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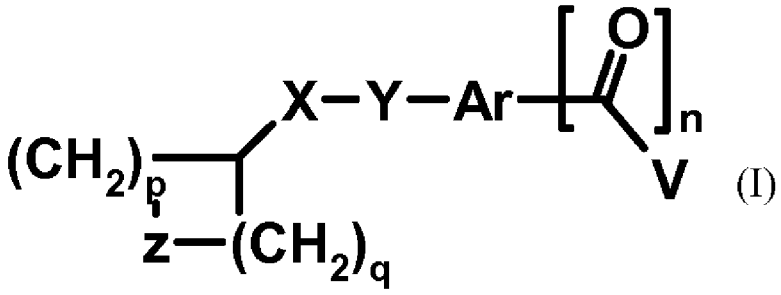
(54) Title: 3-SUBSTITUTED 5-(PYRROLIDINE-1-CARBONYL) PYRROLIDINE AND ITS DERIVATIVES FOR USE IN THE TREATMENT OF METABOLIC DISORDERS



(I)

(57) Abstract: The present invention is directed to therapeutic compounds of formula (I) which have activity as agonists of GPR119 and are useful for the treatment of metabolic disorders including type II diabetes.

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3-SUBSTITUTED 5-(PYRROLIDINE-1-CARBONYL) PYRROLIDINE AND ITS DERIVATIVES FOR USE IN THE TREATMENT OF METABOLIC DISORDERS

BACKGROUND OF THE INVENTION

The present invention is directed to therapeutic compounds useful for the treatment of metabolic disorders including type II diabetes. In particular, the present invention is directed to compounds which have activity as agonists of GPR119.

Drugs aimed at the pathophysiology associated with 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) places people at high risk of coronary artery disease, and is characterized by a cluster of risk factors including central obesity (excessive fat tissue in the abdominal region), glucose intolerance, high triglycerides and low HDL cholesterol, and high blood pressure. Myocardial ischemia and microvascular disease is an established morbidity associated with untreated or poorly controlled metabolic syndrome.

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.

There is a continuing need for novel antidiabetic agents, particularly ones that are well tolerated with few adverse effects and in particular for agents which are weight neutral or preferably cause weight loss.

GPR119 (previously referred to as GPR116) is a GPCR identified as SNORF25 in WO00/50562 which discloses both the human and rat receptors, US 6468756 also discloses the mouse receptor (accession numbers: AAN95194 (human), AAN95195 (rat) and ANN95196 (mouse)).

In humans, GPR119 is expressed in the pancreas, small intestine, colon and adipose tissue. The expression profile of the human GPR119 receptor indicates its potential utility as a target for the treatment of diabetes.

GPR119 agonists have been shown to stimulate the release of GLP-1 from the GI tract. In doing so, GPR119 agonists (1) enhance glucose-dependent insulin release from the pancreas leading to improvements in oral glucose tolerance; (2) attenuate disease progression by increasing β-cell cAMP concentrations; and (3) induce weight loss possibly through GLP-1's ability to reduce food intake.

WO2005/061489, WO2006/070208, WO2006/067532, WO2006/067531, WO2007/003960, WO2007/003961, WO2007/003962, WO2007/003964, WO2007/116229, WO2007/116230, WO2007/138362, WO2008/081204, WO2008/081205, WO2008/081206, WO2008/081207, WO2008/081208, WO2009/050522, WO2009/050971, WO2010/004343, WO2010/004344, WO2010/004345, WO2010/004347 and WO2010/001166 disclose GPR119 receptor agonists.

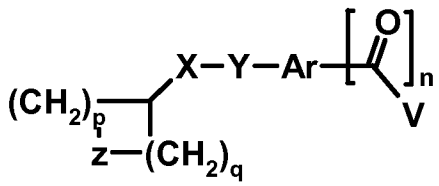
Dipeptidyl peptidase IV (DPP-IV) is a ubiquitous, yet highly specific, serine protease that cleaves N-terminal dipeptides from polypeptides with L-proline or L-alanine at the penultimate position. Studies with DPP-IV inhibitors show the principle role of DPP-IV is in the inactivation GLP-1. By extending the duration of action of GLP-1, insulin secretion is stimulated, glucagon release inhibited, and gastric emptying slowed. DPP-IV inhibitors are of use for the treatment of type II diabetes, examples of DPP-IV inhibitors include vildagliptin, sitagliptin, alogliptin and saxagliptin.

The possibility of using a combination of a GPR119 agonist and a DPP-IV inhibitor has been suggested, but this requires the administration of two separately formulated products to the patient or the co-formulation of two active ingredients with the inherent problems of achieving compatability in the physicochemical, pharmacokinetic and pharmacodynamic properties of the two active ingredients. WO2009/034388, published after the priority date of the present application, discloses compounds having dual activity as agonists of GPR119 and inhibitors of DPP-IV.

SUMMARY OF THE INVENTION

The present invention is directed to compounds which have activity as agonists of GPR119 and may also be inhibitors of DPP-IV and are useful for the treatment of metabolic disorders including type II diabetes.

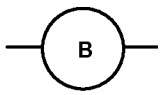
The present invention therefore provides compounds of formula (I) and pharmaceutically acceptable salts thereof:



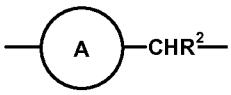
(I)

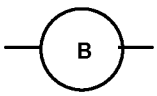
wherein p and q are independently 1 or 2;

Z is N-C(O)OR^4, N-C(O)NR^{4}R^5, N–S(O)$_2$N(C$_{1-3}$alkyl)R^4, N-heteroaryl or N-CH$_2$-heteroaryl, and when p and q are both 2, Z may also be N-CH$_2$-phenyl, in which phenyl is optionally substituted by one or two groups independently selected from C$_{1-4}$ alkyl, C$_{1-4}$ haloalkyl and halogen;

Y is CH$_2$, CF$_2$, CHF, O, NR^1, C(O) or  , where B is a 5-membered heteroaryl ring containing one or more heteroatoms selected from N, O and S;

when Y is CH$_2$, CF$_2$, CHF, O, NR^1 or C(O), X is an unbranched or branched C$_{2-4}$ alkylene group;

when Y is O or NR^1, X, may also be  , where A is a 5-membered heteroaryl ring containing one or more heteroatoms selected from N, O and S;

and when Y is  , X is -O-CHR^3-;

Ar is a para-substituted phenyl or a para-substituted 6-membered heteroaryl ring containing one or two nitrogen atoms, optionally substituted by one or two groups selected from C$_{1-4}$ alkyl, C$_{1-4}$ alkoxy, C$_{2-6}$alkoxyalkyl, cyano, C$_{1-4}$ haloalkyl and halogen;

R^1 is hydrogen or C$_{1-4}$alkyl;

R^2 is hydrogen or C$_{1-4}$alkyl;

R^3 is hydrogen or C$_{1-4}$alkyl;

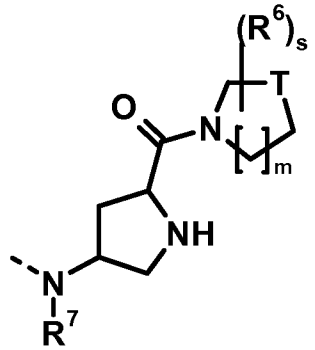
R^4 is aryl, heteroaryl, C$_{2-6}$ alkyl, C$_{3-6}$ cycloalkyl, which cycloalkyl is optionally

substitiuted by C_{1-4}alkyl, C_{4-6}heterocyclyl, heterocyclylC_{1-4}alkyl, C_{2-6}alkoxyalkyl, arylC_{1-4}alkyl, heteroarylC_{1-4}alkyl or C_{4-6}cycloalkylC_{1-4}alkyl, which cycloalkylC_{1-4}alkyl is optionally substituted by C_{1-4} alkyl;

when Z includes heteroaryl, or when R^4 is or includes aryl or heteroaryl, said aryl or heteroaryl may be optionally substituted by one or two groups selected from halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl and C_{3-6} cycloalkyl optionally substituted by C_{1-4}alkyl,

R5 is hydrogen or C1–4alkyl;

V is



in which T is CH_2, and, when m is 1, T may also be S;

when T is CH_2, R^6 is fluoro or cyano, and when T is S, R^6 is cyano;

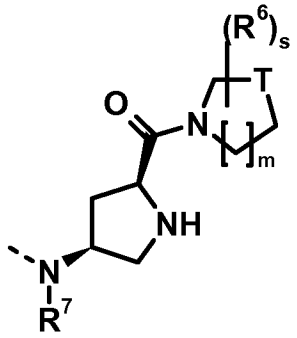
R^7 is hydrogen or C_{1-4}alkyl;

n is 0 or 1;

m is 0 or 1; and

s is 0, 1 or 2.

In some embodiments, the compounds of the invention may have a V group with the stereochemistry as defined below (compounds of formula (Ia)), such compounds may exhibit DPP-IV inhibitory activity:



(Ia)

DETAILED DESCRIPTION OF THE INVENTION

In some embodiments of the invention each p and q are independently 1 or 2, i.e. forming a 4-, 5- or 6-membered ring. p and q may be the same, i.e. forming a 4- or 6-membered ring. Suitably p and q may both be 2.

In some embodiments Z is N-C(O)OR^4.

R^4 may be C_{2-6} alkyl such for example as propyl or butyl, e.g. isopropyl or tert-butyl.

Alternatively Z may be N-heteroaryl, wherein the heteroaryl group is optionally substituted by one or two groups selected from C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-5} hydroxyalkyl, C_{2-4} alkoxyalkyl, C_{3-6} cycloalkyl optionally substituted by C_{1-4} alkyl or halo, C_{1-4} alkoxy, heterocyclyl, heterocyclylalkyl, heteroarylalkyl, alkylamino, alkylaminoalkyl, cyano and halogen.

When Z is N-heteroaryl, suitable heteroaryl groups are optionally substituted oxadiazole, pyrimidine, pyridine, pyridazine, thiazole, tetrazole, benzothiazole and thiadiazole, e.g., oxadiazole, tetrazole, pyridine and pyrimidine.

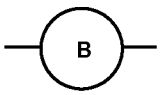
In some embodiments Z may comprise 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, pyridin-2-yl, pyrimidin-2-yl or tetrazol-5-yl, which may be substituted by any of the aforementioned substituents.

Typically, said 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl or tetrazol-5-yl may be substituted by C_{1-4} alkyl, such as propyl (e.g., 3-isopropyl-1,2,4-oxadiazol-5-yl, 5-isopropyl-1,2,4-oxadiazol-3-yl or 2-isopropyl-2H-tetrazol-5-yl), C_{1-4} haloalkyl,such as difluoromethyl or fluoromethylethyl, C_{1-5} hydroxyalkyl (e.g. 1-hydroxyethyl), C_{2-4} alkoxyalkyl, such as methoxymethyl, or heterocyclyl.

Suitably said C_{1-5} hydroxyalkyl group may be C_{1-3} hydroxyalkyl, e.g. hydroxyethyl.

Pyridin-2-yl or pyrimidin-2-yl may be unsubstituted or substituted with one or more halo groups, e.g. 5-chloro- or 5-fluoro- pyrimidin- or pyridine-2-yl, C_{1-4} alkyl, such as ethyl, propyl or butyl (e.g. 5-isopropyl- or 5-ethylpyrimidin-2-yl or 5-isopropylpyridin-2-yl), .

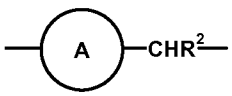
In a further alternative, Z may be -CH_2-phenyl, wherein the phenyl is optionally substituted by one or two groups independently selected from C_{1-4} alkyl, C_{1-4} haloalkyl and halo.

Y may be CH_2, O, NR^1 or 

, where B is a 5-membered heteroaryl ring containing one or more heteroatoms selected from N, O and S, for example oxadiazole, e.g. [1,2,4] oxadiazole, or thiazole.

X is suitably a branched or unbranched C_{2-4}alkylene group. In some embodiments, for instance when Y is CH_2, O or NR^1, especially when Y is O, X may be C_{2-3}alkylene, suitably propyl, which is optionally substituted by 1 or 2 methyl groups, e.g. n-propyl or 1-methylpropyl, where the methyl group is typically on the carbon atom adjacent to the ring containing Z.

When Y is a heteroaryl ring, X is suitably –O-CH_2-.

When X is 

, where A is a 5-membered heteroaryl ring containing one or more heteroatoms selected from N, O and S, suitable heteroaryl rings include oxadiazole, thiazole, triazole, tetrazole and pyrazole.

Ar may be phenyl, pyridyl or pyriminidyl. Optionally Ar may be substituted by a single methyl or fluoro group, typically in the 3-position. In some embodiments Ar may be substituted by two methyl or fluoro groups, typically in the 3- and 5- positions.

R^1 may be hydrogen or methyl.

R^2 may be hydrogen or methyl.

R^3 may be hydrogen or methyl.

R^7 may be hydrogen.

T may be CH_2.

m may be 1.

While the suitable groups for each variable have generally been listed above separately for each variable, the compounds of the invention include those in which several or each variable in

formula (I) is selected from the suitable groups for each variable. Therefore, this invention is intended to include all combinations of suitable listed groups.

The molecular weight of the compounds of the invention is suitably less than 800, typically less than 600.

The invention also comprehends isotopically-labeled compounds, which are identical to those recited in formulae (I) and (Ia) and following, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number most commonly found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, fluorine, such as ^{3}H, ^{11}C, ^{14}C and ^{18}F.

Compounds of the present invention and salts of said compounds that contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of the present invention. Isotopically-labeled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H, ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. ^{11}C and ^{18}F isotopes are particularly useful in PET (positron emission tomography). PET is useful in brain imaging. Further, substitution with heavier isotopes such as deuterium, i.e., ^{2}H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances, isotopically labeled compounds of formula (I) and (Ia) and following of this invention can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples below, by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent. In one embodiment, the compounds of formula (I) and (Ia) or salts thereof are not isotopically labelled.

As used herein, unless stated otherwise, "alkyl" means carbon chains which may be linear or branched. Examples of alkyl groups include ethyl, propyl, isopropyl, butyl, sec- and tert-butyl. Such alkyl groups may in some embodiments be substituted with one or more halo groups, particularly flouro. Generally a CF_3 group may be replaced by SF_5 without departing from the present invention.

The term "heteroaryl" rings means 5- or 6-membered N-containing heteroaryl rings containing up to 2 additional heteroatoms selected from N, O and S. Examples of such heteroaryl rings are pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl.

Reference to para substitution in relation to the ring Ar refers to the positions of the groups -Y- and -$[C=O]_n$-V on ring Ar.

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 present invention includes all stereoisomers of the compounds of the invention 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 the invention 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 the invention 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'*,*N'*-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, *N*-ethylmorpholine, *N*-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

When the compound of the 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, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like

Since the compounds of the invention 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, wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, A, B, T, V, X, Y, Z, m, n, p, q and s are as defined for formula (I). PG is a protecting group attached to the amine functionality of V, LG is a leaving group and Hal is halogen.

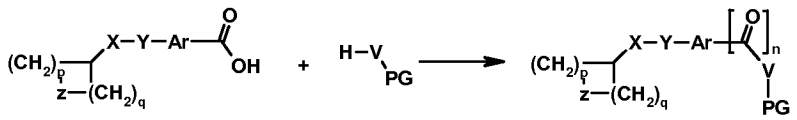
Compounds of formula (I) can be prepared as outlined in Scheme 1. Deprotection of the amine functionality in compounds of formula (II), using standard conditions well known to those with skill in the art, affords compounds of formula (I) as described above.

Scheme 1

II I

Compounds of formula (II) where n is 1 can be prepared as outlined in Scheme 2. Acids of formula (III) can be treated with amines of formula (IV) under standard amide coupling conditions, for example, HOBT and EDCI, in a suitable solvent, such as DCM.

Scheme 2

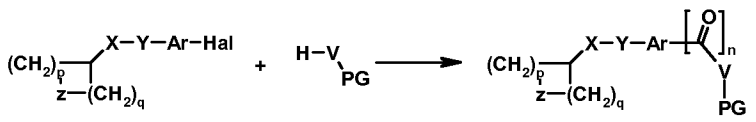


III IV II

Compounds of formula (II) where n is 0 can be prepared as outlined in Scheme 3. Suitable aryl halides of formula (V) can be treated with protected amines of formula (IV) under standard SN_{Ar} conditions, for example, DBU and DMSO at 120°C. Alternatively, compounds of formula (II) can be prepared by reaction of suitable aryl halide of formula (V) with amines of formula (IV) under

Buchwald-Hartwig conditions, such as, $Pd_2(dba)_3$ and BINAP in a suitable solvent, such as toluene at 110°C.

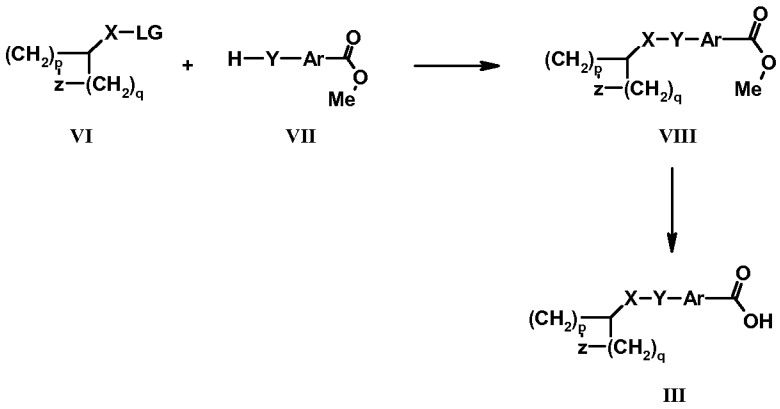
Scheme 3



V IV II

Compounds of formula (III) where X is -A-CHR^2 and Y is O or NR^1 can be prepared as outlined in Scheme 4. Esters of formula (VIII) can be prepared by reaction of compounds of formula (VI) with anilines or phenols of formula (VII) under standard conditions, such as K_2CO_3 in DMF at 80°C. Compounds of formula (III) as described above can be prepared by saponification of esters of formula (VIII) under standard conditions, for example, LiOH in 5:1 methanol / water.

Scheme 4

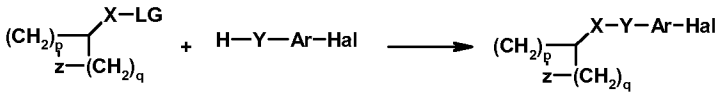


VI VII VIII

III

Compounds of formula (V) where X is an unbranched or a branched C_{2-4} alkylene group or -A-CHR^2 and Y is O or NR^1 can be prepared as outlined in Scheme 5. Compounds of formula (VI) can be treated with aryl halides of formula (IX) under standard conditions, such as K_2CO_3 in DMF at 80°C.

Scheme 5

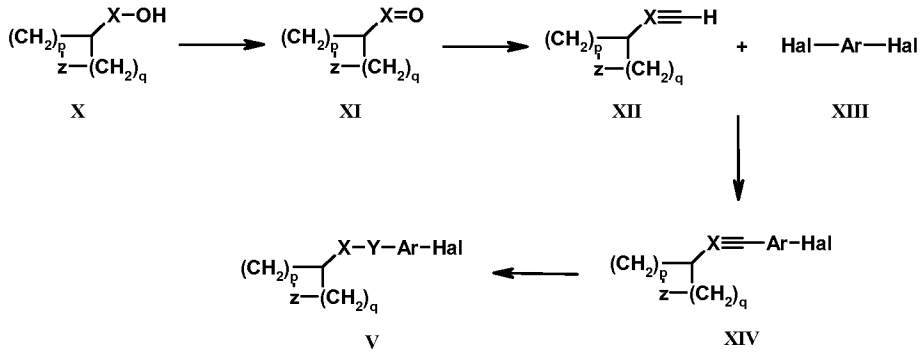


VI IX V

Compounds of formula (V) where X is an unbranched or a branched C_{2-4} alkylene group and Y is CH_2 can be prepared as outlined in Scheme 6. An alkyne of formula (XII) can be prepared from

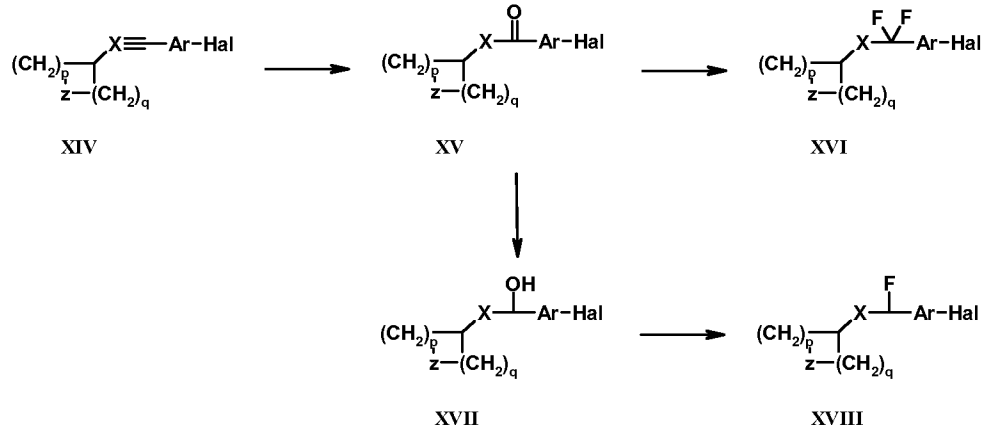
an alcohol of formula (X) by oxidation to the corresponding aldehyde (XI) using a standard oxidizing reagent, such as Dess-Martin Periodinane, and subsequent reaction of the aldehyde of formula (XI) with trimethylsilyldiazomethane, which has previously been treated with a suitable base, such as nBuLi. Alkynes of formula (XIV) can be prepared by reaction of alkynes of formula (XII) with dihaloaryl compounds of formula (XIII) under standard Sonogashira coupling conditions. Compounds of formula (V) as described above can be prepared from alkynes of formula (XIV) under standard reduction conditions, such as 10% palladium on carbon under an atmosphere of hydrogen in a suitable solvent such as methanol.

Scheme 6



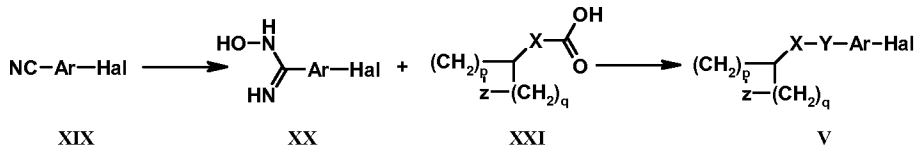
Compounds of formula (V) where X is an unbranched or a branched C_{2-4} alkylene group and Y is CHF, C(O) or CF_2 can be prepared as outlined in Scheme 7. Ketones of formula (XV) can be prepared from alkynes of formula (XIV) by treatment with mercury oxide and sulphuric acid in methanol / water at 80°C. Treatment of ketones of formula (XV) with diethylaminosulfur trifluoride in a suiable solvent, such as DCM, gives difluoro compounds of formula (XVI). Alternatively, alcohols of formula (XVII) can be prepared by treatment of ketones of formula (XV) under standard conditions, for example, sodium borohydride in methanol. Treatment of alcohols of formula (XVII) with diethylaminosulfur trifluoride in a suitable solvent, such as DCM, gives monofluoro compounds of formula (XVIII).

Scheme 7



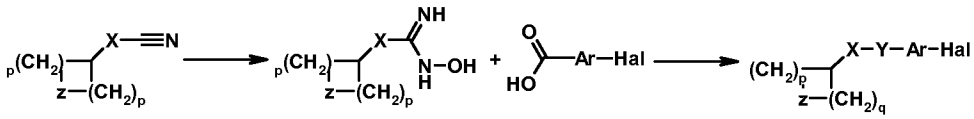
Compounds of formula (V) where Y is -B-, X is -O-CHR^3- and B is specifically a 1,2,4-oxadiazol-5-yl can be prepared as outlined in Scheme (8). Amidoximes of formula (XX) can be prepared by reaction of nitriles of formula (XIX) and hydroxylamine hydrochloride in the prescence of a suitable base such as K_2CO_3 in a suitable solvent such as ethanol/water at 78°C. Building blocks of formula (V) as described above can be prepared by reaction of amidoxime of formula (XX) with acid of formula (XXI) under standard conditions, such as isobutyl chloroformate and triethylamine, in a suitable solvent such as DMF.

Scheme 8



Compounds of formula (V) where Y is -B-, X is -O-CHR^3- and B is specifically a 1,2,4-oxadiazol-3-yl can be prepared as outlined in Scheme 9. Amidoximes of formula (XXIII) can be prepared by reaction of nitriles of formula (XXII) and hydroxylamine hydrochloride in the prescence of a suitable base such as K_2CO_3 in a suitable solvent such as ethanol/water at 78°C. Building blocks of formula (V) as described above can be prepared by reaction of amidoxime of formula (XXIII) with acid of formula (XXIV) under standard conditions, such as isobutyl chloroformate and triethylamine, in a suitable solvent such as DMF.

Scheme 9



XXII XXIII XXIV V

Examples and syntheses of building blocks of formula (III) where X is an unbranched or a branched C_{2-4} alkylene group have been described elsewhere: Bradley *et.al.*, WO2007/003962 and Bertram *et.al.*, WO2008/081205.

Examples and syntheses of building blocks of formula (III) where Y is -B- and X is -O-CHR^3- have been described elsewhere: Bradley *et.al.*, WO2007/003960.

Examples and syntheses of building blocks (IV) have been described elsewhere: Zhao *et.al.*, *Bioorg. Med. Chem. Lett.*, **2005**, 15 3992-3995; Fumihiko *et.al.*, *Bioorg. Med. Chem. Lett.*, **2005**, 15 2441-2445; Corbett *et.al.*, *Bioorg. Med. Chem. Lett.*, **2007**, 17 6707-6713.

Examples and syntheses of building blocks of formula (VI) where X is -A-CHR^2 have been described elsewhere: Chen *et.al.*, WO2008/083238 and Ma *et.al.*, WO2009/014910.

Examples and syntheses of building blocks of formula (VI) and (X) where X is an unbranched or a branched C_{3-4} alkylene group have been described elsewhere: Bradley *et.al.*, WO2007/003962 and Alper *et.al.*, WO2008/097428.

Examples and syntheses of building blocks of formula (XXI), (XXII) and (XXIII) where X is -O-CHR^3 have been described elsewhere: Bradley *et.al.*, WO2007/003960.

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 syntheses 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.

The processes for the production of the compounds of formula (I) and intermediates thereto as described above are also included as further aspects of the present invention.

Any novel intermediates as defined in the Schemes above or in the Examples, are also included within the scope of the invention. Therefore according to a further aspect of the invention there there are provided compounds of formulae (II), (V), (VIII), (XII), (XIV), (XV), (XVI), (XVII) and (XVIII) as defined above. The preferred groups for variables recited above in relation to the compounds of formula (I) also apply to the intermediate compounds.

As indicated above the compounds of the invention are useful as GPR119 agonists, e.g. for the treatment and/or prophylaxis of diabetes. For such use the compounds of the invention will generally be administered in the form of a pharmaceutical composition.

The compounds of the invention may also be useful as dual GPR119 agonists/DPP-IV inhibitors, e.g. for the treatment and/or prophylaxis of diabetes. For such use the compounds of the invention will generally be administered in the form of a pharmaceutical composition.

The invention also provides a compound of the invention, or a pharmaceutically acceptable salt thereof, for use as a pharmaceutical.

The invention also provides a pharmaceutical composition comprising a compound of the invention, 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 the invention, or a pharmaceutically acceptable salt thereof.

Moreover, the invention also provides a pharmaceutical composition for the treatment of disease by modulating GPR119 and optionally DPP-IV, resulting in the prophylactic or therapeutic treatment of diabetes, comprising a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of compound of the invention, 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 the invention, 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 the invention, 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 the invention, 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 the invention, 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 the invention, 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 the invention may be used in the treatment of diseases or conditions in which GPR119 and optionally DPP-IV play a role.

Thus the invention also provides a method for the treatment of a disease or condition in which GPR119 and optionally DPP-IV play a role comprising a step of administering to a subject in need thereof an effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof. Such diseases or conditions diabetes, obesity, 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 compounds of the invention may also be used for treating metabolic diseases such as metabolic syndrome (syndrome

X), impaired glucose tolerance, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL levels and hypertension.

The invention also provides a method for the treatment of type II diabetes, comprising a step of administering to a patient in need thereof an effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof.

The invention also provides a method for the treatment of obesity, metabolic syndrome (syndrome X), impaired glucose tolerance, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL levels or hypertension comprising a step of administering to a patient in need thereof an effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof.

The invention also provides a compound of the invention, 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 the invention, 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 the invention may exhibit advantageous properties compared to known compounds or combination therapies for the treatment of diabetes.

The compounds of the invention, 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 the invention or a different disease or condition. The therapeutically active compounds may be administered simultaneously, sequentially or separately.

The compounds of the invention 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 e.g. metformin, $\alpha 2$ 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, lipoxygenase inhibitors, somostatin analogs, glucokinase activators, glucagon antagonists, insulin signalling agonists, PTP1B inhibitors, gluconeogenesis inhibitors, antilypolitic agents, GSK inhibitors, galanin receptor agonists,

anorectic agents, CCK receptor agonists, leptin, serotonergic/dopaminergic antiobesity drugs, reuptake inhibitors e.g. sibutramine, 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 compound of the invention, or a pharmaceutically acceptable salt thereof, and at least one other agent, for example another agent for the treatment of diabetes or obesity, represents a further aspect of the invention.

The present invention also provides a method for the treatment of diabetes in a mammal, such as a human, which method comprises administering an effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, and another agent, for example another agent for the treatment of diabetes or obesity, to a mammal in need thereof.

The invention also provides the use of a compound of the invention, or a pharmaceutically acceptable salt thereof, and another agent for the treatment of diabetes.

The invention also provides the use of a compound of the invention, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in combination with another agent, for the treatment of diabetes.

The compound of the invention, or a pharmaceutically acceptable salt thereof, and the other agent(s) may be co-administered or administered sequentially or separately.

Co-administration includes administration of a formulation which includes both the compound of the invention, or a pharmaceutically acceptable salt thereof, and the other agent(s), or the simultaneous or separate administration of different formulations of each agent. Where the pharmacological profiles of the compound of the invention, or a pharmaceutically acceptable salt thereof, and the other agent(s) allow it, coadministration of the two agents may be preferred.

The invention also provides the use of a compound of the invention, or a pharmaceutically acceptable salt thereof, and another agent in the manufacture of a medicament for the treatment of diabetes.

The invention also provides a pharmaceutical composition comprising a compound of the invention, or a pharmaceutically acceptable salt thereof, and another antidiabetic agent, and a pharmaceutically acceptable carrier. The invention also encompasses the use of such compositions in the methods described above.

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 SiO_2 (40–63 mesh) unless specified otherwise. LCMS data were obtained as follows: Atlantis 3μ C_{18} column (3.0 × 20.0 mm, flow rate = 0.85 mL/min) eluting with a H_2O–MeCN solution containing 0.1% HCO_2H over 6 min with UV detection at 220 nm. Gradient information: 0.0–0.3 min 100% H_2O; 0.3–4.25 min: Ramp up to 10% H_2O–90% MeCN; 4.25–4.4 min: Ramp up to 100% MeCN; 4.4–4.9 min: Hold at 100% MeCN; 4.9–6.0 min: Return to 100% H_2O. The mass spectra were obtained using an electrospray ionisation source in either the positive (ES^+) or negative (ES^-) ion modes.

Chiral-HPLC was performed on a Daicel chiral pack IA 250 × 20 mm, 5 µM column.

Abbreviations and acronyms: Boc: *tert*-Butoxycarbonyl; CO_2: Carbon dioxide; DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene; DCM: DME: Dimethoxyethane; Dichloromethane; DMF: Dimethylformamide; DIAD: Diisopropylazodicarboxylate; DMSO: Dimethylsulfoxide; EDCI: (3-Dimethylaminopropyl)ethylcarbodiimide hydrochloride; Et_2O: Diethyl ether; EtOH: Ethanol; EtOAc: Ethyl Acetate; Fmoc: 9H-Fluoren-9-ylmethoxycarbonyl; h: hour(s); H_2O: water; HCl: Hydrochloric acid; HCO_2H: Formic acid; HOBt: 1-Hydroxybenzotriazole monohydrate; HPLC: High performance liquid chromatography; IH: Isohexane; K_2CO_3: Potassium carbonate; M: Molar; MeCN: Acetonitrile; MEK: Methylethyl ketone; MeOH: Methanol; $MgSO_4$: Magnesium sulphate; MIBK: Methylisobutyl ketone; min: minute/s; Na_2CO_3: Sodium carbonate; $NaHCO_3$: Sodium hydrogen carbonate; NMP: N-Methyl-2-pyrrolidone; NaOH: Sodium hydroxide; Na_2SO_4: Sodium sulphate; NH_4OH: Ammonium hydroxide; PPh_3: Triphenylphosphine; RT: Retention time; r.t.: Room temperature; sat: Saturated; SCX: Strong Cation Exchange resin; SiO_2: Silica gel; STMaD: Phosphonic acid cation exchange resin; TBAD: di-*tert*-Butylazodicarboxylate; THF: Tetrahydrofuran; TFA: Trifluoroacetic acid; $ZnCl_2$: Zinc chloride.

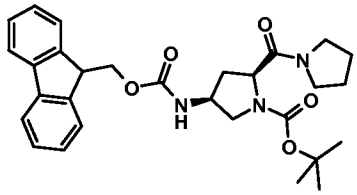
The syntheses of the following compounds have been described elsewhere: 4-(3-hydroxypropyl)piperidine-1-carboxylic acid isopropyl ester and 4-(3-methanesulfonyloxypropyl)piperidine-1-carboxylic acid *tert*-butyl ester: Bradley *et. al.*, WO2007003962; 3-[1-(5-*tert*-butyl-[1,2,4]oxadiazol-3-yl)piperidin-4-yl]propan-1-ol and *tert*-butyl 4-

((*R*)-3-hydroxy-1-methylpropyl)piperidine-1-carboxylate: Bertram *et. al.*, WO2008081205; *tert*-butyl 4-(3-hydroxypropyl)piperidine-1-carboxylate: *Tetrahedron* **1999**, *55*, 11619–11639; 3-piperidin-4-ylpropan-1-ol hydrochloride:

Alper *et. al.*, WO2008097428; 6-hydroxy-2-methylnicotinic acid ethyl ester: *Tetrahedron*, **1974**, 30, 623-32; 2-chloro-5-isopropylpyridine: *J. Med.Chem.*, **1980**, *23*, 1, 92-95; 4-hydroxy-2-methylbenzoic acid methyl ester: Aquino *et. al.* WO2008157330; 4-(3-hydroxypropyl)piperidine-1-carbonitrile and (*R*)-3-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]butan-1-ol: Fyfe *et. al.*, WO2008081204; 3-[1-(5-isopropyl-[1,2,4]oxadiazol-3-yl)piperidin-4-yl]propan-1-ol: Fyfe *et. al.*, WO2008081206; 3-[1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]propan-1-ol: Bertram *et. al.*, WO2008081207.

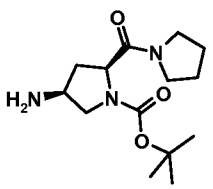
All other compounds were available from commercial sources.

Preparation 1: (2*S*,4*S*)-4-(9H-Fluoren-9-ylmethoxycarbonylamino)-2-(pyrrolidine-1-carbonyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester



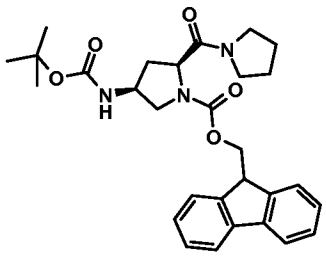
To a solution of (2*S*,4*S*)-4-(9H-fluoren-9-ylmethoxycarbonylamino)pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester (425 mg, 1.00 mmol) and HOBt (175 mg, 1.14 mmol) in DCM (4 mL), under argon, was added EDCI (250 mg, 1.30 mmol), and the reaction was stirred at r.t. for 15 min. A solution of pyrrolidine (75 μL, 0.90 mmol) in DCM (1 mL) was added, dropwise, and the resulting reaction was stirred at r.t.for 16 h. The mixture was diluted with DCM, washed with water, sat. Na_2CO_3 solution (x 2), and brine, then dried ($MgSO_4$). Removal of the solvent *in vacuo* and purification by column chromatography (EtOAc) afforded the title compound: RT = 4.07 min, m/z (ES^+) = 506.2 $[M + H]^+$.

Preparation 2: (2*S*,4*S*)-4-Amino-2-(pyrrolidine-1-carbonyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester



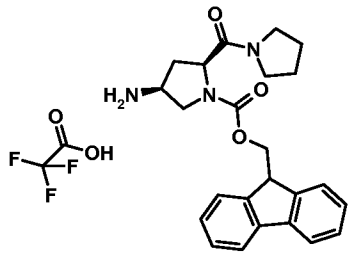
To a solution of (2*S*,4*S*)-4-(9H-fluoren-9-ylmethoxycarbonylamino)-2-(pyrrolidine-1-carbonyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (**Preparation 1**, 6.5 g, 12.8 mmol) in DCM (50 mL) was added piperidine (5 mL) and the reaction was stirred at r.t. for 45 min. A further portion of piperidine (5 mL) was added to the mixture and stirring continued for 75 min. The reaction solvent was concentrated *in vacuo*, azeotroping with toluene to obtain a solid residue. The residue was triturated with MeOH and the filtrate collected. The remaining precipitate was passed down an SCX cartridge, eluting with MeOH then NH_4OH in MeOH, and the basic fraction was collected. The filtrate was purified by column chromatography, then combined with the product from SCX purification to afford the title compound: RT = 1.97 min, m/z (ES^+) = 284.2 $[M + H]^+$.

Preparation 3: (2*S*,4*S*)-4-*tert*-Butoxycarbonylamino-2-(pyrrolidine-1-carbonyl)pyrrolidine-1-carboxylic acid 9H-fluoren-9-ylmethyl ester



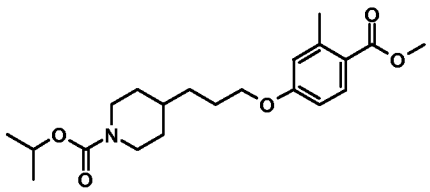
The title compound was prepared by reacting (2*S*,4*S*)-4-*tert*-butoxycarbonylaminopyrrolidine-1,2-dicarboxylic acid 1-(9H-fluoren-9-ylmethyl)ester with pyrrolidine employing the procedure outlined in **Preparation 1**: RT = 4.05 min, m/z (ES^+) = 506.3 $[M + H]^+$.

Preparation 4: (2*S*,4*S*)-4-Amino-2-(pyrrolidine-1-carbonyl)pyrrolidine-1-carboxylic acid 9H-fluoren-9-ylmethyl ester trifluoroacetate.



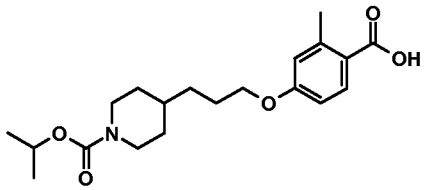
To a solution of (2*S*,4*S*)-4-*tert*-butoxycarbonylamino-2-(pyrrolidine-1-carbonyl)pyrrolidine-1-carboxylic acid 9H-fluoren-9-ylmethyl ester (**Preparation 3**, 1.05 g, 2.97 mmol) in DCM (20 mL), under argon, was added TFA (4 mL), and the reaction was stirred at r.t. for 45 min. The solvent was concentrated *in vacuo* to afford the title compound: RT = 2.72 min, m/z (ES^+) = 406.2 $[M + H]^+$.

Preparation 5: 4-[3-(4-Methoxycarbonyl-3-methylphenoxy)-propyl]piperidine-1-carboxylic acid isopropyl ester



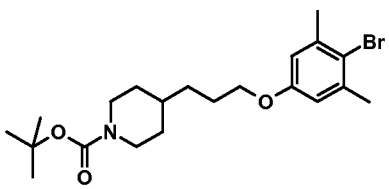
To a solution of 4-hydroxy-2-methylbenzoic acid methyl ester (1.00 g, 6.02 mmol), 4-(3-hydroxypropyl)piperidine-1-carboxylic acid isopropyl ester (1.38 g, 6.02 mmol) and PPh_3 (1.73 g, 6.62 mmol) in THF (50 mL) was added DIAD (1.80 mL, 9.03 mmol), dropwise, and the resulting mixture was stirred at r.t. for 1 h. The solvent was removed *in vacuo*, then the residue was triturated with Et_2O and IH to remove excess PPh_3. The remaining material was purified by column chromatography (IH:EtOAc, 4:1) to afford the title compound: RT = 4.36 min, m/z (ES^-) = 376.5 [M + H]$^-$.

Preparation 6: 4-[3-(4-Carboxy-3-methylphenoxy)propyl]piperidine-1-carboxylic acid isopropyl ester



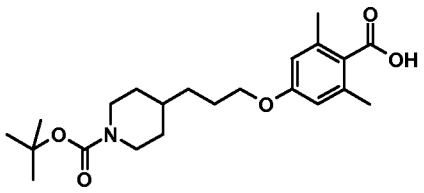
A combination of 4-[3-(4-methoxycarbonyl-3-methylphenoxy)-propyl]piperidine-1-carboxylic acid isopropyl ester (**Preparation 5**, 1.95 g, 5.17 mmol) and lithium hydroxide monohydrate (2.17 g, 51.60 mmol) in a mixture of MeOH (30 mL) and water (6 mL) was stirred at r.t. for 16 h. To the mixture was added water, and the solution was extracted with Et_2O. The aqueous phase was acidified to pH 2 and extracted further with Et_2O. The organic layers were combined, dried ($MgSO_4$) and the solvent removed *in vacuo* to afford the title compound: RT = 3.87 min, m/z (ES^-) = 362.4 [M + H]$^-$.

Preparation 7: 4-[3-(4-Bromo-3,5-dimethylphenoxy)propyl]piperidine-1-carboxylic acid *tert*-butyl ester



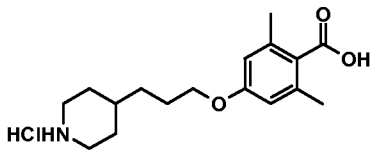
4-Bromo-3,5-dimethylphenol (13.75 g, 68.4 mmol) and K_2CO_3 (18.90 g, 136.8 mmol) were added to a solution of 4-(3-methanesulfonyloxypropyl)piperidine-1-carboxylic acid *tert*-butyl ester (21.98 g, 68.4 mmol) in sulfolane (260 mL) and the resulting solution was heated to 85°C for 4 h. The reaction mixture was diluted with Et_2O (500 mL) and water (500 mL), then the organic layer was washed with water (× 4), 2M NaOH (× 2) and brine, before being dried ($MgSO_4$). Removal of the solvent *in vacuo* and purification by column chromotagraphy (DCM) afforded the title compound: RT = 4.94 min; *m/z* (ES^+) = 426.2 $[M + H]^+$.

Preparation 8: 4-[3-(4-Carboxy-3,5-dimethylphenoxy)propyl]piperidine-1-carboxylic acid *tert*-butyl ester



To a solution of 1.6 M *n*-butyllithium in hexane (20.64 mL, 51.6 mmol) in anhydrous THF (23 mL) at -78°C, under argon, was added a solution of 4-[3-(4-bromo-3,5-dimethyl-phenoxy)propyl]piperidine-1-carboxylic acid *tert*-butyl ester (**Preparation 7**, 11.00 g, 25.8 mmol) in anhydrous THF (34 mL). The reaction mixture was stirred at -78°C for 50 min, then CO_2 gas was bubbled through the reaction mixture as it warmed to ambient temperature (~0.5 h). The reaction mixture was quenched with water and diluted with EtOAc. The aqueous layer was separated and the organic layer was extracted with 2M NaOH (× 2). The basic extracts were combined with the aqueous layer, acidified to pH 1 with 2M HCl and extracted with EtOAc (× 3). The organic fractions were combined, washed with brine and dried ($MgSO_4$). Removal of the solvent *in vacuo* and purification by column chromatography (IH:EtOAc, 3:7) afforded the title compound: RT = 3.93 min; *m/z* (ES^+) = 392.2 $[M + H]^+$.

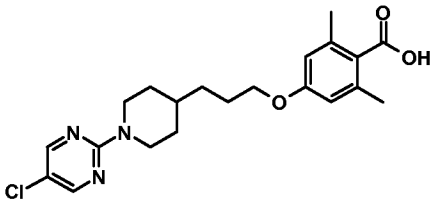
Preparation 9: 2,6-Dimethyl-4-(3-piperidin-4-ylpropoxy)benzoic acid hydrochloride



4M HCl in dioxane (21.95 mL) was added to a stirred solution of 4-[3-(4-carboxy-3,5-dimethylphenoxy)propyl]piperidine-1-carboxylic acid *tert*-butyl ester (**Preparation 8**, 4.91 g, 12.5 mmol) in dioxane (20 mL) at ambient temperature. After 2.5 h, the solid product that had formed was

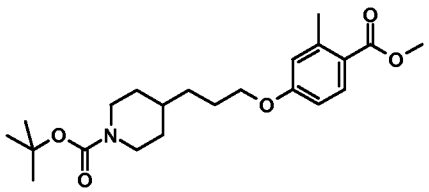
collected by filtration and washed with Et_2O to afford the title compound: RT = 2.50 min; *m/z* (ES^+) = 291.4 $[M + H]^+$.

Preparation 10: 4-{3-[1-(5-Chloropyrimidin-2-yl)piperidin-4-yl]propoxy}-2,6-dimethyl-benzoic acid



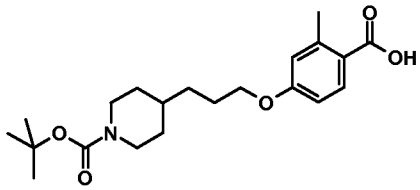
To 2,6-dimethyl-4-(3-piperidin-4-ylpropoxy)benzoic acid hydrochloride (**Preparation 9**, 600 mg, 1.83 mmol) in DMSO (850 µL) was added 2,5-dichloropyrimidine (327 mg, 2.20 mmol), DBU (960 µL, 6.41 mmol) and water (6 drops). The resulting suspension was heated in a sealed tube in a microwave reactor 130°C for 3 h. The reaction mixture was diluted with water, acidified to pH 5 with 2M HCl and extracted with EtOAc (× 3), then the combined organic extracts were washed with brine, before being dried ($MgSO_4$). Removal of the solvent *in vacuo* and purification by column chromatography (IH:EtOAc, 60:40, 40:60) afforded the title compound: RT = 4.20 min; *m/z* (ES^+) = 404.2 $[M + H]^+$.

Preparation 11: 4-[3-(4-Methoxycarbonyl-3-methylphenoxy)propyl]piperidine-1-carboxylic acid *tert*-butyl ester



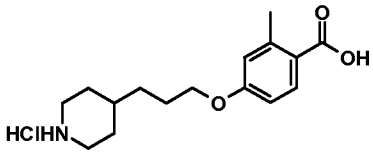
DIAD (8.00 mL, 40.9 mmol) was added to a stirred solution of 4-hydroxy-2-methyl benzoic acid methyl ester (6.00 g, 37.4 mmol), *tert*-butyl 4-(3-hydroxypropyl)piperidine-1-carboxylate (8.25 g, 34.0 mmol) and PPh_3 (10.71 g, 40.9 mmol) in anhydrous THF (60 mL) at ambient temperature. After stirring for 7.5 h, the solvent was removed *in vacuo*, and the residue was dissolved in EtOAc and washed with 2M NaOH (× 2), then brine. The organic layer was dried ($MgSO_4$), concentrated *in vacuo* and the remainder was triturated with IH and Et_2O. The solid produced was filtered and washed with Et_2O. The combined washings and filtrate were concentrated *in vacuo* and purified by column chromatography (IH:EtOAc, 9:1) to afford the title compound: RT = 4.48 min; *m/z* (ES^+) = 392.3 $[M + H]^+$.

Preparation 12: 4-[3-(4-Carboxy-3-methylphenoxy)propyl]piperidine-1-carboxylic acid *tert*-butyl ester



To a solution of 4-[3-(4-methoxycarbonyl-3-methylphenoxy)propyl]piperidine-1-carboxylic acid *tert*-butyl ester (**Preparation 11**, 6.00 g, 15.3 mmol) in MeOH (200 mL) and water (20 mL) was added lithium hydroxide monohydrate (6.43 g, 153.3 mmol) and the resulting mixture was stirred at 40°C for 16 h. The MeOH was removed *in vacuo*, then the residue was dissolved in water (200 mL), washed with EtOAc and acidified to pH 4 with 2M HCl, before being extracted with EtOAc (× 2). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to afford the title compound RT = 4.06 min; *m/z* (ES^+) = 378.2 $[M + H]^+$.

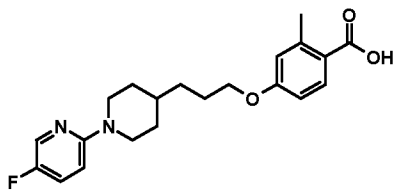
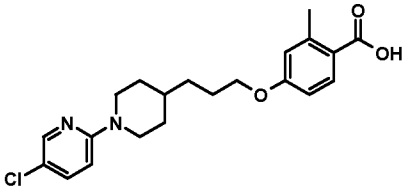
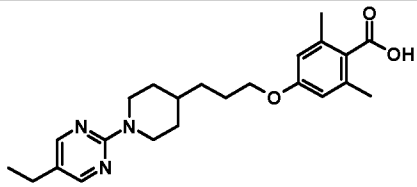
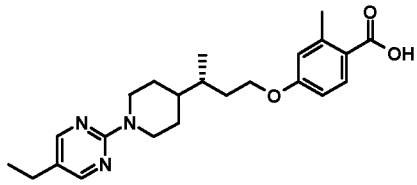
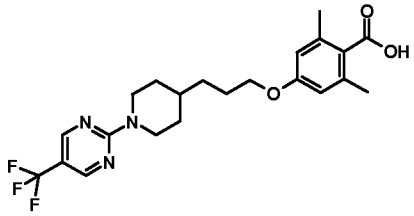
Preparation 13: 2-Methyl-4-(3-piperidin-4-ylpropoxy)benzoic acid hydrochloride



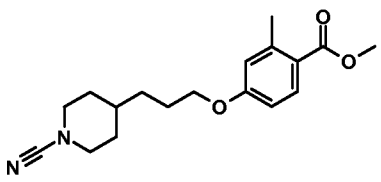
A mixture of 4-[3-(4-carboxy-3-methylphenoxy)propyl]piperidine-1-carboxylic acid *tert*-butyl ester (**Preparation 12**, 126 mg, 0.34 mmol) and 4M HCl in dioxane was stirred at ambient temperature for 1 h. The solvent was removed *in vacuo*, azeotroping with toluene (× 2), to afford the title compound: RT = 2.37 min; *m/z* (ES^+) = 278.2 $[M + H]^+$.

The compounds in **Table 1** were prepared by reacting the appropriate benzoic acid hydrochloride building block with the appropriate 2-fluoropyridine or 2-chloropyrimidine employing a procedure similar to that outlined in **Preparation 10**. The building block used in the synthesis of **Preparation 16** and **17** was prepared employing the methods outlined in WO2003074495:

Table 1:

Prep.	Structure	Name	LCMS
14		4-[3-(5'-Fluoro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)propoxy]-2-methylbenzoic acid	RT = 3.55 min; *m/z* (ES^+) = 373.2 $[M + H]^+$
15		4-[3-(5'-Chloro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)propoxy]-2-methylbenzoic acid	RT = 3.90 min; *m/z* (ES^+) = 389.1 $[M + H]^+$
16		4-{3-[1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl]propoxy}-2,6-dimethylbenzoic acid	RT = 3.95 min; *m/z* (ES^+) = 398.2 $[M + H]^+$
17		4-{(*R*)-3-[1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl]butoxy}-2-methylbenzoic acid	RT = 3.92 min; *m/z* (ES^+) = 398.2 $[M + H]^+$.
18		2,6-Dimethyl-4-{3-[1-(5-trifluoromethylpyrimidin-2-yl)piperidin-4-yl]propoxy}benzoic acid	RT = 4.53 min; *m/z* (ES^+) = 438.2 $[M + H]^+$

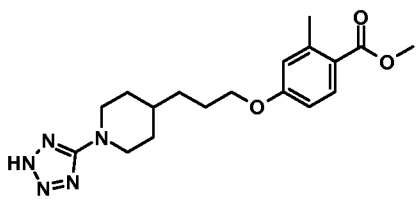
Preparation 19: 4-[3-(1-Cyanopiperidin-4-yl)propoxy]-2-methylbenzoic acid methyl ester



4M HCl in dioxane (7.7 mL) was added to a stirred solution of 4-[3-(4-methoxycarbonyl-3-methylphenoxy)propyl]piperidine-1-carboxylic acid *tert*-butyl ester (**Preparation 11**, 4.00 g, 10.2 mmol) in dioxane (10 mL) at ambient temperature. After 3 h, the mixture was diluted with Et_2O and the solid product formed was collected by filtration and washed with Et_2O to afford the intermediate product, 2-methyl-4-(3-piperidin-4-ylpropoxy)-benzoic acid methyl ester, as the hydrochloride salt: RT = 2.65 min; *m/z* (ES^+) = 292.4 $[M + H]^+$.

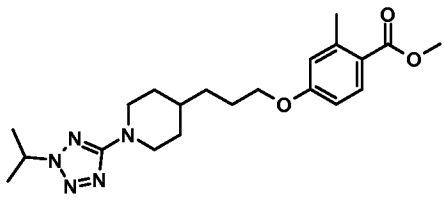
To a stirred solution of the product (10.77 g, 32.9 mmol) in DCM (140 mL) was added a slurry of $NaHCO_3$ (8.30 g, 98.7 mmol) in water (100 mL), at 0°C, and the resulting mixture was treated with a solution of cyanogen bromide (4.18 g, 39.5 mmol) in DCM (22 mL). The reaction mixture was stirred at ambient temperature for 3 h, before being partitioned between water and DCM. The organic phase was separated and dried ($MgSO_4$). Removal of the solvent *in vacuo* afforded the title compound: RT = 3.87 min; *m/z* (ES^+) = 317.2 $[M + H]^+$.

Preparation 20: 2-Methyl-4-{3-[1-(2H-tetrazol-5-yl)piperidin-4-yl]propoxy}benzoic acid methyl ester



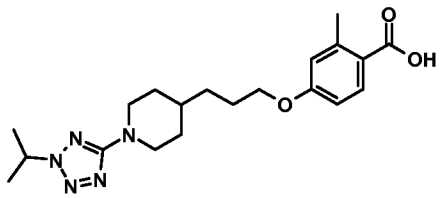
To a solution of 4-[3-(1-cyanopiperidin-4-yl)propoxy]-2-methylbenzoic acid methyl ester (**Preparation 19**, 417 mg, 1.32 mmol) in DMF (7 mL) was added ammonium chloride (106 mg, 1.98 mmol), followed by sodium azide (127 mg, 1.95 mmol), and the reaction was heated to 100°C for 16 h. The mixture was diluted with a mixture of water and brine (1:1), then the solution was extracted with EtOAc. The organic fraction was washed with brine, dried ($MgSO_4$) and the solvent removed *in vacuo*. Crystallisation from EtOAc and IH afforded the title compound: RT = 3.49 min; *m/z* (ES^+) = 360.3 $[M + H]^+$.

Preparation 21: 4-{3-[1-(2-Isopropyl-2H-tetrazol-5-yl)piperidin-4-yl]propoxy}-2-methylbenzoic acid methyl ester



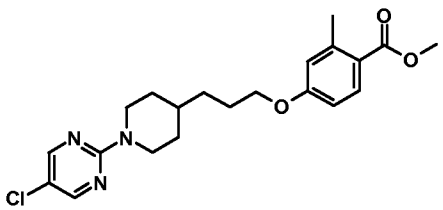
To a solution of 2-methyl-4-{3-[1-(2H-tetrazol-5-yl)piperidin-4-yl]propoxy}benzoic acid methyl ester (**Preparation 20**, 324 mg, 0.9 mmol) in a combination of acetone and DMF (5:1, 6 mL) was added K_2CO_3 (261 mg, 1.9 mmol), followed by 2-iodopropane (300 μL, 3.0 mmol), and the reaction was stirred at 50°C for 3.5 h before being allowed to stir at r.t. for 16 h. The mixture was diluted with a mixture of water and brine (1:1), then the solution was extracted with EtOAc. The organic fraction was washed with brine, dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography (IH:EtOAc, 3:1) afforded the title compound: RT = 4.39 min; *m/z* (ES^+) = 402.4 $[M + H]^+$.

Preparation 22: 4-{3-[1-(2-Isopropyl-2H-tetrazol-5-yl)piperidin-4-yl]propoxy}-2-methylbenzoic acid



To a solution of 4-{3-[1-(2-isopropyl-2H-tetrazol-5-yl)piperidin-4-yl]propoxy}-2-methylbenzoic acid methyl ester (**Preparation 21**, 279 mg, 0.7 mmol), dissolved in a combination of MeOH and water (4:1, 25 mL), was added lithium hydroxide monohydrate (284 mg, 6.8 mmol). The reaction was warmed to 45°C for 28 h before concentrating the reaction solvent to one third its original volume. The mixture was partitioned between EtOAc (100 mL) and water (100 mL), and made acidic by the addition of 1M HCl solution. The aqueous phase was separated and extracted with EtOAc (x 3), then all the organic fractions were combined, washed with brine, and dried ($MgSO_4$). Removal of the solvent *in vacuo* afforded the title compound: RT = 3.86 min; *m/z* (ES^+) = 388.4 $[M + H]^+$.

Preparation 23: 4-{3-[1-(5-Chloropyrimidin-2-yl)piperidin-4-yl]propoxy}-2-methylbenzoic acid methyl ester

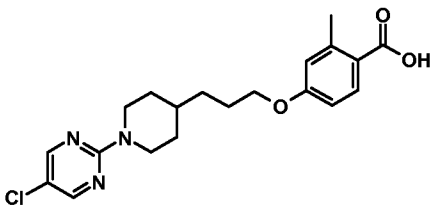


4M HCl in dioxane (7.7 mL) was added to a stirred solution of 4-[3-(4-methoxycarbonyl-3-methylphenoxy)propyl]piperidine-1-carboxylic acid *tert*-butyl ester (**Preparation 11**, 4.00 g, 10.2 mmol) in dioxane (10 mL) at ambient temperature. After 3 h, the mixture was diluted with Et_2O and

the solid product formed was collected by filtration and washed with Et_2O to afford the hydrochloride salt of 2-methyl-4-(3-piperidin-4-ylpropoxy)benzoic acid methyl ester: RT = 2.65 min; *m/z* (ES^+) = 292.4 $[M + H]^+$.

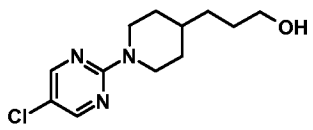
To a stirred solution of the product (1.27 g, 3.9 mmol) in DMSO (12 mL) was added 2,5-dichloropyrimidine (580 mg, 3.9 mmol) and DBU (1.25 mL, 8.54 mmol) and the resulting solution was stirred at 100°C for 16 h. The reaction mixture was diluted with water and extracted with EtOAc (× 2), then the combined organic extracts were washed with brine, before being dried ($MgSO_4$). Removal of the solvent *in vacuo* and purification by column chromatography (IH:EtOAc, 19:1) afforded the title compound: RT = 4.80 min; *m/z* (ES^+) = 404.2 $[M + H]^+$.

Preparation 24: 4-{3-[1-(5-Chloropyrimidin-2-yl)piperidin-4-yl]propoxy}-2-methylbenzoic acid



A mixture of lithium hydroxide monohydrate (308 mg, 7.33 mmol) and 4-{3-[1-(5-chloropyrimidin-2-yl)piperidin-4-yl]propoxy}-2-methylbenzoic acid methyl ester (**Preparation 23**, 1.41 g, 3.49 mmol) in THF (48 mL) and water (4.8 mL) was heated at 65°C for 96 h. The THF was removed *in vacuo*, then the residue was partitioned between 2M NaOH solution and EtOAc. The aqueous phase was acidified to pH 1 with 12M HCl, before being extracted with EtOAc (× 2). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to afford the title compound: RT = 4.27 min; *m/z* (ES^+) = 390.2 $[M + H]^+$.

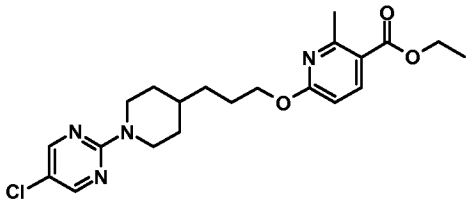
Preparation 25: 3-[1-(5-Chloropyrimidin-2-yl)piperidin-4-yl]propan-1-ol



A stirred solution of 3-piperidin-4-ylpropan-1-ol hydrochloride (15.0 g, 84 mmol) in DMSO (120 mL) was cooled to 0°C, before being treated dropwise with DBU (30.0 mL, 201 mmol) over 5 min. 2,5-Dichloropyrimidine (17.4 g, 117 mmol) was added, portion-wise, then the reaction was heated to 110°C for 4 h. After cooling to r.t., the reaction was poured into water (200 mL) and extracted with EtOAc (3 x 500 mL). The combined organic extracts were washed with 1M HCl (2 x 200 mL), before being dried ($MgSO_4$) and concentrated *in vauoc*. Purification by column chromatography (IH:EtOAc, 6:4) afforded the title compound: ^1H NMR ($CDCl_3$) δ 1.10–1.23 (m,

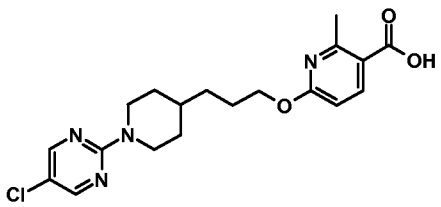
2H), 1.30–1.38 (m, 2H), 1.48–1.57 (m, 1H), 1.58–1.66 (m, 2H), 1.78 (d, 2H), 2.86 (m, 2H), 3.66 (t, 2H), 4.67 (d, 2H), 8.20 (s, 2H).

Preparation 26: 6-{3-[1-(5-Chloropyrimidin-2-yl)piperidin-4-yl]propoxy}-2-methylnicotinic acid ethyl ester



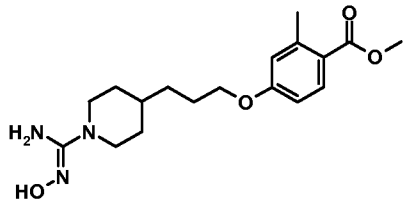
DIAD (2.88 mL, 14.7 mmol) was added dropwise, over 10 min, to a stirred solution of 3-[1-(5-chloropyrimidin-2-yl)piperidin-4-yl]propan-1-ol (**Preparation 25**, 2.50 g, 9.8 mmol), 6-hydroxy-2-methylnicotinic acid ethyl ester (1.95 g, 10.8 mmol), and PPh_3 (3.85 g, 14.7 mmol) in anhydrous THF (40 mL). After 16 h, the THF was removed *in vacuo*, then the residue was partitioned between EtOAc (200 mL) and 1M NaOH (100 mL). The organic layer was washed with brine, before being dried ($MgSO_4$), filtered and concentrated. The remainder was triturated with EtOAc and IH, then purification of the filtrate by column chromatography (IH:EtOAc, 9:1) afforded the title compound: RT = 5.30 min; *m/z* (ES^+) = 419.2 $[M + H]^+$.

Preparation 27: 6-{3-[1-(5-Chloropyrimidin-2-yl)piperidin-4-yl]propoxy}-2-methylnicotinic acid



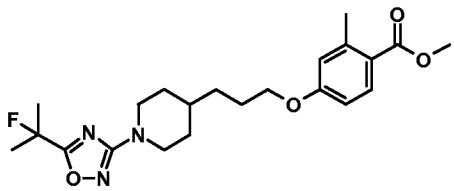
The title compound was prepared from 6-{3-[1-(5-chloropyrimidin-2-yl)piperidin-4-yl]propoxy}-2-methylnicotinic acid ethyl ester (**Preparation 26**, 2.65 g, 6.33 mmol) employing a similar procedure similar to that outlined in **Preparation 12**, but heating the reaction to 60°C, and extracting the product with DCM: RT = 4.49 min; *m/z* (ES^+) = 391.1 $[M + H]^+$.

Preparation 28: 4-{3-[1-(N-Hydroxycarbamimidoyl)piperidin-4-yl]propoxy}-2-methylbenzoic acid methyl ester



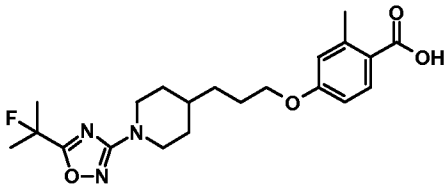
A mixture of aqueous hydroxylamine solution (50 wt%, 3.7 mL) and EtOH (50 mL) was added over a period of 2 h to a stirred solution of 4-[3-(1-cyanopiperidin-4-yl)propoxy]-2-methylbenzoic acid methyl ester (**Preparation 19**, 9.48 g, 30.0 mmol) in EtOH (50 mL). After stirring at ambient temperature for 18 h, the solvent was removed *in vacuo* and the residue was further dried through repeated concentration from toluene to afford the title compound: RT = 2.59 min; *m/z* (ES^+) = 350.2 $[M + H]^+$.

Preparation 29: 4-(3-{1-[5-(1-Fluoro-1-methylethyl)-[1,2,4]oxadiazol-3-yl]piperidin-4-yl}propoxy)-2-methylbenzoic acid methyl ester



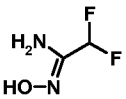
To a solution of 4-{3-[1-(N-hydroxycarbamimidoyl)piperidin-4-yl]propoxy}-2-methylbenzoic acid methyl ester (**Preparation 28**, 2.44 g, 7.0 mmol) and 2-fluoroisobutyric acid (742 mg, 7.0 mmol) in DMF (20 mL) was added HOBt (107 mg, 0.7 mmol), EDCI (1.74 g, 9.1 mmol) and triethylamine (2.2 mL, 16.1 mmol). After stirring at ambient temperature for 18 h the solvent was removed *in vacuo* and the residue was redissolved in EtOAc (400 mL). The EtOAc solution was washed with 1M HCl solution, 1M NaOH solution and brine, before being dried ($MgSO_4$), filtered and concentrated *in vacuo*. purification by column chromatography (IH:EtOAc, 3:1) afforded the title compound: RT = 4.84 min; *m/z* (ES^+) = 420.2 $[M + H]^+$.

Preparation 30: 4-(3-{1-[5-(1-Fluoro-1-methylethyl)-[1,2,4]oxadiazol-3-yl]piperidin-4-yl}propoxy)-2-methylbenzoic acid



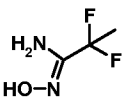
To a solution of 4-(3-{1-[5-(1-fluoro-1-methylethyl)-[1,2,4]oxadiazol-3-yl]piperidin-4-yl}propoxy)-2-methylbenzoic acid methyl ester (**Preparation 29**, 1.59 g, 3.8 mmol) in MeOH (100 mL) and water (20 mL) was added lithium hydroxide monohydrate (1.61 g, 38.4 mmol) and the mixture was stirred at 50°C for 12 h. The MeOH was removed *in vacuo*, then water (100 mL) was added, and the mixture was acidified to pH 3 with 1M HCl solution. The precipitate was extracted into EtOAc, then the combined EtOAc extracts were washed with brine and dried ($MgSO_4$). Filtration and removal of the solvent *in vacuo* afforded the title compound: RT = 4.22 min; *m/z* (ES^+) = 406.2 $[M + H]^+$.

Preparation 31: 2,2-Difluoro-N-hydroxyacetamidine



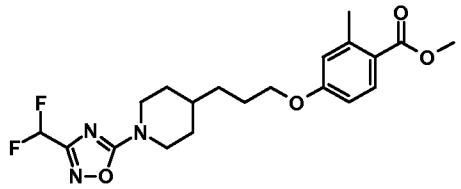
A stirred solution of difluoroacetonitrile (2.21 g, 28.7 mmol) in EtOH (5 mL) was treated carefully with a 50 wt% solution of hydroxylamine in water (2.08 g, 31.6 mmol). The mixture was stirred for a further 16 h, before being concentrated *in vacuo*. The residue was azeotroped with toluene, then the remaining oil was partitioned between EtOAc and water. The aqueous phase was extracted further with EtOAc (x 2), then the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford the title compound: *m/z* (ES^+) = 111.0 $[M + H]^+$.

Preparation 32: 2,2-Difluoro-N-hydroxypropionamidine



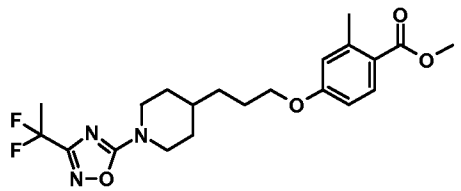
2,2-Difluoropropionitrile was reacted with a 50 wt% solution of hydroxylamine, employing a procedure similar to that outlined in **Preparation 31**, to afford the title compound: *m/z* (ES^+) = 125.0 $[M + H]^+$.

Preparation 33: 4-{3-[1-(3-Difluoromethyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]propoxy}-2-methylbenzoic acid methyl ester



$ZnCl_2$ (1M in Et_2O, 11.4 mL, 11.4 mmol) was slowly added to a stirred solution of 4-[3-(1-cyanopiperidin-4-yl)propoxy]-2-methylbenzoic acid methyl ester (**Preparation 19**, 3.0 g, 9.5 mmol) and 2,2-difluoro-N-hydroxyacetamidine (**Preparation 31**, 1.3g, 11.4 mmol) in EtOAc (30 mL) and the resulting solution was heated to reflux for 3 h. The reaction was cooled to ambient temperature and the solvent removed *in vacuo*. The resulting residue was dissolved in EtOH (30mL) and 12M HCl (3mL), and the mixture was heated to reflux for 12 h. The EtOH was concentrated by half *in vacuo*, and the remainder was adjusted to pH 7 with saturated aqueous $NaHCO_3$ solution. The mixture was extracted with Et_2O (x 2), then the combined extracts were dried ($MgSO_4$). Removal of the solvent *in vacuo* and purification by column chromatography (DCM:EtOAc, 1:1) afforded the title compound: RT = 4.50 min; *m/z* (ES^+) = 410.2 $[M + H]^+$.

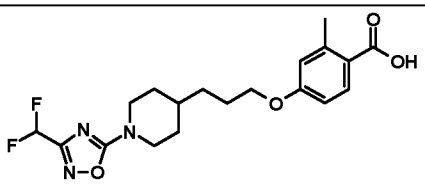
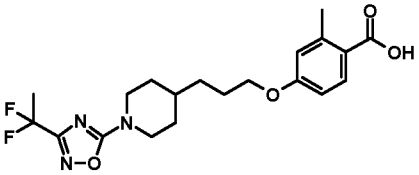
Preparation 34: 4-(3-{1-[3-(1,1-Difluoroethyl)-[1,2,4]oxadiazol-5-yl]piperidin-4-yl}propoxy)-2-methylbenzoic acid methyl ester



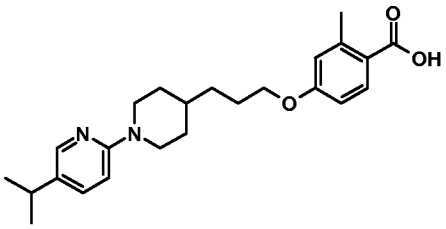
The title compound was prepared by reacting 4-[3-(1-cyanopiperidin-4-yl)propoxy]-2-methylbenzoic acid methyl ester (**Preparation 19**) with 2,2-difluoro-N-hydroxypropionamidine (**Preparation 32**) employing a method similar to that outlined in **Preparation 33**: RT = 4.59 min; *m/z* (ES^+) = 424.22 $[M + H]^+$.

The compounds in **Table 2** were prepared employing a similar method to that outlined in **Preparation 30:**

Table 2:

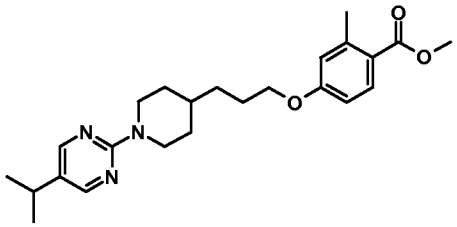
Prep.	Structure	Name	LCMS
35		4-{3-[1-(3-Difluoromethyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]propoxy}-2-methylbenzoic acid	RT = 3.95 min; *m/z* (ES^+) = 396.1 $[M + H]^+$
36		4-(3-{1-[3-(1,1-Difluoroethyl)-[1,2,4]oxadiazol-5-yl]piperidin-4-yl}propoxy)-2-methylbenzoic acid	RT = 4.03 min; *m/z* (ES^+) = 410.2 $[M + H]^+$

Preparation 37: 4-[3-(5'-Isopropyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)propoxy]-2-methylbenzoic acid



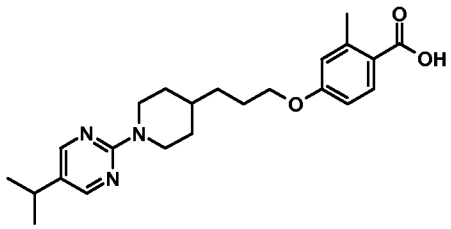
To a solution of 2-methyl-4-(3-piperidin-4-ylpropoxy)benzoic acid hydrochloride (**Preparation 13**, 400 mg, 1.28 mmol) in dioxane (6 mL) was added 2-chloro-5-isopropylpyridine (277 mL, 1.79 mmol), sodium *tert*-butoxide (431 mg, 4.48 mmol) and 2,8,9-triisobutyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]undecane (45 mg, 0.13mmol). Argon was bubbled through the reaction mixture for 40 min, then bis(dibenzylideneacetone)palladium (117 mg, 0.13 mmol) was added. The reaction mixture was bubbled with argon for a further 10 min and then heated in a microwave reactor at 115°C for 1.5 h. The reaction was diluted with methanol, filtered through celite and concentrated *in vacuo*. The residue was diluted with water, acidified to pH 5 with 2M HCl solution and extracted with EtOAc (× 2). The combined organic fractions were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. Crystallisation from MeOH afforded the title compound: RT = 3.05 min; *m/z* (ES^+) = 397.2 $[M + H]^+$.

Preparation 38: 4-{3-[1-(5-Isopropylpyrimidin-2-yl)piperidin-4-yl]propoxy}-2-methylbenzoic acid methyl ester



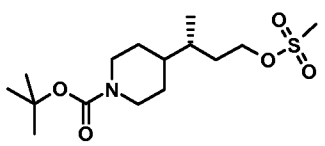
The title compound was prepared by reacting 4-[3-(4-methoxycarbonyl-3-methyl-phenoxy)propyl]piperidine-1-carboxylic acid *tert*-butyl ester (**Preparation 11**) with 2-chloro-5-isopropylpyrimidine employing the procedure outlined in **Preparation 23**: RT = 4.44 min; *m/z* (ES^+) = 412.2 $[M + H]^+$.

Preparation 39: 4-{3-[1-(5-Isopropylpyrimidin-2-yl)piperidin-4-yl]propoxy}-2-methylbenzoic acid



To a solution of 4-{3-[1-(5-isopropylpyrimidin-2-yl)piperidin-4-yl]propoxy}-2-methylbenzoic acid methyl ester (**Preparation 38**, 726 mg, 1.76 mmol) in MeOH (17 mL) and water (3 mL) was added NaOH (704 mg, 17.60 mmol) and the resulting mixture was stirred at 50°C for 16 h. THF (5 mL) was added to the reaction and heating was continued for 72 h. The mixture was cooled to ambient temperature, acidified to pH 1 with 2M HCl solution and extracted with DCM and EtOAc. The combined organic extracts were concentrated *in vacuo* to afford the title compound: RT = 3.90 min; *m/z* (ES^+) = 398.2 $[M + H]^+$.

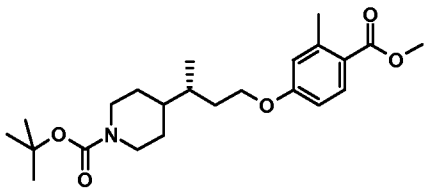
Preparation 40: 4-((*R*)-3-Methanesulfonyloxy-1-methylpropyl)piperidine-1-carboxylic acid *tert*-butyl ester



To a stirred solution of *tert*-butyl 4-((*R*)-3-hydroxy-1-methylpropyl)piperidine-1-carboxylate and methanesulfonyl chloride (9.8 g, 85.6 mmol) in DCM (200 mL), at 0°C, was added triethylamine

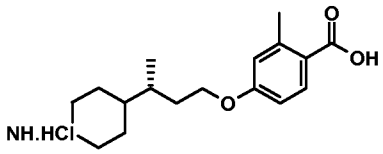
(13.0 mL, 93.4 mmol). The reaction mixture was warmed to ambient temperature and stirred for 3 h. Further methanesulfonyl chloride (5.0 g, 43.7 mmol) and triethylamine (6.9 mL, 49.5 mmol) were added and stirring continued for 10 h. The reaction mixture was partitioned between DCM and water, and the organic phase was washed with 1M HCl, 1M NaOH, then brine, before being dried ($MgSO_4$). Removal of the solvent *in vacuo* and purification by column chromotography (DCM:EtOAc, 19:1) afforded the title compound: RT = 3.65 min; *m/z* (ES^+) = 336.2 $[M + H]^+$.

Preparation 41: 4-[(*R*)-3-(4-Methoxycarbonyl-3-methylphenoxy)-1-methylpropyl]piperidine-1-carboxylic acid *tert*-butyl ester



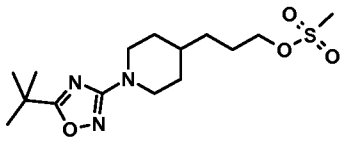
The title compound was prepared by reacting 4-hydroxy-2-methylbenzoic acid methyl ester (8.1 g, 48.7 mmol) with 4-((*R*)-3-methanesulfonyloxy-1-methylpropyl)piperidine-1-carboxylic acid *tert*-butyl ester (**Preparation 40**, 16.3 g, 48.7 mmol) employing a similar method to that outlined in **Preparation 7**: RT = 4.55 min; *m/z* (ES^+) = 406.3 $[M + H]^+$.

Preparation 42: 2-Methyl-4-((*R*)-3-piperidin-4-yl-butoxy)benzoic acid hydrochloride



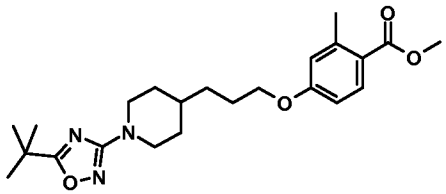
To a solution of 4-[(*R*)-3-(4-methoxycarbonyl-3-methylphenoxy)-1-methylpropyl]piperidine-1-carboxylic acid *tert*-butyl ester (**Preparation 41**, 10.0 g, 24.7 mmol) in MeOH (100 mL) and water (10 mL) was added lithium hydroxide monohydrate (10.4 g, 246.9 mmol) and the resulting mixture was stirred at 50°C for 16 h. The MeOH was concentrated *in vacuo*, then the residue was dissolved in water and acidified to pH 1 with 1M HCl, before being extracted with DCM (x 2). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford the intermediate product 4-[(*R*)-3-(4-carboxy-3-methylphenoxy)-1-methylpropyl]piperidine-1-carboxylic acid *tert*-butyl ester: RT = 4.10 min; *m/z* (ES^+) = 392.30 $[M + H]^+$. The product was stirred with 4M HCl in dioxane for 2 h. Removal of the solvent *in vacuo* afforded the title compound: RT = 2.43 min; *m/z* (ES^+) = 292.2 $[M + H]^+$.

Preparation 43: Methanesulfonic acid 3-[1-(5-*tert*-butyl-[1,2,4]oxadiazol-3-yl)piperidin-4-yl]propyl ester



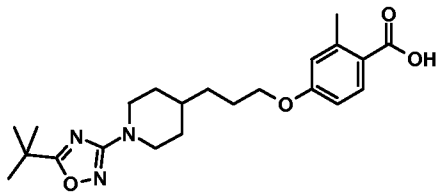
To a stirring solution of 3-[1-(5-*tert*-butyl-[1,2,4]oxadiazol-3-yl)piperidin-4-yl]propan-1-ol (18.5 g, 69 mmol) in DCM (225 mL) was added methanesulfonyl chloride (5.6 mL, 71 mmol), and the reaction was cooled to 0°C. Triethylamine (11.1 mL, 79 mmol) was added, over 15 min, then the reaction was warmed to ambient temperature and allowed to stir for 16 h. The reaction solvent was washed with water (2 x 100 mL), then brine (100 mL), and dried ($MgSO_4$). Removal of the solvent *in vacuo* afforded the title compound: ^{1}H NMR δ_H (400mHz, $CDCl_3$): 1.21 - 1.33 (m, 2H), 1.39 - 1.53 (m, 11H), 1.70 - 1.84 (m, 4H), 2.80 - 2.89 (m, 2H), 3.00 (s, 3H), 3.62 - 3.68 (m, 1H), 3.95 - 4.02 (m, 2H), 4.20 - 4.26 (m, 2H).

Preparation 44: 4-{3-[1-(5-*tert*-Butyl-[1,2,4]oxadiazol-3-yl)piperidin-4-yl]propoxy}-2-methylbenzoic acid methyl ester



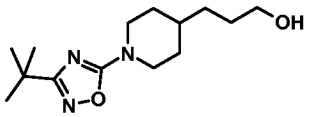
To a solution of methanesulfonic acid 3-[1-(5-*tert*-butyl-[1,2,4]oxadiazol-3-yl)piperidin-4-yl]propyl ester (**Preparation 43**, 22.3 g, 64.6 mmol) and 4-hydroxy-2-methylbenzoic acid methyl ester (10.7 g, 64.5 mmol) in MIBK (300 mL), was added K_2CO_3 (12.9 g, 129.7 mmol), and the reaction was heated to 80°C for 72 h before being allowed to stir at r.t. for a further 72 h. The mixture was poured into water (1000 mL), then the aqueous phase was separated and extracted with Et_2O (2 x 300 mL). The organic fractions were combined, washed with 1M NaOH solution (2 x 150 mL), then water (2 x 300 mL), and dried ($MgSO_4$). Removal of the solvent *in vacuo* afforded the title compound: ^{1}H NMR δ_H (400mHz, $CDCl_3$): 1.22 - 1.35 (m, 2H), 1.38 (s, 9H), 1.40 - 1.54 (m, 3H), 1.75 – 1.88 (m, 4H), 2.59 (s, 3H), 2.80 – 2.91 (m, 2H), 3.85 (s, 3H), 3.98 - 4.04 (m, 4H), 6.70 – 6.73 (m, 2H), 7.90 – 7.93 (d, 1H).

Preparation 45: 4-{3-[1-(5-*tert*-Butyl-[1,2,4]oxadiazol-3-yl)piperidin-4-yl]propoxy}-2-methylbenzoic acid



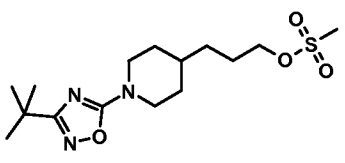
To a solution of 4-{3-[1-(5-*tert*-butyl-[1,2,4]oxadiazol-3-yl)piperidin-4-yl]propoxy}-2-methylbenzoic acid methyl ester (**Preparation 44**, 26.1 g, 62.9 mmol) in MeOH (70 mL) was added a solution of lithium hydroxide monohydrate (13.3 g, 31.6 mmol) in a combination of water (26 mL) and MeOH (20 mL), and the mixture was heated to 55°C for 20 h. The reaction solvent was concentrated *in vacuo*, and the residue was dissolved in water (200 mL). The aqueous solution was warmed to 45°C before being acidified to pH 3 through the addition of 1M HCl solution. The mixture was cooled in an ice bath, then the precipitate was collected, washed with water, and dried under vacuum to afford the title compound: RT = 4.47 min; *m/z* (ES^+) = 402.3 $[M + H]^+$.

Preparation 46: 3-[1-(3-*tert*-Butyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]propan-1-ol



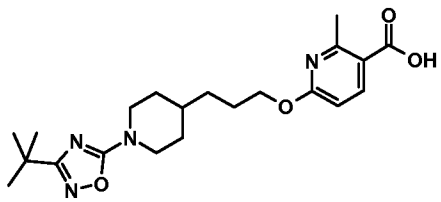
$ZnCl_2$ (0.5M in EtOH, 7.3 mL, 49.9 mmol) was added dropwise, over 10 min, to a stirred solution of 4-(3-hydroxypropyl)piperidine-1-carbonitrile (7.0 g, 41.6 mmol) and N-hydroxy-2,2-dimethylpropionamidine (5.8 g, 49.9 mmol) in EtOH (122.7 mL), and the reaction was stirred at r.t. for 3 h. 12M HCl (24 mL) was added, dropwise, and the resulting mixture was heated to reflux for 16 h. The solvent was removed *in vacuo*, then the residue was diluted with water (200 mL) and adjusted to pH 7 with solid $NaHCO_3$. The mixture was extracted with EtOAc (3 x 200 mL), then the combined extracts were washed with brine, dried ($MgSO_4$), and the solvent removed *in vacuo*. The residue was dissolved in DCM (300 mL), washed with citric acid (2 x 50 mL), and dried ($MgSO_4$). Removal of the solvent *in vacuo* afforded the title compound: RT = 3.09 min; *m/z* (ES^+) = 268.2 $[M + H]^+$.

Preparation 47: Methanesulfonic acid 3-[1-(3-*tert*-butyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]propyl ester



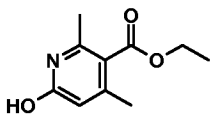
The title compound was prepared from 3-[1-(3-*tert*-butyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]propan-1-ol (**Preparation 46**) employing a similar method to that outlined in **Preparation 43**, but the reaction was complete after 1 h: RT = 3.54 min; *m/z* (ES^+) = 346.1 $[M + H]^+$.

Preparation 48: 6-{3-[1-(3-*tert*-Butyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]propoxy}-2-methylnicotinic acid



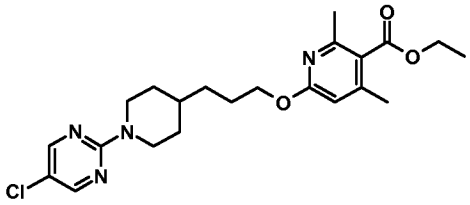
Methanesulfonic acid 3-[1-(3-*tert*-butyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]propyl ester (**Preparation 47**) was condensed with 6-hydroxy-2-methylnicotinic acid ethyl ester employing a similar method to that outlined in **Preparation 7,** but using MEK as the solvent, and heating the reaction for 16 h. The product was hydrolysed, employing a method similar to that outlined in **Preparation 30**, to afford the title compound: RT = 4.15 min; *m/z* (ES^+) = 403.2 $[M + H]^+$.

Preparation 49: 6-Hydroxy-2,4-dimethylnicotinic acid ethyl ester



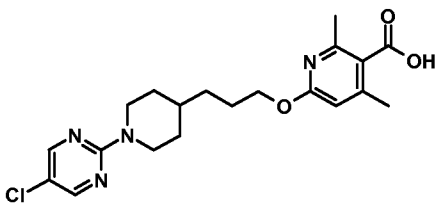
To a solution of 3-aminobut-2-enoic acid ethyl ester (25 mL, 200 mmol) in toluene (150 mL) was added a solution of HCl in dioxane (4M, 100 mL, 400 mmol), and the reaction was heated to 115°C for 16 h. The mixture was cooled to ambient temperature and filtered, then the filtrate was collected and concentrated *in vacuo*. The residue was taken into a combination of IH and EtOAc and an oily residue formed. The filtrate was decanted and the oil discarded. A precipitate, which formed in the filtrate, was removed by filtration, and the remaining solution was purified by column chromatography (EtOAc:MeOH, 9:1), followed by crystallization from IH and EtOAc. The columned product was combined with the precipitate to afford the title compound: RT = 2.40 min; *m/z* (ES^+) = 196.1 $[M + H]^+$

Preparation 50: 6-{3-[1-(5-Chloropyrimidin-2-yl)piperidin-4-yl]propoxy}-2,4-dimethyl-nicotinic acid ethyl ester



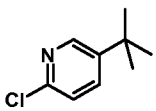
3-[1-(5-Chloropyrimidin-2-yl)piperidin-4-yl]propan-1-ol (**Preparation 25**, 1.55 g, 6.05 mmol) was reacted with 6-hydroxy-2,4-dimethylnicotinic acid ethyl ester (**Preparation 49**, 1.30 g, 6.66 mmol), employing a similar method to that outlined in **Preparation 26**, to afford the title compound: RT = 5.29 min; *m/z* (ES^+) = 433.2 $[M + H]^+$.

Preparation 51: 6-{3-[1-(5-Chloropyrimidin-2-yl)piperidin-4-yl]propoxy}-2,4-dimethylnicotinic acid



6-{3-[1-(5-Chloropyrimidin-2-yl)piperidin-4-yl]propoxy}-2,4-dimethylnicotinic acid ethyl ester (**Preparation 50**, 0.50 g, 1.15 mmol) was hydrolysed, employing a method similar to that outlined in **Preparation 24**, to afford the title compound: RT = 4.24 min; *m/z* (ES^+) = 405.2 $[M + H]^+$.

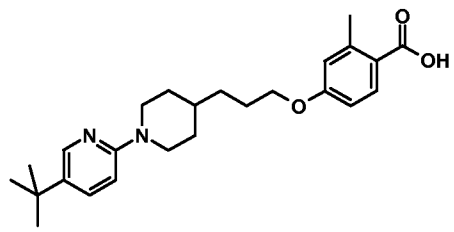
Preparation 52: 5-*tert*-Butyl-2-chloropyridine



To a stirring solution of morpholine (4.0 mL, 46.0 mmol) in anhydrous cyclohexane (40 mL), under argon, was added 3,3-dimethylbutyraldehyde (6.3 mL, 50.0 mmol), dropwise, over 20 min. The resulting solution was heated at 80°C for 16 h, before cooling to ambient temperature and adding EtOAc (40 mL), hydroquinone (20.0 mg, 0.2 mmol) and acetic acid (0.3 mL). The reaction mixture was heated to 78°C and 2-chloroacrylnitrile (5.5 mL, 69.0 mmol) was added, dropwise, over 20 min. Heating at 78°C was continued for 1 h, then HCl gas was bubbled through the reaction mixture for 15 min, before cooling to ambient temperature. Sat. $NaHCO_3$ solution was added to

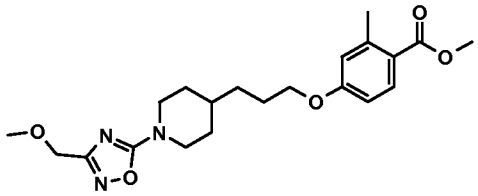
adjust the reaction mixture to pH 8, then the organic phase was separated and the aqueous layer extracted with EtOAc (x 2). The combined organic fractions were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (IH:EtOAc, 9:1) afforded the title compound: RT = 3.42 min; *m/z* (ES^+) = 170.1 $[M + H]^+$.

Preparation 53: 4-[3-(5'-*tert*-Butyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)propoxy]-2-methylbenzoic acid



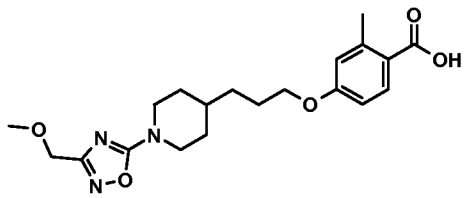
The title compound was prepared by reacting 2-methyl-4-(3-piperidin-4-ylpropoxy)benzoic acid hydrochloride (**Preparation 13**, 400 mg, 1.28 mmol) with 5-*tert*-butyl-2-chloropyridine (**Preparation 52**, 302 mg, 1.79 mmol) employing a similar method to that outlined in **Preparation 37**: RT = 3.07 min; *m/z* (ES^+) = 411.2 $[M + H]^+$.

Preparation 54: 4-{3-[1-(3-Methoxymethyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]propoxy}-2-methylbenzoic acid methyl ester



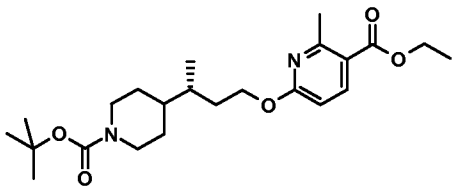
The title compound was prepared by reacting 4-[3-(1-cyanopiperidin-4-yl)propoxy]-2-methylbenzoic acid methyl ester (**Preparation 19**) with N-hydroxy-2-methoxyacetamidine employing a similar method to that outlined in **Preparation 33**, but the reaction was refuluxed in EtOH for only 1 h**:** RT = 3.98 min; *m/z* (ES^+) = 404.2 $[M + H]^+$.

Preparation 55: 4-{3-[1-(3-Methoxymethyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]propoxy}-2-methylbenzoic acid



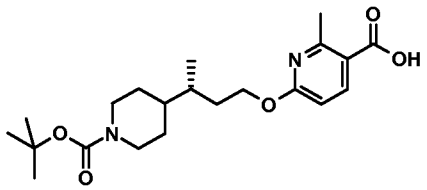
A mixture of lithium hydroxide monohydrate (1.0 g, 23.8 mmol) and 4-{3-[1-(3-methoxymethyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]propoxy}-2-methylbenzoic acid methyl ester (**Preparation 54**, 1.1 g, 2.6 mmol) in a combination of MeOH (10 mL) and water (2 mL) was heated at 50°C for 72 h. The MeOH was removed *in vacuo*, then the residue was partitioned between 2M NaOH solution and EtOAc. The aqueous phase was acidified to pH 1 with 2M HCl, before being extracted with EtOAc (x 3). The combined organic fractions were washed with brine, dried ($MgSO_4$), and the solvent removed *in vacuo* to afford the title compound: RT = 3.47 min; *m/z* (ES^+) = 390.2 [$M + H]^+$.

Preparation 56: 6-[(*R*)-3-(1-*tert*-Butoxycarbonylpiperidin-4-yl)butoxy]-2-methylnicotinic acid ethyl ester



DIAD (5.20 mL, 20.6 mmol) was added to a stirred solution of *tert*-butyl 4-((*R*)-3-hydroxy-1-methylpropyl)piperidine-1-carboxylate (4.56 g, 17.7 mmol), 6-hydroxy-2-methylnicotinic acid ethyl ester (4.44 g, 26.6 mmol) and PPh_3 (6.97 g, 26.6 mmol) in anhydrous THF (50 mL) at ambient temperature. After stirring for 30 min, the solvent was removed *in vacuo*, and the resulting residue was dissolved in EtOAc and washed with 2M NaOH (x 2), then brine. The organic layer was dried ($MgSO_4$), concentrated *in vacuo* to approximately one fifth of the original volume, and IH was added. The precipitate produced was removed by filtration and the remaining filtrate was concentrated *in vacuo* and purified by column chromatography (IH:EtOAc, 17:3) to afford the title compound: RT = 4.75 min; *m/z* (ES^+) = 421.3 [$M + H]^+$.

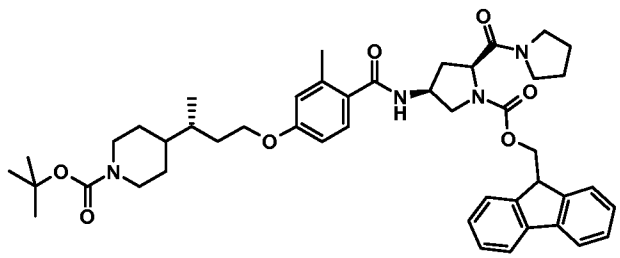
Preparation 57: 6-[(*R*)-3-(1-*tert*-Butoxycarbonylpiperidin-4-yl) butoxy]-2-methylnicotinic acid



To a stirred solution of 6-[(*R*)-3-(1-*tert*-butoxycarbonylpiperidin-4-yl)butoxy]-2-methylnicotinic acid ethyl ester (**Preparation 56**, 3.00 g, 7.14 mmol) in a combination of MeOH (40 mL) and water (4 mL) was added lithium hydroxide monohydrate (3.00 g, 71.4 mmol), and the resulting suspension was stirred at 60°C for 16 h. The solvent was removed *in vacuo*, then the residue

was dissolved in water, acidified to pH 1 with 2M HCl and extracted with DCM (x 3). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the title compound: RT = 4.02 min; *m/z* (ES^+) = 393.3 $[M + H]^+$.

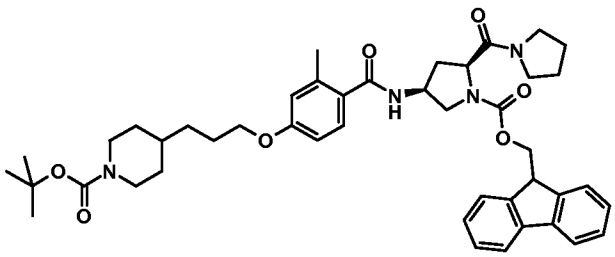
Preparation 58: 4-((*R*)-3-{4-[(3*S*,5*S*)-1-(9H-Fluoren-9-ylmethoxycarbonyl)-5-(pyrrolidine-1-carbonyl)pyrrolidin-3-ylcarbamoyl]-3-methylphenoxy}-1-methylpropyl)piperidine-1-carboxylic acid *tert*-butyl ester



To 4-[(*R*)-3-(4-methoxycarbonyl-3-methylphenoxy)-1-methylpropyl]piperidine-1-carboxylic acid *tert*-butyl ester (**Preparation 41**, 109 mg, 0.27 mmol) and lithium hydroxide monohydrate (65 mg, 2.70 mmol) was added a mixture of MeOH and water (10:1) and the reaction was heated to 50°C for 16 h. The mixture was poured onto 2M HCl, and the resulting solution was extracted with EtOAc. The organic phase was dried ($MgSO_4$), and the solvent removed *in vacuo* to afford the intermediate product 4-[(*R*)-3-(4-Carboxy-3-methylphenoxy)-1-methylpropyl]piperidine-1-carboxylic acid *tert*-butyl ester:

To a solution of the product in NMP (2 mL) was added HOBt (33 mg, 0.22 mmol), followed by EDCI (47 mg, 0.25 mmol), and the reaction was stirred at r.t. for 15 min. Triethylamine (30 µL, 0.22 mmol) was added, followed by (2*S*,4*S*)-4-amino-2-(pyrrolidine-1-carbonyl)pyrrolidine-1-carboxylic acid 9H-fluoren-9-ylmethyl ester trifluoroacetate (**Preparation 4**, 104 mg, 0.20 mmol), and the reaction was allowed to stand at r.t. for 7 h. A second portion of triethylamine (30 µL, 0.22 mmol) was added and the reaction was allowed to stand for a further 17 h. A third portion of triethylamine (30 µL, 0.22 mmol) was added and the reaction allowed to stand for 2 h The mixture was diluted with EtOAc, then the resulting solution was washed with water, sat. $NaHCO_3$ solution (x 2), and dried ($MgSO_4$). Removal of the solvent *in vacuo* afforded the title compound: RT = 4.95 min, m/z (ES^+) = 779.4 $[M + H]^+$.

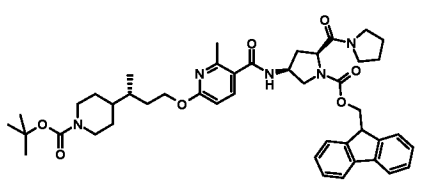
Preparation 59: 4-(3-{4-[(3*S*,5*S*)-1-(9H-Fluoren-9-ylmethoxycarbonyl)-5-(pyrrolidine-1-carbonyl)pyrrolidin-3-ylcarbamoyl]-3-methylphenoxy}propyl)piperidine-1-carboxylic acid *tert*-butyl ester

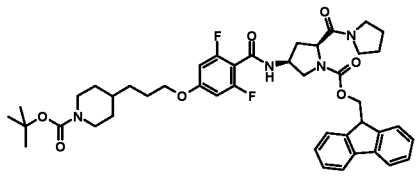
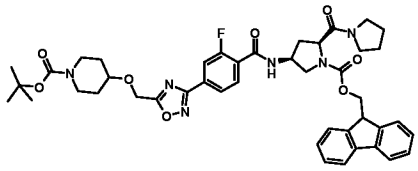


To a solution of 4-[3-(4-carboxy-3-methylphenoxy)propyl]piperidine-1-carboxylic acid *tert*-butyl ester (**Preparation 12**, 68 mg, 0.18 mmol) in NMP (2 mL) was added HOBt (33 mg, 0.22 mmol), followed by EDCI (47 mg, 0.25 mmol), and the reaction was stirred at r.t. for 15 min. Triethylamine (30 μL, 0.22 mmol) was added, followed by (2*S*,4*S*)-4-amino-2-(pyrrolidine-1-carbonyl)pyrrolidine-1-carboxylic acid 9H-fluoren-9-ylmethyl ester trifluoroacetate (**Preparation 4**, 104 mg, 0.20 mmol), and the reaction was allowed to stand at r.t. for 7 h. A second portion of triethylamine (30 μL, 0.22 mmol) was added and the reaction was allowed to stand for a further 17 h. A third portion of triethylamine (30 μL, 0.22 mmol) was added and the reaction allowed to stand for 2 h The mixture was diluted with EtOAc, then the resulting solution was washed with water, sat. $NaHCO_3$ solution (x 2), and dried ($MgSO_4$). Removal of the solvent *in vacuo* afforded the title compound: RT = 4.87 min, m/z (ES^+) = 765.4 $[M + H]^+$.

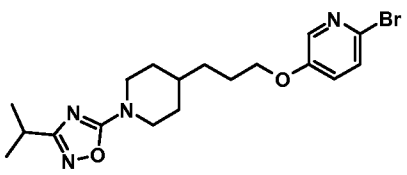
The compounds in **Table 3** were prepared by reacting the appropriate acid building block with (2*S*,4*S*)-4-amino-2-(pyrrolidine-1-carbonyl)pyrrolidine-1-carboxylic acid 9H-fluoren-9-ylmethyl ester trifluoroacetate (**Preparation 4**) employing the method outlined in **Preparation 59**. The building block used in the synthesis of **Preparation 61** was prepared employing the methods outlined in WO2007003962 and the building block used in the synthesis of **Preparation 62** was prepared employing the methods outlined in WO2007003960:

Table 3:

Prep.	Structure	Name	LCMS
60		4-((*R*)-3-{5-[(3*S*,5*S*)-1-(9H-Fluoren-9-ylmethoxycarbonyl)-5-(pyrrolidine-1-carbonyl)pyrrolidin-	RT = 4.90 min; *m/z* (ES^+) = 780.4 $[M + H]^+$

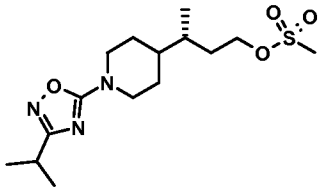
Prep.	Structure	Name	LCMS
		3-ylcarbamoyl]-6-methylpyridin-2-yloxy}-1-methylpropyl)piperidine-1-carboxylic acid *tert*-butyl ester	
61		4-(3-{4-[(3*S*,5*S*)-1-(9H-Fluoren-9-ylmethoxycarbonyl)-5-(pyrrolidine-1-carbonyl)pyrrolidin-3-ylcarbamoyl]-3,5-difluorophenoxy}propyl)piperidine-1-carboxylic acid *tert*-butyl ester	RT = 4.80 min; *m/z* (ES^+) = 787.4 $[M + H]^+$
62		4-(3-{4-[(3*S*,5*S*)-1-(9H-Fluoren-9-ylmethoxycarbonyl)-5-(pyrrolidine-1-carbonyl)pyrrolidin-3-ylcarbamoyl]-3-fluorophenyl}-[1,2,4]oxadiazol-5-ylmethoxy)piperidine-1-carboxylic acid *tert*-butyl ester	RT = 4.52 min; *m/z* (ES^+) = 809.4 $[M + H]^+$

Preparation 63: 2-Bromo-5-{3-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]propoxy}pyridine



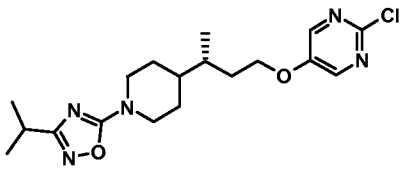
TBAD (1.6g, 6.9 mmol) was added to a stirred solution of 3-[1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]propan-1-ol (1.4 g, 5.8 mmol), 6-bromopyridin-3-ol (1.0 g, 5.8 mmol) and PPh_3 (1.8 g, 6.9 mmol) in anhydrous toluene (40 mL) at ambient temperature. After stirring for 16 h, the reaction mixture was washed with 1M HCl solution, 2M NaOH (x 2) and brine, then dried ($MgSO_4$). Removal of the solvent *in vacuo* and purification by column chromatography (IH:EtOAc, 85:15, 70:30) afforded the title compound: RT = 3.99 min; *m/z* (ES^+) = 409.0, 411.0 [*M* + H]$^+$.

Preparation 64: (*R*)-Methanesulfonic acid-3-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]butyl ester



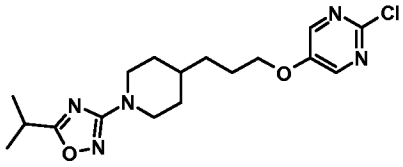
Methanesulfonyl chloride (0.61 mL, 7.9 mmol) and triethylamine (2.01 mL, 15.0 mmol) were added to a solution of (*R*)-3-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]butan-1-ol (2.0 g, 7.5 mmol) in DCM (30 mL) at 0°C. After stirring for 10 min, the reaction was diluted with DCM (100mL) and poured into saturated aqueous $NaHCO_3$ solution (100 mL). The organic layer was separated, washed with 0.1M HCl (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (EtOAc:IH, 1:1) afforded the title compound: RT = 3.42 min; *m/z* (ES^+) = 346.1 [*M* + H]$^+$.

Preparation 65: (*R*)-2-Chloro-5-{3-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]butoxy}pyrimidine



A combination of (*R*)-methanesulfonic acid-3-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]butyl ester (**Preparation 64**, 560 mg, 1.62 mmol), 2-chloro-5-hydroxypyrimidine (423 mg, 3.24 mmol) and K_2CO_3 (447 mg, 3.24 mmol) in DMF (4 mL) was heated to 70°C for 24h. The reaction mixture was diluted with water (75 mL) and extracted with EtOAc (2 x 75 mL). The combined organic fractions were washed with 1M NaOH solution, then brine, and dried ($MgSO_4$). Removal of the solvent *in vacuo* afforded the title compound: RT = 4.14 min; *m/z* (ES^+) = 380.1 [*M* + H]$^+$.

Preparation 66: 2-Chloro-5-{3-[1-(5-isopropyl-[1,2,4]oxadiazol-3-yl)piperidin-4-yl]propoxy}pyrimidine



To a solution of 3-[1-(5-isopropyl-[1,2,4]oxadiazol-3-yl)piperidin-4-yl]propan-1-ol (759 mg, 3.0 mmol) in DCM (15 mL) was added triethylamine (0.50 mL, 3.6 mmol) and the mixture was cooled to 0°C. Methanesulfonyl chloride (0.23 mL, 3.0 mmol) was added and the reaction was warmed to r.t. over 15 min. 1M HCl (80 mL) was added and the resulting mixture poured into EtOAc (150 mL). The organic layer was separated, washed with 1M HCl (80 mL), brine (100 mL), dried ($MgSO_4$), and the solvent removed *in vacuo*. To a solution of the material in DMF (10 mL) was added 2-chloro-5-hydroxypyrimidine (390 mg, 3.0 mmol) and K_2CO_3 (828 mg, 6.0 mmol), and the mixture was heated to 85°C for 16 h. DMF was removed *in vacuo* and the residue was re-dissolved in EtOAc. The organic solution was washed with brine (x 2), dried ($MgSO_4$), and the solvent removed *in vacuo*. Recrystalisation from the minimal volume of MeOH afforded the title compound: RT = 4.22 min *m/z* (ES^+) = 366.2 $[M + H]^+$.

Examples

The compounds in **Examples Table 1** were prepared employing the general procedure outlined below:

General Procedure A:

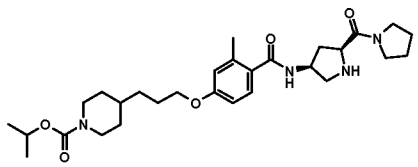
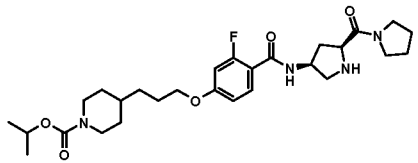
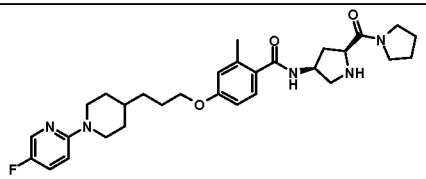
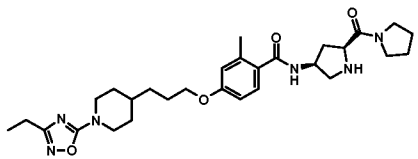
To a combination of acid building block (0.13 mmol), EDCI (32 mg, 0.17 mmol) and HOBt (22 mg, 0.14 mmol) was added NMP (3 mL), and the reaction was shaken for 15 min. A solution of (2*S*,4*S*)-4-amino-2-(pyrrolidine-1-carbonyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (**Preparation 2**, 40 mg, 0.14 mmol) in NMP (2 mL) was added to the mixture, and the reaction was shaken at ambient temperature for 16 h. The mixture was diluted with EtOAc, washed with water, 2M HCl solution, and sat. $NaHCO_3$ solution (x 2), then dried ($MgSO_4$). Removal of the solvent *in vacuo* afforded the intermediate Boc-protected product:

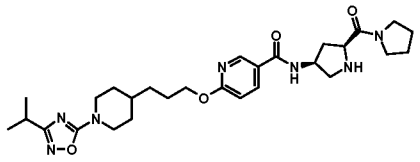
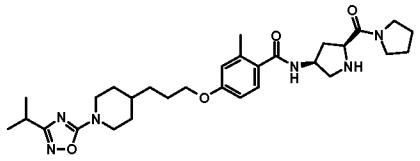
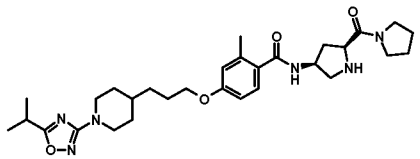
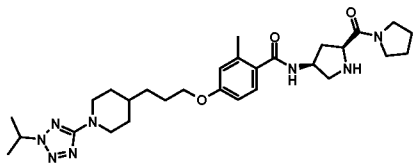
To a solution of the product in DCM (4 mL) was added added TFA (1 mL), and the reaction was shaken for 2 h. **Purification method A**: The crude mixture was passed directly down an SCX cartridge, eluting with MeOH followed by NH_4OH in MeOH. The basic fraction was collected and concentrated *in vacuo* to afford the title compound as the free amine. **Purification method B**: As purification method A but the product was purified further by preparative HPLC to afford the title

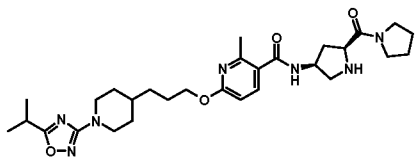
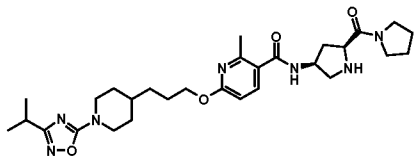
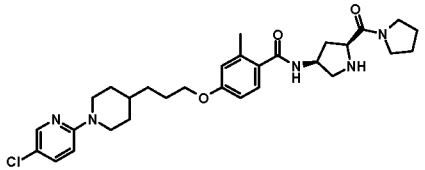
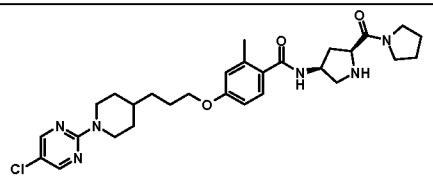
compound as the trifluoroacetate salt. **Purification method C**: As purification method B. After preparative HPLC the product was passed down a second SCX cartridge, eluting with MeOH followed by NH_4OH in MeOH. The basic fraction was collected and concentrated *in vacuo* to afford the title compound as the free amine.

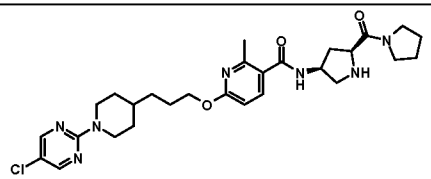
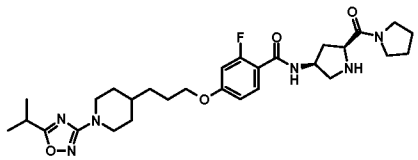
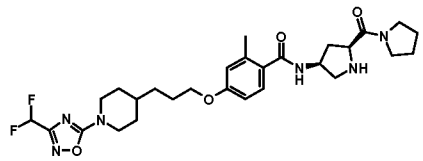
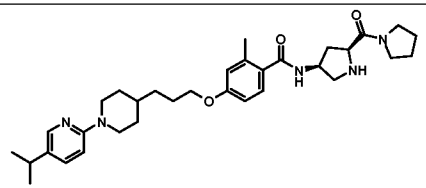
Examples Table 1

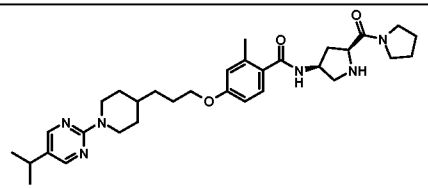
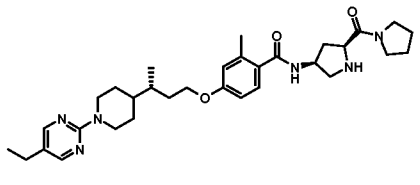
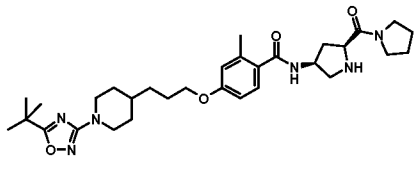
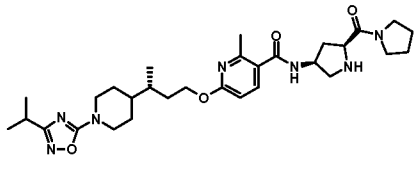
The building block used in the synthesis of **Example 2** was prepared employing the methods outlined in WO2007/003962. The building block used in the synthesis of **Examples 4**, **6**, **7, 14** and **24** were prepared employing the methods outlined in WO2008081205. The building blocks used in the synthesis of **Examples 5**, **9, 10** and **20** were prepared employing the methods outlined in WO2008/081207:

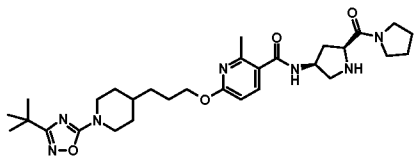
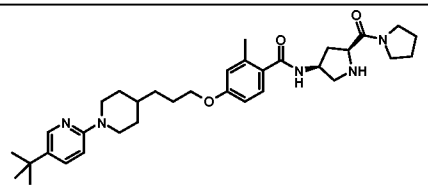
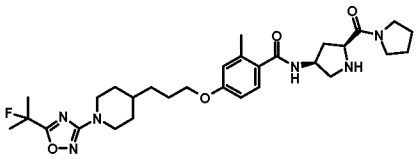
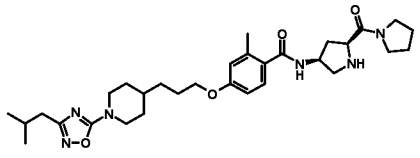
Ex.	Structure	Name	Purification Method	LCMS
1		4-(3-{3-Methyl-4-[(3*S*,5*S*)-5-(pyrrolidine-1-carbonyl)-pyrrolidin-3-ylcarbamoyl]-phenoxy}propyl)piperidine-1-carboxylic acid isopropyl ester	A	RT = 2.88 min, m/z (ES^+) = 529.3 [M + H]$^+$.
2		4-(3-{3-Fluoro-4-[(3*S*,5*S*)-5-(pyrrolidine-1-carbonyl)-pyrrolidin-3-yl-carbamoyl]phenoxy}propyl)piperidine-1-carboxylic acid isopropyl ester	A	RT = 2.80 min; *m/z* (ES^+) = 533.3 [M + H]$^+$
3		4-[3-(5'-Fluoro-3,4,5,6-tetrahydro-2H-[1,2']-bipyridinyl-4-yl)propoxy]-2-methyl-N-[(3*S*,5*S*)-5-(pyrrolidine-1-carbonyl)-pyrrolidin-3-yl]benzamide	B	RT = 2.62 min; *m/z* (ES^+) = 538.4 [M + H]$^+$
4		4-{3-[1-(3-Ethyl-[1,2,4]-oxadiazol-5-yl)piperidin-4-yl]propoxy}-2-methyl-N-[(3*S*,5*S*)-5-(pyrrolidine-1-carbonyl)pyrrolidin-3-yl]-benzamide	A	RT = 2.72 min; *m/z* (ES^+) = 539.3 [M + H]$^+$

Ex.	Structure	Name	Purification Method	LCMS
5		6-{3-[1-(3-Isopropyl-[1,2,4]-oxadiazol-5-yl)piperidin-4-yl]propoxy}-N-[(3*S*,5*S*)-5-(pyrrolidine-1-carbonyl)-pyrrolidin-3-yl]nicotinamide	C	RT = 2.70 min; *m/z* (ES^+) = 540.3 $[M + H]^+$
6		4-{3-[1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]propoxy}-2-methyl-N-[(3*S*,5*S*)-5-(pyrrolidine-1-carbonyl)pyrrolidin-3-yl]benzamide	A	RT = 2.85 min; *m/z* (ES^+) = 553.4 $[M + H]^+$
7		4-{3-[1-(5-Isopropyl-[1,2,4]oxadiazol-3-yl)piperidin-4-yl]propoxy}-2-methyl-N-[(3*S*,5*S*)-5-(pyrrolidine-1-carbonyl)-pyrrolidin-3-yl]benzamide	A	RT = 2.92 min; *m/z* (ES^+) = 553.4 $[M + H]^+$
8		4-{3-[1-(2-Isopropyl-2H-tetrazol-5-yl)piperidin-4-yl]propoxy}-2-methyl-N-[(3*S*,5*S*)-5-(pyrrolidine-1-carbonyl)pyrrolidin-3-yl]-benzamide	A	RT = 2.92 min; *m/z* (ES^+) = 553.4 $[M + H]^+$

Ex.	Structure	Name	Purification Method	LCMS
9		6-{3-[1-(5-Isopropyl-[1,2,4]oxadiazol-3-yl)piperidin-4-yl]propoxy}-2-methyl-N-[(3*S*,5*S*)-5-(pyrrolidine-1-carbonyl)-pyrrolidin-3-yl]nicotinamide	A	RT = 2.75 min; *m/z* (ES^+) = 554.3 $[M + H]^+$
10		6-{3-[1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]-propoxy}-2-methyl-N-[(3*S*,5*S*)-5-(pyrrolidine-1-carbonyl)-pyrrolidin-3-yl]nicotinamide	A	RT = 2.84 min; *m/z* (ES^+) = 554.3 $[M + H]^+$
11		4-[3-(5'-Chloro-3,4,5,6-tetrahydro-2H-[1,2']-bipyridinyl-4-yl)-propoxy]-2-methyl-N-[(3*S*,5*S*)-5-(pyrrolidine-1-carbonyl)-pyrrolidin-3-yl]benzamide	B	RT = 2.93 min; *m/z* (ES^+) = 554.3 $[M + H]^+$
12		4-{3-[1-(5-Chloropyrimidin-2-yl)piperidin-4-yl]-propoxy}-2-methyl-N-[(3*S*,5*S*)-5-(pyrrolidine-1-carbonyl)pyrrolidin-3-yl]-benzamide	A	RT = 3.18 min; *m/z* (ES^+) = 555.3 $[M + H]^+$

Ex.	Structure	Name	Purification Method	LCMS
13		6-{3-[1-(5-Chloropyrimidin-2-yl)piperidin-4-yl]-propoxy}-2-methyl-N-[(3*S*,5*S*)-5-(pyrrolidine-1-carbonyl)pyrrolidin-3-yl]nicotinamide	A	RT = 2.95 min; *m/z* (ES^+) = 556.2 $[M + H]^+$
14		2-Fluoro-4-{3-[1-(5-isopropyl-[1,2,4]oxadiazol-3-yl)piperidin-4-yl]-propoxy}-N-[(3*S*,5*S*)-5-(pyrrolidine-1-carbonyl)-pyrrolidin-3-yl]benzamide	A	RT = 3.04 min; *m/z* (ES^+) = 557.2 $[M + H]^+$
15		4-{3-[1-(3-Difluoromethyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]propoxy}-2-methyl-N-[(3*S*,5*S*)-5-(pyrrolidine-1-carbonyl)-pyrrolidin-3-yl]benzamide	A	RT = 2.79 min; *m/z* (ES^+) = 561.3 $[M + H]^+$
16		4-[3-(5'-Isopropyl-3,4,5,6-tetrahydro-2H-[1,2']-bipyridinyl-4-yl)propoxy]-2-methyl-N-[(3*S*,5*S*)-5-(pyrrolidine-1-carbonyl)-pyrrolidin-3-yl]benzamide	B	RT = 2.73 min; *m/z* (ES^+) = 562.4 $[M + H]^+$

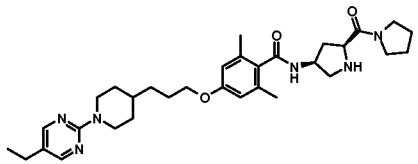
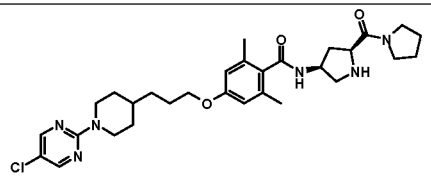
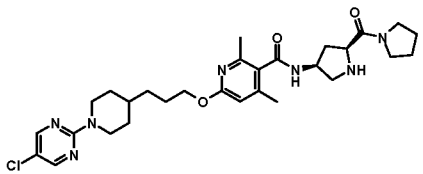
Ex.	Structure	Name	Purification Method	LCMS
17		4-{3-[1-(5-Isopropyl-pyrimidin-2-yl)piperidin-4-yl]propoxy}-2-methyl-N-[(3*S*,5*S*)-5-(pyrrolidine-1-carbonyl)pyrrolidin-3-yl]-benzamide	A	RT = 2.93 min; *m/z* (ES^+) = 563.4 $[M + H]^+$
18		4-{(*R*)-3-[1-(5-Ethyl-pyrimidin-2-yl)piperidin-4-yl]butoxy}-2-methyl-N-[(3*S*,5*S*)-5-(pyrrolidine-1-carbonyl)-pyrrolidin-3-yl]-benzamide	A	RT = 2.87 min; *m/z* (ES^+) = 563.3 $[M + H]^+$
19		4-{3-[1-(5-*tert*-Butyl-[1,2,4]oxadiazol-3-yl)piperidin-4-yl]propoxy}-2-methyl-N-[(3*S*,5*S*)-5-(pyrrolidine-1-carbonyl)-pyrrolidin-3-yl]benzamide	A	RT = 3.04 min; *m/z* (ES^+) = 567.3 $[M + H]^+$
20		6-{(*R*)-3-[1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]butoxy}-2-methyl-N-[(3*S*,5*S*)-5-(pyrrolidine-1-carbonyl)pyrrolidin-3-yl]nicotinamide	A	RT = 2.80 min; *m/z* (ES^+) = 568.3 $[M + H]^+$

Ex.	Structure	Name	Purification Method	LCMS
21		6-{3-[1-(3-*tert*-Butyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]propoxy}-2-methyl-N-[(3*S*,5*S*)-5-(pyrrolidine-1-carbonyl)-pyrrolidin-3-yl]nicotinamide	A	RT = 2.92 min; *m/z* (ES^+) = 568.3 $[M + H]^+$
22		4-[3-(5'-*tert*-Butyl-3,4,5,6-tetrahydro-2H-[1,2']-bipyridinyl-4-yl)propoxy]-2-methyl-N-[(3*S*,5*S*)-5-(pyrrolidine-1-carbonyl)-pyrrolidin-3-yl]benzamide	C	RT = 2.48 min; *m/z* (ES^+) = 576.4 $[M + H]^+$
23		4-(3-{1-[5-(1-Fluoro-1-methylethyl)-[1,2,4]-oxadiazol-3-yl]piperidin-4-yl}propoxy)-2-methyl-N-[(3*S*,5*S*)-5-(pyrrolidine-1-carbonyl)pyrrolidin-3-yl]benzamide	A	RT = 3.08 min; *m/z* (ES^+) = 571.3 $[M + H]^+$
24		4-{3-[1-(3-Isobutyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]propoxy}-2-methyl-N-[(3*S*,5*S*)-5-(pyrrolidine-1-carbonyl)-pyrrolidin-3-yl]benzamide	A	RT = 3.03 min; *m/z* (ES^+) = 567.4 $[M + H]^+$

Ex.	Structure	Name	Purification Method	LCMS
25		4-{3-[1-(3-Methoxymethyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]propoxy}-2-methyl-N-[(3*S*,5*S*)-5-(pyrrolidine-1-carbonyl)-pyrrolidin-3-yl]benzamide	C	RT = 2.68 min; *m/z* (ES^+) = 555.3 $[M + H]^+$
26		4-(3-{1-[3-(1,1-Difluoroethyl)-[1,2,4]-oxadiazol-5-yl]piperidin-4-yl}propoxy)-2-methyl-N-[(3*S*,5*S*)-5-(pyrrolidine-1-carbonyl)pyrrolidin-3-yl]-benzamide	A	RT = 3.04 min; *m/z* (ES^+) = 575.3 $[M + H]^+$

The compounds in **Examples Table 2** were prepared employing a similar method to that outlined in **General Procedure A**, but after shaking the amide coupling reaction at ambient temperature for 16 h, the mixture was heated to 60° for a further 16 h:

Examples Table 2:

Ex.	Structure	Name	Purification Method	LCMS
27		4-{3-[1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl]-propoxy}-2,6-dimethyl -N-[(3*S*,5*S*)-5-(pyrrolidine-1-carbonyl)pyrrolidin-3-yl]benzamide	B	RT = 2.84 min; *m/z* (ES^+) = 563.4 [*M* + H]$^+$
28		4-{3-[1-(5-Chloro-pyrimidin-2-yl)piperidin-4-yl]propoxy}-2,6-dimethyl-N-[(3*S*,5*S*)-5-(pyrrolidine-1-carbonyl)-pyrrolidin-3-yl]benzamide	B	RT = 3.09 min; *m/z* (ES^+) = 569.3 [*M* + H]$^+$
29		6-{3-[1-(5-Chloro-pyrimidin-2-yl)-piperidin-4-yl]propoxy}-2,4-dimethyl-N-[(3*S*,5*S*)-5-(pyrrolidine-1-carbonyl)-pyrrolidin-3-yl]-nicotinamide	B	RT = 3.05 min; *m/z* (ES^+) = 570.3 [*M* + H]$^+$

Ex.	Structure	Name	Purification Method	LCMS
30		2,6-Dimethyl-N-[(3*S*,5*S*)-5-(pyrrolidine-1-carbonyl)pyrrolidin-3-yl]-4-{3-[1-(5-trifluoro-methylpyrimidin-2-yl)piperidin-4-yl]-propoxy}benzamide	A	RT = 3.10 min; *m/z* (ES^+) = 603.3 [*M* + H]$^+$

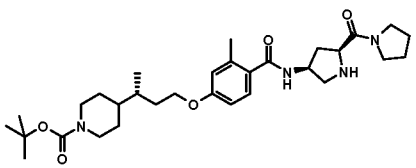
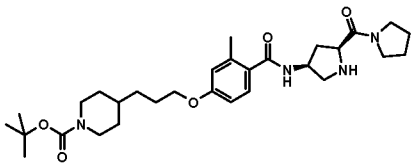
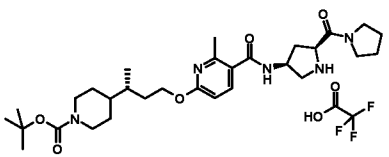
The compounds in **Examples Table 3** were prepared employing the general procedure outlined below:

General procedure B:

To a solution of the appropriate Fmoc-protected amine intermediate (0.12 mmol) in THF (5mL) was added silica 1-propanethiol (1.30 mmol/g, 500 mg, 0.65 mmol), followed by DBU (10 μL, 0.07 mmol), and the reaction was shaken at r.t. for 16 h. If the reaction was incomplete by this stage a further portion of DBU (10 μL, 0.07 mmol) was added, and the reaction shaken until completion. **Purification method A**: The mixture was filtered, then passed down a STMaD cartridge, washing with MeOH followed by 2% NH_4OH in MeOH. The basic fraction was collected and concentrated *in vacuo* to afford the title compound as the free amine. **Purification method B**: As purification method A but the product was purified further by preparative HPLC to afford the title compound as the trifluoroacetate salt. **Purification method C**: As purification method B. After preparative HPLC the product was passed down an SCX cartridge, eluting with MeOH followed by NH_4OH in MeOH. The basic fraction was collected and concentrated *in vacuo* to afford the title compound as the free amine.

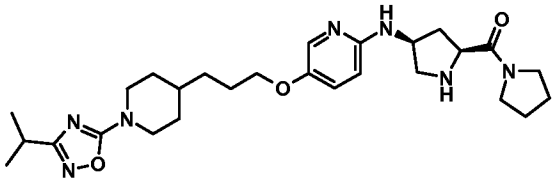
Examples Table 3:

The building block used in the synthesis of **Examples 34** and **35** were prepared employing the methods outlined in WO2007003962.

Ex.	Structure	Name	Purification Method	LCMS
31		4-((*R*)-1-Methyl-3-{3-methyl-4-[(3*S*,5*S*)-5-(pyrrolidine-1-carbonyl)pyrrolidin-3-ylcarbamoyl]phenoxy}-propyl)piperidine-1-carboxylic acid *tert*-butyl ester	C	RT = 3.07 min; *m/z* (ES^+) = 557.4 [*M* + H]$^+$
32		4-(3-{3-Methyl-4-[(3*S*,5*S*)-5-(pyrrolidine-1-carbonyl)pyrrolidin-3-ylcarbamoyl]phenoxy}propyl)piperidine-1-carboxylic acid *tert*-butyl ester	A	RT = 3.00 min; *m/z* (ES^+) = 543.4 [*M* + H]$^+$
33		4-((*R*)-1-Methyl-3-{6-methyl-5-[(3*S*,5*S*)-5-(pyrrolidine-1-carbonyl)pyrrolidin-3-ylcarbamoyl]pyridin-2-yloxy}propyl)piperidine-1-carboxylic acid *tert*-butyl ester trifluoroacetate	B	RT = 3.05 min; *m/z* (ES^+) = 558.4 [*M* + H]$^+$

Ex.	Structure	Name	Purification Method	LCMS
34		4-(3-{3,5-Difluoro-4-[(3*S*,5*S*)-5-(pyrrolidine-1-carbonyl)pyrrolidin-3-ylcarbamoyl]phenoxy}-propyl)piperidine-1-carboxylic acid *tert*-butyl ester	A	RT = 2.93 min; *m/z* (ES^+) = 565.3 [$M+H]^+$
35		4-(3-{3-Fluoro-4-[(3*S*,5*S*)-5-(pyrrolidine-1-carbonyl)pyrrolidin-3-yl-carbamoyl]phenyl}-[1,2,4]oxadiazol-5-yl-methoxy)piperidine-1-carboxylic acid *tert*-butyl ester	A	RT = 2.82 min; *m/z* (ES^+) = 587.3 [$M+H]^+$

Example 36: [(2*S*,4*S*)-4-(5-{3-[1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]propoxy}pyridin-2-ylamino)pyrrolidin-2-yl]pyrrolidin-1-ylmethanone

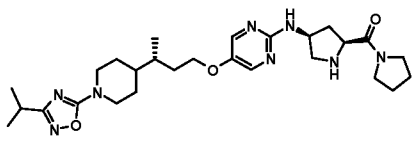
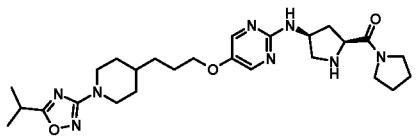


A combination of (*R*)-1-[(*S*)-2-(dicyclohexylphosphino)ferrocenyl]ethyldi-*tert*-butyl phosphine (3.0 mg, 0.05 mmol) and palladium (II) acetate (1.2 mg, 0.05 mmol) in DME (0.25 mL), under argon, was added to a dry solution of 2-bromo-5-{3-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]propoxy}pyridine (**Preparation 63**, 43.0 mg, 0.11 mmol), (2*S*,4*S*)-4-amino-2-(pyrrolidine-1-carbonyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (**Preparation 2**, 30.0 mg, 0.11 mmol) and sodium *tert*-butoxide (14.0 mg, 0.15 mmol) in DME. The reaction was heated to 80°C for 16 h, before being cooled to ambient temperature. The mixture was partitioned between water (2 mL) and DCM (10 mL), then the organic phase was separated, passed down a STMaD cartridge and loaded onto an SCX cartridge, eluting with MeOH followed by NH_4OH in MeOH. The basic fraction was collected and concentrated *in vacuo*, then further purification by preparative HPLC afforded the intermediate product (2*S*,4*S*)-4-(5-{3-[1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]propoxy}pyridin-2-ylamino)-2-(pyrrolidine-1-carbonyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester : RT = 6.73 min *m/z* (ES^+) = 612.5 $[M + H]^+$.

To a solution of the product in DCM (2 mL) was added TFA (0.5 mL), and the reaction was stirred at ambient temperature until complete. The crude mixture was passed down an SCX cartridge, eluting with MeOH followed by NH_4OH in MeOH, and the basic fraction was collected. The solvent was removed *in vacuo*, then the residue was passed down a STMaD cartridge, washing with MeOH followed by NH_4OH in MeOH. The basic fraction was collected and concentrated *in vacuo* to afford the title compound: RT = 2.47 min *m/z* (ES^+) = 512.4 $[M + H]^+$.

The compounds in **Examples Table 4** were prepared employing the method outlined in **Example 36**:

Examples Table 4:

Ex.	Structure	Name	LCMS
37		[(2*S*,4*S*)-4-(5-{(*R*)-3-[1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]butoxy}pyrimidin-2-ylamino)pyrrolidin-2-yl]pyrrolidin-1-ylmethanone	RT = 2.84 min; *m/z* (ES^+) = 527.5 $[M + H]^+$
38		[(2*S*,4*S*)-4-(5-{3-[1-(5-Isopropyl-[1,2,4]oxadiazol-3-yl)piperidin-4-yl]propoxy}pyrimidin-2-ylamino)pyrrolidin-2-yl]pyrrolidin-1-yl methanone	RT = 2.74 min; *m/z* (ES^+) = 513.3 $[M + H]^+$

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

GPR119 cAMP Assay

A stable cell line expressing recombinant human GPR119 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 cell monolayers were washed with phosphate buffered saline and stimulated at 37°C for 30 min 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 produced a concentration-dependent increase in intracellular cAMP level and generally had an EC_{50} of <10 μM. Compounds showing an EC_{50} of less than 1 μM in the cAMP assay may be preferred.

DPP-IV Assay Method

DPP-IV activity was measured by monitoring the cleavage of the fluorogenic peptide substrate, H-Gly-Pro-7-amino-4-methylcoumarin (GP-AMC) whereby the product 7-amino-4-methylcoumarin is quantified by fluorescence at excitation 380 nm and emission 460 nm. Assays were carried out in 96-well plates (Black OptiPlate-96F) in a total volume of 100 μL per well consisting of 50 mM Tris pH 7.6, 100 μM GP-AMC, 10-25 μU recombinant human DPP-IV and a range of inhibitor dilutions in a final concentration of 1% DMSO. Plates were read in a fluorimeter after 30 min incubation at 37°C. Recombinant human DPP-IV residues Asn29-Pro766 was purchased from BioMol.

All of Examples 1 to 38 showed activity in this assay having an IC_{50} of <20 μM. Compounds of the invention of formula (Ia) generally have an IC_{50} of <20 μM.

Activities of a representative group of compounds that were tested in the cAMP assay and the DPP-IV assay are shown in **Table 1** below:

Table 1.

Example No.	cAMP EC_{50} <1μM	cAMP EC_{50} between 1μM and 10μM	DPP-IV IC_{50} <1μM	DPP-IV IC_{50} between 1μM and 20μM
2	+		+	
8	+			+
21	+			+
35		+		+

Anti-diabetic effects of compounds of the invention in an in-vitro model of pancreatic beta cells (HIT-T15)

Cell Culture

HIT-T15 cells (passage 60) were obtained from ATCC, and were cultured in RPMI1640 medium supplemented with 10% fetal calf serum and 30 nM sodium selenite. All experiments were done with cells at less than passage 70, in accordance with the literature, which describes altered properties of this cell line at passage numbers above 81 (Zhang HJ, Walseth TF, Robertson RP. Insulin secretion and cAMP metabolism in HIT cells. Reciprocal and serial passage-dependent relationships. *Diabetes*. 1989 Jan;38(1):44-8).

cAMP assay

HIT-T15 cells were plated in standard culture medium in 96-well plates at 100,000 cells/ 0.1 mL/ well and cultured for 24 h and the medium was then discarded. Cells were incubated for 15min at room temperature with 100μl stimulation buffer (Hanks buffered salt solution, 5mM HEPES, 0.5mM IBMX, 0.1% BSA, pH 7.4). This was discarded and replaced with compound dilutions over the range 0.001, 0.003, 0.01, 0.03, 0.1, 0.3, 1, 3, 10, 30 μM in stimulation buffer in the presence of 0.5% DMSO. Cells were incubated at room temperature for 30 min. Then 75 uL lysis buffer (5mM HEPES, 0.3% Tween-20, 0.1% BSA, pH 7.4) was added per well and the plate was shaken at 900 rpm for 20 min. Particulate matter was removed by centrifugation at 3000rpm for 5 min, then the samples were transferred in duplicate to 384-well plates, and processed following the Perkin Elmer AlphaScreen cAMP assay kit instructions. Briefly 25 μL reactions were set up containing 8 μL

sample, 5 µL acceptor bead mix and 12 µL detection mix, such that the concentration of the final reaction components is the same as stated in the kit instructions. Reactions were incubated at room temperature for 150 min, and the plate was read using a Packard Fusion instrument. Measurements for cAMP were compared to a standard curve of known cAMP amounts (0.01, 0.03, 0.1, 0.3, 1, 3, 10, 30, 100, 300, 1000 nM) to convert the readings to absolute cAMP amounts. Data was analysed using XLfit 3 software.

Representative compounds of the invention were found to increase cAMP at an EC_{50} of less than 10 µM. Compounds showing an EC_{50} of less than 1 µM in the cAMP assay may be preferred.

Insulin secretion assay

HIT-T15 cells are plated in standard culture medium in 12-well plates at 106 cells/ 1 ml/ well and cultured for 3 days and the medium then discarded. Cells are washed x 2 with supplemented Krebs-Ringer buffer (KRB) containing 119 mM NaCl, 4.74 mM KCl, 2.54 mM $CaCl_2$, 1.19 mM $MgSO_4$, 1.19 mM KH_2PO_4, 25 mM $NaHCO_3$, 10 mM HEPES at pH 7.4 and 0.1% bovine serum albumin. Cells are incubated with 1ml KRB at 37°C for 30 min which is then discarded. This is followed by a second incubation with KRB for 30 min, which is collected and used to measure basal insulin secretion levels for each well. Compound dilutions (0, 0.1, 0.3, 1, 3, 10 µM) are then added to duplicate wells in 1ml KRB, supplemented with 5.6 mM glucose. After 30 min incubation at 37°C samples are removed for determination of insulin levels. Measurement of insulin was done using the Mercodia Rat insulin ELISA kit, following the manufacturers' instructions, with a standard curve of known insulin concentrations. For each well, insulin levels are corrected by subtraction of the basal secretion level from the pre-incubation in the absence of glucose. Data is analysed using XLfit 3 software.

Compounds of the invention preferably increase insulin secretion at an EC_{50} of less than 10 µM.

Oral Glucose Tolerance Tests

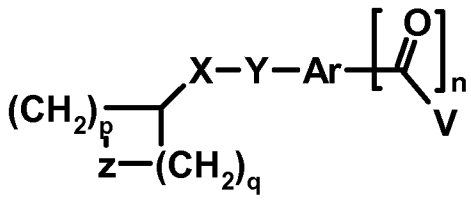
The effects of compounds of the invention on oral glucose (Glc) tolerance may be evaluated in male Sprague-Dawley rats. Food is withdrawn 16 h before administration of Glc and remains withdrawn throughout the study. Rats have free access to water during the study. A cut is made to the animals' tails, then blood (1 drop) is removed for measurement of basal Glc levels 60 min before administration of the Glc load. Then, the rats are weighed and dosed orally with test compound or vehicle (20% aqueous hydroxypropyl-β-cyclodextrin) 45 min before the removal of an additional blood sample and treatment with the Glc load (2 g kg^{-1} p.o.). Blood samples are taken from the cut tip of the tail 5, 15, 30, 60, 120, and 180 min after Glc administration. Blood glucose levels are

measured just after collection using a commercially available glucose-meter (OneTouch® UltraTM from Lifescan). Compounds of the invention preferably statistically reduce the Glc excursion at doses ≤100 mg kg^{-1}.

The effects of compounds of the invention on oral glucose (Glc) tolerance may also be evaluated in male C57Bl/6 or male *ob/ob* mice. Food is withdrawn 5h before administration of Glc and remained withdrawn throughout the study. Mice have free access to water during the study. A cut was made to the animals' tails, then blood (20 µL) is removed for measurement of basal Glc levels 45 min before administration of the Glc load. Then, the mice are weighed and dosed orally with test compound or vehicle (20% aqueous hydroxypropyl-ß-cyclodextrin or 25% aqueous Gelucire 44/14) 30 min before the removal of an additional blood sample (20 µL) and treatment with the Glc load (2-5 g kg^{-1} p.o.). Blood samples (20 µL) are then taken 25, 50, 80, 120, and 180 min after Glc administration. The 20 µL blood samples for measurement of Glc levels are taken from the cut tip of the tail into disposable micro-pipettes (Dade Diagnostics Inc., Puerto Rico) and the sample added to 480 µL of haemolysis reagent. Duplicate 20 µL aliquots of the diluted haemolysed blood are then added to 180 µL of Trinders glucose reagent (Sigma enzymatic (Trinder) colorimetric method) in a 96-well assay plate. After mixing, the samples are left at room temperature for 30 min before being read against Glc standards (Sigma glucose/urea nitrogen combined standard set). Compounds of the invention preferably statistically reduce the Glc excursion at doses ≤100 mg kg^{-1}.

CLAIMS:

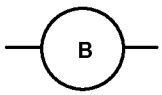
1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



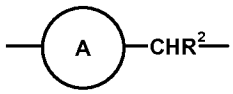
(I)

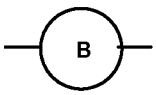
wherein p and q are independently 1 or 2;

Z is N-C(O)OR^4, N-C(O)NR^{4}R^5, N–S(O)$_2$N(C$_{1-3}$alkyl)R^4, N-heteroaryl or N-CH$_2$-heteroaryl, and when p and q are both 2, Z may also be N-CH$_2$-phenyl, in which phenyl is optionally substituted by one or two groups independently selected from C$_{1-4}$ alkyl, C$_{1-4}$ haloalkyl and halogen;

Y is CH$_2$, CF$_2$, CHF, O, NR^1, C(O) or  , where B is a 5-membered heteroaryl ring containing one or more heteroatoms selected from N, O and S;

when Y is CH$_2$, CF$_2$, CHF, O, NR^1 or C(O), X is an unbranched or a branched C$_{2-4}$ alkylene group;

or when Y is O or NR^1, X may also be  , where A is a 5-membered heteroaryl ring containing one or more heteroatoms selected from N, O and S;

and when Y is  , X is -O-CHR^3-;

Ar is a para-substituted phenyl or a para-substituted 6-membered heteroaryl ring containing one or two nitrogen atoms, optionally substituted by one or two groups selected from C$_{1-4}$ alkyl, C$_{1-4}$ alkoxy, C$_{2-6}$alkoxyalkyl, cyano, C$_{1-4}$ haloalkyl and halogen;

R^1 is hydrogen or C$_{1-4}$alkyl;

R^2 is hydrogen or C$_{1-4}$alkyl;

R^3 is hydrogen or C$_{1-4}$alkyl;

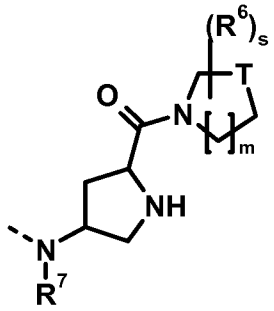
R^4 is aryl, heteroaryl, C$_{2-6}$ alkyl or C$_{3-6}$ cycloalkyl, which cycloalkyl is optionally substitiuted by C$_{1-4}$alkyl, C$_{4-6}$heterocyclyl, heterocyclylC$_{1-4}$alkyl, C$_{2-6}$alkoxyalkyl, arylC$_{1-4}$alkyl,

heteroarylC_{1-4}alkyl or C_{4-6}cycloalkylC_{1-4}alkyl, which cycloalkylC_{1-4}alkyl is optionally substituted by C_{1-4} alkyl;

when Z includes heteroaryl, or when R^4 is or includes aryl or heteroaryl, said aryl or heteroaryl may be optionally substituted by one or two groups selected from halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl and C_{3-6} cycloalkyl optionally substituted by C_{1-4}alkyl,;

R^5 is hydrogen or C_{1-4}alkyl;

V is



in which T is CH_2, or, when m is 1, T may also be S;

when T is CH_2, R^6 is fluoro or cyano; and when T is S, R^6 is cyano;

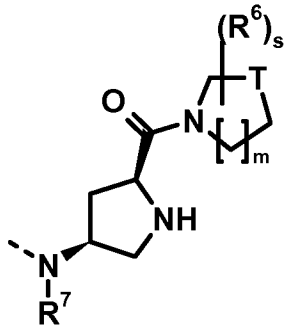
R^7 is hydrogen or C_{1-4}alkyl;

n is 0 or 1;

m is 0 or 1; and

s is 0, 1 or 2.

2. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein the stereochemistry of the V groups is as shown below:



3. A compound according to claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein p and q are 2.

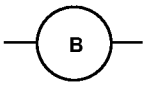
4. A compound according to any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein Z is N-C(O)OR^4.

5. A compound according to claim 4, or a pharmaceutically acceptable salt thereof, wherein R^4 is C_{2-6} alkyl.

6. A compound according to any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein Z is N-heteroaryl, in which the heteroaryl moiety is optionally substituted by one or two groups selected from C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-5} hydroxyalkyl, C_{2-4} alkoxyalkyl, C_{3-6} cycloalkyl optionally substituted by C_{1-4} alkyl or halo, C_{1-4} alkoxy, heterocyclyl, heterocyclylalkyl, heteroarylalkyl, alkylamino, alkylaminoalkyl, cyano and halogen.

7. A compound according to claim 6, or a pharmaceutically acceptable salt thereof, wherein Z is optionally substituted oxadiazole, tertrazole, pyridine or pyrimidine.

8. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein A is oxadiazole, thiazole, triazole, tetrazole or pyrazole.

9. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein Y is CH_2, O, NR^1 or 

, where B is a 5-membered heteroaryl ring containing one or more heteroatoms selected from N, O and S.

10. A compound according to claim 9, wherein X is a branched or unbranched C_{2-4}alkylene group.

11. A compound according to claim 9, wherein Y is a heteroaryl ring and X is–O-CH_2-.

12. A compound according to claim 9 or claim 10, or a pharmaceutically acceptable salt thereof, wherein B is oxadiazole or thiazole.

13. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein Ar is phenyl, pyridyl or pyriminidyl.

14. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R^1 is hydrogen or methyl.

15. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R^2 is hydrogen or methyl.

16. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R^3 is hydrogen or methyl.

17. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R^7 is hydrogen.

18. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein T is CH_2.

19. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein m is 1.

20. A compound as defined in any one of Examples 1 to 38 as the free base or a pharmaceutically acceptable salt thereof.

21. A pharmaceutical composition comprising a compound according to any one of claims to 20, or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

22. A method for the treatment of a disease or condition in which GPR119 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 20, or a pharmaceutically acceptable salt thereof.

23. A method for the treatment of a disease or condition in which GPR119 and DPP-IV play 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 20, or a pharmaceutically acceptable salt thereof.

24. A method for the treatment of type II 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 20, or a pharmaceutically acceptable salt thereof.

25. A method for the treatment of obesity, metabolic syndrome (syndrome X), impaired glucose tolerance, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL levels or hypertension comprising a step of administering to a patient in need thereof an effective amount of a compound according to any one of claims 1 to 20, or a pharmaceutically acceptable salt thereof.

26. Use of a compound according to any one of claims 1 to 20 in the manufacture of a medicament for use in the treatment of type II diabetes, obesity, metabolic syndrome (syndrome X), impaired glucose tolerance, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL levels or hypertension.

27. A compound as claimed in any one of claims 1 to 20 for use in a method of treatment of type II diabetes, obesity, metabolic syndrome (syndrome X), impaired glucose tolerance, hyperlipidaemia, hypertriglyceridaemia, hypercholesterolaemia, low HDL levels or hypertension in humans.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/055864

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/454 A61K31/506 A61K31/4545 A61P3/10
ADD.

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)
A61K

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)
EPO-Internal, BEILSTEIN Data, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2009/034388 A1 (PROSIDION LTD [GB]; BARBA OSCAR [GB]; BRADLEY STUART EDWARD [GB]; FYFE) 19 March 2009 (2009-03-19) compounds 1-33 pages 80-83	1-27
X	WO 2009/123992 A1 (METABOLEX INC [US]; WILSON MARIA E [US]; JOHNSON JEFFREY [US]; CLEMENS) 8 October 2009 (2009-10-08) claims 1-5	1-27
X	WO 2007/003960 A1 (PROSIDION LTD [GB]; BRADLEY STUART EDWARD [GB]; DAWSON GRAHAM JOHN [GB) 11 January 2007 (2007-01-11) compounds 1-238 pages 66-69	1-27

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 May 2011	20/05/2011

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Renard, Delphine

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/055864

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/067531 A1 (PROSIDION LTD [GB]; FYFE MATTHEW COLIN THOR [GB]; GARDNER LISA SARAH [) 29 June 2006 (2006-06-29) compounds 1-136 pages 44-47 -----	1-27
X	EP 1 308 439 A1 (WELFIDE CORP [JP] MITSUBISHI PHARMA CORP [JP] MITSUBISHI TANABE PHARMA) 7 May 2003 (2003-05-07) tables 1-40 paragraphs [0042] - [0046] -----	1-27
X	SAKASHITA H ET AL: "[(S)-gamma-(Arylamino)prolyl]thiazolidine compounds as a novel series of potent and stable DPP-IV inhibitors", BIOORGANIC & MEDICINAL CHEMISTRY, PERGAMON, GB, vol. 14, no. 11, 1 June 2006 (2006-06-01), pages 3662-3671, XP025133265, ISSN: 0968-0896, DOI: DOI:10.1016/J.BMC.2006.01.022 [retrieved on 2006-06-01] compounds 3, 11, 12a-m -----	1-27

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2011/055864

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2009034388 A1	19-03-2009	EP 2200609 A1	30-06-2010
		JP 2010539152 T	16-12-2010
		US 2010286112 A1	11-11-2010
WO 2009123992 A1	08-10-2009	AR 072352 A1	25-08-2010
		AU 2009231906 A1	08-10-2009
		CA 2719507 A1	08-10-2009
		CN 102026636 A	20-04-2011
		EP 2280704 A1	09-02-2011
		KR 20100134659 A	23-12-2010
		SM AP201000118 A	19-01-2011
		US 2009270404 A1	29-10-2009
WO 2007003960 A1	11-01-2007	EP 1907383 A1	09-04-2008
		JP 2008545007 T	11-12-2008
		US 2009325924 A1	31-12-2009
WO 2006067531 A1	29-06-2006	AU 2005317769 A1	29-06-2006
		BR PI0516407 A	02-09-2008
		CA 2591922 A1	29-06-2006
		EP 1838311 A1	03-10-2007
		JP 2008525416 T	17-07-2008
		KR 20070091038 A	06-09-2007
		NZ 556017 A	30-10-2009
		US 2008312281 A1	18-12-2008
EP 1308439 A1	07-05-2003	AT 411285 T	15-10-2008
		AT 450504 T	15-12-2009
		AU 7775401 A	25-02-2002
		AU 2001277754 B2	29-09-2005
		BR 0113146 A	24-06-2003
		CA 2418656 A1	21-02-2002
		CN 1441779 A	10-09-2003
		DK 1308439 T3	12-01-2009
		EP 1950199 A1	30-07-2008
		EP 1930319 A1	11-06-2008
		ES 2311534 T3	16-02-2009
		ES 2334858 T3	16-03-2010
		HU 0300746 A2	28-10-2003
		WO 0214271 A1	21-02-2002
		JP 4101053 B2	11-06-2008
		NO 20030619 A	26-02-2003
		NZ 524618 A	27-08-2004
		PT 1308439 E	12-12-2008
		US 2005245538 A1	03-11-2005
		US 2004106655 A1	03-06-2004