 1H), 3.60(m, 1H), 3.90(s, 3H), 4.60(m, 1H), 6.90(d, 1H), 7.80(m, 2H). MS APCI+ m/z 239 $[MH]^+$

Preparation 24-b

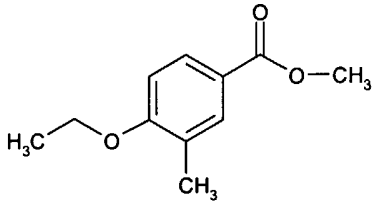
4-(2-methoxy-(1*R*)-methyl-ethoxy)-3-methyl-benzoic acid methyl ester



The title compound was prepared from the product of preparation 23 and (2*S*)-1-methoxy-propan-2-ol, using the method described for preparation 21, in 94% yield. ^{1}H NMR($CDCl_3$, 400MHz) δ: 1.40(d, 3H), 2.20(s, 3H), 3.40(s, 3H), 3.50(m, 1H), 3.60(m, 1H), 3.90(s, 3H), 4.60(m, 1H), 6.90(d, 2H), 7.80(d, 2H)
MS APCI+ m/z 239 $[MH]^+$

Preparation 25

4-Ethoxy-3-methyl-benzoic acid methyl ester

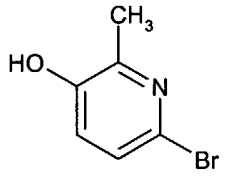


A solution of the product of preparation 23 (13.6g, 81.8mmol) and potassium carbonate (17.0g, 123mmol) in N,N-dimethylformamide (150mL), was stirred at room temperature for 10 minutes. Ethyl iodide (19.18g, 123 mmol) was added and the mixture was stirred at 60°C for 2 hours. The reaction mixture was then concentrated *in vacuo* and partitioned between ethyl acetate (250mL) and water (250mL). The organic layer was washed with brine (2x250mL), dried over magnesium sulfate and concentrated *in vacuo* to a give a pale yellow oil. The oil was then azeotroped with dichloromethane (3x100mL) to afford the title compound as pale yellow crystals in quantitative yield, 15.9g.

^{1}H NMR(DMSO-D_6, 400MHz) δ: 1.40(t, 3H), 2.20(s, 3H), 3.82(s, 3H), 4.10(q, 2H), 6.78 (d, 1H), 7.58 (d, 2H). MS APCI+ m/z 195 $[MH]^+$

Preparation 26

6-Bromo-2-methyl-pyridin-3-ol

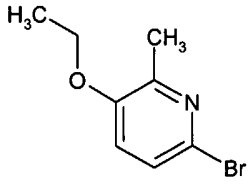


A solution of bromine (24.9g, 0.47mol) in 0.5M sodium hydroxide solution (175mL). was added dropwise to an ice cooled solution of 2-methyl-3-pyridinol (11.4g, 0.104mol) in 0.5M sodium hydroxide solution (175mL). After standing for 24 hours, the solution was acidified to pH7 with concentrated hydrochloric acid and the mixture was stirred for 18 hours. The reaction mixture was then filtered off and the residue was stirred in dichloromethane for 1 hour. The precipitate that formed was filtered off to give the title product as a solid in 20% yield (3.83g).

^{1}H NMR(DMSO-D_6, 400MHz) δ: 2.15(s, 3H), 7.15(d, 1H), 7.20(d, 1H), 10.1(s, 1H) MS APCI+ m/z 188 $[MH]^+$

Preparation 27

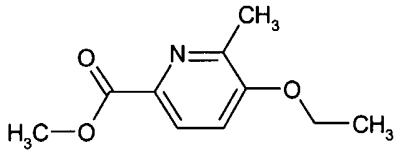
6-Bromo-3-ethoxy-2-methyl-pyridine



The product of preparation 26 (3.83, 20.3mmol) and potassium carbonate (5.6g, 40.6mmol), were dissolved in N,N-dimethylformamide (40mL), and cooled to 0°C. Iodoethane (2mL, 24.4mmol) was added dropwise and the solution was stirred for 12 hours. The mixture was then treated with additional iodoethane (0.8mL) and stirred at 45°C for a further 8 hours. The solvent was evaporated under reduced pressure and azeotroped with toluene. The residue was taken up in dichloromethane and washed with water, sodium hydrogen carbonate solution and brine. The organic layer was dried over magnesium sulfate, concentrated *in vacuo* and the residual brown liquid was passed through a silica pad to yield the title compound, 4.4g, (72.7%). ^{1}H NMR($CDCl_3$, 400MHz) δ: 1.25(t, 3H), 2.25(s, 3H), 4.00(q, 2H), 6.95(d, 1H), 7.20(d, 1H). MS APCI+ m/z 218 $[MH]^+$

Preparation 28

5-Ethoxy-6-methyl-pyridine-2-carboxylic acid methyl ester

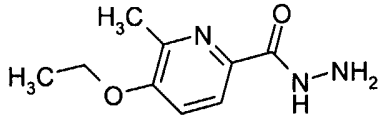


The bromo product of preparation 27 (0.5g, 2.31mmol), dichloro-bis(triphenylphosphine)palladium (0.05g, 0.07mmol) and triethylamine (0.45mL, 3.47mmol) were dissolved in a mixture of methanol (1.3mL) and acetonitrile (5mL), and transferred to a sealed vessel. The vessel was heated to 60°C and the mixture was stirred under 60psi of carbon monoxide gas for 18 hours. The solvent was then removed under reduced pressure and the residue was dissolved in dichloromethane and washed with water, sodium hydrogen carbonate solution and brine. The layers were separated and the aqueous layer was basified with sodium hydroxide and re-extracted with dichloromethane. The combined organic fractions were dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by column chromatography on silica gel, eluting with pentane:ethyl acetate, 99:1, afforded the title compound as a solid,

2.2g. ^{1}H NMR($CDCl_3$, 400MHz) δ: 1.50(t, 3H), 2.55(s, 3H), 3.95(s, 3H), 4.10(q, 2H), 7.10(d, 1H) 8.00(d, 1H). MS APCI+ m/z 196 $[MH]^+$

Preparation 29

5-Ethoxy-6-methyl-pyridine-2-carboxylic acid hydrazide

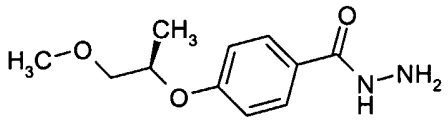


The ester of preparation 28 (2.2g, 11.3mmol) was dissolved in methanol (25mL) and the solution was treated dropwise with hydrazine monohydrate (1.6mL, 33.8mmol). The reaction mixture was heated under reflux for 18 hours and then cooled in a refrigerator. The resulting precipitate was collected by filtration and washed with methanol to give the title compound in 81.8% yield (1.8g)

^{1}H NMR($CDCl_3$, 400MHz) δ: 1.45(t, 3H), 2.45(s, 3H), 4.00(d, 2H), 4.10(q, 2H), 7.10(d, 1H) 7.95(d, 1H), 8.80(s, 1H). MS APCI+ m/z 196 $[MH]^+$

Preparation 30

4-(2-Methoxy-(1*R*)-1-methyl-ethoxy)-benzoic acid hydrazide

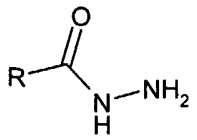


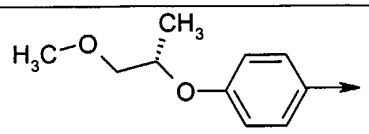
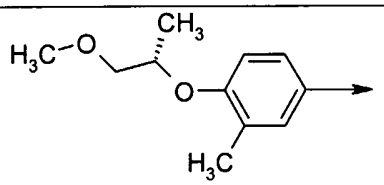
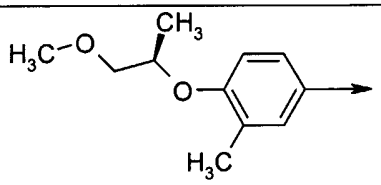
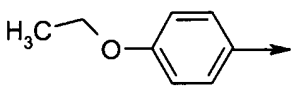
The ester of preparation 21 (33.5g, 149mmol) was dissolved in methanol (250mL) and the solution was treated dropwise with hydrazine monohydrate (21.8mL, 450mmol). The reaction mixture was heated under reflux for 18 hours and then concentrated *in vacuo*. The residue was treated with hydrazine monohydrate (21.8mL, 450mmol) and methanol (200mL) and was heated under reflux for a further 18 hours. The solvent was evaporated under reduced pressure and the residue was taken up in dichloromethane and washed with water and brine. The organic phase was dried over magnesium sulfate and concentrated *in vacuo* to yield the title product, 28.8g.

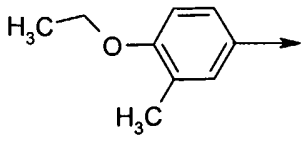
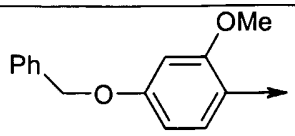
^{1}H NMR($CDCl_3$, 400MHz) δ: 1.30(d, 3H), 3.40(s, 3H), 3.50(m, 1H), 3.60(m, 1H), 4.60(m, 1H), 6.90(d, 2H), 7.70(d, 2H). MS APCI+ m/z 225 $[MH]^+$

Preparations 31 to 35

The following compounds, of the general formula shown below, were prepared by the method described for preparation 30 using the appropriate ester as outlined below.



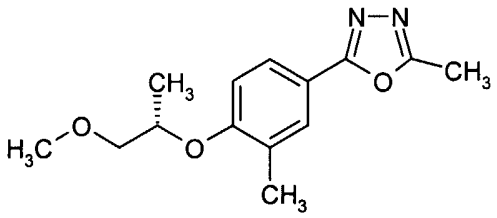
No.	R	Data	Yield
31	 Prepared from the compound of preparation 22	^{1}H NMR($CDCl_3$, 400MHz) δ: 1.35(d, 3H), 3.40(s, 3H), 3.50(m, 1H), 3.60(m, 1H), 4.10(s, 2H), 4.60(m, 1H), 6.80(d, 2H), 7.20(s, 1H) 7.70(d, 2H). MS APCI+ m/z 225 $[MH]^+$	28.7g (63%)
32a	 Prepared from the compound of preparation 24a	^{1}H NMR($CDCl_3$, 400MHz) δ: 1.30(d, 3H), 2.15(s, 3H) 3.40(s, 3H), 3.50(m, 1H), 3.60(m, 1H), 4.05(s, 2H), 4.60(m, 1H), 6.90(d, 1H), 7.25(s, 1H), 7.50(m, 2H). MS APCI+ m/z 239 $[MH]^+$	10.6g 95%)
32b	 Prepared from the compound of preparation 24b	^{1}H NMR($CDCl_3$, 400MHz) δ: 1.40(d, 3H), 2.20(s, 3H) 3.40(s, 3H), 3.50(m, 1H), 3.60(m, 1H), 4.60(m, 1H), 6.90(d, 1H), 7.20(s, 1H), 7.60(m, 2H). MS APCI+ m/z 239 $[MH]^+$	10.1g (88%)
33	 Prepared from the compound benzoic acid 4-ethoxymethyl ester	^{1}H NMR(DMSO-D_6, 400MHz) δ: 1.30(t, 3H), 3.34(bs, 1H), 4.00(q, 2H), 4.41(bs, 1H), 6.92(d, 2H), 7.77(d, 2H), 9.57(s, 1H) MS APCI+ m/z 181 $[MH]^+$	14.6 g (79%)

34	 Prepared from the compound of preparation 25	^{1}H NMR(DMSO-D_6, 400MHz) δ: 1.40(t, 3H), 2.20(s, 3H), 4.00(q, 2H), 6.78 (d, 1H), 7.58 (d, 2H), MS APCI+ m/z 195 $[MH]^+$	10.9g (69%)
35	 Prepared from the compound benzoic acid, 2-methoxy-4-(phenylmethoxy)	^{1}H NMR($CDCl_3$, 400MHz) δ: 3.91(s, 3H), 5.11(s, 2H), 6.57(s, 1H), 6.68(d, 1H), 7.33-7.45(m, 4H), 8.15(d, 1H), 8.81(s, 1H) MS APCI+ m/z 273 $[MH]^+$	19.1g 83%)

Product 35: 2-methoxy-4-(phenylmethoxy) benzoic acid methyl ester used, prepared as described in *J. Med. Chem.*, 1985, 28(6), 717-727

Preparation 36

2-[4-(2-Methoxy-(1*S*)-methyl-ethoxy)-3-methyl-phenyl]-5-methyl-[1,3,4]oxadiazole

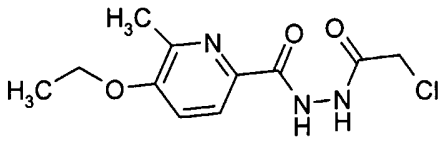


To a suspension of N,N-dimethylacetamide dimethyl acetal (2.4mL, 16.7mmol) in N,N-dimethylformamide (20mL) was added (4-ethoxyphenyl)-acyl hydrazine (2g, 11.1mmol) and the mixture was heated at 60°C for 18 hours. The solvent was concentrated *in vacuo* and the residue was twice azeotroped with toluene. Toluene (30mL) and *para*-toluenesulfonic acid (150mg, cat) were added to the reaction vessel and the mixture was heated under reflux for 18 hours. A further amount of *para*-toluenesulfonic acid was then added and heating continued for a further 4 hours before the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate and washed with water, citric acid, sodium hydrogen carbonate solution and brine. The organic layer was dried over sodium sulfate and concentrated *in vacuo* to give a pale brown oil in 78% yield, 0.512mg. ^{1}H NMR($CDCl_3$ 400MHz) δ: 1.44(d, 3H), 2.15(s, 3H), 2.60(s, 3H), 3.40(s, 3H), 3.60(m, 1H), 3.65(m, 1H), 4.60(m, 1H), 6.95(d, 1H) 7.80(m, 2H).

MS APCI+ m/z 263 $[MH]^+$

Preparation 37

5-Ethoxy-6-methyl-pyridine-2-carboxylic acid N'-(2-chloro-acetyl)-hydrazide

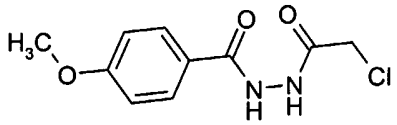


The hydrazide of preparation 29 (1.5g, 7.7mmol), chloroacetyl chloride (0.74mL, 9.2mmol) and 4-methylmorpholine (1.3mL, 11.6mmol) were dissolved in dichloromethane (100mL) and the reaction was stirred at room temperature for 3 hours. The solvent was then concentrated *in vacuo* to a low volume and the mixture was cooled to 4°C for 30 minutes. The resulting precipitate was collected by filtration, washed with dichloromethane and water and dried to afford the title compound, 1.04g.

^1H NMR($CDCl_3$, 400MHz) δ: 1.45(t, 3H), 2.45(s, 3H), 4.05(q, 2H), 4.20(s, 2H), 7.10(d, 1H) 7.95(d, 1H), 9.10(d, 1H), 10.00(d, 1H). MS APCI+ m/z 272 $[MH]^+$

Preparation 38

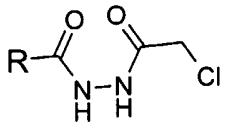
4-Methoxy-benzoic acid N'-(2-chloro-acetyl)-hydrazide

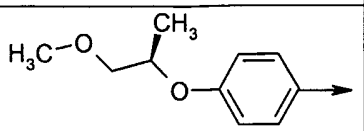
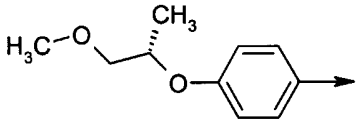
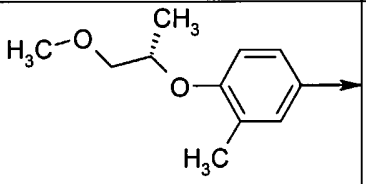
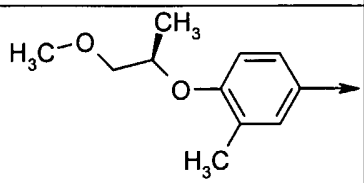
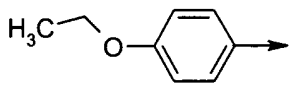


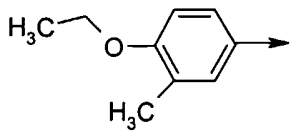
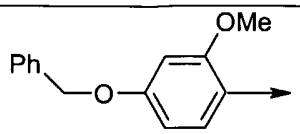
4-Methoxy-benzoic acid hydrazide (50.0g, 301mmol), chloroacetyl chloride (35mL, 440mmol) and 4-methylmorpholine (30g, 300mmol) were dissolved in dichloromethane (500mL) and the reaction was stirred at room temperature for 18 hours. The mixture was filtered, washing through with dichloromethane, and the collected residue was triturated with dichloromethane to yield the title product, 72.6g. MS ES+ m/z 243 $[MH]^+$

Preparations 39-44

The following compounds, of the general formula shown below, were prepared by the method described for preparation 38 using the appropriate hydrazide as outlined in the table below

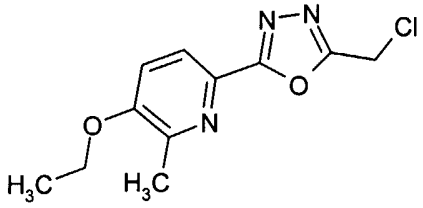


No.	R	Data	Yield
39	 Prepared from the compound of preparation 30	^{1}H NMR(DMSO-D_6, 400MHz) δ: 1.20(d, 3H), 3.29(s, 3H), 3.45(m, 2H), 4.16(s, 2H), 4.72(m, 1H), 6.99(d, 2H), 7.81(d, 2H), 10.34(d, 1H), 13.00(d, 2H) MS ES+ m/z 301 $[MH]^+$	13.9g (36%)
40	 Prepared from the compound of preparation 31	^{1}H NMR($CDCl_3$, 400MHz) δ: 1.20(d, 3H), 3.30(s, 3H), 3.80(m, 2H), 4.20(s, 2H), 4.70(m, 1H), 7.00(d, 2H), 7.80(d, 2H), 10.20(d, 1H), 13.00(d, 2H) MS APCI+ m/z 301 $[MH]^+$	27.2g (88%)
41a	 Prepared from the compound of preparation 32a	^{1}H NMR($CDCl_3$, 400MHz) δ: 1.30(d, 3H), 2.20(s, 3H), 3.40(s, 3H), 3.50(m, 1H), 3.60(m, 1H), 4.20(s, 2H), 4.70(m, 1H), 6.90(d, 1H), 7.60(m, 2H), 8.95(d, 1H) 9.50(d, 1H) MS APCI+ m/z 315 $[MH]^+$	7.1g (54%)
41b	 Prepared from the compound of preparation 32b	^{1}H NMR($CDCl_3$, 400MHz) δ: 1.30(d, 3H), 2.20(s, 3H), 3.40(s, 3H), 3.50(m, 1H), 3.60(m, 1H), 4.20(s, 2H), 4.70(m, 1H), 6.90(d, 1H), 7.60(m, 2H), 8.95(d, 1H) 9.50(d, 1H) MS APCI+ m/z 315 $[MH]^+$	10.3g (86%)
42	 Prepared from the compound of preparation 33	^{1}H NMR(DMSO-D_6, 400MHz) δ: 1.33(t, 3H), 4.07(q, 2H), 4.15(s, 2H), 6.96(d, 2H), 7.81(d, 2H), 10.25(m, 2H) MS APCI+ m/z 257 $[MH]^+$	16.7g (77%)

43	 Prepared from the compound of preparation 34	^{1}H NMR(DMSO-D_6, 400MHz) δ: 1.33(t, 3H), 2.18(s, 3H), 4.10(q, 2H), 4.20(s, 2H), 6.96(d, 1H), 7.65-7.75(m, 2H), 10.30(m, 2H) MS APCI+ m/z 271 $[MH]^+$	5.9g 90%)
44	 Prepared from the compound of preparation 35	^{1}H NMR(DMSO-D_6, 400MHz) δ: 3.89(s, 3H), 4.16(s, 2H), 5.18(s, 2H), 6.70-6.77(m, 2H), 7.32-7.47(m, 5H), 7.78(d, 1H), 9.87(s, 1H), 10.59(s, 1H) MS APCI+ m/z 349 $[MH]^+$	17.7g (73%)

Preparation 45

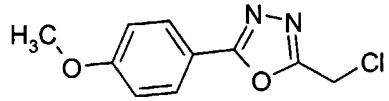
6-(5-Chloromethyl-[1,3,4]oxadiazol-2-yl)-3-ethoxy-2-methyl-pyridine



The product of preparation 37 (0.109g, 0.4mmol) was added to phosphorous oxychloride (3mL) and the reaction mixture was heated under reflux for 25 hours. The mixture was allowed to cool to room temperature and was concentrated *in vacuo*. The residue was taken up in ethyl acetate and water (500mL) and treated with saturated sodium hydrogen carbonate solution. The phases were separated and the aqueous layer was re-extracted with ethyl acetate. The combined organic fractions were washed with sodium hydrogen carbonate solution and brine, dried over magnesium sulfate and concentrated *in vacuo* to give a pale brown solid. Purification by column chromatography on silica gel, eluting with ethyl acetate: pentane, 90:10 to 70:30, afforded the title compound as a white solid in quantitative yield, 0.105g. ^{1}H NMR($CDCl_3$, 400MHz) δ: 1.50(t, 3H), 2.60(s, 3H), 4.10(q, 2H), 4.80(s, 2H), 7.20(d, 1H), 8.10(d, 1H). MS APCI+ m/z 254 $[MH]^+$

Preparation 46

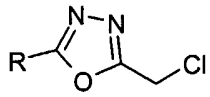
2-Chloromethyl-5-(4-methoxy-phenyl)-[1,3,4]oxadiazole

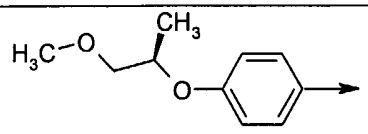
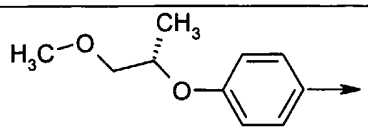


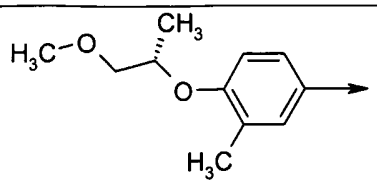
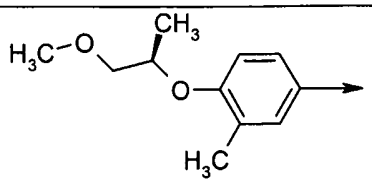
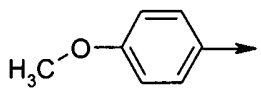
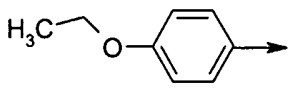
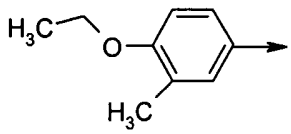
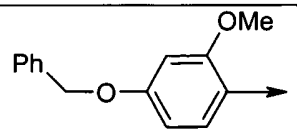
The product of preparation 38 (72.6g, 300mmol) was added to phosphorous oxychloride (200mL) and the reaction mixture heated to 110°C for 5 hours. The mixture was then allowed to cool to room temperature and was concentrated *in vacuo*. The residue was taken up in ethyl acetate (500mL) and water (500mL) and treated with a saturated sodium hydrogen carbonate solution. The phases were separated and the aqueous layer was extracted with ethyl acetate (2x200mL). The organics were combined, dried over magnesium sulfate and concentrated *in vacuo* to yield the title product, 53.0g. ^{1}H NMR($CDCl_3$, 400MHz) δ: 3.88(s, 3H), 4.76(s, 2H), 7.01(d, 2H), 8.01(d, 2H). MS APCI+ m/z 225 $[MH]^+$

Preparations 47 to 54

The following compounds, of the general formula shown below, were prepared by the method described for preparation 46 using the appropriate chloroacetyl hydrazide as outlined in the table below.



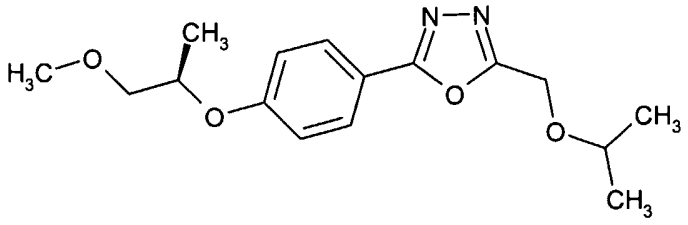
No.	R	Data	Yield
47	 Prepared from the compound of preparation 39	^{1}H NMR($CDCl_3$, 400MHz) δ: 1.40(d, 3H), 3.40(s, 3H), 3.50(m, 1H), 3.60(m, 1H), 4.60(m, 1H), 4.80(s, 2H), 7.00(d, 2H), 8.00(d, 2H). MS ES+ m/z 283 $[MH]^+$	8.2g (66%)
48	 Prepared from the compound of preparation 41	^{1}H NMR($CDCl_3$, 400MHz) δ: 1.40(d, 3H), 3.40(s, 3H), 3.50(m, 1H), 3.60(m, 1H), 4.60(m, 1H), 4.80(s, 2H), 7.00(d, 2H), 8.00(d, 2H). MS ES+ m/z 283 $[MH]^+$	12.7g (80%)

49	 Prepared from the compound of preparation 41a	^{1}H NMR($CDCl_3$, 400MHz) δ: 1.35(d, 3H), 2.30(s, 3H), 3.40(s, 3H), 3.60(m, 1H), 3.65(m, 1H), 4.65(m, 1H), 4.75(s, 2H), 7.00(d, 1H), 8.00(m, 2H). MS ES+ m/z 297 $[MH]^+$	6.2g (93%)
50	 Prepared from the compound of preparation 41b	^{1}H NMR($CDCl_3$, 400MHz) δ: 1.40(d, 3H), 2.30(s, 3H), 3.40(s, 3H), 3.50(m, 1H), 3.70(m, 1H), 4.60(m, 1H), 4.80(s, 2H), 7.00(d, 1H), 7.90(m, 2H). MS ES+ m/z 297 $[MH]^+$	7.9g (81%)
51	 Prepared from the compound benzoic acid 4-methoxy-2-(chloroacetyl)-hydrazide	^{1}H NMR($CDCl_3$, 400MHz) δ: 3.38(s, 3H), 4.76(s, 2H), 7.01 (d, 2H), 8.01(d, 2H) MS APCI+ m/z 225 $[MH]^+$	53.0g (90%)
52	 Prepared from the compound of preparation 42	^{1}H NMR(DMSO-D_6, 400MHz) δ: 1.33(t, 3H), 4.07(q, 2H), 4.15(s, 2H), 6.96 (d, 2H), 7.81(d, 2H), MS APCI+ m/z 239 $[MH]^+$	16.7g, (77%)
53	 Prepared from the compound of preparation 43	^{1}H NMR(DMSO-D_6, 400MHz) δ: 1.46(t, 3H), 2.25(s, 3H), 4.10(q, 2H), 4.78(s, 2H), 6.85-6.95(d, 1H), 7.85-7.9(m, 2H) MS APCI+ m/z 253 $[MH]^+$	4.8g, (86%)
54	 Prepared from the compound of preparation 44	^{1}H NMR($CDCl_3$, 400MHz) δ: 3.94(s, 3H), 4.77(s, 2H), 5.14(s, 2H), 6.65-6.69(m, 2H), 7.34-7.46(m, 5H), 7.88(d, 1H).	12.5g (75%)

		MS APCI+ m/z 331 $[MH]^+$	

Preparation 55

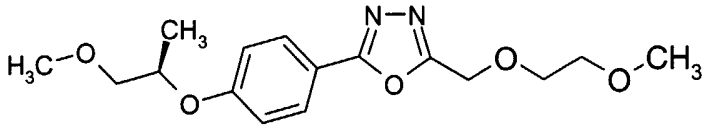
2-Isopropoxymethyl-5-[4-(2-methoxy-(1*R*)-methyl-ethoxy)-phenyl]-[1,3,4]oxadiazole



Sodium metal (34mg, 1.51mmol), was dissolved in *iso*-propyl alcohol (20mL) heated to 45°C. On cooling to room temperature, the product of preparation 47 (300mg, 1.01mmol) was added to the formed sodium *iso*-propoxide and the mixture was allowed to stir for 18 hours. The solvent was then evaporated under reduced pressure and the residue was dissolved in ethyl acetate and washed with water and brine. The organic phase was dried over sodium sulfate and concentrated *in vacuo* to give the title compound in 54% yield, (168mg). ^{1}H NMR($CDCl_3$, 400MHz) δ: 1.24(d, 6H), 1.34(d, 3H), 3.39(s, 3H), 3.50(m, 1H), 3.61(m, 1H), 3.78(m, 1H), 4.68(m, 1H), 4.73(s, 2H), 7.03(d, 2H), 7.97(d, 2H). MS APCI+ m/z 307 $[MH]^+$

Preparation 56

2-(2-Methoxy-ethoxymethyl)-5-[4-(2-methoxy-(1*R*)-methyl-ethoxy)-phenyl]-[1,3,4]oxadiazole

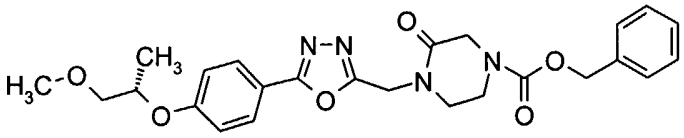


To a 60% dispersion of NaH (81mg, 2.02mmol), in tetrahydrofuran (20mL) was added 2-methoxyethanol (0.12mL, 1.52mmol) and the mixture was allowed to stir for 15 minutes at room temperature. The product of preparation 47 (300mg, 1.01mmol) was added in tetrahydrofuran (20mL) and stirring continued for a further 2 hours. The solvent was then evaporated under reduced pressure and the residue was dissolved in ethyl acetate and washed with water and brine. The organic phase was dried over sodium sulfate and concentrated *in vacuo* to yield the title compound, 321mg. ^{1}H NMR($CDCl_3$, 400MHz) δ: 1.40(d, 3H), 2.00(s,

3H), 3.40(s, 3H), 3.43-3.60(m, 2H) 3.70(m, 2H), 4.16(m, 2H) 4.63(m, 1H), 4.81(s, 2H), 6.90(d, 2H), 7.93(d, 2H). MS APCI+ m/z 323 $[MH]^+$

Preparation 57

4-{5-[4-(2-Methoxy-(1*S*)-methyl-ethoxy)-phenyl]-[1,3,4]oxadiazol-2-ylmethyl}-3-oxo-piperazine-1-carboxylic acid benzyl ester

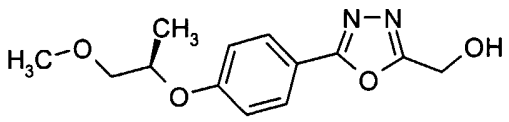


A solution of potassium carbonate (136mg, 2.4mmol) suspended in tetrahydrofuran (3mL) was cooled to 0°C. Tetrabutylammonium bromide (130mg, 0.40mmol), 4-benzyloxycarbonyl piperazin-2-one (568mg, 2.43mmol), and the product of preparation 48 (572mg, 2.02mmol), were added in tetrahydrofuran (3mL) and the mixture was allowed to warm to room temperature and stir for 18 hours. The solvent was then evaporated under reduced pressure and the residue was dissolved in ethyl acetate and washed with water and brine. The organic phase was dried over magnesium sulfate and concentrated in vacuo to give an oil. Purification by column chromatography on silica gel, eluting with pentane:diethyl ether 90:10 to 20:80, gave the title compound as a pale brown foam in 70% yield, (679mg).

^{1}H NMR($CDCl_3$, 400MHz) δ: 1.40(d, 3H), 3.40(s, 3H), 3.50(m, 1H), 3.55(t, 2H), 3.60(m, 1H), 3.80(t, 2H), 4.15(s, 2H), 4.64(m, 1H), 4.90(s, 2H), 5.15(s, 2H), 7.00(d, 2H), 7.40(m, 5H), 7.95(d, 2H). MS APCI+ m/z 481 $[MH]^+$

Preparation 58

{5-[4-(2-Methoxy-(1*R*)-methyl-ethoxy)-phenyl]-[1,3,4]oxadiazol-2-l}-methanol

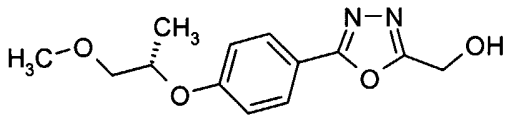


To the product of preparation 47 (3.65g, 12.9mmol) stirred in N,N-dimethylformamide (20mL), was added potassium acetate (2.66g, 27.16mmol) and the mixture was heated at 50°C for 18 hours. The solvent was then evaporated under reduced pressure to give a brown residue that was dissolved in ethyl acetate, washed with 2N hydrochloric acid, water and brine. The organic

phase was dried over sodium sulfate and the solvent was evaporated under reduced pressure under reduced pressure. The residue was dissolved in methanol and treated with 10% sodium carbonate solution. The reaction mixture was heated at 50°C for 90 minutes before the solvent was removed *in vacuo*. The residue was taken up in ethyl acetate, washed with 2N hydrochloric acid and brine, dried over sodium sulfate and concentrated *in vacuo* to afford title compound in 84% yield, (2.86g). ^{1}H NMR($CDCl_3$, 400MHz) δ: 1.25(d, 3H), 3.30(s, 1H), 3.33(m, 5H), 4.63(m, 1H), 4.87 (s, 2H), 7.95(d, 2H), 7.94(d, 2H)

Preparation 59

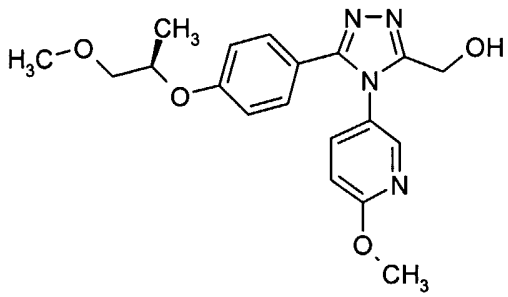
{5-[4-(2-Methoxy-1-methyl-ethoxy)-phenyl]-[1,3,4]oxadiazol-2-yl}-methanol



The title compound was prepared by the method described for preparation 58 using the chloro product of preparation 48, in 93% yield. ^{1}H NMR($CDCl_3$, 400MHz) δ: 1.35(d, 3H), 3.30(s, 1H), 3.40(s, 3H), 3.50(m, 1H), 3.60(m, 1H), 4.65(m, 1H), 4.90(s, 2H), 7.00(d, 2H), 8.00(d, 2H). MS APCI+ m/z 265 $[MH]^+$

Preparation 60

[5-[4-(2-Methoxy-1-methyl-ethoxy)-phenyl]-4-(6-methoxy-pyridin-3-yl)-4H-[1,2,4]triazol-3-yl]-methanol

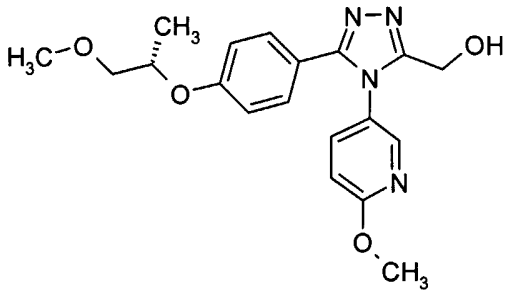


The product of preparation 58 (2.86g, 10.83mmol), 5-amino-2-methoxypyridine (2.02g, 16.24mmol) and *para*-toluenesulfonic acid (cat) were heated under reflux in xylene (50mL) for 90 minutes. The solvent was then evaporated under reduced pressure and the residue was dissolved in dichloromethane (50mL) and washed with 2N sodium hydroxide, water and brine. The organic phase was dried over sodium sulfate and concentrated *in vacuo* to give a red oil that was

decolourised by charcoal in methanol to give the title compound in 59% yield, (2.37g). ^{1}H NMR($CDCl_3$, 400MHz) δ: 1.40(d, 3H), 3.40(s, 3H), 3.50(m, 1H), 3.60(m, 1H), 4.00(s, 3H) 4.50(m, 1H), 4.70(s, 2H), 6.80(m, 3H), 7.30(d, 2H), 7.60(d, 1H), 8.20(s, 1H). MS APCI+ m/z 371 $[MH]^+$

Preparation 61

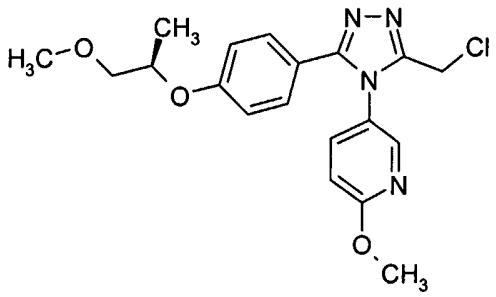
[5-[4-(2-Methoxy-1-methyl-ethoxy)-phenyl]-4-(6-methoxy-pyridin-3-yl)-4H-[1,2,4]triazol-3-yl]-methanol



The title compound was prepared by the method described for preparation 60 using the product of preparation 59 and 5-amino-2-methoxypyridine, 67% yield. ^{1}H NMR($CDCl_3$, 400MHz) δ: 1.25(d, 3H), 3.40(s, 3H), 3.50(m, 1H), 3.55(m, 1H), 3.90 (brs, 1H), 4.00(s, 3H), 4.30(m, 1H), 4.65(s, 2H), 6.80(m, 3H), 7.30(d, 2H), 7.60(d, 1H), 8.20(s, 1H). MS APCI+ m/z 371 $[MH]^+$

Preparation 62

5-{3-Chloromethyl-5-[4-(2-methoxy-(1*R*)-methyl-ethoxy)-phenyl]-[1,2,4]triazol-4-yl}-2-methoxy-pyridine



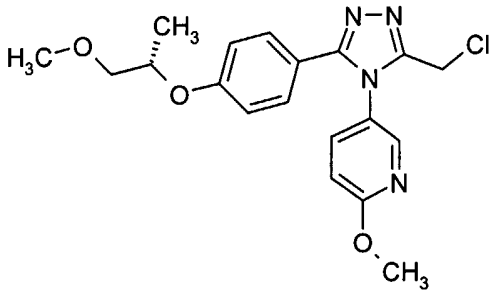
The product of preparation 60 (2.36g, 6.37mmol) and methanesulfonyl chloride (0.986mL, 12.74mmol) were added to a solution of triethylamine (1.93g, 2.66mL, 19.11mmol) dissolved in dichloromethane (50mL). After stirring at room temperature for 18 hours, the reaction mixture was washed with water, citric acid

and brine. The organic layer was separated, dried over sodium sulfate and concentrated *in vacuo* to yield the title compound, 1.97g (80%)

^{1}H NMR($CDCl_3$, 400MHz) δ: 1.40(d, 3H), 3.40(s, 3H), 3.50(m, 1H), 3.60(m, 1H), 4.00(s, 3H) 4.55(m, 1H), 4.60(s, 2H), 6.90(m, 3H), 7.40(d, 2H), 7.50(d, 1H), 8.20(s, 1H). MS APCI+ m/z 389 $[MH]^+$

Preparation 63

5-{3-Chloromethyl-5-[4-(2-methoxy-(1*S*)-methyl-ethoxy)-phenyl]-[1,2,4]triazol-4-yl}-2-methoxy-pyridine

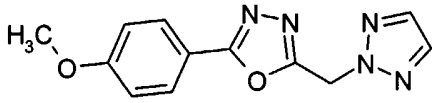


The title compound was prepared from the product of preparation 61, using the method described for preparation 62, in 40% yield.

^{1}H NMR($CDCl_3$, 400MHz) δ: 1.30(d, 3H), 3.40(s, 3H), 3.45(m, 1H), 3.55(m, 1H), 4.00(s, 3H), 4.55(m, 1H), 4.60(s, 2H), 6.85(m, 3H), 7.40(d, 2H), 7.50(d, 1H), 8.20(s, 1H). MS APCI+ m/z 389 $[MH]^+$

Preparation 64

2-(4-Methoxy-phenyl)-5-[1,2,3]triazol-2-ylmethyl-[1,3,4]oxadiazole



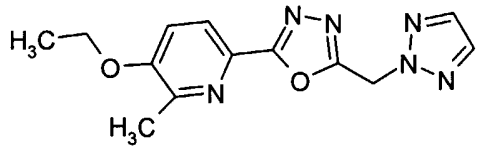
The chloro compound of preparation 46 (12.9g, 66mmol), 1H-1,2,3-triazole (5.0g, 72.4mmol) and potassium carbonate (18.2g, 132mmol) were dissolved in N,N-dimethylformamide (200mL) and stirred at room temperature for 2 hours. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between ethyl acetate (300mL) and water (300mL). The aqueous layer was extracted with ethyl acetate (200mL) and the combined organics were dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by

column chromatography on silica gel, eluting with pentane:ethyl acetate 70:30 to 0:100, to yield the title product, 5.80g, (34%).

^{1}H NMR($CDCl_3$, 400MHz) δ: 3.86(s, 3H), 5.91(s, 2H), 6.98(d, 2H), 7.76(s, 2H), 7.95(m, 2H). MS APCI+ m/z 258 $[MH]^+$

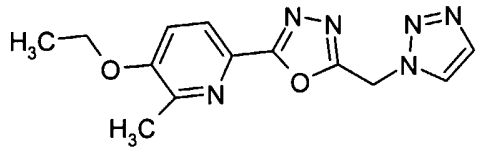
Preparation 65

3-Ethoxy-2-methyl-6-(5-[1,2,3]triazol-2-ylmethyl-[1,3,4]oxadiazol-2-yl)-pyridine



and **preparation 66**

3-Ethoxy-2-methyl-6-(5-[1,2,3]triazol-1-ylmethyl-[1,3,4]oxadiazol-2-yl)-pyridine



The compounds of preparations 65 and 66 were prepared by the method described for preparation 64 using the chloro compound of preparation 45. 660mg of the desired products were produced as a mixture of isomers.

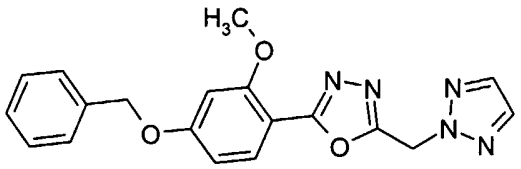
MS ES+ m/z 287 $[MH]^+$

Preparation 67 and 68

The title compounds of preparations 67 and 68 were prepared by the method described for preparation 64 using the chloro compound of preparation 54. A crude mixture of isomers was produced that was purified by column chromatography on silica gel. Elution with ethyl acetate:pentane:methanol:0.88 ammonia, 50:50:1:0.1, afforded the product of preparation 67 in 39% yield. Further elution with ethyl acetate:methanol 98:2 afforded the product of preparation 68 in 52% yield.

Preparation 67

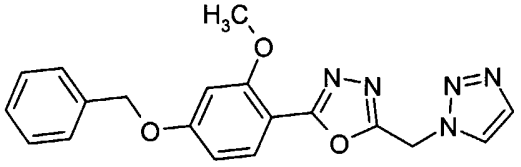
2-(4-Benzyloxy-2-methoxy-phenyl)-5-[1,2,3]triazol-2-ylmethyl-[1,3,4]oxadiazole



^{1}H NMR($CDCl_3$, 400MHz) δ: 3.89(s, 3H), 5.12(s, 2H), 5.92(s, 2H), 6.61-6.64(m, 2H), 7.33-7.45(m, 5H), 7.70(s, 2H), 7.80(d, 1H). MS ES+ m/z 364 $[MH]^+$

Preparation 68

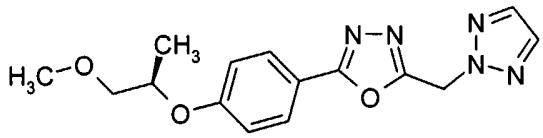
2-(4-Benzyloxy-2-methoxy-phenyl)-5-[1,2,3]triazol-1-ylmethyl-[1,3,4]oxadiazole



^{1}H NMR($CDCl_3$, 400MHz) δ: 3.90(s, 3H), 5.12(s, 2H), 5.90(s, 2H), 6.63-6.66(m, 2H), 7.36-7.45(m, 5H), 7.78(d, 2H), 7.82(d, 1H). MS ES+ m/z 364 $[MH]^+$

Preparation 69

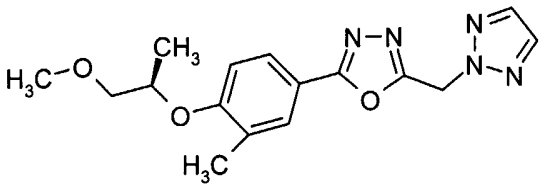
2-[4-(2-Methoxy-(1*R*)-1-methyl-ethoxy)-phenyl]-5-[1,2,3]triazol-2-ylmethyl-[1,3,4]oxadiazole



The chloro compound of preparation 47 (750mg, 2.79mmol), 1H-1,2,3-triazole (289mg, 4.19mmol) and potassium carbonate (770mg, 5.58mmol) were dissolved in acetonitrile (25mL) and stirred at room temperature for 18 hours. The solvent was then evaporated under reduced pressure and the residue was taken up in ethyl acetate (25mL) and washed with water (25mL), 2M sodium hydroxide solution (25mL) and brine (25mL). The ethyl acetate phase was dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with dichloromethane:methanol 100:0 to 98:2 to yield the title product, 650mg. MS ES+ m/z 317 $[MH]^+$

Preparation 70

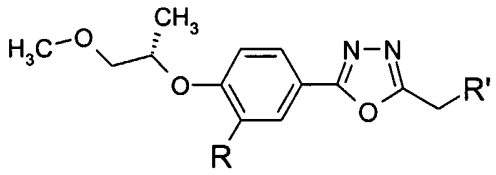
2-[4-(2-Methoxy-1-methyl-ethoxy)-3-methyl-phenyl]-5-[1,2,3]triazol-2-ylmethyl-[1,3,4]oxadiazole

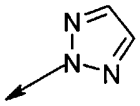
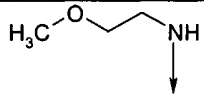


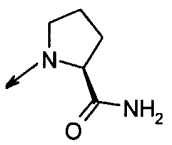
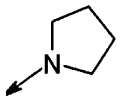
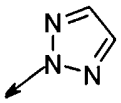
The title compound was prepared by a similar method to preparation 69 using the chloro product of preparation 50 and 1,2,3-triazole, in quantitative yield.
^{1}H NMR($CDCl_3$, 400MHz) δ: 1.34(d, 3H), 2.25(s, 3H) 3.40(s, 3H), 3.50(m, 1H), 3.60(m, 1H), 4.60(m, 1H), 5.90(d, 2H), 6.93(m, 2H), 7.70(s, 1H), 7.80(d, 1H), 7.90(d, 1H). MS APCI+ m/z 330 $[MH]^+$

Preparations 71 to 76

The following compounds, of the general formula shown below, were prepared by the method described for preparation 69 using the products of preparation 48/49 and the appropriate amine as outlined in the table below.

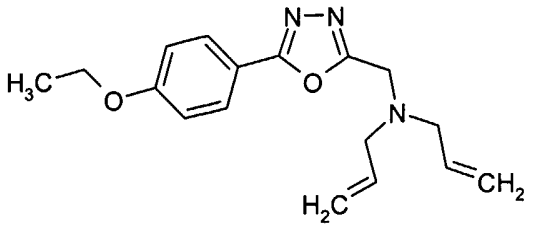


No.	R	R'	Data	Yield
71	H	 Prepared from the compound of preparation 48 and 1,2,3-triazole	^{1}H NMR($CDCl_3$, 400MHz) δ: 1.35(d, 3H), 3.40(s, 3H), 3.50(m, 1H), 3.60(m, 1H), 4.60(m, 1H), 5.90(d, 2H), 7.00(m, 2H), 7.70(s, 2H), 7.80(d, 1H), 7.90(d, 1H). MS APCI+ m/z 316 $[MH]^+$	1.11g (99%)
72	H	 Prepared from the compound of preparation 48	^{1}H NMR($CDCl_3$, 400MHz) δ: 1.35(d, 3H), 2.90(t, 2H), 3.35(s, 3H), 3.45(s, 3H), 3.50(m, 1H), 3.55(t, 2H), 3.60(m, 1H), 4.10(s, 2H), 4.50(m, 1H), 7.00(d, 2H), 8.60(d, 2H).	357mg (91%)

		and 2-methoxy-ethylamine	MS APCI+ m/z 322 $[MH]^+$	
73	H	 Prepared from the compound of preparation 48 and L-(-)-prolanamide hydrochloride	^{1}H NMR($CDCl_3$, 400MHz) δ: 1.40(d, 3H), 1.90(m, 2H), 2.00(m, 1H), 2.30(m, 1H), 2.70(q, 1H), 3.30(m, 1H), 3.40(s, 3H), 3.45(m, 1H), 3.50(m, 1H), 3.60(m, 1H), 4.10(m, 2H), 4.60(m, 1H), 7.00(d, 2H), 7.20(m, 1H), 7.95(d, 2H). MS APCI+ m/z 361 $[MH]^+$	538mg (86%)
74	H	 Prepared from the compound of preparation 48 and pyrrolidine	^{1}H NMR($CDCl_3$, 400MHz) δ: 1.40(d, 3H), 1.80(m, 4H), 2.70(m, 4H), 3.40(s, 3H), 3.50(m, 1H), 3.60(m, 1H), 4.00(s, 2H), 4.62(m,1H), 7.00(d, 2H), 8.00(d, 2H) MS APCI+ m/z 318 $[MH]^+$	523mg (95%)
75	H	HN-CH_3 Prepared from the compound of preparation 49 and methylamine	^{1}H NMR($CDCl_3$, 400MHz) δ: 1.30(d, 3H), 2.00(bs, 1H), 2.50(s, 3H), 3.40(s, 3H), 3.50(m, 1H), 3.60(m, 1H), 4.05(s, 2H), 4.60(m, 1H), 7.00(d, 2H), 7.95(d, 2H) MS APCI+ m/z 278 $[MH]^+$	203mg (88%)
76	CH_3	 Prepared from the compound of preparation 49 and 1,2,3-triazole	^{1}H NMR($CDCl_3$, 400MHz) δ: 1.40(d, 3H), 2.25(s, 3H), 3.40(s, 3H), 3.50(m, 1H), 3.60(m, 1H), 4.60(m, 1H), 5.90(d, 2H), 7.00(m, 2H), 7.70(s, 1H), 7.80(m, 3H), MS APCI+ m/z 330 $[MH]^+$	660mg (92%)

Preparation 77

Diallyl-[5-(4-ethoxy-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-amine

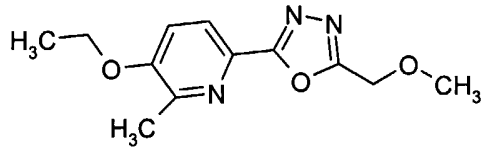


The chloro product of preparation 52 (0.2g, 0.84mmol), diallylamine (98mg, 1.01mmol) and potassium carbonate (221mg, 1.68mmol) were dissolved in dimethyl sulfoxide (1mL) and stirred for 3 hours. The mixture was then diluted with ethyl acetate (40mL) and washed with water (3x10mL), sodium hydrogen carbonate solution (2x10mL) and brine (10mL). The organic phase was dried over magnesium sulfate and evaporated under reduced pressure, to give a pink oil. Purification by column chromatography on silica gel, eluting with dichloromethane:methanol, 95:5, afforded the title compound as a colourless oil in 65.6% yield, 165mg.

^{1}H NMR($CDCl_3$, 400MHz) δ: 1.50(t, 3H), 3.20(d, 4H), 3.95(s, 2H), 4.10(q, 2H), 5.10(m, 4H), 5.90(m, 2H), 7.00(d, 2H), 8.00(d, 2H). MS ES+ m/z 300 $[MH]^+$

Preparation 78

3-Ethoxy-6-(5-methoxy-[1,3,4]oxadiazol-2-yl)-2-methyl-pyridine

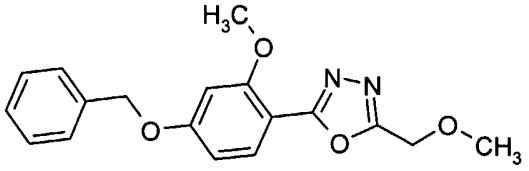


The chloro compound of preparation 45 (298mg, 1.18mmol), and sodium methoxide (0.3mL, 2.36mmol), were stirred in methanol (3.5mL) for 6 hours at room temperature. The solvent was then evaporated under reduced pressure and the residue was dissolved in ethyl acetate and washed with water, sodium hydrogen carbonate solution and brine. The organic phase was dried over magnesium sulfate, concentrated *in vacuo* and azeotroped with diethyl ether to give title compound a white solid in 51% yield, 149mg.

^{1}H NMR($CDCl_3$, 400MHz) δ: 1.50(t, 3H), 2.60(s, 3H), 3.50(s, 3H), 4.15(q, 2H), 4.70(s, 2H), 7.15(d, 1H), 8.00(d, 1H). MS ES+ m/z 250 $[MH]^+$

Preparation 79

2-(4-Benzyloxy-2-methoxy-phenyl)-5-methoxymethyl-[1,3,4]oxadiazole

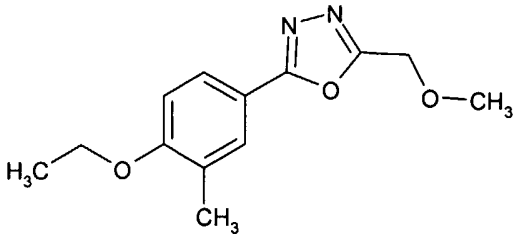


The chloro compound of preparation 54 (3.00g, 9.07mmol) was dissolved in methanol (40mL) and treated with sodium methoxide (2.30g). The reaction mixture was heated to 50°C for 4 hours and was then allowed to stand at room temperature for 18 hours. The solvent was evaporated under reduced pressure and the residue was partitioned between ethyl acetate and sodium hydrogen carbonate solution. The organic phase was washed with brine, dried over magnesium sulfate and concentrated *in vacuo* to yield the title product, 2.88g.

^{1}H NMR($CDCl_3$, 400MHz) δ: 3.48(s, 3H), 3.93(s, 3H), 4.70(s, 2H), 5.13(s, 2H), 6.64-6.68(m, 2H), 7.32-7.46(m, 5H), 7.88(d, 1H). MS ES+ m/z 327 $[MH]^+$

Preparation 80

2-(4-Ethoxy-3-methyl-phenyl)-5-methoxymethyl-[1,3,4]oxadiazole

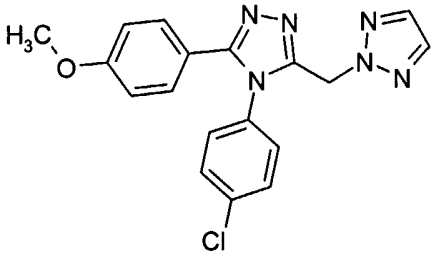


The title compound was prepared from the chloro product of preparation 53 using the method described for preparation79, as a white solid in 86% yield.

^{1}H NMR($CDCl_3$, 400MHz) δ: 1.44(t, 3H), 2.22(s, 3H), 3.45(s, 3H), 4.16(q, 2H), 4.65(s, 2H), 6.83(d, 1H), 7.83(m, 2H). MS ES+ m/z 249 $[MH]^+$

Preparation 81

2-[4-(4-Chloro-phenyl)-5-(4-methoxy-phenyl)-4H-[1,2,4]triazol-3-ylmethyl]-2H-[1,2,3]triazole

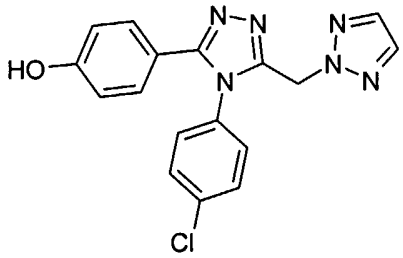


The product of preparation 64 (4.90g, 19mmol), 4-chloroaniline (3.70g, 29mmol) and *para*-toluenesulfonic acid (100mg) were dissolved in xylene (150mL) and heated to 140°C for 8 hours. The reaction mixture was allowed to cool to room temperature and the crystals that formed were filtered off and dried *in vacuo* to yield the title product, 8.24g.

^{1}H NMR($CDCl_3$, 400MHz) δ: 3.77(s, 3H), 5.71(s, 2H), 6.80(d, 2H), 7.05(d, 2H), 7.34(d, 2H), 7.37(d, 2H), 7.52(s, 2H). MS APCI+ m/z 367 $[MH]^+$

Preparation 82

4-[4-(4-Chloro-phenyl)-5-[1,2,3]triazol-2-ylmethyl-4H-[1,2,4]triazol-3-yl]-phenol

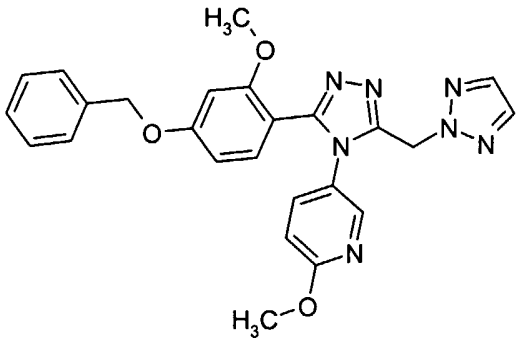


The ether of preparation 81 (1.50g, 4.1mmol) and boron tribromide (12.3mL, 12.3mmol) were dissolved in dichloromethane (30mL) and heated under reflux for 18 hours. The resulting precipitate was filtered off, taken up in methanol and treated with 1M sodium hydroxide solution (150mL). The solution was re-filtered and acidified to pH 4 with 2M hydrochloric acid, and the precipitate that formed was collected by filtration and dried *in vacuo* to yield the title product, 1.40g.

^{1}H NMR($CDCl_3$, 400MHz) δ: 5.78(s, 2H), 6.72(d, 2H), 7.17(d, 2H), 7.21(d, 2H), 7.45(d, 2H), 7.59(s, 2H). MS ES+ m/z 351 $[MH]^+$

Preparation 83

5-[3-(4-Benzyloxy-2-methoxy-phenyl)-5-[1,2,3]triazol-2-ylmethyl-[1,2,4]triazol-4-yl]-2-methoxy-pyridine

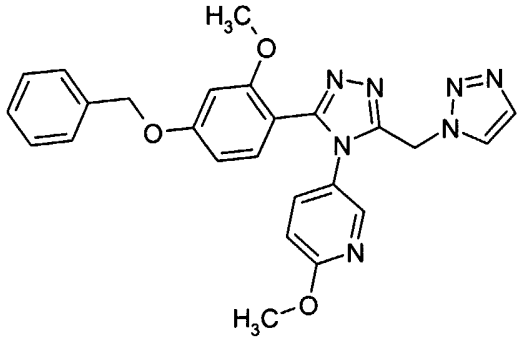


The product of preparation 67 (2.20g, 6.05mmol), 2-methoxy-pyridin-2-ylamine (530mg, 6.60mmol) and *para*-toluenesulfonic acid (50mg, cat) were dissolved in xylene (30mL) and heated at 140°C for 18 hours. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between ethyl acetate and sodium hydrogen carbonate solution. The organic phase was washed with brine, dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by column chromatography on silica gel, eluting with 98:2 dichloromethane:methanol and then with pentane:ethyl acetate 50:50 to 0:100, yielded the title product, 1.80g.

^{1}H NMR($CDCl_3$, 400MHz) δ: 3.44(s, 3H), 3.90(s, 3H), 5.03(s, 2H), 5.75(s, 2H), 6.34(d, 1H), 6.59(m, 1H), 6.63(d, 1H), 7.18(m, 1H), 7.32-7.39(m, 5H), 7.46(d, 1H), 7.54(s, 2H), 7.82(d, 1H). MS APCI+ m/z 470 $[MH]^+$

Preparation 84

5-[3-(4-Benzyloxy-2-methoxy-phenyl)-5-[1,2,3]triazol-1-ylmethyl-[1,2,4]triazol-4-yl]-2-methoxy-pyridine

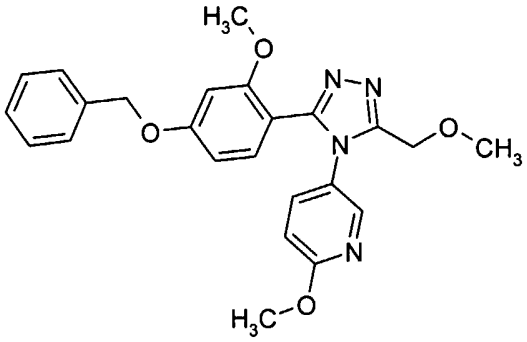


The title compound was prepared from the product of preparation 68 by the method described for preparation 83, in 93% yield.

^{1}H NMR($CDCl_3$, 400MHz) δ: 3.43(s, 3H), 3.93(s, 3H), 5.03(s, 2H), 5.68(s, 2H), 6.36(d, 1H), 6.60(d, 1H), 6.72(d, 1H), 7.15(m, 1H), 7.32-7.40(m, 5H), 7.42(d, 1H), 7.72(s, 1H), 7.80(d, 1H), 7.84(s, 1H). MS APCI+ m/z 470 $[MH]^+$

Preparation 85

5-[3-(4-Benzyloxy-2-methoxy-phenyl)-5-methoxymethyl-[1,2,4]triazol-4-yl]-2-methoxy-pyridine

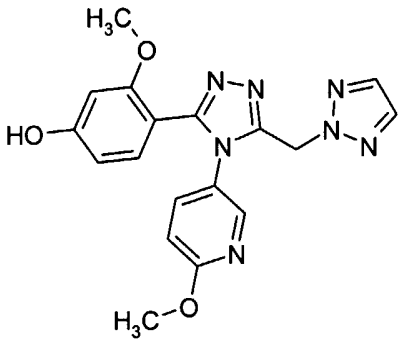


The title product was prepared by the method described for preparation 83 using the product of preparation 79. 2.38g of the desired product were produced.

^{1}H NMR($CDCl_3$, 400MHz) δ: 3.39(s, 3H), 3.45(s, 3H), 3.94(s, 3H), 4.49(s, 2H), 5.05(s, 2H), 6.37(s, 1H), 6.61(d, 1H), 6.72(d, 1H), 7.32-7.48(m, 7H), 7.98(s, 1H). MS APCI+ m/z 433 $[MH]^+$

Preparation 86

3-Methoxy-4-[4-(6-methoxy-pyridin-3-yl)-5-[1,2,3]triazol-2-ylmethyl-4H-[1,2,4]triazol-3-yl]-phenol



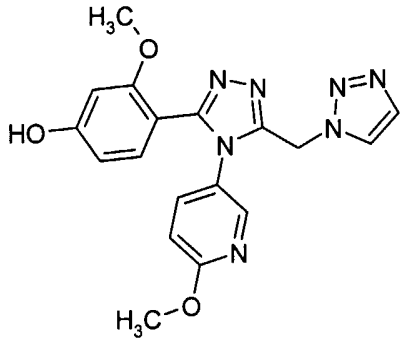
The benzyl protected alcohol of preparation 83 (1.70g, 3.62mmol) and 10% Pd/C (200mg) were added to ethanol (20mL) and the reaction mixture was stirred at room temperature, under 60psi of hydrogen, for 18 hours. The mixture was then

filtered through Arbocel®, washing through with ethanol and dichloromethane, and the filtrate was evaporated under reduced pressure. The residue was dissolved in dichloromethane, dried over magnesium sulfate and concentrated *in vacuo*. Trituration of the residue with ether yielded the title product, 1.26g.

^{1}H NMR($CDCl_3$, 400MHz) δ: 3.35(s, 3H), 3.90(s, 3H), 5.72(s, 2H), 6.25(s, 1H), 6.35(d, 1H), 6.61(d, 1H), 7.15(dd, 2H), 7.54(s, 2H), 7.81(s, 1H).
MS APCI+ m/z 378 $[M-H]^-$

Preparation 87

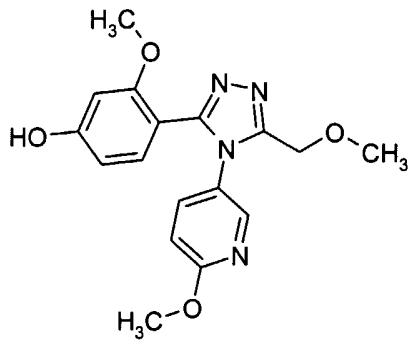
3-Methoxy-4-[4-(6-methoxy-pyridin-3-yl)-5-[1,2,3]triazol-1-ylmethyl-4H-[1,2,4]triazol-3-yl]-phenol



The title product was prepared from the product of preparation 84 by the method described for preparation 86, in 87% yield. ^{1}H NMR($CDCl_3$, 400MHz) δ: 3.32(s, 3H), 3.91(s, 3H), 5.65(m, 2H), 6.26(s, 1H), 6.36(d, 1H), 6.68(d, 1H), 7.17(t, 2H), 7.70(s, 1H), 7.80(m, 2H). MS APCI+ m/z 378 $[M-H]^-$

Preparation 88

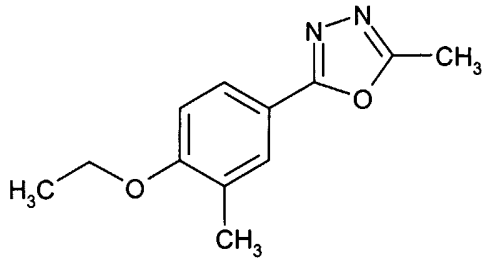
3-Methoxy-4-[5-methoxymethyl-4-(6-methoxy-pyridin-3-yl)-4H-[1,2,4]triazol-3-yl]-phenol



The title product was prepared from the product of preparation 85 using the method described for preparation 86, in 93% yield. ^{1}H NMR($CDCl_3$, 400MHz) δ: 3.33(s, 3H), 3.37(s, 3H), 3.93(s, 3H), 4.47(s, 2H), 6.28(d, 1H), 6.40(m, 1H), 6.72(d, 1H), 7.20(d, 1H), 7.42(m, 1H), 7.98(d, 1H). MS ES+ m/z 343 $[MH]^+$

Preparation 89

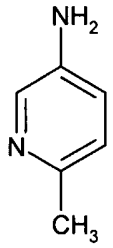
2-(4-Ethoxy-3-methyl-phenyl)-5-methyl-[1,3,4]oxadiazole



The title compound was prepared from the hydrazine product of preparation 34 and N,N-dimethylacetamide dimethyl acetal using the method described for preparation4. Re-crystallisation with hexane:ethyl acetate, 90:10, afforded 7.2g of desired product (64%). ^{1}H NMR($CDCl_3$, 400MHz) δ: 1.42(t, 3H), 2.29(s, 3H), 2.60(s, 3H), 4.12(q, 2H), 6.82(d, 1H), 7.81(m, 2H). MS APCI+ m/z 219 $[MH]^+$

Preparation 90

6-methyl-pyridin-3-ylamine

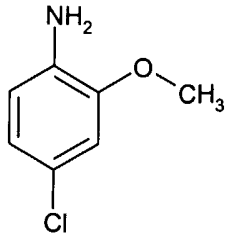


Iron powder (10g) was added to a well-stirred solution of 2-methyl-5-nitro-pyridine, [(46g, 330mmol) Monatshefte fűr chemie, 1950 81(4) 479] dissolved in acetic acid (500mL). The mixture was heated under reflux for 1.5 hours, cooled, and a further portion of iron powder (2g) was added. The reaction mixture was stirred under reflux for an additional 5 hours, cooled and left to stand for 18 hours. The iron powder was then filtered off and the filtrate was evaporated under reduced pressure. The residue was taken up in water and chloroform and was treated with potassium carbonate. The organic phase was washed with

water, dried over magnesium sulfate and concentrated *in vacuo* to produce the title compound as a semi-solid (17.2g). BPt. 130°C@ 1mmHg

Preparation 91

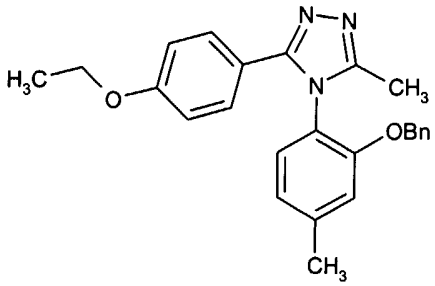
4-Chloro-2-methoxy-phenylamine



To a suspension of 5-chloro-2-nitroanisole (10g, 53mmol) and potassium bicarbonate (28g, 280mmol) in methanol (150mL) and water (150mL) was added sodium dithionite (28g, 159 mmol). The mixture was allowed to stir at room temperature for 2 hours. The reaction mixture was acidified to pH1 with concentrated hydrochloric acid and the resulting brown suspension was heated for 2 hours at 60°C before the solvent was evaporated under reduced pressure. The residual aqueous solution was washed with ethyl acetate, basified with sodium hydroxide pellets and re-extracted with ethyl acetate. The combined organic phase was washed with brine, dried over sodium sulfate and concentrated *in vacuo* to give the title compound in 64% yield (5.35g). ^{1}H NMR(DMSO-D_6, 400MHz) δ: 3.66(s, 3H), 4.76(bs, 2H), 6.52(m, 1H), 6.65(m, 1H), 6.79(m, 1H)

Preparation 92

4-(2-Benzyloxy-4-methyl-phenyl)-3-(4-ethoxy-phenyl)-5-methyl-4H-[1,2,4]triazole



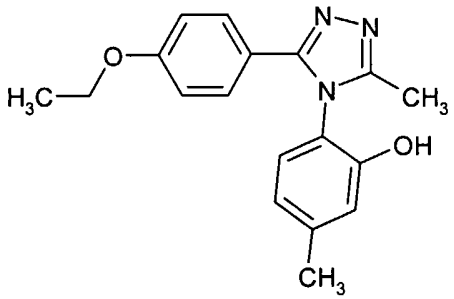
The product of preparation 4 (294mg, 1.44mmol), 2-benzyloxy-4-methyl-phenylamine [(360 mg, 1.44mmol), Tetrahedron, 2000, 56 (37), 7163-7171, compound 6] and *para*-toluenesulfonic acid (50mg, cat) were dissolved in xylene

(6mL) and stirred at 140°C for 30 hours. The solvent was then evaporated under reduced pressure and the residue was purified by column chromatography on silica gel, eluting with dichloromethane:methanol:0.88 ammonia, 99:1:0.1, to give a brown coloured oil. Trituration with diethyl ether afforded the title compound as a white solid in 54% yield (304mg).

^{1}H NMR(DMSO-D_6, 400MHz) δ: 1.39(t, 3H), 2.29(s, 3H), 2.40(s, 3H), 3.99(q, 2H), 4.97(m, 2H) 6.75(m, 2H), 6.84-6.89(m, 2H) 7.01-7.06(m, 3H), 7.24-7.27(m, 3H), 7.35 (m, 2H). MS APCI+ m/z 400 $[MH]^+$. Microanalysis: found (%) C (74.94), H (6.29), N (10.55); $C_{25}H_{25}N_3O_2$ requires: (%) C (75.16), H (6.31), N (10.52)

Preparation 93

2-[3-(4-Ethoxy-phenyl)-[1,2,4]triazol-4-yl]-5-methyl-phenol

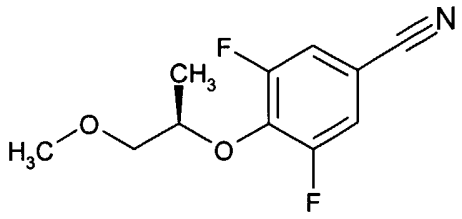


The benzyl-protected alcohol of preparation 92 (290mg, 0.73mmol) and 10% Pd/C (30mg) was added to ethanol (10mL) and the mixture was stirred under 60psi of hydrogen gas for 18 hours. The reaction mixture was then filtered through Arbocel®, washing through with ethanol, and the filtrate was evaporated under reduced pressure. The residue was taken up in dichloromethane and 1N sodium hydroxide and the aqueous layer was separated, acidified with concentrated hydrochloric acid and extracted with dichloromethane. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated *in vacuo* to yield the title product, 208mg, (93%).

^{1}H NMR(DMSO-D_6, 400MHz) δ: 1.35(t, 3H), 2.22(s, 3H), 2.34(s, 3H), 3.93(q, 2H), 6.61-6.72 (m, 5H), 7.26-7.33(m, 3H). MS APCI+ m/z 310 $[MH]^+$

Preparation 94

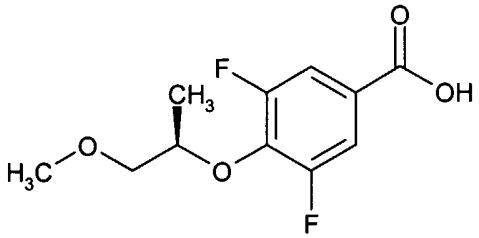
3,5-Difluoro-4-(2-methoxy-(1*R*)-methyl-ethoxy)-benzonitrile



3,4,5-Trifluorobenzonitrile (5g, 31.83mmol) and (2*R*)-1-methoxy-propan-2-ol (3.44g, 38.2mmol) were dissolved in tetrahydrofuran (60mL) and cooled to –5°C. Sodium hydride (60% dispersion in mineral oil, 1.53g, 38.20mmol) was slowly added and the mixture was stirred for 1 hour. The reaction vessel was then warmed to room temperature and stirring continued for a further for 18 hours. The solvent was evaporated under reduced pressure and the residue was partitioned between dichloromethane (200mL) and water (200mL). The organic phase was washed with brine, dried over sodium sulfate and was concentrated *in vacuo* to form an oily residue. The residue was then azeotroped with pentane (x5) and dichloromethane (x5) to give the title compound as a pale yellow oil in 94% yield (6.8g). ^{1}H NMR($CDCl_3$, 400MHz) δ: 1.38(d, 3H), 3.37(s, 3H), 3.53(m, 1H), 3.59(m, 1H), 4.60 (m, 1H), 7.21(d, 2H)

Preparation 95

3,5-Difluoro-4-(2-methoxy-1-methyl-ethoxy)-benzoic acid

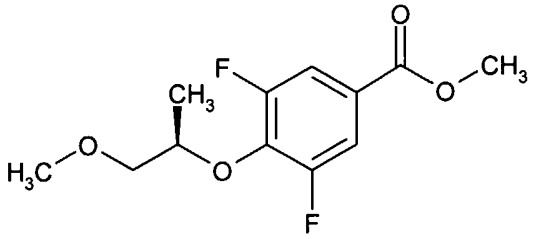


The product of preparation 94 (6.8g, 29.9mmol), and hydrochloric acid (20%, 60mL) were heated under reflux in acetic acid (60mL) for 42 hours. The reaction mixture was then concentrated under reduced pressure to a low volume (20mL) and was partitioned between ethyl acetate (100mL) and water (100mL). The organic layer was washed with potassium carbonate solution (10%, 2x100mL) and the aqueous washings were acidified with 2N hydrochloric acid and extracted with dichloromethane (3x100mL). The combined organic extracts were washed with brine, dried over magnesium sulfate and concentrated *in vacuo* to give the title compound as a gum in 75% yield (5.5g).

^{1}H NMR($CDCl_3$, 400MHz) δ: 1.38(d, 3H), 3.40(s, 3H), 3.56(m, 1H), 3.63(m, 1H), 4.65(m, 1H), 7.64(d, 2H). MS APCI+ m/z 264 [MNH_4^+]

Preparation 96

3,5-Difluoro-4-(2-methoxy-1-methyl-ethoxy)-benzoic acid methyl ester

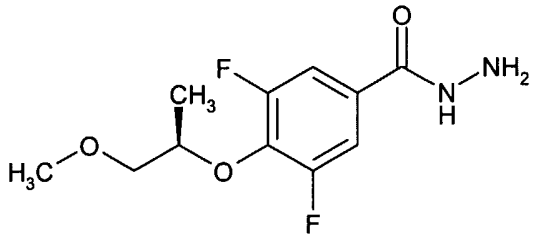


The title compound was prepared from the product of preparation 95 using the method described for preparation 23. Purification by column chromatography on silica gel, eluting with pentane:diethyl diethyl ether, 100:0 to 90:10, gave a crude compound that was azeotroped with dichloromethane (5x50mL) to produce the title product as a clear oil in 65% yield, (3.8g).

^{1}H NMR($CDCl_3$, 400MHz) δ: 1.37(d, 3H), 3.39(s, 3H), 3.56(m, 1H), 3.61(m, 1H), 3.91 (s, 3H), 4.58(m, 1H), 7.60(d, 2H). MS APCI+ m/z 278 [MNH_4^+]

Preparation 97

3,5-Difluoro-4-(2-methoxy-1-methyl-ethoxy)-benzoic acid hydrazide

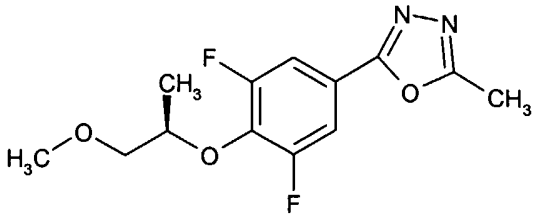


The title compound was prepared from the product of preparation 96 using the method described for preparation 30, as a white solid in 57% yield.

^{1}H NMR($CDCl_3$, 400MHz) δ: 1.37(d, 3H), 3.38(s, 3H), 3.52(m, 1H), 3.60(m, 1H), 4.09(brs, 2H), 4.58(m, 1H), 7.35(d, 2H), 7.44(brs, 1H). MS APCI+ m/z 261 [MH^+]

Preparation 98

2-[3,5-Difluoro-4-(2-methoxy-1-methyl-ethoxy)-phenyl]-5-methyl-[1,3,4]oxadiazole

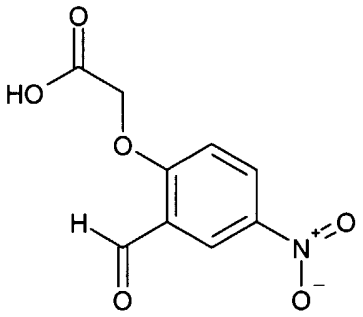


The title compound was prepared from the product of preparation 97 using the method described for preparation 4. 280mg of the desired product were produced as a light brown gum in 98% yield.

^{1}H NMR($CDCl_3$, 400MHz) δ: 1.38(d, 3H), 2.91(s, 3H), 3.38(s, 3H), 3.52(m, 1H), 3.61(m, 1H), 4.59(m, 1H), 7.59(d, 2H). MS APCI+ m/z 211

Preparation 99

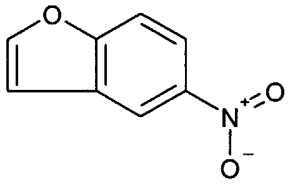
(2-Formyl-4-nitro-phenoxy)-acetic acid



O-formyl phenoxyacetic acid (100g, 0.56mol) was added to fuming nitric acid (333mL) and the solution was stirred at 0°C for 2 hours. The reaction was then quenched with hydrochloric acid/water (50:50, 2.5L) and filtered. The residue was washed with water and dried under reduced pressure to yield the title compound as a yellow powder in 90% yield. m.p. 187-190°C

Preparation 100

5-Nitro-benzofuran

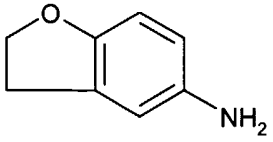


The product of preparation 100 (94.7g, 31mmol) and acetic anhydride (875mL) were heated at 60°C until the solution cleared. Anhydrous sodium acetate (94.7g, 1.15mol) was then added and heating continued for 45 minutes. The

reaction was quenched with water (12L) and the aqueous solution was basified to pH 10 with concentrated ammonium hydroxide solution and filtered. Trituration of the residue with diethyl ether (3x200mL) afforded the title compound as a pale yellow powder in 19% yield, 12.9g. m.p. 111-113°C. MS ES^+ m/z 163 $[MH]^+$

Preparation 101

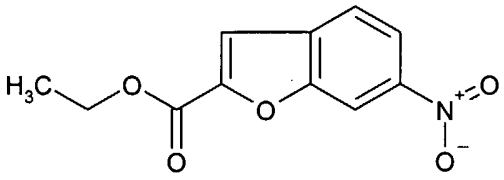
2,3-Dihydro-benzofuran-5-ylamine



The product of preparation 100 (5.0g, 31mmol) and 10% Pd/C (1.25g) was added to ethanol (100mL) and the mixture was stirred under 55psi of hydrogen gas for 5 hours. The reaction mixture was then filtered through Celite and the filtrate was concentrated *in vacuo* to afford the title product as a pale brown powder in 92% yield. MS ES^+ m/z 135 $[M^+]$. m.p. 73-77°C

Preparation 102

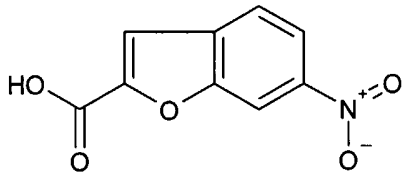
6-Nitro-benzofuran-2-carboxylic acid ethyl ester



Diethyl bromomalonate (6.31g, 26.5mmol) and potassium carbonate (3g, 21.7mmol) were added to a solution of 2-hydroxy-4-nitro-benzaldehyde [(4.27g, 29.5mmol) *Eur. J. Med. Chem*] in 2-butanone (12.5mL) and the mixture was heated under reflux for 90 minutes. The reaction mixture was then evaporated under reduced pressure and the residue was diluted with water (50mL) and extracted with ethyl acetate (3x25mL). The combined organic extracts were dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by column chromatography on silica gel, eluting with hexane:ethyl acetate, 83:17, afforded the title compound as a yellow solid in 40% yield, 2.1g. MS EI^+ m/z 236 $[MH]^+$

Preparation 103

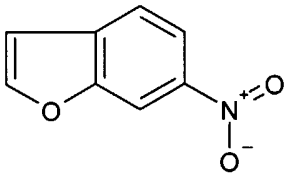
6-Nitro-benzofuran-2-carboxylic acid



The product of preparation 102 (3.5g, 14.9mmol) and potassium hydroxide (880mg, 15.6mmol) were heated under reflux in ethanol (52mL) for one hour. The mixture was then treated with further potassium hydroxide (613mg, 10.9mmol), and heating continued for a further 30 minutes. The solvent was evaporated under reduced pressure and the residue was dissolved in water (50mL) and acidified to pH4 with concentrated hydrochloric acid. The resulting precipitate was collected by filtration, washed with water and dried to yield the title compound as a pale brown solid in 92% yield.

Preparation 104

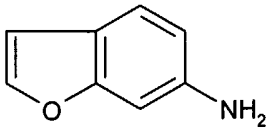
6-Nitro-benzofuran



The product of preparation 103 (3.8g, 18.3mmol), and copper powder (1.14g, 17.9mmol) were thoroughly mixed together and added to quinoline (22.5mL). The mixture was heated at 200°C for 15 minutes, cooled to room temperature and filtered through celite washing through with ethyl acetate (3x50mL). The filtrate was partitioned between ethyl acetate (150mL) and 2N hydrochloric acid (150mL) and the aqueous layer was separated and re-extracted with ethyl acetate (4x35mL). The organic layers were combined, dried over magnesium sulfate and concentrated *in vacuo* to yield a dark brown solid. Purification by column chromatography on silica gel, eluting with of the solid by column chromatography on silica gel, eluting with hexane:ethyl acetate, 85:15, afforded the title compound as a yellow solid in 63% yield.

Preparation 105

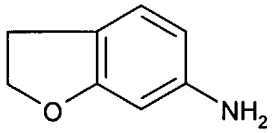
Benzofuran-6-ylamine



The product of preparation 104 (1.88g, 11.4mmol), N,N- dimethylhydrazine (7.2g, 120mmol) and iron chloride (41mg, 0.15mmol) were suspended in ethanol (30mL) and heated under reflux for 20 hours. The reaction mixture was then filtered through celite washing through with ethanol (4x10mL). The filtrate was dried over magnesium sulfate and evaporated under reduced pressure. Purification of the residue by column chromatography on silica gel, eluting with hexane:ethyl acetate, 75:25, afforded the title compound as a white solid in 79% yield

Preparation 106

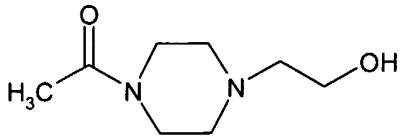
2,3-Dihydro-benzofuran-6-ylamine



The product of preparation 105 (600mg, 4.5mmol) and 10% Pd/C (600mg) was added to ethanol (10mL) and the mixture was stirred under 55psi of hydrogen gas for 30 minutes. The reaction mixture was then filtered through celite, washing through with dichloromethane and the filtrate was concentrated *in vacuo* to afford the title product as a clear crystalline solid in 99% yield.

Preparation 107

1-[4-(2-Hydroxy-ethyl)-piperazin-1-yl]-ethanone

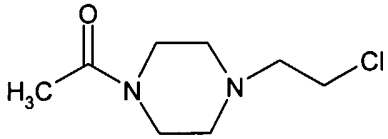


N-(2-Hydroxyethyl) piperazine (7.81g, 60mmol) and triethylamine (8.36mL, 66mmol) were dissolved in dichloromethane (100mL). Acetyl chloride (9.3mL, 60mmol) in dichloromethane (20mL) was added and the mixture was stirred for 2

hours at room temperature. The solvent was then evaporated under reduced pressure and the residue was dissolved in diethyl ether, dried over magnesium sulfate, and concentrated *in vacuo* to afford the title compound as a colourless oil in 73% yield.

Preparation 108

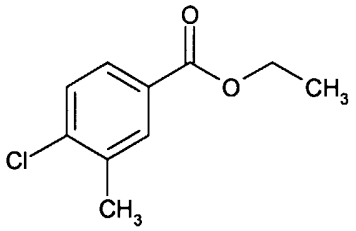
1-[4-(2-Chloro-ethyl)-piperazin-1-yl]-ethanone



The product of preparation 107 (3g, 17.4mmol) was dissolved in chloroform (30mL), and the resulting solution was cooled to 0°C. Thionyl chloride (10mL) was added over 20 minutes and the reaction mixture was heated under reflux for 90 minutes. The solvent was then evaporated under reduced pressure and the residue was stirred in acetone (100mL) to give a brown precipitate. The precipitate was filtered off and re-crystallised from ethanol:ethyl acetate, 33:66, to afford the title compound as a solid in 54% yield. m.p. 215-218°C

Preparation 109

4-Chloro-3-methyl-benzoic acid ethyl ester

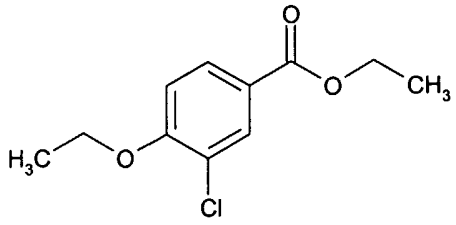


Ethyl iodide (1.4mL, 17.6mmol) and potassium carbonate (6g, 44mmol) were added to a solution of 4-chloro-3-methylbenzoic acid (1.5g, 8.8mmol) in N,N-dimethylformamide (15mL) and the mixture was stirred for 18 hours at room temperature. The reaction mixture was then diluted with water and extracted with ethyl acetate. The organic solution was dried over magnesium sulfate and concentrated *in vacuo* to afford the title compound in 98% yield, 1.7g.

^{1}H NMR (400MHz, $CDCl_3$) δ: 1.40(t, 3H), 2.42(s, 3H), 4.36(q, 2H), 7.38(d, 1H), 7.78(dd, 1H), 7.91(d, 1H)

Preparation 110

3-Chloro-4-ethoxy-benzoic acid ethyl ester

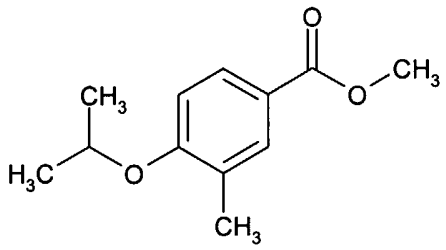


The title compound was prepared from ethyl 3-chloro-4-hydroxybenzoate and ethyl iodide, using the method described for preparation 109, as a white crystalline solid in 54% yield.

^{1}H NMR (400MHz, $CDCl_3$) δ: 1.40(t, 3H), 1.50(t, 3H), 4.18(q, 2H), 6.93(d, 1H), 7.92(dd, 1H), 8.04(d, 1H); LRMS ESI m/z 229 $[M+H]^+$

Preparation 111

4-Isopropoxy-3-methyl-benzoic acid methyl ester

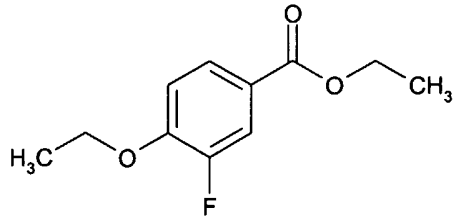


The title compound was prepared from methyl 3-methyl-4-hydroxybenzoate (*J. Am Chem Soc*, 1979,101(23), 7001) and 2-bromopropane, using the method of preparation 109, as a light brown liquid in quantitative yield.

^{1}H NMR (400MHz, $CDCl_3$) δ: 1.28(d, 6H), 2.14(s, 3H), 3.78(s, 3H), 4.56(m, 1H), 6.75(d, 1H), 7.75(m, 2H)

Preparation 112

4-Ethoxy-3-fluoro-benzoic acid ethyl ester



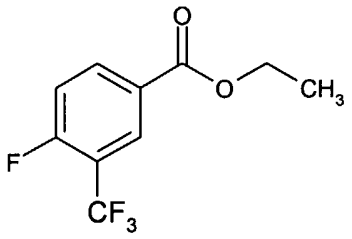
Ethyl iodide (10.5mL, 128mmol) and potassium carbonate (44g, 320mmol) were added to a solution of 3-fluoro-4-hydroxybenzoic acid (5g, 32mmol) in N,N-

dimethylformamide (50mL) and the mixture was stirred for 18 hours at room temperature. The reaction mixture was then diluted with water and extracted with ethyl acetate. The organic solution was dried over magnesium sulfate and concentrated *in vacuo* to afford the title compound in 80% yield, 5.42g.

^{1}H NMR (400MHz, $CDCl_3$) δ: 1.39(t, 3H), 1.44(t, 3H), 4.18(q, 2H), 4.37(q, 2H), 6.97(m, 1H), 7.77(dd, 1H), 7.80(d, 1H); LRMS ESI m/z 235 $[M+Na]^+$

Preparation 113

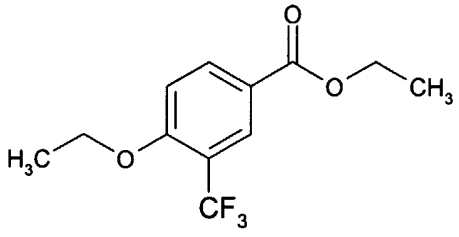
4-Fluoro-3-trifluoromethyl-benzoic acid ethyl ester



Concentrated sulfuric acid (0.3mL) was added to a solution of 4-fluoro-3-(trifluoromethyl)benzoic acid (10g, 48mmol) in ethanol (70mL) and the resulting mixture was heated under reflux for 18 hours. The solvent was then evaporated under reduced pressure and the residue was dissolved in ethyl acetate (150mL) and washed with sodium hydrogen carbonate solution and brine. The organic solution was dried over magnesium sulfate and concentrated *in vacuo* to give a brown liquid. The liquid was purified by column chromatography on silica gel, eluting with ethyl acetate:pentane, 10:90, to afford the title compound as a colourless oil in 74% yield 7.9g. ^{1}H NMR (400MHz, $CDCl_3$) δ: 1.40(t, 3H), 4.40(q, 2H), 7.25(m, 1H), 8.25(m, 1H), 8.32(d, 1H)

Preparation 114

4-Ethoxy-3-trifluoromethyl-benzoic acid ethyl ester



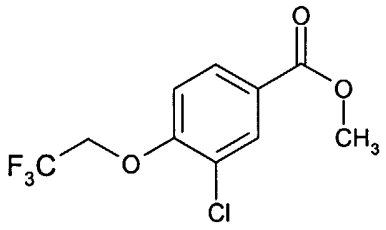
The product of preparation 113 (7.8g, 34mmol) was added to an ice-cold suspension of sodium (2g, 87mmol) in ethanol (200mL) and the mixture was

heated under reflux for 42 hours. The reaction mixture was then concentrated *in vacuo* and the residue was partitioned between dichloromethane and water. The organic solution was then separated, dried over magnesium sulfate and concentrated *in vacuo* to afford the title compound in 36% yield, 3.2g.

^{1}H NMR (400MHz, $CDCl_3$) δ: 1.40(t, 3H), 1.48(t, 3H), 4.20(q, 2H), 4.38(q, 2H), 7.00(d, 1H), 8.18(dd, 1H), 8.26(d, 1H); LRMS ESI m/z 263 $[M+H]^+$

Preparation 115

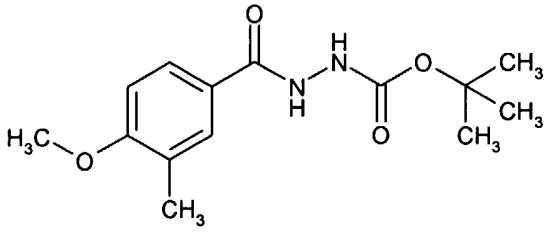
3-Chloro-4-(2,2,2-trifluoro-ethoxy)-benzoic acid methyl ester



A mixture of methyl 3-chloro-4-hydroxybenzoate (1g, 5.4mmol), 1,1,1-trifluoro-2-iodoethane (1.04mL, 10.8mmol) and sodium hydride (60% dispersion in mineral oil 886mg, 22.1mmol) in N,N-dimethylformamide (10mL) was stirred for 18 hours at room temperature. The mixture was then partitioned between ethyl acetate and water and the organic layer was separated, washed with brine, dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with dichloromethane:methanol, 100:0 to 97.5:2.5, to afford the title compound in 35% yield, 0.5g. ^{1}H NMR (400MHz, $CDCl_3$) δ: 3.90(s, 3H), 4.85(m, 2H), 6.98(d, 1H), 7.90(dd, 1H), 8.07(d, 1H)

Preparation 116

tert-Butyl 2-(4-methoxy-3-methylbenzoyl)hydrazinecarboxylate

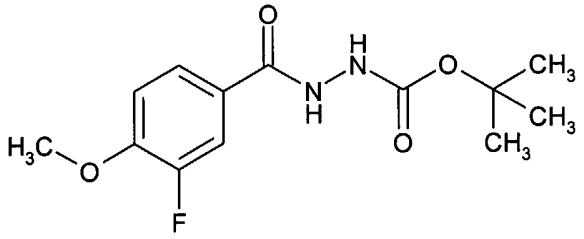


A mixture of 4-methoxy-2-methylbenzoic acid (5g, 30.12mmol), *tert*-butyl carbazate (3.97g, 30.12mmol) and 1-(3-dimethylaminopropyl)-3-

ethylcarbodiimide (11.54g, 60.24mmol) in N,N-dimethylformamide (50mL) was stirred at room temperature for 20 hours. The mixture was then diluted with saturated sodium hydrogen carbonate solution (150mL) and extracted with diethyl ether (3x100mL). The combined organic solution was dried over magnesium sulfate and concentrated *in vacuo* to afford the title compound in 80% yield, 6.71g. ^{1}H NMR (400MHz, $CDCl_3$) δ: 1.25(s, 9H), 2.25(s, 3H), 3.80(s, 3H), 6.75(m, 2H), 7.45(dd, 1H); LRMS ESI m/z 303 $[M+H]^+$

Preparation 117

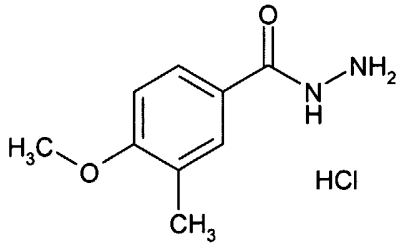
tert-Butyl 2-(3-fluoro-4-methoxybenzoyl)hydrazinecarboxylate



The title compound was prepared from 2-fluoro-4-methoxybenzoic acid and *tert*-butyl carbazate, using a method similar to that used for preparation 116, in 42% yield. ^{1}H NMR (400MHz, $CDCl_3$) δ: 1.41(s, 9H), 3.80(s, 3H), 6.80(m, 2H), 8.05(dd, 1H); LRMS ESI m/z 307 $[M+Na]^+$

Preparation 118

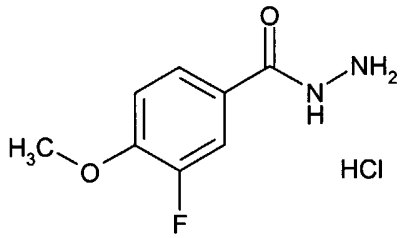
4-Methoxy-3-methyl-benzoic acid hydrazide hydrochloride



A solution of the product of preparation 116 (8.43g, 30.12mmol) in ethyl acetate (100mL) was added to hydrochloric acid (4N in dioxane, 100mL) and the mixture was stirred at room temperature for 18 hours. The reaction mixture was then concentrated *in vacuo* to afford the title compound as a solid in quantitative yield, 6.49g. ^{1}H NMR (400MHz, $CDCl_3$) δ: 2.40(s, 3H), 3.80(s, 3H), 6.80(m, 2H), 7.50(m, 1H); LRMS ESI m/z 181 $[M+H]^+$

Preparation 119

3-Fluoro-4-methoxy-benzoic acid hydrazide hydrochloride

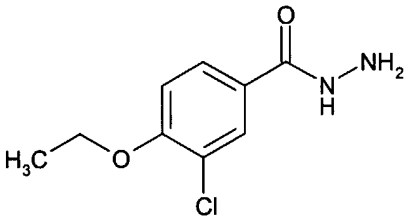


The title compound was prepared from the product of preparation 117, using the method used for preparation 118, in quantitative yield, 2.58g.

^{1}H NMR (400MHz, $CDCl_3$) δ: 3.80(s, 3H), 6.90(m, 2H), 7.70(m, 1H)

Preparation 120

3-Chloro-4-ethoxy-benzoic acid hydrazide

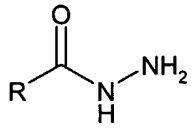


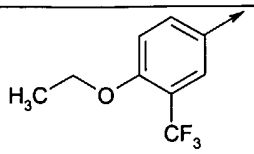
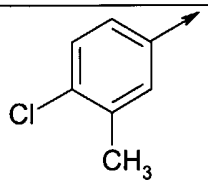
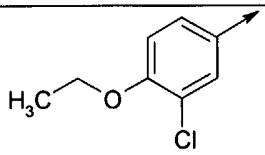
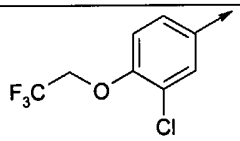
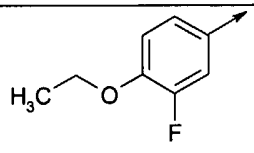
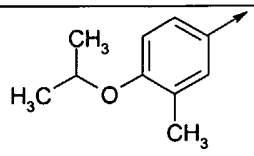
Hydrazine monohydrate (3.5mL, 72mmol) was added to a solution of ethyl-3-chloro-4-ethoxybenzoate (5.2g, 22mmol) in methanol (35mL) and the mixture was heated under reflux for 18 hours. The reaction mixture was then cooled in an ice bath and the precipitate that formed was filtered off, washed with diethyl ether and dried to afford the title compound as a white powder in quantitative yield.

^{1}H NMR (400MHz, DMSO-d_6) δ: 1.38(t, 3H), 3.30(bs, 2H), 4.17(q, 2H), 7.18(d, 1H), 7.78(dd, 1H), 7.86(d, 1H), 9.72(1H, bs); LRMS ESI m/z 215 $[M+H]^+$

Preparations 121 to 126

The following compounds, of the general formula shown below, were prepared by the method described for preparation 120, using the appropriate ester and hydrazine monohydrate as outlined in the table below.



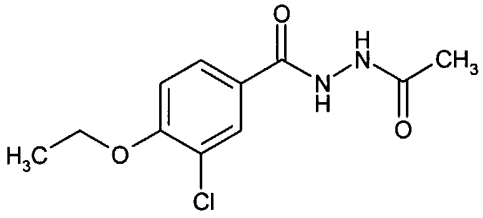
No.	R	Data	Yield
121	 Prepared from the compound of preparation 114	^{1}H NMR (400MHz, DMSO-d_6) δ: 1.37(t, 3H), 4.20(q, 2H), 4.50(bs, 2H), 7.30(d, 1H), 8.08(m, 2H), 9.82(1H, bs); LRMS ESI m/z 249 $[M+H]^+$	Quant
122	 Prepared from the compound of preparation 109	^{1}H NMR (400MHz, DMSO-d_6) δ: 2.35(s, 3H), 7.47(d, 1H), 7.62(dd, 1H), 7.78(d, 1H), 9.70-9.90(bs, 1H); LRMS ESI m/z 183 $[M-H]^-$	82%
123	 Prepared from the compound of preparation 110	^{1}H NMR (400MHz, DMSO-d_6) δ: 1.38(t, 3H), 3.35(bs, 2H), 4.16(q, 2H), 7.18(d, 1H), 7.78(dd, 1H), 7.96(d, 1H), 9.72(1H, bs); LRMS ESI m/z 215 $[M+H]^+$	67%
124	 Prepared from the compound of preparation 115	^{1}H NMR (400MHz, DMSO-d_6) δ: 4.95(q, 2H), 7.35(d, 1H), 7.84(dd, 1H), 7.95(d, 1H); LRMS ESI m/z 267 $[M-H]^-$	Quant
125	 Prepared from the compound of preparation 112	^{1}H NMR (400MHz, DMSO-d_6) δ: 1.38(t, 3H), 4.17(q, 2H), 4.42(bs, 2H), 7.20(m, 1H), 7.61(s, 1H), 7.63(m, 1H), 9.68(s, 1H); LRMS ESI m/z 221 $[M+Na]^+$	85%
126		^{1}H NMR (400MHz, DMSO-d_6) δ: 1.26(d, 6H), 2.10(s, 3H), 4.38(bs, 2H), 4.64(m, 1H), 6.95(m, 1H), 7.60(m, 2H); LRMS ESI m/z 231	53%

	Prepared from the compound of preparation 111	$[M+Na]^+$	

Preparation 126: further hydrazine monohydrate (0.5eq) added after heating under reflux for 18 hours. Heated then resumed for an additional 6 hours.

Preparation 127

3-Chloro-4-ethoxy-benzoic acid N'-acetyl-hydrazide

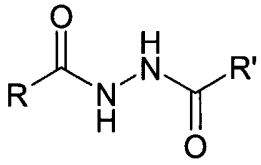


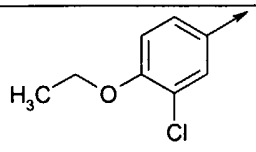
Acetyl chloride (1mL, 14mmol) was added to an ice-cold solution of the product of preparation 123 (2g, 9.35mmol) and *N*-methylmorpholine (1.54mL, 14mmol) in dichloromethane (50mL) and the mixture was stirred for 18 hours at room temperature. The resulting precipitate was filtered off and dried to afford the title compound in 92% yield.

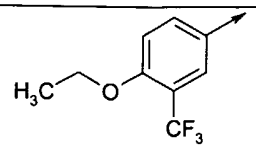
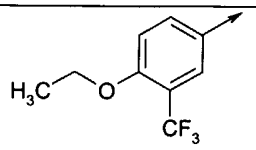
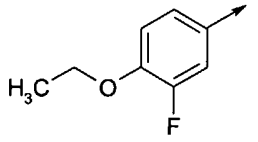
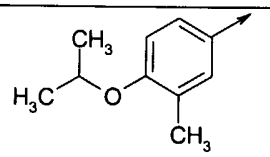
^{1}H NMR (400MHz, DMSO-d_6) δ: 1.38(t, 3H), 1.90(s, 3H), 4.20(q, 2H), 7.22(d, 1H), 7.82(dd, 1H), 7.92(d, 1H), 9.95(1H, s), 10.22(1H, s); LRMS ESI m/z 257 $[M+H]^+$

Preparations 128 to 132

The following compounds, of the general formula shown below, were prepared by the method described for preparation 127 using the appropriate hydrazide and acid chloride as outlined in the table below.

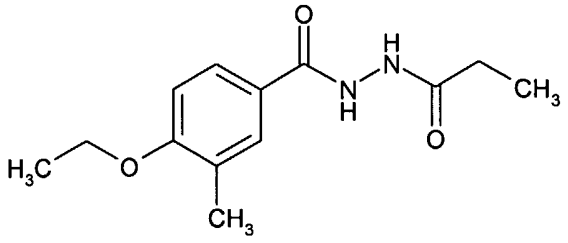


No.	R	R'	Data	Yield
128	 Prepared from the	CH_2OCH_3	^{1}H NMR (400MHz, DMSO-d_6) δ: 1.38(t, 3H), 3.36(s, 3H), 3.95(s, 2H), 4.18(q, 2H), 7.24(d, 1H), 7.84(dd, 1H),	90%

	compound of preparation 123 and methoxyacetyl chloride		7.94(d, 1H), 9.94(1H, s), 10.28(1H, s); LRMS ESI m/z 287 $[M+H]^+$	
129	 Prepared from the compound of preparation 121 and acetyl chloride	CH_3	^{1}H NMR (400MHz, DMSO-d_6) δ: 1.38(t, 3H), 1.92(s, 3H), 4.22(q, 2H), 7.38(d, 1H), 8.16(m, 2H), 9.90(1H, s), 10.38(1H, s); LRMS ESI m/z 290 $[M+H]^+$	45%
130	 Prepared from the compound of preparation 121 and methoxyacetyl chloride	CH_2OCH_3	^{1}H NMR (400MHz, DMSO-d_6) δ: 1.38(t, 3H), 3.38(s, 3H), 3.95(s, 2H), 4.25(q, 2H), 7.40(d, 1H), 8.18(m, 2H), 9.96(1H, s), 10.44(1H, s); LRMS ESI m/z 321 $[M+H]^+$	70%
131	 Prepared from the compound of preparation 125 and methoxyacetyl chloride	CH_2OCH_3	^{1}H NMR (400MHz, DMSO-d_6) δ: 1.39(t, 3H), 3.38(s, 3H), 3.96(s, 2H), 4.18(q, 2H), 7.25(m, 1H), 7.70(m, 2H), 9.85(s, 1H), 10.25(s, 1H); LRMS ESI m/z 269 $[M-H]^-$	70%
132	 Prepared from the compound of preparation 126 and methoxyacetyl chloride	CH_2OCH_3	^{1}H NMR (400MHz, $CDCl_3$) δ: 1.36(d, 6H), 2.20(s, 3H), 3.50(s, 3H), 4.08(s, 2H), 4.60(m, 1H), 6.82(d, 1H), 7.64(m, 2H), 8.64(d, 1H), 9.08(d, 1H); LRMS ESI m/z 303 $[M+Na]^+$	71%

Preparation 133

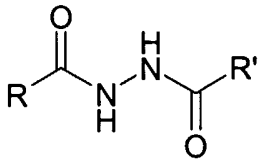
4-Ethoxy-3-methyl-benzoic acid N'-propionyl-hydrazide

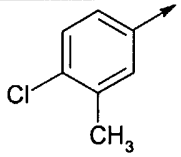


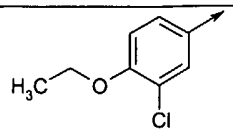
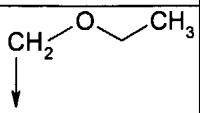
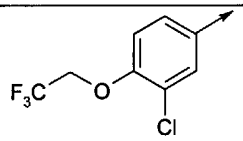
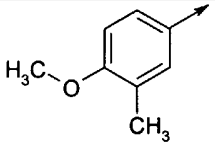
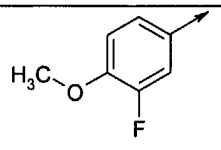
Propionyl chloride (394μL, 4.54mmol) was added to an ice-cold solution of the product of preparation 34 (800mg, 4.12mmol) and triethylamine (1.15mL, 8.25mmol) in dichloromethane (10mL) and the mixture was stirred for 3 hours at room temperature. Further propionyl chloride (200μL, 2.30mmol) was then added and the reaction mixture was stirred for an additional 18 hours at room temperature. The mixture was then diluted with water and the aqueous layer was separated and re-extracted with dichloromethane (2x10mL). The combined organic solution was washed with brine, dried over sodium sulfate and concentrated *in vacuo*. Purification of the residue by column chromatography on silica gel, eluting with dichloromethane:methanol, 100:0 to 95:5, afforded the title compound in quantitative yield. ^{1}H NMR (400MHz, $CDCl_3$) δ: 1.20(t, 3H), 1.43(t, 3H), 2.20(s, 3H), 2.34(q, 2H), 4.05(q, 2H), 6.77(d, 1H), 7.59-7.66(m, 2H), 9.01(1H, bs), 9.16(1H, bs); LRMS APCI m/z 251 $[M+H]^+$

Preparations 134 to 138

The following compounds, of the general formula shown below, were prepared by the method described for preparation 133, using the appropriate hydrazide and acid chloride as outlined in the table below.

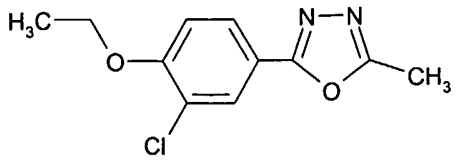


No.	R	R'	Data	Yield
134		CH_2OCH_3	^{1}H NMR (400MHz, $CDCl_3$) δ: 2.38(s, 3H), 3.50(s, 3H), 4.10(s, 2H), 7.38(d, 1H),	64%

	Prepared from the compound of preparation 122 and methoxyacetyl chloride		7.56(dd, 1H), 7.68(d, 1H), 9.04(d, 1H), 9.70-9.90(d, 1H); LRMS ESI m/z 183 $[M-H]^-$	
135	 Prepared from the compound of preparation 123 and ethoxyacetyl chloride		^{1}H NMR (400MHz, $CDCl_3$) δ: 1.17(t, 3H), 1.38(t, 3H), 3.55(q, 2H), 3.96(s, 2H), 4.20(q, 2H), 7.25(d, 1H), 7.84(dd, 1H), 7.95(d, 1H); LRMS ESI m/z 301 $[M+H]^+$	78%
136	 Prepared from the compound of preparation 124 and methoxyacetyl chloride	CH_2OCH_3	^{1}H NMR (400MHz, $CDCl_3$) δ: 3.45(s, 3H), 4.00(s, 2H), 4.50(m, 2H), 7.20(d, 1H), 7.88(dd, 1H), 7.91(d, 1H); LRMS ESI m/z 339 $[M-H]^-$	99%
137	 Prepared from the compound of preparation 118 and methoxyacetyl chloride	CH_2OCH_3	^{1}H NMR (400MHz, $CDCl_3$) δ: 2.40(s, 3H), 3.50(s, 3H), 3.80(s, 3H), 4.50(s, 2H), 6.80(m, 2H), 7.40(m, 1H); LRMS ESI m/z 275 $[M+Na]^+$	Quant
138	 Prepared from the compound of preparation 119 and methoxyacetyl chloride	CH_2OCH_3	^{1}H NMR (400MHz, $CDCl_3$) δ: 3.50(s, 3H), 3.85(s, 3H), 4.50(s, 2H), 7.10(m, 2H), 7.80(m, 1H); LRMS ESI m/z 279 $[M+Na]^+$	Quant

Preparation 139

2-(3-Chloro-4-ethoxy-phenyl)-5-methyl-[1,3,4]oxadiazole

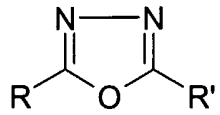


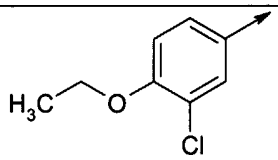
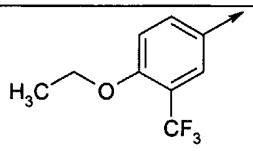
A mixture of the product of preparation 127 (2g, 7mmol) and phosphorus oxychloride (15mL) was heated at 110°C for 2 hours. The reaction mixture was then concentrated *in vacuo* and the residue was partitioned between ethyl acetate and saturated sodium hydrogen carbonate solution. The organic layer was separated, dried over magnesium sulfate and concentrated *in vacuo* to afford the title compound as a foam in 60% yield, 1g

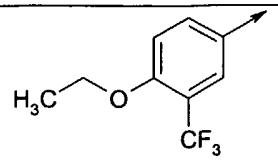
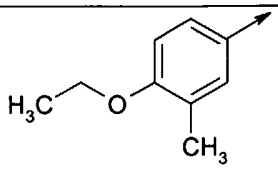
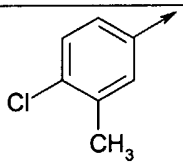
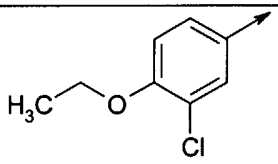
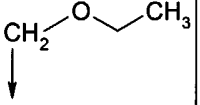
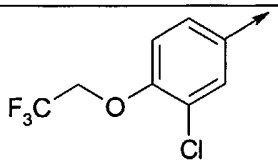
^{1}H NMR (400MHz, $CDCl_3$) δ: 1.52(t, 3H), 2.61(s, 3H), 4.20(q, 2H), 7.01(d, 1H), 7.92(dd, 1H), 8.04(d, 1H); LRMS ESI m/z 239 $[M+H]^+$

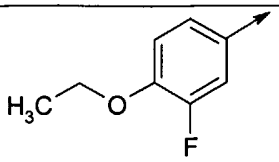
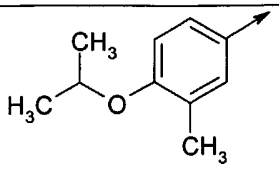
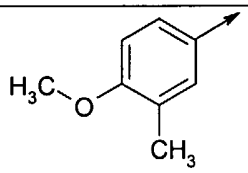
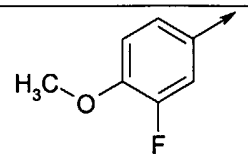
Preparations 140 to 150

The following compounds, of the general formula shown below, were prepared by the method described for preparation 139 using the appropriate hydrazide and phosphorus oxychloride as outlined in the table below.



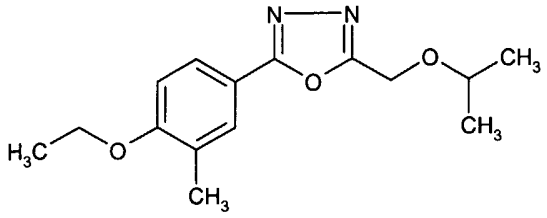
No.	R	R'	Data	Yield
140	 Prepared from the compound of preparation 128	CH_2OCH_3	^{1}H NMR (400MHz, $CDCl_3$) δ: 1.52(t, 3H), 3.50(s, 3H), 4.18(q, 2H), 4.76(s, 2H), 7.20 (d, 1H), 7.95(dd, 1H), 8.05(d, 1H); LRMS ESI m/z 269 $[M+H]^+$	72%
141	 Prepared from the compound of	CH_3	^{1}H NMR (400MHz,$CDCl_3$) δ: 1.50(t, 3H), 2.62(s, 3H), 4.20(q, 2H), 7.10(d, 1H), 8.20(m, 2H); LRMS ESI m/z 273 $[M+H]^+$	92%

	preparation 129			
142	 Prepared from the compound of preparation 130	CH_2OCH_3	^{1}H NMR (400MHz, DMSO-d_6) δ: 1.50(t, 3H), 3.50(s, 3H), 4.20(q, 2H), 4.65(s, 2H), 7.10(d, 1H), 8.22(d, 1H), 8.30(1H, s); LRMS ESI m/z 325 $[M+Na]^+$	85%
143	 Prepared from the compound of preparation 133	CH_2CH_3	^{1}H NMR (400MHz, $CDCl_3$) δ: 1.42(t, 3H), 1.45(t, 3H), 2.26(s, 3H), 2.92(q, 2H), 4.09(q, 2H), 6.87(d, 1H), 7.79-7.83(m, 2H); LRMS APCI m/z 233 $[M+H]^+$	70%
144	 Prepared from the compound of preparation 134	CH_2OCH_3	^{1}H NMR (400MHz, $CDCl_3$) δ: 2.44(s, 3H), 3.50(s, 3H), 4.75(s, 2H), 7.48(d, 1H), 7.84(dd, 1H), 7.96(d, 1H); LRMS ESI m/z 239 $[M+H]^+$	73%
145	 Prepared from the compound of preparation 135		^{1}H NMR (400MHz, $CDCl_3$) δ: 1.25(t, 3H), 1.55(t, 3H), 3.66(q, 2H), 4.18(q, 2H), 4.76(s, 2H), 7.01(d, 1H), 7.95(dd, 1H), 8.08(d, 1H); LRMS ESI m/z 305 $[M+Na]^+$	41%
146	 Prepared from the compound of preparation 136	CH_2OCH_3	^{1}H NMR (400MHz, $CDCl_3$) δ: 3.45(s, 3H), 4.50(q, 2H), 4.70(s, 2H), 7.08(d, 1H), 7.98(dd, 1H), 8.16(d, 1H); LRMS ESI m/z 323 $[M+H]^+$	74%

147	 Prepared from the compound of preparation 131	CH_2OCH_3	^{1}H NMR (400MHz, $CDCl_3$) δ: 1.50(t, 3H), 3.50(s, 3H), 4.19(q, 2H), 4.70(s, 2H), 7.05(m, 1H), 7.80(m, 2H); LRMS ESI m/z 275 $[M+Na]^+$	94%
148	 Prepared from the compound of preparation 13	CH_2OCH_3	^{1}H NMR (400MHz, $CDCl_3$) δ: 1.40(d, 6H), 2.24(s, 3H), 3.48(s, 3H), 4.64(m, 1H), 4.72(s, 2H), 6.90(d, 1H), 7.86(m, 2H); LRMS ESI m/z 285 $[M+Na]^+$	64%
149	 Prepared from the compound of preparation 137	CH_2OCH_3	^{1}H NMR (400MHz, $CDCl_3$) δ: 2.65(s, 3H), 3.50(s, 3H), 3.85(s, 3H), 4.70(s, 2H), 6.80(m, 2H), 8.00(m, 1H); LRMS ESI m/z 235 $[M+H]^+$	30%
150	 Prepared from the compound of preparation 138	CH_2OCH_3	^{1}H NMR (400MHz, $CDCl_3$) δ: 3.50(s, 3H), 3.90(s, 3H), 4.70(s, 2H), 6.80(m, 2H), 7.90(m, 1H); LRMS ESI m/z 239 $[M+H]^+$	26%

Preparation 151

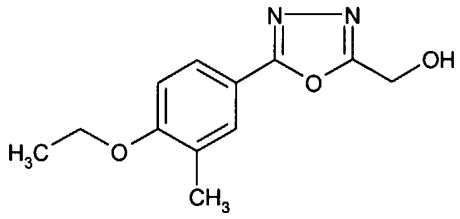
2-(4-Ethoxy-3-methyl-phenyl)-5-isopropoxymethyl-[1,3,4]oxadiazole



Isopropanol (3.6mL, 47.5mmol) was added to a suspension of sodium hydride (60% dispersion in mineral oil, 1.9g, 47.5mmol) in N,N-dimethylformamide (40mL) at 0°C. The reaction mixture was then allowed to warm to room temperature and was stirred for 30 minutes. A solution of the product of preparation 53 (8g, 31.7mmol) in N,N-dimethylformamide (10mL) was added and the mixture was stirred at room temperature for 18 hours. The reaction mixture was then diluted with water and extracted with ethyl acetate (3x50mL). The combined organic layer was washed with brine (2x50mL), dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by column chromatography on silica gel, eluting with petroleum ether:ethyl acetate, 75:25, then afforded the title compound in 18% yield, 1.1g.

Preparation 152

[5-(4-Ethoxy-3-methyl-phenyl)-[1,3,4]oxadiazol-2-yl]-methanol

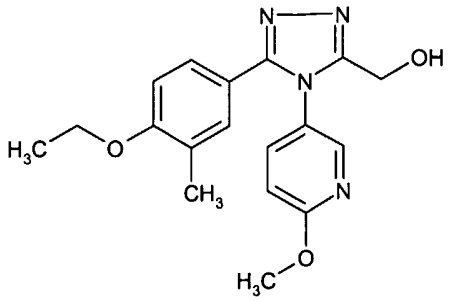


The title compound was prepared from the product of preparation 53, using the method of preparation 58, as a white solid in 97% yield.

^{1}H NMR (400MHz, $CDCl_3$) δ: 1.45(t, 3H), 2.27(s, 3H), 3.30-3.40(t, 1H), 4.10(q, 2H), 4.93(d, 2H), 6.80-6.90(m, 1H), 7.80-7.85(m, 2H); LRMS APCI m/z 235 $[M+H]^+$

Preparation 153

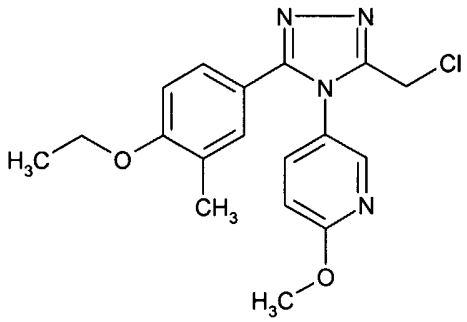
[5-(4-Ethoxy-3-methyl-phenyl)-4-(6-methoxy-pyridin-3-yl)-4H-[1,2,4] triazol-3-yl]-methanol



The title compound was prepared form the product of preparation 152 and 5-amino-2-methoxypyridine, using the method of example 74, as a white solid in 69% yield. ^{1}H NMR (400MHz, $CDCl_3$) δ: 1.41(t, 3H), 2.10(s, 3H), 3.95-4.05(m, 5H), 4.60-4.70(m, 3H), 6.63(d, 1H), 6.83(d, 1H), 7.00(d, 1H), 7.25(s, 1H), 7.65(d, 1H), 8.10(s, 1H); LRMS APCI m/z 341 $[M+H]^+$

Preparation 154

5-[3-Chloromethyl-5-(4-ethoxy-3-methyl-phenyl)-[1,2,4]triazol-4-yl]-2-methoxy-pyridine

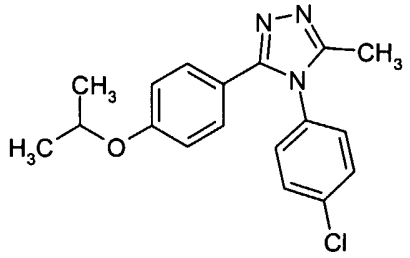


The title compound was prepared from the product of preparation 153, using the similar method for preparation 62, as a solid in 42% yield.

^{1}H NMR (400MHz, $CDCl_3$) δ: 1.43(t, 3H), 2.18(s, 3H), 3.95-4.05(m, 5H), 4.60(s, 2H), 6.66(d, 1H), 6.88(d, 1H), 7.07(d, 1H), 7.39(s, 1H), 7.47(d, 1H), 8.15(s, 1H); LRMS APCI m/z 359 $[M+H]^+$

Example 1

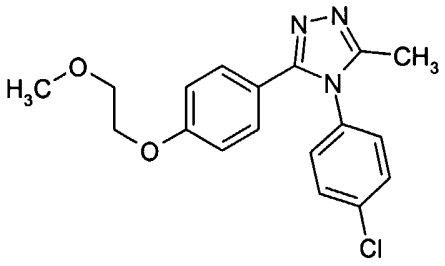
4-(4-Chloro-phenyl)-3-(4-isopropoxy-phenyl)-5-methyl-4H-[1,2,4]triazole



The alcohol of preparation 6 (200mg, 0.70mmol) was dissolved in N,N-dimethylformamide (2mL) and tetrahydrofuran (1mL) and the solution was added dropwise to a stirred solution of sodium hydride in mineral oil (60%, 35mg, 0.87mmol) in tetrahydrofuran (1mL). The mixture was stirred at room temperature for 1 hour before being treated with 2-bromopropane (35mg, 0.70mmol). The reaction mixture was stirred at room temperature for a further 48 hours and was then quenched with water (5mL) and extracted with ethyl acetate (4x10mL). The combined organics were washed with 1M sodium hydroxide solution, dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with dichloromethane:methanol:0.88 ammonia 98:2:0.2, to yield the title product, 200mg. ^{1}H NMR(DMSO-D_6, 400MHz) δ: 1.22(d, 6H), 2.20(s, 3H), 4.60(m, 1H), 6.87(m, 2H), 7.22(m, 2H), 7.45(m, 2H), 7.61(m, 2H). MS ES+ m/z 328 $[MH]^+$

Example 2

4-(4-Chloro-phenyl)-3-[4-(2-methoxy-ethoxy)-phenyl]-5-methyl-4H-[1,2,4]triazole

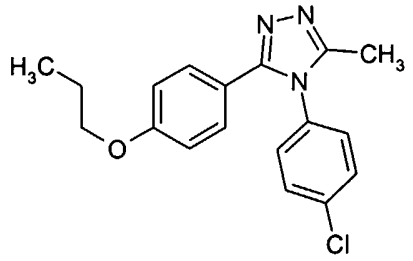


The title compound was prepared by the method described for example 1, using 2-bromoethyl methyl ether, as a white solid in 39% yield.

^{1}H NMR(DMSO-D_6, 400MHz) δ: 2.21(s, 3H), 3.27(s, 3H), 3.62(t, 2H), 4.07(t, 2H), 6.91(m, 2H), 7.24(m, 2H), 7.44(m, 2H), 7.60(m, 2H). MS ES+ m/z 344 $[MH]^+$

Example 3

4-(4-Chloro-phenyl)-3-methyl-5-(4-propoxy-phenyl)-4H-[1,2,4]triazole

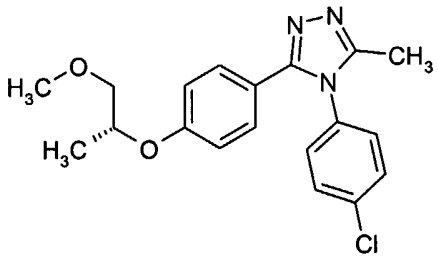


The title compound was prepared by the method described for example 1, using 1-bromopropane, as a white solid in 56% yield.

^{1}H NMR($CDCl_3$, 400MHz) δ: 1.00(t, 3H), 1.77(m, 2H), 2.33(s, 3H), 3.88(t, 2H), 6.78(m, 2H), 7.12(m, 2H), 7.29(m, 2H), 7.47(m, 2H). MS APCI+ m/z 328 $[MH]^+$

Example 4

4-(4-Chloro-phenyl)-3-[4-((1*R*)-2-methoxy-1-methyl-ethoxy)-phenyl]-5-methyl-4H-[1,2,4]triazole

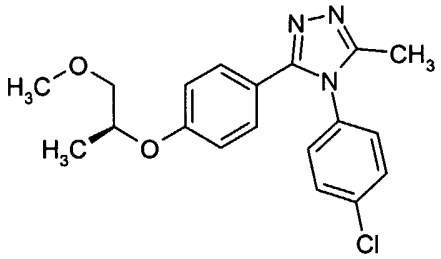


The alcohol of preparation 6 (325mg, 1.14mmol), (2*R*)-methoxypropan-2-ol (130μL, 1.39mmol) and triphenylphosphine (600mg, 2.29mmol) were dissolved in tetrahydrofuran (5mL) and the mixture was treated with a solution of dibenzyl azodicarboxylate (525mg, 2.28mmol) in tetrahydrofuran (2.5mL). The reaction mixture was stirred at room temperature for 3 hours and then diluted with dichloromethane (10mL) and treated with triethylsilane (1mL) and trifluoroacetic acid (15mL). The mixture was stirred at room temperature for a further 18 hours and was then concentrated *in vacuo*. The residue was taken up in 10% sodium carbonate solution (10mL) and was extracted with dichloromethane (50mL). The organic phase was dried over magnesium sulfate and concentrated *in vacuo*. The purification of the crude product by column chromatography on silica gel, eluting with dichloromethane:methanol: 0.88 ammonia, 100:0:0 to 97.5:2.5:0.25, afforded the title product, 73mg.

^{1}H NMR($CDCl_3$, 400MHz) δ: 1.27(d, 3H), 2.32(s, 3H), 3.38(s, 3H), 3.42-3.48(m, 1H), 3.51-3.57(m, 1H), 4.52(m, 1H), 6.82(m, 2H), 7.12(m, 2H), 7.28(m, 2H), 7.47(m, 2H). MS ES+ m/z 358 $[MH]^+$

Example 5

4-(4-Chloro-phenyl)-3-[4-((1*S*)-2-methoxy-1-methyl-ethoxy)-phenyl]-5-methyl-4H-[1,2,4]triazole

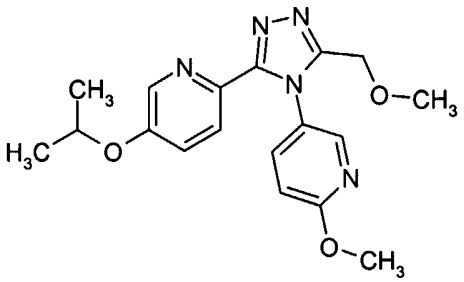


The title compound was prepared by the method described for example 4, using (2*S*)-methoxypropan-2-ol, as a white foam in 74% yield.

^{1}H NMR($CDCl_3$, 400MHz) δ: 1.27(d, 3H), 2.32(s, 3H), 3.38(s, 3H), 3.42-3.48(m, 1H), 3.51-3.57(m, 1H), 4.52(m, 1H), 6.82(m, 2H), 7.12(m, 2H), 7.28(m, 2H), 7.47(m, 2H). MS ES+ m/z 358 $[MH]^+$

Example 6

5-Isopropoxy-2-[5-(methoxymethyl)-4-(4-methoxyphenyl)-4*H*-1,2,4-triazol-3-yl]pyridine



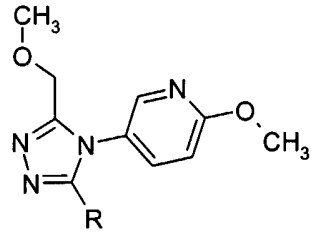
A solution of the product of preparation 13 (60mg, 0.19mmol), triphenylphosphine (100mg, 0.38mmol) and isopropyl alcohol (20μL, 0.26mmol) in tetrahydrofuran (1mL), was treated with a solution of dibenzyl azodicarboxylate (88mg, 0.38mmol) in tetrahydrofuran (1mL). The reaction mixture was stirred at room temperature for 18 hours and was then diluted with dichloromethane (2mL). The mixture was treated with triethylsilane (1mL) and trifluoroacetic acid (5mL) and stirred at room temperature for 3 hours. The solvent was evaporated under

reduced pressure and the residue was basified with 10% sodium carbonate solution (3mL) and extracted with dichloromethane. The organic phase was dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with dichloromethane:methanol:0.88 ammonia 100:0:0 to 95:5:0.5 to yield the title product, 49mg.

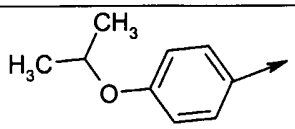
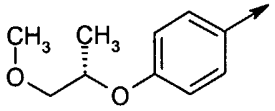
^{1}H NMR(DMSO-D_6, 400MHz) δ: 1.25(d, 6H), 3.16(s, 3H), 3.85(s, 3H), 4.40(s, 2H), 4.71(m, 1H), 6.91(d, 1H), 7.49(dd, 1H), 7.73(dd, 1H), 7.96(d, 1H), 7.99(d, 1H), 8.16(d, 1H). MS APCI+ m/z 356 $[MH]^+$

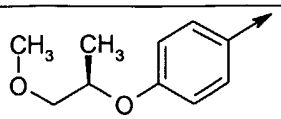
Examples 7 to 22

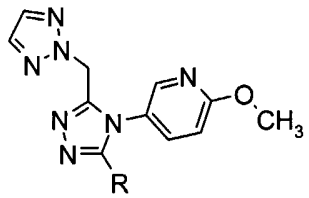
The following compounds of the general formula shown below were prepared by the method described for example 6 using the appropriate alcohols as indicated in the table below.



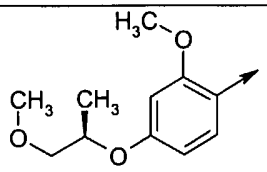
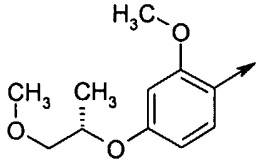
Compound of preparation 20

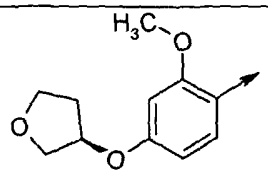
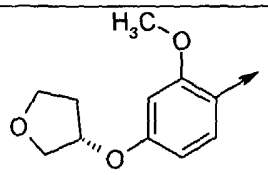
Ex.	R	Data	Yield
7	 Prepared from isopropanol	^{1}H NMR($CDCl_3$, 400MHz) δ: 1.32(d, 6H), 3.25(s, 3H), 3.99(s, 3H), 4.47(s, 2H), 4.54(d, 1H), 6.81(d, 2H), 6.83(d, 1H), 7.38(d, 2H), 7.50(dd, 1H), 8.12(d, 1H) MS APCI+ m/z 355 $[MH]^+$	139mg (61%)
8	 Prepared from (1*S*)-1-methyl-2-methoxypropanol	^{1}H NMR($CDCl_3$, 400MHz) δ: 1.29(d, 3H), 3.35(s, 3H), 3.38(s, 3H), 3.46(m, 1H), 3.55(m, 1H), 3.99(s, 3H), 4.47(s, 2H), 4.54(m, 1H), 6.83(d, 1H), 6.86(d, 2H), 7.37(d, 2H), 7.48(m, 1H), 8.11(d, 1H). MS APCI+ m/z 385 $[MH]^+$	145mg (60%)

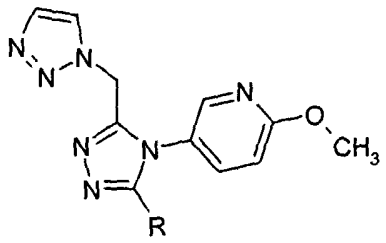
9	 Prepared from (1*R*)-1-methyl-2-methoxypropanol	^{1}H NMR($CDCl_3$, 400MHz) δ: 1.29(d, 3H), 3.35(s, 3H), 3.38(s, 3H), 3.46(m, 1H), 3.55(m, 1H), 3.99(s, 3H), 4.47(s, 2H), 4.54(m, 1H), 6.83(d, 1H), 6.86(d, 2H), 7.37(d, 2H), 7.48(m, 1H), 8.11(d, 1H). MS APCI+ m/z 385 $[MH]^+$	91mg (38%)



Compound of preparation 86

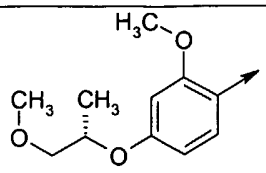
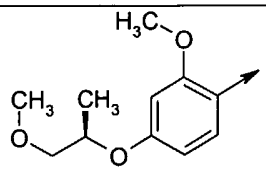
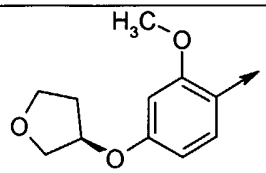
Ex.	R	Data	Yield
10	 Prepared from (1*R*)-1-methyl-2-methoxypropanol	^{1}H NMR($CDCl_3$, 400MHz) δ: 1.28(d, 3H), 3.39(s, 3H), 3.44(s, 3H), 3.45-3.57(m, 4H), 3.90(s, 3H), 4.52-4.58(m, 1H), 5.74(s, 2H), 6.31(s, 1H), 6.54(d, 1H), 6.61(d, 1H), 7.17(m, 1H), 7.42(d, 1H), 7.54(s, 2H), 7.82(d, 1H). MS APCI+ m/z 452 $[MH]^+$ Microanalysis found (%); C(58.16), H(5.59), N(21.50); $C_{22}H_{25}N_7O_4$ requires (%); C(58.53), H(5.58), N(21.72)	135mg (56%)
11	 Prepared from (1*S*)-1-methyl-2-methoxypropanol	^{1}H NMR($CDCl_3$, 400MHz) δ: 1.30(d, 3H), 3.39(s, 3H), 3.44(s, 3H), 3.45-3.57(m, 4H), 3.90(s, 3H), 4.51-4.58(m, 1H), 5.74(s, 2H), 6.31(s, 1H), 6.54(d, 1H), 6.62d, 1H), 7.16(m, 1H), 7.43(d, 1H), 7.54(s, 2H), 7.82(d, 1H). MS APCI+ m/z 452 $[MH]^+$ Microanalysis found (%); C(58.07), H(5.60), N(21.34); $C_{22}H_{25}N_7O_4$ 0.05 H_2O requires (%); C(58.41), H(5.59), N(21.67)	131mg (55%)

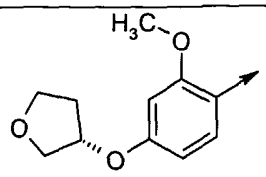
12	 Prepared from *R*-(-)-3-hydroxyl-tetrahydrofuran	^{1}H NMR($CDCl_3$, 400MHz) δ: 2.09-2.28(m, 2H), 3.45(s, 3H), 3.86-3.89(m, 4H), 3.90(s, 3H), 4.89(m, 1H), 5.74(d, 2H), 6.26(s, 1H), 6.45(d, 1H), 6.64(d, 1H), 7.18(m, 1H), 7.46(d, 1H), 7.54(s, 2H), 7.81(d, 1H). MS APCI+ m/z 450 $[MH]^+$ Microanalysis found (%); C(58.25), H(5.21), N(21. 41); $C_{22}H_{23}N_7O_4$ 0.1 H_2O requires (%); C(57.96), H(5.11), N(21.41)	216mg (91%)
13	 Prepared from *S*-(+)-3-hydroxyl-tetrahydrofuran	^{1}H NMR($CDCl_3$, 400MHz) δ: 2.09-2.28(m, 2H), 3.45(s, 3H), 3.86-3.89(m, 4H), 3.90(s, 3H), 4.89(m, 1H), 5.74(d, 2H), 6.26(s, 1H), 6.45(d, 1H), 6.64(d, 1H), 7.18(m, 1H), 7.46(d, 1H), 7.54(s, 2H), 7.81(d, 1H). MS APCI+ m/z 450 $[MH]^+$ Microanalysis found (%); C(58.20), H(5.22), N(21.34); $C_{22}H_{23}N_7O_4$ 0.1 H_2O requires (%); C(57.96), H(5.11), N(21.41)	202mg (85%)

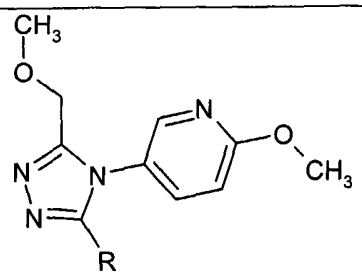


Compound of preparation 87

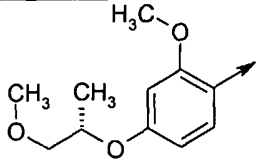
Ex.	R	Data	Yield

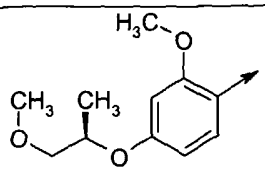
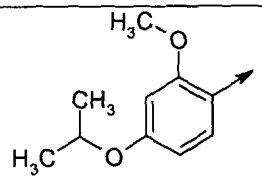
14	 Prepared from (1*S*)-1-methyl-2-methoxypropanol	^{1}H NMR($CDCl_3$, 400MHz) δ: 1.29(d, 3H), 3.38(s, 3H), 3.42(s, 3H), 3.43-3.57(m, 2H), 3.92(s, 3H), 4.50-4.58(m, 1H), 5.67(s, 2H), 6.31(d, 1H), 6.53(m, 1H), 6.69 (d, 1H), 7.14(m, 1H), 7.39(d, 1H), 7.71(s, 1H), 7.79(d, 1H), 7.83(s, 1H). MS ES+ m/z 452 $[MH]^+$ Microanalysis: Found (%); C(57.54), H(5.62), N(21.27); $C_{22}H_{25}N_7O_4$ 0.3 H_2O requires(%);C(57.84), H(5.65), N(21.46)	195mg (80%)
15	 Prepared from (1*R*)-1-methyl-2-methoxypropanol	^{1}H NMR($CDCl_3$, 400MHz) δ: 1.30(d, 3H), 3.39(s, 3H), 3.42(s, 3H), 3.44-3.57(m, 2H), 3.93(s, 3H), 4.51(m, 1H), 5.67(s, 2H), 6.32(d, 1H), 6.54(m, 1H), 6.70(d, 1H), 7.15(m, 1H), 7.40(d, 1H), 7.71(s, 1H), 7.80(d, 1H), 7.83(s, 1H). MS ES+ m/z 452 $[MH]^+$. Microanalysis: Found (%); C(57.23), H(5.66), N(20.88); $C_{22}H_{25}N_7O_4$ 0.6 H_2O requires (%); C(57.16), H(5.71), N(21.21)	135mg (56%)
16	 Prepared from *R*-(-)-3-hydroxyl-tetrahydrofuran	^{1}H NMR($CDCl_3$, 400MHz) δ: 2.09-2.26(m, 2H), 3.44(s, 3H), 3.86-4.00(m, 4H), 3.93(s, 3H), 4.89(m, 1H), 5.67(s, 2H), 6.26(d, 1H), 6.45(m, 1H), 6.70(d, 1H), 7.13(m, 1H), 7.41(d, 1H), 7.70(s, 1H), 7.79(d, 1H), 7.82(s, 1H). MS APCI+ m/z 450 $[MH]^+$ Microanalysis : found (%); C(56.44), H(5.12), N(20.29); $C_{22}H_{23}N_7O_4$ 0.3mol DCM requires (%); C(56.39), H(5.01), N(20.64)	98mg (41%)

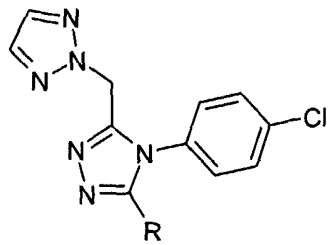
17	 Prepared from *S*-(+)-3-hydroxyl-tetrahydrofuran	^{1}H NMR($CDCl_3$, 400MHz) δ: 2.09-2.26(m, 2H), 3.44(s, 3H), 3.86-4.00(m, 4H), 3.93(s, 3H), 4.89(m, 1H), 5.67(s, 2H), 6.26(d, 1H), 6.45(m, 1H), 6.70(d, 1H), 7.13(m, 1H), 7.41(d, 1H), 7.70(s, 1H), 7.79(d, 1H), 7.82(s, 1H). MS APCI+ m/z 450 $[MH]^+$ Microanalysis : found (%); C(57.56), H(5.27), N(20.79); $C_{22}H_{23}N_7O_4$ 0.2 DCM requires (%); C(57.16), H(5.06), N(21.02)	147mg (62%)



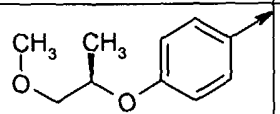
Compound of preparation 88

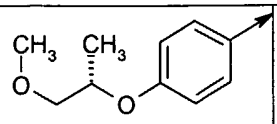
Ex.	R	Data	Yield
18	 Prepared from (1*S*)-1-methyl-2-methoxypropanol	^{1}H NMR($CDCl_3$, 400MHz) δ: 1.30(d, 3H), 3.37(s, 3H), 3.39(s, 3H), 3.43(s, 3H), 3.45-3.58(m, 2H), 3.93(s, 3H), 4.48(s, 2H), 4.52-4.58(m, 1H), 6.33(d, 1H), 6.55(m, 1H), 6.72(d, 1H), 7.42-7.45(m, 2H), 7.98(d, 1H). MS APCI+ m/z 415 $[MH]^+$. Microanalysis : found (%); C(59.58), H(6.43), N(13.19); $C_{21}H_{26}N_4O_5$ 0.1 DCM requires (%); C(59.92), H(6.24), N(13.05)	126mg (52%)

19	 Prepared from (1*R*)-1-methyl-2-methoxypropanol	^{1}H NMR($CDCl_3$, 400MHz) δ: 1.30(d, 3H), 3.37(s, 3H), 3.39(s, 3H), 3.43(s, 3H), 3.45-3.58(m, 2H), 3.93(s, 3H), 4.48(s, 2H), 4.52-4.58(m, 1H), 6.33(d, 1H), 6.55(m, 1H), 6.72(d, 1H), 7.42-7.45(m, 2H), 7.98(d, 1H). 126mg. MS APCI+ m/z 415 $[MH]^+$ Microanalysis : found (%); C(60.38), H(6.28), N(13.38); $C_{21}H_{26}N_4O_5$ 0.05 DCM requires (%); C(59.92), H(6.24), N(13.05)	222mg (92%)
20	 Prepared from isopropanol	^{1}H NMR($CDCl_3$, 400MHz) δ: 1.33(d, 6H), 3.37(s, 3H), 3.43(s, 3H), 3.93(s, 3H), 4.48(s, 2H), 4.52-4.58(m, 1H), 6.26(d, 1H), 6.51(d, 1H), 6.72(d, 1H), 7.42-7.45(m, 2H), 7.99(d, 1H). MS APCI+ m/z 395 $[MH]^+$ Microanalysis : found (%); C(61.47), H(6.38), N(14.25); $C_{20}H_{24}N_4O_4$ 0.1 DCM requires (%); C(61.44), H(6.21), N(14.26)	201mg (90%)



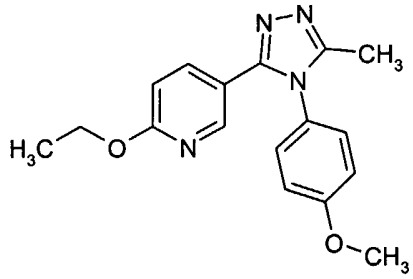
Compound of preparation 7

Ex.	R	Data	Yield
21	 Prepared from (1*R*)-1-methyl-2-methoxypropanol	^{1}H NMR($CDCl_3$, 400MHz) δ: 1.29(d, 3H), 3.39(s, 3H), 3.46(m, 1H), 3.56(m, 1H), 4.53(m, 1H), 5.71(s, 2H), 6.82(d, 2H), 7.02(d, 2H), 7.31(d, 2H), 7.37(d, 2H), 7.53(s, 2H). MS APCI+ m/z 425 $[MH]^+$	118mg (27%)

22	 Prepared from (1*S*)-1-methyl-2-methoxypropanol	^{1}H NMR($CDCl_3$, 400MHz) δ: 1.29(d, 3H), 3.39(s, 3H), 3.46(m, 1H), 3.56(m, 1H), 4.53(m, 1H), 5.71(s, 2H), 6.82(d, 2H), 7.02(d, 2H), 7.31(d, 2H), 7.37(d, 2H), 7.53(s, 2H). MS APCI+ m/z 425 $[MH]^+$	95mg (22%)

Example 23

2-Ethoxy-5-[4-(4-methoxy-phenyl)-5-methyl-4H-[1,2,4]triazol-3-yl]-pyridine



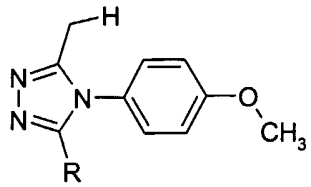
The product of preparation 8 (215mg, 1.05mmol) was added to a solution of *para*-toluenesulfonic acid monohydrate (10mg, 0.15mmol) and 4-methoxy-phenylamine (387mg, 3.14mmol) in xylene (10mL) and the reaction mixture was heated at 150°C for 18 hours. The solvent was then evaporated under reduced pressure and the residue was taken up in ethyl acetate and sodium hydrogen carbonate solution. The organic phase was separated and purified by column chromatography on silica gel, eluting with dichloromethane:methanol:0.88 ammonia, 100:0:0 to 97.5:2.5:0.25, to yield the title compound, 200mg.

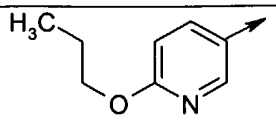
^{1}H NMR($CDCl_3$, 400MHz) δ: 1.34(t, 3H), 2.31(s, 3H), 3.86(s, 3H), 4.29(q, 2H), 6.65(m, 1H), 6.99(m, 2H), 7.11(m, 2H), 7.73(m, 1H), 8.07(m, 1H).

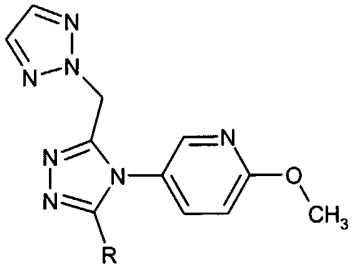
MS APCI+ m/z 311 $[MH]^+$

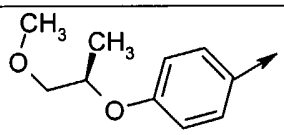
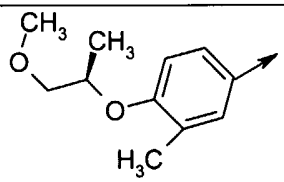
Examples 24-29

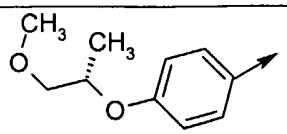
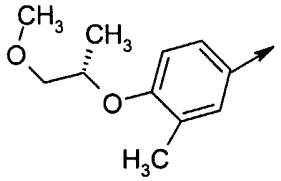
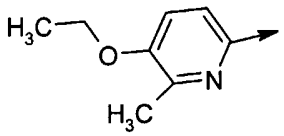
The following compounds, of the general formula shown below, were prepared by the method described for example 23 using the appropriate amine and oxadiazole starting materials as outlined in the table below.



Ex.	R	Data	Yield
24	 Prepared from the compound of preparation 9 and 4-methoxyphenylamine	^{1}H NMR($CDCl_3$, 400MHz) δ: 0.98(t, 3H), 1.75(m, 2H), 2.31(s, 3H), 3.86(s, 3H), 4.18(t, 2H), 6.66(m, 1H), 6.99(m, 2H), 7.11(m, 2H), 7.75(m, 1H), 8.06(m, 1H). MS APCI+ m/z 325 $[MH]^+$	33mg (15%)

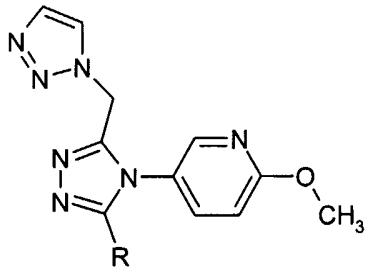


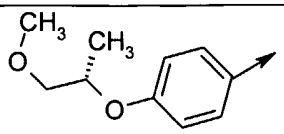
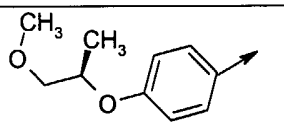
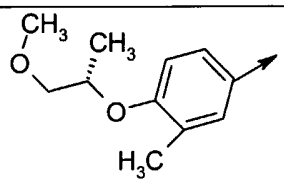
Ex.	R	Data	Yield
25	 Prepared from the compound of preparation 69 and 2-methoxy-5-aminopyridine	^{1}H NMR($CDCl_3$, 400MHz) δ: 1.20(d, 3H), 3.40(s, 3H), 3.50(t, 1H), 3.60(t, 1H), 3.90(s, 3H), 4.50(m, 1H), 5.70(s, 2H), 6.70(d, 1H), 6.80(d, 2H), 7.20(d, 1H), 7.30(d, 2H), 7.50(s, 2H), 7.90(s, 1H). MS ES+ m/z 422 $[MH]^+$	1.44g (13%)
26	 Prepared from the compound of preparation 70 and 2-methoxy-5-aminopyridine	^{1}H NMR($CDCl_3$, 400MHz) δ: 1.30(d, 3H), 2.10(s, 3H), 3.40(s, 3H), 3.50(m, 1H), 3.60(m, 1H), 3.90(s, 3H), 4.50(m, 1H), 5.70(s, 2H), 6.70(m, 2H), 6.80(d, 1H), 7.20(d, 1H), 7.40(s, 1H), 7.60(s, 2H), 7.90(s, 1H). MS ES+ m/z 436 $[MH]^+$	124mg (12%)

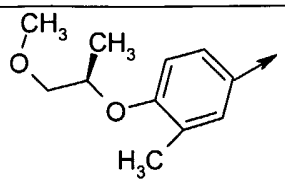
27	 Prepared from the compound of preparation 71 and 2-methoxy-5-aminopyridine	^{1}H NMR($CDCl_3$, 400MHz) δ: 1.30(d, 3H), 3.40(s, 3H), 3.45(m, 1H), 3.55(m, 1H), 4.00(s, 3H), 4.50(m, 1H), 5.70(s, 2H), 6.10(d, 1H), 6.30(d, 2H), 7.20(d, 1H), 7.35(d, 2H), 7.50(s, 2H), 7.90(s, 1H) MS APCI+ m/z 422 $[MH]^+$	392mg (26%)
28	 Prepared from the compound of preparation 76 and 2-methoxy-5-aminopyridine	^{1}H NMR($CDCl_3$, 400MHz) δ: 1.30(d, 3H), 2.10(s, 3H), 3.40(s, 3H), 3.45(m, 1H), 3.60(m, 1H), 4.00(s, 3H), 4.50(m, 1H), 5.70(s, 2H), 6.70 (d, 2H), 7.00(d, 1H), 7.2 (d, 1H), 7.35(s, 1H), 7.55(s, 2H), 7.90(s, 1H). MS APCI+ m/z 436 $[MH]^+$ Microanalysis found (%); C(59.98), H(5.75), N(22.04); $C_{22}H_{25}N_7O_3$ requires (%); C(60.32), H(5.76), N(22.34)	313mg (36%)
29	 Prepared from the compound of preparation 65 and 2-methoxy-5-aminopyridine	^{1}H NMR($CDCl_3$, 400MHz) δ: 1.40(t, 3H), 2.10(s, 3H), 3.95(s, 3H), 4.05(q, 2H), 5.70(s, 2H), 6.70(d, 1H), 7.10(d, 1H), 7.30(d, 1H), 7.60(s, 2H), 7.90(d, 1H), 8.00(d, 1H). MS APCI+ m/z 393 $[MH]^+$ Microanalysis found (%); C(57.55), H(5.14), N(28.31); $C_{19}H_{20}N_8O_2$ 0.12 H_2O requires (%); C(57.84), H(5.17), N(28.40)	144mg (16%)

Examples 30a-32

The following compounds, of the general formula shown below, were prepared from the appropriate oxadiazole starting material as outlined in the table below by the method described for preparation 83 then followed by the method of preparation for example 23.

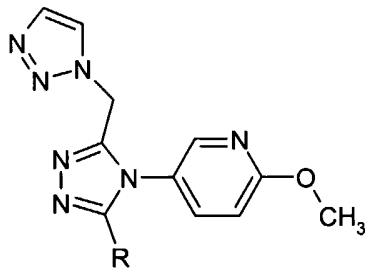


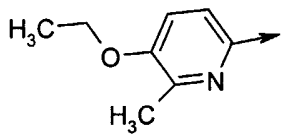
Ex.	R	Data	Yield
30a	 Prepared from the compounds of preparation 68	^{1}H NMR($CDCl_3$, 400MHz) δ: 1.30(d, 3H), 3.40(s, 3H), 3.45(m, 1H), 3.55(m, 1H), 4.00(s, 3H), 4.50(m, 1H), 5.65(s, 2H), 6.80(d, 1H), 6.85(d, 2H), 7.20(d, 1H), 7.35(d, 2H), 7.70(s, 1H), 7.80(s, 1H), 7.90(s, 1H). MS APCI+ m/z 422 $[MH]^+$	416mg (28%)
30b	 Prepared from the compounds of preparation 47	^{1}H NMR($CDCl_3$, 400MHz) δ: 1.20(d, 3H), 3.40(s, 3H), 3.50(m, 1H), 3.55(m, 1H), 3.90(s, 3H), 4.50(m, 1H), 5.60(s, 2H), 6.80(m, 3H), 7.20(d, 1H), 7.30(d, 2H), 7.60(s, 1H), 7.7(s, 1H), 7.90(s, 1H). MS ES+ m/z 422 $[MH]^+$	212mg (18%)
31	 Prepared from the compounds of preparation 49	^{1}H NMR($CDCl_3$, 400MHz) δ: 1.30(d, 3H), 2.10(s, 3H), 3.40(s, 3H), 3.50(m, 1H), 3.60(m, 1H), 4.00(s, 3H), 4.50(m, 1H), 5.60(s, 2H), 6.70(d, 1H), 6.80(d, 1H), 7.00(d, 1H), 7.30(s, 1H), 7.40(d, 1H) 7.70(s, 1H), 7.80(s, 1H), 7.90(s, 1H) MS APCI+ m/z 436 $[MH]^+$ Microanalysis found (%); C(59.90), H(5.85), N(22.05); $C_{22}H_{25}N_7O_3$ 0.07 DCM requires (%); C(60.05), H(5.74), N(22.21)	226mg (26%)

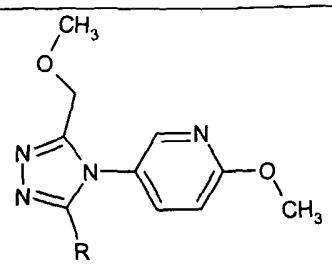
32	 Prepared from the compounds of preparation 50	^{1}H NMR($CDCl_3$, 400MHz) δ: 1.30(d, 3H), 2.20(s, 3H), 3.40(s, 3H), 3.50(m, 1H), 3.60(m, 1H), 4.00(s, 3H), 4.50(m, 1H), 5.60(s, 2H), 6.75(d, 1H), 6.80(d, 1H), 7.00(d, 1H), 7.20(d, 1H), 7.40(d, 1H) 7.70(s, 1H), 7.80(s, 1H), 7.90(s, 1H) MS APCI+ m/z 436 $[MH]^+$	261mg (25%)

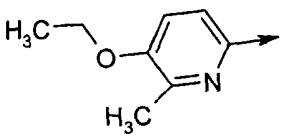
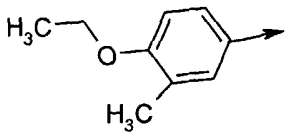
Examples 33-43

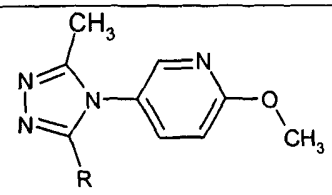
The following compounds, of the general formula shown below, were prepared by the method described for example 23 with the additional purifications below where appropriate, using the appropriate amine and oxadiazole starting materials as outlined in the table below.



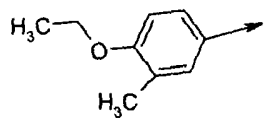
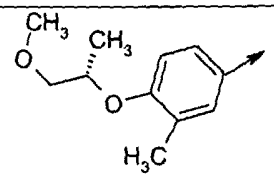
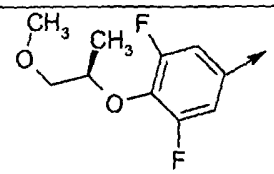
Ex.	R	Data	Yield
33	 Prepared from the compound of preparation 66 and 2-methoxy-5-aminopyridine	^{1}H NMR($CDCl_3$, 400MHz) δ: 1.40(t, 3H), 2.05(s, 3H), 4.00(s, 3H), 4.05(q, 2H), 5.65 (s, 2H), 6.80(d, 1H), 7.10(d, 1H), 7.30(d, 1H), 7.75(s, 2H), 7.90(d, 1H), 8.00(d, 1H). MS APCI+ m/z 393 $[MH]^+$ Microanalysis found (%); C(57.42), H(5.17), N(28.12); $C_{19}H_{20}N_8O_2$ 0.12 H_2O requires (%); C(57.76), H(5.18), N(28.36)	178mg (20%)

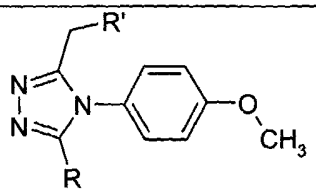


Ex.	R	Data	Yield
34	 Prepared from the compound of preparation 78 and 2-methoxy-5-aminopyridine	^{1}H NMR($CDCl_3$, 400MHz) δ: 1.40(t, 3H), 2.15(s, 3H), 3.35(s, 3H), 4.00(s, 3H), 4.05(q, 2H), 4.45(s, 2H), 6.80(d, 1H), 7.10(d, 1H), 7.60(d, 1H), 7.90(d, 1H), 8.05(s, 1H) MS APCI+ m/z 393 $[MH]^+$	73mg (56%)
35	 Prepared from the compound of preparation 80 and 2-methoxy-5-aminopyridine	^{1}H NMR($CDCl_3$, 400MHz) δ: 1.42(t, 3H), 2.18(s, 3H), 3.37(s, 3H), 3.95-4.05(m, 5H), 4.45(s, 2H), 6.65(d, 1H), 6.8-6.85(m, 1H) 7.37 (brs, 1H), 7.45-7.5(m, 2H), 8.05(s, 1H). MS APCI+ m/z 355 $[MH]^+$. Microanalysis found (%); C(62.82), H(6.21), N(15.25); $C_{19}H_{22}N_4O_3$ 0.5 H_2O requires (%); C(62.80), H(6.38), N(15.42)	140mg (60%)

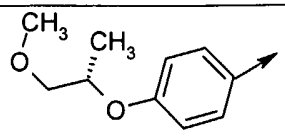
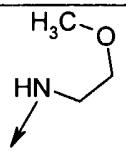
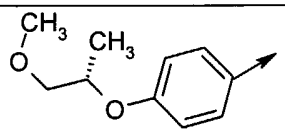
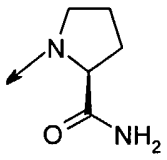
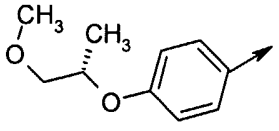
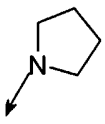


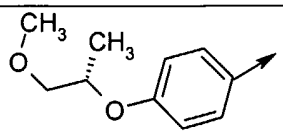
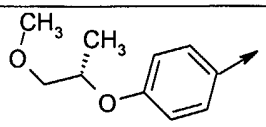
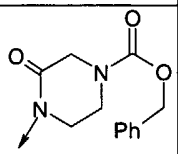
Ex.	R	Data	Yield

36	 Prepared from the compound of preparation 89 and 2-methoxy-5-aminopyridine	^{1}H NMR($CDCl_3$, 400MHz) δ: 1.40(t, 3H), 2.20(s, 3H), 2.40(s, 3H), 4.00(m, 5H), 6.60(d, 1H), 6.80(d, 1H) 7.00(d, 1H), 7.40(m, 2H), 8.00 (s, 1H) MS APCI+ m/z 325 $[MH]^+$	329mg (40%)
37	 Prepared from the compound of preparation 39 and 2-methoxy-5-aminopyridine	^{1}H NMR($CDCl_3$, 400MHz) δ: 1.30(d, 3H), 2.15(s, 3H), 2.35(s, 3H), 3.40(s, 3H), 3.50(m, 1H), 3.60(m, 1H), 4.00(s, 3H), 4.51(m, 1H), 6.75(d, 1H), 6.85(d, 1H) 7.00(d, 1H), 7.40(m, 2H), 8.00(s, 1H) MS APCI+ m/z 369 $[MH]^+$	151mg (21%)
38	 Prepared from the compound of preparation 98 and 2-methoxy-5-aminopyridine	^{1}H NMR($CDCl_3$, 400MHz) δ: 1.30(d, 3H), 2.38(s, 3H), 3.37(s, 3H), 3.49(m, 1H), 3.59(m, 1H), 4.00(s, 3H), 4.45(m, 1H), 6.92(d, 1H), 7.00(d, 2H), 7.40(d, 1H), 8.03(s, 1H). MS APCI+ m/z 391 $[MH^+]$. Microanalysis: found (%) C (58.26), H (5.10), N (14.30); $C_{19}H_{20}N_4O_3F_2$ requires: (%) C (58.46), H (5.16), N (14.35)	170mg (44%)



Ex.	R	R'	Data	Yield

39	 Prepared from the compound of preparation 72 and 2-methoxy-5-aminopyridine		^{1}H NMR($CDCl_3$, 400MHz) δ: 1.25(d, 3H), 2.20(m, 1H), 2.80(t, 2H), 3.30(s, 3H), 3.40(s, 3H), 3.45(m, 3H), 3.55(m, 1H), 3.80(s, 2H), 4.00(s, 3H), 4.50(m, 1H), 6.80(m, 3H), 7.35(d, 2H), 7.50(d, 1H), 8.10(s, 1H) MS APCI+ m/z 423 $[MH]^+$	53mg (16%)
40	 Prepared from the compound of preparation 73 and 2-methoxy-5-aminopyridine		^{1}H NMR($CDCl_3$, 400MHz) δ: 1.30(d, 3H), 1.80(m, 1H), 1.90(m, 1H), 2.20(m, 1H), 2.65(q, 1H), 3.10(m, 2H), 3.4(s, 3H), 3.50-3.60(m, 2H), 3.70-3.90(m, 2H), 4.00(s, 3H), 4.50(m, 1H), 5.00(s, 1H), 6.80(s, 1H), 6.85(m, 3H), 7.35(d, 2H), 7.38(d, 1H), 7.90(d, 1H), 8.10(s, 1H) MS APCI+ m/z 467 $[MH]^+$	280mg. (58%)
41	 Prepared from the compound of preparation 74 and 2-methoxy-5-aminopyridine		^{1}H NMR($CDCl_3$, 400MHz) δ: 1.30(d, 3H), 1.70(m, 4H), 2.50(m, 4H), 3.40(s, 3H), 3.45(m, 1H), 3.55(m, 1H), 3.60(s, 2H), 4.00(s, 3H), 4.50(m, 1H), 6.80(d, 1H), 6.85(d, 2H), 7.35(d, 2H), 7.50(d, 1H), 8.10(s, 1H). MS APCI+ m/z 424 $[MH]^+$	250mg (36%)

42	 Prepared from the compound of preparation 75 and 2-methoxy-5-aminopyridine	HN-CH_3	^{1}H NMR($CDCl_3$, 400MHz) δ: 1.30(d, 3H), 1.70(br, 1H), 2.40(s, 3H), 3.40(s, 3H), 3.50(m, 1H), 3.60(m, 1H), 3.70(s, 2H), 4.00(s, 3H), 4.55(m, 1H), 6.85(m, 3H), 7.35(d, 2H), 7.50(d, 1H), 8.10(s, 1H). MS APCI+ m/z 384 $[MH]^+$	63mg (24%)
43	 Prepared from the compound of preparation 57 and 2-methoxy-5-aminopyridine		^{1}H NMR($CDCl_3$, 400MHz) δ: 1.30(d, 3H), 3.40(s, 3H), 3.45(m, 1H), 3.6(m, 3H), 3.70(t, 2H), 4.00(m, 5H), 4.60(m, 1H), 4.65(s, 2H), 5.10(s, 2H), 6.80(m, 4H), 7.40 (m, 7H), 8.10(s, 1H). MS APCI+ m/z 587 $[MH]^+$	613mg (77%)

Examples 29 and 41: Compounds were purified by column chromatography on silica gel eluting with pentane:ethyl acetate 50:50 to 0:100

Example 33: This compound was purified by column chromatography on silica gel eluting with ethyl acetate: methanol 97:3

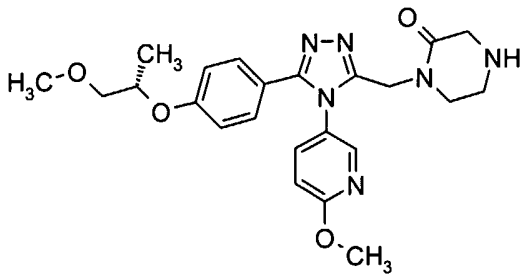
Example 34: This compound was purified by column chromatography on silica gel eluting with ethyl acetate: pentane: methanol, 20:80:0 to 98.5:0: 1.5

Example 40: This compound was purified by column chromatography on silica gel eluting with pentane:ethyl acetate 50:50 to 10:90.

Example 43: This compound was purified by column chromatography on silica gel, eluting with by ethyl acetate:methanol, 100:0 to 97:3

Example 44

1-{5-[4-(2-Methoxy-(1*S*)-methyl-ethoxy)-phenyl]-4-phenyl-4H-[1,2,4]triazol-3-ylmethyl}-piperazin-2-one

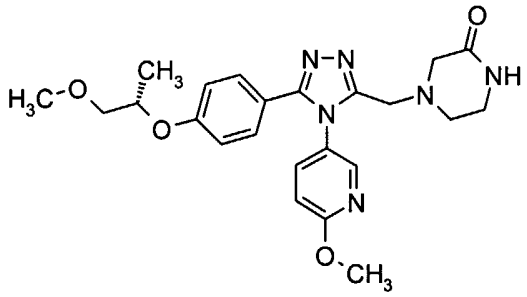


The product of example 43 (0.5g, 0.85mmol) and 10% Pd/C (200mg) was added to ethanol (5mL) and the reaction mixture was stirred at room temperature, under 60psi of hydrogen gas, for 18 hours. The mixture was then filtered through Arbocel®, washing through with ethanol, and the filtrate was evaporated under reduced pressure. Purification of the residue by column chromatography on silica gel, eluting with dichloromethane:methanol:0.88 ammonia, 97:3:1, afforded the title compound in quantitative yield (256mg).

^{1}H NMR($CDCl_3$, 400MHz) δ: 1.30(d, 3H), 1.80(brs, 1H) 3.10(t, 2H), 3.40(m, 5H), 3.5 (m, 1H), 3.55(m, 3H), 4.00(s, 3H), 4.55(m, 1H), 4.65(s, 2H), 6.80(m, 3H), 7.35(d, 2H), 7.45(d, 1H), 8.00(s, 1H). MS APCI+ m/z 453 $[MH]^+$

Example 45

4-{5-[4-(2-Methoxy-(1*S*)-methyl-ethoxy)-phenyl]-4-phenyl-4H-[1,2,4]triazol-3-ylmethyl}-piperazin-2-one



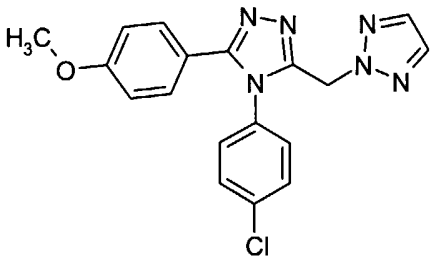
Potassium carbonate (68mg, 0.49mmol) was added to the chloro compound of preparation 63 (95.5mg, 0.24mmol) and piperazin-2-one [(36.9mg, 0.37mmol), *Tet. Lett.*, 35 (51), 9545-8; 1994] in acetonitrile (3mL). The resulting mixture was stirred at room temperature for 18 hours and at 45°C for a further 18 hours. The solvent was then evaporated under reduced pressure and the residue was re-dissolved in dichloromethane and washed with water and sodium hydrogen carbonate solution. The organic phase was dried over magnesium sulfate and concentrated *in vacuo* to give a brown oil. Purification by column chromatography

on silica gel, eluting with dichloromethane:methanol:0.88 ammonia, 97:3:0.3, gave the title product as a pale yellow foam in 62% yield (69.1mg).

^{1}H NMR($CDCl_3$, 400MHz) δ: 1.30(d, 3H), 2.80(t, 2H), 3.10(s, 2H), 3.30(t, 2H), 3.40(s, 3H), 3.45(m, 1H), 3.60(m, 3H), 4.00(s, 3H), 5.90(s, 1H), 6.80(m, 3H), 7.35(d, 2H), 7.45(d, 1H), 8.00(s, 1H). MS APCI+ m/z 453 $[MH]^+$

Example 46

2-[4-(4-Chloro-phenyl)-5-(4-methoxy-phenyl)-4H-[1,2,4]triazol-3-ylmethyl]-2H-[1,2,3]triazole

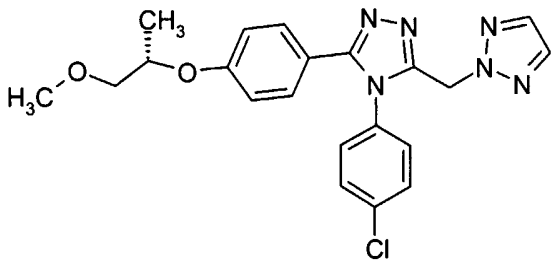


The product of preparation 64 (4.9g, 19mmol), 4-chloroaniline (3.7g, 29mmol) and *para*-toluenesulfonic acid (100mg, cat) were heated under reflux in xylene (150mL), for 8 hours. The solution was then allowed to cool and stand for 18 hours. The resulting precipitate was collected by filtration and dried to give the title compound as a pale pink solid in 77% yield (8.24g).

^{1}H NMR($CDCl_3$, 400MHz) δ: 3.77(s, 3H), 5.71(s, 2H), 6.80(d, 2H), 7.05(d, 2H), 7.34(d, 2H), 7.37(d, 2H), 7.52(s, 2H). MS APCI+ m/z 367 $[MH]^+$

Example 47

2-{4-(4-Chloro-phenyl)-5-[4-(2-methoxy-(1*S*)-methyl-ethoxy)-phenyl]-4H-[1,2,4]triazol-3-ylmethyl}-2H-[1,2,3]triazole



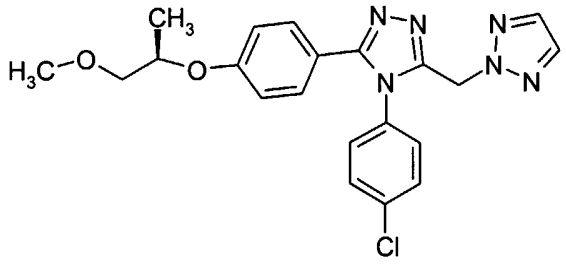
The product of preparation 7 (225mg, 0.64mmol), (2*R*)-1-methoxy-propan-2-ol (0.09g, 1mmol) and triphenylphosphine (262mg, 1mmol) were dissolved in tetrahydrofuran (7mL) and the mixture was cooled to 0°C. Dibenzyl

azodicarboxylate (230mg, 1mmol) was added dropwise and the reaction mixture stirred at room temperature for 18 hours. The reaction mixture was concentrated to low volume *in vacuo*, treated with triethylsilane (10mL) and cooled to 0°C. Trifluoroacetic acid (4mL) was added dropwise and the solution was stirred at room temperature for a further 18 hours. The solvent was concentrated *in vacuo* and the residue taken up in dichloromethane (12mL) and sodium hydrogen carbonate. The mixture was then filtered through a phase separation tube and the filtrate was concentrated *in vacuo*. Purification by column chromatography on silica gel, eluting with dichloromethane: methanol, 100:0 to 99.75:0.25, afforded the title compound as a white foam in 22% yield (95mg).

^{1}H NMR($CDCl_3$, 400MHz) δ: 1.29(d, 3H), 3.39(s, 3H), 3.46(m, 1H), 3.56(m, 1H) 4.53 (m, 1H), 5.71(s, 2H), 6.83(d, 2H), 7.05(d, 2H), 7.33(d, 2H), 7.36(d, 2H) 7.52(s, 2H). MS APCI+ m/z 425 $[MH]^+$

Example 48

2-{4-(4-Chloro-phenyl)-5-[4-(2-methoxy-(1*R*)-methyl-ethoxy)-phenyl]-4H-[1,2,4]triazol-3-ylmethyl}-2H-[1,2,3]triazole

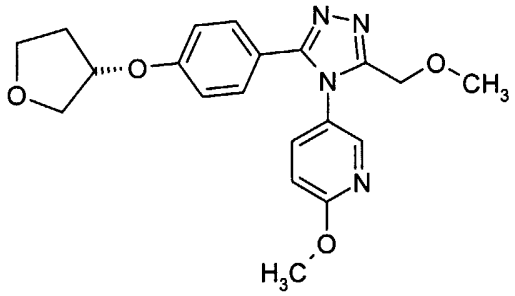


The title compound was prepared as in the method described for example 47, using the product of preparation 7 and (2*S*)-1-methoxy-propan-2-ol, as a white foam in 27% yield.

^{1}H NMR($CDCl_3$, 400MHz) δ: 1.29(d, 3H), 3.39(s, 3H), 3.46(m, 1H), 3.56(m, 1H), 4.53 (m, 1H), 5.71(s, 2H), 6.82 (d, 2H), 7.02 (d, 2H), 7.31(d, 2H), 7.37(d, 2H) 7.53(s, 2H). MS APCI+ m/z 425 $[MH]^+$

Example 49

2-Methoxy-5-{(3*S*)-methoxymethyl-5-[4-(tetrahydro-furan-3-yloxy)-phenyl]-[1,2,4]triazol-4-yl}-pyridine

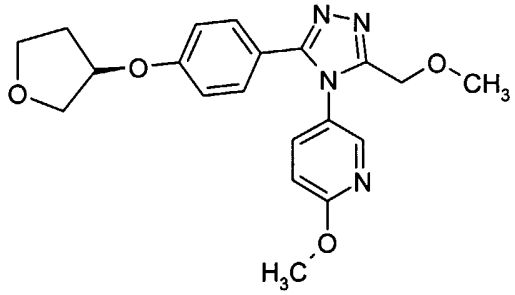


The title compound was prepared as in the method described for example 47, using the alcohol product of preparation 20 and (*S*)-(+)-3-hydroxytetrahydrofuran, as a gummy solid in 52% yield.

^{1}H NMR($CDCl_3$, 400MHz) δ: 2.07-2.25(m, 2H), 3.35(s, 3H), 3.86-4.00(m, 4H), 3.99(s, 3H), 4.47(s, 2H), 4.89-4.92(m, 1H), 6.80(d, 2H), 6.85(d, 1H), 7.40(d, 2H), 7.52(m, 1H) 8.11(d, 1H). MS APCI+ m/z 383 $[MH]^+$

Example 50

2-Methoxy-5-{(3*R*)-methoxymethyl-5-[4-(tetrahydro-furan-3-yloxy)-phenyl]-[1,2,4]triazol-4-yl}-pyridine

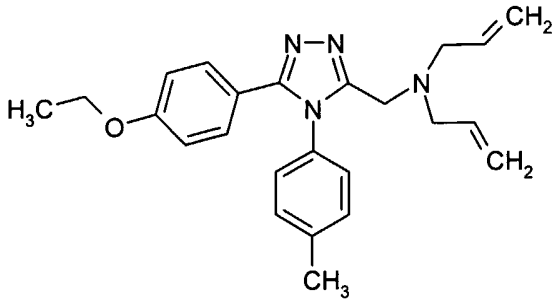


The title compound was prepared as in the method described for example 47, using the alcohol product of preparation 20 and (*R*)-(-)-3-hydroxytetrahydrofuran, as a gummy solid in 33% yield.

^{1}H NMR($CDCl_3$, 400MHz) δ: 2.08-2.26(m, 2H), 3.35(s, 3H), 3.86-4.00(m, 4H), 4.00(s, 3H), 4.48(s, 2H), 4.90-4.93(m, 1H), 6.81(d, 2H), 6.85(d, 1H), 7.41(d, 2H), 7.53(m, 1H) 8.13(d, 1H). MS APCI+ m/z 383 $[MH]^+$

Example 51

Diallyl-[5-(4-ethoxy-phenyl)-4-p-tolyl-4H-[1,2,4]triazol-3-ylmethyl]-amine



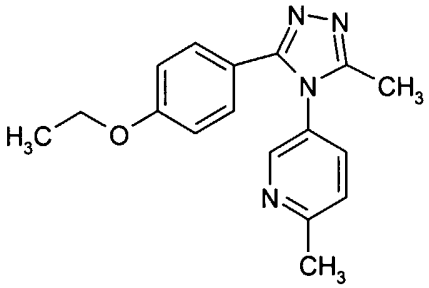
The product of preparation 77 (0.15g, 0.5mmol) was added to a solution of *para*-toluenesulfonic acid monohydrate (10mg, cat) and *p*-toluidine (80.3mg, 0.75mmol) in xylene (8mL) and the reaction mixture was heated to 150°C for 18 hours. The solvent was evaporated under reduced pressure and the residue was taken up in ethyl acetate and sodium hydrogen carbonate solution. The organic phase was separated, dried over sodium sulfate and concentrated *in vacuo*. Purification by column chromatography on silica gel, using an elution gradient of ethyl acetate:pentane of 10:90 to 70:30 yielded the title product, 144mg.

^{1}H NMR($CDCl_3$, 400MHz) δ: 1.40(t, 3H), 2.40(s, 3H), 3.05(d, 4H), 3.60(s, 2H), 4.00(q, 2H), 5.00(m, 4H), 5.55(m, 2H), 6.80(d, 2H), 7.10(d, 2H), 7.30(d, 2H), 7.40(d, 2H). MS APCI+ m/z 389 $[MH]^+$

Microanalysis found (%); C(73.45), H(7.26), N(14.11); $C24H_{28}N_4O$ 0.11 ethyl acetate requires (%); C(73.72), H(7.31), N(14.07)

Example 52

5-[3-(4-Ethoxy-phenyl)-5-methyl-[1,2,4]triazol-4-yl]-2-methyl-pyridine



The products of preparations 4 (150mg, 1.32mmol) and 90 (250mg, 1.2mmol) were dissolved in xylene (5mL) and heated at 150°C for 18 hours. The reaction mixture was then concentrated *in vacuo* to 2.5ml and heated for one further hour. The solvent was evaporated under reduced pressure and the residue was partitioned between dichloromethane and water (x3). The dichloromethane layer was collected and washed with brine, dried over sodium sulfate and concentrated

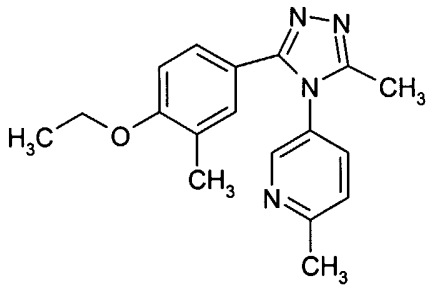
in vacuo. The residue was purified by column chromatography on silica gel, eluting with dichloromethane/methanol/0.88 ammonia 95:5:0.5, to give a clear oil. Trituration with diethyl ether afforded the title compound as a white solid in 17% yield (61mg).

^{1}H NMR($CDCl_3$, 400MHz) δ: 1.40(t, 3H), 2.39(s, 3H), 2.67(s, 3H), 4.00(q, 2H), 6.81(d, 2H) 7.2-7.4(m, 4H), 8.41(s, 1H). MS APCI+ m/z 295 $[MH]^+$

Microanalysis: found (%) C (68.77), H (6.19), N (18.78); $C_{17}H_{18}N_4O$ 0.1 H_2O requires: (%) C (68.95), H (6.19), N (18.92)

Example 53

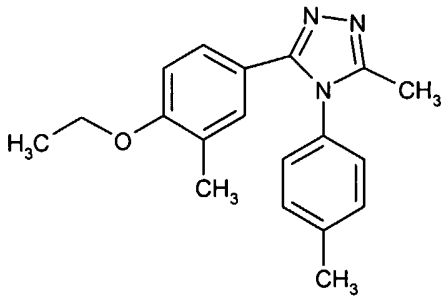
5-[3-(4-Ethoxy-3-methyl-phenyl)-5-methyl-[1,2,4]triazol-4-yl]-2-methyl-pyridine



The title compound was prepared as in the method described for example 52 using the oxadiazole product of preparation 89 and the amine product of preparation 90. Purification by column chromatography on silica gel, eluting with dichloromethane:methanol:0.88 ammonia, 99:1:0.1 to 90:10:1, afforded the title compound in 36% yield. ^{1}H NMR($CDCl_3$, 400MHz) δ: 1.40(t, 3H), 2.15(s, 3H), 2.35(s, 3H), 2.67(s, 3H), 4.00(q, 2H), 6.67(d, 1H), 7.00(d, 1H), 7.25-7.40(m, 3H), 8.40(s, 1H). MS APCI+ m/z 309 $[MH]^+$. Microanalysis: found (%) C (69.87), H (6.57), N (18.07); $C_{18}H_{20}N_4O$ requires: (%) C (70.10), H (6.53), N (18.17)

Example 54

3-(4-Ethoxy-3-methyl-phenyl)-5-methyl-4-p-tolyl-4H-[1,2,4]triazole

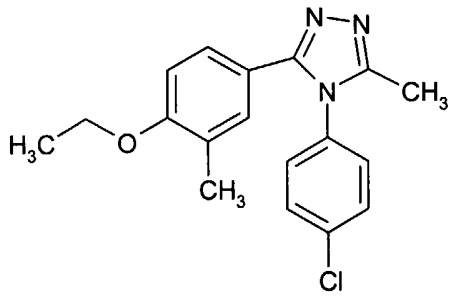


The title compound was prepared as in the method described for example 52, using the oxadiazole product of preparation 89 and toluidine, as a white solid in 83% yield. ^{1}H NMR($CDCl_3$, 400MHz) δ: 1.40(t, 3H), 2.10(s, 3H), 2.30(s, 3H), 2.43(s, 3H), 3.98(q, 2H), 6.60-6.65 (d, 1H), 6.98-7.10(m, 3H) 7.25-7.35(m, 2H), 7.38(brs, 1H). MS APCI+ m/z 308 $[MH]^+$

Microanalysis: found (%) C (73.6), H (6.85), N (13.56); $C_{19}H_{21}N_3O$ 0.1 H_2O requires: (%) C (73.81), H (6.91), N (13.59)

Example 55

4-(4-Chloro-phenyl)-3-(4-ethoxy-3-methyl-phenyl)-5-methyl-4H-[1,2,4]triazole

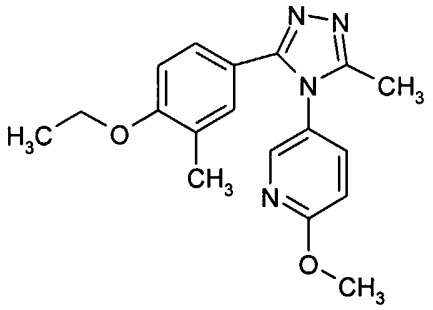


The title compound was prepared as in the method described for example 52, using the oxadiazole product of preparation 89 and 4-chloroaniline, in 55% yield. ^{1}H NMR($CDCl_3$, 400MHz) δ: 1.40(t, 3H), 2.20(s, 3H), 2.40(s, 3H), 4.00(q, 2H), 6.60(d, 1H), 7.00(d, 1H) 7.20(d, 2H), 7.40(s, 1H) 7.50(d, 2H)

MS APCI+ m/z 350 $[MNa^+]$

Example 56

5-[3-(4-Ethoxy-3-methyl-phenyl)-5-methyl-[1,2,4]triazol-4-yl]-2-methoxy-pyridine

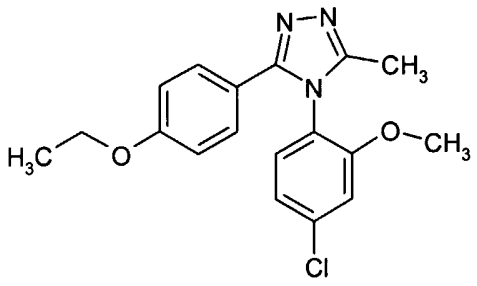


The title compound was prepared as in the method described for example 52 using the oxadiazole product of preparation 89 and 5-amino-2-methoxypyridine, in 44% yield. ^{1}H NMR($CDCl_3$, 400MHz) δ: 1.40(t, 3H), 2.15(s, 3H), 2.35(s, 3H), 4.00(m, 5H), 6.67(d, 1H), 6.80(d, 1H), 7.00(d, 1H), 7.40(m, 2H) 8.40(s, 1H)

MS APCI+ m/z 323 $[M-H]^-$

Example 57

4-(4-Chloro-2-methoxy-phenyl)-3-(4-ethoxy-phenyl)-5-methyl-4H-[1,2,4]triazole

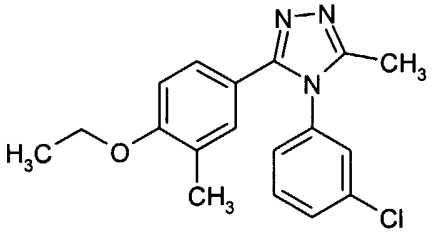


The products of preparations 4 (1g, 4.9mmol) and 91 (926mg, 5.88mmol) were dissolved in xylene (20ml) and the reaction mixture was heated for 10 hours at 150°C. Heating was continued for 4.5 hours with portions of *para*-toluenesulfonic acid (100mg) added to the mixture at regular intervals until tlc analysis showed all of the starting material to be consumed. The reaction mixture was then taken up into 2N hydrochloric acid and ethyl acetate and partitioned. The aqueous layer was basified with sodium hydroxide pellets and re-extracted with ethyl acetate. The combined organic phase was dried over sodium sulfate and evaporated to give a dark brown oil. Trituration with diethyl ether formed a dark brown solid that was re-crystallised from ethyl acetate to produce the title compound as a beige solid (340mg). Evaporation of the ethyl acetate gave a further residue that was purified by column chromatography on silica gel, eluting with dichloromethane:methanol:0.88 ammonia, 98.2:0.2, to afford further amounts of product giving a total yield of 37% (629mg).

^{1}H NMR($CDCl_3$, 400MHz) δ: 1.39(t, 3H), 2.27(s, 3H), 3.73(s, 3H), 3.99(q, 2H), 6.78 (d, 2H), 7.02-7.06(m, 3H), 7.31(d, 2H). MS APCI+ m/z 344 $[MH]^+$

Example 58

4-(3-chloro-phenyl)-3-(4-ethoxy-3-methyl-phenyl)-5-methyl-4H-[1,2,4]triazole



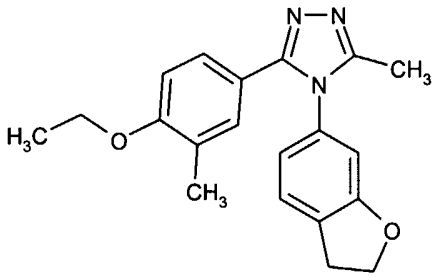
The products of preparations 89 (120mg, 0.55mmol) and 3-chloroaniline (140mg, 1.1mmol) were dissolved in xylene (5mL) and heated at 150°C for 18 hours. The reaction mixture was then concentrated *in vacuo* to 2.5ml and heated for one further hour. The solvent was then evaporated under reduced pressure and the residue was partitioned between ethyl acetate (15mL) and sodium hydrogen carbonate solution (9mL). The organic phase was separated and washed with further sodium hydrogen carbonate solution and brine, dried over magnesium sulfate and concentrated *in vacuo* to give an oil. Purification of the oil by column chromatography on silica gel, eluting with dichloromethane:methanol, 100:0 to 95:5, afforded the title compound as a white solid in 72% yield, (130mg).

^{1}H NMR($CDCl_3$, 400MHz) δ: 1.40(t, 3H), 2.12(s, 3H), 2.38(s, 3H), 3.99(q, 2H), 6.66 (d, 1H), 7.00-7.55(m, 6H). MS APCI+ m/z 328 $[MH]^+$

Microanalysis: found (%) C (64.96), H (5.59), N (12.63); $C_{18}H_{18}ClN_3O$ 0.25 H_2O requires: (%) C (65.06), H (5.61), N (12.64)

Example 59

4-(2,3-Dihydro-benzofuran-6-yl)-3-(4-ethoxy-3-methyl-phenyl)-5-methyl-4H-[1,2,4]triazole

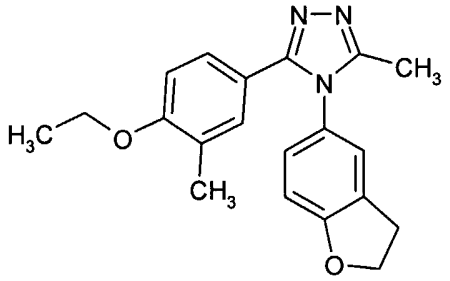


A solution of the product of preparation 89 (100mg, 0.46mmol), the product of preparation 106 (93mg, 0.69mmol) and *para*-toluenesulfonic acid (cat) was heated under reflux in xylene (10mL) for 18 hours. The solvent was then evaporated under reduced pressure and the residue was partitioned between ethyl acetate and water. The organic layer was separated, washed with sodium hydrogen carbonate solution and brine, dried over sodium sulfate and concentrated *in vacuo*. Purification by column chromatography on silica gel, eluting with dichloromethane:methanol, 100:0 to 97:3, gave the title compound in 41% yield, 63mg. ^{1}H NMR($CDCl_3$, 400MHz) δ: 1.40(t, 3H), 2.20(s, 3H), 2.38(s,

3H), 3.30(t, 2H), 4.00(q, 2H), 4.70(t, 2H) 6.60(m, 3H), 7.10(d, 1H), 7.30(m, 1H) 7.40(s, 1H). MS APCI+ m/z 336 $[MH]^+$

Example 60

4-(2,3-Dihydro-benzofuran-5-yl)-3-(4-ethoxy-3-methyl-phenyl)-5-methyl-4H-[1,2,4]triazole



The title compound was prepared as in the method described for example 59, using the products of preparations 89 and 101, as a pale yellow foam in 41% yield. ^1H NMR($CDCl_3$, 400MHz) δ: 1.40(t, 3H), 2.15(s, 3H), 2.30(s, 3H), 3.25(t, 2H), 4.00(q, 2H), 4.70(t, 2H), 6.65(d, 1H), 6.85(d, 1H), 6.95(m, 2H), 7.05(d, 1H), 7.40(s, 1H). MS APCI+ m/z 336 $[MH]^+$

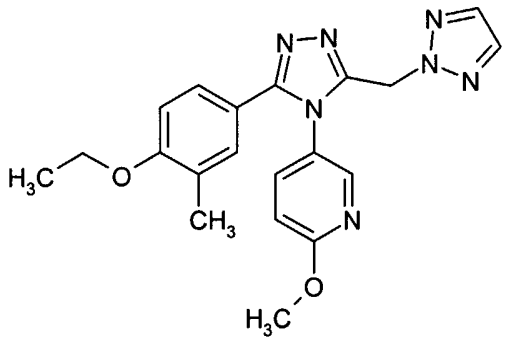
Examples 61 and 62

The product of preparation 53 (500mg, 1.98mmol), 1H-1,2,3-triazole (204mg, 2.96mmol) and potassium carbonate (546mg, 3.96mmol) were stirred for 18 hours in a mixture of acetonitrile (5mL) and N,N-dimethylformamide (2mL). The solvent was then evaporated under reduced pressure and the residue was partitioned between ethyl acetate (20mL) and water (10mL). The organic phase was separated, washed with 1M hydrochloric acid (3x10mL), sodium hydrogen carbonate solution (10mL) and brine (10mL), dried over magnesium sulfate and concentrated *in vacuo* to provide an intermediate residue. The residue was then dissolved in xylene (7mL) and 2-methoxy-5-aminopyridine (491mg, 4mmol) and *para*-toluenesulfonic acid (cat) were added. The reaction mixture was heated at 140°C for 6 hours then the solvent was evaporated under reduced pressure. The resulting black residue was partitioned between ethyl acetate (30mL) and water (10mL). The organic phase was separated, washed with citric acid (2x10mL), sodium hydrogen carbonate solution (10mL) and brine (10mL), dried over

magnesium sulfate and concentrated *in vacuo* to provide a pale yellow oil. Purification by column chromatography on silica gel, eluting with pentane:ethyl acetate, 80:20 to 20:80, afforded the title compound of example 61 as a solid in quantitative yield, 230mg. Further elution with pentane:ethyl acetate, 10:90 to 0:100, afforded the product of example 62 in quantitative yield.

Example 61

5-[3-(4-Ethoxy-3-methyl-phenyl)-5-[1,2,3]triazol-2-ylmethyl-[1,2,4]triazol-4-yl]-2-methoxy-pyridine

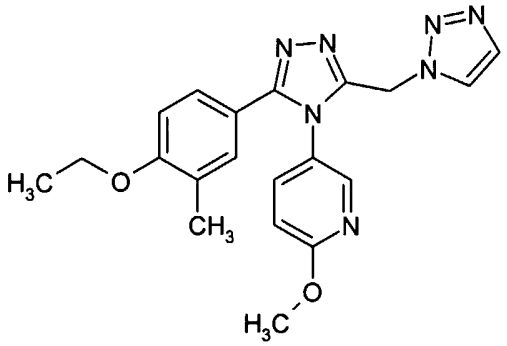


^{1}H NMR($CDCl_3$, 400MHz) δ: 1.40(t, 3H), 2.15(s, 3H), 3.95-4.05(m, 5H), 5.70(s, 2H) 6.65-6.75 (m, 2H), 7.00-7.05(m, 1H), 7.18-7.25 (m, 1H), 7.35(m, 1H), 7.55(s, 2H) 7.90(s, 1H). MS APCI+ m/z 392 $[MH]^+$

Microanalysis: found (%) C (61.06), H (5.40), N (24.80); $C_{20}H_{21}N_7O_2$ requires: (%) C (61.36), H (5.40), N (25.05)

Example 62

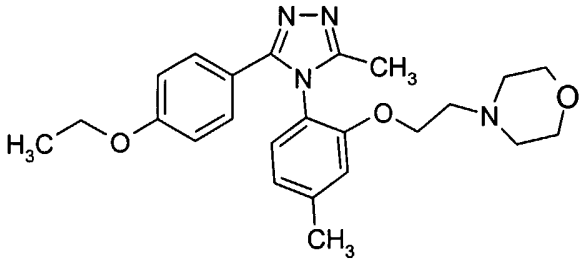
5-[3-(4-Ethoxy-3-methyl-phenyl)-5-[1,2,3]triazol-1-ylmethyl-[1,2,4]triazol-4-yl]-2-methoxy-pyridine



^{1}H NMR($CDCl_3$, 400MHz) δ: 1.40(t, 3H), 2.15(s, 3H), 3.95-4.05(m, 5H), 5.65(s, 2H) 6.65-6.75 (d, 1H), 6.78-6.82(d, 1H), 7.00-7.05(brd, 1H), 7.15-7.20(d, 1H), 7.35(s, 1H), 7.70(s, 1H) 7.80(s, 1H), 7.90(brs, 1H). MS APCI+ m/z 392 $[MH]^+$
Microanalysis: found (%) C (61.20), H (5.36), N (24.86); $C_{20}H_{21}N_7O_2$ requires: (%) C (61.36), H (5.40), N (25.05)

Example 63

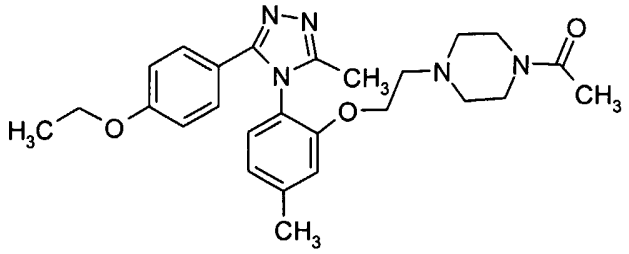
4-(2-{2-[3-(4-Ethoxy-phenyl)-5-methyl-[1,2,4]triazol-4-yl]-5-methyl-phenoxy}-ethyl)-morpholine



4-(2- Chloroethyl)morpholine hydrochloride (81mg, 0.45mmol)was added to the product of preparation 93 (90mg, 0.3mmol) and potassium carbonate (121mg, 0.9mmol), dissolved in N,N-dimethylformamide (2ml). The mixture was stirred at room temperature for 18 hours and at 60°C for 4 hours. The reaction mixture was then partitioned between ethyl acetate and sodium hydrogen carbonate solution and the organic phase was washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with dichloromethane:methanol:0.88 ammonia, 98:2:0.2, to give a colourless oil. Trituration with diethyl ether yielded the title compound as a white solid, 72mg (57%).
^{1}H NMR($CDCl_3/D_2O$, 400MHz) δ: 1.36(t, 3H), 2.25(s, 3H), 2.32-2.64(brm, 9H), 3.62 (brm, 4H), 3.98(m, 3H), 4.12(brm, 1H), 6.76(m, 2H), 6.82-6.88(m, 2H), 7.00-7.04(m, 1H), 7.36(m, 2H). MS ES m/z 445 (100%) $[MNa]^+$
Microanalysis: found (%) C (67.8), H (7.25), N (12.99); $C_{24}H_{30}N_4O_3$ 0.1 Et_2O requires: (%) C (68.17), H (7.27), N (13.03)

Example 64

1-[4-(3-{2-[3-(4-Ethoxy-phenyl)-5-methyl-[1,2,4]triazol-4-yl]-5-methyl-phenyl}-propyl)-piperazin-1-yl]-ethanone

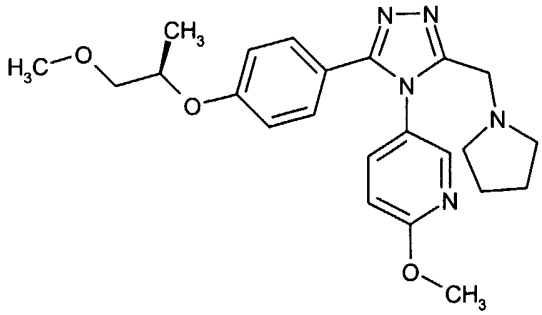


To the products of preparation 93 (90mg, 0.3mmol) and preparation 108 (100mg, 0.45mmol), dissolved in N,N-dimethylformamide (2ml), was added potassium carbonate (121mg, 0.9mmol) and potassium iodide (73mg 0.45mmol). The mixture was heated at 60°C for 2hours but tlc analysis showed that only starting material was present after this time. Further amounts of the product of preparation 108 (100mg, 4.5mmol), potassium carbonate, (121mg, 0.9mmol) and N,N-dimethylformamide (2ml) were added to the reaction vessel and the mixture was heated at 80°C for 18 hours . The solvent was then evaporated under reduced pressure and the residue was taken up into ethyl acetate and water. The organic layer was washed with brine, dried over sodium sulfate and concentrated *in vacuo* to give orange coloured oil. Purification by column chromatography on silica gel, eluting with dichloromethane:methanol:0.88 ammonia, 94:4:0.4, produced a clear oil. Trituration with diethyl ether and ethyl acetate then afforded the title compound as a white solid, 24mg (18%). ^{1}H NMR($CDCl_3/D_2O$, 400MHz) δ: 1.33(t, 3H), 1.97(s, 3H), 2.18(s, 3H), 2.16 -2.35(m, 4H), 2.36(s, 3H), 3.23(brm, 2H), 3.45(brm, 2H), 3.92(q, 2H), 3.90-4.03(brm, 2H), 6.70(d, 2H), 6.77(s, 2H), 6.80(d, 1H), 7.30(d, 2H). MS APCI m/z 464 (100%) $[MH]^+$

Microanalysis: found (%) C (66.68), H (7.14), N (14.82); $C_{26}H_{33}N_5O_3$ 0.2 H_2O requires: (%) C (66.84), H (7.21), N (14.99)

Example 65

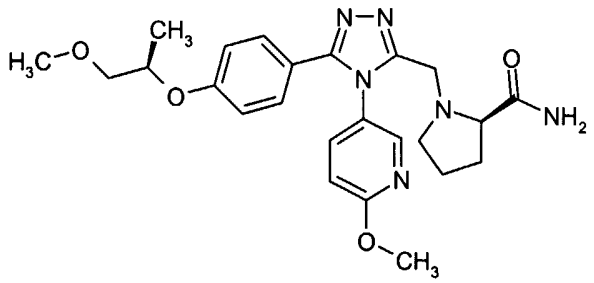
2-Methoxy-5-{3-[4-(2-methoxy-(1*R*)-methyl-ethoxy)-phenyl]-5-pyrrolidin-1-ylmethyl-[1,2,4]triazol-4-yl}-pyridine



The product of preparation 62 (100mg, 0.26mmol) and pyrrolidine (0.04mL 0.514mmol) were stirred in acetonitrile (10ml) at room temperature for 2 hours. The solvent was then evaporated under reduced pressure to provide an oil that was dissolved in dichloromethane (25mL) and washed with water and citric acid. The aqueous layer was basified with sodium hydroxide and re-extracted with dichloromethane and the combined organic fractions were concentrated *in vacuo* to afford the title compound in 44% yield, 48mg. ^{1}H NMR($CDCl_3$, 400MHz) δ: 1.30(d, 3H), 1.80(m, 4H), 2.60(m, 4H) 3.40(s, 3H), 3.50(m, 1H), 3.6(m, 3H), 4.0(s, 3H) 4.60(m, 1H), 6.80(d, 1H), 6.90(d, 2H), 7.40(d, 2H), 7.60(d, 1H), 8.10(s, 1H). MS APCI+ m/z 424 $[MH]^+$

Example 66

1-[5-[4-(2-Methoxy-(1*R*)-methyl-ethoxy)-phenyl]-4-(6-methoxy-pyridin-3-yl)-4H-[1,2,4]triazol-3-ylmethyl]-pyrrolidine-(2*R*)-carboxylic acid amide

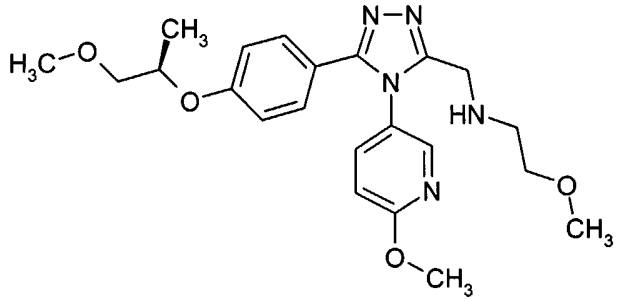


A mixture of the product of preparation 62 (100mg, 0.26mmol), L-prolinamide (44mg, 0.39mmol) and potassium carbonate (72mg, 0.51mmol) were stirred in acetonitrile (10ml), for 18 hours at room temperature, and for 6 hours at 45°C. The solvent was then evaporated under reduced pressure and the residue was taken up in ethyl acetate and washed with water and brine. The organic phase was dried over sodium sulfate, concentrated *in vacuo*, and purified by column chromatography on silica gel, eluting with dichloromethane:methanol:0.88 ammonia, 98:2:0.2, to yield the title compound, 24mg.

^{1}H NMR($CDCl_3$, 400MHz) δ: 1.30(d, 3H), 1.80(m, 2H), 2.20(t, 1H), 2.60(m, 1H), 3.10(t, 1H), 3.20(m, 1H) 3.40(s, 3H), 3.50(m, 1H), 3.60(m, 1H), 3.80(d, 1H), 3.90(d, 1H) 4.00(s, 3H) 4.60(m, 1H), 5.10(s, 1H), 6.80(d, 1H), 6.90(d, 2H), 7.30(d, 2H), 7.40(d, 1H), 8.10(s, 1H). MS APCI+ m/z 467 $[MH]^+$

Example 67

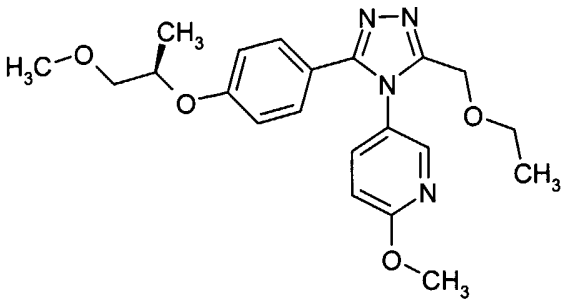
(2-Methoxy-ethyl)-[5-[4-(2-methoxy-(1*R*)-methyl-ethoxy)-phenyl]-4-(6-methoxy-pyridin-3-yl)-4H-[1,2,4]triazol-3-ylmethyl]-amine



The product of preparation 62 (150mg, 0.39mmol), 2-methoxyethylamine (44mg, 0.58mmol) and potassium carbonate (107mg, 0.77mmol) were stirred in acetonitrile (10ml), for 18 hours at room temperature. The solvent was then evaporated under reduced pressure and the residue was taken up in ethyl acetate (25mL) and washed with water and brine. The organic phase was dried over sodium sulfate, concentrated *in vacuo*, and purified by column chromatography on silica gel, eluting with dichloromethane:methanol, 96:4, to yield the title compound, 51mg. ^{1}H NMR($CDCl_3$, 400MHz) δ: 1.30(d, 3H), 1.80(s, 1H), 2.80(t, 2H), 3.30(s, 3H), 3.40(s, 3H), 3.50(m, 3H), 3.60(m, 1H), 3.80(s, 2H), 4.00(s, 3H) 4.60(m, 1H), 6.80(m, 3H), 7.40(d, 2H), 7.50(d, 1H), 8.10(s, 1H) MS APCI+ m/z 428 $[MH]^+$

Example 68

5-{3-Ethoxymethyl-5-[4-(2-methoxy-(1*R*)-methyl-ethoxy)-phenyl]-[1,2,4]triazol-4-yl}-2-methoxy-pyridine



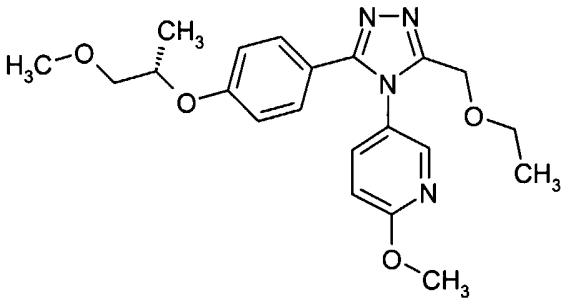
The product of preparation 62 (150g, 0.39mmol), and sodium ethoxide (52mg, 0.77mmol) were stirred in ethanol, (20mL), for 17 hours at room temperature. The solvent was then evaporated under reduced pressure and the residue was taken up in dichloromethane and washed with water, sodium hydrogen carbonate solution and citric acid. The organic phase was dried over sodium sulfate and concentrated *in vacuo*. Purification by column chromatography on silica gel, eluting with dichloromethane:methanol, 98:2, afforded the title compound, 55mg.

^{1}H NMR($CDCl_3$, 400MHz) δ: 1.2(t, 3H), 1.3(d, 3H), 3.4(s, 3H), 3.5(m, 4H), 4.0(s, 3H), 4.5(s, 2H), 4.6 (m, 1H), 6.8(m, 3H), 7.4(d, 2H), 7.5(d, 1H), 8.1(s, 1H)

MS APCI+ m/z 399 $[MH]^+$

Example 69

5-{3-Ethoxymethyl-5-[4-(2-methoxy-(1*S*)-methyl-ethoxy)-phenyl]-[1,2,4]triazol-4-yl}-2- methoxy-pyridine

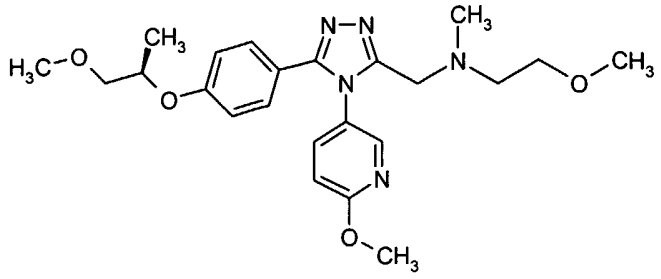


The title compound was prepared by the method described for example 68, using the chloro product of preparation 63, in 87% yield.

^{1}H NMR($CDCl_3$, 400MHz) δ: 1.20(t, 3H), 1.30(d, 3H), 3.40(s, 3H), 3.50(m, 4H), 4.00(s, 3H), 4.50(s, 2H), 4.60(m, 1H), 6.80(m, 3H), 7.40(d, 2H), 7.50(d, 1H), 8.10(s, 1H). MS APCI+ m/z 399 $[MH]^+$

Example 70

(2-Methoxy-ethyl)-[5-[4-(2-methoxy-(1*R*)-methyl-ethoxy)-phenyl]-4-(6-methoxy-pyridin-3-yl)-4H-[1,2,4]triazol-3-ylmethyl]-methyl-amine

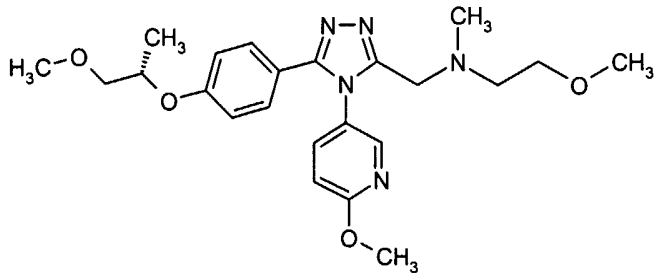


The product of preparation 62 (150mg, 0.39mmol), N-(2-methoxyethyl)methylamine (41mg, 0.58mmol) and potassium carbonate (107mg, 0.77mmol) were stirred in acetonitrile (10mL), for 18 hours at room temperature. The solvent was then evaporated under reduced pressure and the residue was taken up in ethyl acetate (25mL) and washed with water and brine. The organic phase was dried over sodium sulfate and concentrated *in vacuo*. Purification by column chromatography on silica gel, eluting with dichloromethane:methanol:0.88 ammonia 97:3:0.3, afforded the title compound, 30mg.

^{1}H NMR($CDCl_3$, 400MHz) δ: 1.30(d, 3H), 2.25(s, 3H), 2.60(t, 2H), 3.20(s, 3H), 3.30(t, 2H), 3.40(s, 3H), 3.50(m, 2H), 3.60(s, 2H), 3.96(s, 3H) 4.50(m, 1H), 6.80(m, 3H), 7.40(d, 2H), 7.60(d, 1H), 8.10(s, 1H). MS APCI+ m/z 442 $[MH]^+$

Example 71

(2-Methoxy-ethyl)-[5-[4-(2-methoxy-(1*S*)-methyl-ethoxy)-phenyl]-4-(6-methoxy-pyridin-3-yl)-4H-[1,2,4]triazol-3-ylmethyl]-methyl-amine

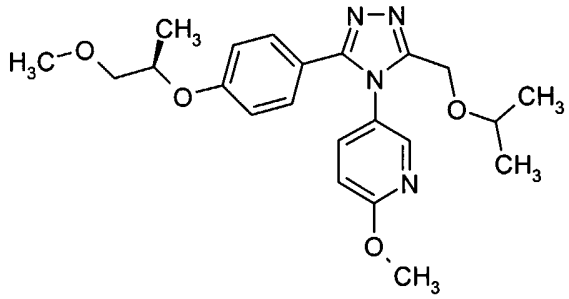


The title compound was prepared by the method described for example 70 using the chloro product of preparation 61, in 67% yield.

^{1}H NMR($CDCl_3$, 400MHz) δ: 1.30(d, 3H), 2.30(s, 3H), 2.60(t, 2H), 3.20(s, 3H), 3.30(t, 2H), 3.40(s, 3H), 3.45(m, 1H), 3.60(m, 3H), 4.00(s, 3H), 4.55(m, 1H), 6.80(m, 3H), 7.40(d, 2H), 7.60(d, 1H), 8.10(s, 1H). MS APCI+ m/z 442 $[MH]^+$

Example 72

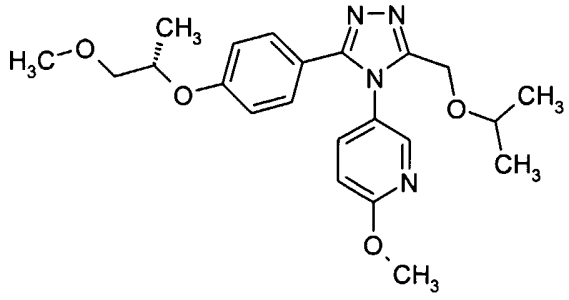
5-{3-Isopropoxymethyl-5-[4-(2-methoxy-(1*R*)-methyl-ethoxy)-phenyl]-[1,2,4]triazol-4-yl}-2-methoxy-pyridine



The product of preparation 55 (160mg, 0.52mmol), 2-methoxy-5-aminopyridine (129mg, 1.04mmol) and *para*-toluenesulfonic acid (cat) were heated under reflux in xylene (15mL), for 18 hours. The solvent was then evaporated under reduced pressure and the residue was dissolved in ethyl acetate and washed with sodium hydrogen carbonate solution, water and brine. The organic phase was dried over sodium sulfate and concentrated *in vacuo*. Purification by column chromatography on silica gel, eluting with dichloromethane:methanol, 97:3, afforded the title compound in 53% yield, (116mg). ^{1}H NMR($CDCl_3$, 400MHz) δ: 1.00(d, 6H), 1.20(d, 3H), 3.40(s, 3H), 3.45(d, 1H) 3.50(m, 2H), 4.00(s, 3H), 4.40(s, 2H), 4.50(m, 1H), 6.80(m, 3H), 7.30(d, 2H), 7.50(d, 1H), 8.10(s, 1H)
MS APCI+ m/z 413 $[MH]^+$

Example 73

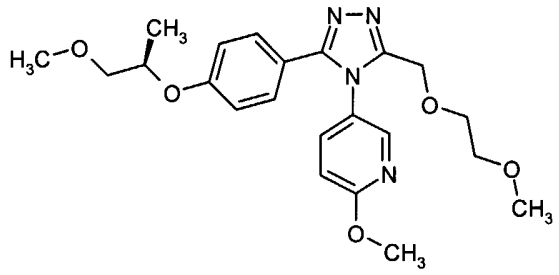
5-{3-Isopropoxymethyl-5-[4-(2-methoxy-(1*S*)-methyl-ethoxy)-phenyl]-[1,2,4]triazol-4-yl}-2-methoxy-pyridine



The product of preparation 61 (95mg, 0.24mmol) was added to a solution of sodium hydride (60% in mineral oil, 20mg, 0.49mmol), dissolved in 2-hydroxypropane (2mL) and the mixture was allowed to stir for 18 hours. The solvent was then evaporated under reduced pressure and the residue was dissolved in ethyl acetate and washed with water and brine. The organic phase was dried over magnesium sulfate and condensed *in vacuo*. Purification by column chromatography on silica gel, eluting with pentane:ethyl acetate, 100:0 to 0:100 gave the title compound in 28% yield, (28.5mg). ^{1}H NMR($CDCl_3$, 400MHz) δ: 1.05(d, 6H), 1.30(d, 3H), 3.40(s, 3H), 3.50(m, 1H) 3.60(m, 2H), 4.00(s, 3H), 4.40(s, 2H), 4.50(m, 1H), 6.80(m, 3H), 7.35(d, 2H), 7.50(d, 1H), 8.10(s, 1H)
MS APCI+ m/z 413 $[MH]^+$

Example 74

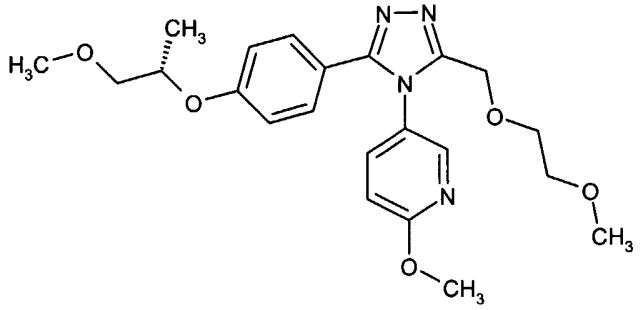
2-Methoxy-5-{3-(2-methoxy-ethoxymethyl)-5-[4-(2-methoxy-(1*R*)-methyl-ethoxy)-phenyl]-[1,2,4]triazol-4-yl}-pyridine



The product of preparation 56 (320mg, 99.3mmol), 2-methoxy-5-aminopyridine (247mg, 199mmol) and *para*-toluenesulfonic acid (cat) were heated under reflux in xylene (15mL), for 18 hours. The solvent was then evaporated under reduced pressure and the residue was dissolved in ethyl acetate (30mL) and washed with sodium hydrogen carbonate solution, water and brine. The organic phase was dried over sodium sulfate, concentrated *in vacuo*. Purification by column chromatography on silica gel, eluting with dichloromethane:methanol, 97:3, provided 52mg of the title compound. ^{1}H NMR($CDCl_3$, 400MHz) δ: 1.30(d, 3H), 3.35(s, 3H), 3.40(s, 3H) 3.50(m, 3H), 3.60(t, 1H), 3.65(d, 2H), 4.00(s, 3H), 4.50(m, 1H), 4.60(s, 2H) 6.80(m, 3H), 7.30(d, 2H), 7.50(d, 1H) 8.10(s, 1H)
MS APCI+ m/z 429 $[MH]^+$

Example 75

2-Methoxy-5-{3-(2-methoxy-ethoxymethyl)-5-[4-(2-methoxy-(1*S*)-methyl-ethoxy)-phenyl]-[1,2,4]triazol-4-yl}-pyridine

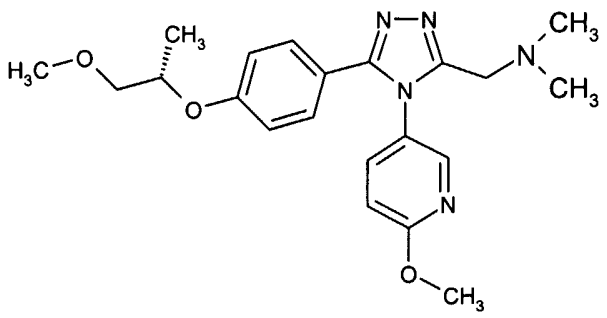


The product of preparation 62 (100mg, 0.26mmol) was added to a solution of sodium hydride (60% in mineral oil, 20.5mg, 0.51mmol), dissolved in 2-methoxyethanol (2mL) and the mixture was allowed to stir for 18 hours. The solvent was then evaporated under reduced pressure and the residue was dissolved in pentane. After standing for 48 hours, the solvent was evaporated under reduced pressure and the residue was dissolved in dichloromethane and washed with sodium hydrogen carbonate solution and water. The organic phase was separated, dried over magnesium sulfate and condensed *in vacuo* to give the title compound as a colourless gum in 85% yield (93.4mg).

^{1}H NMR($CDCl_3$, 400MHz) δ: 1.30(d, 3H), 3.35(s, 3H), 3.40(s, 3H) 3.50(m, 3H), 3.55(m, 1H), 3.60(m, 2H), 4.00(s, 3H), 4.55(m, 1H), 4.60(s, 2H), 6.80(m, 3H), 7.35(d, 2H), 7.50(d, 1H), 8.10(s, 1H). MS APCI+ m/z 429 $[MH]^+$

Example 76

[5-[4-(2-Methoxy-(1*S*)-methyl-ethoxy)-phenyl]-4-(6-methoxy-pyridin-3-yl)-4H-1,2,4]triazol-3-ylmethyl]-dimethyl-amine



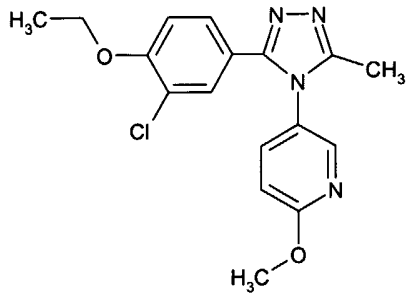
The product of preparation 63 (0.107g, 0.275mmol) was added to dimethylamine (3mL in ethanol) and the mixture was allowed to stir at room temperature for 18

hours. The solvent was then evaporated under reduced pressure and the residue was taken up in dichloromethane and washed with water, sodium hydrogen carbonate solution and brine. The organic phase was dried over sodium sulfate and concentrated *in vacuo* to give a pink coloured oil. Purification by column chromatography on silica gel, eluting with dichloromethane:methanol: 0.88 ammonia, 99:1:0.1 to 95:5:0.5, afforded the title compound in 72% yield, (79.3mg)

^{1}H NMR($CDCl_3$, 400MHz) δ: 1.30(d, 3H), 2.20(s, 6H), 3.35(s, 3H), 3.38(s, 3H) 3.40(s, 2H), 3.50(m, 1H), 3.60(m, 1H), 4.50(m, 1H), 6.80(m, 3H), 7.35(d, 2H), 7.55(d, 1H), 8.10(s, 1H). MS APCI+ m/z 398 $[MH]^+$

Example 77

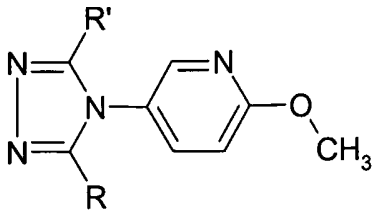
5-[3-(3-Chloro-4-ethoxy-phenyl)-5-methyl-[1,2,4]triazol-4-yl]-2-methoxy-pyridine

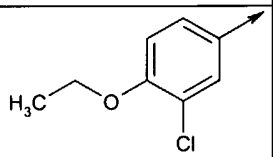
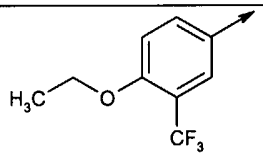
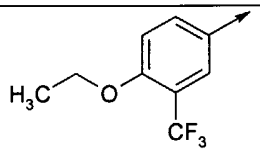
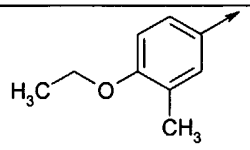


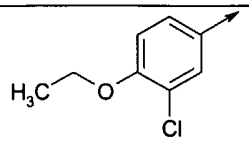
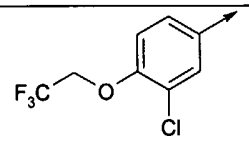
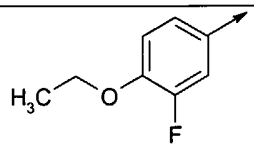
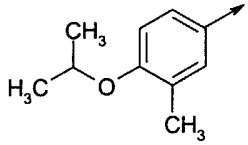
The title compound was prepared from the product of preparation 139 and 5-amino-2-methoxypyridine, using a similar method to that described for example 74, as a brown oil in 31% yield. ^{1}H NMR (400MHz, $CDCl_3$) δ: 1.44(t, 3H), 2.38(s, 3H), 4.02(s, 3H), 4.10(q, 2H), 6.82(d, 1H), 6.88(d, 1H), 7.20(dd, 1H), 7.38(dd, 1H), 7.50(d, 1H), 8.05(d, 1H); LRMS ESI m/z 345 $[M+H]^+$

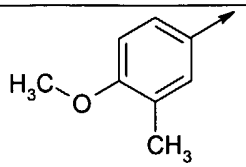
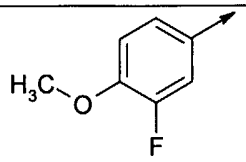
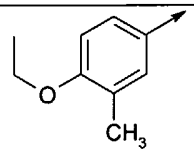
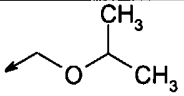
Examples 78 to 90

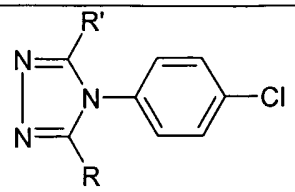
The following compounds, of the general formulae shown below, were prepared by the method described for example 74, with the additional purification for example 84 given below, using the appropriate oxadiazole and amine (1.0-2.0eq) as outlined in the table below. The reaction mixtures were heated under reflux until tlc analysis indicated that all starting material had been consumed.

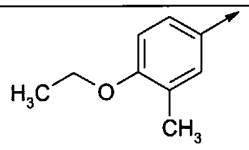


Ex.	R	R'	Data	Yield
78	 Prepared from the compound of preparation 140 and 2-methoxy-5-aminopyridine	CH_2OCH_3	^{1}H NMR (400MHz, $CDCl_3$) δ: 1.46(t, 3H), 3.37(3H, s), 4.02(s, 3H), 4.10(q, 2H), 4.48(s, 2H), 6.84(d, 1H), 6.87(d, 1H), 7.22(dd, 1H), 7.50(dd, 1H), 7.56(d, 1H), 8.05(d, 1H); LRMS ESI m/z 375 $[M+H]^+$	51%
79	 Prepared from the compound of preparation 141 and 2-methoxy-5-aminopyridine	CH_3	^{1}H NMR (400MHz,$CDCl_3$) δ: 1.42(t, 3H), 2.50(s, 3H), 4.02(s, 3H), 4.15(q, 2H), 6.95(m, 2H), 7.64(m, 3H), 8.12(d, 1H); LRMS ESI m/z 379 $[M+H]^+$	34%
80	 Prepared from the compound of preparation 142 and 2-methoxy-5-aminopyridine	CH_2OCH_3	^{1}H NMR (400MHz, $CDCl_3$) δ: 1.42(t, 3H), 3.38(s, 3H), 4.00(s, 3H), 4.35(q, 2H), 4.50(s, 2H), 6.86(d, 1H), 6.94(d, 1H), 7.55(dd, 1H), 7.59(dd, 1H), 7.70(d, 1H), 8.10(d, 1H); LRMS ESI m/z 431 $[M+Na]^+$	37%
81		CH_2CH_3	^{1}H NMR (400MHz, $CDCl_3$) δ: 1.29(t, 3H), 1.39(t, 3H), 2.12(s, 3H), 2.68(q, 2H),	47%

	Prepared from the compound of preparation 143 and 2-methoxy-5-aminopyridine		3.98(q, 2H), 3.99(s, 3H), 6.67(d, 1H), 6.85(d, 1H), 7.08(dd, 1H), 7.32(d, 1H), 7.41(dd, 1H), 8.06(d, 1H); LRMS APCI m/z 339 $[M+H]^+$	
82	 Prepared from the compound of preparation 145 and 2-methoxy-5-aminopyridine	$CH_2OCH_2CH_3$	^1H NMR(400MHz, $CDCl_3$) δ: 1.15(t, 3H), 1.45(t, 3H), 3.50(q, 2H), 3.98(s, 3H), 4.10(q, 2H), 4.50(s, 2H), 6.82(m, 2H), 7.20(dd, 1H), 7.50(dd, 1H), 7.55(d, 1H), 8.10(d, 1H); LRMS ESI m/z 389 $[M+H]^+$	42%
83	 Prepared from the compound of preparation 146 and 2-methoxy-5-aminopyridine	CH_2OCH_3	^1H NMR (400MHz, $CDCl_3$) δ: 3.36(s, 3H), 4.01(s, 3H), 4.40(q, 2H), 4.50(s, 2H), 6.90(m, 2H), 7.50(m, 2H), 7.60(d, 1H), 8.10(d, 1H); LRMS ESI m/z 429 $[M+H]^+$	29%
84	 Prepared from the compound of preparation 147 and 2-methoxy-5-aminopyridine	CH_2OCH_3	^1H NMR(400MHz, $CDCl_3$) δ: 1.42(t, 3H), 3.37(s, 3H), 4.00(s, 3H), 4.10(q, 2H), 4.45(s, 2H), 6.86(m, 2H), 7.18(m, 2H), 7.50(dd, 1H), 8.10(d, 1H); LRMS ESI m/z 381 $[M+Na]^+$	38%
85		CH_2OCH_3	^1H NMR(400MHz, $CDCl_3$) δ: 1.34(d, 6H), 2.10(s, 3H), 3.38(s, 3H), 3.98(s,	7%

	Prepared from the compound of preparation 148 and 2-methoxy-5-aminopyridine		3H), 4.46(s, 2H), 4.52(m, 1H), 6.70(d, 1H), 6.82(d, 1H), 7.08(dd, 1H), 7.36(d, 1H), 7.48(dd, 1H), 8.10(d, 1H); LRMS ESI m/z 369 $[M+H]^+$	
86	 Prepared from the compound of preparation 149 and 2-methoxy-5-aminopyridine	CH_2OCH_3	^1H NMR (400MHz, $CDCl_3$) δ: 2.10(s, 3H), 3.40(s, 3H), 3.75(s, 3H), 3.95(s, 3H), 4.50(s, 2H), 6.75(m, 3H), 7.10(m, 1H), 7.40(m, 1H), 8.00(m, 1H); LRMS ESI m/z 341 $[M+H]^+$	19%
87	 Prepared from the compound of preparation 150 and 2-methoxy-5-aminopyridine	CH_2OCH_3	^1H NMR (400MHz, $CDCl_3$) δ: 3.20(s, 3H), 3.80(s, 3H), 3.95(s, 3H), 4.45(s, 2H), 6.50(m, 1H), 6.80(m, 2H), 7.50(m, 2H), 8.00(m, 1H); LRMS ESI m/z 345 $[M+H]^+$	46%
88	 Prepared from the compound of preparation 151 and 2-methoxy-5-aminopyridine		^1H NMR(400MHz, $CDCl_3$) δ: 1.14(d, 6H), 1.35(t, 3H), 2.10(s, 3H), 3.52(m, 1H), 3.90-4.00(m, 5H), 4.44(s, 2H), 6.62(m, 1H), 6.76(m, 1H), 7.00(m, 1H), 7.30(m, 1H), 7.44(m, 1H), 8.07(m, 1H); LRMS ESI m/z 383 $[M+H]^+$	36%

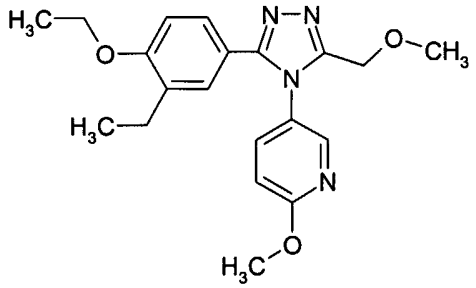


Ex.	R	R'	Data	Yield
89	 Prepared from the compound of preparation 80 and 4-chloroanaline	CH_2OCH_3	^{1}H NMR (400MHz, $CDCl_3$) δ: 1.38(t, 3H), 2.12(s, 3H), 3.30(s, 3H), 3.96 (q, 2H), 4.40(s, 2H), 6.63(d, 1H), 6.96(d, 1H), 7.21(d, 2H), 7.30(s, 1H), 7.42(d, 2H); LRMS ESI m/z 358 $[M+H]^+$	59%

Example 84: was further purified by column chromatography on silica gel, eluting with ethyl acetate:pentane, 80:20 to 100:0.

Example 90

5-[3-(4-Ethoxy-3-ethyl-phenyl)-5-methoxymethyl-[1,2,4]triazol-4-yl]-2-methoxy-pyridine

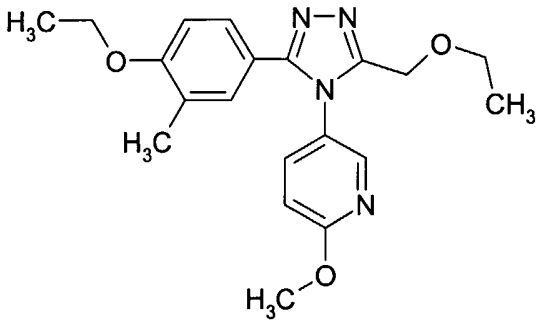


^{t}Butyl lithium (1M in pentane, 4mL, 4mmol) was added to a solution of the product of example 78 (200mg, 0.54mmol) in diethyl ether (9mL) at -78°C, and the mixture was stirred for 30 minutes. Ethyl bromide (0.44mL, 5.90mmol) was added and the mixture was stirred for a further 30 minutes at -78°C. The reaction mixture was then allowed to warm to room temperature and was diluted with water (30mL) and stirred for 15 minutes. The mixture was extracted with ethyl acetate (2x50mL) and the combined organic solution was washed with brine, dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by HPLC using a Phenomenex Luna C18 system, eluting with

water/acetonitrile/trifluoroacetic acid (5:95:0.1):acetonitrile, 95:5 to 5:95, to afford the title compound as a brown oil, 3mg. ^{1}H NMR (400MHz, $CDCl_3$) δ: 1.45(m, 8H), 3.50(s, 3H), 4.00(s, 3H), 4.10(m, 2H), 4.45(s, 2H), 6.85(m, 2H), 7.35(m, 1H), 7.50(m, 2H), 8.10(d, 1H); LRMS ESI m/z 368 $[M+H]^+$

Example 91

5-[3-(4-Ethoxy-3-methyl-phenyl)-5-ethoxymethyl-[1,2,4]triazol-4-yl]-2-methoxy-pyridine

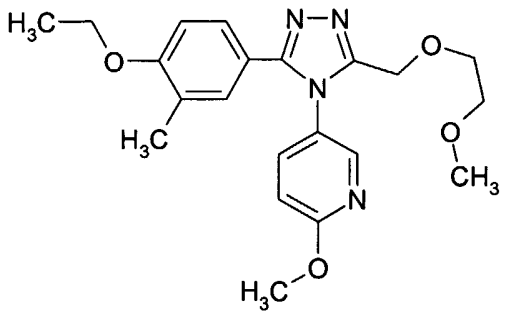


The product of preparation 154 (100mg, 0.28mmol) was added to a solution of sodium metal (13mg, 0.56mmol) in ethanol (10mL) and the mixture was heated at 50°C for 1 hour. The reaction mixture was then concentrated *in vacuo* and the residue was dissolved in ethyl acetate (20mL) and washed with water and brine. The organic solution was dried over sodium sulfate and concentrated *in vacuo* to afford the title compound in 54% yield.

^{1}H NMR (400MHz, $CDCl_3$) δ: 1.20(t, 3H), 1.40 (t, 3H), 2.20(s, 3H), 3.50(q, 2H), 4.00(m, 5H), 4.50(s, 2H), 6.70(d, 1H), 6.80(d, 1H), 7.10(d, 1H), 7.40(s, 1H), 7.50(d, 1H), 8.20(s, 1H); LRMS APCI m/z 369 $[M+H]^+$

Example 92

5-[3-(4-Ethoxy-3-methyl-phenyl)-5-(2-methoxy-ethoxymethyl)-[1,2,4]triazol-4-yl]-2-methoxy-pyridine

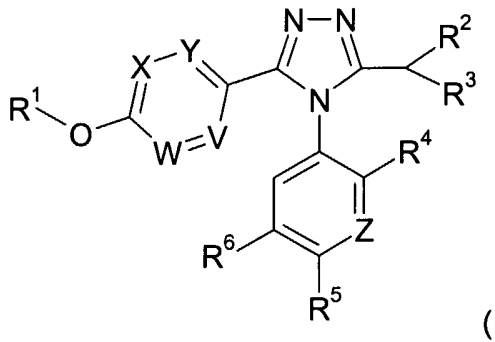


Sodium hydride (60% dispersion in mineral oil, 10mg, 0.25mmol) and the product of preparation 154 (75mg, 0.21mmol) were added to a solution of 2-methoxyethanol (25μL, 0.31mmol) in tetrahydrofuran (3mL) and the mixture was stirred for 2 hours at room temperature. The reaction mixture was then concentrated *in vacuo* and the residue was dissolved in ethyl acetate (20mL) and washed with water and brine. The organic solution was dried over sodium sulfate and concentrated *in vacuo* to afford the title compound in 77% yield, 64.2mg.

^{1}H NMR (400MHz, $CDCl_3$) δ: 1.41(t, 3H), 2.15(s, 3H), 3.35(s, 3H), 3.47(m, 2H), 3.65(m, 2H), 4.00(m, 5H), 4.58(s, 2H), 6.67(d, 1H), 6.83(d, 1H), 7.07(m, 1H), 7.37(s, 1H), 7.52-7.57(m, 1H), 8.10(s, 1H); LRMS APCI m/z 399 $[M+H]^+$; Microanalysis found (%); C(63.15), H(6.60), N(14.04); $C_{21}H_{26}N_4O_4$ requires (%); C(63.29), H(6.57), N(14.07)

Claims

1. A compound of of formula (I)



(I)

wherein:

V, W, X and Y, which may be the same or different, represent CH, C-(C_1-C_6)alkyl, C-halo, C-CF_3, C-CN, C-NH(C_1-C_6)alkyl, C-N((C_1-C_6)alkyl)$_2$, C-C(O)(C_1-C_6)alkyl, C-C(O)O(C_1-C_6)alkyl, C-C(O)NH(C_1-C_6)alkyl, C-C(O)N((C_1-C_6)alkyl)$_2$, C-C(O)OH, C-O(C_1-C_6)alkyl, C-C(O)NH_2 or N;

Z is CH or N;

R^1 is selected from:

i) (C_1-C_6)alkyl, which is optionally substituted by one or more substituents each independently selected from O(C_1-C_6)alkyl, CF_3 and phenyl; and

ii) a 5-8 membered saturated or partially saturated heterocycle containing 1-3 heteroatoms each independently selected from N, O and S; said ring being optionally substituted with one or more groups selected from CN, halo, (C_1-C_6)alkyl, O(C_1-C_6)alkyl, NH(C_1-C_6)alkyl, N((C_1-C_6)alkyl)$_2$, CO(C_1-C_6)alkyl, C(O)O(C_1-C_6)alkyl, C(O)NH(C_1-C_6)alkyl, C(O)N((C_1-C_6)alkyl)$_2$, C(O)OH and C(O)NH_2;

R^2 is selected from:

i) H;

ii) $(C_1$-$C_6)$alkyl, which is optionally substituted by $O(C_1$-$C_6)$alkyl or phenyl;

iii) $O(C_1$-$C_6)$alkyl, which is optionally substituted by $O(C_1$-$C_6)$alkyl;

iv) $NH(C_1$-$C_6)$alkyl, said alkyl group being optionally substituted by $O(C_1$-$C_6)$alkyl;

v) $N((C_1$-$C_6)alkyl)_2$, wherein one or both of said alkyl groups may be optionally substituted by $O(C_1$-$C_6)$alkyl;

vi) $N(CH_2CH=CH_2)_2$;

vii) a 5-8 membered N-linked saturated or partially saturated heterocycle containing 1-3 heteroatoms, each independently selected from N, O and S, wherein at least one heteroatom is N and said ring may optionally incorporate one or two carbonyl groups; said ring being optionally substituted with one or more groups selected from CN, halo, $(C_1$-$C_6)$alkyl, $O(C_1$-$C_6)$alkyl, $NH(C_1$-$C_6)$alkyl, $N((C_1$-$C_6)alkyl)_2$, $C(O)(C_1$-$C_6)$alkyl, $C(O)O(C_1$-$C_6)$alkyl, $C(O)NH(C_1$-$C_6)$alkyl, $C(O)N((C_1$-$C_6)alkyl)_2$, $C(O)OH$, $C(O)NH_2$ and $C(O)OCH_2Ph$; and

viii) a 5-7 membered N-linked aromatic heterocycle containing 1-3 heteroatoms each independently selected from N, O and S, wherein at least one heteroatom is N; said ring being optionally substituted with one or more groups selected from CN, halo, $(C_1$-$C_6)$alkyl, $O(C_1$-$C_6)$alkyl, $NH(C_1$-$C_6)$alkyl, $N((C_1$-$C_6)alkyl)_2$, $C(O)(C_1$-$C_6)$alkyl, $C(O)O(C_1$-$C_6)$alkyl, $C(O)NH(C_1$-$C_6)$alkyl, $C(O)N((C_1$-$C_6)alkyl)_2$, $C(O)OH$, $C(O)NH_2$ and $C(O)OCH_2Ph$;

R^3 is selected from H, $(C_1$-$C_6)$alkyl and $O(C_1$-$C_6)$alkyl;

R^4 is selected from H, $(C_1$-$C_6)$alkyl and $O(C_1$-$C_6)$alkyl, wherein said alkoxy group may be optionally substituted with a 5-8 membered N-linked saturated or partially saturated heterocycle containing 1-3 heteroatoms each independently selected from N, O and S, wherein at least one heteroatom is N; said ring being optionally substituted with one or more $C(O)(C_1$-$C_6)$alkyl groups;

R^5 is selected from H, halo, $(C_1\text{-}C_6)$alkyl, $O(C_1\text{-}C_6)$alkyl, $NH(C_1\text{-}C_6)$alkyl and $N((C_1\text{-}C_6)alkyl)_2$; and

R^6 is H, $(C_1\text{-}C_6)$alkyl, $O(C_1\text{-}C_6)$alkyl or halo;

or R^5 and R^6 may be joined to form a $(C_1\text{-}C_4)$alkylene link, said link optionally incorporating 1-2 heteroatoms each independently selected from N, O and S;

a tautomer thereof or a pharmaceutically acceptable salt, solvate or polymorph of said compound or tautomer;

with the proviso that when:

(a) any three of V, W, X and Y represent CH and the other represents CH, C-$(C_1\text{-}C_6)$alkyl, C-halo, C-$NH(C_1\text{-}C_6)$alkyl or C-$N((C_1\text{-}C_6)alkyl)_2$; and
R^2 is H or $(C_1\text{-}C_6)$alkyl; and
R^3 is H or $(C_1\text{-}C_6)$alkyl; and
R^4 is other than H, then
R^1 is selected from:
i) $(C_1\text{-}C_6)$alkyl, which is optionally substituted by one or more substituents each independently selected from $O(C_1\text{-}C_6)$alkyl and CF_3; and
ii) a 5-6 membered saturated heterocycle containing 1-2 oxygen atoms;
said ring being optionally substituted with one or more groups selected from CN, halo, $(C_1\text{-}C_6)$alkyl, $O(C_1\text{-}C_6)$alkyl, $NH(C_1\text{-}C_6)$alkyl, $N((C_1\text{-}C_6)alkyl)_2$, $CO(C_1\text{-}C_6)$alkyl, $C(O)O(C_1\text{-}C_6)$alkyl, $C(O)NH(C_1\text{-}C_6)$alkyl, $C(O)N((C_1\text{-}C_6)alkyl)_2$, C(O)OH and $C(O)NH_2$; or

(b) any two of V, W, X and Y represent CH and the other two represent CH, C-$(C_1\text{-}C_4)$alkyl, C-halo, C-CF_3, C-$NH(C_1\text{-}C_4)$alkyl, C-$N((C_1\text{-}C_4)alkyl)_2$ or C-$O(C_1\text{-}C_4)$alkyl; and
R^1 is $(C_1\text{-}C_4)$alkyl; and
R^2 is H or $(C_1\text{-}C_3)$alkyl; and
R^3 is H or $(C_1\text{-}C_3)$alkyl; and
R^4 is H, $(C_1\text{-}C_4)$alkyl or $(C_1\text{-}C_4)$alkoxy; then

Z is N.

2. A compound according to claim 1 wherein X and W are each independently selected from CH, C-(C_1-C_6)alkyl, C-halo, C-CF_3 and N; and V and Y are each independently selected from CH, C-O(C_1-C_6)alkyl and N.

3. A compound according to claim 2 wherein W is selected from CH, C-F and N; X is selected from CH, CCH_3, C-F, C-Cl and N; V is selected from CH and N; and Y is selected from CH, C-OCH_3 and N.

4. A compound according to any one of claims 1 to 3 wherein R^1 is selected from:

i) (C_1-C_4)alkyl, which is optionally substituted by one or more substituents each independently selected from O(C_1-C_3)alkyl and CF_3; and

ii) a 5-6 membered saturated heterocycle containing 1-2 oxygen atoms.

5. A compound according to claim 4 wherein R^1 is selected from methyl, ethyl, n-propyl, isopropyl, 2,2,2-trifluoroethyl, 2-methoxyethyl, 2-methoxyprop-1-yl, 1-methoxyprop-2-yl and tetrahydrafuran-3-yl.

6. A compound according to any one of claims 1 to 5 wherein R^2 is selected from:

i) H;

ii) (C_1-C_3)alkyl, which is optionally substituted by O(C_1-C_3)alkyl;

iii) O(C_1-C_3)alkyl, which is optionally substituted by O(C_1-C_3)alkyl;

iv) NH(C_1-C_3)alkyl, said alkyl group being optionally substituted by O(C_1-C_3)alkyl;

v) N((C_1-C_3)alkyl)$_2$, wherein one or both of said alkyl groups may be optionally substituted by O(C_1-C_3)alkyl;

vi) N($CH_2CH{=}CH_2$)$_2$;

vii) a 5-6 membered N-linked saturated heterocycle containing 1-2 nitrogen atoms; said ring may optionally incorporate one or two

carbonyl groups; said ring being optionally substituted by $C(O)NH_2$ or $C(O)OCH_2Ph$; and

viii) a 5-6 membered N-linked aromatic heterocycle containing 1-3 heteroatoms each independently selected from N, O and S, wherein at least two heteroatoms are N; and

R^3 is H or $(C_1\text{-}C_6)$alkyl.

7. A compound according to claim 6 wherein R^2 is selected from H, CH_3, OCH_3, OCH_2CH_3, $OCH(CH_3)_2$, $OCH_2CH_2OCH_3$, $NHCH_3$, $N(CH_3)_2$, $NHCH_2CH_2OCH_3$, $N(CH_3)CH_2CH_2OCH_3$, $N(CH_2CH{=}CH_2)_2$, pyrrolidin-1-yl, pyrrolidin-1-yl-2-carboxylic acid amide, 2,5-dioxopiperazin-4-yl-1-carboxylic acid benzyl ester, piperazin-1-yl-2-one and piperazin-4-yl-2-one; and

R^3 is H.

8. A compound according to any one of claims 1 to 7 wherein:

R^4 is selected from H and $O(C_1\text{-}C_6)$alkyl, wherein said alkoxy group may be optionally substituted with a 5-8 membered N-linked saturated or partially saturated heterocycle containing 1-3 heteroatoms each independently selected from N, O and S, wherein at least one heteroatom is N; said ring being optionally substituted with one or more $C(O)(C_1\text{-}C_6)$alkyl groups;

R^5 is H, chloro, fluoro, $(C_1\text{-}C_3)$alkyl or $O(C_1\text{-}C_3)$alkyl; and

R^6 is H, chloro or fluoro; or

R^5 and R^6 may be joined to form a link, said link being $(C_1\text{-}C_3)$alkylene, said alkylene link optionally incorporating 1-2 heteroatoms each independently selected from N and O.

9. A compound according to claim 8 wherein:

R^4 is selected from H, methoxy, 2-(morpholin-4-yl)ethoxy, 2-(1-acetyl-piperazin-4-yl)ethoxy;

R^5 is H, chloro, methyl or methoxy; and

R^6 is H or chloro;

or R^5 and R^6 may be joined to form a link, said link being ethoxy.

10. A compound according to claim 1, which is selected from:

5-[3-(3-chloro-4-ethoxy-phenyl)-5-ethoxymethyl-[1,2,4]triazol-4-yl]-2-methoxy-pyridine;
2-methoxy-5-{3-[2-methoxy-4-(2-methoxy-1-methyl-ethoxy)-phenyl]-5-[1,2,3]triazol-2-ylmethyl-[1,2,4]triazol-4-yl}-pyridine;
2-methoxy-5-{3-[2-methoxy-4-(2-methoxy-1-methyl-ethoxy)-phenyl]-5-[1,2,3]triazol-2-ylmethyl-[1,2,4]triazol-4-yl}-pyridine;
5-[3-(4-ethoxy-3-methyl-phenyl)-5-(2-methoxy-ethoxymethyl)-[1,2,4]triazol-4-yl]-2-methoxy-pyridine;
3-ethoxy-6-[5-methoxymethyl-4-(6-methoxy-pyridin-3-yl)-4H-[1,2,4]triazol-3-yl]-2-methyl-pyridine;
3-ethoxy-6-[5-methoxymethyl-4-(6-methoxy-pyridin-3-yl)-4H-[1,2,4]triazol-3-yl]-2-trifluoromethyl-pyridine;
6-[5-isopropoxymethyl-4-(6-methoxy-pyridin-3-yl)-4H-[1,2,4]triazol-3-yl]-3-methoxy-2-methyl-pyridine; and
3-ethoxy-6-[5-ethyl-4-(6-methoxy-pyridin-3-yl)-4H-[1,2,4]triazol-3-yl]-2-methyl-pyridine;
and tautomers thereof and pharmaceutically acceptable salts, solvates and polymorphs of said compound or tautomer.

11. A pharmaceutical composition comprising a compound of formula (I) as claimed in any one of claims 1 to 10, or pharmaceutically acceptable salts, solvates or polymorphs thereof, and a pharmaceutically acceptable diluent or carrier.

12. A compound of formula (I) as claimed in any one of claims 1 to 10 or a pharmaceutically acceptable salt, solvate or polymorph thereof, for use as a medicament.

13. A method of treatment of a disorder or condition where inhibition of oxytocin is known, or can be shown, to produce a beneficial effect, in a mammal, comprising administering to said mammal a therapeutically effective amount of a compound of formula (I) as claimed in any one of claims 1 to 10, without the proviso, or a pharmaceutically acceptable salt, solvate or polymorph thereof.

14. A method according to claim 13 wherein the disorder or condition is selected from sexual dysfunction, male sexual dysfunction, female sexual dysfunction, hypoactive sexual desire disorder, sexual arousal disorder, orgasmic disorder, sexual pain disorder, premature ejaculation, preterm labour, complications in labour, appetite and feeding disorders, benign prostatic hyperplasia, premature birth, dysmenorrhoea, congestive heart failure, arterial hypertension, liver cirrhosis, nephrotic hypertension, ocular hypertension, obsessive compulsive disorder and neuropsychiatric disorders.

15. Use of a compound of formula (I) as claimed in any one of claims 1 to 10, without the proviso, or a pharmaceutically acceptable salt, solvate or polymorph thereof, in the preparation of a medicament for the treatment of a disorder or condition, which is selected from sexual dysfunction, male sexual dysfunction, female sexual dysfunction, hypoactive sexual desire disorder, sexual arousal disorder, orgasmic disorder, sexual pain disorder, premature ejaculation, preterm labour, complications in labour, appetite and feeding disorders, benign prostatic hyperplasia, premature birth, dysmenorrhoea, congestive heart failure, arterial hypertension, liver cirrhosis, nephrotic hypertension, ocular hypertension, obsessive compulsive disorder and neuropsychiatric disorders.

16. A method according to claim 14 or use according to claim 15 wherein the disorder or condition is selected from sexual arousal disorder, orgasmic disorder, sexual pain disorder and premature ejaculation.