Title: HETEROCYCLIC DERIVATIVES AS GPCR RECEPTOR AGONISTS

Abstract: Compounds of Formula (I), R1-A-V-B-R2, or pharmaceutically acceptable salts thereof, are agonists of GPR116 and are useful as regulators of satiety, e.g. for the treatment of obesity, and for the treatment of diabetes.
TITLE OF THE INVENTION

HETEROCYCLIC DERIVATIVES AS GPCR RECEPTOR AGONISTS

BACKGROUND OF THE INVENTION

The present invention is directed to G-protein coupled receptor (GPCR) agonists. In particular, the present invention is directed to agonists of GPR116 that are useful as regulators of satiety, e.g. for the treatment of obesity, and for the treatment of diabetes.

Obesity is characterized by an excessive adipose tissue mass relative to body size. Clinically, body fat mass is estimated by the body mass index (BMI; weight(kg)/height(m)^2), or waist circumference. Individuals are considered obese when the BMI is greater than 30 and there are established medical consequences of being overweight. It has been an accepted medical view for some time that an increased body weight, especially as a result of abdominal body fat, is associated with an increased risk for diabetes, hypertension, heart disease, and numerous other health complications, such as arthritis, stroke, gallbladder disease, muscular and respiratory problems, back pain and even certain cancers.

Pharmacological approaches to the treatment of obesity have been mainly concerned with reducing fat mass by altering the balance between energy intake and expenditure. Many studies have clearly established the link between adiposity and the brain circuitry involved in the regulation of energy homeostasis. Direct and indirect evidence suggest that serotonergic, dopaminergic, adrenergic, cholinergic, endocannabinoid, opioid, and histaminergic pathways in addition to many neuropeptide pathways (e.g. neuropeptide Y and melanocortins) are implicated in the central control of energy intake and expenditure. Hypothalamic centres are also able to sense peripheral hormones involved in the maintenance of body weight and degree of adiposity, such as insulin and leptin, and fat tissue derived peptides.

Drugs aimed at the pathophysiology associated with insulin dependent Type I diabetes and non-insulin dependent Type II diabetes have many potential side effects and do not adequately address the dyslipidaemia and hyperglycaemia in a high proportion of patients. Treatment is often focused at individual patient needs using diet, exercise, hypoglycaemic agents and insulin, but there is a continuing need for novel antidiabetic agents, particularly ones that may be better tolerated with fewer adverse effects.

Similarly, metabolic syndrome (syndrome X) which is characterized by hypertension and its associated pathologies including atherosclerosis, lipidemia, hyperlipidemia and hypercholesterolemia have been associated with decreased insulin sensitivity which can lead to abnormal blood sugar levels when challenged. Myocardial ischemia and microvascular disease is an established morbidity associated with untreated or poorly controlled metabolic syndrome.

There is a continuing need for novel antiobesity and antidiabetic agents, particularly ones that are well tolerated with few adverse effects.

GPR116 is a GPCR identified as SNORF25 in WO00/50562 which discloses both the human and rat receptors, US 6,468,756 also discloses the mouse receptor (accession numbers: AAN95194 (human), AAN95195 (rat) and ANN95196 (mouse)).

In humans, GPR116 is expressed in the pancreas, small intestine, colon and adipose tissue. The expression profile of the human GPR116 receptor indicates its potential utility as a target for the treatment of obesity and diabetes.
Williams J.P., Combinatorial Chemistry & High Throughput Screening, 2000, 3, 43-50 discloses the compounds 4-(5-piperidin-4-yl-[1,2,4]oxadiazol-3-yl)pyridine and 4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)piperidine-1-carboxylic acid butyl ester, synthesised as part of a compound library designed to identify dopamine D₄ ligands.

The compounds 4-[5-(4-butylocyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine and 3-[5-(4-propylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine (Chem Div) and 3-[5-(4-butylocyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine (Chembridge) are / were commercially available. No pharmaceutical utility has been suggested for these compounds.

The present invention relates to agonists of GPR116 which are useful as peripheral regulators of satiety, e.g. for the treatment of obesity, and for the treatment of diabetes.

SUMMARY OF THE INVENTION

Compounds of formula (I):

$$R^1\cdot A\cdot V\cdot B\cdot R^2$$

(I)

or pharmaceutically acceptable salts thereof, are agonists of GPR116 and are useful as regulators of satiety, e.g. in the prophylactic or therapeutic treatment of obesity, and for the treatment of diabetes.

DETAILS OF DESCRIPTION OF THE INVENTION

The present invention is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof:

$$R^1\cdot A\cdot V\cdot B\cdot R^2$$

(I)

wherein V is a 5-membered heteroaryl ring containing up to four heteroatoms selected from O, N and S, optionally substituted by C₄ alkyl;

A is -CH=CH- or (CH₂)n;

B is -CH=CH- or (CH₂)m, where one of the CH₂ groups may be replaced by O, NR₅, S(O)m, C(O) or C(O)NR₅;

n is independently 0, 1, 2 or 3;

m is independently 0, 1 or 2;

R¹ is 3- or 4-pyridyl, 4- or 5-pyrimidinyl or 2-pyrazinyl, any of which may be optionally substituted by one or more substituents selected from halo, C₁₄ alkyl, C₁₄ fluoroalkyl, C₂₄ alkenyl, C₂₄ alkynyl, C₃₇ cycloalkyl, aryl, OR₅, CN, NO₂, S(O)mR₅, CON(R₅)₂, N(R₅)₂,

NR₅COR₅, NR₅SO₂R₅, SO₂N(R₅)₂, a 4- to 7-membered heterocyclyl group or a 5- or 6-membered heteroaryl group;

R² is 4- to 7-membered cycloalkyl substituted by R₅, C(O)OR₅, C(O)R₅ or S(O)₂R₅, or 4- to 7-membered heterocyclyl, containing one or two nitrogen atoms which is unsubstituted or substituted by C(O)OR₅, C(O)R₅, S(O)mR₅, C(O)NHR₅, P(O)(OR₅)₂ or a 5- or 6-membered nitrogen containing heteroaryl group;

R₃ is C₃₈ alkyl, C₃₈ alkenyl or C₃₈ alkynyl, any of which may be optionally substituted with up to 5 fluoro or chloro atoms, and may contain a CH₂ group that may be replaced by O, or C₃₇ cycloalkyl, aryl, heterocyclyl, heteroaryl, C₁₄ alkylC₃₇ cycloalkyl, C₁₄ alkylaryl, C₁₄ alkylheterocyclyl or C₁₄ alkylheteroaryl, any of which may be optionally substituted with one or
more substituents selected from halo, C₄₋₅ alkyl, C₄₋₅ fluoroalkyl, OR⁺, CN, CO₂C₄₋₅ alkyl, N(R⁺)₂ and NO₂;

R¹ is C₂₋₅ alkyl, C₂₋₅ alkenyl or C₂₋₅ alkynyl, any of which may be optionally substituted with up to 5 fluoro or chloro atoms, and may contain a CH₂ group that may be replaced by O, or C₃₋₇ cycloalkyl, aryl, heterocyclyl, heteroaryl, C₄₋₅ alkylC₃₋₇ cycloalkyl, C₄₋₅ alkylaryl, C₄₋₅ alkylheterycyclyl or C₄₋₅ alkyheterycyclyl, any of which may be substituted with one or more substituents selected from halo, C₄₋₅ alkyl, C₄₋₅ fluoroalkyl, OR⁺, CN, CO₂C₄₋₅ alkyl, N(R⁺)₂ and NO₂;

R² is hydrogen, C(O)R⁷, S(O)₂R⁸, C₃₋₇ cycloalkyl or C₄₋₅ alkyl optionally substituted by OR⁺, C₃₋₇ cycloalkyl, aryl, heterocyclyl or heteroaryl, wherein the cyclic groups may be substituted with one or more substituents selected from halo, C₁₋₂ alkyl, C₁₋₂ fluoroalkyl, OR⁺, CN, N(R⁺)₂ and NO₂;

R³ are independently hydrogen, C₄₋₅ alkyl, C₃₋₇ cycloalkyl, aryl, heterocyclyl or heteroaryl, wherein the cyclic groups may be substituted with one or more substituents selected from halo, C₄₋₅ alkyl, C₄₋₅ fluoroalkyl, OR⁺, CN, SO₂CH₃, N(R⁺)₂ and NO₂; or a group N(R⁺)₂ may form a 4- to 7-membered heterocyclic ring optionally containing a further heteroatom selected from O and NR⁺;

R⁴ is hydrogen, C₄₋₅ alkyl, OR⁺, N(R⁺)₂, aryl or heteroaryl;

R⁵ is C₁₋₅ alkyl, C₁₋₅ fluoroalkyl, aryl or heteroaryl;

R⁶ is hydrogen, C₁₋₂ alkyl or C₁₋₂ fluoroalkyl;

R⁷ is hydrogen or C₁₋₄ alkyl;

R⁸ is phenyl; and

R¹² is hydrogen, C₄₋₅ alkyl or C₃₋₇ cycloalkyl;

provided that the compound is not:

a) 4-(5-piperidin-4-yl-[1,2,4]oxadiazol-3-y1)pypidine;
b) 4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-y1)pypidine-1-carboxylic acid 'butyl ester;
c) 4-[5-(4-butylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pypidine;
d) 3-[5-(4-butylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pypidine; or
e) 3-[5-(4-propylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pypidine.

The molecular weight of the compounds of formula (I) is preferably less than 800, more preferably less than 600, especially less than 500.

In the compounds of formula (I) V is preferably a 5-membered heteroaryl ring containing up to three heteroatoms selected from O, N and S of the formula:

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\text{\begin{tikzpicture}[baseline = (current bounding box.center)]
  \node at (0,0) [circle,draw,minimum size=2em] (a) {X};
  \node at (2,0) [circle,draw,minimum size=2em] (b) {Y};
  \node at (1,0) [circle,draw,minimum size=2em] (c) {W};
  \draw (a) -- (b);
  \draw (b) -- (c);
  \draw (c) -- (a);
\end{tikzpicture}}
\]

wherein W, X and Y represent the positions of the heteroatom(s) or otherwise represent CH.

Particular heterocyclic rings which V may represent include oxadiazole, oxazole, isoxazole, thiadiazole, thiazole and pyrazole.

Preferably two of W, X and Y are N, and the other is O.

W is preferably N.

Preferably the n groups of A and B do not both represent 0.

In A, n is preferably 0, 1 or 2, more preferably 0.
In B, n is preferably 2 or 3, more preferably 2.

When one of the CH₂ groups in B is replaced, it is preferably replaced by O, NR₅, S(O)ₘ or C(O); more preferably it is replaced by O or NR₅.

R¹ is preferably 4-pyridyl optionally substituted by 1 or 2 halo, C₁₋₄ alkyl, C₁₋₄ fluoroalkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₅₋₇ cycloalkyl, aryl, OR₆, CN, NO₂, S(O)ₘR₅, CON(R₅)₂, N(R₅)₂, NR₁₀COR₆, NR₁₀SO₂R₆, SO₃N(R₅), 4- to 7-membered heterocyclyl or 5- or 6-membered heteroaryl groups; more preferably 4-pyridyl optionally substituted by halo, C₁₋₄ alkyl C₁₋₄ alkoxy or CN; even more preferably 4-pyridyl, optionally substituted by halo, C₁₋₄ alkyl or CN; and especially 4-pyridyl, optionally substituted by CN.

When R² is a 4- to 7-membered heterocyclyl, containing one or two nitrogen atoms it is preferably substituted, the substitution is preferably on the nitrogen atom.

R² is preferably a 4- to 7-membered cycloalkyl substituted by R³ or C(O)OR³, especially R³, or 4- to 7-membered heterocyclyl containing one nitrogen atom which is substituted by C(O)OR⁴ or a 6-membered nitrogen containing heteroaryl group, more preferably a 4- to 7-membered heterocyclyl containing one nitrogen atom which is substituted by C(O)OR⁴.

A particularly preferred R³ group is piperidinyl, especially 4-piperidinyl, which is substituted on the nitrogen atom by C(O)OR⁴.

R¹ is preferably C₃₋₅ alkyl which may contain a CH₂ group that may be replaced by O, or C₅₋₇ cycloalkyl, more preferably R³ is C₅₋₇ alkyl.

R⁴ is preferably C₂₋₅ alkyl, C₂₋₅ alkenyl or C₂₋₅ alkynyl, any of which may be optionally substituted with up to 5 fluoro or chloro atoms, and may contain a CH₂ group that may be replaced by O, or C₅₋₇ cycloalkyl, aryl, 5- to 6-membered heteroaryl containing one or two nitrogen atoms, C₁₋₄ alkylC₅₋₇ cycloalkyl or C₁₋₄ alkylaryl, any of which may be substituted with one or more substituents selected from halo, C₁₋₄ alkyl, C₁₋₄ fluoroalkyl, OR⁶ and CO₂C₁₋₄ alkyl.

More preferably R⁴ is C₃₋₅ alkyl optionally substituted with up to 5 fluoro or chloro atoms, e.g. 3 fluoro or chloro atoms, and which may contain a CH₂ group that may be replaced by O, or C₅₋₇ cycloalkyl.

R² is preferably hydrogen or C₁₋₄ alkyl, more preferably C₁₋₄ alkyl.

R⁶ is preferably hydrogen, C₁₋₄ alkyl or C₅₋₇ cycloalkyl, more preferably C₁₋₄ alkyl.

R⁷ is preferably hydrogen or C₁₋₄ alkyl.

R⁸ is preferably C₁₋₄ alkyl or C₁₋₄ fluoroalkyl.

While the preferred groups for each variable have generally been listed above separately for each variable, preferred compounds of this invention include those in which several or each variable in formula (I) is selected from the preferred, more preferred or particularly listed groups for each variable. Therefore, this invention is intended to include all combinations of preferred, more preferred and particularly listed groups. The preferences listed above also apply, where applicable, to the compounds of formula (Ia) to (Ie) below.

A particular group of compounds which may be mentioned are the compounds of formula (Ia) and pharmaceutically acceptable salts thereof:

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R¹ X Y R²
A W B
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where two of W, X and Y are N, and the other is O.
A is -CH=CH- or (CH₂)ₙ;
B is -CH=CH- or (CH₂)ₙ where one of the CH₂ groups may be replaced by O, NR²,
S(O)ₙ, C(O) or C(O)NR²;
n is independently 0, 1, 2 or 3;
m is 0, 1 or 2;
R¹ is 3- or 4-pyridyl, 4-pyrimidinyl or 2-pyrazinyl, any of which may be optionally
substituted by one or more substituents selected from halo, C₁₋₄ alkyl, C₁₋₄ fluoroalkyl, C₃₋₇
cycloalkyl, OR⁶, CN, NO₂, S(O)ₙR⁶, N(R⁶)ₙ, CON(R⁶)₂ or a 5- or 6-membered heteroaryl
group;
R² is 4- to 7-membered cycloalkyl substituted by R³, C(O)OR³, C(O)R³ or S(O)₂R³, or
4- to 7-membered heterocycloalkyl, containing one or two nitrogen atoms, which is unsubstituted or
substituted by C(O)OR⁴, C(O)R⁴, S(O)₂R⁴, C(O)NHR⁴, P(O)(OR⁴)₂, or a 5- or 6-membered
nitrogen containing heteroaryl group;
R³ is C₃₋₇ alkyl, C₃₋₇ alkenyl or C₃₋₇ alkynyl, any of which may be optionally substituted
with up to 5 chloro or fluoro atoms, and which may also contain a CH₂ group that may be
replaced by O, or C₃₋₇ cycloalkyl, C₁₋₄ alkylC₃₋₇ cycloalkyl, aryl or C₁₋₄ alkylaryl, wherein the
cycloalkyl groups may be optionally substituted by one or more substituents selected from halo
and C₁₋₄ alkyl, and the aryl groups may be substituted with one or more substituents selected
from halo, C₁₋₄ alkyl, C₁₋₄ fluoroalkyl, OR⁶, COOR⁶, CN, N(R⁶)₂ and NO₂;
R⁴ is C₃₋₇ alkyl, C₃₋₇ alkenyl or C₃₋₇ alkynyl, any of which may be optionally substituted
with up to 5 chloro or fluoro atoms, and which may also contain a CH₂ group that may be
replaced by O, or C₃₋₇ cycloalkyl, C₁₋₄ alkylC₃₋₇ cycloalkyl, aryl or C₁₋₄ alkylaryl, wherein the
cycloalkyl groups may be optionally substituted by one or more substituents selected from halo
and C₁₋₄ alkyl, and the aryl groups may be substituted with one or more substituents selected
from halo, C₁₋₄ alkyl, C₁₋₄ fluoroalkyl, OR⁶, COOR⁶, CN, N(R⁶)₂ and NO₂;
R⁵ are independently hydrogen, C₁₋₄ alkyl or C₁₋₄ alkylC₃₋₇ cycloalkyl;
R⁶ are independently hydrogen, C₁₋₄ alkyl or C₁₋₄ fluoroalkyl;
R⁷ are independently hydrogen, C₁₋₄ alkyl or C₁₋₄ alkylC₃₋₇ cycloalkyl;
R¹² is phenyl; and
R¹¹ is hydrogen, C₁₋₄ alkyl or C₃₋₇ cycloalkyl;
provided that the compound is not:

a) 4-(5-piperidin-4-yl-[1,2,4]oxadiazol-3-yl)pyridine;
b) 4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)piperidine-1-carboxylic acid 'butyl ester;
c) 4-[5-(4-butyicyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine;
d) 3-[5-(4-butyicyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine; or
e) 3-[5-(4-propylcylohexyl)-[1,2,4]oxadiazol-3-yl]pyridine.

A further group of compounds which may be mentioned are the compounds of formula
(Ib) and pharmaceutically acceptable salts thereof:

R¹-A-V-B-R²
( Ib)

wherein V is a 5-membered heteroaryl ring containing up to four heteroatoms selected
from O, N and S;
A is (CH₂)ₙ;
B is (CH₂)ₙ where one of the CH₂ groups may be replaced by O, NR², S(O)ₙ or C(O);

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n is independently 0, 1, 2 or 3;
m is 0, 1 or 2;
R^1 is 3- or 4-pyridyl or 4- or 5-pyrimidinyl, any of which may be optionally substituted by one or more substituents selected from halo, C\textsubscript{1-4} alkyl, C\textsubscript{1-4} fluoroalkyl, C\textsubscript{2-4} alkenyl, C\textsubscript{2-4} alkynyl, C\textsubscript{3-7} cycloalkyl, aryl, OR\textsuperscript{6}, CN, NO\textsubscript{2}, S(O)\textsubscript{m}R\textsuperscript{6}, CON(R\textsuperscript{6})\textsubscript{2}, N(R\textsuperscript{6})\textsubscript{2}, NR\textsuperscript{10}COR\textsuperscript{6}, NR\textsuperscript{10}SO\textsubscript{2}R\textsuperscript{6}, SO\textsubscript{2}N(R\textsuperscript{6})\textsubscript{2}, a 4- to 7-membered heterocyclic group or a 5- or 6-membered heteroaryl group;
R^2 is 4- to 7-membered cycloalkyl substituted by R^3, C(O)OR\textsuperscript{5}, C(O)R\textsuperscript{5} or S(O)\textsubscript{2}R\textsuperscript{5}, or 4- to 7-membered heterocycl, containing one or two nitrogen atoms, which are un-substituted or substituted by C(O)OR\textsuperscript{5}, C(O)R\textsuperscript{5} or S(O)\textsubscript{2}R\textsuperscript{5};
R^3 is C\textsubscript{3-7} alkyl, C\textsubscript{3-7} alkenyl or C\textsubscript{3-7} alkynyl which may contain a CH\textsubscript{2} group that may be replaced by O, C\textsubscript{3-7} cycloalkyl, aryl, heterocyclyl, heteroaryl, C\textsubscript{1-4} alkylC\textsubscript{3-7} cycloalkyl, C\textsubscript{1-4} alkenyl, C\textsubscript{1-4} alkynylC\textsubscript{3-7} cycloalkyl, any of which may be substituted with one or more substituents selected from halo, C\textsubscript{1-4} alkyl, C\textsubscript{1-4} fluoroalkyl, OR\textsuperscript{6}, CN, N(R\textsuperscript{6})\textsubscript{2} and NO\textsubscript{2};
R^4 is C\textsubscript{2-7} alkyl, C\textsubscript{2-7} alkenyl or C\textsubscript{2-7} alkynyl which may contain a CH\textsubscript{2} group that may be replaced by O, or C\textsubscript{2-7} cycloalkyl, aryl, heterocyclyl, heteroaryl, C\textsubscript{1-4} alkylC\textsubscript{3-7} cycloalkyl, C\textsubscript{1-4} alkenyl, C\textsubscript{1-4} alkynylC\textsubscript{3-7} cycloalkyl, any of which may be substituted with one or more substituents selected from halo, C\textsubscript{1-4} alkyl, C\textsubscript{1-4} fluoroalkyl, OR\textsuperscript{6}, CN, N(R\textsuperscript{6})\textsubscript{2} and NO\textsubscript{2};
R^5 is hydrogen, C(O)R\textsuperscript{7}, S(O)\textsubscript{2}R\textsuperscript{8} or C\textsubscript{1-4} alkyl optionally substituted by OR\textsuperscript{6}, C\textsubscript{3-7} cycloalkyl, aryl, heterocyclyl or heteroaryl, wherein the cyclic groups may be substituted with one or more substituents selected from halo, C\textsubscript{1-2} alkyl, C\textsubscript{1-2} fluoroalkyl, OR\textsuperscript{6}, CN, N(R\textsuperscript{6})\textsubscript{2} and NO\textsubscript{2};
R^6 are independently hydrogen, or C\textsubscript{1-4} alkyl, C\textsubscript{3-7} cycloalkyl, aryl, heterocyclyl group or heteroaryl, wherein the cyclic groups may be substituted with one or more substituents selected from halo, C\textsubscript{1-4} alkyl, C\textsubscript{1-4} fluoroalkyl, OR\textsuperscript{9}, CN, SO\textsubscript{2}CH\textsubscript{3}, N(R\textsuperscript{16})\textsubscript{2} and NO\textsubscript{2}; or a group N(R\textsuperscript{16})\textsubscript{2} may form a 4- to 7-membered heterocyclic ring optionally containing a further heteroatom selected from O and NR\textsuperscript{10};
R^7 is hydrogen, C\textsubscript{1-4} alkyl, OR\textsuperscript{6}, N(R\textsuperscript{6})\textsubscript{2} aryl or heteroaryl;
R^8 is C\textsubscript{1-4} alkyl, C\textsubscript{1-4} fluoroalkyl, aryl or heteroaryl;
R^9 is hydrogen, C\textsubscript{1-2} alkyl or C\textsubscript{1-2} fluoroalkyl; and
R\textsuperscript{10} is hydrogen or C\textsubscript{1-4} alkyl;
provided that the compound is not:
a) 4-(5-piperidin-4-yl-[1,2,4]oxadiazol-3-yl)pyridine;
b) 4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)piperidine-1-carboxylic acid 'butyl ester;
c) 4-[5-(4-butylocyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine;
d) 3-[5-(4-butylocyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine; or
e) 3-[5-(4-propylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine.
A further specific group of compounds of the invention which may be mentioned are those of formula (Ic), or a pharmaceutically acceptable salt thereof:
where two of W, X and Y are N, and the other is O;
A is (CH₂)ₙ;
B is (CH₂)ₙ where one of the CH₂ groups may be replaced by O, NR₅, S(O)ₘ or C(O);
n is independently 0, 1, 2 or 3;
m is 0, 1 or 2;
R¹ is 3- or 4-pyridyl or 4-pyrimidinyl any of which may be optionally substituted by one or more substituents selected from halo, C₄₋₅ alkyl, C₄₋₅ fluoroalkyl, C₃₋₇ cycloalkyl, OR₅, CN, NO₂, N(R₆)₂, CON(R₆)₂ or a 5- or 6-membered heteroaryl group;
R² is 4- to 7-membered cycloalkyl substituted by R¹, C(O)OR₃, C(O)R₃ or S(O)₂R₃, or 4- to 7-membered heterocyclyl, containing one or two nitrogen atoms, which is unsubstituted or substituted by C(O)OR₅, C(O)R₅ or S(O)₂R₅;
R³ is C₄₋₅ alkyl, C₃₋₇ alkenyl or C₃₋₇ alkynyl any of which may contain a CH₂ group that may be replaced by O, or C₃₋₇ cycloalkyl, aryl or C₄₋₅ alkylaryl, wherein the aryl groups may be substituted with one or more substituents selected from halo, C₄₋₅ alkyl, C₄₋₅ fluoroalkyl, OR₅, CN, N(R₆)₂ and NO₂;
R⁴ is C₃₋₇ alkyl, C₃₋₇ alkenyl or C₃₋₇ alkynyl any of which may contain a CH₂ group that may be replaced by O, or C₃₋₇ cycloalkyl, aryl or C₄₋₅ alkylaryl, wherein the aryl groups may be substituted with one or more substituents selected from halo, C₄₋₅ alkyl, C₄₋₅ fluoroalkyl, OR₅, CN, N(R₆)₂ and NO₂;
R⁵ are independently hydrogen, C₄₋₅ alkyl or C₄₋₅ fluoroalkyl; and
R⁶ are independently hydrogen and C₄₋₅ alkyl;
provided that the compound is not:
a) 4-(5-piperidin-4-yl-[1,2,4]oxadiazol-3-yl)pyridine;
b) 4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)piperidine-1-carboxylic acid 'butyl ester;
c) 4-[5-(4-butylocyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine;
d) 3-[5-(4-butylocyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine; or
e) 3-[5-(4-propylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine.
A preferred group of compounds of the invention are the compounds of formula (Id), and pharmaceutically acceptable salts thereof:

((Id)

where two of W, X and Y are N, and the other is O;
A is -CH=CH- or (CH₂)ₙ;
B is -CH=CH- or (CH₂)ₙ, where one of the CH₂ groups may be replaced by O, NR₅, S(O)ₘ or C(O);
n is independently 0, 1, 2 or 3, provided that not both n are 0;
m is independently 0, 1 or 2;
R⁸ and R⁹ are independently selected from hydrogen, halo, C₄₋₅ alkyl, C₄₋₅ fluoroalkyl, C₄₋₅ alkenyl, C₄₋₅ alkynyl, C₃₋₇ cycloalkyl, aryl, OR₅, CN, NO₂, S(O)ₘR₆, CON(R₆)₂, N(R₆)₂.
NR^{10}COR^{6}, NR^{10}SO_{2}R^{6}, SO_{2}N(R^{5})_{2}, a 4- to 7-membered heterocycl group and a 5- or 6-
membered heteroaryl group;

Z is C(O)OR^{4}, C(O)R^{2}, S(O)_{2}R^{3}, C(O)NHR^{4} or a 5- or 6-membered nitrogen containing
heteroaryl group;

R^{5} is C_{3-8} alkyl, C_{3-8} alkenyl or C_{3-8} alkynyl, any of which may be optionally substituted
with up to 5 fluoro or chloro atoms, and may contain a CH_{2} group that may be replaced by O, or
C_{3-7} cycloalkyl, aryl, heterocycl, heteroaryl, C_{1-4} alkylC_{3-7} cycloalkyl, C_{1-4} alkylaryl, C_{1-4}
alkylheterocycl or C_{1-4} alkylheteroaryl, any of which may be optionally substituted with one or
more substituents selected from halo, C_{1-4} alkyl, C_{1-4} fluoroalkyl, OR^{6}, CN, CO_{2}C_{1-4} alkyl, N(R^{5})_{2}
and NO_{2};

R^{6} is C_{2-8} alkyl, C_{2-8} alkenyl or C_{2-8} alkynyl, any of which may be optionally substituted
with up to 5 fluoro or chloro atoms, and may contain a CH_{2} group that may be replaced by O, or
C_{3-7} cycloalkyl, aryl, heterocycl, heteroaryl, C_{1-4} alkylC_{3-7} cycloalkyl, C_{1-4} alkylaryl, C_{1-4}
alkylheterocycl or C_{1-4} alkylheteroaryl, any of which may be substituted with one or more
substituents selected from halo, C_{1-4} alkyl, C_{1-4} fluoroalkyl, OR^{6}, CN, CO_{2}C_{1-4} alkyl, N(R^{5})_{2}
and NO_{2};

R^{7} are independently hydrogen, or C_{1-4} alkyl, C_{3-7} cycloalkyl, aryl, heterocycl or
heteroaryl, wherein the cyclic groups may be substituted with one or more substituents selected
from halo, C_{1-4} alkyl, C_{1-4} fluoroalkyl, OR^{6}, CN, SO_{2}CH_{2}, N(R^{10})_{2} and NO_{2}; or a group N(R^{10})_{2}
may form a 4- to 7-membered heterocyclic ring optionally containing a further heteroatom
selected from O and NR^{10};

R^{9} is hydrogen, C_{1-2} alkyl or C_{1-2} fluoroalkyl; and

R^{10} is hydrogen or C_{1-4} alkyl.

A further preferred group of compounds of the invention are the compounds of formula
(Ie), and pharmaceutically acceptable salts thereof:

\[ \text{\chem{R^{1} X Y Q - (CH_{2})_{p} N(O - R^{4})}} \]

wherein one of X and Y is N, and the other is O;

Q is O, NR^{5} or CH_{2};

R is hydrogen, halo, C_{1-4} alkyl, C_{1-4} fluoroalkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7}
cycloalkyl, aryl, OR^{6}, CN, NO_{2}, S(O)_{m}R^{6}, CON(R^{6})_{2}, N(R^{6})_{2}, NR^{10}COR^{6}, NR^{10}SO_{2}R^{6},
SO_{2}N(R^{6})_{2}, a 4- to 7-membered heterocycl group or a 5- or 6-membered heteroaryl group;

R^{4} is C_{2-8} alkyl, C_{2-8} alkenyl or C_{2-8} alkynyl, any of which may be optionally substituted
with up to 5 fluoro or chloro atoms, and contain a CH_{2} group that may be replaced by O, or C_{3-7}
cycloalkyl, aryl, heterocycl, heteroaryl, C_{1-4} alkylC_{3-7} cycloalkyl, C_{1-4} alkylaryl, C_{1-4}
alkylheterocycl or C_{1-4} alkylheteroaryl, any of which may be substituted with one or more
substituents selected from halo, C_{1-4} alkyl, C_{1-4} fluoroalkyl, OR^{6}, CN, CO_{2}C_{1-4} alkyl, N(R^{5})_{2}
and NO_{2};

R^{5} is C_{1-4} alkyl;
R^6 are independently hydrogen, or C_{1-4} alkyl, C_{3-7} cycloalkyl, aryl, heterocyclyl or heteroaryl, wherein the cyclic groups may be substituted with one or more substituents selected from halo, C_{1-4} alkyl, C_{1-4} fluoroalkyl, OR, CN, SO_2CH_3, N(R'^8) and NO_2; or a group N(R'^8) may form a 4- to 7-membered heterocyclic ring optionally containing a further heteroatom selected from O and NR; R^8 is hydrogen, C_{1-2} alkyl or C_{1-2} fluoroalkyl; R'^8 is hydrogen or C_{1-4} alkyl; and
p is 0 or 1.
In the compounds of formula (Ie) R is preferably hydrogen, halo, C_{1-4} alkyl, C_{1-4} alkoxy or CN.
Specific compounds of the invention which may be mentioned are those included in the Examples and pharmaceutically acceptable salts thereof.
Particular compounds which may be mentioned are:
4-(3-Pyridin-4-yl-1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid tert-butyl ester,
4-[5-(2-Cyanopyridin-4-yl)-1,2,4]oxadiazol-3-ylmethoxy]piperidine-1-carboxylic acid tert-butyl ester,
4-(3-Pyridin-4-yl-1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid cyclopentyl ester,
4-(3-Pyridin-4-yl-1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid 2,2,2-trichloroethyl ester,
4-[Ethyl-(3-pyridin-4-yl-1,2,4]oxadiazol-5-ylmethyl)amino]piperidine-1-carboxylic acid tert-butyl ester,
4-[Methyl-(3-pyridin-4-yl-1,2,4]oxadiazol-5-ylmethyl)amino]piperidine-1-carboxylic acid cyclopentyl ester, and
4-[[Methyl-(3-pyridin-4-yl-1,2,4]oxadiazol-5-ylmethyl)amino]methyl]piperidine-1-carboxylic acid 2,2,2-trichloroethyl ester,
and pharmaceutically acceptable salts thereof.
As used herein, unless stated otherwise, “alkyl” as well as other groups having the prefix “alk” such as, for example, alkenyl, alkynyl, and the like, means carbon chains which may be linear or branched or combinations thereof. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, heptyl and the like. “Alkenyl”, “alkynyl” and other like terms include carbon chains having at least one unsaturated carbon-carbon bond.
The term “fluoroalkyl” includes alkyl groups substituted by one or more fluorine atoms, e.g. CH_2F, CHF_2 and CF_3.
The term “cycloalkyl” means carbocycles containing no heteroatoms, and includes monocyclic saturated carbocycles. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.
The term “halo” includes fluorine, chlorine, bromine, and iodine atoms.
The term “aryl” includes phenyl and naphthyl, in particular phenyl.
Unless otherwise indicated the term “heterocyclyl” and “heterocyclic ring” includes 4- to 10-membered monocyclic and bicyclic saturated rings, e.g. 4- to 7-membered monocyclic saturated rings, containing up to three heteroatoms selected from N, O and S. Examples of
heterocyclic rings include oxetane, tetrahydrofuran, tetrahydropyran, oxepane, oxocene, thietane, tetrahydrothiophene, tetrahydrothiopyran, thiepane, thiocone, azetidine, pyrrolidine, piperidine, azepane, azocane, [1,3]dioxane, oxazolidine, piperazone, and the like. Other examples of heterocyclic rings include the oxidised forms of the sulfur-containing rings. Thus, tetrahydrothiophene 1-oxide, tetrahydrothiopyran 1,1-dioxide, tetrahydrothiopyran 1-oxide, and tetrahydrothiopyran 1,1-dioxide are also considered to be heterocyclic rings.

Examples of heterocyclic rings that R² may represent include azetidine, pyrrolidine, piperidine and piperazone. R² heterocyclol groups may also contain additional heteroatoms, e.g. morpholine.

Unless otherwise stated, the term “heteroaryl” includes mono- and bicyclic 5- to 10-membered, e.g. monocyclic 5- or 6-membered, heteroaryl rings containing up to 4 heteroatoms selected from N, O and S. Examples of such heteroaryl rings are furyl, thiethyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl. Bicyclic heteroaryl groups include bicyclic heteroaromatic groups where a 5- or 6-membered heteroaryl ring is fused to a phenyl or another heteroaromatic group. Examples of such bicyclic heteroaromatic rings are benzofuran, benzothiophene, indole, benzoxazole, benzothiazole, indazole, benzimidazole, benzotriazole, quinoline, isoquinoline, quinoxaline, quinazoline and purine.

Compounds described herein may contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention includes all such possible diastereomers as well as their racemic mixtures, their substantially pure resolved enantiomers, all possible geometric isomers, and pharmaceutically acceptable salts thereof. The above formula (I) is shown without a definitive stereochemistry at certain positions. The present invention includes all stereoisomers of formula (I) and pharmaceutically acceptable salts thereof. Further, mixtures of stereoisomers as well as isolated specific stereoisomers are also included. During the course of the synthetic procedures used to prepare such compounds, or in using racemization or epimerization procedures known to those skilled in the art, the products of such procedures can be a mixture of stereoisomers.

When a tautomer of the compound of formula (I) exists, the present invention includes any possible tautomers and pharmaceutically acceptable salts thereof, and mixtures thereof, except where specifically drawn or stated otherwise.

When the compound of formula (I) and pharmaceutically acceptable salts thereof exist in the form of solvates or polymorphic forms, the present invention includes any possible solvates and polymorphic forms. A type of a solvent that forms the solvate is not particularly limited so long as the solvent is pharmacologically acceptable. For example, water, ethanol, propanol, acetone or the like can be used.

The term “pharmaceutically acceptable salts” refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids. When the compound of the present invention is acidic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic bases, including inorganic bases and organic bases. Salts derived from such inorganic bases include aluminum, ammonium, calcium, copper (Ic and ous), ferric, ferrous, lithium, magnesium, potassium, sodium, zinc and the like salts. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from
pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, as well as cyclic amines and substituted amines such as naturally occurring and synthesized substituted amines. Other pharmaceutically acceptable organic non-toxic bases from which salts can be formed include arginine, betaine, caffeine, choline, \( N^1,N^1 \)-dibenzylethlenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, \( N \)-ethylmorpholine, \( N \)-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaïne, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

When the compound of the present invention is basic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothentic, phosphoric, succinic, sulfuric, tartaric, p-toluene sulfonic acid and the like.

Since the compounds of formula (I) are intended for pharmaceutical use they are preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure, especially at least 98% pure (% are on a weight for weight basis).

The compounds of formula (I) can be prepared as described below, in which, for illustrative purposes, \(-V-\) is shown as a group of the formula:

![Diagram](attachment:image)

and \( R^1, R^2, R^3, R^4, A, B, W, X \) and \( Y \) are as defined above.

The compounds of formula (I), in which \( X = N, Y = O \) and \( W = N \), may be prepared according to the method illustrated in Scheme 1. The nitriles of formula 2 are either commercially available or can be synthesised using known techniques. Compounds of formula 2 are treated with hydroxylamine in a suitable solvent, such as ethanol-water, at elevated temperature, to afford amidoximes of formula 3 (synthesis of amidoximes is further described by A. R. Martin et al., J. Med. Chem., 2001, 44, 1560). Compounds of formula 3 are subsequently condensed with acids of formula 4, which are themselves either commercially available or can be readily synthesised using known techniques. The condensation first entails activation of compounds of formula 4 by, for example, formation of the mixed anhydride, in which the acid is treated with a chloroformate, such as isobutychloroformate, in the presence of a suitable base, such as triethylamine, in a suitable solvent, such as THF or toluene, followed by addition of compounds of formula 3. Alternatively, compounds of formula 4 may be activated by conversion to the acid halide, generated by treatment of the acid with, for example, oxalyl chloride in a suitable solvent, such as \( \text{CH}_2\text{Cl}_2\)-DMF. The intermediates arising from the condensation of amidoximes of formula 3 and acids of formula 4 are dissolved in an appropriate solvent, such as toluene or xylene, and heated under reflux, with concomitant removal of water by Dean-Stark apparatus or by molecular sieves, to form oxadiazoles of formula (I). Alternatively, amidoximes of formula 3 can firstly be treated with a suitable base, for example sodium hydride, in an appropriate solvent, such as THF, and subsequently esters of formula 5. Heating of this mixture also generates oxadiazoles of formula (I) (this process is further illustrated by R. H. Mach et al, Bioorg. Med. Chem., 2001, 9, 3113).
Compounds of formula (I) in which X = O, Y = N and W = N may be prepared according to the method outlined in Scheme 2. The nitriles of formula 6 are either commercially available or can be synthesised using known techniques. These are converted to the corresponding amidoximes of formula 7, as described above, and subsequently condensed with acids of formula 8, which are commercially available or can readily be synthesised by those skilled in the art. This condensation is performed in a fashion analogous to that described in Scheme 1, to afford the corresponding oxadiazoles of formula (I).

Compounds of formula (I) in which X = N, Y = N and W = O can be synthesised as outlined in Scheme 3. The acyl chlorides of formula 9 are either commercially available or may be synthesised using known methods. The acid hydrazides of formula 10 can be readily obtained by, for example, treating an ethanolic solution of the corresponding ester with hydrazine (for further details see K. M. Kahn et al, Bioorg. Med. Chem., 2003, 11, 1381). Treating the acyl chlorides of formula 9 with the acid hydrazides of formula 10 in a suitable solvent, such as pyridine, affords compounds of formula 11 (further illustrated by V. N. Kerr et al, J. Am. Chem. Soc., 1960, 82, 186), which are then converted by POCl₃ at elevated temperature to compounds of formula (I) (this process is further described by S-A. Chen et al, J. Am. Chem. Soc., 2001, 123, 2296). Similarly, compounds of formula (I) where X = Y = W = N can be prepared via the condensation of the amidrazone analogue of 10 with the appropriate activated carboxylic acid derivative, such as 9. The reactive groups in this reaction may be exchanged, i.e., an amidrazone of formula R¹–A–C(=NH)NH₂ can form a compound of formula (I) by condensation with an activated carboxylic acid derivative LG–C(=O)–B–R² where LG is halogen or oxycarbonyl (P. H. Olesen et al., J. Med. Chem., 2003, 46, 3333–3341).
Compounds of formula (I) where X = N, Y = N, and W = S can also be prepared from compounds of formula 11 by heating with Lawesson’s reagent in a suitable solvent, such as toluene or acetonitrile (D. Alker et al., J. Med. Chem., 1989, 32, 2381-2388). Compounds of formula (I) where X = S, Y = N and W = N can be formed from compounds of formula 12 (Scheme 4) which are commercially available, or can be readily synthesised from the corresponding carbonyl compound and Lawesson’s reagent under standard conditions. Treating a compound of formula 12 with a compound of formula 13 in a suitable solvent such as dichloromethane at about 20°C gives compounds of formula 14. Compounds of formula 13 can be obtained by treating the corresponding dimethylamide with Meerwein’s reagent (for details see M. Brown US 3,092,637). Compounds of formula 14 are then cyclised using hydroxylamine-O-sulfonic acid in the presence of a base, such as pyridine, in a suitable solvent such as methanol (for further details, see A. MacLeod et al, J. Med. Chem., 1990, 33, 2052).

Scheme 4

The regioisomeric derivatives of formula (I), where X = N, Y = S and W = N, can be formed in a similar manner by reversing the functionality of the reactants so the R¹ fragment contains the acetal moiety and the R² fragment contains the thiocarbonyl.

Compounds of formula (I) where W = O, X = N and Y = CH can be formed from compounds of formula 15 (Scheme 5). Compounds of formula 15 are commercially available or synthesised using known techniques. Chlorides of formula 16 are commercially available, or can readily be formed by chlorinating the corresponding ketone using standard conditions, for example, bubbling chlorine gas through a methanol solution of the ketone (for further details see R. Gallucci & R. Goings, J. Org. Chem., 1981, 46, 2532). Mixing a compound of formula 15 with a chloroform of formula 16 in a suitable solvent, such as toluene, with heating, for instance at about 100°C gives compounds of formula (I) (for further information, see A. Hassner et al, Tetrahedron, 1989, 45, 6249). Compounds of formula (I) where W = O, X = CH and Y = N can be formed in a similar fashion by reversing the functionality of the reactants so the R¹ fragment contains the haloketone moiety and the R² fragment contains the C(O)NH₂.

Scheme 5

Alternatively, compounds of formula (I) where X = S, W = N and Y = CH can also be formed from compounds of formula 16. Heating an compound of formula 15 with phosphorus pentasulfide, followed by the addition of a compound of formula 16 followed by further heating gives compounds of formula (I) (for further details, see R. Kurkij & E. Brown, J. Am. Chem. Soc., 1952, 74, 5778). The regioisomeric compounds where X = CH, W = N and Y = S can be
formed is a similar fashion by reversing the functionality of the reactants, so the $R^1$ fragment contains the halo ketone moiety and the $R^2$ fragment contains the $\text{C(O)NH}_2$.

Compounds of formula I where $W = N$, $X = O$ and $Y = \text{CH}$ can be formed from compounds of formula 15 and formula 17 (Scheme 6) under similar conditions to those outlined for Scheme 5. Compounds of formula I where $W = S$, $X = N$ and $Y = \text{CH}$ can also be formed from compounds of formula 15 and formula 17 using the conditions involving phosphorus pentasulfide described above.

Scheme 6

\[
\begin{array}{c}
\text{R}^1\text{A} \text{O} \text{NH}_2 + \text{O} \text{Cl} \text{B} \text{R}^2 \\
\rightarrow \\
\text{R}^1\text{A} \text{O} \text{Y} \text{B} \text{R}^2
\end{array}
\]

Compounds of formula (I) where $X = O$, $Y = N$ and $W = \text{CH}$, and where $X = N$, $Y = O$ and $W = \text{CH}$ can be formed from compounds of formula 20 (Scheme 7). Acylation of compounds of formula 18 with a compound of formula 19, where $Q$ is alkoxide or chloride, can occur under standard conditions, for example, deprotonation of ketone 18 with a suitable base, such as lithium diisopropylamide or potassium ethoxide, in a suitable solvent, such as tetrahydrofuran, generally at low temperature. Treatment of compounds of formula 20 with hydroxylamine, in a suitable solvent, such as ethanol, at elevated temperature, for example $75^\circ\text{C}$, yields compounds of formula (I) as a mixture of both regioisomers of the isoxazole. Using standard separation techniques, such as chromatography on silica gel, the individual isomers can be isolated (for further details, see M. Rowley et al, J. Med. Chem., 1997, 40, 2374).

Scheme 7

\[
\begin{array}{c}
\text{R}^1\text{A} \text{O} + \text{O} \text{Q} \text{B} \text{R}^2 \\
\rightarrow \\
\text{R}^1\text{A} \text{O} \text{B} \text{R}^2
\end{array}
\]

Compounds of formula (I) where $X = S$, $Y = N$ and $W = \text{CH}$ can be formed by hydrogenation of a compound of formula (I) where $X = O$, $Y = N$ and $W = \text{CH}$, with platinum oxide in a suitable solvent such as ethanol, followed by heating with phosphorus pentasulfide to give compounds of formula (I) where $X = S$, $Y = N$ and $W = \text{CH}$ (for further details, see G. Wiegand et al, J. Med. Chem., 1971, 14, 1015). For details of the synthesis of the regioisomer where $X = N$, $Y = S$ and $W = \text{CH}$ also see G. Wiegand \textit{ibid}).

Compounds of formula (I) where $X = N$, $Y = N$ and $W = \text{CH}$ can be formed from compounds of formula 20. Treatment of compounds of formula 20 with hydrazine in a suitable solvent, such as methanol, would give rise to compounds of formula (I) where $X = N$, $Y = N$ and $W = \text{CH}$ (this process is further illustrated by R. Baker et al, J. Med. Chem., 1997, 40, 2374).

Compounds of formula (I) in which $X = \text{CH}$, $Y = N$ and $W = \text{N}$ can be synthesised as described in Scheme 8. Bromides of formula 23 are either commercially available or may be synthesised from the corresponding ketone by, for example, treating an aqueous solution of the ketone with Br$_2$ and HBr (as described by J. Y. Becker et al, Tetrahedron Lett., 2001, 42, 1571). The amidines of formula 22 may be synthesised by known methods, for example by treatment of the corresponding alkyl imidates of formula 21 with ammonia in a suitable solvent, such as
ethanol (as detailed by D. A. Pearson et al., J. Med. Chem., 1996, 39, 1372). The imidates of formula 21 may in turn be generated by, for example, treatment of the corresponding nitrile with HCl in a suitable solvent, such as methanol (for further details see J. P. Lokensgard et al., J. Org. Chem., 1985, 50, 5609). Reaction of amidines of formula 22 with bromides of formula 23 in a suitable solvent, such as DMF, affords compounds of formula (I) (illustrated by N. J. Liverton et al., J. Med. Chem., 1999, 42, 2180).

The regioisomeric compounds where $X = N$, $Y = CH$ and $W = N$ can be formed in a similar fashion by reversing the functionality of the reactants, so the $R^1$ fragment contains the amide moiety and the $R^2$ fragment contains the bromide.

Compounds of formula (I) in which $X = CH$, $Y = CH$ and $W = N$ can be synthesised as illustrated in Scheme 9. Diketones of formula 25 are readily accessible by, for example, the condensation of ketones of formula 24, which are commercially available or are readily synthesised using known techniques, with bromides of formula 23 in a suitable solvent, such as benzene using an appropriate catalyst. Illustrative examples are described by O. G. Kulinkovich et al., Synthesis, 2000, 9, 1259. Using a Paal-Knorr reaction, diketones of formula 25 may be treated with, for example, ammonium carbonate in a suitable solvent, such as ethanol at elevated temperature (for further details see R. A. Jones et al., Tetrahedron, 1996, 52, 8707) to afford compounds of formula (I).

Compounds of formula (I) in which $R^2$ contains either a carbamate or a sulfonamide group may be synthesised as described in Scheme 10. Compounds of formula 26, in which $P$ represents a suitable protecting group, for example tert-butoxycarbonyl (Boc), may be synthesised as outlined in Schemes 1-9 above. The protecting group is firstly removed under suitable conditions to afford compounds of formula 27. In the case of the Boc group this can be achieved by treatment of compounds of formula 26 with a suitable acid, such as trifluoroacetic acid, in an appropriate solvent, such as CH$_2$Cl$_2$. Treatment of compounds of formula 27 with chloroformates of formula 28, which are generally commercially available or can be readily synthesised, in a suitable solvent, such as CH$_2$Cl$_2$, in the presence of a suitable base, such as triethylamine, affords compounds of formula (I). Similarly, compounds of formula 27 may be reacted with sulfonyl chlorides of formula 29, which are generally commercially available or
can readily be synthesised, in a suitable solvent, such as CH₂Cl₂, in the presence of a suitable base, such as triethylamine, to afford compounds of formula (I). Compounds of formula (I) in which R² contains a urea moiety may be prepared by reacting a compound of formula 13 with an isocyanate of formula O=\text{C}=\text{N}-\text{R}³. Furthermore, compounds of formula (I) in which R² is a 4–7-membered heterocyclyl substituted with a heteroaryl group may be prepared by reacting the amine 27 with the appropriate heteroaryl chloride or bromide under Pd(0) catalysis in the presence of a suitable ligand and base (Urgaonkar, S.; Hu, J.-H.; Verkade, J. G. J. Org. Chem. 2003, 68, 8416–8423).

![Scheme 10](image)

Compounds of formula (I) in which R² contains an amide group may be synthesised from compounds of formula 27 and a suitable acid (R²COOH), or activated derivative thereof, in an amide bond forming reaction.

Compounds of formula (I) where R² contains an ester moiety may be synthesised as illustrated in Scheme 11. Compounds of formula 30 in which R is an alkyl group, for example a methyl group, may be synthesised using procedures described in Schemes 1–9. The alkyl group is firstly removed under appropriate conditions to afford compounds of formula 31. For example, when R = Me compounds of formula 30 may be hydrolysed in the presence of a suitable alkali, for example LiOH, in a suitable solvent, such as water-methanol. The acids of formula 31 are then condensed with alcohols of formula 32, which are commercially available or can be synthesised using known techniques. The condensation may be achieved by, for example, treating compounds of formula 31 with alcohols of formula 32 in the presence of thionyl chloride, giving rise to compounds of formula (I).

![Scheme 11](image)

Compounds of formula (I) where R² contains an ether group may also be synthesised from compounds of formula 30 as illustrated in Scheme 12. Compounds of formula 30 may be converted to the corresponding alcohol 33 by the action of a suitable reducing agent, for example diisobutylaluminium hydride, in a suitable solvent, such as CH₂Cl₂, and can then be treated firstly with a suitable base, such as sodium hydride, in a suitable solvent, such as THF,
followed by an appropriate alkylating agent, such as an alkyl halide of formula 34 to afford compounds of formula (I).

Scheme 12

Compounds of formula (I) where B contains a NR₂ group where R₂ is hydrogen can be further transformed into compounds of formula (I) where R₂ is CO(R), SO₂R₂, or an optionally substituted C₆H₄ alkyl group using standard techniques known to those with skill in the art for acylation, sulfonation and reductive amination, respectively.

Compounds of the formula (I) where R¹ is pyridyl optionally substituted with CN can be prepared from the corresponding unsubstituted pyridine by the Reissert reaction (Fife, W. K. *J. Org. Chem.* 1983, 48, 1375–1377). Similar reactions can be used to prepare the compounds where R¹ is pyridyl optionally substituted with halogen (Walters, M. A.; Shay, J. J. *Tetrahedron Lett.* 1995, 36, 7575–7578). The compounds where R¹ is pyridyl optionally substituted with halogen can be transformed into the corresponding compounds where R¹ is pyridyl optionally substituted with C₆H₄ alkyl by transition metal-catalysed cross-coupling reactions (Fürstner, A., et al. *J. Am. Chem. Soc.* 2002, 124, 13856–13863).

Other compounds of formula (I) may be prepared by methods analogous to those described above or by methods known per se.

Further details for the preparation of the compounds of formula (I) are found in the examples.

The compounds of formula (I) may be prepared singly or as compound libraries comprising at least 2, for example 5 to 1,000, compounds and more preferably 10 to 100 compounds of formula (I). Compound libraries may be prepared by a combinatorial “split and mix” approach or by multiple parallel synthesis using either solution or solid phase chemistry, using procedures known to those skilled in the art.

During the synthesis of the compounds of formula (I), labile functional groups in the intermediate compounds, e.g. hydroxy, carboxy and amino groups, may be protected. The protecting groups may be removed at any stage in the synthesis of the compounds of formula (I) or may be present on the final compound of formula (I). A comprehensive discussion of the ways in which various labile functional groups may be protected and methods for cleaving the resulting protected derivatives is given in, for example, Protective Groups in Organic Chemistry, T.W. Greene and P.G.M. Wuts, (1991) Wiley-Interscience, New York, 2nd edition.

Any novel intermediates as defined above are also included within the scope of the invention.

As indicated above the compounds of formula (I) are useful as GPR116 agonists, e.g. for the treatment and/or prophylaxis of obesity and diabetes. For such use the compounds of formula (I) will generally be administered in the form of a pharmaceutical composition.

The invention also provides a compound of formula (I), including the compounds of provisos c) to e), or a pharmaceutically acceptable salt thereof, for use as a pharmaceutical.

The invention also provides a pharmaceutical composition comprising a compound of
formula (I), including the compounds of provisos c) to e), in combination with a pharmaceutically acceptable carrier.

Preferably the composition is comprised of a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of a compound of formula (I), including the compounds of provisos c) to e), or a pharmaceutically acceptable salt thereof.

Moreover, the invention also provides a pharmaceutical composition for the treatment of disease by modulating GPR116, as a regulators of satiety, e.g. resulting in the prophylactic or therapeutic treatment of obesity, or for the treatment of diabetes, comprising a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of compound of formula (I), including the compounds of provisos a) to e), or a pharmaceutically acceptable salt thereof.

The pharmaceutical compositions may optionally comprise other therapeutic ingredients or adjuvants. The compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

In practice, the compounds of formula (I), including the compounds of provisos a) to e), or pharmaceutically acceptable salts thereof, can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g. oral or parenteral (including intravenous).

Thus, the pharmaceutical compositions can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion, or as a water-in-oil liquid emulsion. In addition to the common dosage forms set out above, the compound of formula (I), including the compounds of provisos a) to e), or a pharmaceutically acceptable salt thereof, may also be administered by controlled release means and/or delivery devices. The compositions may be prepared by any of the methods of pharmacy. In general, such methods include a step of bringing into association the active ingredient with the carrier that constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both. The product can then be conveniently shaped into the desired presentation.

The compounds of formula (I), including the compounds of provisos a) to e), or pharmaceutically acceptable salts thereof, can also be included in pharmaceutical compositions in combination with one or more other therapeutically active compounds.

The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen.

In preparing the compositions for oral dosage form, any convenient pharmaceutical media may be employed. For example, water, glycols, oils, alcohols, flavoring agents,
preservatives, coloring agents, and the like may be used to form oral liquid preparations such as suspensions, elixirs and solutions; while carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like may be used to form oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules are the preferred oral dosage units whereby solid pharmaceutical carriers are employed. Optionally, tablets may be coated by standard aqueous or nonaqueous techniques.

A tablet containing the composition of this invention may be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Each tablet preferably contains from about 0.05mg to about 5g of the active ingredient and each cachet or capsule preferably containing from about 0.05mg to about 5g of the active ingredient.

For example, a formulation intended for the oral administration to humans may contain from about 0.5mg to about 5g of active agent, compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Unit dosage forms will generally contain between from about 1mg to about 2g of the active ingredient, typically 25mg, 50mg, 100mg, 200mg, 300mg, 400mg, 500mg, 600mg, 800mg, or 1000mg.

Pharmaceutical compositions of the present invention suitable for parenteral administration may be prepared as solutions or suspensions of the active compounds in water. A suitable surfactant can be included such as, for example, hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Further, a preservative can be included to prevent the detrimental growth of microorganisms.

Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder, or the like. Further, the compositions can be in a form suitable for use in transdermal devices. These formulations may be prepared, using a compound of formula (I), or a pharmaceutically acceptable salt thereof, via conventional processing methods. As an example, a cream or ointment is prepared by admixing hydrophilic material and water, together with about 5wt% to about 10wt% of the compound, to produce a cream or ointment having a desired consistency.

Pharmaceutical compositions of this invention can be in a form suitable for rectal administration wherein the carrier is a solid. It is preferable that the mixture forms unit dose
suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in molds.

In addition to the aforementioned carrier ingredients, the pharmaceutical formulations described above may include, as appropriate, one or more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, preservatives (including anti-oxidants) and the like. Furthermore, other adjuvants can be included to render the formulation isotonic with the blood of the intended recipient. Compositions containing a compound of formula (I), or pharmaceutically acceptable salts thereof, may also be prepared in powder or liquid concentrate form.

Generally, dosage levels on the order of 0.01mg/kg to about 150mg/kg of body weight per day are useful in the treatment of the above-indicated conditions, or alternatively about 0.5mg to about 7g per patient per day. For example, obesity may be effectively treated by the administration of from about 0.01 to 50mg of the compound per kilogram of body weight per day, or alternatively about 0.5mg to about 3.5g per patient per day.

It is understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The compounds of formula (I), including the compounds of provisos a) to e), may be used in the treatment of diseases or conditions in which GPR116 plays a role.

Thus the invention also provides a method for the treatment of a disease or condition in which GPR116 plays a role comprising a step of administering to a subject in need thereof an effective amount of a compound of formula (I), including the compounds of provisos a) to e), or a pharmaceutically acceptable salt thereof.

Diseases or conditions in which GPR116 plays a role include obesity and diabetes. In the context of the present application the treatment of obesity is intended to encompass the treatment of diseases or conditions such as obesity and other eating disorders associated with excessive food intake e.g. by reduction of appetite and body weight, maintenance of weight reduction and prevention of rebound and diabetes (including Type 1 and Type 2 diabetes, impaired glucose tolerance, insulin resistance and diabetic complications such as neuropathy, nephropathy, retinopathy, cataracts, cardiovascular complications and dyslipidaemia). And the treatment of patients who have an abnormal sensitivity to ingested fats leading to functional dyspepsia.

The invention also provides a method for the regulation of satiety comprising a step of administering to a subject in need thereof an effective amount of a compound of formula (I), including the compounds of provisos a) to e), or a pharmaceutically acceptable salt thereof.

The invention also provides a method for the treatment of obesity comprising a step of administering to a subject in need thereof an effective amount of a compound of formula (I), including the compounds of provisos a) to e), or a pharmaceutically acceptable salt thereof.

The invention also provides a method for the treatment of diabetes, including Type 1 and Type 2 diabetes comprising a step of administering to a patient in need thereof an effective amount of a compound of formula (I), including the compounds of provisos a) to e), or a pharmaceutically acceptable salt thereof.
The invention also provides a compound of formula (I), including the compounds of provisos a) to e), or a pharmaceutically acceptable salt thereof, for use in the treatment of a condition as defined above.

The invention also provides the use of a compound of formula (I), including the compounds of provisos a) to e), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a condition as defined above.

In the methods of the invention the term “treatment” includes both therapeutic and prophylactic treatment.

The compounds of formula (I), including the compounds of provisos a) to e), or pharmaceutically acceptable salts thereof, may be administered alone or in combination with one or more other therapeutically active compounds. The other therapeutically active compounds may be for the treatment of the same disease or condition as the compounds of formula (I), including the compounds of provisos a) to e), or a different disease or condition. The therapeutically active compounds may be administered simultaneously, sequentially or separately.

The compounds of formula (I), including the compounds of provisos a) to e), may be administered with other active compounds for the treatment of obesity and/or diabetes, for example insulin and insulin analogs, gastric lipase inhibitors, pancreatic lipase inhibitors, sulfonyl ureas and analogs, biguanides, α2 agonists, glitazones, PPAR-γ agonists, mixed PPAR-α/γ agonists, RXR agonists, fatty acid oxidation inhibitors, α-glucosidase inhibitors, β-agonists, phosphodiesterase inhibitors, lipid lowering agents, glycogen phosphorylase inhibitors, antiobesity agents e.g. pancreatic lipase inhibitors, MCH-1 antagonists and CB-1 antagonists (or inverse agonists), amylin antagonists, lipooxygenase inhibitors, somostatin analogs, glucokinase activators, glucagon antagonists, insulin signalling agonists, PTP1B inhibitors, gluconeogenesis inhibitors, antilypotic agents, GSK inhibitors, galanin receptor agonists, anorectic agents, CCK receptor agonists, leptin, serotoninergic/dopaminergic antiobesity drugs, CRF antagonists, CRF binding proteins, thyromimetic compounds, aldose reductase inhibitors, glucocorticoid receptor antagonists, NHE-1 inhibitors or sorbitol dehydrogenase inhibitors.

Combination therapy comprising the administration of a GPR116 agonist and at least one other antiobesity agent represents a further aspect of the invention.

The present invention also provides a method for the treatment of obesity in a mammal, such as a human, which method comprises administering an effective amount of a GPR116 agonist and another antiobesity agent, to a mammal in need thereof.

The invention also provides the use of a GPR116 agonist and another antiobesity agent for the treatment of obesity.

The invention also provides the use of a GPR116 agonist in the manufacture of a medicament for use in combination with another antiobesity agent, for the treatment of obesity.

The GPR116 agonist and the other antiobesity agent(s) may be co-administered or administered sequentially or separately.

Co-administration includes administration of a formulation which includes both the GPR116 agonist and the other antiobesity agent(s), or the simultaneous or separate administration of different formulations of each agent. Where the pharmacological profiles of the GPR116 agonist and the other antiobesity agent(s) allow it, coadministration of the two agents may be preferred.
The invention also provides the use of a GPR116 agonist and another antiobesity agent in the manufacture of a medicament for the treatment of obesity.

The invention also provides a pharmaceutical composition comprising a GPR116 agonist and another antiobesity agent, and a pharmaceutically acceptable carrier. The invention also encompasses the use of such compositions in the methods described above.

GPR116 agonists which may be used in the combination therapies according to this aspect of the invention include those compounds described herein and also those disclosed in WO04/065380 and WO04/076413.

GPR116 agonists are of particular use in combination with centrally acting antiobesity agents as such combinations may avoid the risk of adverse side effects which may be encountered if two centrally acting antiobesity agents are administered in combination.


Other diseases or conditions in which GPR116 has been suggested to play a role include those described in WO 00/50562 and US 6,468,756, for example cardiovascular disorders, hypertension, respiratory disorders, gestational abnormalities, gastrointestinal disorders, immune disorders, musculoskeletal disorders, depression, phobias, anxiety, mood disorders and Alzheimer’s disease.

All publications, including, but not limited to, patents and patent application cited in this specification, are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as fully set forth.

The invention will now be described by reference to the following examples which are for illustrative purposes and are not to be construed as a limitation of the scope of the present invention.

EXAMPLES
Materials and methods

Column chromatography was carried out on SiO2 (40–63 mesh) unless specified otherwise.

LCMS data were obtained as follows: Atlantis 3μ C18 column (2.1 × 30.0mm, flow rate = 0.85ml/min) eluting with a H2O–MeCN solution containing 0.1% HCO3H over 6min with UV detection at 220nm. Gradient information: 0.0–0.3min 100% H2O; 0.3–4.25 min: Ramp to 10% H2O–90% CH3CN; 4.25min–4.4min: Ramp to 100% CH3CN; 4.4–4.9min: Hold at 100% MeCN;
4.9–6.0 min: Return to 100% H$_2$O. The mass spectra were obtained using an electrospray ionisation source in either the positive (ES$^+$) ion or negative ion (ES$^-$) mode. Atmospheric Pressure Chemical Ionisation (APCI) spectra were obtained on a FinniganMat SSQ 7000C instrument.

$^1$H nmr spectra were recorded on a Varian Mercury 400 spectrometer, operating at 400 MHz. Chemical shifts are reported as ppm relative to tetramethylsilane (δ=0).

HPLC was performed using a Phenomenex™ 10μC$_{18}$ column (210 × 21mm) eluting with a H$_2$O-C$_2$H$_5$CN solution at 20ml/min, with UV detection at 220nm. Typical gradient: 0-0.5min, 10% CH$_3$CN-90%H$_2$O; 0.5min-10min, ramp to 90% CH$_3$CN-10%H$_2$O and hold at 90%CH$_3$CN-10%H$_2$O for 5min; 15min-16min, return to 10% CH$_3$CN-90%H$_2$O.

The syntheses of the following compounds have been reported previously:


(N-Hydroxycarbamimidoylmethyl)carbamic acid tert-butyl ester: WO03/082861;


N-Hydroxy-2-pyridin-3-yacetamide and N-hydroxy-2-pyridin-4-yacetamide: WO 01/047901;

4-Mercaptopiperidine-1-carboxylic acid tert-butyl ester: US Patent 5,317,025;


3-Pyridin-4-yl-[1,2,4]oxadiazole-5-carboxylic acid ethyl ester: EP647635;

4-(3-Bromo-2-oxopropyl)piperidine-1-carboxylic acid tert-butyl ester: WO04/013137.

Abbreviations and acronyms: Ac: Acetyl; Boc: tert-Butyloxycarbonyl; t-Bu: tert-Butyl; CDI: 1,1'-Carbonyldimidazole; dba: dibenzylideneacetone; DMF: N,N-Dimethylformamide; Et: Ethyl; HPLC: High performance liquid chromatography; IH: Isohexane; LDA: Lithium diisopropylamide; mCPBA: 3-Chloroper oxybenzoic acid; Me: Methyl; PDC: Pyridinium dichromate; RP-HPLC: Reverse phase high performance liquid chromatography; RT: Retention time; rt: Room temperature; TFA: Trifluoroacetic acid; THF: Tetrahydrofuran; TMS: Trimethylsilyl.

**Preparation 1**: 4-Carboxymethoxy piperidine-1-carboxylic acid tert-butyl ester

\[
\begin{align*}
\text{HO} & \quad \text{O} \\
\text{N} & \quad \text{O} \\
\end{align*}
\]

Sodium hydride (596mg of a 60% dispersion in oil, 14.9mmol) was added portionwise to a stirred solution of tert-butyl-4-hydroxypiperidine-1-carboxylate (1.0g, 5mmol) in anhydrous THF (20ml) at rt. After 15min, bromoacetic acid (1.38g, 9.94mmol) was introduced and stirring continued for 5h. Additional bromoacetic acid (5mmol) and sodium hydride (5mmol) were added and stirring continued for 24h. The reaction was quenched with water (2ml) and diluted with EtOAc (20ml), which was washed with saturated aqueous NaHCO$_3$ (20ml). Using dilute HCl, the aqueous phase was acidified to pH 2 and the precipitate extracted into EtOAc (50ml).
The organic phase was dried (MgSO₄), evaporated and the residue was purified by flash chromatography (5% AcOH in IH-EtOAc, 7:3 to 1:1) to afford the title acid: RT = 2.89 min; m/z (ES⁺) = 260.3 [M+H]+.

**Preparation 2: 2-Chloro-N-hydroxyisonicotinamidine**

\[
\text{Cl} \quad \text{NH₂} \\
\text{N} \quad \text{O} \\
\text{H} \quad \text{OH}
\]

A solution of sodium carbonate (382 mg, 3.61 mmol) and ammonium hydroxide hydrochloride salt (502 mg, 7.22 mmol) in water (10 ml) was added to 2-chloro-4-cyanopyridine (1.0 g, 7.22 mmol) and the mixture heated to 80°C. Sufficient ethanol (10 ml) was then added to give a homogeneous solution. After 18 h, the solution was cooled and the ethanol removed in vacuo. The solid precipitate was collected by filtration, washed with ethanol and CH₂Cl₂ then dried, affording the title compound: RT = 0.86 min; m/z (ES⁺) = 172.1 [M+H]+.

**Preparation 3: trans-4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)cyclohexanecarboxylic acid methyl ester**

\[
\text{N} \quad \text{O} \\
\text{N} \quad \text{O} \\
\text{H} \quad \text{O}
\]

A solution of cyclohexane-1,4-dicarboxylic acid monomethyl ester (1.053g, 5.66 mmol) and triethylamine (800 μl, 5.66 mmol) in toluene (30 ml) was cooled to 0°C and isobutylchloroformate (735 μl, 5.66 mmol) introduced dropwise. The mixture was stirred at rt for 30 min whereupon activated, powdered 3Å molecular sieves (5 g) and N-hydroxyisonicotinamide (705 mg, 5.14 mmol) were added. The mixture was heated under reflux for 18 h, cooled and filtered through celite. The solvent was removed in vacuo and the residue purified by flash chromatography (IH-EtOAc, 1:1) to afford the title compound: RT = 3.20 min; m/z (ES⁺) = 288.2 [M+H]+.

**Preparation 4: trans-4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)cyclohexanecarboxylic acid**

Water (0.5 ml) and lithium hydroxide (9.2 mg, 0.22 mmol) were added to a stirred solution of 4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)cyclohexanecarboxylic acid methyl ester (Preparation 3, 30 mg, 104 μmol) in THF (1.5 ml). The mixture was heated at 60°C for 1.5 h, cooled and the THF removed in vacuo. Water (5 ml) was added, the aqueous washed with EtOAc (5 ml) and carefully acidified with 1 M HCl to pH 4. The resulting precipitate was extracted into 3% MeOH in EtOAc (2 × 15 ml) and the combined organic phases dried (MgSO₄) and evaporated to afford the title compound: RT = 2.74 min, m/z (ES⁺) = 274.2 [M+H]+.
Preparation 5: cis-[3-(3-Pyridin-4-yl)-1,2,4]oxadiazol-5-yl)cyclopentyl)methanol

Sodium hydride (100mg of a 60% dispersion in oil, 2.5mmol) was added to a solution of 
N-hydroxyisonicotinamide (344mg, 2.5mmol) in anhydrous THF (3ml) and the mixture heated 
under reflux for 1h. cis-Methyl-3-hydroxymethylcyclopentane-1-carboxylate (396mg, 2.5mmol) 
was added in one portion and heating was continued for 18h. After cooling, the solution was 
filtered through celite and the filtrate concentrated in vacuo. The residue was purified by flash 
chromatography (1H:EtOAc, 1: 1 to 0:1) to afford the title compound: RT = 2.59 min, m/z (ES^+) 
= 246.1 [M+H]^+.

Preparation 6: trans-4-(3-Pyridin-4-yl)-1,2,4]oxadiazol-5-yl)cyclohexylmethanol

A solution of trans-4-(3-pyridin-4-yl)-1,2,4]oxadiazol-5-yl)cyclohexanecarboxylic acid 
methyl ester (Preparation 3, 200mg, 0.696mmol) in dry CH2Cl2 (13ml) was cooled to -30°C 
and diisobutylaluminium hydride (1.59ml of a 1M solution in toluene, 1.59mmol) introduced 
dropwise. After 30min the reaction was quenched with 2M HCl (6ml), the mixture warmed to rt 
and partitioned between 2M HCl (10ml) and CH2Cl2 (10ml). The aqueous phase was neutralised 
using 2M NaOH then extracted with CH2Cl2 (4x20ml). The combined organics were dried 
(MgSO4) and evaporated to afford the title compound: RT = 2.59 min, m/z (ES^+) = 260.2 
[M+H]^+.

Preparation 7: trans-N-Hydroxy-4-pentylcyclohexylamidine

A solution of potassium carbonate (2.49g, 18mmol) and NH2OH.HCl (2.50g, 36mmol) 
in water (15ml) was added to trans-4-pentylcyclohexanecarbonitrile (4.30g, 24mmol) and the 
mixture heated to 80°C. Sufficient ethanol (approx. 45ml) was then added to give a homogeneous solution. After 10h, the solution was cooled, diluted with water (200ml) and the 
solid material collected by filtration. The solid was dissolved in EtOAc (150ml) and the 
resulting solution washed with brine (50ml) and dried (MgSO4). The solvent was reduced in 
volume to 15ml and hexane (60ml) added to precipitate the title compound, which was collected 
by filtration: RT = 2.86 min, m/z (ES^+) = 213.2 [M+H]^+.

Preparation 8: (3-Pyridin-4-yl)-1,2,4]oxadiazol-5-ylmethyl)carbamic acid tert-butyl ester
A solution of tert-butoxycarbonylaminoacetic acid (1.0g, 5.71mmol) and triethylamine (802µl, 5.71mmol) in toluene (30ml) was cooled to 0°C and isobutylchloroformate (740µl, 5.71mmol) introduced dropwise. The reaction mixture was stirred at 0°C for 10min and at rt for 30min, whereupon N-hydroxysonicotinamidine (652mg, 4.76mmol) and powdered 3Å molecular sieves (4g) were added. After heating under reflux for 12h the reaction was cooled, filtered through celite and the solvent removed in vacuo. The residue was dissolved in EtOAc (200ml) and washed with water (30ml) and saturated aqueous NaHCO₃ (30ml), then dried (MgSO₄). The solvent was removed and the residue purified by flash chromatography (IH-EtOAc, 2:3) to afford the title compound: RT = 2.97 min; m/z (ES⁺) = 277.1 [M+H]⁺.

**Preparation 9: C-(3-Pyrind-4-yl-[1,2,4]oxadiazol-5-yl)methylamine**

Trifluoroacetic acid (6.5ml) was added to a solution of (3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)carbamic acid tert-butyl ester (Preparation 8, 420mg, 1.52mmol) in CH₂Cl₂ (10ml) and the mixture stirred at rt for 2h. The solvent was evaporated and the residue dissolved in EtOAc (100ml). After washing with saturated aqueous Na₂CO₃ (25ml), the aqueous phase was re-extracted with 5% MeOH in CH₂Cl₂ (7x25ml) and the combined organic phases dried (MgSO₄). The solvent was removed to afford the title compound: RT = 0.25min; m/z (ES⁺) = 177.1 [M+H]⁺.

**Preparation 10: 3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethylcarbolic acid isobutyl ester**

Isobutylichloroformate (11.67ml, 90mmol) was added to a solution of hydroxyacetic acid (3.42g, 45mmol) and triethylamine (12.65ml, 90mmol) in toluene (220ml) at 0°C. After stirring at rt for 1h, N-hydroxysonicotinamidine (6.17g, 45mmol) and powdered 3Å molecular sieves (20g) were added. After heating under reflux for 18h, the cooled mixture was filtered through celite, the solvent evaporated and the residue purified by flash chromatography (IH-EtOAc, 1:1) to afford the title compound: RT = 3.51min; m/z (ES⁺) = 278.0 [M+H]⁺.

**Preparation 11: (3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)methanol**

A stirred solution of 3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethylcarbolic acid isobutyl ester (Preparation 10, 5.94g, 21.45mmol) in methanol (75ml) at rt was treated with 2M
aqueous sodium hydroxide (11.8ml, 23.6mmol). After 10min the solvent was removed and the residue purified by flash chromatography (EtOAc) to afford the title compound: RT = 1.30min; m/z (ES⁺) = 178.0 [M+H]⁺.

**Preparation 12**: Methanesulfonic acid 3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl ester

![Methanesulfonic acid 3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl ester](image)

Methanesulfonyl chloride (0.50ml, 6.50mmol) was added to a stirred solution of (3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)methanol (1g, 5.65mmol) and triethylamine (0.953ml, 6.78mmol) in CH₂Cl₂ (30ml) at 0°C. After 10min, water (20ml) was added and the aqueous phase extracted with CH₂Cl₂ (20ml). The combined organic phases were dried (MgSO₄) and evaporated to afford the title compound: RT = 2.32min; m/z (ES⁺) = 256.0 [M+H]⁺.

**Preparation 13**: 4-Carbamoylmethoxyxypiperidine-1-carboxylic acid tert-butyl ester

![4-Carbamoylmethoxyxypiperidine-1-carboxylic acid tert-butyl ester](image)

A solution of 4-carboxymethoxyxypiperidine-1-carboxylic acid tert-butyl ester (Preparation 1, 14.13g, 54.7mmol) and triethylamine (7.68ml, 65.6mmol) in anhydrous THF (250ml) was cooled to 0°C and isobutylchloroformate (8.51ml, 65.6mmol) introduced dropwise. After stirring at 0°C for 30min, the reaction mixture was cooled to -20°C and added rapidly via cannula to a solution of 0.7M ammonia in anhydrous CH₂Cl₂ (250ml, 180mmol) at -70°C. The reaction was allowed to warm to rt and stirred for 1h. The mixture was diluted with CH₂Cl₂ (250ml) and washed with saturated aqueous NaHCO₃ (200ml), 0.5M HCl (200ml) and brine (200ml) then dried (MgSO₄). The solvent was evaporated and the residue purified by flash chromatography (IH-THF 3:7) to afford the title compound: δH (CDCl₃) 1.49 (9H, s), 1.53-1.60 (2H, m), 1.85-1.92 (2H, m), 3.11 (2H, m), 3.58 (1H, m), 3.76-3.83 (2H, m), 3.98 (2H, s), 6.19 (1H, bs), 6.56 (1H, bs).

**Preparation 14**: 4-Cyanomethoxyxypiperidine-1-carboxylic acid tert-butyl ester

![4-Cyanomethoxyxypiperidine-1-carboxylic acid tert-butyl ester](image)

A solution of 4-carbamoylmethoxyxypiperidine-1-carboxylic acid tert-butyl ester (Preparation 13, 235mg, 0.91mmol) and triethylamine (140μl, 1mmol) in anhydrous CH₂Cl₂ (5ml) was cooled to 0°C and a solution of trichloroacetyl chloride (174mg, 0.96mmol) in anhydrous CH₂Cl₂ added dropwise. The reaction mixture was stirred at rt for 1h, the solvent was removed and the residue purified by flash chromatography (IH-EtOAc, 1:1) to afford the title compound: δH (CDCl₃) 1.50 (9H, s), 1.58-1.65 (2H, m), 1.89-1.95 (2H, m), 3.20 (2H, m), 3.74-3.79 (3H, m), 4.33 (2H, s).
Preparation 15: 4-[(N-Hydroxycarbamimidoylmethoxy)piperidine-1-carboxylic acid tert-butyl ester

A solution of potassium carbonate (119mg, 0.86mmol) and NH₂OH.HCl (119mg, 1.71mmol) in water (0.5ml) was added to 4-cyanomethoxypiperidine-1-carboxylic acid tert-butyl ester (Preparation 14, 206mg, 0.857mmol) in ethanol (2ml). The mixture was heated at 75°C for 0.75h, cooled and the ethanol evaporated. The residue was diluted with EtOAc (50ml) and washed with water (2x10ml) and brine (10ml) then dried (MgSO₄). The solvent was removed to afford the title compound: δ_H (CDCl₃) 1.50 (9H, s), 1.50-1.60 (2H, m), 1.85-1.92 (2H, m), 3.13 (2H, m), 3.56 (1H, m), 3.77-3.84 (2H, m), 4.05 (2H, s), 4.82 (2H, bs); RT = 2.70min, m/z (ES⁻) = 274.0 [M+H]⁺.

Preparation 16: 4-[(2-Oxo-2-[N-(pyridine-4-carbonyl)hydrazino]ethoxy)piperidine-1-carboxylic acid tert-butyl ester

A solution of 4-carboxymethoxypiperidine-1-carboxylic acid tert-butyl ester (Preparation 1, 1.25g, 4.82mmol), ethyl-(3-dimethylaminopropyl)carbodiimide (924mg, 4.82mmol) and N-hydroxybenzotriazole (651mg, 4.82mmol) in anhydrous CH₂Cl₂ (30ml) were stirred at rt for 10min. Isonicotinic acid hydrazide (601mg, 4.38mmol) was added in one portion and stirring continued for a further 18h. The reaction mixture was diluted with CH₂Cl₂ (150ml) and washed with water (30ml), saturated aqueous NaHCO₃ (30ml) and brine (30ml). After drying (MgSO₄) the solvent was removed to afford the title compound: RT = 2.89min; m/z (ES⁻) = 379.1 [M+H]⁺.

Preparation 17: 4-[(5-(Piperidin-4-yloxyethyl)]=[1,2,4]oxadiazol-3-yl]pyridine

The tert-butoxycarbonyl group of 4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid tert-butyl ester (Example 1) was removed using the procedure described in Example 51, affording the title compound: RT = 1.84min; m/z (ES⁺) = 261.2 [M+H]⁺.
Preparation 18: 4-Thiocarbamoylemethoxypiperidine-1-carboxylic acid tert-butyl ester

![Chemical Structure]

A solution of 4-carbamoylmethoxypiperidine-1-carboxylic acid tert-butyl ester (Preparation 13, 67.5mg, 260μmol) and Lawesson’s reagent (116mg, 287μmol) in dimethoxyethane (1.5ml) was stirred at rt for 24h. The solvent was evaporated and the residue purified by flash chromatography (5%MeOH in CH₂Cl₂) to afford the title compound: δ_H (CDCl₃) 1.50 (9H, s), 1.55-1.63 (2H, m), 1.88-1.95 (2H, m), 3.12 (2H, ddd), 3.59-3.66 (1H, m), 3.79-3.87 (2H, m), 4.40, (2H, s), 7.65 (1H, bs), 8.04 (1H, bs).

Preparation 19: trans-4-Pentyl-cyclohexanecarboxylic acid N'-(pyridine-4-carbonyl)hydrazide

![Chemical Structure]

Isonicotinic acid hydrazide was reacted with 4-pentylcyclohexane carboxylic acid in a similar fashion to that described in Preparation 16 to afford the title compound: RT = 4.79min; m/z (ES⁺) = 318.0 [M+H]⁺.

Preparation 20: 3-(2-Cyanopyridin-4-yl)propionic acid

![Chemical Structure]

A solution of K₂CO₃ (1.67g, 12.1mmol) in H₂O (30ml) was added to a stirred solution of 3-(2-cyanopyridin-4-yl)propyl acetate (4.94g, 24.2mmol) in MeOH (130ml). After 25min, the MeOH was removed under reduced pressure, then the aqueous phase was extracted three times with EtOAc. The combined organic extracts were dried (MgSO₄), filtered, and concentrated to give a residue that was purified by column chromatography (iH–EtOAc, 1:3) to furnish 4-(3-hydroxypropyl)pyridine-2-carbonitrile: m/z (ES⁺) = 163.1 [M+H]⁺. A solution of this alcohol (500mg, 3.1mmol) in DMF (20ml) was treated with PDC (7g, 18.6mmol) and H₂O (0.5ml). The reaction was stirred for 16h, before being washed with brine, before being dried (MgSO₄), filtered, and concentrated to give the title compound: m/z (ES⁺) = 177.0 [M+H]⁺.

Preparation 21: 4-(3-Aminomethyl-[1,2,4]oxadiazol-5-yl)pyridine-2-carbonitrile
NEt$_3$ (6.6ml, 47.3mmol) was added to a stirred solution of 2-cyanoisonicotinic acid (7.00g, 47.3mmol) in toluene (500ml). The mixture was cooled to 0°C, before being treated with isobutyl chloroformate (6.1ml, 47.3mmol). Stirring was continued at 0°C for 10 min, then the mixture was allowed to warm to rt over 1h, before being treated with (N-hydroxycarbamimidoylmethyl)carbamic acid tert-butyl ester (7.44g, 39.4mmol) and dried 4Å molecular sieves (40g). The reaction was heated under reflux for 16h. On cooling, the mixture was filtered through celite, washing with MeOH. The combined filtrates were concentrated in vacuo, then the residue was dissolved in EtOAc. The EtOAc solution was washed with saturated aqueous Na$_2$CO$_3$ and brine, before being dried (MgSO$_4$). Filtration, solvent evaporation, and column chromatography (IH–EtOAc, 7:3) furnished [5-(2-cyanopyridin-4-yl)-1,2,4]oxadiazol-3-ylmethyl]carbamic acid tert-butyl ester: $m/z$ (ES$^+$) = 603.2 [2M+H]$^+$. A stirred solution of this carbamate (1.95g, 6.5mmol) in CHCl$_3$ (50ml) was treated with TMS–I (2.2ml, 15.6mmol). After 10min, the reaction was treated with MeOH (2.5ml, 62.2mmol), then stirring was continued for a further 10min. The solvents were evaporated off under reduced pressure, then the residue was dissolved in MeOH and adsorbed onto SiO$_2$. Column chromatography (EtOAc then EtOAc–MeOH, 9:1) afforded the title compound: $m/z$ (ES$^+$) = 202.0 [M+H]$^+$.  

**Preparation 22:** 4-(3,5-Dioxo-5-pyrinid-4-ylpentyl)piperidine-1-carboxylic acid tert-butyl ester

CDI (0.63g, 3.9mmol) was added to a solution of 4-(2-carboxyethyl)piperidine-1-carboxylic acid tert-butyl ester (1.00g, 3.9mmol) in anhydrous THF (7.6ml), then the mixture was stirred for 45min. In a separate vessel, 4-acyethylpyridine (0.49g, 4.1mmol) was added slowly to a stirred solution of LDA (2.04ml of a 2.0M solution in heptane–THF–ethylenbenzene, 4.1mmol) in anhydrous THF (15.3ml) at –78°C. After 45 min, the solution of the acylimidazole was added slowly via cannula to the lithiated 4-acyethylpyridine while maintaining the temperature at –78°C. The reaction was allowed to warm to rt over 2h, before being diluted with EtOAc (150ml). The solution was washed with 10% aqueous citric acid (2 × 15ml), saturated aqueous NaHCO$_3$ (2 × 15ml), and brine (20ml), before being dried (MgSO$_4$). Filtration, concentration, and purification by RP-HPLC afforded the title compound: $m/z$ (ES$^+$) = 261.2 [M–Boc+H]$^+$.  

**Preparation 23:** 4-(2,4-Dideox-4-pyrindin-4-ylbutoxy)piperidine-1-carboxylic acid tert-butyl ester
Condensation of 4-acetylpyridine with 4-carboxymethoxypiperidine-1-carboxylic acid 
tert-butyl ester (Preparation 1), employing the protocol described in Preparation 22, afforded 
the title compound: m/z (ES⁺) = 263.2 [M−Boc+H]+.

Preparation 24: 4-(2,4-Dixo-4-pyridin-4-ylbutyl)piperidine-1-carboxylic acid tert-butyl ester

Condensation of 4-acetylpyridine with 4-carboxymethylpiperidine-1-carboxylic acid 
tert-butyl ester, utilising the protocol described in Preparation 22, afforded the title compound: 
m/z (ES⁺) = 247.2 [M−Boc+H]+.

Preparation 25: 4-[3-(Piperidin-4-yloxymethyl)-1,2,4]oxadiazol-5-yl]pyridine-2-carbonitrile

To a stirred solution of 4-[5-(2-cyanopyridin-4-yl)-1,2,4]oxadiazol-3-
ylmethoxy]piperidine-1-carboxylic acid tert-butyl ester (Example 42, 2.0g, 5.2mmol) in 
chloroform (100ml) under argon, was added trimethylsilyl iodide (2.95ml, 20.8mmol) and the 
reaction mixture stirred for 1h. MeOH was added until a solution formed then sodium 
thiosulphate (6.6g, 41.5mmol) was added and the reaction mixture stirred vigorously for 10min. 
The solids were removed by filtration and the filtrate adsorbed onto silica gel. Purification via 
column chromatography (DCM-MeOH, 9:1) afforded the title compound: RT = 1.92min; m/z 
(ES⁺) = 286.0 [M+H]+.

Example 1: 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid tert-
butyl ester

A stirred solution of triethylamine (123µl, 0.87mmol) and 4-carboxymethoxypiperidine-
1-carboxylic acid tert-butyl ester (Preparation 1, 227mg, 0.87mmol) in toluene (10ml) was
treated with isobutylchloroformate (113µl, 0.87mmol). After 20min, activated powdered 3Å molecular sieves (0.7g) and N-hydroxysisonicotinamide (100mg, 0.73mmol) were added and the mixture heated under reflux for 18h. On cooling, the mixture was filtered through celite, the solvent removed *in vacuo* and the residue purified by flash chromatography (II-EtOAc, 7:13) to afford the title compound: RT = 3.29min; *m/z* (ES⁺) 361.3 [M+H]⁺; δH (CDCl₃) 1.40 (9H, s), 1.55-1.63 (2H, m), 1.80-1.92 (2H, m), 3.05-3.15 (2H, m), 3.64-3.79 (3H, m), 4.80 (2H, s), 7.90 (2H, d), 8.75 (2H, d).

The [1,2,4]oxadiazoles in Table 1 were synthesised from the appropriate amidoxime and the corresponding acid, in a similar manner to that described in Example 1.

<table>
<thead>
<tr>
<th>Ex</th>
<th>Structure</th>
<th>Name</th>
<th>RT (min)</th>
<th><em>m/z</em> (ES⁺)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td><img src="image1" alt="Structure" /></td>
<td>4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)piperidine-1-carboxylic acid tert-butyl ester</td>
<td>3.52</td>
<td>331.3 [M+H]⁺</td>
</tr>
<tr>
<td>3</td>
<td><img src="image2" alt="Structure" /></td>
<td>3-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid tert-butyl ester</td>
<td>3.29</td>
<td>361.3 [M+H]⁺</td>
</tr>
<tr>
<td>4</td>
<td><img src="image3" alt="Structure" /></td>
<td>4-[5-(4-Pentylecyclohexylmethyl)-[1,2,4]oxadiazol-3-yl]pyridine</td>
<td>4.97</td>
<td>314.3 [M+H]⁺</td>
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<tr>
<td>5</td>
<td><img src="image4" alt="Structure" /></td>
<td><em>trans</em>-2-Chloro-4-[5-(4-pentylecyclohexane)-[1,2,4]oxadiazol-3-yl]pyridine</td>
<td>5.19</td>
<td>334.3 [M+H]⁺</td>
</tr>
<tr>
<td>6</td>
<td><img src="image5" alt="Structure" /></td>
<td><em>trans</em>-4-[5-(4-Pentylecyclohexane)-[1,2,4]oxadiazol-3-ylmethyl]pyridine</td>
<td>3.77</td>
<td>314.3 [M+H]⁺</td>
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<td>pIC50</td>
<td>Molecular Weight</td>
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</tr>
<tr>
<td>7</td>
<td><img src="image1" alt="Structure" /></td>
<td>4-(3-Pyridin-4-ylmethyl[1,2,4]oxadiazol-5-yl)piperidine-1-carboxylic acid tert-butyl ester</td>
<td>2.67</td>
<td>345.2 [M+H]^+</td>
</tr>
<tr>
<td>8</td>
<td><img src="image2" alt="Structure" /></td>
<td>trans-3-[5-(4-Pentylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine</td>
<td>3.92</td>
<td>314.3 [M+H]^+</td>
</tr>
<tr>
<td>9</td>
<td><img src="image3" alt="Structure" /></td>
<td>4-[5-(4-Butylcyclohexane)-[1,2,4]oxadiazol-3-yl]pyridine</td>
<td>4.69</td>
<td>286.2 [M+H]^+</td>
</tr>
<tr>
<td>10</td>
<td><img src="image4" alt="Structure" /></td>
<td>4-[5-(4-n-Propylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine</td>
<td>4.42</td>
<td>272.3 [M+H]^+</td>
</tr>
<tr>
<td>11</td>
<td><img src="image5" alt="Structure" /></td>
<td>trans-4-[5-(4-Pentylcyclohexane)-[1,2,4]oxadiazol-3-yl]pyridine</td>
<td>4.87</td>
<td>300.3 [M+H]^+</td>
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<tr>
<td>12</td>
<td><img src="image6" alt="Structure" /></td>
<td>4-[2-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)-ethyl]piperidine-1-carboxylic acid tert-butyl ester</td>
<td>3.84</td>
<td>359.2 [M+H]^+</td>
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<tr>
<td>13</td>
<td><img src="image7" alt="Structure" /></td>
<td>4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)piperidine-1-carboxylic acid tert-butyl ester</td>
<td>3.67</td>
<td>345.2 [M+H]^+</td>
</tr>
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</table>

The compounds in Table 2 were also prepared according to the method described in Example 1.
Table 2

<table>
<thead>
<tr>
<th>Ex</th>
<th>Structure</th>
<th>Name</th>
<th>RT (min)</th>
<th>m/z (ES&lt;sup&gt;+&lt;/sup&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td><img src="image" alt="Structure" /></td>
<td>3-[5-(4-Propylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine</td>
<td>4.42</td>
<td>272.3 [M+H]&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td>15</td>
<td><img src="image" alt="Structure" /></td>
<td>3-[5-(4-Butylcyclohexane)-[1,2,4]oxadiazol-3-yl]pyridine</td>
<td>4.76</td>
<td>286.3 [M+H]&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Example 16:** *trans*-4-[3-(4-Pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine-2-carboxylic acid methylamide

![Structure](image)

A stirred solution of *trans*-4-[5-(4-pentylcyclohexane)-[1,2,4]oxadiazol-3-yl]pyridine (Example 11, 100mg, 0.33mmol) and H<sub>2</sub>SO<sub>4</sub> (17.8μl, 0.33mmol) in N-methylformamide (2ml) was cooled to 0°C. Solid FeSO<sub>4</sub>·7H<sub>2</sub>O (23mg, 83μmol) was added followed by H<sub>2</sub>O<sub>2</sub> (63μl of a 27% solution in water, 0.5mmol) and the mixture stirred at 0°C for 2h. A solution of 1M aqueous sodium citrate (1ml) was added and the mixture extracted with CH<sub>2</sub>Cl<sub>2</sub> (2x5ml). The combined organic phases were washed with water (2x5ml), saturated aqueous NaHCO<sub>3</sub> (2x5ml) and brine (5ml) then dried (MgSO<sub>4</sub>). The solvent was removed and the residue purified by flash chromatography (IH-EtOAc, 17:3 to 7:3) to afford the title compound: RT = 4.86min, m/z (ES<sup>+</sup>) = 357.4 [M+H]<sup>+</sup>.

**Example 17:** *trans*-4-[5-(4-Pentylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine-2-carboxylic acid amide

![Structure](image)

A stirred solution of *trans*-4-[5-(4-pentylcyclohexane)-[1,2,4]oxadiazol-3-yl]pyridine (Example 11) and H<sub>2</sub>SO<sub>4</sub> in formamide was treated with FeSO<sub>4</sub>·7H<sub>2</sub>O and H<sub>2</sub>O<sub>2</sub> in a similar way to that described in Example 16 to afford the title compound: RT = 4.66min, m/z (ES<sup>+</sup>) = 343.4 [M+H]<sup>+</sup>.

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Example 18: trans-4-[3-(4-Pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine

A solution of isonicotinic acid (36.2mg, 290μmol) and triethylamine (30mg, 290μmol) in anhydrous THF (3ml) was cooled to 0°C and isobutylchloroformate (39mg, 280μmol) was added. The mixture was stirred at rt for 1h and solid trans-N-hydroxy-4-pentylcyclohexylamidine (Preparation 7, 50mg, 235μmol) added in one portion. After 45min the reaction was diluted with EtOAc (12ml), washed with saturated aqueous NaHCO₃ (3ml) and brine (6ml), then dried (MgSO₄). After evaporation of the solvent, the residue was dissolved in toluene (5ml) and solution heated under gentle reflux for 2h. The solvent was removed and the residue purified by flash chromatography (IH-EtOAc, 2:1) to afford the title compound: RT = 4.97min; m/z (ES⁺) = 300.3 [M+H]⁺.

The [1,2,4]oxadiazoles in Table 3 were synthesized by reacting the appropriate acid with trans-N-hydroxy-4-pentylcyclohexylamidine (Preparation 7), in a manner similar to that described in Example 18.

<table>
<thead>
<tr>
<th>Ex</th>
<th>Structure</th>
<th>Name</th>
<th>RT (min)</th>
<th>m/z (ES⁺)</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td><img src="image" alt="Structure" /></td>
<td>trans-2-Chloro-4-[3-(4-pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine</td>
<td>5.14</td>
<td>334.3 [M+H]⁺</td>
</tr>
<tr>
<td>20</td>
<td><img src="image" alt="Structure" /></td>
<td>trans-3-[3-(4-Pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine</td>
<td>5.11</td>
<td>300.3 [M+H]⁺</td>
</tr>
<tr>
<td>21</td>
<td><img src="image" alt="Structure" /></td>
<td>trans-2-Methyl-3-[3-(4-pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine</td>
<td>4.92</td>
<td>314.3 [M+H]⁺</td>
</tr>
<tr>
<td>22</td>
<td><img src="image" alt="Structure" /></td>
<td>trans-2-Chloro-6-methyl-4-[3-(4-pentylcyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine</td>
<td>5.39</td>
<td>348.3 [M+H]⁺</td>
</tr>
<tr>
<td>23</td>
<td>(\text{trans-4-}[3-(4-\text{Pentylcyclohexyl})-\text{[1,2,4]oxadiazol-5-yl}]\text{pyridine-2-carbonitrile})</td>
<td>4.91</td>
<td>366.4</td>
<td>([\text{M+H+CH}_3\text{CN}]^+)</td>
</tr>
<tr>
<td>24</td>
<td>(\text{trans-2-Chloro-3-}[3-(4-\text{pentylycyclohexyl})-\text{[1,2,4]oxadiazol-5-yl}]\text{pyridine})</td>
<td>4.99</td>
<td>334.3</td>
<td>([\text{M+H}]^+)</td>
</tr>
<tr>
<td>25</td>
<td>(\text{trans-2-Chloro-6-methyl-3-}[3-(4-\text{pentylycyclohexyl})-\text{[1,2,4]oxadiazol-5-yl}]\text{pyridine})</td>
<td>5.34</td>
<td>348.3</td>
<td>([\text{M+H}]^+)</td>
</tr>
<tr>
<td>26</td>
<td>(\text{trans-2-Methyl-5-}[3-(4-\text{pentylycyclohexyl})-\text{[1,2,4]oxadiazol-5-yl}]\text{pyridine})</td>
<td>4.80</td>
<td>314.3</td>
<td>([\text{M+H}]^+)</td>
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<tr>
<td>27</td>
<td>(\text{trans-3-Methyl-5-}[3-(4-\text{pentylycyclohexyl})-\text{[1,2,4]oxadiazol-5-yl}]\text{pyridine})</td>
<td>4.94</td>
<td>314.3</td>
<td>([\text{M+H}]^+)</td>
</tr>
<tr>
<td>28</td>
<td>(\text{trans-2,6-Dichloro-4-}[3-(4-\text{pentylycyclohexyl})-\text{[1,2,4]oxadiazol-5-yl}]\text{pyridine})</td>
<td>5.37</td>
<td>368.3</td>
<td>([\text{M+H}]^+)</td>
</tr>
<tr>
<td>29</td>
<td>(\text{trans-2-Chloro-6-methoxy-4-}[3-(4-\text{pentylycyclohexyl})-\text{[1,2,4]oxadiazol-5-yl}]\text{pyridine})</td>
<td>5.44</td>
<td>364.3</td>
<td>([\text{M+H}]^+)</td>
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<tr>
<td>30</td>
<td>(\text{trans-5-}[3-(4-\text{Pentylcyclohexyl})-\text{[1,2,4]oxadiazol-5-yl}]\text{-2-}[1,2,4]\text{triazol-1-ylpyridine})</td>
<td>5.36</td>
<td>367.4</td>
<td>([\text{M+H}]^+)</td>
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<tr>
<td>No.</td>
<td>Molecular Structure</td>
<td>Chemical Formula</td>
<td>Retention Time</td>
<td>Mass Spectrum</td>
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<tr>
<td>31</td>
<td><img src="image1" alt="Molecule 31" /></td>
<td>2-[3-(4-Pentylycyclohexyl)-[1,2,4]oxadiazol-5-yl]pyrazine</td>
<td>4.72</td>
<td>301.2 [M+H]^+</td>
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<tr>
<td>32</td>
<td><img src="image2" alt="Molecule 32" /></td>
<td>4-[3-(4-Pentylycyclohexyl)-[1,2,4]oxadiazol-5-yl]pyrimidine</td>
<td>4.86</td>
<td>301.2 [M+H]^+</td>
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<tr>
<td>33</td>
<td><img src="image3" alt="Molecule 33" /></td>
<td>trans-5-[3-(4-Pentylycyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine-2-carbonitrile</td>
<td>5.16</td>
<td>325.2 [M+H]^+</td>
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<tr>
<td>34</td>
<td><img src="image4" alt="Molecule 34" /></td>
<td>trans-5-Chloro-2-methylsulfanyl-4-[3-(4-pentylycyclohexyl)-[1,2,4]oxadiazol-5-yl]pyrimidine</td>
<td>5.32</td>
<td>381.1 [M+H]^+</td>
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<tr>
<td>35</td>
<td><img src="image5" alt="Molecule 35" /></td>
<td>trans-2-Fluoro-5-[3-(4-pentylycyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine</td>
<td>5.12</td>
<td>318.2 [M+H]^+</td>
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<tr>
<td>36</td>
<td><img src="image6" alt="Molecule 36" /></td>
<td>trans-2-Fluoro-4-[3-(4-pentylycyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine</td>
<td>5.07</td>
<td>318.2 [M+H]^+</td>
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<tr>
<td>37</td>
<td><img src="image7" alt="Molecule 37" /></td>
<td>trans-2-Imidazol-1-yl-5-[3-(4-pentylycyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine</td>
<td>4.49</td>
<td>366.2 [M+H]^+</td>
</tr>
<tr>
<td>38</td>
<td><img src="image8" alt="Molecule 38" /></td>
<td>trans-2-Methyl-4-[3-(4-pentylycyclohexyl)-[1,2,4]oxadiazol-5-yl]pyridine</td>
<td>5.05</td>
<td>314.2 [M+H]^+</td>
</tr>
</tbody>
</table>
Example 41: 4-(5-Pyridin-4-yl-[1,2,4]oxadiazol-3-ylmethoxy)piperidine-1-carboxylic acid tert-butyl ester

\[
\text{\begin{center}
\begin{tikzpicture}
\end{tikzpicture}
\end{center}}
\]

A solution of isonicotinic acid (31mg, 250\(\mu\)mol) and triethylamine (51mg, 500 \(\mu\)mol) in anhydrous THF was cooled to 0°C and isobutylchloroformate (34mg, 250\(\mu\)mol) was added. The reaction was stirred at rt for 0.5h and solid 4-(N-hydroxycarbamimidoylmethoxy)piperidine-1-carboxylic acid tert-butyl ester (Preparation 15, 54.5mg, 200\(\mu\)mol) added in one portion. After stirring for 40min the solvent was removed, EtOAc added to the residue, and the mixture passed through a small plug of silica, eluting with EtOAc. Following evaporation, the residue was dissolved in toluene (4ml) and heated under reflux for 15h. The solvent was then evaporated and the residue purified by flash chromatography (EtOAc) to afford the title compound: RT = 3.65min, \(m/z\) (ES\(^{+}\)) = 361.2 \([M+H]^{+}\).

The [1,2,4]oxadiazoles in Table 4 were synthesized by condensing the appropriate acid with a suitable amidoxime, in a manner similar to that described in Example 41.

<table>
<thead>
<tr>
<th>Ex</th>
<th>Structure</th>
<th>Name</th>
<th>RT (min)</th>
<th>(m/z) (ES(^{+}))</th>
</tr>
</thead>
</table>
| 42 | \[
\text{\begin{center}
\begin{tikzpicture}
\end{tikzpicture}
\end{center}}
\]
4-[5-(2-Cyanopyridin-4-yl)-[1,2,4]oxadiazol-3-ylmethoxy]piperidine-1-carboxylic acid tert-butyl ester | 3.82 | 386.1 \([M+H]^{+}\) |
<table>
<thead>
<tr>
<th>No.</th>
<th>Structure</th>
<th>Molecular Formula</th>
<th>Molecular Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>43</td>
<td>(E)-4-[5-(2-Pyridin-3-ylvinyl)-1,2,4-oxadiazol-3-ylmethoxy]piperidine-1-carboxylic acid tert-butyl ester</td>
<td>3.49</td>
<td>387.2 [M+H]^+</td>
</tr>
<tr>
<td>44</td>
<td>(E)-4-[5-(2-Pyridin-3-ylvinyl)-1,2,4-oxadiazol-3-yl]piperidine-1-carboxylic acid tert-butyl ester</td>
<td>3.52</td>
<td>357.2 [M+H]^+</td>
</tr>
<tr>
<td>45</td>
<td>(E)-4-[5-(2-Pyridin-3-ylvinyl)-1,2,4-oxadiazol-3-ylmethyl]piperidine-1-carboxylic acid tert-butyl ester</td>
<td>3.62</td>
<td>271.2 [M-Boc+H]^+</td>
</tr>
<tr>
<td>46</td>
<td>(E)-4-[5-(2-Pyridin-4-ylvinyl)-1,2,4-oxadiazol-3-yl]piperidine-1-carboxylic acid tert-butyl ester</td>
<td>3.26</td>
<td>357.2 [M+H]^+</td>
</tr>
<tr>
<td>47</td>
<td>4-[5-(2-Pyridin-4-yl-ethyl)-1,2,4-oxadiazol-3-yl]piperidine-1-carboxylic acid tert-butyl ester</td>
<td>2.76</td>
<td>359.1 [M+H]^+</td>
</tr>
<tr>
<td>48</td>
<td>4-[5-[2-(2-Cyanopyridin-4-yl)ethyl]-1,2,4-oxadiazol-3-yl]piperidine-1-carboxylic acid tert-butyl ester</td>
<td>3.70</td>
<td>384.2 [M+H]^+</td>
</tr>
<tr>
<td>49</td>
<td>4-[5-[2-(2-Cyanopyridin-4-yl)ethyl]-1,2,4-oxadiazol-3-ylmethoxy]piperidine-1-carboxylic acid tert-butyl ester</td>
<td>3.74</td>
<td>414.2 [M+H]^+</td>
</tr>
<tr>
<td>50</td>
<td>4-[5-[2-(2-Cyanopyridin-4-yl)ethyl]-1,2,4-oxadiazol-3-ylmethyl]piperidine-1-carboxylic acid tert-butyl ester</td>
<td>3.76</td>
<td>398.2 [M+H]^+</td>
</tr>
</tbody>
</table>
Example 51: 4-(3-Piperidin-4-yl-[1,2,4]oxadiazol-3-yl)pyridine

Trifluoroacetic acid (20ml) was added to a stirred solution of 4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)piperidine-1-carboxylic acid tert-butyl ester (Example 2, 1.64g, 4.96mmol) in CH₂Cl₂ (35ml). After 2.5h at rt, the solvent was evaporated under reduced pressure. The residual solid was suspended in EtOAc (150ml) and washed with saturated aqueous Na₂CO₃ (20ml). The aqueous was separated and extracted with EtOAc (3x30ml). The combined organic extracts were dried (MgSO₄) and evaporated under reduced pressure to afford the title compound: RT = 3.48min, m/z (ES⁺) = 231.2 [M+H]⁺.

Example 52: 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)piperidine-1-carboxylic acid isobutyl ester

A solution of pyridine (18µl, 0.22mmol) and 4-(5-piperidin-4-yl-[1,2,4]oxadiazol-3-yl)pyridine (Example 51, 50mg, 0.22mmol) in CH₂Cl₂ (4ml) was treated with isobutylchloroformate (54mg, 0.43mmol). The reaction was stirred at rt for 18h then quenched with saturated aqueous NaHCO₃ (1ml). The organic phase was separated, evaporated and the residue purified by flash chromatography (IH-EtOAc, 1:1 to 0:1) to afford the title compound: RT = 3.42min, m/z (ES⁺) = 331.2 [M+H]⁺.

The [1,2,4]oxadiazoles in Table 4 were synthesized in a manner similar to that described in Example 52.

<table>
<thead>
<tr>
<th>Ex</th>
<th>Structure</th>
<th>Name</th>
<th>RT (min)</th>
<th>m/z (ES⁺)</th>
</tr>
</thead>
<tbody>
<tr>
<td>53</td>
<td><img src="image1" alt="Structure" /></td>
<td>4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)piperidine-1-carboxylic acid 2-methoxyethyl ester</td>
<td>2.77</td>
<td>333.2 [M+H]⁺</td>
</tr>
<tr>
<td>54</td>
<td><img src="image2" alt="Structure" /></td>
<td>4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)piperidine-1-carboxylic acid ethyl ester</td>
<td>3.19</td>
<td>303.2 [M+H]⁺</td>
</tr>
</tbody>
</table>
**Example 55**: 3,3-Dimethyl-1-[4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)piperidin-1-yl]butan-1-one

A solution of pyridine (18μl, 0.22mmol) and 4-(5-piperidin-4-yl-[1,2,4]oxadiazol-3-yl)pyridine (Example 51, 50mg, 0.22mmol) in CH₂Cl₂ (4ml) was treated with 3,3-dimethylbutanoyl chloride (58mg, 0.43mmol). The reaction was stirred at rt for 18h then quenched with saturated aqueous NaHCO₃ (1ml). The organic phase was separated, evaporated and the residue purified by flash chromatography (IH-ElOAc, 1:1 to 0:1) to afford the title compound: RT = 3.11 min, m/z (ES⁺) = 329.3 [M+H]⁺.

**Example 56**: 2-Cyclopentyl-1-[4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)piperidin-1-yl]ethanone

4-[5-(Piperidin-4-yl)oxymethyl-[1,2,4]oxadiazol-3-yl]pyridine (Example 51) was reacted with cyclopentylacetyl chloride, in a similar manner to that described in Example 55, to afford the title compound: RT = 3.44 min, m/z (ES⁺) = 341.3 [M+H]⁺.

**Example 57**: 4-[5-[1-(Butane-1-sulfonyle)]piperidin-4-yl-[1,2,4]oxadiazol-3-yl]pyridine

A solution of pyridine (18μl, 0.22mmol) and 4-(5-piperidin-4-yl-[1,2,4]oxadiazol-3-yl)pyridine (Example 51, 50mg, 0.22mmol) in CH₂Cl₂ (4ml) was treated with butane-1-sulfonyl chloride (56μl, 0.43mmol). The reaction was stirred at rt for 18h then quenched with saturated aqueous NaHCO₃ (1ml). The organic phase was separated, dried (MgSO₄) and evaporated. The residue was dissolved in ElOAc (5ml) and extracted into 2M HCl (10ml). The aqueous phase was then basified using 2M NaOH to pH = 8 and extracted with CH₂Cl₂ (2x10ml). The combined organic phases were dried (MgSO₄) and evaporated to afford the title compound: RT = 3.29 min, m/z (ES⁺) = 351.2 [M+H]⁺.

**Example 58**: 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)piperidine-1-carboxylic acid propylamide
1-Propylisocyanate (13 μl, 137 μmol) was added to a solution of 4-(5-piperidin-4-yl-1,2,4]oxadiazol-3-yl)pyridine (Example 51, 15.8 mg, 69 μmol) in CH₂Cl₂ (0.7 ml). After stirring 18 h at rt, the solvent was removed to afford the title compound: RT = 2.72 min; m/z (ES⁺) = 316.3 [M+H]⁺.

**Example 59: 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)piperidine-1-carboxylic acid tert-butylamide**

![Chemical structure](image)

*tert*-Butylisocyanate was reacted with 4-(5-piperidin-4-yl-[1,2,4]oxadiazol-3-yl)pyridine (Example 51) in a similar fashion to that described in Example 58 to afford the title compound: RT = 3.04 min; m/z (ES⁺) = 330.3 [M+H]⁺.

The carbamate esters in Table 5 were produced by reaction of 4-[5-(piperidin-4-yloxy)methyl]-[1,2,4]oxadiazol-3-yl]pyridine (Preparation 17) with the appropriate chloroformate, in a fashion similar to that described in Example 52.

**Table 5**

<table>
<thead>
<tr>
<th>Ex</th>
<th>Structure</th>
<th>Name</th>
<th>RT (min)</th>
<th>m/z (ES⁺)</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td><img src="image" alt="Chemical structure" /></td>
<td>4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)methoxy)piperidine-1-carboxylic acid cyclopentyl ester</td>
<td>3.51</td>
<td>373.4 [M+H]⁺</td>
</tr>
<tr>
<td>61</td>
<td><img src="image" alt="Chemical structure" /></td>
<td>4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)methoxy)piperidine-1-carboxylic acid benzyl ester</td>
<td>3.64</td>
<td>395.3 [M+H]⁺</td>
</tr>
<tr>
<td>62</td>
<td><img src="image" alt="Chemical structure" /></td>
<td>4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)methoxy)piperidine-1-carboxylic acid isobutyl ester</td>
<td>3.49</td>
<td>361.3 [M+H]⁺</td>
</tr>
<tr>
<td>63</td>
<td><img src="image" alt="Chemical structure" /></td>
<td>4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)methoxy)piperidine-1-carboxylic acid ethyl ester</td>
<td>3.03</td>
<td>333.3 [M+H]⁺</td>
</tr>
<tr>
<td>No.</td>
<td>Structural Formula</td>
<td>Molecular Formula</td>
<td>Molecular Weight</td>
<td>Mass Spectral Data</td>
</tr>
<tr>
<td>-----</td>
<td>-------------------</td>
<td>------------------</td>
<td>------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>64</td>
<td><img src="image1" alt="Image" /></td>
<td>4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid cycloheptyl ester</td>
<td>3.92</td>
<td>401.1 [M+H]$^+$</td>
</tr>
<tr>
<td>65</td>
<td><img src="image2" alt="Image" /></td>
<td>4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid methyl ester</td>
<td>2.86</td>
<td>319.3 [M+H]$^+$</td>
</tr>
<tr>
<td>66</td>
<td><img src="image3" alt="Image" /></td>
<td>4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid 2-methoxyethyl ester</td>
<td>2.95</td>
<td>363.2 [M+H]$^+$</td>
</tr>
<tr>
<td>67</td>
<td><img src="image4" alt="Image" /></td>
<td>4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid isopropyl ester</td>
<td>3.34</td>
<td>347.2 [M+H]$^+$</td>
</tr>
<tr>
<td>68</td>
<td><img src="image5" alt="Image" /></td>
<td>4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid 4-methoxyphenyl ester</td>
<td>3.74</td>
<td>411.1 [M+H]$^+$</td>
</tr>
<tr>
<td>69</td>
<td><img src="image6" alt="Image" /></td>
<td>4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid 2,2,2-trichloroethyl ester</td>
<td>3.81</td>
<td>434.8 [M+H]$^+$</td>
</tr>
<tr>
<td>70</td>
<td><img src="image7" alt="Image" /></td>
<td>4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid 4-chlorophenyl ester</td>
<td>3.79</td>
<td>415.1 [M+H]$^+$</td>
</tr>
<tr>
<td>71</td>
<td><img src="image8" alt="Image" /></td>
<td>4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid phenyl ester</td>
<td>3.54</td>
<td>381.1 [M+H]$^+$</td>
</tr>
<tr>
<td>72</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid 2-ethylhexyl ester</td>
<td>4.27</td>
<td>417.2 [M+H]^+</td>
</tr>
<tr>
<td>73</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid propyl ester</td>
<td>3.40</td>
<td>347.1 [M+H]^+</td>
</tr>
<tr>
<td>74</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid hexyl ester</td>
<td>3.95</td>
<td>389.1 [M+H]^+</td>
</tr>
<tr>
<td>75</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid (IR,2S,5R)-2-isopropyl-5-methylcyclohexyl ester</td>
<td>4.44</td>
<td>443.2 [M+H]^+</td>
</tr>
<tr>
<td>76</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid (IS,2R,5S)-2-isopropyl-5-methylcyclohexyl ester</td>
<td>4.39</td>
<td>443.2 [M+H]^+</td>
</tr>
<tr>
<td>77</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid 2,2-dimethylpropyl ester</td>
<td>3.92</td>
<td>375.1 [M+H]^+</td>
</tr>
<tr>
<td>78</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid naphthalen-1-yl ester</td>
<td>3.90</td>
<td>431.1 [M+H]^+</td>
</tr>
<tr>
<td></td>
<td>Structure</td>
<td>Chemical Formula</td>
<td>Mass (M+H)$^+$</td>
<td></td>
</tr>
<tr>
<td>----</td>
<td>-----------</td>
<td>------------------</td>
<td>----------------</td>
<td></td>
</tr>
<tr>
<td>79</td>
<td><img src="image" alt="Structure 79" /></td>
<td>4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid 2-methoxyphenyl ester</td>
<td>3.67</td>
<td>411.1 [M+H]$^+$</td>
</tr>
<tr>
<td>80</td>
<td><img src="image" alt="Structure 80" /></td>
<td>4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid 3-trifluoromethoxyphenyl ester</td>
<td>3.87</td>
<td>449.0 [M+H]$^+$</td>
</tr>
<tr>
<td>81</td>
<td><img src="image" alt="Structure 81" /></td>
<td>4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid prop-2-ynyl ester</td>
<td>3.36</td>
<td>343.1 [M+H]$^+$</td>
</tr>
<tr>
<td>82</td>
<td><img src="image" alt="Structure 82" /></td>
<td>4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid but-2-ynyl ester</td>
<td>3.40</td>
<td>357.2 [M+H]$^+$</td>
</tr>
<tr>
<td>83</td>
<td><img src="image" alt="Structure 83" /></td>
<td>4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid pentyl ester</td>
<td>3.90</td>
<td>375.2 [M+H]$^+$</td>
</tr>
<tr>
<td>84</td>
<td><img src="image" alt="Structure 84" /></td>
<td>4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid $p$-tolyl ester</td>
<td>3.72</td>
<td>395.2 [M+H]$^+$</td>
</tr>
<tr>
<td>85</td>
<td><img src="image" alt="Structure 85" /></td>
<td>4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid 2-chlorophenyl ester</td>
<td>3.72</td>
<td>415.1 [M+H]$^+$</td>
</tr>
<tr>
<td>86</td>
<td><img src="image" alt="Structure 86" /></td>
<td>4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid naphthalen-2-yl ester</td>
<td>3.97</td>
<td>431.1 [M+H]$^+$</td>
</tr>
</tbody>
</table>
4-[5-((Piperidin-4-yloxymethyl)-[1,2,4]oxadiazol-3-yl)pyridine (Preparation 17) was reacted with the appropriate acid chloride, in a manner similar to that described in Example 55, to afford the amides in Table 6.

### Table 6

<table>
<thead>
<tr>
<th>Ex</th>
<th>Structure</th>
<th>Name</th>
<th>RT (min)</th>
<th>m/z (ES&lt;sup&gt;+&lt;/sup&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>90</td>
<td><img src="image" alt="Structure" /></td>
<td>3-Methyl-1-[4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidin-1-yl]-butan-1-one</td>
<td>3.04</td>
<td>345.2 [M+H]&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td>91</td>
<td><img src="image" alt="Structure" /></td>
<td>Phenyl-[4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidin-1-yl]methanone</td>
<td>3.29</td>
<td>365.2 [M+H]&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td>92</td>
<td><img src="image" alt="Structure" /></td>
<td>1-[4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidin-1-yl]butan-1-one</td>
<td>2.90</td>
<td>331.2 [M+H]&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
4-[5-(Piperidin-4-yloxy)methyl]-[1,2,4]oxadiazol-3-yl]pyridine (Preparation 17) was reacted with the appropriate sulfonyl chloride, in a fashion similar to that described in Example 57, to afford the sulfonamides in Table 7.

Table 7

| 97 | 4-[5-[1-(Butane-1-sulfonyl)] piperidin-4-yloxy)methyl]-[1,2,4]oxadiazol-3-yl]pyridine | 3.34 | 381.2 [M+H]^+ |
| 98 | 4-[5-[1-(Propane-1-sulfonyl)] piperidin-4-yloxy)methyl]-[1,2,4]oxadiazol-3-yl]pyridine | 3.12 | 367.1 [M+H]^+ |
The compounds in Table 8 were synthesized by reacting 4-[5-(piperidin-4-yloxy)methyl]-[1,2,4]oxadiazol-3-yl]pyridine (Preparation 17) with the appropriate isocyanate, in a manner similar to that described in Example 58.

Table 8

<table>
<thead>
<tr>
<th>Ex</th>
<th>Structure</th>
<th>Name</th>
<th>RT (min)</th>
<th>m/z (ES⁺)</th>
</tr>
</thead>
<tbody>
<tr>
<td>99</td>
<td><img src="image" alt="Structure" /></td>
<td>4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid tert-butylamide</td>
<td>2.95</td>
<td>360.4 [M+H]⁺</td>
</tr>
<tr>
<td>100</td>
<td><img src="image" alt="Structure" /></td>
<td>4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid o-tolylamide</td>
<td>3.44</td>
<td>394.4 [M+H]⁺</td>
</tr>
</tbody>
</table>

Example 101: trans-4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)cyclohexanecarboxylic acid propyl ester

![Structure](image)

Thionyl chloride (11.5μl, 0.1mmol) was added to a solution of trans-4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)cyclohexanecarboxylic acid (Preparation 4, 22mg, 0.08mmol) in 1-propanol (2ml). The mixture was heated under reflux for 2h, cooled and the solvent removed in vacuo. The residue was dissolved in EtOAc (10ml), washed with saturated aqueous NaHCO₃ (3ml) and brine (5ml), then dried (MgSO₄). Removal of the solvent afforded the title compound: RT = 3.67min, m/z (ES⁺) = 316.3 [M+H]⁺.

The esters in Table 9 were synthesised in a manner similar to that described in Example 101.

Table 9

<table>
<thead>
<tr>
<th>Ex</th>
<th>Structure</th>
<th>Name</th>
<th>RT (min)</th>
<th>m/z (ES⁺)</th>
</tr>
</thead>
<tbody>
<tr>
<td>102</td>
<td><img src="image" alt="Structure" /></td>
<td>trans-4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)cyclohexanecarboxylic acid butyl ester</td>
<td>3.92</td>
<td>330.3 [M+H]⁺</td>
</tr>
</tbody>
</table>
Example 104: *trans*-4-[5-(4-Propoxymethylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine

A solution of *trans*-4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)cyclohexylmethylmethanol (Preparation 6, 50mg, 0.19mmol) in THF (2.5ml) was stirred with sodium hydride (27mg of a 60% dispersion in oil, 0.68mmol) for 1h then 1-bromopropane (70µl, 0.77mmol) and tetrabutylammonium iodide (7mg, 19µmol) were added. The mixture was stirred at rt for 72h, the solvent removed and the residue dissolved in CH₂Cl₂ (10ml). After washing with water (3ml), the organic phase was dried (MgSO₄) and evaporated. Purification of the residue by flash chromatography (IH-EtOAc, 7:3) afforded the title compound: RT = 3.92min, m/z (ES⁺) = 302.3 [M+H]⁺.

Example 105: *trans*-4-[5-(4-Butoxymethylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine

A solution of 4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)cyclohexylmethylmethanol (Preparation 6) in THF was treated with sodium hydride, 1-bromobutane and tetrabutylammonium iodide, as described for Example 104, to afford the title compound: RT = 4.16min, m/z (ES⁺) = 316.3 [M+H]⁺.

Example 106: *cis*-4-[5-(3-Butoxymethylcyclopentyl)-[1,2,4]oxadiazol-3-yl]pyridine

A solution of *cis*-3-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)cyclopentyl)methanol (Preparation 5, 40mg, 0.16mmol) in anhydrous THF (2ml) was treated with sodium hydride (23mg of a 60% dispersion in oil, 0.57mmol) and tetrabutylammonium iodide (6mg, 16µmol). After stirring the mixture at rt for 10min, 1-bromobutane (59µl, 0.65mmol) was introduced and stirring continued for 72h. The solvent was removed in vacuo, the residue dissolved in CH₂Cl₂ (20ml) and washed with water (2x5ml). The organic phase was dried (MgSO₄) and evaporated. Flash chromatography (IH-EtOAc, 7:3) afforded the title compound: RT = 3.99min, m/z (ES⁺) = 302.3 [M+H]⁺.
Example 107: cis-4-[5-(3-Propoxymethylcyclopentyl)-[1,2,4]oxadiazol-3-yl]pyridine

 cis-[3-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-yl)cyclopentyl]methanol (Preparation 5) was reacted with 1-bromopropane in the presence of tetraethylammonium iodide, using a similar procedure to that described in Example 106, to afford the title compound: RT = 3.69 min, m/z (ES⁺) = 288.3 [M+H]⁺.

Example 108: cis-4-[5-(3-Butoxymethylcyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine

 cis-Methyl-3-hydroxymethylcyclohexane-1-carboxylate was reacted with N-hydroxyisonicotinamidine, using the reaction conditions described in Preparation 5, to afford cis-[3-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)cyclohexyl]methanol: RT = 2.70 min, m/z (ES⁺) = 246.1 [M+H]⁺. This was subsequently alkylated with 1-bromobutane, under similar conditions to those described in Example 106, to afford the title compound: RT = 4.11 min, m/z (ES⁺) = 316.3 [M+H]⁺.

Example 109: 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)-3,4,5,6-tetrahydro-2H-[1,3]bipyridinyl

 Sodium tert-butoxide (86 mg, 900 µmol) was added to a solution of 3-chloropyridine (23 mg, 200 µmol), 4-[5-(piperidin-4-ylmethoxy)-[1,2,4]oxadiazol-3-yl]pyridine (Preparation 17, 65 mg, 250 µmol), Pd₂dba₃ (4 mg, 4 µmol) and 2,8,9-trisobutyl-2,5,8,9-tetraaza-1-phospha bicyclo[3.3.3]undecane (6 mg, 16 µmol) in toluene (3 ml) and the resulting mixture heated at 80°C for 48 h. After cooling and filtering through celite, the solvent was removed and the residue purified by HPLC to afford the title compound: RT = 2.64 min; m/z (ES⁺) = 338.0 [M+H]⁺.

The compounds in Table 10 were prepared in a similar fashion to that described in Example 109.
Table 10

<table>
<thead>
<tr>
<th>Ex</th>
<th>Structure</th>
<th>Name</th>
<th>RT (min)</th>
<th>m/z (ES&lt;sup&gt;+&lt;/sup&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>110</td>
<td><img src="image1" alt="Structure" /></td>
<td>2-[4-(3-Pyridin-4-yl-&lt;br&gt;[1,2,4]oxadiazol-5-ylmethoxy)piperidin-1-yl]pyrazine</td>
<td>3.24</td>
<td>339.0 &lt;br&gt;[M+H]&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td>111</td>
<td><img src="image2" alt="Structure" /></td>
<td>2-[4-(3-Pyridin-4-yl-&lt;br&gt;[1,2,4]oxadiazol-5-ylmethoxy)piperidin-1-yl]pyrimidine</td>
<td>3.19</td>
<td>339.0 &lt;br&gt;[M+H]&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Example 112: (4-Pentylcyclohexyl)-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amine

![Structure](image3)

A solution of C-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)methylamine (Preparation 9, 50mg, 284mmol), 4-pentylcyclohexanone (64ml, 340mmol) and sodium triacetoxyborohydride (96mg, 450mmol) in CH<sub>2</sub>Cl<sub>2</sub> (4ml) were stirred 18h at rt. The reaction was quenched by the addition of 2M aqueous sodium hydroxide (2ml) and the mixture diluted with EtOAc (25ml). The organic phase was separated, washed with brine (5ml) and dried (MgSO<sub>4</sub>). The solvent was removed and the residue purified by flash chromatography (IH-EtOAc, 1:1) to afford the title compound: RT = 3.12 min; m/z (ES<sup>+</sup>) = 329.3 [M+H]<sup>+</sup>.

The amines in Table 11 were synthesized in a manner similar to that described in Example 112.

Table 11

<table>
<thead>
<tr>
<th>Ex</th>
<th>Structure</th>
<th>Name</th>
<th>RT (min)</th>
<th>m/z (ES&lt;sup&gt;+&lt;/sup&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>113</td>
<td><img src="image4" alt="Structure" /></td>
<td>(4-Pentylcyclohexyl-methyl)-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amine</td>
<td>3.19</td>
<td>343.2 &lt;br&gt;[M+H]&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td>114</td>
<td><img src="image5" alt="Structure" /></td>
<td>4-[(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amino]piperidin-1-carboxylic acid tert-butyl ester</td>
<td>2.42</td>
<td>360.2 &lt;br&gt;[M+H]&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
Example 117: Methyl-(4-pentylcyclohexyl)-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amine

A solution of (4-pentylcyclohexyl)-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amine (Example 112, 30.9mg, 94μmol) in dichloroethane (1.3ml) at rt was treated with formaldehyde (8.4ml of a 37% aqueous solution, 103μmol) and sodium triacetoxyborohydride (28mg, 132μmol). After stirring for 48h, the solvent was removed and 2M aqueous sodium hydroxide (1ml) added. The mixture was extracted into EtOAc (25ml) which was dried (MgSO₄) and evaporated. The residue was purified by flash chromatography (IH-EtOAc 7:3) to afford the title compound: RT = 3.37min; m/z (ES⁺) = 343.2 [M+H]⁺.

The amines in Table 12 were synthesized in a manner similar to that described in Example 117.

Table 12

<table>
<thead>
<tr>
<th>Ex</th>
<th>Structure</th>
<th>Name</th>
<th>RT (min)</th>
<th>m/z (ES⁺)</th>
</tr>
</thead>
<tbody>
<tr>
<td>118</td>
<td></td>
<td>Methyl-(4-pentylcyclohexylmethyl)-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amine</td>
<td>4.05</td>
<td>357.2 [M+H]⁺</td>
</tr>
<tr>
<td>119</td>
<td></td>
<td>4-[[Methyl-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amino]piperidine-1-carboxylic acid tert-butyl ester]</td>
<td>2.82</td>
<td>374.2 [M+H]⁺</td>
</tr>
<tr>
<td></td>
<td>Structure</td>
<td>Chemical Formula</td>
<td>Molecular Weight (g/mol)</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>-----------</td>
<td>------------------</td>
<td>--------------------------</td>
<td></td>
</tr>
<tr>
<td>120</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>4-[Ethyl-(3-pyridin-4-yl-1,2,4]oxadiazol-5-ylmethyl)amino)piperidine-1-carboxylic acid tert-butyl ester</td>
<td>3.01</td>
<td>388.2 [M+H]+</td>
</tr>
<tr>
<td>121</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>4-[Propyl-(3-pyridin-4-yl-1,2,4]oxadiazol-5-ylmethyl)amino)piperidine-1-carboxylic acid tert-butyl ester</td>
<td>3.39</td>
<td>402.2 [M+H]+</td>
</tr>
<tr>
<td>122</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>4-[Cyclopropylmethyl-(3-pyridin-4-yl-1,2,4]oxadiazol-5-ylmethyl)amino)piperidine-1-carboxylic acid tert-butyl ester</td>
<td>3.17</td>
<td>414.1 [M+H]+</td>
</tr>
<tr>
<td>123</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>4-[Butyl-(3-pyridin-4-yl-1,2,4]oxadiazol-5-ylmethyl)amino)piperidine-1-carboxylic acid tert-butyl ester</td>
<td>3.45</td>
<td>416.1 [M+H]+</td>
</tr>
<tr>
<td>124</td>
<td><img src="image5.png" alt="Structure" /></td>
<td>4-[[Methyl-(3-pyridin-4-yl-1,2,4]oxadiazol-5-ylmethyl)amino][methyl]-piperidine-1-carboxylic acid tert-butyl ester</td>
<td>3.12</td>
<td>388.2 [M+H]+</td>
</tr>
<tr>
<td>125</td>
<td><img src="image6.png" alt="Structure" /></td>
<td>4-[[Ethyl-(3-pyridin-4-yl-1,2,4]oxadiazol-5-ylmethyl)amino][methyl]-piperidine-1-carboxylic acid tert-butyl ester</td>
<td>3.22</td>
<td>402.2 [M+H]+</td>
</tr>
<tr>
<td>126</td>
<td><img src="image7.png" alt="Structure" /></td>
<td>4-[[5-(2-Cyanopyridin-4-yl)-1,2,4]oxadiazol-3-ylmethyl]ethylamino]-piperidine-1-carboxylic acid tert-butyl ester</td>
<td>2.77</td>
<td>413.2 [M+H]+</td>
</tr>
</tbody>
</table>

**Example 127:** 4-[Methyl-(3-pyridin-4-yl-1,2,4]oxadiazol-5-ylmethyl)amino)piperidine-1-carboxylic acid cyclopentyl ester
The tert-butoxycarbonyl group of 4-[methyl-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amino]piperidine-1-carboxylic acid tert-butyl ester (Example 119) was removed using the procedure described in Example 51 to afford methylpiperidin-4-yl-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amine: RT = 0.65min; m/z (ES⁺) = 274.0 [M+H]⁺. Derivatisation of methylpiperidin-4-yl-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amine with cyclopentylchloroformate, using the procedure described for Example 52, afforded the title compound: RT = 3.02min; m/z (ES⁺) = 386.0 [M+H]⁺.

Example 128: 4-([Methyl-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amino]methyl)piperidine-1-carboxylic acid 2,2,2-trichloroethyl ester

The tert-butoxycarbonyl group of 4-([methyl(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amino]methyl)piperidine-1-carboxylic acid tert-butyl ester (Example 124) was removed using the procedure described in Example 51 to afford methylpiperidin-4-ylmethyl-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amine: RT = 0.75min; m/z (ES⁺) = 288.0 [M+H]⁺. Derivatisation of methylpiperidin-4-ylmethyl-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)amine with 2,2,2-trichloroethylchloroformate, using the procedure described for Example 52, afforded the title compound: RT = 3.51min; m/z (ES⁺) = 461.9 [M+H]⁺.

Example 129: 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxymethyl)piperidine-1-carboxylic acid tert-butyl ester

Sodium hydride (19.5mg, 0.49mmol) was added to a solution of (3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)methanol (Preparation 11, 86mg, 0.49mmol) in anhydrous THF (3ml). After stirring at rt for 5min, 15-crown-5 (97μl, 0.49mmol) was added followed by 4-methanesulfonyloxymethylpiperidin-1-carboxylic acid tert-butyl ester (143mg, 0.487mmol). The reaction mixture was heated in a microwave oven (750W) at 100°C for 15min, cooled and the solvent evaporated. The residue was taken up in CH₂Cl₂ (100ml), washed with water (10ml), dried (MgSO₄) and the solvent evaporated. The residue was purified by flash chromatography (IH-EtOAc, 1:1) to afford the title compound: RT = 3.67min; m/z (ES⁺) = 375.2 [M+H]⁺.
**Example 130:** 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl)piperazine-1-carboxylic acid tert-butyl ester

![Chemical structure](image)

Methanesulfonic acid 3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl ester (**Preparation 12**, 56mg, 0.22mmol) and potassium carbonate (30mg, 0.22mmol) were added to a solution of piperazine-1-carboxylic acid tert-butyl ester (37mg, 0.2mmol) in acetonitrile (4ml). The stirred mixture was heated under reflux for 18h, the solvent removed and the residue dissolved in EtOAc-water (90:10, 50ml). The organic phase was separated, washed with brine, dried (MgSO₄) and the solvent removed to give a residue which was purified by flash chromatography (IH-EtOAc, 4:1), affording the title compound: RT = 3.26min; m/z (ES⁺) = 346.1 [M+H]⁺.

**Example 131:** 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethylsulfanyl)piperidine-1-carboxylic acid tert-butyl ester

![Chemical structure](image)

t-BuOK (92mg, 823μmol) and methanesulfonic acid 3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethyl ester (**Preparation 12**, 150mg, 588μmol) were added to a stirred solution of 4-mercaptotetrahydrofuran-1-carboxylic acid tert-butyl ester (191mg, 881μmol) in anhydrous THF (10ml). After 100min, the reaction mixture was diluted with Et₂O, before being washed with NaHCO₃ and brine. The organic layer was dried (MgSO₄), filtered, and concentrated, then the residue was purified by column chromatography (IH-EtOAc, 3:2) to afford the title compound: RT = 3.77min; m/z (ES⁺) = 377.2 [M+H]⁺.

**Example 132:** 4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethanesulfonyl)piperidine-1-carboxylic acid tert-butyl ester

![Chemical structure](image)

mCPBA (111mg of 65% pure, 418μmol) was added to a stirred solution of 4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethylsulfanyl)piperidine-1-carboxylic acid tert-butyl ester (**Example 131**, 105mg, 279μmol) in CH₂Cl₂ (7ml). After 110min, the reaction was quenched with saturated aqueous Na₂CO₃. The organic layer was washed with brine, dried (MgSO₄), filtered, and concentrated. Column chromatographic purification (4:1 EtOAc–IH) afforded the title compound: RT = 3.40min; m/z (ES⁺) = 353.1 [M–t-Bu+2H]⁺.

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Example 133: 4-(5-Pyridin-4-yl-[1,3,4]oxadiazol-2-ylmethoxy)piperidine-1-carboxylic acid tert-butyl ester

![Chemical structure](image)

Triethylamine (149µl, 1.06mmol) was added to stirred solution of 4-{2-oxo-2-[[N-(pyridine-4-carbonyl)hydrazino]ethoxy]piperidine-1-carboxylic acid tert-butyl ester (Preparation 16, 200mg, 0.53mmol) and 2-chloro-1,3-dimethyl-2-imidazolinium hexafluorophosphate (147mg, 0.53mmol) in CH$_2$Cl$_2$ (10ml). After 18h at rt, the solvent was reduced to a small volume and this mixture purified by flash chromatography (EtOAc), affording the title compound: RT = 3.42min; m/z (ES$^+$) = 361.1 [M+H]$^+$.  

Example 134: 3-Pyridin-4-yl-[1,2,4]oxadiazole-5-carboxylic acid (4-pentylcyclohexyl)amide

![Chemical structure](image)

A solution of 3-pyridin-4-yl-[1,2,4]oxadiazole-5-carboxylic acid ethyl ester (50.5mg, 0.23mmol) and 4-pentylcyclohexylamine (39mg, 0.23mmol) in anhydrous toluene (2ml) was treated with trimethylaluminium (345µl of a 2M solution in hexanes, 0.69mmol). After stirring at rt for 18h, saturated aqueous NaHCO$_3$ (2ml) was added and the mixture diluted with CH$_2$Cl$_2$ (25ml). The organic phase was separated, washed with brine (5ml) and dried (MgSO$_4$). The solvent was evaporated and the residue purified by flash chromatography to afford the title compound: RT = 4.14min; m/z (ES$^+$) = 343.2 [M+H]$^+$.  

Example 135: [4-(3-Pyridin-4-yl-[1,2,4]oxadiazol-5-ylmethoxy)piperidin-1-yl]phosphonic acid diphenyl ester

![Chemical structure](image)

A solution of pyridine (31µl, 0.38mmol) and 4-[5-(piperidin-4-yloxy)methyl]-[1,2,4]oxadiazol-3-yl]pyridine (Preparation 17, 49mg, 0.19mmol) in CH$_2$Cl$_2$ (4ml) was treated with phosphorochloridic acid diphenyl ester (103mg, 0.38mmol). The reaction was stirred at rt for 18h then quenched with saturated aqueous NaHCO$_3$ (1ml). The organic phase was separated, evaporated and the residue purified by HPLC to afford the title compound: RT = 3.79min, m/z (ES$^+$) = 493.1 [M+H]$^+$.  

Example 136: 4-(4-Pyridin-4-yl-thiazol-2-ylmethoxy)piperidine-1-carboxylic acid tert-butyl ester
A solution of 2-bromo-1-pyridin-4-yl-ethanone hydrobromide (35mg, 124µmol) and 4-thiocarbamoylmethoxy-piperidine-1-carboxylic acid tert-butyl ester (Preparation 18, 34mg, 124µmol) in methanol (2ml) was heated at 60°C for 1.5h. The reaction mixture was diluted with EtOAc (60ml), washed with saturated aqueous NaHCO₃ (15ml) and brine (15ml) then dried (MgSO₄). The solvent was removed and the residue purified by flash chromatography (EtOAc) to afford the title compound: RT = 2.95min, m/z (ES⁺) = 376.1 [M+H]⁺.

**Example 137:** 4-(2-Pyridin-4-yl-thiazol-4-ylmethyl)piperidine-1-carboxylic acid tert-butyl ester

4-(3-Bromo-2-oxopropyl)piperidine-1-carboxylic acid tert-butyl ester was reacted with thiosisonicotinamide in a manner similar to that described in Example 136 to afford the title compound: RT = 3.39min, m/z (ES⁺) = 360.1 [M+H]⁺.

**Example 138:** trans-4-[5-(4-Pentyl-cyclohexyl)-[1,3,4]thiadiazol-2-yl]pyridine

A solution of 4-pentyl-cyclohexanecarboxylic acid N′-(pyridine-4-carbonyl)hydrazide (Preparation 19, 50mg, 0.158mmol) and Lawesson’s reagent (127mg, 0.32mmol) in toluene (2ml) was heated under reflux for 18h. The solvent was evaporated and the residue purified by flash chromatography (IH-EtOAc, 4:1 then EtOAc) to afford the title compound: RT = 5.02min; m/z (ES⁺) = 316.0 [M+H]⁺.

**Example 139:** 4-(5-Pyridin-4-yl-[1,3,4]thiadiazol-2-ylmethoxy)piperidine-1-carboxylic acid tert-butyl ester

4-(2-Oxo-2-[N′-(pyridine-4-carbonyl)hydrazino]ethoxy)piperidine-1-carboxylic acid tert-butyl ester (Preparation 16) was treated with Lawesson’s reagent in a similar manner to that described in Example 138, affording the title compound: RT = 3.47min, m/z (ES⁺) = 377.1 [M+H]⁺.
Example 140: 4-(5-Pyridin-4-yl-4H-[1,2,4]triazol-3-ylmethoxy)piperidine-1-carboxylic acid tert-butyl ester

A solution of 4-carboxymethoxypiperidine-1-carboxylic acid tert-butyl ester (Preparation 1, 255mg, 0.952mmol) and triethylamine (138μl, 0.982mmol) in toluene was cooled to 0°C and isobutylchloroformate (127μl, 0.982mmol) added. After stirring at rt for 45min 4-pyrindinecarboximidic acid hydrazide (100mg, 0.82mmol) and 3Å powdered molecular sieves (0.82g) were added and the reaction heated under reflux for 18h. On cooling, the mixture was filtered through celite, the filtrate evaporated and the residue dissolved in EtOAc (50ml). After washing with saturated aqueous Na₂CO₃ (10ml) and brine (10ml), the solvent was removed and the residue purified by flash chromatography (EtOAc then 5%MeOH in EtOAc) to afford the title compound: RT = 2.81min; m/z (ES⁺) = 360.1 [M+H]⁺.

Example 141: 4-[2-(5-Pyridin-4-yl-isoxazol-3-yl)ethyl]piperidine-1-carboxylic acid tert-butyl ester

HONH₂·HCl (29mg, 418μmol) and Na₂CO₃ (29mg, 277μmol) were added to a stirred solution of 4-(3,5-dioxo-5-pyridin-4-ylpentyl)piperidine-1-carboxylic acid tert-butyl ester (Preparation 22, 98mg, 271μmol) in EtOH (0.75ml) and H₂O (0.45ml). The reaction was heated at 70°C (bath) for 4h, then the solvents were removed under reduced pressure. The residue was purified by RP-HPLC to afford the title compound: RT = 3.57min; m/z (ES⁺) = 358.3 [M+H]⁺.

Example 142: 4-(5-Pyridin-4-yl-isoxazol-3-ylmethoxy)piperidine-1-carboxylic acid tert-butyl ester

Condensation of HONH₂ with 4-(2,4-dioxo-4-pyridin-4-ylbutoxy)piperidine-1-carboxylic acid tert-butyl ester (Preparation 23), as outlined in Example 141, afforded the title compound: RT = 3.34min; m/z (ES⁺) = 360.3 [M+H]⁺.

Example 143: 4-(5-Pyridin-4-yl-isoxazol-3-ylmethyl)piperidine-1-carboxylic acid tert-butyl ester
Condensation of HONH₂ with 4-(2,4-dioxo-4-pyridin-4-ylbutyl)piperidine-1-carboxylic acid tert-butyl ester (Preparation 24), as outlined in Example 141, afforded the title compound: RT = 3.47 min; m/z (ES⁺) = 344.3 [M+H]⁺.

Examples 144 and 145: 4-[2-(1-Methyl-5-pyridin-4-yl-1H-pyrazol-3-yl)ethyl]piperidine-1-carboxylic acid tert-butyl ester and 4-[2-(2-Methyl-5-pyridin-4-yl-2H-pyrazol-3-yl)ethyl]piperidine-1-carboxylic acid tert-butyl ester

MeNHNH₂ (16 mg, 348 µmol) was added to a stirred solution of 4-(3,5-dioxo-5-pyridin-4-yl-pentyl)piperidine-1-carboxylic acid tert-butyl ester (Preparation 22, 96 mg, 268 µmol) in EtOH (1 ml). The reaction was heated under reflux for 4 h, then the solvents were removed under reduced pressure. The residue was purified by RP-HPLC to afford Example 144: RT = 3.22 min; m/z (ES⁺) = 371.3 [M+H]⁺; and Example 145: RT = 2.99 min; m/z (ES⁺) = 371.3 [M+H]⁺.

Example 146: (E)-4-[5-(2-(2-Cyanopyridin-4-yl)vinyl]-[1,2,4]oxadiazol-3-yl)piperidine-1-carboxylic acid tert-butyl ester

A solution of mCPBA (9.4 mg of 77% pure, 42 µmol) in CHCl₃ (0.5 ml) was added to a stirred solution of (E)-4-[5-(2-pyridin-4-ylvinyl]-[1,2,4]oxadiazol-3-yl)piperidine-1-carboxylic acid tert-butyl ester (Example 46, 15 mg, 42 µmol) in CHCl₃ (1 ml) at 0°C. The mixture was stirred at 20°C for 16 h, before being treated with more mCPBA (2.5 mg of 77% pure, 11 µmol). After 2 h, the reaction was concentrated, then the residue was purified by column chromatography (EtOAc then THF) to yield (E)-4-[5-(1-oxopyridin-4-yl)vinyl]-[1,2,4]oxadiazol-3-yl)piperidine-1-carboxylic acid tert-butyl ester: m/z (ES⁺) = 373.3 [M+H]⁺. This N-oxide (13 mg, 35 µmol) was treated with TMS-CN (14 µl, 130 µmol), NEt₃ (10 µl, 70 µmol), CH₂Cl₂ (250 µl) and Mes₂NOCl (3 µl). After 18 h, the solvents were evaporated and the residue purified by column chromatography (IH–EtOAc, 1:1) to afford the title compound: RT = 3.99 min; m/z (ES⁺) = 382.3 [M+H]⁺.
Example 147: 4-[(5-[2-(2H-Tetrazol-5-yl)pyridin-4-yl]-[1,2,4]oxadiazol-3-ylmethoxy]-piperidine-1-carboxylic acid \textit{tert}-butyl ester

\[ \text{Structure Image} \]

To a stirred solution of 4-[5-(2-cyanopyridin-4-yl)-[1,2,4]oxadiazol-3-ylmethoxy]piperidine-1-carboxylic acid \textit{tert}-butyl ester (Example 42, 52mg, 0.14mmol) in DMF (3ml) heated to 90°C was added sodium azide (9mg, 0.15mmol) as a suspension in DMF (2ml). After 3h, sodium azide (18mg, 0.29mmol) was added in one portion and the reaction mixture stirred at 90°C for a further 16h. The reaction mixture was allowed to cool to rt then all solvents were removed in vacuo. The residue was suspended in EtOAc then filtered through a sinter, washing with EtOAc. The solid was partitioned between EtOAc (20ml) and water (10ml) containing AcOH (5 drops). The layers were separated then the aqueous extracted with EtOAc (3x20ml). The combined organics were washed with brine (20ml), dried (MgSO₄), filtered and concentrated in vacuo to afford the title compound which needed no further purification: RT = 3.44min; \textit{m/z} (ES⁺) = 429.1 [M+H]⁺.

Example 148: 4-[5-(2-Cyanopyridin-4-yl)-[1,2,4]oxadiazol-3-ylmethoxy]piperidine-1-carboxylic acid isopropyl ester

\[ \text{Structure Image} \]

To a stirred solution of 4-[3-(piperidin-4-yloxymethyl)-[1,2,4]oxadiazol-5-yl]pyridine-2-carbonitri le (Preparation 25, 300mg, 1.1mmol) in DCM (10ml) was added triethylamine (0.3ml, 2.1mmol). The resulting solution was transferred to a stirred solution of isopropylchloroformate (2.1ml of a 1M solution in PhMe, 2.1mmol) in DCM (30ml) and stirring was continued for 30min at rt. The reaction mixture was diluted with EtOAc (30ml) then washed successively with water (50ml), saturated aqueous sodium carbonate (50ml) and brine (50ml). The organics were dried (MgSO₄) then adsorbed onto silica gel. Purification via chromatography (EtOAc-I.H, 1:1) afforded the title compound: RT = 3.44min; \textit{m/z} (ES⁺) = 372.04 [M+H]⁺.

Example 149: 4-[5-(2-Cyanopyridin-4-yl)-[1,2,4]oxadiazol-3-ylmethoxy]piperidine-1-carboxylic acid phenyl ester
To a stirred solution of 4-[3-(piperidin-4-yloxyethyl)-1,2,4]oxadiazol-5-yl]pyridine-2-carbonitrile (Preparation 25, 700mg, 2.5mmol) in DCM (30ml) was added triethylamine (0.7ml, 4.9mmol). The resulting solution was transferred to a stirred solution of phenylchloroformate (0.62ml, 4.9mmol) in DCM (30ml) and stirring was continued for 30min at rt. The reaction mixture was diluted with EtOAc (250ml) then washed successively with water (100mL), saturated aqueous sodium carbonate (100ml) and brine (100ml). The organics were dried (MgSO₄) then adsorbed onto silica gel. Purification via chromatography (EtOAc-I.H, 1:1 to 3:2) afforded the title compound: RT = 3.63min; m/z (ES⁺) = 406.01 [M+H]⁺.

The biological activity of the compounds of the invention may be tested in the following assay systems:

**Yeast Reporter Assay**

The yeast cell-based reporter assays have previously been described in the literature (e.g. see Miret J. J. et al, 2002, J. Biol. Chem., 277:6881-6887; Campbell R.M. et al, 1999, Bioorg. Med. Chem. Lett., 9:2413-2418; King K. et al, 1990, Science, 250:121-123; WO 99/14344; WO 00/12704; and US 6,100,042). Briefly, yeast cells have been engineered such that the endogenous yeast G-alpha (GPA1) has been deleted and replaced with G-protein chimera constructed using multiple techniques. Additionally, the endogenous yeast alpha-cell GPCR, Ste3 has been deleted to allow for a homologous expression of a mammalian GPCR of choice. In the yeast, elements of the pheromone signaling transduction pathway, which are conserved in eukaryotic cells (for example, the mitogen-activated protein kinase pathway), drive the expression of Fus1. By placing β-galactosidase (LacZ) under the control of the Fus1 promoter (Fus1p), a system has been developed whereby receptor activation leads to an enzymatic read-out.

Yeast cells were transformed by an adaptation of the lithium acetate method described by Agatep et al, (Agatep, R. et al, 1998, Transformation of Saccharomyces cerevisiae by the lithium acetate/single-stranded carrier DNA/polyethylene glycol (LiAc/ss-DNA/PEG) protocol. Technical Tips Online, Trends Journals, Elsevier). Briefly, yeast cells were grown overnight on yeast tryptone plates (YT). Carrier single-stranded DNA (10μg), 2μg of each of two Fus1p-LacZ reporter plasmids (one with URA selection marker and one with TRP), 2μg of GPR116 (human or mouse receptor) in yeast expression vector (2μg origin of replication) and a lithium acetate/polyethylene glycol/TE buffer was pipetted into an Eppendorf tube. The yeast expression plasmid containing the receptor/ no receptor control has a LEU marker. Yeast cells were inoculated into this mixture and the reaction proceeds at 30°C for 60min. The yeast cells were then heat-shocked at 42°C for 15min. The cells were then washed and spread on selection plates. The selection plates are synthetic defined yeast media minus LEU, URA and TRP (SD-
LUT). After incubating at 30°C for 2-3 days, colonies that grow on the selection plates were then tested in the LacZ assay.

In order to perform fluorimetric enzyme assays for β-galactosidase, yeast cells carrying the human or mouse GPR116 receptor were grown overnight in liquid SD-LUT medium to an unsaturated concentration (i.e. the cells were still dividing and had not yet reached stationary phase). They were diluted in fresh medium to an optimal assay concentration and 90μl of yeast cells are added to 96-well black polystyrene plates (Costar). Compounds, dissolved in DMSO and diluted in a 10% DMSO solution to 10X concentration, were added to the plates and the plates placed at 30°C for 4h. After 4h, the substrate for the β-galactosidase was added to each well. In these experiments, Fluorescein di (β-D-galactopyranoside) was used (FDG), a substrate for the enzyme that releases fluorescein, allowing a fluorimetric read-out. 20μl per well of 500μM FDG/2.5% Triton X100 was added (the detergent was necessary to render the cells permeable). After incubation of the cells with the substrate for 60min, 20μl per well of 1M sodium carbonate was added to terminate the reaction and enhance the fluorescent signal. The plates were then read in a fluorimeter at 485/535nm.

The compounds of the invention give an increase in fluorescent signal of at least ~ 1.5-fold that of the background signal (i.e. the signal obtained in the presence of 1% DMSO without compound).

cAMP Assay

A stable cell line expressing recombinant human GPR116 was established and this cell line was used to investigate the effect of compounds of the invention on intracellular levels of cyclic AMP (cAMP). The cells monolayers were washed with phosphate buffered saline and stimulated at 37°C for 30min with various concentrations of compound in stimulation buffer plus 1% DMSO. Cells were then lysed and cAMP content determined using the Perkin Elmer AlphaScreen™ (Amplified Luminescent Proximity Homogeneous Assay) cAMP kit. Buffers and assay conditions were as described in the manufacturer’s protocol. Compounds of the invention showed a concentration-dependant increase in intracellular cAMP level and generally had an EC50 of <10μM.

In vivo feeding study

The effect of compounds of the invention on body weight and food and water intake was examined in freely-feeding male Sprague-Dawley rats maintained on reverse-phase lighting. Test compounds and reference compounds were dosed by appropriate routes of administration (e.g. intraperitoneally or orally) and measurements made over the following 24 h. Rats were individually housed in polypropylene cages with metal grid floors and a temperature of 21±4°C and 55±20% humidity. Polypropylene trays with cage pads were placed beneath each cage to detect any food spillage. Animals were maintained on a reverse phase light-dark cycle (lights off for 8 h from 09:30-17:30 h) during which time the room was illuminated by red light. Animals had free access to a standard powdered rat diet and tap water during a two week acclimatization period. The diet was contained in glass feeding jars with aluminum lids. Each lid had a 3-4 cm hole in it to allow access to the food. Animals, feeding jars and water bottles were weighed (to the nearest 0.1 g) at the onset of the dark period. The feeding jars and water bottles were subsequently measured 1, 2, 4, 6 and 24 h after animals were dosed with a
compound of the invention and any significant differences between the treatment groups at baseline compared to vehicle-treated controls.

Selected compounds of the invention showed a statistically significant hyperphagic effect at one or more time points at a dose of < 100mg/kg.
WHAT IS CLAIMED IS:

1. A compound of formula (I), pharmaceutically acceptable salt thereof:

   \[ R^1-A-V-B-R^2 \]

   \[ (I) \]

   wherein \( V \) is a 5-membered heteroaryl ring containing up to four heteroatoms selected from O, N and S, optionally substituted by C<sub>1-4</sub> alkyl;

   A is \(-\text{CH} = \text{CH}-\) or \((\text{CH}_2)_n\);

   B is \(-\text{CH} = \text{CH}-\) or \((\text{CH}_2)_m\), where one of the \( \text{CH}_2 \) groups may be replaced by O, NR<sup>5</sup>, S(O)<sub>n</sub>, C(O) or C(O)NR<sup>12</sup>;

   n is independently 0, 1, 2 or 3;

   m is independently 0, 1 or 2;

   \( R^1 \) is 3- or 4-pyridyl, 4- or 5-pyrimidinyl or 2-pyrazinyl, any of which may be optionally substituted by one or more substituents selected from halo, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> fluoroalkyl, C<sub>2-4</sub> alkynyl, C<sub>2-4</sub> alkylnyl, C<sub>3-7</sub> cycloalkyl, aryl, OR<sup>5</sup>, CN, NO<sub>2</sub>, S(O)<sub>n</sub>R<sup>5</sup>, CON(R<sup>9</sup>)<sub>2</sub>, N(R<sup>6</sup>)<sub>2</sub>, NR<sup>10</sup>OR<sup>6</sup>, NR<sup>10</sup>SO<sub>2</sub>R<sup>6</sup>, SO<sub>2</sub>N(R<sup>6</sup>)<sub>2</sub> a 4- to 7-membered heterocyclic group or a 5- or 6-membered heteroaryl group;

   \( R^2 \) is 4- to 7-membered cycloalkyl substituted by R<sup>3</sup>, C(O)OR<sup>3</sup>, C(O)R<sup>3</sup> or S(O)<sub>n</sub>R<sup>3</sup>, or 4- to 7-membered heterocyclic, containing one or two nitrogen atoms which is unsubstituted or substituted by C(O)OR<sup>4</sup>, C(O)R<sup>4</sup>, S(O)<sub>n</sub>R<sup>4</sup>, C(O)NHR<sup>4</sup>, P(O)(OR<sup>11</sup>)<sub>2</sub> or a 5- or 6-membered nitrogen containing heteroaryl group;

   \( R^3 \) is C<sub>3-8</sub> alkyl, C<sub>3-8</sub> alkenyl or C<sub>3-8</sub> alkynyl, any of which may be optionally substituted with up to 5 fluoro or chloro atoms, and may contain a CH<sub>2</sub> group that may be replaced by O, or C<sub>3-7</sub> cycloalkyl, aryl, heterocyclic, heteroaryl, C<sub>1-4</sub> alkylC<sub>3-7</sub> cycloalkyl, C<sub>1-4</sub> alkylnyl, C<sub>1-4</sub> alkylheterocyclyl or C<sub>1-4</sub> alkylheteroaryl, any of which may be optionally substituted with one or more substituents selected from halo, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> fluoroalkyl, OR<sup>6</sup>, CN, CO<sub>2</sub>C<sub>1-4</sub> alkyl, N(R<sup>6</sup>)<sub>2</sub> and NO<sub>2</sub>;

   \( R^4 \) is C<sub>2-8</sub> alkyl, C<sub>2-8</sub> alkenyl or C<sub>2-8</sub> alkynyl, any of which may be optionally substituted with up to 5 fluoro or chloro atoms, and may contain a CH<sub>2</sub> group that may be replaced by O, or C<sub>3-7</sub> cycloalkyl, aryl, heterocyclic, heteroaryl, C<sub>1-4</sub> alkylC<sub>3-7</sub> cycloalkyl, C<sub>1-4</sub> alkylnyl, C<sub>1-4</sub> alkylheterocyclyl or C<sub>1-4</sub> alkylheteroaryl, any of which may be substituted with one or more substituents selected from halo, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> fluoroalkyl, OR<sup>6</sup>, CN, CO<sub>2</sub>C<sub>1-4</sub> alkyl, N(R<sup>6</sup>)<sub>2</sub> and NO<sub>2</sub>;

   \( R^5 \) is hydrogen, C(O)R<sup>7</sup>, S(O)<sub>n</sub>R<sup>5</sup>, C<sub>3-7</sub> cycloalkyl or C<sub>1-4</sub> alkyl optionally substituted by OR<sup>5</sup>, C<sub>3-7</sub> cycloalkyl, aryl, heterocyclic or heteroaryl, wherein the cyclic groups may be substituted with one or more substituents selected from halo, C<sub>1-2</sub> alkyl, C<sub>1-2</sub> fluoroalkyl, OR<sup>6</sup>, CN, N(R<sup>6</sup>)<sub>2</sub> and NO<sub>2</sub>;

   \( R^6 \) are independently hydrogen C<sub>1-4</sub> alkyl, C<sub>3-7</sub> cycloalkyl, aryl, heterocycl or heteroaryl, wherein the cyclic groups may be substituted with one or more substituents selected from halo, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> fluoroalkyl, OR<sup>9</sup>, CN, SO<sub>2</sub>CH<sub>3</sub>, N(R<sup>10</sup>)<sub>2</sub> and NO<sub>2</sub>; or a group N(R<sup>10</sup>)<sub>2</sub> may form a 4- to 7-membered heterocyclic ring optionally containing a further heteroatom selected from O and NR<sup>10</sup>;

   \( R^7 \) is hydrogen, C<sub>1-4</sub> alkyl, OR<sup>6</sup>, N(R<sup>6</sup>)<sub>2</sub>, aryl or heteroaryl;
R^8 is C\textsubscript{1-4} alkyl, C\textsubscript{1-4} fluoroalkyl, aryl or heteroaryl;
R^9 is hydrogen, C\textsubscript{1-2} alkyl or C\textsubscript{1-2} fluoroalkyl;
R^10 is hydrogen or C\textsubscript{1-4} alkyl;
R^11 is phenyl; and
R^12 is hydrogen, C\textsubscript{1-4} alkyl or C\textsubscript{3-7} cycloalkyl;
provided that the compound is not:
a) 4-(5-piperidin-4-yl-[1,2,4]oxadiazol-3-yl)pyridine;
b) 4-(3-pyridin-4-yl-[1,2,4]oxadiazol-5-yl)piperidine-1-carboxylic acid butyl ester;
c) 4-[5-(4-butylocyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine;
d) 3-[5-(4-butylocyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine; or
e) 3-[5-(4-propylocyclohexyl)-[1,2,4]oxadiazol-3-yl]pyridine.

2. A compound according to claim 1, or a pharmaceutically acceptable salt thereof,
wherein V represents a 5-membered heteroaryl ring containing up to three heteroatoms selected
from O, N and S of the formula:

\[ \text{X} \]

\[ \text{Y} \]

\[ \text{W} \]

wherein W, X and Y represent the positions of the heteroatom(s) or otherwise represent
CH.

3. A compound according to claim 2, or a pharmaceutically acceptable salt thereof,
wherein two of W, X and Y are N, and the other is O.

4. A compound according to claim 2 or 3, or a pharmaceutically acceptable salt thereof,
wherein W is N.

5. A compound according to any one of the preceding claims, or a pharmaceutically
acceptable salt thereof, wherein the n groups of A and B do not both represent 0.

6. A compound according to any one of the preceding claims, or a pharmaceutically
acceptable salt thereof, wherein in A, n is 0, 1 or 2.

7. A compound according to any one of the preceding claims, or a pharmaceutically
acceptable salt thereof, wherein in B, n is 2 or 3.

8. A compound according to any one of the preceding claims, or a pharmaceutically
acceptable salt thereof, wherein R^1 is 4-pyridyl optionally substituted by 1 or 2 halo, C\textsubscript{1-4} alkyl,
C\textsubscript{1-4} fluoroalkyl, C\textsubscript{2-4} alkenyl, C\textsubscript{2-4} alkynyl, C\textsubscript{3-7} cycloalkyl, aryl, OR^6, CN, NO\textsubscript{2}, S(O)\textsubscript{m}R^6, CON(R^6)\textsubscript{2}, N(R^6)\textsubscript{2}, NR\textsuperscript{10}COR^6, NR\textsuperscript{10}SO\textsubscript{2}R^6, SO\textsubscript{2}N(R^6)\textsubscript{2}, 4- to 7-membered heterocyclyl or 5- or
6-membered heteroaryl groups.

9. A compound according to claim 8, or a pharmaceutically acceptable salt thereof;
wherein R^1 is 4-pyridyl optionally substituted by halo, C\textsubscript{1-4} alkyl C\textsubscript{1-4} alkoxy or CN.
10. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein $R^4$ is a 4- to 7-membered cycloalkyl substituted by $R^3$, or 4- to 7-membered heterocyclyl containing one nitrogen atom which is substituted by C(O)OR^4.

11. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein $R^3$ is C$_{3-4}$ alkyl which may contain a CH$_2$ group that may be replaced by O, or C$_{3-7}$ cycloalkyl.

12. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein $R^4$ is C$_{2-8}$ alkyl, C$_{2-8}$ alkenyl or C$_{2-8}$ alkynyl, any of which may be optionally substituted with up to 5 fluoro or chloro atoms, and may contain a CH$_2$ group that may be replaced by O, or C$_{3-7}$ cycloalkyl, aryl, 5- to 6-membered heteroaryl containing one or two nitrogen atoms, C$_{1-4}$ alkylC$_{3-7}$ cycloalkyl or C$_{1-4}$ alkyaryl, any of which may be substituted with one or more substituents selected from halo, C$_{1-4}$ alkyl, C$_{1-4}$ fluoroalkyl, OR$^6$ and CO$_2$C$_{1-4}$ alkyl.

13. A compound according to claim 12, or a pharmaceutically acceptable salt thereof, wherein $R^4$ is C$_{3-4}$ alkyl optionally substituted with up to 5 fluoro or chloro atoms, and which may contain a CH$_2$ group that may be replaced by O, or C$_{3-7}$ cycloalkyl.

14. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein $R^5$ is C$_{1-4}$ alkyl.

15. A compound of formula (I) as defined in any one of Examples 1, 3 to 8, 10 to 13, 16 to 50, or 52 to 149, or a pharmaceutically acceptable salt thereof.

16. A compound according to claim 1 having the formula (Id), or a pharmaceutically acceptable salt thereof:

![Diagram](Id)

where two of W, X and Y are N, and the other is O;

A is -CH=CH- or (CH$_2$)$_n$;

B is -CH=CH- or (CH$_2$)$_n$ where one of the CH$_2$ groups may be replaced by O, NR$^5$, S(O)$_m$ or C(O);

$n$ is independently 0, 1, 2 or 3, provided that not both $n$ are 0;

$m$ is independently 0, 1 or 2;

$R^4$ and $R^7$ are independently selected from hydrogen, halo, C$_{1-4}$ alkyl, C$_{1-4}$ fluoroalkyl, C$_{2-4}$ alkenyl, C$_{2-4}$ alkynyl, C$_{3-7}$ cycloalkyl, aryl, OR$^5$, CN, NO$_2$, S(O)$_m$R$^5$, CON(R$^5$)$_2$, N(R$^5$)$_2$, NR$^{10}$COR$^6$, NR$^{10}$SO$_2$R$^6$, SO$_2$N(R$^5$)$_2$, a 4- to 7-membered heterocyclyl group and a 5- or 6-membered heteroaryl group;
Z is C(O)OR, C(O)R, S(O)2R, C(O)NHR or a 5- or 6-membered nitrogen containing heteroaryl group;

R is C3-8 alkyl, C3-8 alkenyl or C3-8 alkynyl, any of which may be optionally substituted with up to 5 fluoro or chloro atoms, and may contain a CH2 group that may be replaced by O, or C3-7 cycloalkyl, aryl, heterocyclyl, heteroaryl, C1-4 alkylC3-7 cycloalkyl, C1-4 alkyllaryl, C1-4 alkylheterocyclyl or C1-4 alkylheteroaryl, any of which may be optionally substituted with one or more substituents selected from halo, C1-4 alkyl, C1-4 fluoroalkyl, OR, CN, CO2C1-4 alkyl, N(R)2 and NO2;

R is C2-8 alkyl, C2-8 alkenyl or C2-8 alkynyl, any of which may be optionally substituted with up to 5 fluoro or chloro atoms, and may contain a CH2 group that may be replaced by O, or C3-7 cycloalkyl, aryl, heterocyclyl, heteroaryl, C1-4 alkylC3-7 cycloalkyl, C1-4 alkyllaryl, C1-4 alkylheterocyclyl or C1-4 alkylheteroaryl, any of which may be substituted with one or more substituents selected from halo, C1-4 alkyl, C1-4 fluoroalkyl, OR, CN, CO2C1-4 alkyl, N(R)2 and NO2;

R is hydrogen or C1-4 alkyl;

R are independently hydrogen, or C1-4 alkyl, C3-7 cycloalkyl, aryl, heterocyclyl or heteroaryl, wherein the cyclic groups may be substituted with one or more substituents selected from halo, C1-4 alkyl, C1-4 fluoroalkyl, OR, CN, SO2CH3, N(R)2 and NO2; or a group N(R)2 or may form a 4- to 7-membered heterocyclic ring optionally containing a further heteroatom selected from O and NR;

R is hydrogen, C1-2 alkyl or C1-2 fluoroalkyl; and

R is hydrogen or C1-4 alkyl.

A compound according to claim having the formula (Ie), or a pharmaceutically acceptable salt thereof:

wherein one of X and Y is N, and the other is O;

Q is O, NR or CH2;

R is hydrogen, halo, C1-4 alkyl, C1-4 fluoroalkyl, C2-4 alkenyl, C2-4 alkynyl, C3-7 cycloalkyl, aryl, OR, CN, NO2, S(O)2R, CON(R)2, N(R)2, NR10COR, NR10SO2R, SO2N(R)2, a 4- to 7-membered heterocyclyl group or a 5- or 6-membered heteroaryl group;

R is C2-8 alkyl, C2-8 alkenyl or C2-8 alkynyl, any of which may be optionally substituted with up to 5 fluoro or chloro atoms, and contain a CH2 group that may be replaced by O, or C3-7 cycloalkyl, aryl, heterocyclyl, heteroaryl, C1-4 alkylC3-7 cycloalkyl, C1-4 alkyllaryl, C1-4 alkylheterocyclyl or C1-4 alkylheteroaryl, any of which may be substituted with one or more substituents selected from halo, C1-4 alkyl, C1-4 fluoroalkyl, OR, CN, CO2C1-4 alkyl, N(R)2 and NO2;

R is C1-4 alkyl;
R^6_{1} are independently hydrogen, or C_{1-4} alkyl, C_{3-7} cycloalkyl, aryl, heterocyclyl or heteroaryl, wherein the cyclic groups may be substituted with one or more substituents selected from halo, C_{1-4} alkyl, C_{1-4} fluoroalkyl, OR^9, CN, SO_{2}CH_{3}, N(R^{10})_{2} and NO_{2}; or a group N(R^{10})_{2} may form a 4- to 7-membered heterocyclic ring optionally containing a further heteroatom selected from O and NR^{10};

R^9 is hydrogen, C_{1-2} alkyl or C_{1-2} fluoroalkyl;
R^{10} is hydrogen or C_{1-4} alkyl; and
p is 0 or 1.

18. A pharmaceutical composition comprising a compound according to any one of claims 1 to 17, including the compounds of provisos c) to e), or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

19. A method for the treatment of a disease or condition in which GPR116 plays a role comprising a step of administering to a subject in need thereof an effective amount of a compound according to any one of claims 1 to 17, including the compounds of provisos a) to e), or a pharmaceutically acceptable salt thereof.

20. A method for the regulation of satiety comprising a step of administering to a subject in need thereof an effective amount of a compound according to any one of claims 1 to 17, including the compounds of provisos a) to e), or a pharmaceutically acceptable salt thereof.

21. A method for the treatment of obesity comprising a step of administering to a subject in need thereof an effective amount of a compound according to any one of claims 1 to 17, including the compounds of provisos a) to e), or a pharmaceutically acceptable salt thereof.

22. A method for the treatment of diabetes comprising a step of administering to a subject in need thereof an effective amount of a compound according to any one of claims 1 to 17, including the compounds of provisos a) to e), or a pharmaceutically acceptable salt thereof.
## INTERNATIONAL SEARCH REPORT

**A. CLASSIFICATION OF SUBJECT MATTER**

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<th>C07D413/06</th>
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According to International Patent Classification (IPC) or to both national classification and IPC.

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched.

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

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**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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Further documents are listed in the continuation of box C.

Patient family members are listed in annex.

**Date of the actual completion of the international search**

21 April 2005

**Date of mailing of the international search report**

28/04/2005

Name and mailing address of the ISA

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Authorized officer

Samsam Bakhtiar, M
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