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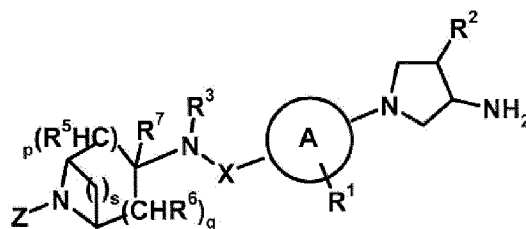
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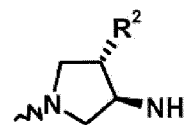
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(54) Title: 1,4 DI SUBSTITUTED PYRROLIDINE - 3 - YL -AMINE DERIVATIVES AND THEIR USE FOR THE TREATMENT OF METABOLIC DISORDERS



(I)



(Ia)

(57) Abstract: Therapeutic compounds are disclosed having the general formula (1) that are useful for the treatment of metabolic disorders, including type II diabetes. The compounds have activity as agonists of GPR1 19. Compounds having the stereochemistry of formula (Ia) may also demonstrate DPP-IV inhibitory activity.



**1,4 DISUBSTITUTED PYRROLIDINE - 3 - YL -AMINE DERIVATIVES AND THEIR USE
FOR THE TREATMENT OF METABOLIC DISORDERS**

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 6,468,756 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

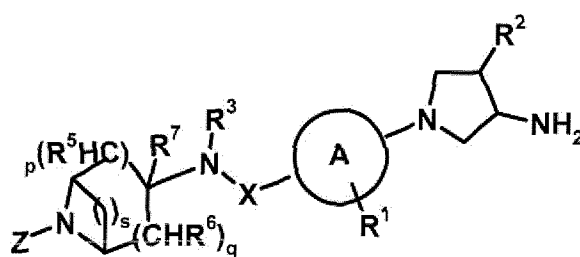
cAMP concentrations; and (3) induce weight loss possibly through GLP-1's ability to reduce food intake.

International Patent Applications WO 2005/061489, WO 2006/070208, WO 2006/067532, WO 2006/067531, WO 2007/003960, WO 2007/003961, WO 2007/003962, WO 2007/003964, WO 2007/116229, WO 2007/116230, WO 2008/081204, WO 2008/081205, WO 2008/081206, WO 2008/081207, WO 2008/081208, WO 2009/050522, WO 2009/050523, WO 2010/001166, WO 2010/004343, WO 2010/004344, WO 2010/004345, WO 2010/004346, WO 2010/004347 and WO 2010/004348 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 has been suggested, however 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 compatibility in the physicochemical and pharmacokinetic and pharmacodynamic properties of the two active ingredients. WO 2009/034388, WO 2010/103333, WO 2010/103334 and WO 2010/103333 disclose dual GPR119 agonists and DPP-IV inhibitors. The compounds of the invention preferably have dual activity as agonists of GPR119 and inhibitors of DPP-IV

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



(I)

wherein A is a para-linked phenyl, pyridinyl, pyrimidinyl, pyrazinyl or triazinyl;

R¹ is hydrogen, halo, cyano, C₁₋₄alkyl, C₁₋₄haloalkyl, C₁₋₄alkoxy or C₂₋₆alkoxyalkyl;

R² is selected from the group consisting of:

(a) phenyl optionally substituted by one or more halo, methyl or halomethyl groups,

(b) pyridyl optionally substituted by one or more halo, methyl or halomethyl groups and

(c) *N*-pyridonyl optionally substituted by one or more halo, methyl or halomethyl groups

5 R^3 is methyl, C_{3-6} cycloalkyl, 4 to 6 membered saturated heterocyclyl (comprising 1 or 2 ring heteroatoms selected from N, O and S) or C_{2-4} alkyl wherein the C_{3-6} cycloalkyl and C_{2-4} alkyl are optionally substituted by fluoro, cyano, hydroxy or C_{1-2} alkyloxy;

p and q are each 0, 1 or 2, provided that $0 \leq p+q \leq 2$;

Z is selected from the group consisting of:

10 (a) $C(O)OR^4$,

(b) $C(O)R^4$,

(c) $S(O)_2R^4$,

(d) a 5- or 6-membered N-containing heteroaryl ring optionally

containing 1 to 3 additional heteroatoms selected from N, O and S, or a 8 to 10 membered fused

15 bicyclic system optionally containing 1 to 3 heteroatoms selected from N, O and S, wherein the heteroaryl ring or fused bicyclic system is optionally substituted by one or two groups independently selected from halo, cyano, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{2-4} alkoxyalkyl, heterocyclyl (a 4 to 6 membered saturated heterocycle comprising 1 or 2 ring heteroatoms selected from N, O and S), heterocyclyl C_{1-4} alkyl (wherein the heterocyclyl is a 4 to 6 membered saturated heterocycle
20 comprising 1 or 2 ring heteroatoms selected from N, O and S) and C_{3-6} cycloalkyl optionally substituted by C_{1-4} alkyl, C_{1-4} alkoxy or halo;

and (e) $-CH_2$ -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;

and when Z is optionally substituted $-CH_2$ -phenyl then p and q are both 0 or 1;

25 R^4 is selected from the group consisting of:

a) C_{1-6} alkyl,

b) phenyl,

c) C_{2-6} alkoxyalkyl,

d) C_{3-6} cycloalkyl optionally substituted by C_{1-4} alkyl

30 e) C_{3-6} cycloalkyl C_{1-4} alkyl optionally substituted by C_{1-4} alkyl, and

f) 4 to 6 membered saturated heterocycle comprising 1 or 2 ring heteroatoms selected from N, O and S, and

g) 5 or 6 membered heteroaryl ring containing 1 to 4 heteroatoms selected from N, O and S optionally substituted by one or two groups selected from halo, cyano,

C₁₋₄alkyl, C₁₋₄haloalkyl, C₁₋₄alkoxy, C₂₋₄alkoxyalkyl, 4 to 6 membered saturated heterocycle comprising 1 or 2 ring heteroatoms selected from N, O and S and C₃₋₆cycloalkyl wherein the cycloalkyl is optionally substituted by C₁₋₄alkyl or halo:

5 X is selected from C(O) or S(O)₂ with the proviso that when X is S(O)₂ then R³ is methyl, p and q are both 1 and Z is a 5 to 6 membered heteroaryl ring;

each of R⁵ and R⁶ is independently hydrogen, halo, C₁₋₂alkyl, C₁₋₂haloalkyl or C₁₋₃alkoxy; alternatively R⁵ and R⁶ can be joined to form an azabicyclo[3.3.1]nonane, a 3-oxa-7-azabicyclo[3.3.1]nonane or an azabicyclo[3.2.1]octane;

10 R⁷ is hydrogen, halo, C₁₋₂alkyl, C₁₋₂haloalkyl or C₁₋₃alkoxy;

s is 0, 2 or 3

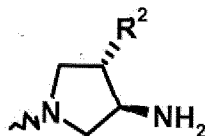
and when R⁵ and R⁶ are both hydrogen then s is 0, 2 or 3,

and when at least one of R⁵ and R⁶ is halo, C₁₋₂alkyl, C₁₋₂haloalkyl or C₁₋₃alkoxy, then s

is 0

15 and pharmaceutically acceptable salts thereof.

In particular the invention provides compounds of formula I having the stereochemistry defined below; such compounds may demonstrate DPP-IV inhibitory activity:



20 p and q are independently 0, 1 or 2 provided that p+q does not exceed 2, i.e., forming a 4-, 5- or 6-membered ring. In some embodiments, p and q may be the same, i.e., forming a 4- or 6-membered ring. Suitably p and q are both 1.

25 A is suitably pyridine, pyrimidine or pyrazine typically pyridine or pyrimidine, e.g., 2- or 3-pyridyl or 2- or 5-pyrimidinyl, where the 2-, 3- or 5- refers to the point of attachment of the pyrrolidine ring (X being attached in the para position and R¹ being attached at any suitable position).

R¹ is suitably hydrogen, halogen or cyano. R¹ is preferably hydrogen.

The ring of R² may optionally be substituted by 1, 2 or 3 substituents. In certain embodiments R² is optionally substituted by 1 or 2 substituents and in further embodiments it is
30 substituted by 2 or 3 substituents. R² is preferably optionally substituted by 1, 2, or 3 substituents independently selected from halo and methyl. R² is preferably optionally substituted by 1 or 2

substituents independently selected from halo and methyl. R^2 is suitably phenyl substituted by 1, 2 or 3 groups selected from halo and methyl groups. R^2 is suitably phenyl substituted by 2 or 3 halo groups. Halo is suitably fluoro. R^2 may be an optionally substituted phenyl or pyridyl, e.g. an optionally substituted phenyl or 2-pyridyl. Examples of R^2 include phenyl, 2-pyridinyl, 4-fluoro-2-pyridinyl, 5-fluoro-2-pyridinyl, 4-methyl-2-pyridinyl, 5-methyl-2-pyridinyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 2,3,4-trifluorophenyl, 2,3,5-trifluorophenyl, 2,3,6-trifluorophenyl, 2,4,5-trifluorophenyl, 2,4,6-trifluorophenyl, 2-fluoro-5-methylphenyl and 2,4-difluoro-5-methylphenyl.

R^3 may suitably be methyl, C_{3-6} cycloalkyl or C_{2-4} alkyl wherein the C_{2-4} alkyl is optionally substituted by fluoro, cyano, hydroxy or C_{1-2} alkoxy. Suitable examples of R^3 include methyl, ethyl, n-propyl, i-propyl, cyclopropyl, $CH_2CH_2OCH_3$ and CH_2CF_3 .

p and q are independently 0, 1 or 2 provided that $p+q$ does not exceed 2, i.e., forming a 4-, 5- or 6-membered ring. In some embodiments, p and q may be the same, i.e., forming a 4- or 6-membered ring. Suitably p and q are both 1. In certain embodiments p is 1 and q is 0. In other embodiments p is 0 and q is 1.

In certain embodiments Z is $-C(O)OR^4$. In further embodiments Z is $C(O)R^4$. In still further embodiments it is $S(O)_2R^4$.

R^4 may suitably be alkyl, C_{2-6} alkoxyalkyl, C_{3-6} cycloalkyl or C_{3-6} cycloalkylalkyl, wherein said C_{3-6} cycloalkyl or C_{3-6} cycloalkyl C_{1-4} alkyl is optionally substituted by C_{1-4} alkyl.

Examples of R^4 include methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, i-butyl or t-butyl, cyclopropyl and 1-methylcyclopropyl. In certain embodiments R^4 is propyl, especially isopropyl.

Z may be a heteroaryl group optionally substituted by one or two groups selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{2-4} alkoxyalkyl, 4 to 6 membered saturated heterocyclyl comprising 1 or 2 ring heteroatoms selected from N, O and S, C_{4-6} heterocyclyl C_{1-4} alkyl (wherein the heterocyclyl is a 4 to 6 membered saturated heterocycle comprising 1 or 2 ring heteroatoms selected from N, O and S) and C_{3-6} cycloalkyl wherein the cycloalkyl is optionally substituted by C_{1-4} alkyl or halo. Preferred C_{1-4} haloalkyls are perfluoroalkyls, e.g. CF_3 , CF_2Me and CHF_2 .

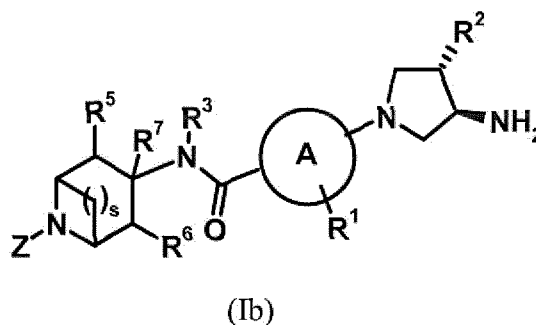
When Z is heteroaryl, suitable heteroaryl groups include oxadiazole, pyrimidine, pyridazine, thiazole, tetrazole, benzothiazole and thiadiazole, e.g., oxadiazole and pyrimidine. In some embodiments Z may comprise 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, pyrimidin-2-yl or a 2H-tetrazol-5-yl, which may be substituted by any of the aforementioned substituents.

When Z is a substituted heteroaryl suitable substituents include ethyl, i-propyl, t-butyl, cyclopropyl, chloro, 1-methylcyclopropyl, CF_3 , CH_2F , CF_2H , $\text{CH}(\text{OMe})\text{Me}$, $\text{C}(\text{Me})_2\text{OH}$, $\text{C}(\text{Me})_2\text{F}$, CF_2Me , CH_2OMe and 2-tetrahydrofuranlyl.

In a further alternative, when p and q are both 0 or 1, Z may be $-\text{CH}_2$ -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. Particular embodiments include those wherein Z is $-\text{CH}_2$ -phenyl optionally substituted by one or two halo or methyl groups, e.g. 4-fluorophenyl

R^7 is preferably hydrogen.

X is suitably $\text{C}(\text{O})$, therefore the compounds of the invention may have the formula:



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

The invention also includes isotopically labeled compounds, which are similar to those recited in formulae (I), (Ia) and (Ib) 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 ^3H , ^{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 ^3H , ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^3H , and carbon-14, i.e., ^{14}C , isotopes are particularly preferred for their ease of preparation and detectability. ^{11}C and ^8F 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., ^2H , 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), (Ia)

and (Ib) 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), (Ia) and (Ib) or salts thereof are not isotopically labelled.

5 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 fluoro. When used herein the term "cycloalkyl" refers to a 3 to 6 C saturated carbocycle moiety e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. When used herein the
10 term 'heterocyclyl' refers to a 4 to 6 membered saturated heterocycle comprising 1 or 2 ring heteroatoms selected from N, O and S. Examples of heterocycles include tetrahydrofuran, pyrrolidine, tetrahydropyran, piperidine, oxetane and azetidine. When used herein the term "heteroaryl" refers to a 5- or 6-membered heteroaryl ring optionally containing one or more, e.g. 1, 2 or 3 heteroatoms selected from N, O and S, or a 8 to 10 membered fused bicyclic system optionally
15 containing one or more, e.g. 1, 2 or 3 heteroatoms selected from N, O and S. Examples of heteroaryl rings include pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, tetrazolyl and benzothiazolyl.

 Compounds described herein may contain one or more asymmetric centers and may thus
20 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
25 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
30 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
35 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.

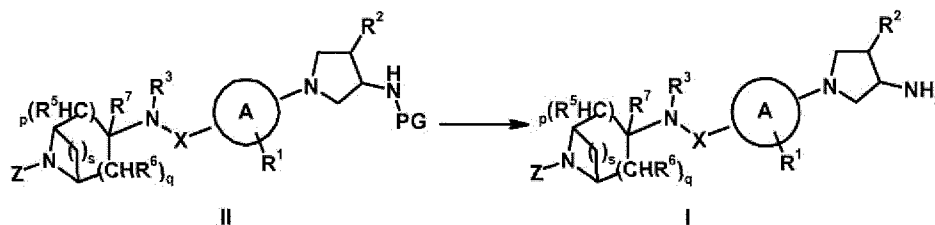
When the compound of the invention is basic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic, trifluoroacetic 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, X, Z, p, q, r and s are as defined for formula (I). PG is a protecting group, LG is a leaving group, Hal is halogen, Het is heteroaryl.

Compounds of formula (I) can be prepared as outlined in Scheme 1. Removal of the protecting group PG from the amine functionality in compounds of formula (II) can be achieved using standard conditions well known to those skilled in the art.

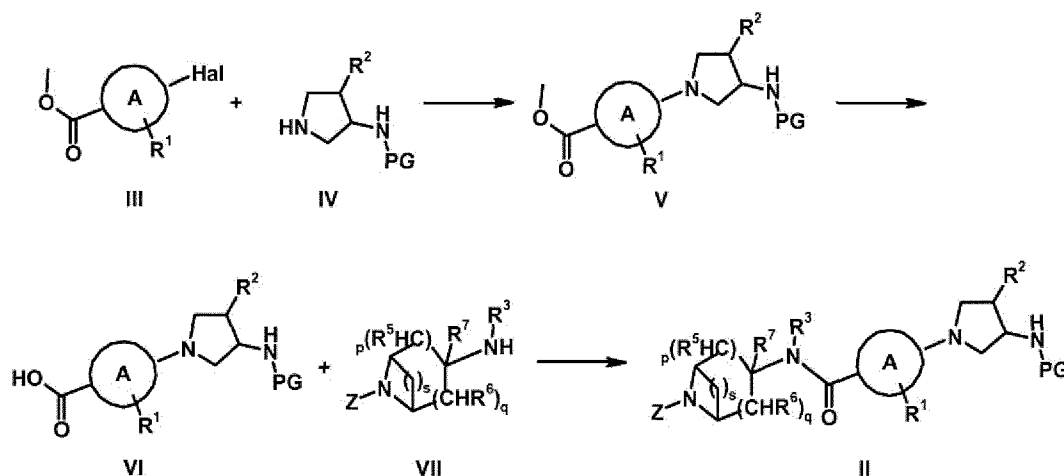
Scheme 1



Compounds of formula (II) where X is C(O) can be prepared as outlined in Scheme 2.

- Esters of formula (V) can be prepared by S_NAr displacement of suitable haloaromatic compounds of formula (III) with amines of formula (IV) under standard conditions, for example, DBU and DMSO at 80 - 100°C. Acids of formula (VI) can be prepared from esters of formula (V) under standard conditions, for example, LiOH, water and methanol at room temperature. Amides of formula (II) can be prepared from acids of formula (VI) with amines of formula (VII) under standard amide coupling conditions, for example, HOBt and EDCI, in a suitable solvent, such as DCM.

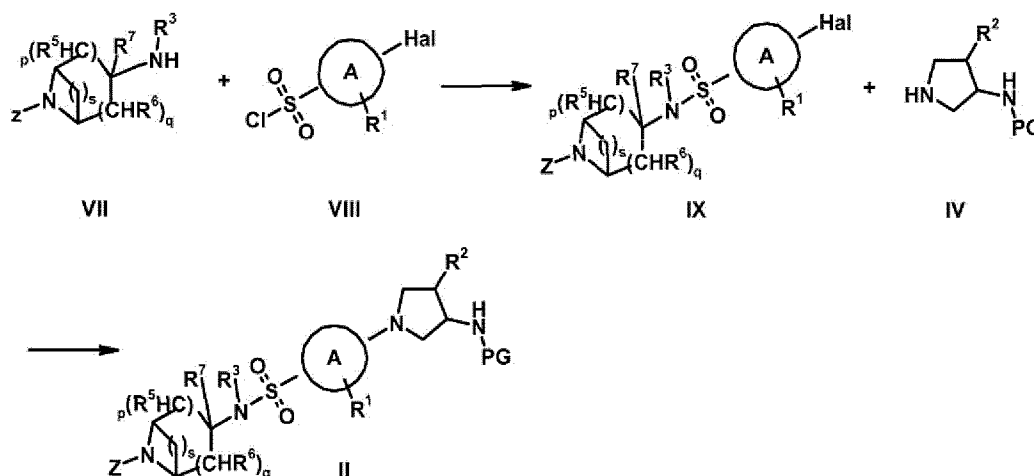
Scheme 2



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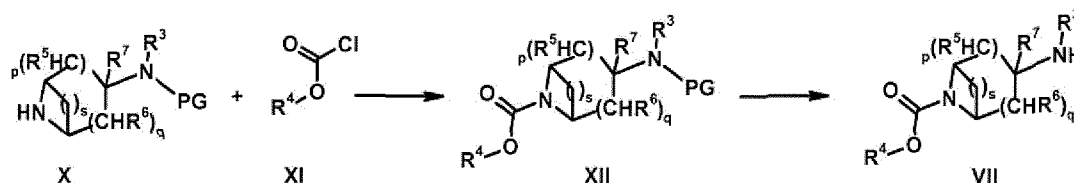
- Compounds of formula (II) where X is $S(O)_2$ can be prepared as outlined in Scheme 3. Sulfonamides of formula (IX) can be prepared by reaction of amine of formula (VII) with sulfonyl chloride of formula (VIII) under standard conditions, for example, triethylamine in a suitable solvent, such as DCM. Compounds of formula (II) can be prepared by S_NAr displacement of suitable haloaromatic compounds of formula (IX) with amines of formula (IV) under standard conditions, for example, DBU and DMSO at 80 - 100°C.

Scheme 3



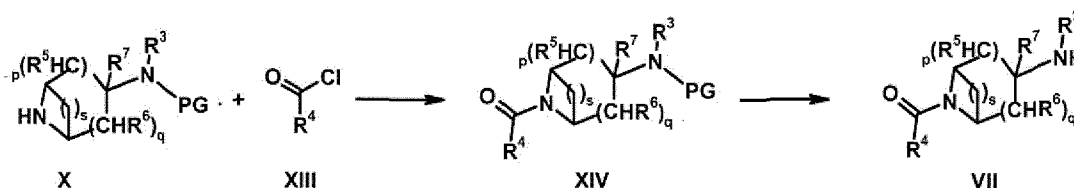
Compounds of formula (VII) where Z is C(O)OR⁴ can be prepared as outlined in Scheme 4. Carbamates of formula (XII) can be prepared from amines of formula (X) and chloroformates of formula (XI) under standard conditions, for example, triethylamine in a suitable solvent, such as DCM. Removal of the protecting group PG from the amine functionality in compounds of formula (XII) can be achieved using standard conditions well known to those skilled in the art.

Scheme 4



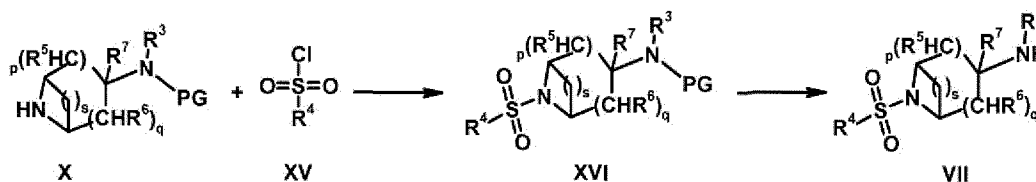
Compounds of formula (VII) where Z is C(O)R⁴ can be prepared as outlined in Scheme 5. Amides of formula (XIV) can be prepared from amines of formula (X) and acid chlorides of formula (XIII) under standard conditions, for example, triethylamine in a suitable solvent, such as DCM. Removal of the protecting group PG from the amine functionality in compounds of formula (XIV) can be achieved using standard conditions well known to those skilled in the art.

Scheme 5



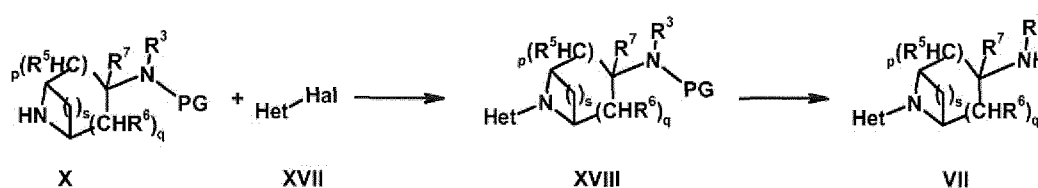
Compounds of formula (VII) where Z is S(O)₂R⁴ can be prepared as outlined in Scheme 6. Sulfonamides of formula (XVI) can be prepared from amines of formula (X) and sulfonyl chlorides of formula (XV) under standard conditions, for example, triethylamine in a suitable solvent, such as DCM. Removal of the protecting group PG from the amine functionality in compounds of formula (XVI) can be achieved using standard conditions well known to those skilled in the art.

Scheme 6



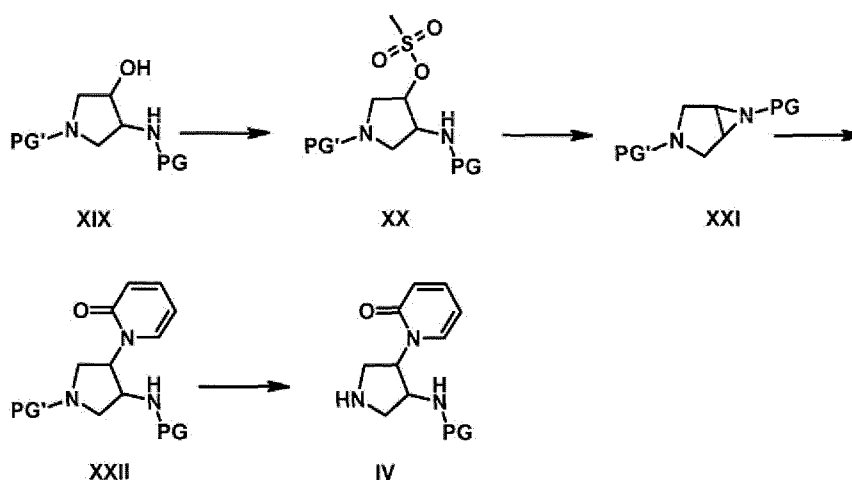
Compounds of formula (VII) where Z is heteroaryl can be prepared as outlined in Scheme 7. Compounds of formula (XVIII) can be prepared by S_NAr displacement of suitable haloaromatic compounds of formula (XVII) with amines of formula (X) under standard conditions, for example, DBU and DMSO at 80 - 100°C. Alternatively, compounds of formula (XVIII) can be prepared by reaction of suitable haloaromatic compounds of formula (XVII) with amines of formula (X) under Buchwald-Hartwig conditions, such as, $Pd_2(dba)_3$ and BINAP in a suitable solvent, such as toluene at 110°C. Removal of the protecting group PG from the amine functionality in compounds of formula (XVIII) can be achieved using standard conditions well known to those skilled in the art.

Scheme 7



Compounds of formula (IV) where R^2 is *N*-pyridonyl can be prepared as outlined in Scheme 8. Compounds of formula (XX) can be prepared from alcohols of formula (XIX) under standard conditions, for example, methanesulfonyl chloride and triethylamine in a suitable solvent, such as, THF at 0°C. Diazabicyclo compounds of formula (XXI) can be prepared from compounds of formula (XX) by treatment with sodium hydride in a suitable solvent, such as, THF at 0°C. Compounds of formula (XXII) can be prepared from compounds of formula (XXI), pyrid-2-one and potassium *tert*-butoxide in a suitable solvent, such as, NMP in a microwave reactor at 100°C. Removal of the protecting group PG' from the amine functionality in compounds of formula (XXII) can be achieved using standard conditions well known to those skilled in the art.

Scheme 8



Examples and syntheses of building blocks of formula (IV) have been described elsewhere: Benbow *et.al.*, WO2007148185; Backes *et.al.*, *Bioorg. Med. Chem. Lett.*, **2007**, 17 2005-2012; Pei *et.al.*, *J. Med. Chem.*, **2007**, 50 (8), 1983-1987; Cox *et.al.*, *Bioorg. Med. Chem. Lett.*, **2007**, 17 4579-4583; Wright *et.al.*, *Bioorg. Med. Chem. Lett.*, **2007**, 17 5638-5642.

5 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.

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

15 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.

20 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 is provided a compound of any one of formulae (II), (VI), (VII), (IX), (XVI) and (XVIII) as defined
25 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.

30 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.

35 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
5 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
10 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
15 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.

20 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.

25 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
30 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
35 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, $\alpha 2$ 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 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, 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 antiobesity 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 SiO₂ (40–63 mesh) unless specified otherwise. LCMS data were obtained as follows:

LCMS-method 1: Atlantis 3 μ C₁₈ column (3.0 × 20.0mm, flow rate = 0.85mL/min) eluting with a H₂O–MeCN solution containing 0.1% HCO₂H over 6 min with UV detection at 220 nm. Gradient information: 0.0–0.3 min 100% H₂O; 0.3–4.25 min: Ramp up to 10% H₂O–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% H₂O. The mass spectra were obtained using an electrospray ionisation source in either the positive (ES⁺) or negative (ES[−]) ion modes.

LCMS-method 2: Phenomenex Kinetex C18 column (3.0x30mm, 2.6 μ M, flow rate 1.0mL/min) eluting with a H₂O–MeCN solution containing 0.1% HCO₂H over 2 min with UV detection at 220 nm. Gradient information: 0.0–0.1 min 2% MeCN 98% H₂O to 5% MeCN 95% H₂O; 0.1–1.50 min: Ramp up to 100% MeCN; 1.5–1.75min: Hold at 100% MeCN; 1.75–1.8min: 100% MeCN to 2% MeCN 98% H₂O ; 1.8–2.0 min: Hold at 2% MeCN 98% H₂O. The mass spectra were obtained using an electrospray ionisation source in both the positive (ES⁺) or negative (ES[−]) ion modes.

LCMS-method 3 data were obtained as follows: Xbridge C18 column (3.0 × 150mm, 5 μ M, flow rate 1.0mL/min) eluting with an MeCN–10mM NH₄HCO₃ solution over 5 min with UV detection at 215 – 350nm. Gradient information: 0–0.1 min: hold at 5% MeCN 95% NH₄HCO₃; 0.1–3.0 min: 5% MeCN 95%NH₄HCO₃ to 5% NH₄HCO₃ 95% MeCN; 3.0–3.9min: hold at 5% NH₄HCO₃ 95% MeCN. The mass spectra were obtained using an electrospray ionisation source in the positive (ES⁺) mode.

LCMS –method 4 data were obtained as follows: Xbridge C₁₈ column (2.1 × 50mm, 2.5 μ M, flow rate 0.8mL/min) eluting with an MeCN–10mM NH₄HCO₃ solution over 1.5 min with UV detection at 215 – 350nm. Gradient information: 0–0.8 min: 98% MeCN 2% NH₄HCO₃ to 98% NH₄HCO₃ 2% MeCN; 0.8–1.2min: hold at 98% NH₄HCO₃ 2% MeCN. The mass spectra were obtained using an electrospray ionisation source in the positive (ES⁺) mode.

LCMS-method 5 data were obtained as follows: Xbridge C₁₈ column (2.1 × 5.0mm, 2.55 μ M, flow rate 0.8mL/min) eluting with an MeCN–10mM NH₄HCO₃ solution over 5 min with UV detection at 215 – 350nm. Gradient information: 0–4 min: 98% MeCN 2% NH₄HCO₃ to 98% NH₄HCO₃ 2% MeCN; 4–4.6min: hold at 98% NH₄HCO₃ 2% MeCN. The mass spectra were obtained using an electrospray ionisation source in the positive (ES⁺) mode.

Unless otherwise stated LCMS-method 1 was employed for analysis.

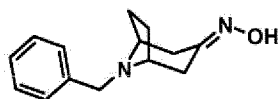
Preparative HPLC purification was carried out using either a standard or basic method. Standard method: Gemini-NX C₁₈ column (21.2 × 100mm, 5 μ M, flow rate 20mL/min) eluting with a H₂O–MeCN solution containing 0.1% HCO₂H using a 10 minute gradient with UV detection at 220 nm.

Basic method: XBridge Prep C₁₈ column (19 x 100mm, 5μM, flow rate 20mL/min) eluting with a H₂O–MeCN solution containing 0.2% NH₄OH using a 10 minute gradient with UV detection at 220 nm. Unless otherwise stated, the standard method was employed for purification.

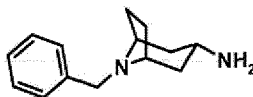
Chiral-HPLC was performed on a Daicel chiralpak IA 250 × 20 mm, 5 μM column.

- 5 Abbreviations and acronyms: AcOH: Acetic acid; Aq: Aqueous; BOP: (Benzotriazol-1-yl)oxytris(dimethylamino)phosphonium hexafluorophosphate; DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene; DCE: 1, 2-Dichloroethane; DCM: Dichloromethane; DEA: Diethylamine; DIPEA: Diisopropylethylamine; DMAP: Dimethylpyridin-4-ylamine; EDCI: (3-Dimethylaminopropyl)ethylcarbodiimide hydrochloride; Et₂O: Diethyl ether; EtOH: Ethanol; EtOAc: Ethyl acetate; h: hour(s); HCl: Hydrochloric acid; HCO₂H: Formic acid; H₂O: Water; HOBt: 1-Hydroxybenzotriazole monohydrate; HPLC: High performance liquid chromatography; IH: Isohexane; IPA: Isopropyl alcohol; IMS: Industrial methylated spirits; M: Molar; MeCN: Acetonitrile; MeOH: Methanol; MgSO₄: Magnesium sulfate; min: minute/s; PPA: 1-Propanephosphonic acid cyclic anhydride; NaHCO₃: Sodium hydrogen carbonate; NaOH: Sodium hydroxide; Na₂SO₄: Sodium sulfate; NH₃: Ammonia; NH₄Cl: Ammonium chloride; NH₄HCO₃: Ammonium carbamate; NH₄OH: Ammonium hydroxide; RT: Retention time; r.t.: Room temperature; Sat: saturated; SCX: Strong Cation Exchange resin; SiO₂: Silica gel; THF: Tetrahydrofuran; TFA: Trifluoroacetic acid; TMSCl: Trimethylsilyl Chloride.
- 20 The syntheses of the following compounds have been described elsewhere: 2,2-Difluoro-*N*-hydroxyacetamidine and 2,2-Difluoro-*N*-hydroxy-propionamidine: Bertram, L., *et al.*, WO2010004348; 2-Fluoro-*N*-hydroxy-2-methyl-propionamidine: Azimioara, M. *et al.*, WO2011044001; (3-Benzyl-3-aza-bicyclo[3.2.1]oct-8-yl)-carbamic acid tert-butyl ester, Arányi, P. *et al.*, WO2005021536.
- 25 All other compounds were available from commercial sources.

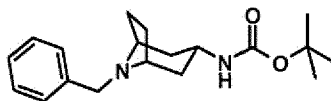
Preparation 1: 8-Benzyl-8-aza-bicyclo[3.2.1]octan-3-one oxime



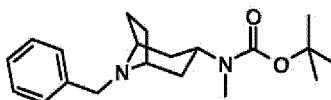
- To a solution of 8-benzyl-8-aza-bicyclo[3.2.1]octan-3-one (10.0g, 46.4mmol) in EtOH (250mL) was added hydroxylamine hydrochloride (3.23g, 46.4mmol) and pyridine (4.13mL, 51.1mmol) and the mixture was heated to reflux for 18 h. The reaction mixture was cooled to r.t. and a saturated solution of sodium bicarbonate added. The resulting suspension was filtered and the filtrate concentrated *in vacuo*. The residue was dissolved in DCM and washed with water (x2), then brine. The organics were then dried (MgSO₄), filtered and concentrated *in vacuo* to afford the title compound. RT = 0.43 min; *m/z* (ES⁺) = 231.25 [*M* + H]⁺ (LCMS Method - 2).
- 30
- 35

Preparation 2: 8-Benzyl-8-aza-bicyclo[3.2.1]oct-3-ylamine

To an oven dried, argon purged 3-necked flask containing anhydrous toluene (100mL, 900mmol) was added sodium metal (5.13g, 223mmol) in pieces. The mixture was heated to reflux before the slow addition of a solution of 8-benzyl-8-aza-bicyclo[3.2.1]octan-3-one oxime (**Preparation 1**, 4.67g, 20.3mmol) in pentan-1-ol (30mL) and toluene (40mL) over 15 min (hydrogen gas evolution). The mixture was heated for a further 2 h before cooling to 80 °C and isopropanol added (75mL). The mixture heated at 80 °C for 1 h before cooling to room temperature. The mixture was diluted with water (200mL) and concentrated HCl added until pH1 was obtained. The layers were separated and the organic layer basified with sodium hydroxide pellets until a pH of 12 was obtained. The mixture was extracted with ethyl acetate (x2), the combined organics dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by column chromatography (DCM:7M ammonia in MeOH, 93:7) afforded the title *exo*-compound. m/z (ES⁺) = 217.25 [$M + H$]⁺ (LCMS Method - 2).

Preparation 3: (8-Benzyl-8-aza-bicyclo[3.2.1]oct-3-yl)-carbamic acid *tert*-butyl ester

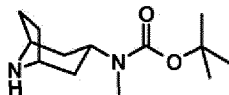
To a solution of 8-benzyl-8-aza-bicyclo[3.2.1]oct-3-ylamine (**Preparation 2**, 1.88g, 8.69mmol) in THF (75mL) was added di-*tert*-butyldicarbonate (1.99g, 9.12mmol) and the mixture allowed to stir at r.t. under argon for 18 h. The mixture was concentrated *in vacuo* and the residue dissolved in ethyl acetate, washed with water (x2), then brine. The organics were dried (MgSO₄), filtered and the filtrate concentrated *in vacuo* to afford the title compound. RT = 0.68 min; m/z (ES⁺) = 317.34 [$M + H$]⁺ (LCMS Method - 2).

Preparation 4: 8-Benzyl-8-aza-bicyclo[3.2.1]oct-3-yl)-methyl-carbamic acid *tert*-butyl ester

To an argon purged, 2-necked flask containing anhydrous THF (80mL) was added lithium aluminum hydride (0.554g, 14.6mmol) and the suspension cooled to 0 °C. A solution of (8-benzyl-8-aza-bicyclo[3.2.1]oct-3-yl)-carbamic acid *tert*-butyl ester (**Preparation 3**, 1.54g, 4.87mmol) in THF (20mL) was added dropwise and the mixture allowed to warm to room temperature before heating to reflux for 4 h. The mixture was then cooled to r.t. and water slowly added (0.5mL) followed by aqueous sodium hydroxide solution (2M, 0.75mL) then water (1.5mL). The mixture was filtered

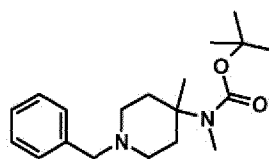
through celite and di-*tert*-butyldicarbonate (1.06g, 4.87mmol) added to the filtrate. The mixture was allowed to stir at room temperature under argon for 18 h. The mixture was concentrated *in vacuo*, the residue dissolved in DCM (100mL) and washed with 1M sodium hydroxide solution (30mL) then brine. The organics were dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by column chromatography (DCM to DCM:7M ammonia in methanol 95:5) afforded the title compound. RT = 0.72 min; *m/z* (ES⁺) = 331.37 [*M* + H]⁺ (LCMS Method - 2).

Preparation 5: (8-Aza-bicyclo[3.2.1]oct-3-yl)-methyl-carbamic acid *tert*-butyl ester



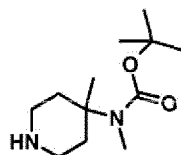
A solution of 8-benzyl-8-aza-bicyclo[3.2.1]oct-3-yl)-methyl-carbamic acid *tert*-butyl ester (**Preparation 4**, 2.0g, 6.0mmol) in methanol (0.05M) was passed through an H-Cube apparatus (10% Pd/C Catcart, 50 °C, 8 bar) at a flow rate of 1mL per min. The solvent was removed *in vacuo* to afford the title compound: *m/z* (ES⁺) = 241.30 [*M* + H]⁺ (LCMS Method-2).

Preparation 6: (1-Benzyl-4-methyl-piperidin-4-yl)-methyl-carbamic acid *tert*-butyl ester

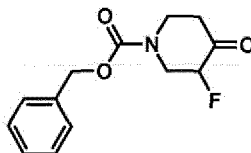


The title compound was synthesized from (1-benzyl-4-methyl-piperidin-4-yl)-carbamic acid *tert*-butyl ester employing a procedure similar to that outlined in **Preparation 4**: ¹H NMR δ_H (301MHz, CDCl₃): 7.36 - 7.15 (m, 5H), 3.47 (s, 2H), 2.83 (s, 3H), 2.51 - 2.16 (m, 8H), 1.85 - 1.68 (m, 2H), 1.44 (s, 9H), 1.24 (s, 3H).

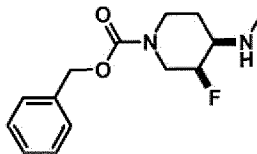
Preparation 7: Methyl-(4-methyl-piperidin-4-yl)-carbamic acid *tert*-butyl ester



To a suspension of 10% Pd/C (700mg) in MeOH (500mL) in an autoclave was added (1-benzyl-4-methyl-piperidin-4-yl)-methyl-carbamic acid *tert*-butyl ester (**Preparation 6**, 9.0g, 28.26mmol) and the mixture hydrogenated (40 psi, 75 °C) for 4 h. The mixture was then filtered through celite and the filtrate concentrated *in vacuo* to afford the title compound: ¹H NMR δ_H (301MHz, CDCl₃): 2.88 - 2.69 (m, 5H), 2.28 - 2.07 (m, 2H), 1.76 - 1.57 (m, 4H), 1.44 (s, 9H), 1.26 (s, 3H).

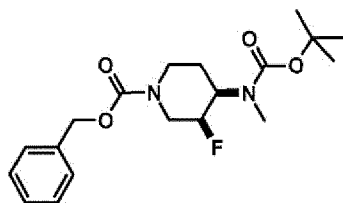
Preparation 8: 3-Fluoro-4-oxo-piperidine-1-carboxylic acid benzyl ester

To a solution of 4-oxo-piperidine-1-carboxylic acid benzyl ester (15g, 64mmol) in anhydrous DMF (80mL) was added anhydrous triethylamine (22mL, 150mmol) and the reaction heated to 80 °C for 18 h. TMSCl (9.8mL, 77mmol) was added followed by triethylamine (22mL) and the reaction heated to 80 °C for 18 h. The reaction was cooled to room temperature, diluted with hexane and washed with water then brine solution. The organics were dried (sodium sulfate), filtered and concentrated *in vacuo*. To a solution of the residue in MeCN (300 mL) at 0 °C under argon was added 1-chloromethyl-4-fluoro-1,4-diazaonibicyclo[2.2.2]octane bis(tetrafluoroborate) (25g, 71mmol) portion wise and the mixture allowed to warm to room temperature and stirred for 18 h. The mixture was concentrated *in vacuo* and the residue partitioned between water and ethyl acetate. The organics were then washed with brine, dried (sodium sulfate), filtered and concentrated *in vacuo*. Purification by flash chromatography (hexane:EtOAc 7:3 - 1:1) afforded the title compound: ¹H NMR δ_H (400MHz, CDCl₃): 7.41-7.39 (m, 5H), 5.35 (s, 2H), 4.91-4.80 (m, 1H), 4.60-4.49 (m, 1H), 4.29-4.23 (m, 1H), 3.41-3.36 (m, 2H), 2.69-2.55 (m, 2H).

Preparation 9: *cis*-3-Fluoro-4-methylamino-piperidine-1-carboxylic acid benzyl ester

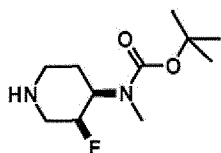
To a solution of 3-fluoro-4-oxo-piperidine-1-carboxylic acid benzyl ester (**Preparation 8**, 4.00g, 15.9mmol) in anhydrous 1,2-dichloroethane (40mL) was added a solution of methylamine in MeOH (2M, 24mL, 48mmol) and the mixture stirred for 2 h at r.t. before the addition of sodium triacetoxyborohydride (5.1g, 24mmol). The reaction was stirred at r.t. for 18 h before the addition of saturated potassium carbonate solution and the organics extracted with DCM. The organics were then dried (sodium sulfate), filtered and concentrated *in vacuo*. Purification by flash chromatography (1:2:97 7N ammonia in MeOH:MeOH:DCM) afforded the title compound: RT = 0.56 min, *m/z* (ES⁺) = 267.3 [*M* + H]⁺ (LCMS Method - 2).

Preparation 10: *cis*-4-(*tert*-Butoxycarbonyl-methyl-amino)-3-fluoro-piperidine-1-carboxylic acid benzyl ester



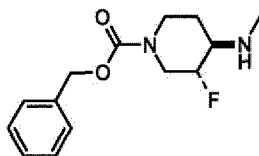
To a solution of *cis*-3-fluoro-4-methylamino-piperidine-1-carboxylic acid benzyl ester (**Preparation 9**, 542mg, 2.04mmol) in DCM (10 mL) was added triethylamine (0.851mL, 6.10mmol) followed by di-*tert*-butyldicarbonate (444mg, 2.04mmol) and the mixture stirred at r.t. for 18 h. The mixture was diluted with water and the organics dried (sodium sulfate), filtered and concentrated *in vacuo*. Purification by flash chromatography (hexane - 7:3 hexane:ethyl acetate) afforded the title compound. RT = 1.28 min, m/z (ES^+) = 389.3 $[M + Na]^+$ (LCMS Method - 2).

Preparation 11: *cis*-3-Fluoro-piperidin-4-yl)-methyl-carbamic acid *tert*-butyl ester



To a solution of *cis*-4-(*tert*-butoxycarbonyl-methyl-amino)-3-fluoro-piperidine-1-carboxylic acid benzyl ester (**Preparation 10**, 634mg, 1.73mmol) in EtOH (20 mL) and 1,4-cyclohexadiene (4.05mL, 43.2mmol) was added 10% Pd/C (150mg, 4.2mmol) as a slurry in EtOH under argon. The reaction was stirred at r.t. for 18 h then filtered through celite and concentrated *in vacuo*. The crude residue was loaded onto a SCX cartridge, washed with methanol, eluted with 7N ammonia in MeOH and concentrated *in vacuo* to afford the title compound: 1H NMR δ_H (400MHz, $CDCl_3$): 4.79-4.66 (m, 1H), 4.27-4.18 (m, 1H), 3.31-3.20 (m, 2H), 2.92 (s, 3H), 2.78-2.71 (m, 2H), 2.09-1.85 (dq, $J = 14, 6$ Hz, 1H), 1.57-1.50 (m, 10H).

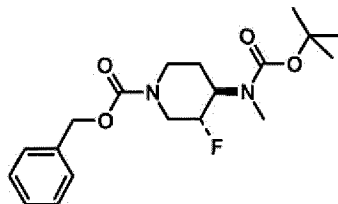
Preparation 12: *trans*-3-Fluoro-4-methylamino-piperidine-1-carboxylic acid benzyl ester



To a solution of 3-fluoro-4-oxo-piperidine-1-carboxylic acid benzyl ester (**Preparation 8**, 1.00g, 3.98mmol) in anhydrous MeOH (10mL) was added AcOH (0.5mL, 9mmol) followed by a solution of methylamine in MeOH (2 M, 6mL). The mixture was stirred at r.t. for 1 h before the addition of sodium cyanoborohydride (0.38g, 6.0mmol) portion wise over 5 min. After 3 h the

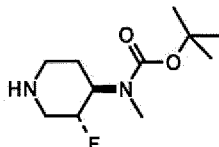
reaction was quenched with a saturated solution of sodium bicarbonate and the organics extracted with ethyl acetate. The organics were then dried (sodium sulfate), filtered and concentrated *in vacuo*. Purification by flash chromatography (97:3 DCM:MeOH then 1:5:94 7N ammonia in MeOH:MeOH:DCM) afforded the title compound. RT = 0.56 min, m/z (ES^+) = 267.3 $[M + Na]^+$ (Method -2).

Preparation 13: *trans*-4-(*tert*-Butoxycarbonyl-methyl-amino)-3-fluoro-piperidine-1-carboxylic acid benzyl ester



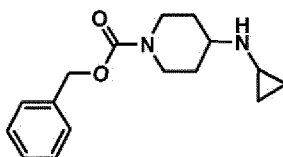
The title compound was synthesized from *trans*-3-fluoro-4-methylamino-piperidine-1-carboxylic acid benzyl ester (**Preparation 12**) employing a procedure similar to that outlined in **Preparation 10**: 1H NMR δ_H (400MHz, $CDCl_3$): 7.48 - 7.32 (m, 5H), 5.17 (s, 2H), 4.67 - 4.36 (m, 2H), 4.36 - 4.17 (m, 2H), 2.91 - 2.77 (m, 5H), 1.85 - 1.69 (m, 2H), 1.50 (s, 9H).

Preparation 14: (*trans*-3-Fluoro-piperidin-4-yl)-methyl-carbamic acid *tert*-butyl ester



The title compound was synthesized from *trans*-4-(*tert*-butoxycarbonyl-methyl-amino)-3-fluoro-piperidine-1-carboxylic acid benzyl ester (**Preparation 13**) employing a procedure similar to that outlined in **Preparation 11**: 1H NMR δ_H (400MHz, $CDCl_3$): 4.64 - 4.39 (m, 1H), 4.31 - 3.89 (m, 1H), 3.52 - 3.39 (m, 1H), 3.12 - 3.01 (m, 1H), 2.86 (br. s., 3H), 2.74 - 2.56 (m, 2H), 1.83 - 1.62 (m, 2H), 1.50 (s, 9H).

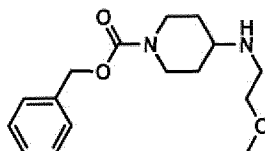
Preparation 15: 4-Cyclopropylamino-piperidine-1-carboxylic acid benzyl ester



To a solution of 4-oxo-piperidine-1-carboxylic acid benzyl ester (10g, 43.1mmol) in DCM (100mL) was added acetic acid (3.7mL, 64.6mmol) and cyclopropylamine (3.7g, 64.6mmol). The mixture was cooled to 10 °C, sodium triacetoxyborohydride (13.7g, 64.6mmol) added and the

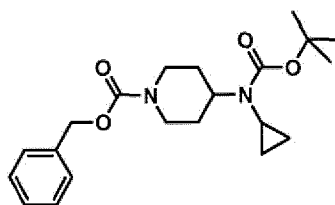
mixture was stirred at room temperature for 18 h. The reaction mixture was quenched with water and washed with NaHCO₃. The aqueous layer was extracted with DCM (3x), the organics dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by column chromatography (DCM:7M ammonia in MeOH, 95:5) afforded the title compound: RT = 0.78 min; *m/z* (ES⁺) = 275.5 [*M* + H]⁺ (LCMS Method - 4).

Preparation 16: 4-(2-Methoxy-ethylamino)-piperidine-1-carboxylic acid benzyl ester



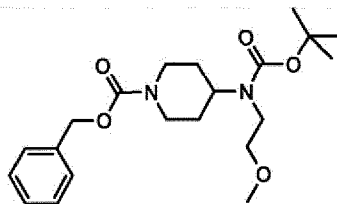
The title compound was synthesized from 4-oxo-piperidine-1-carboxylic acid benzyl ester and 2-methoxy-ethylamine employing a procedure similar to that outlined in **Preparation 15**: ¹H NMR δ_H (301MHz, CDCl₃): 7.40 – 7.27 (m, 5H), 5.12 (s, 2H), 4.24 – 4.01 (m, 2H), 3.49 (t, *J*=5.0 Hz, 2H), 3.35 (s, 3H), 2.74 - 2.98 (m, 4H), 2.71 – 2.55 (m, 1H), 1.96 – 1.76 (m, 2H), 1.39 – 1.19 (m, 2H).

Preparation 17: 4-(*tert*-Butoxycarbonyl-cyclopropyl-amino)-piperidine-1-carboxylic acid benzyl ester



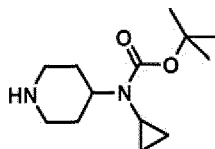
To a solution of 4-cyclopropylamino-piperidine-1-carboxylic acid benzyl ester (**Preparation 15**, 11.79g, 43.13mmol) in THF (118mL) was added aqueous sodium carbonate solution (2N, 151mL) followed by di-*tert*-butyldicarbonate (11.3g, 51.75mmol) and the mixture stirred at r.t. for 18 h. The mixture was diluted with DCM, washed with water and the organics dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by column chromatography (heptane:EtOAc, 50:50) afforded the title compound: ¹H NMR δ_H (301MHz, CDCl₃): 7.43 - 7.28 (m, 5H), 5.12 (s, 2H), 4.39 -4.14 (m, 2H), 3.88 -3.70 (m, 1H), 2.89 -2.66 (m, 2H), 2.38 -2.25 (m, 1H), 2.03 -1.18 (m, 2H), 1.79 -1.63 (m, 2H), 1.45 (s, 9H), 0.79-0.69 (m, 2H), 0.67-0.58 (m, 2H).

Preparation 18: 4-[*tert*-Butoxycarbonyl-(2-methoxy-ethyl)-amino]-piperidine-1-carboxylic acid benzyl ester



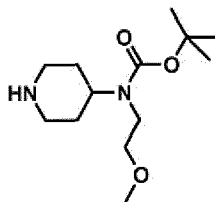
The title compound was synthesized from 4-(2-methoxy-ethylamino)-piperidine-1-carboxylic acid benzyl ester (**Preparation 16**) employing a procedure similar to that outlined in **Preparation 17**: ^1H NMR δ_{H} (301MHz, CDCl_3): 7.41 – 7.28 (m, 5H), 5.12 (s, 2H), 4.39 – 4.14 (m, 2H), 3.47 – 3.36 (m, 2H), 3.32 (s, 3H), 3.29 – 3.14 (m, 2H), 2.91 – 2.69 (m, 3H), 1.80 – 1.59 (m, 4H), 1.46 (s, 9H).

Preparation 19: Cyclopropyl-piperidin-4-yl-carbamic acid *tert*-butyl ester

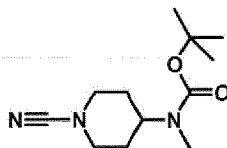


To a solution of 5% Pd/C (0.50g) in IMS (100mL) was added 4-(*tert*-butoxycarbonyl-cyclopropyl-amino)-piperidine-1-carboxylic acid benzyl ester (**Preparation 17**, 14.92g, 39.9mmol) and the mixture hydrogenated at 40 bar for 18 h at room temperature. The mixture was then filtered through celite and the filtrate concentrated *in vacuo* to afford the title compound: ^1H NMR δ_{H} (301MHz, CDCl_3): 3.81 -3.66 (m, 1H), 3.19 - 3.07 (m, 2H), 2.71 - 2.56 (m, 2H), 2.38 - 2.27 (m, 1H), 2.08 -1.98 (m, 1H), 1.98 - 1.81 (m, 2H), 1.79 - 1.67 (m, 2H), 1.46 (s, 9H), 0.80 - 0.70 (m, 2H), 0.70 - 0.61 (m, 2H).

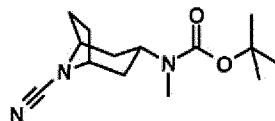
Preparation 20: (2-Methoxy-ethyl)-piperidin-4-yl-carbamic acid *tert*-butyl ester



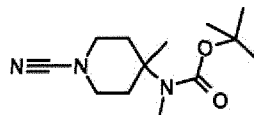
The title compound was synthesized from 4-[*tert*-butoxycarbonyl-(2-methoxy-ethyl)-amino]-piperidine-1-carboxylic acid benzyl ester employing a procedure similar to that outlined in **Preparation 18**: RT = 0.63 min; m/z (ES^+) = 259.49 [$M + \text{H}$] $^+$ (LCMS Method - 4).

Preparation 21: (1-Cyano-piperidin-4-yl)-methyl-carbamic acid *tert*-butyl ester

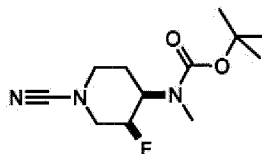
To a solution of methyl-piperidin-4-yl-carbamic acid *tert*-butyl ester (2.08g, 9.68mmol) in DCM (25mL) was added a slurry of NaHCO₃ (2.44g, 29.1mmol) in water (6mL). The resulting reaction mixture was cooled to 0 °C and a solution of cyanogen bromide (1.23g, 11.6mmol) in DCM (3mL) was added dropwise over 1 min, before warming to r.t. and stirring for 2.5 h. The reaction mixture was diluted with water, the layers separated and the aqueous layer extracted with DCM. The combined organic extracts were washed with brine, dried (MgSO₄), filtered and concentrated *in vacuo* to afford the title compound: RT = 3.12 min; *m/z* (ES⁺) = 240.17 [*M* + H]⁺.

Preparation 22: (8-Cyano-8-aza-bicyclo[3.2.1]oct-3-yl)-methyl-carbamic acid *tert*-butyl ester

The title compound was synthesized from (8-aza-bicyclo[3.2.1]oct-3-yl)-methyl-carbamic acid *tert*-butyl ester (**Preparation 5**) employing a procedure similar to that outlined in **Preparation 21**: RT = 1.05 min; *m/z* (ES⁺) = 266.3 [*M* + H]⁺ (LCMS Method - 2).

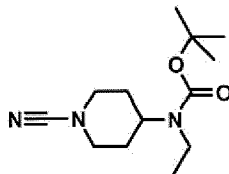
Preparation 23: (1-Cyano-4-methyl-piperidin-4-yl)-methyl-carbamic acid *tert*-butyl ester

The title compound was synthesized from methyl-(4-methyl-piperidin-4-yl)-carbamic acid *tert*-butyl ester (**Preparation 7**) employing a procedure similar to that outlined in **Preparation 21**: ¹H NMR δ_H (301MHz, CDCl₃): 3.29 - 3.11 (m, 4H), 2.80 (s, 3H), 2.56 - 2.42 (m, 2H), 1.78 - 1.62 (m, 2H), 1.44 (s, 9H), 1.25 (s, 3H).

Preparation 24: (*cis*-1-Cyano-3-fluoro-piperidin-4-yl)-methyl-carbamic acid *tert*-butyl ester

The title compound was synthesized from (*cis*-3-fluoro-piperidin-4-yl)-methyl-carbamic acid *tert*-butyl ester (**Preparation 11**) employing a procedure similar to that outlined in **Preparation 21**: RT = 0.97 min; m/z (ES^+) = 280.29 [$M + H$] $^+$ (LCMS Method - 2).

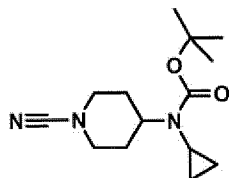
5 **Preparation 25: (1-Cyano-piperidin-4-yl)-ethyl-carbamic acid *tert*-butyl ester**



The title compound was synthesized from ethyl-piperidin-4-yl-carbamic acid *tert*-butyl ester employing a procedure similar to that outlined in **Preparation 21**: RT = 3.43 min; m/z (ES^+) = 254.16 [$M + H$] $^+$.

10

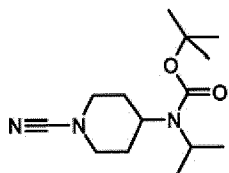
Preparation 26: (1-Cyano-piperidin-4-yl)-cyclopropyl-carbamic acid *tert*-butyl ester



The title compound was synthesized from cyclopropyl-piperidin-4-yl-carbamic acid *tert*-butyl ester (**Preparation 19**) employing a procedure similar to that outlined in **Preparation 21**: RT = 1.07 min; m/z (ES^+) = 288.32 [$M + H$] $^+$ (LCMS Method - 2).

15

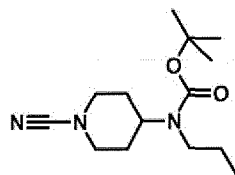
Preparation 27: (1-Cyano-piperidin-4-yl)-isopropyl-carbamic acid *tert*-butyl ester



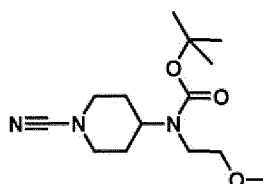
The title compound was synthesized from isopropyl-piperidin-4-yl-carbamic acid *tert*-butyl ester employing a procedure similar to that outlined in **Preparation 21**: 1H NMR δ_H (301MHz, $CDCl_3$): 3.56 - 3.38 (m, 3H), 3.17 - 2.96 (m, 3H), 2.26 - 1.92 (m, 2H), 1.69 - 1.57 (m, 2H), 1.48 (s, 9H), 1.20 (d, $J=6.4$ Hz, 6H).

20

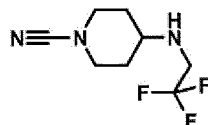
25

Preparation 28: (1-Cyano-piperidin-4-yl)-propyl-carbamic acid *tert*-butyl ester

The title compound was synthesized from piperidin-4-yl-propyl-carbamic acid *tert*-butyl ester employing a procedure similar to that outlined in **Preparation 21**: ^1H NMR δ_{H} (301MHz, CDCl_3): 4.14 - 3.88 (m, 1H), 3.56 - 3.37 (m, 2H), 3.17 - 2.89 (m, 4H), 1.99 - 1.63 (m, 4H), 1.60 - 1.48 (m, 2H), 1.45 (s, 9H), 0.93 - 0.83 (m, 3H).

Preparation 29: (1-Cyano-piperidin-4-yl)-(2-methoxy-ethyl)-carbamic acid *tert*-butyl ester

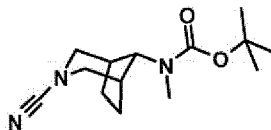
The title compound was synthesized from (2-methoxy-ethyl)-piperidin-4-yl-carbamic acid *tert*-butyl ester (**Preparation 20**) employing a procedure similar to that outlined in **Preparation 21**: ^1H NMR δ_{H} (301MHz, CDCl_3): 3.56 - 3.38 (m, 5H), 3.33 (s, 3H), 3.31 - 3.20 (m, 2H), 3.15 - 2.98 (m, 2H), 2.03 - 3.15 (m, 2H), 1.77 - 1.64 (m, 2H), 1.46 (s, 9H).

Preparation 30: 4-(2,2,2-Trifluoro-ethylamino)-piperidine-1-carbonitrile

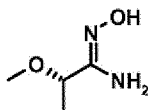
The title compound was synthesized from piperidin-4-yl-(2,2,2-trifluoro-ethyl)-amine employing a procedure similar to that outlined in **Preparation 21**: ^1H NMR δ_{H} (301MHz, CDCl_3): 3.46 (dt, $J=13.2, 4.0$ Hz, 2H), 3.29 - 3.12 (m, 2H), 3.11 - 2.94 (m, 2H), 2.84 - 2.68 (m, 1H), 1.91 (dd, $J=13.1, 3.4$ Hz, 2H), 1.57 - 1.39 (m, 2H), 1.34 - 1.08 (m, 1H).

Preparation 31: (3-Benzyl-3-aza-bicyclo[3.2.1]oct-8-yl)-methyl-carbamic acid *tert*-butyl ester

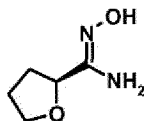
The title compound was synthesized from (3-benzyl-3-aza-bicyclo[3.2.1]oct-8-yl)-carbamic acid *tert*-butyl ester employing a procedure similar to that outlined in **Preparation 4**. The crude mixture was then taken on without further purification to **Preparation 32**.

Preparation 32: (3-Cyano-3-aza-bicyclo[3.2.1]oct-8-yl)-methyl-carbamic acid *tert*-butyl ester

To a suspension of 10% Pd/C (2.5g) in MeOH (500mL) in an autoclave was added (3-benzyl-3-aza-bicyclo[3.2.1]oct-8-yl)-methyl-carbamic acid *tert*-butyl ester (**Preparation 31**, 32.8g, 0.1mol) and the mixture hydrogenated (40 psi, 80°C) for 5 h. The mixture was then filtered through celite and the filtrate concentrated *in vacuo*. To a solution of a portion of the residue (700mg, 2.9mmol) in DCM (7mL) was added a slurry of NaHCO₃ (730mg) in water (4mL). The resulting reaction mixture was cooled to 0 °C and a solution of cyanogen bromide (310mg, 2.9mmol) in DCM (3mL) was added dropwise over 1 min, before warming to r.t. and stirring for 18 h. The reaction mixture was diluted with water, the layers separated and the aqueous layer extracted with DCM. The combined organic extracts were washed with brine, dried (MgSO₄), filtered and concentrated *in vacuo*. The stereoisomers were separated by column chromatography (90:10 to 80:10 heptane:EtOAc, then 60:40 heptane:EtOAc) to afford the title compound: ¹H NMR δ_H (301MHz, CDCl₃): 3.77 - 3.66 (m, 1H), 3.43 - 3.32 (m, 2H), 3.28 - 3.16 (m, 2H), 2.81 (s, 3H), 2.49 - 2.34 (m, 2H), 1.95 - 1.78 (m, 4H), 1.46 (s, 9H).

Preparation 33: (S)-N-Hydroxy-2-methoxypropionamidine

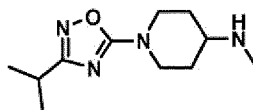
To a solution of (S)-2-methoxypropionitrile (910mg, 10.69mmol) in IMS (10mL) was added hydroxylamine (50% in water, 1.55mL, 23.52mmol) and the reaction was heated to 80 °C for 16 h. On cooling, the solvent was removed *in vacuo* and the product recrystallised from heptane:EtOAc (1:1). The mother liquor was concentrated *in vacuo* and crystallised for a second time. Both crops of material were combined and dried under vacuum to afford the title compound: RT = 0.33 min; *m/z* (ES⁺) = 119.0 [*M* + H]⁺ (LCMS Method - 2).

Preparation 34: (S)-N-Hydroxytetrahydrofuran-2-carboxamidine

To a solution of (S)-tetrahydrofuran-2-carbonitrile (1000mg, 10.3mmol) in IMS (7mL) was added hydroxylamine (50% in water, 750μL, 11.3mmol) and the reaction was heated to 70 °C for 18 h. On cooling, the solvent was removed *in vacuo*, azeotroping with toluene. The residue was purified

by column chromatography (EtOAc) to afford the title compound. ^1H NMR δ_{H} (300MHz, CDCl_3): 4.85 (bs, 2H), 4.44 – 4.32 (m, 1H), 4.00 – 3.74 (m, 2H), 2.20 – 1.80 (m, 4H).

Preparation 35: [1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-methyl-amine



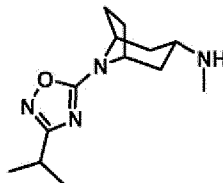
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To a solution of (1-cyano-piperidin-4-yl)-methyl-carbamic acid *tert*-butyl ester (**Preparation 21**, 1.00g, 4.18mmol) and *N*-hydroxy-isobutyramidine (512mg, 5.01mmol) in EtOH (20mL) was added a solution of zinc dichloride (683mg, 5.01mmol) in EtOH (7mL) and the resulting reaction mixture was stirred at r.t. for 2 h. Aqueous HCl solution (11.7 M, 1.07mL, 12.5mmol) was added and the reaction mixture stirred at 50 °C for 16 h and at r.t. for 120 h. The solvent was removed *in vacuo* and the residue triturated with MeCN. The solid was removed by filtration and the filtrate concentrated *in vacuo*, dissolved in water and washed with EtOAc. The aqueous was basified to pH12 with 2M aqueous NaOH solution, extracted with EtOAc and the resulting emulsion was filtered through celite. The layers of the filtrate were separated and the aqueous was extracted with EtOAc (3 x). The combined organic extracts were washed with brine, dried (MgSO_4), filtered and concentrated *in vacuo* to afford the title compound: RT = 1.68 min; m/z (ES^+) = 225.13 [$M + \text{H}$] $^+$.

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Preparation 36: 8-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-8-aza-bicyclo[3.2.1]oct-3-yl]-methyl-amine

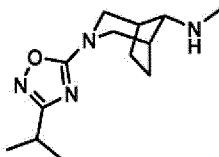


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The title compound was synthesized from (8-cyano-8-aza-bicyclo[3.2.1]oct-3-yl)-methyl-carbamic acid *tert*-butyl ester (**Preparation 22**) and *N*-hydroxy-isobutyramidine employing a procedure similar to that outlined in **Preparation 35**: RT = 0.55 min; m/z (ES^+) = 251.28 [$M + \text{H}$] $^+$ (LCMS Method - 2).

25

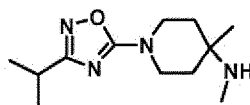
Preparation 37: [3-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-3-aza-bicyclo[3.2.1]oct-8-yl]-methyl-amine



The title compound was synthesized from (3-cyano-3-aza-bicyclo[3.2.1]oct-8-yl)-methyl-carbamic acid *tert*-butyl ester (**Preparation 32**) and *N*-hydroxy-isobutyramidine employing a procedure similar to that outlined in **Preparation 35**: RT = 0.64 min; m/z (ES^+) = 251.5 [$M + H$] $^+$ (LCMS Method - 3).

5

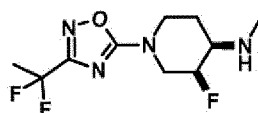
Preparation 38: [1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-4-methyl-piperidin-4-yl]-methyl-amine



The title compound was synthesized from (1-cyano-4-methyl-piperidin-4-yl)-methyl-carbamic acid *tert*-butyl ester (**Preparation 23**) employing a procedure similar to that outlined in

10 **Preparation 35**: RT = 0.62 min; m/z (ES^+) = 239.4 [$M + H$] $^+$ (LCMS Method - 4).

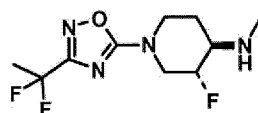
Preparation 39: *cis*-{1-[3-(1,1-Difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-3-fluoro-piperidin-4-yl}-methyl-amine



15 The title compound was synthesized from *cis*-1-cyano-3-fluoro-piperidin-4-yl)-methyl-carbamic acid *tert*-butyl ester (**Preparation 24**) employing a procedure similar to that outlined in **Preparation 35**: RT = 0.42 min; m/z (ES^+) = 265.3 [$M + H$] $^+$ (LCMS Method - 2).

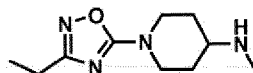
Preparation 40: *trans*-{1-[3-(1,1-Difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-3-fluoro-piperidin-4-yl}-methyl-amine

20



To a cooled solution of *trans*-3-fluoro-piperidin-4-yl)-methyl-carbamic acid *tert*-butyl ester (**Preparation 14**, 95mg, 0.41mmol) in DCM (5mL) was added a solution of sodium bicarbonate (93.7mg, 1.12mmol) in water (1mL) and a solution of cyanogen bromide (43mg, 0.41mmol) in DCM (2mL) dropwise over 5 min. The mixture was stirred at 0 °C for 1 h then at r.t. for 10 min. The organics were separated using a phase separator and concentrated *in vacuo*. The residue was then dissolved in EtOH and the title compound synthesized employing a procedure similar to that outlined in **Preparation 35**: RT = 0.46 min; m/z (ES^+) = 265.2 [$M + H$] $^+$ (LCMS Method - 2).

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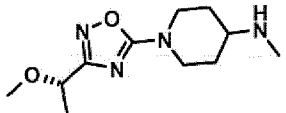
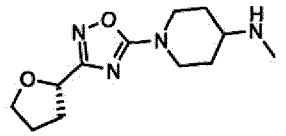
Preparation 41: [1-(3-Ethyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-methyl-amine

The title compound was synthesized from (1-cyano-piperidin-4-yl)-methyl-carbamic acid *tert*-butyl ester (**Preparation 21**) and *N*-hydroxy-propionamidine employing a procedure similar to that outlined in **Preparation 35**: RT = 0.43 min; m/z (ES^+) = 211.24 [$M + H$] $^+$ (LCMS Method - 2).

The following compounds were prepared by reacting (1-cyano-piperidin-4-yl)-methyl-carbamic acid *tert*-butyl ester (**Preparation 21**) with the appropriate amidoxime intermediate employing a procedure similar to that outlined in **Preparation 35**:

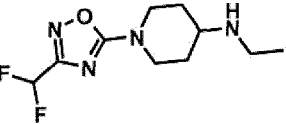
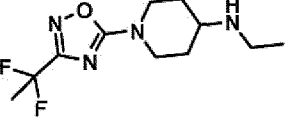
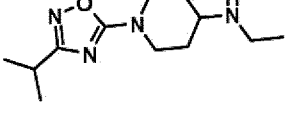
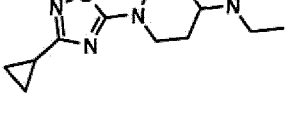
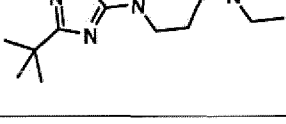
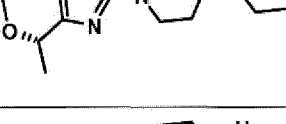
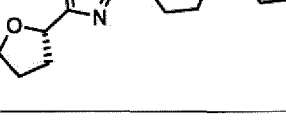
10

Prep.	Structure	Name	Spectral Data
42		[1-(3-Difluoromethyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-methyl-amine	1H NMR δ_H (300MHz, $CDCl_3$): 6.5 (t, $J=52.8$ Hz, 1H), 4.2-4.05 (m, 2H), 3.3-3.2 (m, 2H), 2.6-2.7 (m, 1H), 2.45 (s, 3H), 2.1-1.9 (m, 2H), 1.55-1.35 (m, 2H).
43		[1-(3- <i>tert</i> -Butyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-methyl-amine	RT = 2.37 min; m/z (ES^+) = 239.2 [$M + H$] $^+$ (LCMS Method - 3).
44		{1-[3-(1,1-Difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-methyl-amine	RT = 2.04 min; m/z (ES^+) = 247.1 [$M + H$] $^+$ (LCMS Method - 3).
45		[1-(3-Cyclopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-methyl-amine	RT = 2.03 min; m/z (ES^+) = 223.1 [$M + H$] $^+$ (LCMS Method - 3).
46		{1-[3-(1-Fluoro-1-methyl-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-methyl-amine	RT = 1.31 min; m/z (ES^+) = 243.4 [$M + H$] $^+$ (LCMS Method - 5).
47		Methyl-[1-(3-trifluoromethyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-amine	RT = 1.58 min; m/z (ES^+) = 251.4 [$M + H$] $^+$ (LCMS Method - 5).

Prep.	Structure	Name	Spectral Data
48		{1-[3-((<i>S</i>)-1-Methoxy-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-methyl-amine	RT = 1.82 min; m/z (ES^+) = 241.2 [$M + H$] $^+$ (LCMS Method - 3).
49		Methyl-{1-[(<i>S</i>)-3-(tetrahydrofuran-2-yl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-amine	RT = 1.86 min; m/z (ES^+) = 253.2 [$M + H$] $^+$ (LCMS Method - 3).

The following compounds were prepared by reacting (1-cyano-piperidin-4-yl)-ethyl-carbamic acid *tert*-butyl ester (**Preparation 25**) with the appropriate amidoxime intermediate employing a procedure similar to that outlined in **Preparation 35**:

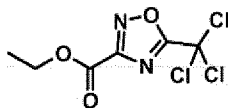
5

Prep.	Structure	Name	Spectral Data
50		[1-(3-Difluoromethyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-ethyl-amine	RT = 1.98 min; m/z (ES^+) = 247.2 [$M + H$] $^+$ (LCMS Method - 3).
51		{1-[3-(1,1-Difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-ethyl-amine	RT = 2.18 min; m/z (ES^+) = 261.2 [$M + H$] $^+$ (LCMS Method - 3).
52		Ethyl-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-amine	RT = 2.27 min; m/z (ES^+) = 239.3 [$M + H$] $^+$ (LCMS Method - 3).
53		[1-(3-Cyclopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-ethyl-amine	RT = 2.18 min; m/z (ES^+) = 237.2 [$M + H$] $^+$ (LCMS Method - 3).
54		[1-(3- <i>tert</i> -Butyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-ethyl-amine	RT = 1.65 min; m/z (ES^+) = 253.3 [$M + H$] $^+$ (LCMS Method - 5).
55		Ethyl-{1-[3-((<i>S</i>)-1-methoxy-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-amine	RT = 1.16 min; m/z (ES^+) = 255.19 [$M + H$] $^+$ (LCMS Method - 5).
56		Ethyl-{1-[(<i>S</i>)-3-(tetrahydrofuran-2-yl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-amine	RT = 2.04 min; m/z (ES^+) = 267.2 [$M + H$] $^+$ (LCMS Method - 3).

The following compounds were prepared by reacting the appropriate cyano-piperidinyl intermediate with the appropriate amidoxime intermediate employing a procedure similar to that outlined in

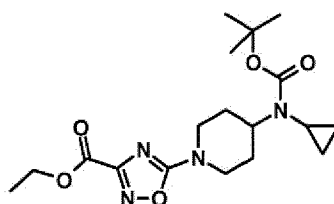
Preparation 35:

Prep.	Structure	Name	Spectral Data
57		{1-[3-(1,1-Difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-isopropyl-amine	RT = 1.74 min; m/z (ES^+) = 275.5 [$M + H$] $^+$ (LCMS Method - 5).
58		{1-[3-(1,1-Difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-propyl-amine	1H NMR δ_H (301MHz, $CDCl_3$): 4.11 (dt, $J=13.3, 3.7$ Hz, 2H), 3.33 -3.14 (m, 2H), 2.85 - 2.67 (m, 1H), 2.60 (t, $J=7.3$ Hz, 2H), 2.14 - 1.88 (m, 5H), 1.64 - 1.34 (m, 4H), 1.07 - 0.83 (m, 3H).
59		Cyclopropyl-{1-[3-(1,1-difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-amine	1H NMR δ_H (301MHz, $CDCl_3$): 4.10 (dt, $J=13.3, 3.9$ Hz, 2H), 3.32 - 3.14 (m, 2H), 2.96 - 2.77 (m, 1H), 2.20 - 2.08 (m, 1H), 2.08 - 1.90 (m, 4H), 1.62 - 1.36 (m, 3H), 0.52 - 0.43 (m, 2H), 0.38 - 0.29 (m, 2H).
60		{1-[3-(1,1-Difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-(2,2,2-trifluoroethyl)-amine	RT = 0.79 min; m/z (ES^+) = 315.4 [$M + H$] $^+$ (LCMS Method - 4).
61		{1-[3-(1,1-Difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-(2-methoxyethyl)-amine	RT = 1.49 min; m/z (ES^+) = 291.4 [$M + H$] $^+$ (LCMS Method - 5).
62		Cyclopropyl-{1-[3-((S)-1-methoxy-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-amine	RT = 1.40 min; m/z (ES^+) = 267.5 [$M + H$] $^+$ (LCMS Method - 5).
63		Cyclopropyl-[1-(3-methoxymethyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-amine	RT = 0.42 min; m/z (ES^+) = 253.26 [$M + H$] $^+$ (LCMS Method - 2).

Preparation 64: 5-Trichloromethyl-[1,2,4]oxadiazole-3-carboxylic acid ethyl ester

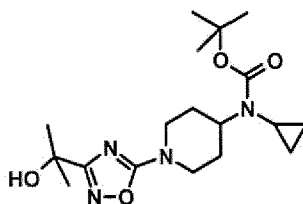
To a suspension of ethyl-2-oximinooxamate (1.26g, 9.54mmol) in toluene (13mL, 120mmol) was added perchloroacetic anhydride (1.74mL, 9.54mmol) and the resulting reaction mixture was heated at 110 °C for 17 h, prior to removal of the solvent *in vacuo*. The residue was dissolved in EtOAc (80mL), washed with saturated aqueous NaHCO₃ solution (2x) and concentrated *in vacuo* to afford the title compound: ¹H NMR δ_H (400 MHz, CDCl₃): 4.58 (q, *J*=7.29 Hz, 2 H), 1.50 (t, *J*=7.22 Hz, 3 H).

Preparation 65: 5-[4-(*tert*-Butoxycarbonyl-cyclopropyl-amino)-piperidin-1-yl]-[1,2,4]oxadiazole-3-carboxylic acid ethyl ester



To a solution of cyclopropyl-piperidin-4-yl-carbamic acid *tert*-butyl ester (**Preparation 19**: 1.0g, 4.2mmol) in DMF (5.0mL) under an argon atmosphere was added trichloromethyl-[1,2,4]oxadiazole-3-carboxylic acid ethyl ester (**Preparation 64**, 0.7g, 3mmol) and the reaction mixture heated to 50 °C for 2.5 h. The reaction was diluted with EtOAc before washing with water (2x) and finally brine. The EtOAc layer was dried over magnesium sulfate before filtering and concentrating *in vacuo*. Purification by column chromatography (2:1 – 3:2 heptane:EtOAc) afforded the title compound: RT = 1.23 min; *m/z* (ES⁺) = 381.36 [*M* + H]⁺ (LCMS Method - 2).

Preparation 66: Cyclopropyl-{1-[3-(1-hydroxy-1-methyl-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-carbamic acid *tert*-butyl ester

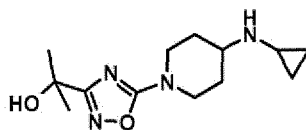


To a solution of 5-[4-(*tert*-butoxycarbonyl-cyclopropyl-amino)-piperidin-1-yl]-[1,2,4]oxadiazole-3-carboxylic acid ethyl ester (**Preparation 65**, 380mg, 1.0mmol) in anhydrous THF (8mL) at -20°C was added a solution of methylmagnesium bromide in diethyl ether (3M, 1.6mL, 5.0mmol). The reaction was allowed to stir at -20 °C for 1.5 h before the addition of a

saturated aqueous solution of ammonium chloride. The mixture was concentrated *in vacuo* and the residue partitioned between EtOAc and water. The organics were washed with water and brine then dried (MgSO₄), filtered and concentrated *in vacuo* to afford the title compound: RT = 1.04 min; *m/z* (ES⁺) = 367.37 [M + H]⁺ (LCMS Method - 2).

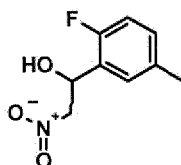
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Preparation 67: 2-[5-(4-Cyclopropylamino-piperidin-1-yl)-[1,2,4]oxadiazol-3-yl]-propan-2-ol



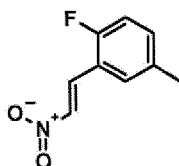
To a solution of cyclopropyl-{1-[3-(1-hydroxy-1-methyl-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-carbamic acid *tert*-butyl ester (**Preparation 66**, 20mg, 0.05mmol) in DCM (400μL) at 0 °C was added TFA (100μL, 1mmol). The reaction mixture was allowed to stir for 1 h before concentrating *in vacuo*. The residue was dissolved in MeOH and loaded onto a SCX cartridge. The product was eluted with a 7M ammonia in MeOH solution and concentrated *in vacuo* to afford the title compound: RT = 0.44 min; *m/z* (ES⁺) = 267.30 [M + H]⁺ (LCMS Method - 2).

Preparation 68: 1-(2-Fluoro-5-methyl-phenyl)-2-nitro-ethanol



To a solution of 2-fluoro-5-methyl-benzaldehyde (5.0g, 36.2mmol) and nitromethane (2.35mL, 43.5mmol) in MeOH (90mL) at 0 °C was added a solution of NaOH (1.52g, 38.0mmol) in H₂O (15mL) dropwise over 10 min and the resulting reaction mixture was stirred at r.t. for 50 min. The reaction mixture was poured into saturated aqueous NH₄Cl solution and extracted with DCM (3 x). The combined organics were washed with brine, dried (MgSO₄), filtered and concentrated *in vacuo* to afford the title compound: ¹H NMR δ_H (300MHz, CDCl₃): 7.34-7.30 (m, 1H), 7.15-7.10 (m, 1H), 7.0-6.9 (m, 1H), 5.71-5.70 (m, 1H), 4.63-4.57 (m, 2H), 2.93 (br. s, 1H), 2.33 (s, 3H).

Preparation 69: 1-Fluoro-4-methyl-2-((E)-2-nitro-vinyl)-benzene



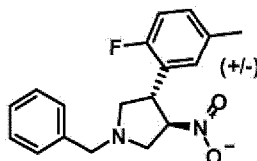
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To a solution of 1-(2-fluoro-5-methyl-phenyl)-2-nitro-ethanol (**Preparation 68**, 7.18g, 36.1mmol) in acetic anhydride (6.8mL, 22.2mmol) was added DMAP (300mg, 2.5mmol) and the resulting reaction mixture was stirred at r.t. for 19 h. The reaction mixture was slowly poured into

saturated aqueous NaHCO_3 solution and stirred vigorously for 1 h. The solid was collected by filtration, washing with saturated aqueous NaHCO_3 solution, then H_2O to afford the title compound: ^1H NMR δ_{H} (300MHz, CDCl_3): 8.04-7.99 (d, $J=13.76$ Hz, 1H), 7.74-7.69 (d, $J=13.76$ Hz, 1H), 7.30-7.26 (m, 2H), 7.1-7.0 (m, 1H), 2.36 (s, 3H).

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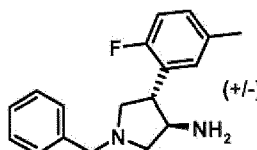
Preparation 70: (*trans*)-1-Benzyl-3-(2-fluoro-5-methyl-phenyl)-4-nitro-pyrrolidine



To a solution of 1-fluoro-4-methyl-2-((*E*)-2-nitro-vinyl)-benzene (**Preparation 68**, 6.38g, 35.3mmol) in DCM (70mL) at 10 °C was added TFA (0.27mL, 3.52mmol), followed by dropwise addition of *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine (9.52mL, 38.8mmol) in DCM (30mL). The resulting reaction mixture was stirred at r.t. for 1.5 h, poured into saturated aqueous NaHCO_3 solution and extracted with DCM (3 x). The combined organic extracts were washed with brine, dried (MgSO_4), filtered and concentrated *in vacuo* to afford the title compound: ^1H NMR δ_{H} (300MHz, CDCl_3): 7.35-7.26 (m, 5H), 7.1-7.0 (m, 2H), 7.0-6.9 (m, 1H), 5.04-5.02 (m, 1H), 4.17-4.15 (m, 1H), 3.77-3.65 (m, 2H), 3.5-3.46 (m, 1H), 3.3-3.26 (m, 1H), 3.1-3.0 (m, 1H), 2.65-2.60 (m, 1H), 2.30 (s, 3H).

15

Preparation 71: (*trans*)-Benzyl-4-(2-fluoro-5-methyl-phenyl)-pyrrolidin-3-ylamine



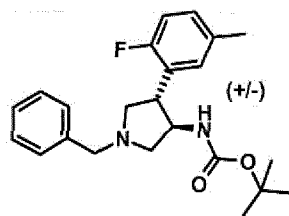
20

To a solution of (*trans*)-1-benzyl-3-(2-fluoro-5-methyl-phenyl)-4-nitro-pyrrolidine (**Preparation 70**, 11.4g, 35.3mmol) in AcOH (90mL) at 30 °C was added zinc (13.8g, 212mmol) portion wise over 30 min. The resulting reaction mixture was stirred at 30 °C for 1 h, then filtered through celite washing with AcOH. The filtrate was concentrated *in vacuo*, the remainder dissolved in DCM (30mL) and poured slowly into saturated aqueous NaHCO_3 solution (900mL). The resulting mixture was stirred at r.t. for 16 h, the layers separated and the aqueous extracted with DCM (2 x). The combined organic extracts were dried (MgSO_4), filtered and concentrated *in vacuo*. Purification by column chromatography (DCM:MeOH, 19:1 to 9:1 to 17:3 to 4:1 to 7:3 to 3:2) afforded the title compound: RT = 3.06 min; m/z (ES^+) = 285.1 [$M + \text{H}$] $^+$ (LCMS Method - 3).

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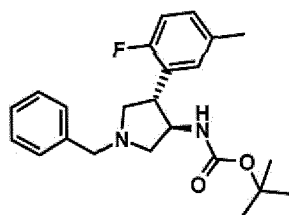
30

Preparation 72: [(*trans*)-1-Benzyl-4-(2-fluoro-5-methyl-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester



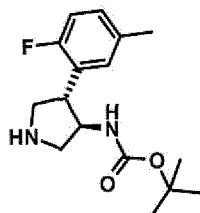
To a solution of (*trans*)-benzyl-4-(2-fluoro-5-methyl-phenyl)-pyrrolidin-3-ylamine (**Preparation 71**, 5.6g, 19.7mmol) in THF (80mL) at 0 °C was added triethylamine (5.65mL, 40mmol) and di-*tert*-butyldicarbonate (5.15g, 23.6mmol) in THF (30mL) and the resulting reaction mixture was stirred at r.t. for 21 h. The reaction mixture was poured into water, extracted with EtOAc (3 x) and the combined organic extracts washed with brine, dried (MgSO₄), filtered and concentrated *in vacuo*. The resulting oil was dissolved in IH, allowed to stand at r.t. and the solid collected by filtration, washing with IH, to afford the title compound; RT = 3.36 min; *m/z* (ES⁺) = 385.1 [*M* + H]⁺ (LCMS Method - 3).

Preparation 73: [(3*R*,4*S*)-1-Benzyl-4-(2-fluoro-5-methyl-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester



The title compound was afforded via chiral HPLC separation of [(*trans*)-1-benzyl-4-(2-fluoro-5-methyl-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester (**Preparation 72**): IH:IPA:DEA 96:4:0.1, 15ml/min, 270nm, RT = 8.2 min.

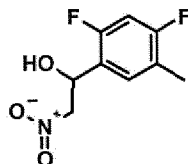
Preparation 74: [(3*R*,4*S*)-4-(2-Fluoro-5-methyl-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester



A solution of [(3*R*,4*S*)-1-benzyl-4-(2-fluoro-5-methyl-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester (**Preparation 73**, 2.4g, 6.2mmol) in MeOH (124mL) was passed through an H-Cube apparatus (10% Pd/C Catcart 70, 100 bar, 50 °C) at a flow rate of 1mL per min. The solvent was

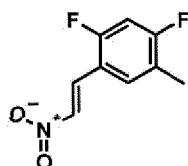
removed *in vacuo* to afford the title compound: RT = 2.42 min; m/z (ES⁺) = 295.32 [$M + H$]⁺.

Preparation 75: 1-(2,4-Difluoro-5-methyl-phenyl)-2-nitro-ethanol



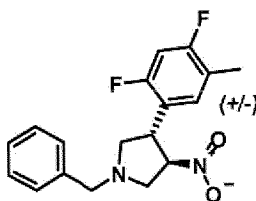
To a solution of 2,4-difluoro-5-methyl-benzaldehyde (15.0g, 96.1mmol) and nitromethane (7.33g, 120mmol) in IPA (150mL) at 0°C was added a solution of NaOH (5.22g, 131mmol) in H₂O (20mL) dropwise over 10 min and the resulting reaction mixture was stirred at r.t. for 1 h. Water (90mL) and saturated aqueous NH₄Cl solution (105mL) were added and extracted with DCM (3 x 250mL). The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by column chromatography (IH:EtOAc, 9:1 to 7:1 to 4:1 to 3:1) afforded the title compound: ¹H NMR δ_H (300MHz, CDCl₃): 7.38-7.34 (m, 1H), 6.82-6.76 (m, 1H), 5.69-5.66 (m, 1H), 4.61-4.51 (m, 2H), 2.95 (s, 1H), 2.28 (s, 3H).

Preparation 76: 1,5-Difluoro-2-methyl-4-((E)-2-nitro-vinyl)-benzene

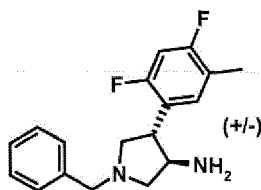


The title compound was synthesized from 1-(2,4-difluoro-5-methyl-phenyl)-2-nitro-ethanol (**Preparation 75**, 14.5g, 66.9mmol) employing a procedure similar to that outlined in **Preparation 69**: ¹H NMR δ_H (400MHz, CDCl₃): 7.99-7.96 (d, $J=13.73$ Hz, 1H), 7.68-7.65 (d, $J=13.73$ Hz, 1H), 7.34-7.3 (m, 1H), 6.91-6.89 (m, 1H), 2.27 (s, 3H).

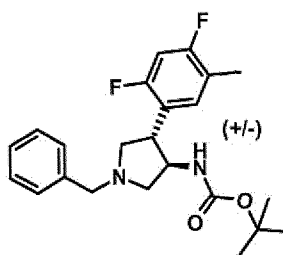
Preparation 77: (trans)-1-Benzyl-3-(2,4-difluoro-5-methyl-phenyl)-4-nitro-pyrrolidine



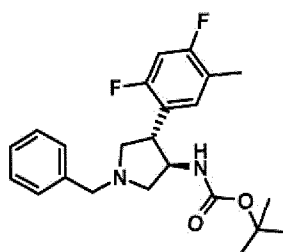
The title compound was synthesized from 1,5-difluoro-2-methyl-4-((E)-2-nitro-vinyl)-benzene (**Preparation 76**, 12.0g, 60.3mmol) employing a procedure similar to that outlined in **Preparation 70**: RT = 1.00 min; m/z (ES⁺) = 333.2 [$M + H$]⁺ (LCMS Method - 4).

Preparation 78: (*trans*)-1-Benzyl-4-(2,4-difluoro-5-methyl-phenyl)-pyrrolidin-3-ylamine

The title compound was synthesized from (*trans*)-1-benzyl-3-(2,4-difluoro-5-methyl-phenyl)-4-nitro-pyrrolidine (**Preparation 77**, 21.0g, 63.3mmol) employing a procedure similar to that outlined in **Preparation 71**: RT = 0.93 min; m/z (ES^+) = 303.2 [$M + H$] $^+$ (LCMS Method - 4).

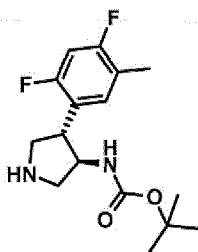
Preparation 79: [(*trans*)-1-Benzyl-4-(2,4-difluoro-5-methyl-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester

The title compound was synthesised from (*trans*)-1-benzyl-4-(2,4-difluoro-5-methyl-phenyl)-pyrrolidin-3-ylamine (**Preparation 78**, 9.5g, 31.5mmol) employing a procedure similar to that outlined in **Preparation 72**: RT = 3.25 min; m/z (ES^+) = 403.3 [$M + H$] $^+$ (LCMS Method - 5).

Preparation 80: [(3*R*,4*S*)-1-Benzyl-4-(2,4-difluoro-5-methyl-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester

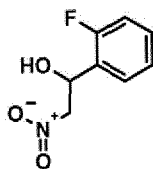
The title compound was afforded via chiral HPLC separation of [(*trans*)-1-benzyl-4-(2,4-difluoro-5-methyl-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester (**Preparation 79**): IH:IPA:DEA 96:4:0.1, 15ml/min, 270nm, RT = 9.0 min.

Preparation 81: [(3*R*,4*S*)-4-(2,4-Difluoro-5-methyl-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester



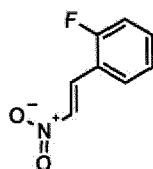
A solution of [(3*R*,4*S*)-1-benzyl-4-(2,4-difluoro-5-methyl-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester (**Preparation 80**, 1.97g, 4.9mmol) in MeOH (100 mL) was passed through an H-Cube apparatus (10% Pd/C Catcart 70, 80 bar, 50 °C) at a flow rate of 1mL per min. The solvent was removed *in vacuo* to afford the title compound: RT = 0.68 min; m/z (ES^+) = 313.32 [$M + H$] $^+$ (LCMS Method - 2).

Preparation 82: 1-(2-Fluoro-phenyl)-2-nitro-ethanol

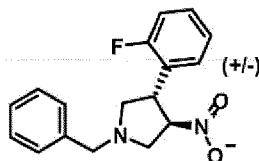


The title compound was synthesized from 2-fluoro-benzaldehyde (41g, 330mmol) employing a procedure similar to that outlined in **Preparation 68**: 1H NMR δ_H (300MHz, $CDCl_3$): 7.60-7.50 (m, 1H), 7.40-7.29 (m, 1H), 7.23-7.13 (1H, m), 7.12-7.01 (m, 1H), 5.8-5.68 (m, 1H), 4.69-4.52 (m, 2H), 3.15-3.0 (m, 1H).

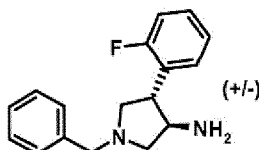
Preparation 83: 1-Fluoro-2-((*E*)-2-nitro-vinyl)-benzene



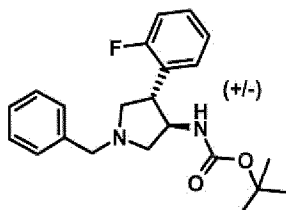
The title compound was synthesized from 1-(2-fluoro-phenyl)-2-nitro-ethanol (**Preparation 82**, 59g, 319mmol) employing a procedure similar to that outlined in **Preparation 69**: 1H NMR δ_H (400MHz, $CDCl_3$): 8.05 (d, $J=13.79$ Hz, 1H), 7.72 (d, $J=13.79$ Hz, 1H), 7.55-7.42 (m, 2H), 7.28-7.12 (m, 2H).

Preparation 84: (*trans*)-1-Benzyl-3-(2-fluoro-phenyl)-4-nitro-pyrrolidine

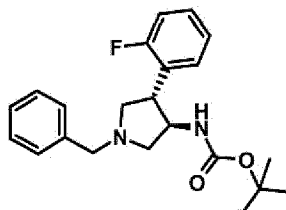
The title compound was synthesized from 1-fluoro-2-((*E*)-2-nitro-vinyl)-benzene (**Preparation 83**, 26.5g, 159mmol) employing a procedure similar to that outlined in **Preparation 70**: RT = 0.90 min; m/z (ES^+) = 301.2 [$M + H$] $^+$ (LCMS Method - 4).

Preparation 85: (*trans*)-1-Benzyl-4-(2-fluoro-phenyl)-pyrrolidin-3-ylamine

The title compound was synthesized from (*trans*)-1-benzyl-3-(2-fluoro-phenyl)-4-nitro-pyrrolidine (**Preparation 84**, 54.5g, 181mmol) employing a procedure similar to that outlined in **Preparation 71**: RT = 0.75 min; m/z (ES^+) = 271.2 [$M + H$] $^+$ (LCMS Method - 4).

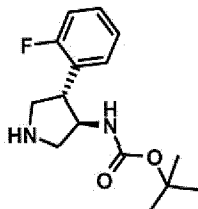
Preparation 86: [(*trans*)-1-Benzyl-4-(2-fluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester

The title compound was synthesised from (*trans*)-1-benzyl-4-(2-fluoro-phenyl)-pyrrolidin-3-ylamine (**Preparation 85**, 11.7g, 43.3mmol) employing a procedure similar to that outlined in **Preparation 72**: RT = 3.00 min; m/z (ES^+) = 371.3 [$M + H$] $^+$ (LCMS Method - 5).

Preparation 87: [(3*R*,4*S*)-1-Benzyl-4-(2-fluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester

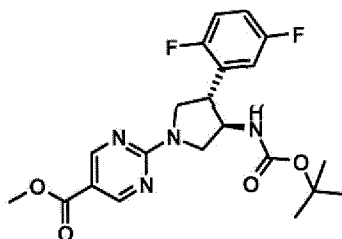
The title compound was afforded via chiral HPLC separation of [(*trans*)-1-benzyl-4-(2-fluorophenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester (**Preparation 86**): IH:IPA:n-butylamine 96:4:0.1, 15ml/min, 270nm, RT = 10.6 min.

5 **Preparation 88: [(3*R*,4*S*)-4-(2-Fluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester**



The title compound was synthesised from [(3*R*,4*S*)-1-benzyl-4-(2-fluorophenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester (**Preparation 87**, 880mg, 2.37mmol) employing a procedure similar to that outlined in **Preparation 74**: RT = 0.63 min; m/z (ES^+) = 281.3 [$M + H$] $^+$ (LCMS
10 Method - 2).

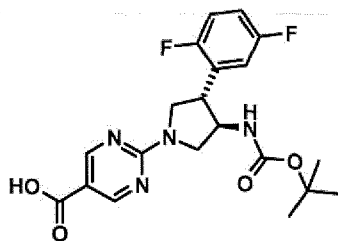
Preparation 89: 2-[(3*R*,4*S*)-3-*tert*-Butoxycarbonylamino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid methyl ester



15 To a solution of 2-chloro-pyrimidine-5-carboxylic acid methyl ester (2.1g, 12mmol) and [(3*R*,4*S*)-4-(2,5-difluorophenyl)pyrrolidin-3-yl]carbamic acid *tert*-butyl ester (**Preparation 206**, 4.0g, 13mmol) in DCE (100mL) was added triethylamine (3.3mL, 23mmol) and the resulting reaction mixture was stirred at r.t. for 16 h. The reaction mixture was diluted with DCM (200mL), washed with water (200mL) and brine (400mL), dried (MgSO₄), filtered and concentrated *in vacuo*.
20 The remainder was triturated with MeOH and the solid collected by filtration to afford the title compound: RT = 3.95 min; m/z (ES^+) = 435.18 [$M + H$] $^+$.

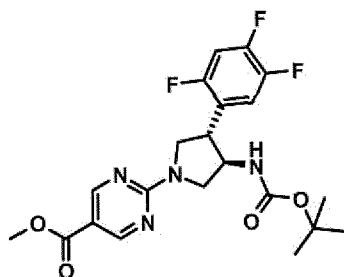
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Preparation 90: 2-[(3*R*,4*S*)-3-*tert*-Butoxycarbonylamino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid



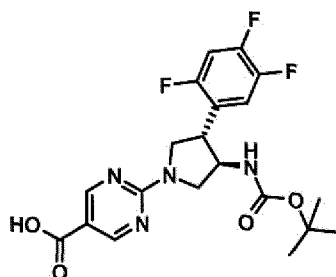
To a solution of 2-[(3*R*,4*S*)-3-*tert*-butoxycarbonylamino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid methyl ester (**Preparation 89**, 3.89g, 8.95mmol) in THF (100mL) was added aqueous NaOH solution (1M, 50mL, 50mmol) and the resulting reaction mixture was stirred at r.t. for 16 h. The reaction mixture was acidified to pH 6 using 2M aqueous HCl solution and extracted with EtOAc (3 x 200mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo*. The remainder was triturated with Et₂O and the solid collected by filtration to afford the title compound: RT = 3.50 min; *m/z* (ES⁺) = 421.19 [*M* + H]⁺.

Preparation 91: 2-[(3*R*,4*S*)-3-*tert*-Butoxycarbonylamino-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid methyl ester



The title compound was synthesized from 2-chloro-pyrimidine-5-carboxylic acid methyl ester (350mg, 3.85mmol) and [(3*R*,4*S*)-4-(2,4,5-trifluorophenyl)pyrrolidin-3-yl]carbamic acid *tert*-butyl ester (**Preparation 212**, 784mg, 2.48mmol) employing a procedure similar to that outlined in **Preparation 89**: RT = 1.29 min; *m/z* (ES⁺) = 453.00 [*M* + H]⁺ (LCMS Method - 2).

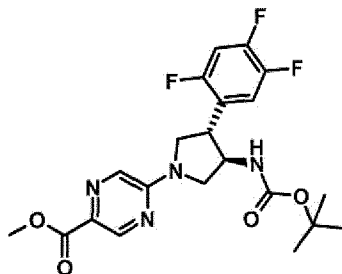
Preparation 92: 2-[(3*R*,4*S*)-3-*tert*-Butoxycarbonylamino-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid



The title compound was synthesized from 2-[(3*R*,4*S*)-3-*tert*-butoxycarbonylamino-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid methyl ester (**Preparation 91**, 820mg, 1.8mmol) employing a procedure similar to that outlined in **Preparation 90**: RT = 1.11 min; m/z (ES^+) = 439.3 [$M + H$] $^+$ (LCMS Method - 2).

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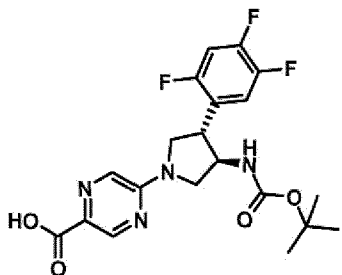
Preparation 93: 5-[(3*R*,4*S*)-3-*tert*-Butoxycarbonylamino-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-1-yl]-pyrazine-2-carboxylic acid methyl ester



The title compound was synthesized from 2,5-chloro-pyrazine-2-carboxylic acid methyl ester (292mg, 1.69mmol) and [(3*R*,4*S*)-4-(2,4,5-trifluorophenyl)pyrrolidin-3-yl]carbamic acid *tert*-butyl ester (**Preparation 212**, 1.07g, 3.38mmol) employing a procedure similar to that outlined in **Preparation 89**: RT = 1.18 min; m/z (ES^+) = 453.38 [$M + H$] $^+$ (LCMS Method - 2).

Preparation 94: 5-[(3*R*,4*S*)-3-*tert*-Butoxycarbonylamino-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-1-yl]-pyrazine-2-carboxylic acid

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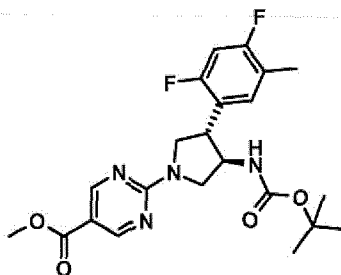


The title compound was synthesized from 5-[(3*R*,4*S*)-3-*tert*-butoxycarbonylamino-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-1-yl]-pyrazine-2-carboxylic acid methyl ester (**Preparation 93**, 400mg, 0.884mmol) employing a procedure similar to that outlined in **Preparation 90**: RT = 1.05 min; m/z (ES^+) = 439.33 [$M + H$] $^+$ (LCMS Method - 2).

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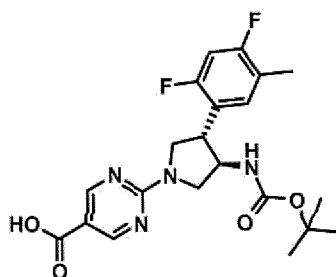
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Preparation 95: 2-[(3*R*,4*S*)-3-*tert*-Butoxycarbonylamino-4-(2,4-difluoro-5-methyl-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid methyl ester



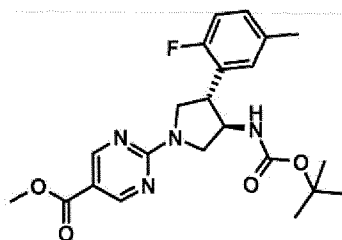
The title compound was synthesized from 2-chloro-pyrimidine-5-carboxylic acid methyl ester (295mg, 1.71mmol) and [(3*R*,4*S*)-4-(2,4-difluoro-5-methyl-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester (**Preparation 81**, 640mg, 2.05mmol) employing a procedure similar to that outlined in **Preparation 89**: RT = 1.33 min; m/z (ES^+) = 449.38 [$M + H$] $^+$ (LCMS Method - 2).

Preparation 96: 2-[(3*R*,4*S*)-3-*tert*-Butoxycarbonylamino-4-(2,4-difluoro-5-methyl-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid



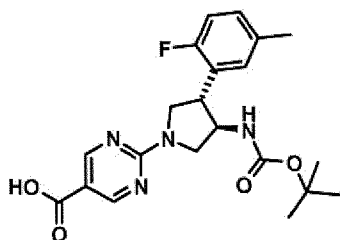
To a solution of 2-[(3*R*,4*S*)-3-*tert*-butoxycarbonylamino-4-(2,4-difluoro-5-methyl-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid methyl ester (**Preparation 95**, 767mg, 1.71mmol) in THF (5.5mL), MeOH (2.8mL) and water (2.5mL) was added lithium hydroxide monohydrate (86.1mg, 2.05mmol) and the resulting reaction mixture was heated at 30 °C for 5.5 h. The solvent was removed *in vacuo*, water was added and the mixture acidified to pH 1 with aqueous HCl solution (1M) prior to extraction with EtOAc. The organic extract was dried (MgSO₄), filtered and concentrated *in vacuo* to afford the title compound: RT = 1.14 min; m/z (ES^+) = 435.39 [$M + H$] $^+$ (LCMS Method - 2).

Preparation 97: 2-[(3*R*,4*S*)-3-*tert*-Butoxycarbonylamino-4-(2-fluoro-5-methyl-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid methyl ester



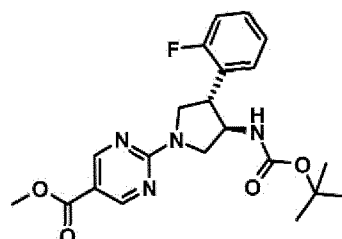
The title compound was synthesized from 2-chloro-pyrimidine-5-carboxylic acid methyl ester (375mg, 2.17mmol) and [(3*R*,4*S*)-4-(2-fluoro-5-methyl-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester (**Preparation 74**, 704mg, 2.39mmol), employing a procedure similar to that outlined in **Preparation 89**: RT = 1.32 min; m/z (ES^+) = 431.39 [$M + H$] $^+$ (LCMS Method - 2).

Preparation 98: 2-[(3*R*,4*S*)-3-*tert*-Butoxycarbonylamino-4-(2-fluoro-5-methyl-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid



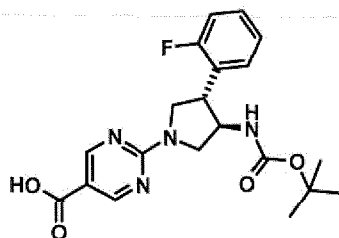
The title compound was synthesized from 2-[(3*R*,4*S*)-3-*tert*-butoxycarbonylamino-4-(2-fluoro-5-methyl-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid methyl ester (**Preparation 97**, 850mg, 2.0mmol), employing a procedure similar to that outlined in **Preparation 90**: RT = 1.13 min; m/z (ES^+) = 417.38 [$M + H$] $^+$ (LCMS Method - 2).

Preparation 99: 2-[(3*R*,4*S*)-3-*tert*-Butoxycarbonylamino-4-(2-fluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid methyl ester



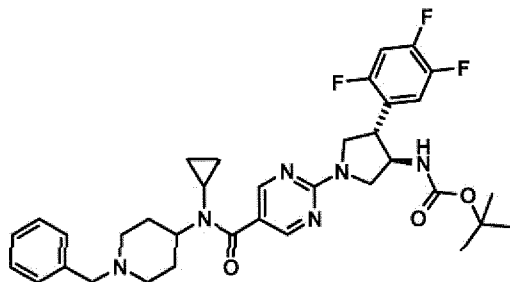
The title compound was synthesized from 2-chloro-pyrimidine-5-carboxylic acid methyl ester (271mg, 1.57mmol) and [(3*R*,4*S*)-4-(2-fluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester (**Preparation 88**, 440mg, 1.57mmol), employing a procedure similar to that outlined in **Preparation 89**: RT = 1.24 min; m/z (ES^+) = 417.33 [$M + H$] $^+$ (LCMS Method - 2).

Preparation 100: 2-[(3*R*,4*S*)-3-*tert*-butoxycarbonylamino-4-(2-fluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid



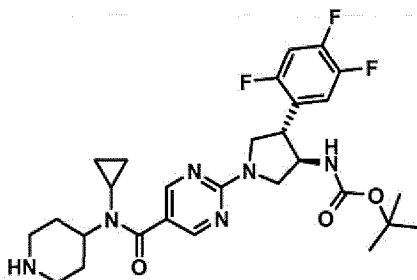
The title compound was synthesized from 2-[(3*R*,4*S*)-3-*tert*-butoxycarbonylamino-4-(2-fluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid methyl ester (**Preparation 99**, 460mg, 1.1mmol), employing a procedure similar to that outlined in **Preparation 90**: RT = 1.06 min; m/z (ES^+) = 403.30 [$M + H$] $^+$ (LCMS Method - 2).

Preparation 101: [(3*R*,4*S*)-1-{5-[(1-Benzyl-piperidin-4-yl)-cyclopropyl-carbamoyl]-pyrimidin-2-yl}-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester



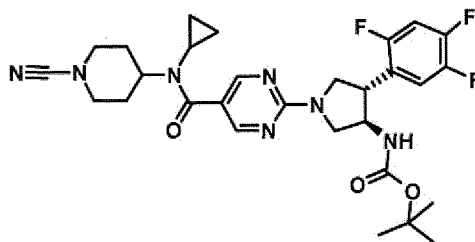
To a solution of 2-[(3*R*,4*S*)-3-*tert*-butoxycarbonylamino-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid (**Preparation 92**, 400mg, 900 μ mol) in THF (12mL) was added EDCI (289mg, 1.50mmol), HOBt (2.30mg, 1.50mmol) and DIPEA (421 μ L, 2.42mmol). The resulting reaction mixture was stirred at r.t. for 20 min prior to the addition of (1-benzyl-piperidin-4-yl)-cyclopropyl-amine (320mg, 1.4mmol) in THF (3mL) and the resulting reaction mixture was stirred at r.t. for 16 h. The solvent was removed *in vacuo*, then the residue was dissolved in EtOAc, washed with aqueous NaOH solution (2M, 2 x) and brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (EtOAc) afforded a crude product which was dissolved in DCM and added to an SCX cartridge. The SCX cartridge was washed with MeOH then eluted with 7M NH_3 in MeOH and the basic fraction was concentrated *in vacuo* to afford the title compound: RT = 0.93 min; m/z (ES^+) = 651.57 [$M + H$] $^+$ (LCMS Method - 2).

Preparation 102: [(3*R*,4*S*)-1-[5-(Cyclopropyl-piperidin-4-yl-carbamoyl)-pyrimidin-2-yl]-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester



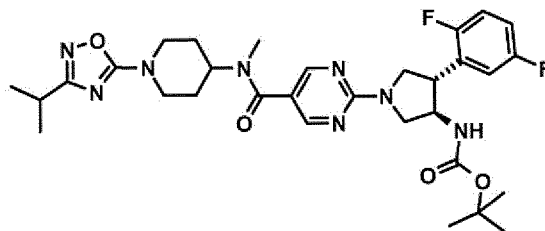
A solution of [(3*R*,4*S*)-1-{5-[(1-benzyl-piperidin-4-yl)-cyclopropyl-carbamoyl]-pyrimidin-2-yl}-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester (**Preparation 101**, 162mg, 249μmol) in EtOH (5mL) was reacted on the H-cube cube (10% Pd/C Catcart 70, 50 bar, 70 °C) at a flow rate of 1 mL/min. The resulting solution was concentrated *in vacuo* and the remainder was re-dissolved in EtOH (25mL) and reacted on the H-cube (10% Pd/C Catcart 70, 100 bar, 75 °C) at a flow rate of 1 mL/min. The resulting solution was concentrated *in vacuo* and the remainder was re-dissolved in EtOH (35mL) and reacted on the H-cube (10% Pd/C Catcart 70, 100 bar, 80 °C) at a flow rate of 0.7 mL/min. The resulting solution was concentrated *in vacuo* to afford the title compound: RT = 0.81 min; *m/z* (ES⁺) = 561.57 [*M* + H]⁺ (LCMS Method - 2).

Preparation 103: [(3*R*,4*S*)-1-{5-[(1-Cyano-piperidin-4-yl)-cyclopropyl-carbamoyl]-pyrimidin-2-yl}-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester



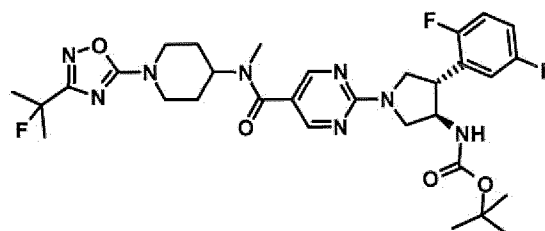
To a solution of [(3*R*,4*S*)-1-[5-(cyclopropyl-piperidin-4-yl-carbamoyl)-pyrimidin-2-yl]-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester (**Preparation 102**, 78.2mg, 139μmol) in DCM (500μL) was added a slurry of NaHCO₃ (35mg, 420μmol) in water (400μL), followed by cyanogen bromide (18mg, 170μmol) in DCM (500μL). The resulting reaction mixture was stirred at r.t. for 1.25 h, then diluted with DCM and water. The layers were separated, the aqueous layer extracted with DCM (3 x) and the combined organic extracts were washed with brine, dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by column chromatography (EtOAc:IH, 4:1) afforded the title compound: RT = 1.16 min; *m/z* (ES⁺) = 586.52 [*M* + H]⁺ (LCMS Method - 2).

Preparation 104: [(3*R*,4*S*)-4-(2,5-Difluoro-phenyl)-1-(5-{[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-methyl-carbamoyl}-pyrimidin-2-yl)-pyrrolidin-3-yl]-carbamic ester *tert*-butyl ester



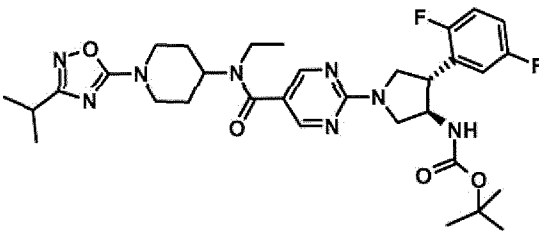
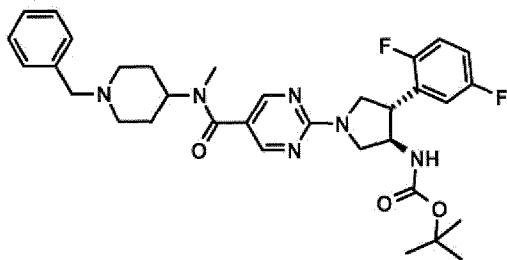
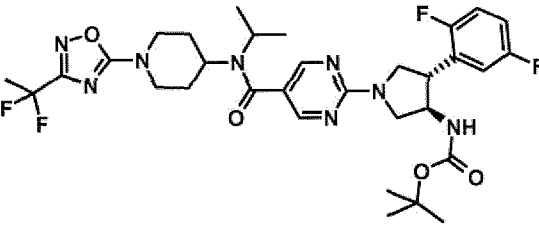
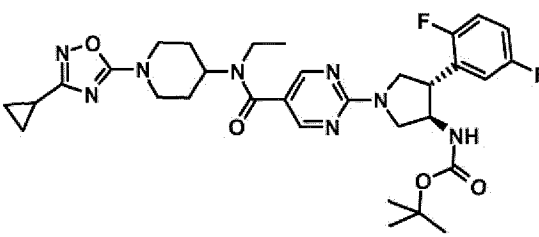
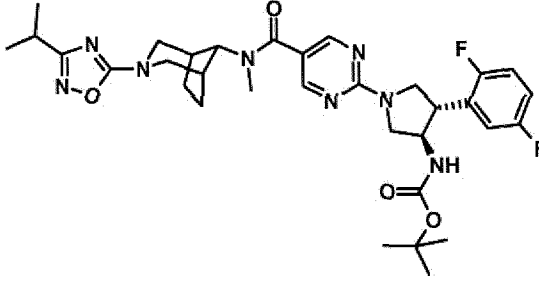
5 To a solution of 2-[(3*R*,4*S*)-3-*tert*-butoxycarbonylamino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid (**Preparation 90**, 120mg, 280μmol) in THF (4mL) was added EDCI (71.1mg, 371μmol), HOBt (56.8mg, 371μmol) and DIPEA (99.4μL, 571μmol). The resulting reaction mixture was stirred at r.t. for 20 min prior to the addition of [1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-methyl-amine (**Preparation 35**, 96.0mg, 428μmol), then
 10 stirred at r.t. for 16 h. The solvent was removed *in vacuo* and the remainder dissolved in EtOAc, washed with aqueous NaOH solution (2M, 2 x), aqueous citric acid solution (10%, 2 x) and brine, dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by column chromatography (EtOAc:IH, 4:1 to 9:1) afforded the title compound: RT = 3.87 min; *m/z* (ES⁺) = 627.33 [*M* + H]⁺.

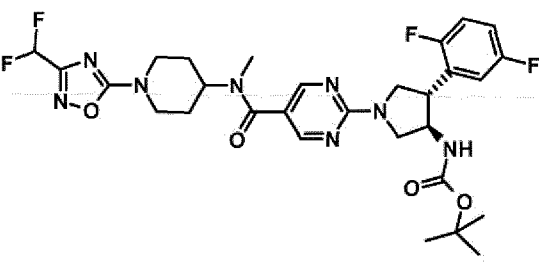
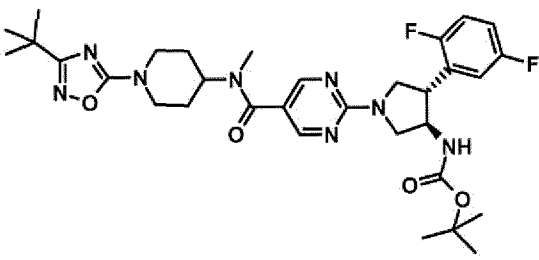
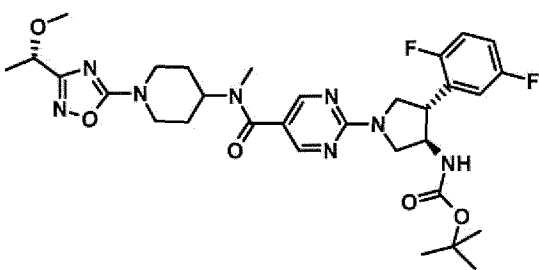
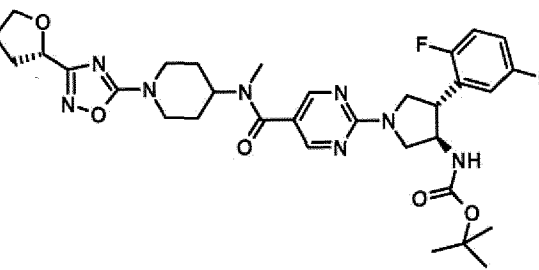
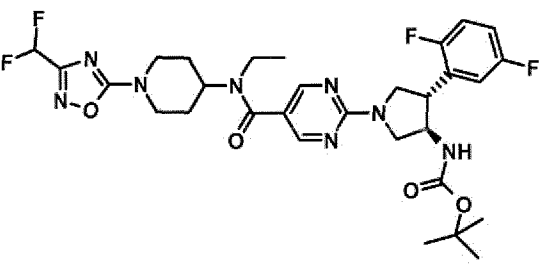
15 **Preparation 105: {(3*R*,4*S*)-4-(2,5-Difluoro-phenyl)-1-[5-({1-[3-(1-fluoro-1-methyl-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-methyl-carbamoyl)-pyrimidin-2-yl]-pyrrolidin-3-yl}-carbamic acid *tert*-butyl ester**

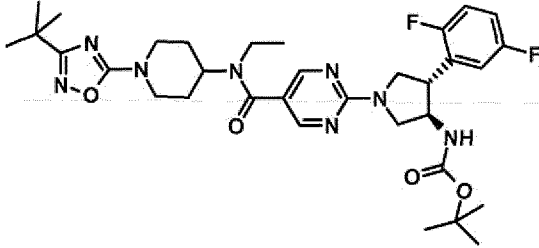
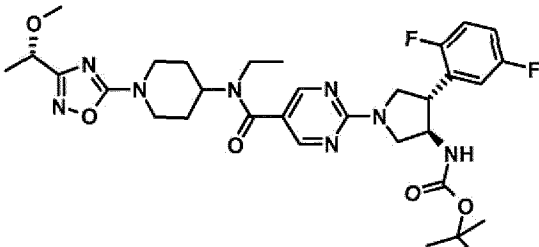
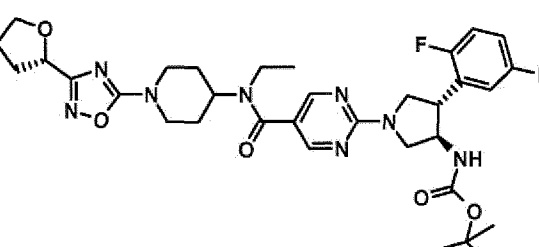
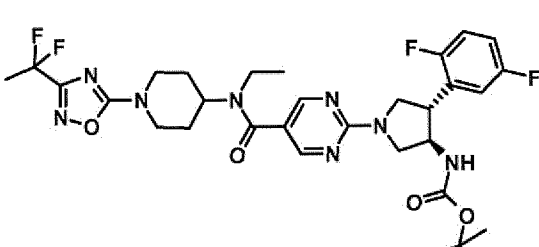
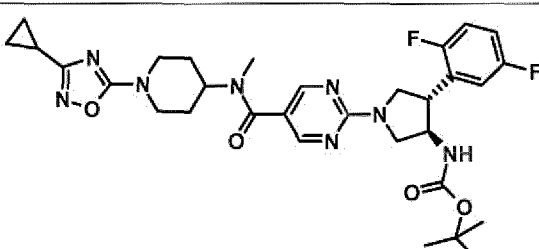


To a solution of 2-[(3*R*,4*S*)-3-*tert*-butoxycarbonylamino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid (**Preparation 90**, 70mg, 166μmol) in DCM (2mL) was added {1-[3-(1-fluoro-1-methyl-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-methyl-amine (**Preparation 46**, 40mg, 166μmol) and DIPEA (87μL, 499μmol) followed by PPA (50% w/w in EtOAc, 149μL, 250μmol). The resulting reaction mixture was stirred at r.t. under argon for 3 h. After this time the mixture was diluted with water and filtered through a hydrophobic frit and concentrated *in vacuo*.
 20 Purification by column chromatography (DCM to 2:98 MeOH:DCM) afforded the title compound: RT = 1.23 min; *m/z* (ES⁺) = 645.45 [*M* + H]⁺ ((LCMS Method - 2).

The following compounds were prepared by reacting 2-[(3*R*,4*S*)-3-*tert*-butoxycarbonylamino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid (**Preparation 90**) with the appropriate amine intermediate employing a procedure similar to that outlined in **Preparation 104**:

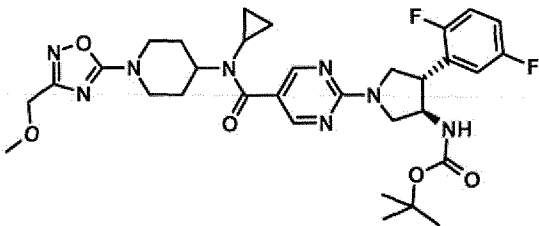
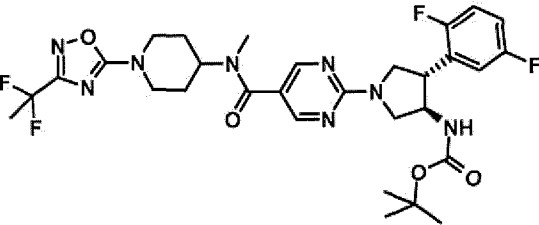
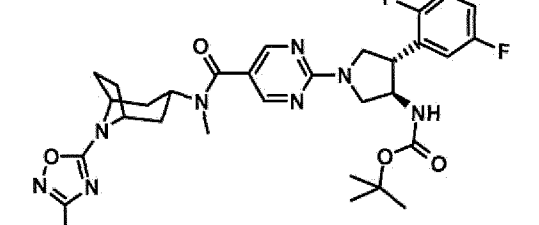
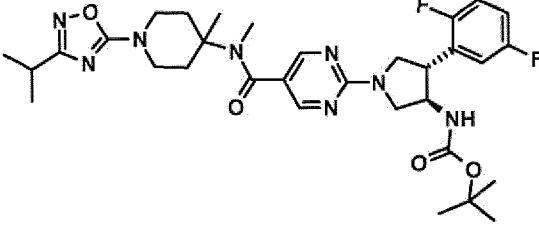
Prep.	Structure	Name	LCMS Data
106		[(3 <i>R</i> ,4 <i>S</i>)-4-(2,5-Difluoro-phenyl)-1-(5-{ethyl-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-carbamoyl}-pyrimidin-2-yl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 1.26 min; <i>m/z</i> (ES ⁺) = 641.59 [<i>M</i> + H] ⁺ (LCMS Method - 2).
107		[(3 <i>R</i> ,4 <i>S</i>)-1-{5-[(1-Benzyl-piperidin-4-yl)-methyl-carbamoyl]-pyrimidin-2-yl}-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 2.85 min; <i>m/z</i> (ES ⁺) = 607.58 [<i>M</i> + H] ⁺ .
108		(3 <i>R</i> ,4 <i>S</i>)-1-[5-({1-[3-(1,1-Difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-isopropyl-carbamoyl)-pyrimidin-2-yl]-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 1.34 min; <i>m/z</i> (ES ⁺) = 677.46 [<i>M</i> + H] ⁺ (LCMS Method - 2).
109		[(3 <i>R</i> ,4 <i>S</i>)-1-(5-{[1-(3-Cyclopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-ethyl-carbamoyl}-pyrimidin-2-yl)-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 1.25 min; <i>m/z</i> (ES ⁺) = 639.4 [<i>M</i> + H] ⁺ (LCMS Method - 2).
110		[(3 <i>R</i> ,4 <i>S</i>)-4-(2,5-Difluoro-phenyl)-1-(5-{[3-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-3-aza-bicyclo[3.2.1]oct-8-yl]-methyl-carbamoyl}-pyrimidin-2-yl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 1.29 min; <i>m/z</i> (ES ⁺) = 653.46 [<i>M</i> + H] ⁺ (LCMS Method - 2).

111		[(3 <i>R</i> ,4 <i>S</i>)-1-(5-{[1-(3-Difluoromethyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-methyl-carbamoyl}-pyrimidin-2-yl)-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 3.88 min; <i>m/z</i> (ES ⁺) = 635.16 [<i>M</i> + H] ⁺ (LCMS Method - 1).
112		[(3 <i>R</i> ,4 <i>S</i>)-1-(5-{[1-(3- <i>tert</i> -Butyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-methyl-carbamoyl}-pyrimidin-2-yl)-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 4.08 min; <i>m/z</i> (ES ⁺) = 641.23 [<i>M</i> + H] ⁺ (LCMS Method - 1).
113		{(3 <i>R</i> ,4 <i>S</i>)-4-(2,5-Difluoro-phenyl)-1-[5-(1-[3-((<i>S</i>)-1-methoxy-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl]-methyl-carbamoyl)-pyrimidin-2-yl]-pyrrolidin-3-yl}-carbamic acid <i>tert</i> -butyl ester	RT = 3.67 min; <i>m/z</i> (ES ⁺) = 643.21 [<i>M</i> + H] ⁺ (LCMS Method - 1).
114		{(3 <i>R</i> ,4 <i>S</i>)-4-(2,5-Difluoro-phenyl)-1-[5-(methyl-{1-[(<i>S</i>)-3-(tetrahydro-furan-2-yl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-carbamo-yl)-pyrimidin-2-yl]-pyrrolidin-3-yl}-carbamic acid <i>tert</i> -butyl ester	RT = 3.68 min; <i>m/z</i> (ES ⁺) = 655.23 [<i>M</i> + H] ⁺ (LCMS Method - 1).
115		[(3 <i>R</i> ,4 <i>S</i>)-1-(5-{[1-(3-Difluoromethyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-ethyl-carbamoyl}-pyrimidin-2-yl)-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 3.98 min; <i>m/z</i> (ES ⁺) = 649.16 [<i>M</i> + H] ⁺ (LCMS Method - 1).

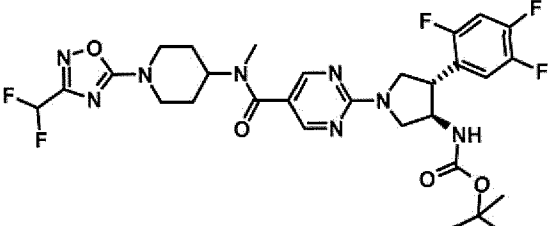
116		[(3 <i>R</i> ,4 <i>S</i>)-1-(5-{[1-(3- <i>tert</i> -Butyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-ethyl-carbamoyl}-pyrimidin-2-yl)-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 4.25 min; <i>m/z</i> (ES ⁺) = 655.25 [<i>M</i> + H] ⁺ (LCMS Method - 1).
117		{(3 <i>R</i> ,4 <i>S</i>)-4-(2,5-Difluoro-phenyl)-1-[5-(ethyl-{1-[3-((<i>S</i>)-1-methoxy-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-carbamoyl)-pyrimidin-2-yl]-pyrrolidin-3-yl}-carbamic acid <i>tert</i> -butyl ester	RT = 3.77 min; <i>m/z</i> (ES ⁺) = 657.17 [<i>M</i> + H] ⁺ (LCMS Method - 1).
118		{(3 <i>R</i> ,4 <i>S</i>)-4-(2,5-Difluoro-phenyl)-1-[5-(ethyl-{1-[(<i>S</i>)-3-(tetrahydro-furan-2-yl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-carbamoyl)-pyrimidin-2-yl]-pyrrolidin-3-yl}-carbamic acid <i>tert</i> -butyl ester	RT = 3.82 min; <i>m/z</i> (ES ⁺) = 669.16 [<i>M</i> + H] ⁺ (LCMS Method - 1).
119		[(3 <i>R</i> ,4 <i>S</i>)-1-[5-({1-[3-(1,1-Difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl]-ethyl-carbamoyl)-pyrimidin-2-yl]-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 4.14 min; <i>m/z</i> (ES ⁺) = 663.16 [<i>M</i> + H] ⁺ (LCMS Method - 1).
120		[(3 <i>R</i> ,4 <i>S</i>)-1-(5-{[1-(3-Cyclopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-methyl-carbamoyl}-pyrimidin-2-yl)-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 3.87 min; <i>m/z</i> (ES ⁺) = 625.18 [<i>M</i> + H] ⁺ (LCMS Method - 1).

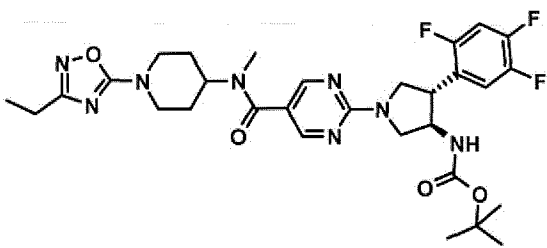
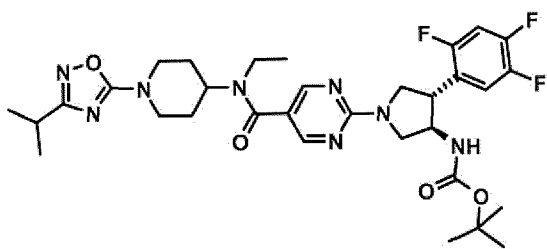
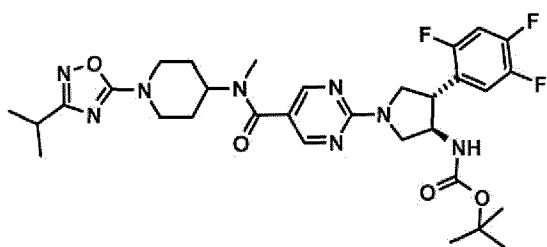
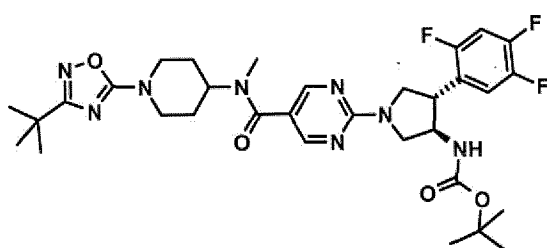
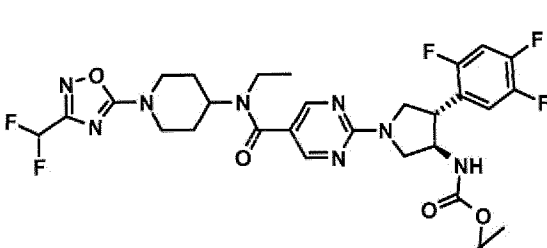
The following compounds were prepared by reacting 2-[(3*R*,4*S*)-3-*tert*-butoxycarbonylamino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid (**Preparation 90**) with the appropriate amine intermediate employing a procedure similar to that outlined in **Preparation 105**:

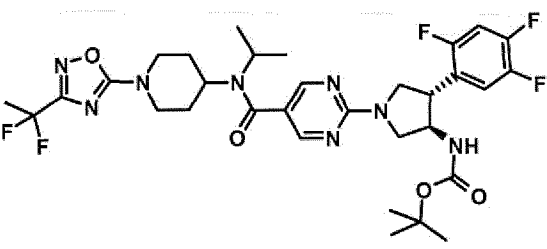
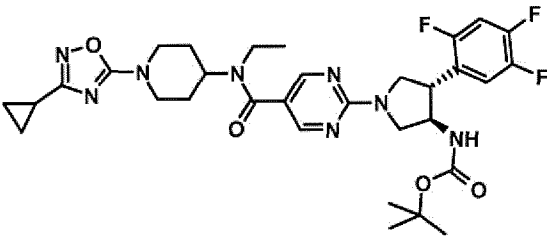
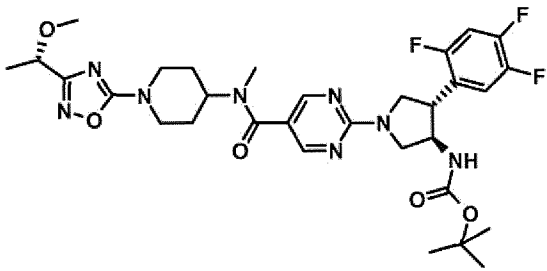
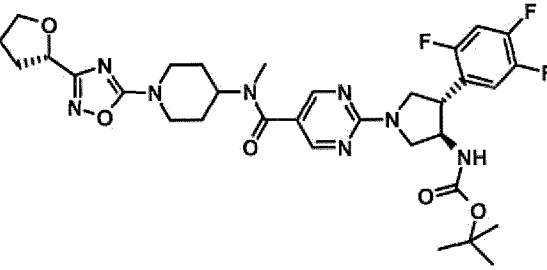
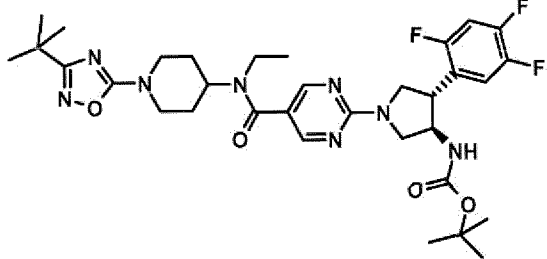
Prep.	Structure	Name	LCMS Data
121		[(3 <i>R</i> ,4 <i>S</i>)-1-[5-({1-[3-(1,1-Difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-propyl-carbamoyl)-pyrimidin-2-yl]-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 1.34 min; <i>m/z</i> (ES ⁺) = 677.45 [<i>M</i> + H] ⁺ (LCMS Method - 2).
122		[(3 <i>R</i> ,4 <i>S</i>)-1-[5-(Cyclopropyl-{1-[3-(1,1-difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-carbamoyl)-pyrimidin-2-yl]-4-(2,5-difluorophenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 1.31 min; <i>m/z</i> (ES ⁺) = 675.53 [<i>M</i> + H] ⁺ (LCMS Method - 2).
123		[(3 <i>R</i> ,4 <i>S</i>)-1-[5-(Cyclopropyl-{1-[3-(1-hydroxy-1-methyl-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-carbamoyl)-pyrimidin-2-yl]-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 1.13 min; <i>m/z</i> (ES ⁺) = 669.46 [<i>M</i> + H] ⁺ (LCMS Method - 2).
124		[(3 <i>R</i> ,4 <i>S</i>)-1-[5-({1-[3-(1,1-Difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-(2-methoxy-ethyl)-carbamoyl]-pyrimidin-2-yl]-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 1.27 min; <i>m/z</i> (ES ⁺) = 693.47 [<i>M</i> + H] ⁺ (LCMS Method - 2).
125		[(3 <i>R</i> ,4 <i>S</i>)-1-[5-(Cyclopropyl-{1-[3-((<i>S</i>)-1-methoxy-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-carbamoyl)-pyrimidin-2-yl]-4-(2,5-difluorophenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 1.21 min; <i>m/z</i> (ES ⁺) = 669.46 [<i>M</i> + H] ⁺ (LCMS Method - 2).

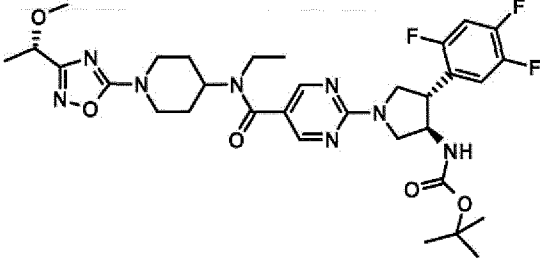
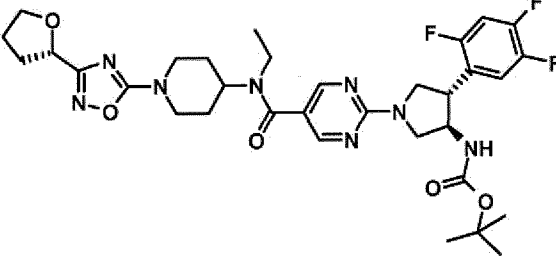
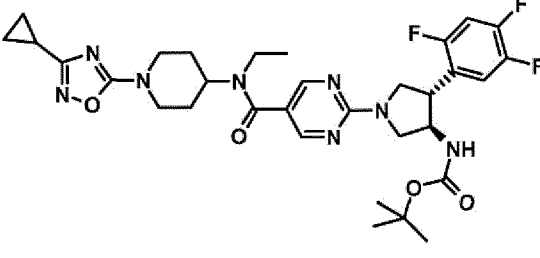
126		[(3 <i>R</i> ,4 <i>S</i>)-1-(5-{Cyclopropyl-[1-(3-methoxymethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-carbamoyl)-pyrimidin-2-yl)-4-(2,5-difluorophenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 1.19 min; <i>m/z</i> (ES ⁺) = 655.48 [<i>M</i> + H] ⁺ (LCMS Method - 2).
127		[(3 <i>R</i> ,4 <i>S</i>)-1-[5-({1-[3-(1,1-Difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-methyl-carbamoyl)-pyrimidin-2-yl)-4-(2,5-difluorophenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 1.26 min; <i>m/z</i> (ES ⁺) = 649.48 [<i>M</i> + H] ⁺ (LCMS Method - 2).
128		[(3 <i>R</i> ,4 <i>S</i>)-4-(2,5-Difluoro-phenyl)-1-(5-{[8-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-8-aza-bicyclo[3.2.1]oct-3-yl]-methyl-carbamoyl}-pyrimidin-2-yl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 1.26 min; <i>m/z</i> (ES ⁺) = 653.47 [<i>M</i> + H] ⁺ (LCMS Method - 2).
129		[(3 <i>R</i> ,4 <i>S</i>)-4-(2,5-Difluoro-phenyl)-1-(5-{[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-4-methyl-piperidin-4-yl]-methyl-carbamoyl}-pyrimidin-2-yl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 1.32 min; <i>m/z</i> (ES ⁺) = 641.50 [<i>M</i> + H] ⁺ (LCMS Method - 2).

The following compounds were prepared by reacting 2-[(3*R*,4*S*)-3-*tert*-butoxycarbonylamino-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid (**Preparation 92**) with the appropriate amine intermediate employing a procedure similar to that outlined in **Preparation 104**:

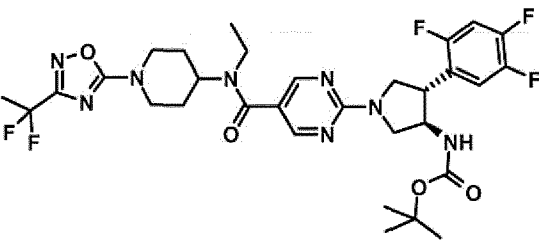
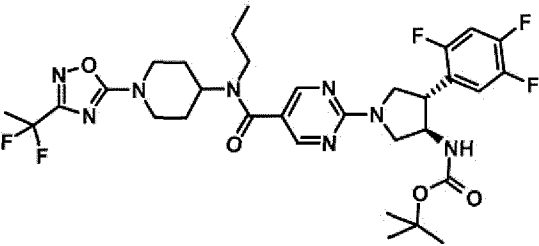
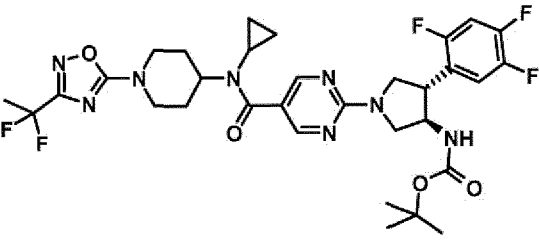
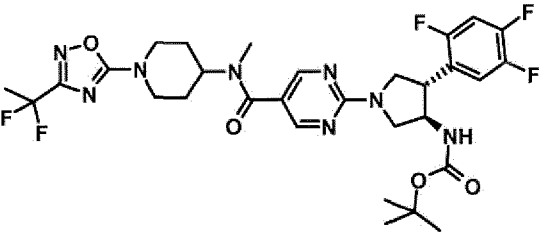
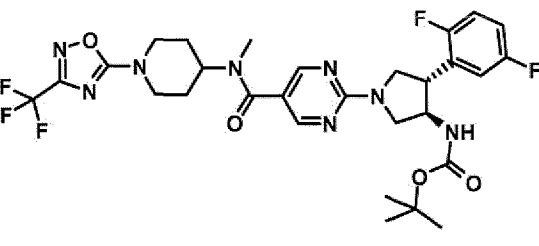
Prep.	Structure	Name	LCMS Data
130		[(3 <i>R</i> ,4 <i>S</i>)-1-(5-{[1-(3-Difluoromethyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-methyl-carbamoyl}-pyrimidin-2-yl)-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 3.92 min; <i>m/z</i> (ES ⁺) = 653.1 [<i>M</i> + H] ⁺ (LCMS Method - 1).

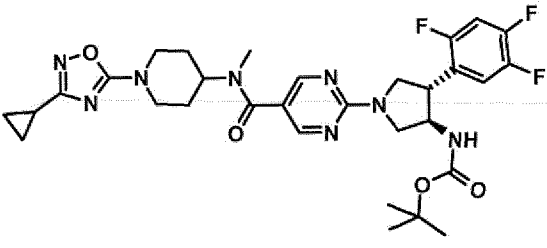
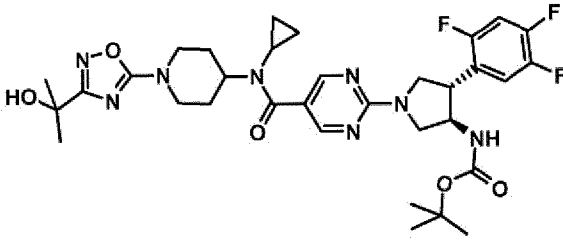
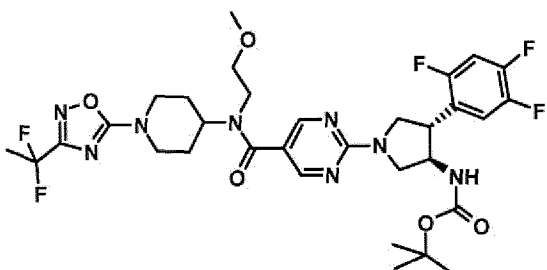
Prep.	Structure	Name	LCMS Data
131		[(3 <i>R</i> ,4 <i>S</i>)-1-(5-{[1-(3-Ethyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-methyl-carbamoyl}-pyrimidin-2-yl)-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 1.18 min; <i>m/z</i> (ES ⁺) = 631.6 [<i>M</i> + H] ⁺ (LCMS Method - 2).
132		[(3 <i>R</i> ,4 <i>S</i>)-1-(5-{Ethyl-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-carbamoyl}-pyrimidin-2-yl)-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 1.29 min; <i>m/z</i> (ES ⁺) = 659.57 [<i>M</i> + H] ⁺ (LCMS Method - 2).
133		[(3 <i>R</i> ,4 <i>S</i>)-1-(5-{[1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-methyl-carbamoyl}-pyrimidin-2-yl)-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 1.25 min; <i>m/z</i> (ES ⁺) = 645.6 [<i>M</i> + H] ⁺ (LCMS Method - 2).
134		[(3 <i>R</i> ,4 <i>S</i>)-1-(5-{[1-(3- <i>tert</i> -Butyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-methyl-carbamoyl}-pyrimidin-2-yl)-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 1.32 min; <i>m/z</i> (ES ⁺) = 659.6 [<i>M</i> + H] ⁺ (LCMS Method - 2).
135		[(3 <i>R</i> ,4 <i>S</i>)-1-(5-{[1-(3-Difluoromethyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-ethyl-carbamoyl}-pyrimidin-2-yl)-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 1.26 min; <i>m/z</i> (ES ⁺) = 667.54 [<i>M</i> + H] ⁺ (LCMS Method - 2).

Prep.	Structure	Name	LCMS Data
136		(3 <i>R</i> ,4 <i>S</i>)-1-[5-({1-[3-(1,1-Difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-isopropyl-carbamoyl)-pyrimidin-2-yl]-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 1.36 min; <i>m/z</i> (ES ⁺) = 695.45 [<i>M</i> + H] ⁺ (LCMS Method - 2).
137		[(3 <i>R</i> ,4 <i>S</i>)-1-(5-{[1-(3-Cyclopropyl-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl]-ethyl-carbamoyl}-pyrimidin-2-yl)-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 1.27 min; <i>m/z</i> (ES ⁺) = 657.5 [<i>M</i> + H] ⁺ (LCMS Method - 2).
138		[(3 <i>R</i> ,4 <i>S</i>)-1-[5-({1-[3-((<i>S</i>)-1-Methoxy-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-methyl-carbamoyl)-pyrimidin-2-yl]-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 3.77 min; <i>m/z</i> (ES ⁺) = 661.19 [<i>M</i> + H] ⁺ (LCMS Method - 1).
139		[(3 <i>R</i> ,4 <i>S</i>)-1-[5-(Methyl-{1-[(<i>S</i>)-3-(tetrahydro-furan-2-yl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-carbamoyl)-pyrimidin-2-yl]-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 3.43 min; <i>m/z</i> (ES ⁺) = 673.20 [<i>M</i> + H] ⁺ (LCMS Method - 1).
140		[(3 <i>R</i> ,4 <i>S</i>)-1-(5-{[1-(3- <i>tert</i> -Butyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-ethyl-carbamoyl}-pyrimidin-2-yl)-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 4.37 min; <i>m/z</i> (ES ⁺) = 673.26 [<i>M</i> + H] ⁺ (LCMS Method - 1).

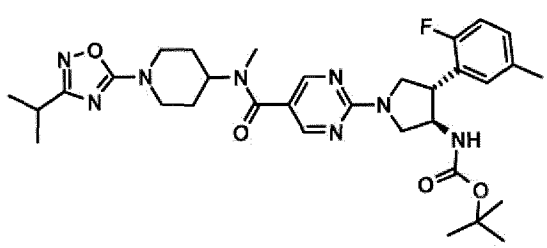
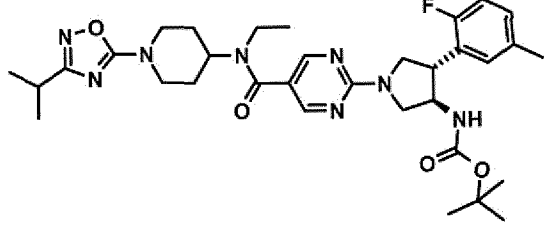
Prep.	Structure	Name	LCMS Data
141		[(3 <i>R</i> ,4 <i>S</i>)-1-[5-(Ethyl-{1-[3-((<i>S</i>)-1-methoxy-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-carbamoyl)-pyrimidin-2-yl]-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 3.87 min; <i>m/z</i> (ES ⁺) = 675.21 [<i>M</i> + H] ⁺ (LCMS Method - 1).
142		[(3 <i>R</i> ,4 <i>S</i>)-1-[5-(Ethyl-{1-[(<i>S</i>)-3-(tetrahydro-furan-2-yl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-carbamoyl)-pyrimidin-2-yl]-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 3.92 min; <i>m/z</i> (ES ⁺) = 687.23 [<i>M</i> + H] ⁺ (LCMS Method - 1).
143		(3 <i>R</i> ,4 <i>S</i>)-1-(5-{[1-(3-Cyclopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-ethyl-carbamoyl}-pyrimidin-2-yl)-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 4.09 min; <i>m/z</i> (ES ⁺) = 657.21 [<i>M</i> + H] ⁺ (LCMS Method - 1).

The following compounds were prepared by reacting the appropriate acid intermediate with the appropriate amine intermediate employing a procedure similar to that outlined in **Preparation 105**:

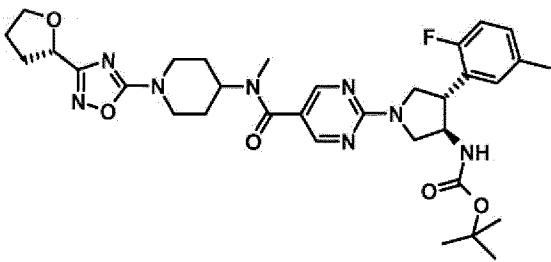
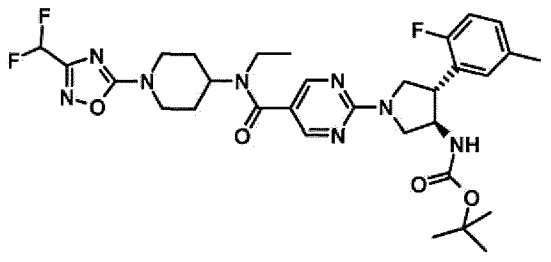
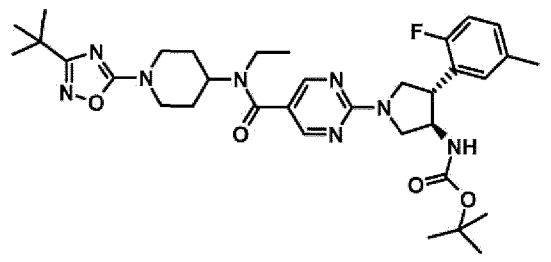
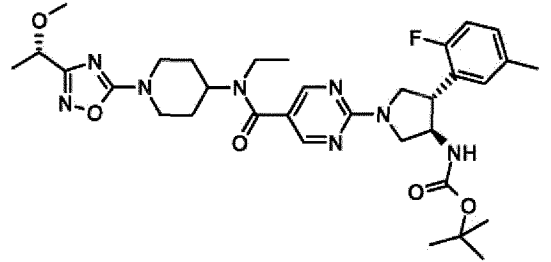
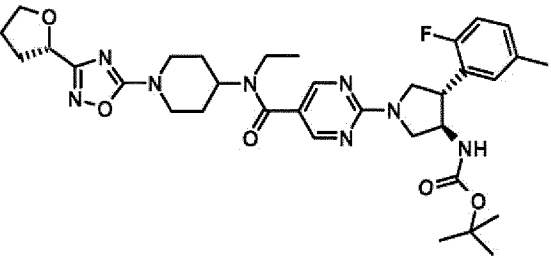
Prep.	Structure	Name	LCMS Data
144		[(3 <i>R</i> ,4 <i>S</i>)-1-[5-({1-[3-(1,1-Difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-ethyl-carbamoyl)-pyrimidin-2-yl]-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 1.30 min; <i>m/z</i> (ES ⁺) = 681.50 [<i>M</i> + H] ⁺ (LCMS Method - 2).
145		[(3 <i>R</i> ,4 <i>S</i>)-1-[5-({1-[3-(1,1-Difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-propyl-carbamoyl)-pyrimidin-2-yl]-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 1.36min; <i>m/z</i> (ES ⁺) = 695.44 [<i>M</i> + H] ⁺ (LCMS Method - 2).
146		[(3 <i>R</i> ,4 <i>S</i>)-1-[5-(Cyclopropyl-{1-[3-(1,1-difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-carbamoyl)-pyrimidin-2-yl]-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 1.33 min; <i>m/z</i> (ES ⁺) = 693.42 [<i>M</i> + H] ⁺ (LCMS Method - 2).
147		(3 <i>R</i> ,4 <i>S</i>)-1-[5-({1-[3-(1,1-Difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-methyl-carbamoyl)-pyrimidin-2-yl]-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 1.27 min; <i>m/z</i> (ES ⁺) = 667.48 [<i>M</i> + H] ⁺ (LCMS Method - 2).
148		[(3 <i>R</i> ,4 <i>S</i>)-1-(5-{Methyl-[1-(3-trifluoromethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-carbamoyl)-pyrimidin-2-yl]-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 1.31 min; <i>m/z</i> (ES ⁺) = 653.39 [<i>M</i> + H] ⁺ (LCMS Method - 2).

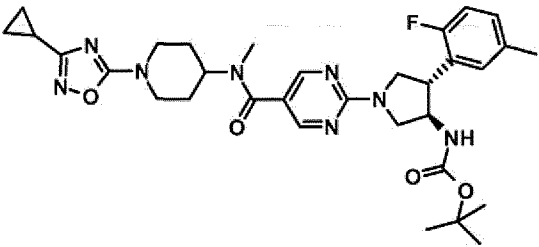
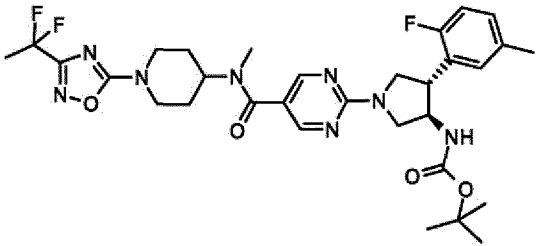
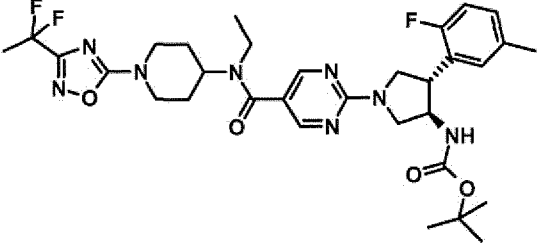
149		[(3 <i>R</i> ,4 <i>S</i>)-1-(5-{[1-(3-Cyclopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-methylcarbamoyl}-pyrimidin-2-yl)-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 1.23 min; <i>m/z</i> (ES ⁺) = 651.49 [<i>M</i> + H] ⁺ (LCMS Method - 2).
150		[(3 <i>R</i> ,4 <i>S</i>)-1-[5-(Cyclopropyl-{1-[3-(1-hydroxy-1-methyl-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-carbamoyl)-pyrimidin-2-yl]-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 1.15 min; <i>m/z</i> (ES ⁺) = 687.46 [<i>M</i> + H] ⁺ (LCMS Method - 2).
151		[(3 <i>R</i> ,4 <i>S</i>)-1-{5-[{1-[3-(1,1-Difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-(2-methoxy-ethyl)-carbamoyl]-pyrimidin-2-yl}-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 1.29 min; <i>m/z</i> (ES ⁺) = 711.43 [<i>M</i> + H] ⁺ (LCMS Method - 2).

The following compounds were prepared by reacting 2-[(3*R*,4*S*)-3-*tert*-butoxycarbonylamino-4-(2-fluoro-5-methyl-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid (**Preparation 98**) with the appropriate amine intermediate employing a procedure similar to that outlined in **Preparation 104**:

Prep.	Structure	Name	LCMS Data
152		[(3 <i>R</i> ,4 <i>S</i>)-4-(2-Fluoro-5-methyl-phenyl)-1-(5-{[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-methylcarbamoyl}-pyrimidin-2-yl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 1.26 min; <i>m/z</i> (ES ⁺) = 623.57 [<i>M</i> + H] ⁺ (LCMS Method - 2).
153		[(3 <i>R</i> ,4 <i>S</i>)-1-(5-{Ethyl-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-carbamoyl}-pyrimidin-2-yl)-4-(2-fluoro-5-methyl-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 4.15 min; <i>m/z</i> (ES ⁺) = 637.32 [<i>M</i> + H] ⁺ (LCMS Method - 1).

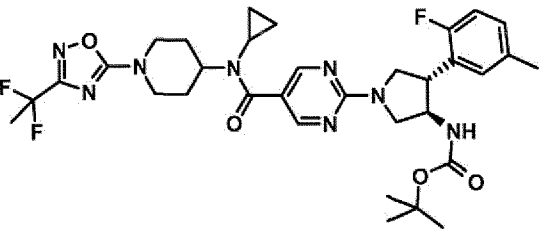
Prep.	Structure	Name	LCMS Data
154		[(3 <i>R</i> ,4 <i>S</i>)-1-(5-{[1-(3-Ethyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-methyl-carbamoyl}-pyrimidin-2-yl)-4-(2-fluoro-5-methyl-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 1.20 min; <i>m/z</i> (ES ⁺) = 609.62 [<i>M</i> + H] ⁺ (LCMS Method - 2).
155		[(3 <i>R</i> ,4 <i>S</i>)-1-(5-{[1-(3-Cyclopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-ethyl-carbamoyl}-pyrimidin-2-yl)-4-(2-fluoro-5-methyl-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 1.30 min; <i>m/z</i> (ES ⁺) = 635.4 [<i>M</i> + H] ⁺ (LCMS Method - 2).
156		[(3 <i>R</i> ,4 <i>S</i>)-1-(5-{[1-(3-Difluoromethyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-methyl-carbamoyl}-pyrimidin-2-yl)-4-(2-fluoro-5-methyl-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 4.02 min; <i>m/z</i> (ES ⁺) = 631.19 [<i>M</i> + H] ⁺ (LCMS Method - 1).
157		[(3 <i>R</i> ,4 <i>S</i>)-1-(5-{[1-(3- <i>tert</i> -Butyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-methyl-carbamoyl}-pyrimidin-2-yl)-4-(2-fluoro-5-methyl-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 4.27 min; <i>m/z</i> (ES ⁺) = 637.22 [<i>M</i> + H] ⁺ (LCMS Method - 1).
158		{(3 <i>R</i> ,4 <i>S</i>)-4-(2-Fluoro-5-methyl-phenyl)-1-[5-({[1-(3-((<i>S</i>)-1-methoxy-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-methyl-carbamoyl)-pyrimidin-2-yl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 3.82 min; <i>m/z</i> (ES ⁺) = 639.19 [<i>M</i> + H] ⁺ (LCMS Method - 1).

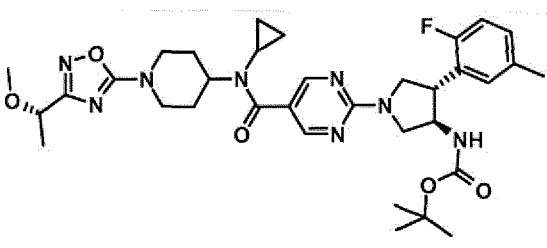
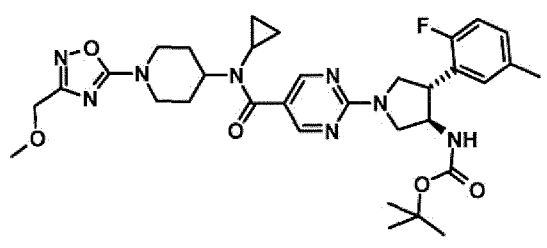
Prep.	Structure	Name	LCMS Data
159		{(3 <i>R</i> ,4 <i>S</i>)-4-(2-Fluoro-5-methyl-phenyl)-1-[5-(methyl-{1-[(<i>S</i>)-3-(tetrahydro-furan-2-yl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-carbamoyl)-pyrimidin-2-yl]-pyrrolidin-3-yl}-carbamic acid <i>tert</i> -butyl ester	RT = 3.79 min; <i>m/z</i> (ES ⁺) = 651.20 [<i>M</i> + H] ⁺ (LCMS Method - 1).
160		[(3 <i>R</i> ,4 <i>S</i>)-1-(5-{[1-(3-Difluoromethyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-ethyl-carbamoyl}-pyrimidin-2-yl)-4-(2-fluoro-5-methyl-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 4.12 min; <i>m/z</i> (ES ⁺) = 645.17 [<i>M</i> + H] ⁺ (LCMS Method - 1).
161		[(3 <i>R</i> ,4 <i>S</i>)-1-(5-{[1-(3- <i>tert</i> -Butyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-ethyl-carbamoyl}-pyrimidin-2-yl)-4-(2-fluoro-5-methyl-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 4.42 min; <i>m/z</i> (ES ⁺) = 651.29 [<i>M</i> + H] ⁺ (LCMS Method - 1).
162		[(3 <i>R</i> ,4 <i>S</i>)-1-[5-(Ethyl-{1-[3-((<i>S</i>)-1-methoxy-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-carbamoyl)-pyrimidin-2-yl)-4-(2-fluoro-5-methyl-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 3.90 min; <i>m/z</i> (ES ⁺) = 653.20 [<i>M</i> + H] ⁺ (LCMS Method - 1).
163		[(3 <i>R</i> ,4 <i>S</i>)-1-[5-(Ethyl-{1-[(<i>S</i>)-3-(tetrahydro-furan-2-yl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-carbamoyl)-pyrimidin-2-yl)-4-(2-fluoro-5-methyl-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 3.91 min; <i>m/z</i> (ES ⁺) = 665.24 [<i>M</i> + H] ⁺ (LCMS Method - 1).

Prep.	Structure	Name	LCMS Data
164		[(3 <i>R</i> ,4 <i>S</i>)-1-(5-{[1-(3-Cyclopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-methyl-carbamoyl}-pyrimidin-2-yl)-4-(2-fluoro-5-methyl-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 4.02 min; <i>m/z</i> (ES ⁺) = 621.23 [<i>M</i> + H] ⁺ (LCMS Method - 1).
165		[(3 <i>R</i> ,4 <i>S</i>)-1-[5-({1-[3-(1,1-Difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-methyl-carbamoyl)-pyrimidin-2-yl]-4-(2-fluoro-5-methyl-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 4.15 min; <i>m/z</i> (ES ⁺) = 645.20 [<i>M</i> + H] ⁺ (LCMS Method - 1).
166		[(3 <i>R</i> ,4 <i>S</i>)-1-[5-({1-[3-(1,1-Difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-ethyl-carbamoyl)-pyrimidin-2-yl]-4-(2-fluoro-5-methyl-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 4.25 min; <i>m/z</i> (ES ⁺) = 659.22 [<i>M</i> + H] ⁺ (LCMS Method - 1).

The following compounds were prepared by reacting 2-[(3*R*,4*S*)-3-*tert*-butoxycarbonylamino-4-(2-fluoro-5-methyl-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid (**Preparation 98**) with the appropriate amine intermediate employing a procedure similar to that outlined in **Preparation 105**:

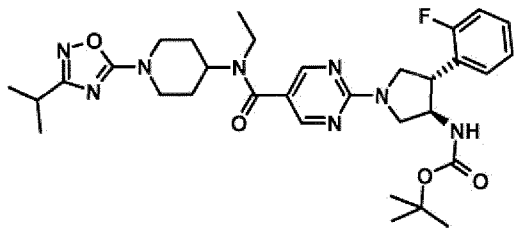
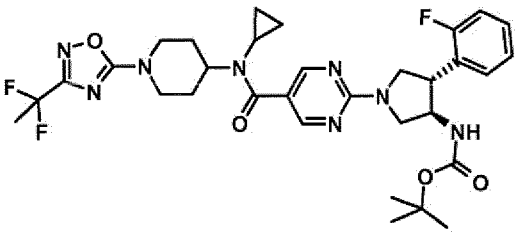
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Prep.	Structure	Name	LCMS Data
167		[(3 <i>R</i> ,4 <i>S</i>)-1-[5-(Cyclopropyl-{1-[3-(1,1-difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl} carbamoyl)-pyrimidin-2-yl]-4-(2-fluoro-5-methyl-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 1.35 min; <i>m/z</i> (ES ⁺) = 671.46 [<i>M</i> + H] ⁺ (LCMS Method - 2).

Prep.	Structure	Name	LCMS Data
168		[(3R,4S)-1-[5-(Cyclopropyl-{1-[3-((S)-1-methoxy-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-carbamoyl)-pyrimidin-2-yl]-4-(2-fluoro-5-methyl-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 1.25 min; <i>m/z</i> (ES ⁺) = 665.49 [<i>M</i> + H] ⁺ (LCMS Method - 2).
169		[(3R,4S)-1-(5-{Cyclopropyl-[1-(3-methoxymethyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-carbamoyl}-pyrimidin-2-yl)-4-(2-fluoro-5-methyl-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 1.23 min; <i>m/z</i> (ES ⁺) = 651.49 [<i>M</i> + H] ⁺ (LCMS Method - 2).

The following compounds were prepared by reacting 2-[(3R,4S)-3-*tert*-butoxycarbonylamino-4-(2-fluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid (**Preparation 100**) with the appropriate amine intermediate employing a procedure similar to that outlined in **Preparation 105**:

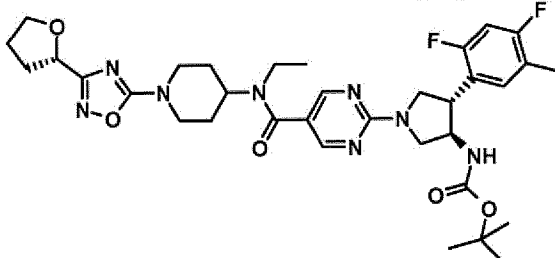
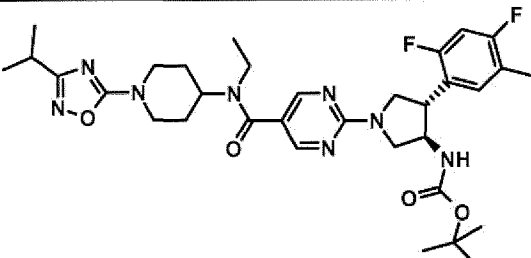
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Prep.	Structure	Name	LCMS Data
170		[(3R,4S)-1-(5-{Ethyl-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-carbamoyl}-pyrimidin-2-yl)-4-(2-fluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 1.25 min; <i>m/z</i> (ES ⁺) = 623.46 [<i>M</i> + H] ⁺ (LCMS Method - 2).
171		[(3R,4S)-1-[5-(Cyclopropyl-{1-[3-(1,1-difluoroethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-carbamoyl)-pyrimidin-2-yl]-4-(2-fluorophenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 1.30 min; <i>m/z</i> (ES ⁺) = 657.44 [<i>M</i> + H] ⁺ (LCMS Method - 2).

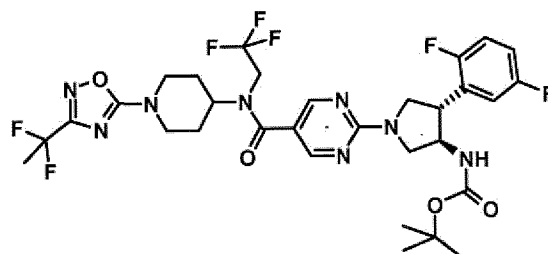
The following compounds were prepared by reacting 2-[(3R,4S)-3-*tert*-butoxycarbonylamino-4-(2,4-difluoro-5-methyl-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid (**Preparation 96**) and the appropriate amine intermediate employing a procedure similar to that outlined in **Preparation 104**:

Prep.	Structure	Name	LCMS Data
172		[(3 <i>R</i> ,4 <i>S</i>)-1-(5-{[1-(3-Difluoromethyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-methyl-carbamoyl}-pyrimidin-2-yl)-4-(2,4-difluoro-5-methyl-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 4.07 min; <i>m/z</i> (ES ⁺) = 649.07 [<i>M</i> + H] ⁺ (LCMS Method - 1).
173		[(3 <i>R</i> ,4 <i>S</i>)-1-[5-({1-[3-(1,1-Difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-methyl-carbamoyl)-pyrimidin-2-yl]-4-(2,4-difluoro-5-methyl-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 4.20 min; <i>m/z</i> (ES ⁺) = 663.10 [<i>M</i> + H] ⁺ (LCMS Method - 1).
174		[(3 <i>R</i> ,4 <i>S</i>)-1-(5-{[1-(3-Cyclopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-methyl-carbamoyl}-pyrimidin-2-yl)-4-(2,4-difluoro-5-methyl-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 4.02 min; <i>m/z</i> (ES ⁺) = 639.13 [<i>M</i> + H] ⁺ (LCMS Method - 1).
175		[(3 <i>R</i> ,4 <i>S</i>)-1-(5-{[1-(3- <i>tert</i> -Butyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-methyl-carbamoyl}-pyrimidin-2-yl)-4-(2,4-difluoro-5-methyl-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 4.34 min; <i>m/z</i> (ES ⁺) = 655.17 [<i>M</i> + H] ⁺ (LCMS Method - 1).
176		{(3 <i>R</i> ,4 <i>S</i>)-4-(2,4-Difluoro-5-methyl-phenyl)-1-[5-({1-[3-((<i>S</i>)-1-methoxy-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-methyl-carbamoyl)-pyrimidin-2-yl]-pyrrolidin-3-yl}-carbamic acid <i>tert</i> -butyl ester	RT = 3.85 min; <i>m/z</i> (ES ⁺) = 657.13 [<i>M</i> + H] ⁺ (LCMS Method - 1).

Prep.	Structure	Name	LCMS Data
177		{(3 <i>R</i> ,4 <i>S</i>)-4-(2,4-Difluoro-5-methyl-phenyl)-1-[5-(methyl-{1-[(<i>S</i>)-3-(tetrahydro-furan-2-yl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-carbamoyl)-pyrimidin-2-yl]-pyrrolidin-3-yl}-carbamic acid <i>tert</i> -butyl ester	RT = 3.84 min; <i>m/z</i> (ES ⁺) = 669.14 [<i>M</i> + H] ⁺ (LCMS Method - 1).
178		[(3 <i>R</i> ,4 <i>S</i>)-1-(5-{[1-(3-Difluoromethyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-ethyl-carbamoyl}-pyrimidin-2-yl)-4-(2,4-difluoro-5-methyl-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 4.18 min; <i>m/z</i> (ES ⁺) = 663.13 [<i>M</i> + H] ⁺ (LCMS Method - 1).
179		[(3 <i>R</i> ,4 <i>S</i>)-1-[5-({1-[3-(1,1-Difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-ethyl-carbamoyl)-pyrimidin-2-yl]-4-(2,4-difluoro-5-methyl-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 4.35 min; <i>m/z</i> (ES ⁺) = 677.13 [<i>M</i> + H] ⁺ (LCMS Method - 1).
180		[(3 <i>R</i> ,4 <i>S</i>)-1-(5-{[1-(3- <i>tert</i> -Butyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-ethyl-carbamoyl}-pyrimidin-2-yl)-4-(2,4-difluoro-5-methyl-phenyl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 4.49 min; <i>m/z</i> (ES ⁺) = 669.19 [<i>M</i> + H] ⁺ (LCMS Method - 1).
181		{(3 <i>R</i> ,4 <i>S</i>)-4-(2,4-Difluoro-5-methyl-phenyl)-1-[5-(ethyl-{1-[3-((<i>S</i>)-1-methoxy-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-carbamoyl)-pyrimidin-2-yl]-pyrrolidin-3-yl}-carbamic acid <i>tert</i> -butyl ester	RT = 4.05 min; <i>m/z</i> (ES ⁺) = 671.16 [<i>M</i> + H] ⁺ (LCMS Method - 1).

Prep.	Structure	Name	LCMS Data
182		{(3R,4S)-4-(2,4-Difluoro-5-methyl-phenyl)-1-[5-(ethyl-{1-[(S)-3-(tetrahydro-furan-2-yl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-carbamoyl)-pyrimidin-2-yl]-pyrrolidin-3-yl}-carbamic acid <i>tert</i> -butyl ester	RT = 3.98 min; <i>m/z</i> (ES ⁺) = 683.15 [<i>M</i> + H] ⁺ (LCMS Method - 1).
183		(3R,4S)-4-(2,4-Difluoro-5-methyl-phenyl)-1-(5-{ethyl-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-carbamoyl}-pyrimidin-2-yl)-pyrrolidin-3-yl]-carbamic acid <i>tert</i> -butyl ester	RT = 4.22 min; <i>m/z</i> (ES ⁺) = 655.19 [<i>M</i> + H] ⁺ (LCMS Method - 1).

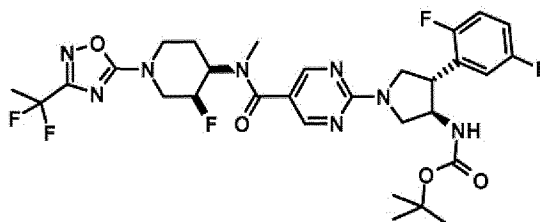
Preparation 184: [(3R,4S)-1-{5-[[1-[3-(1,1-Difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl]-(2,2,2-trifluoro-ethyl)-carbamoyl]-pyrimidin-2-yl}-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester



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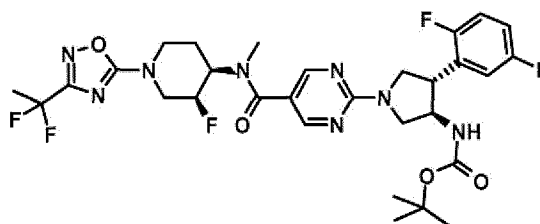
To a suspension of 2-[(3R,4S)-3-*tert*-butoxycarbonylamino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid (**Preparation 90**, 150mg, 360μmol) in DCM (3mL) was added pyridine (38μL, 460μmol), DMF (20μL, 200μmol) followed by the dropwise addition of oxalyl chloride (36μL, 430μmol) under argon. The reaction mixture was stirred at r.t. for 1 h. To this was added a solution of {1-[3-(1,1-difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-(2,2,2-trifluoro-ethyl)-amine (**Preparation 60**, 120mg, 390μmol) and pyridine (38μL) in DCM (2mL) and the mixture stirred at r.t. for 18 h. The reaction mixture was diluted with EtOAc and washed with water (15mL) then a saturated solution of sodium carbonate (15mL). The organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by preparative HPLC (standard method) to afford the title compound: RT = 1.37 min; *m/z* (ES⁺) = 717.43 [*M* + H]⁺ (LCMS Method - 2).

Preparation 185: [(3*R*,4*S*)-1-[5-({1-[3-(1,1-Difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-3-fluoro-piperidin-4-yl}-methyl-carbamoyl)-pyrimidin-2-yl]-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester



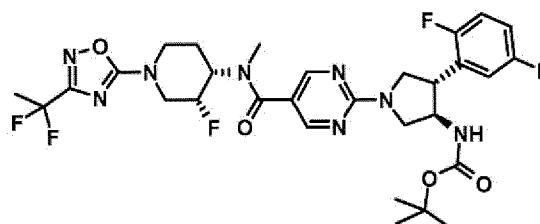
The title compound was prepared by reacting 2-[(3*R*,4*S*)-3-*tert*-butoxycarbonylamino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid (**Preparation 90**) with *cis*-{1-[3-(1,1-difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-3-fluoro-piperidin-4-yl}-methyl-amine (**Procedure 39**) employing a procedure similar to that outlined in **Preparation 105** to afford the title compound as a mixture of diastereoisomers: RT = 1.30 min; m/z (ES^+) = 667.44 [$M + H$] $^+$ (LCMS Method - 2).

Preparation 186: [(3*R*,4*S*)-1-[5-({(3*S*,4*R*)-1-[3-(1,1-Difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-3-fluoro-piperidin-4-yl}-methyl-carbamoyl)-pyrimidin-2-yl]-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester



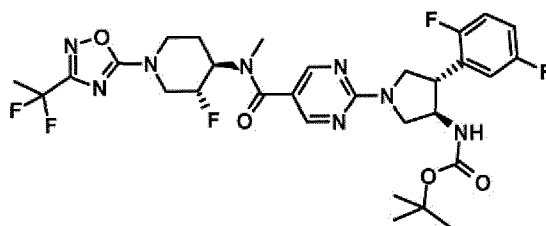
[(3*R*,4*S*)-1-[5-({1-[3-(1,1-Difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-3-fluoro-piperidin-4-yl}-methyl-carbamoyl)-pyrimidin-2-yl]-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester (**Preparation 185**) was separated via chiral HPLC: MTBE:MeOH:IH 35:35:30, 15ml/min, 270nm, RT = 12.1 min to afford the title single diastereomer with arbitrarily assigned stereochemistry: RT = 1.30 min; m/z (ES^+) = 667.44 [$M + H$] $^+$ (LCMS Method - 2).

Preparation 187: [(3*R*,4*S*)-1-[5-({(3*R*,4*S*)-1-[3-(1,1-Difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-3-fluoro-piperidin-4-yl}-methyl-carbamoyl)-pyrimidin-2-yl]-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester



[(3*R*,4*S*)-1-[5-({1-[3-(1,1-Difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-3-fluoro-piperidin-4-yl}-methyl-carbamoyl)-pyrimidin-2-yl]-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester (**Preparation 185**) was separated via chiral HPLC: MTBE:MeOH:IH 35:35:30, 15ml/min, 270nm, RT = 9.7 min to afford the title single diastereomer with arbitrarily assigned stereochemistry. RT = 1.30 min; m/z (ES^+) = 667.44 [$M + H$] $^+$ (LCMS Method - 2).

Preparation 188: [(3*R*,4*S*)-1-[5-({(3*R*,4*R*)-1-[3-(1,1-Difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-3-fluoro-piperidin-4-yl}-methyl-carbamoyl)-pyrimidin-2-yl]-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester



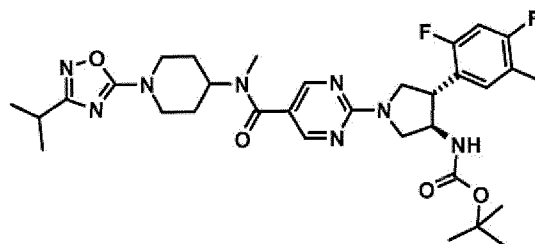
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The title compound was prepared by reacting 2-[(3*R*,4*S*)-3-*tert*-butoxycarbonylamino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid (**Preparation 90**) with *trans*-{1-[3-(1,1-difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-3-fluoro-piperidin-4-yl}-methyl-amine (**Procedure 40**) employing a procedure similar to that outlined in **Preparation 105** to afford the title compound as a mixture of diastereoisomers. The diastereomers were separated via chiral HPLC: MTBE:MeOH 80:20, 15ml/min, 270nm, RT = 9.7 min to afford the title single diastereomer with arbitrarily assigned stereochemistry: RT = 1.26 min; m/z (ES^+) = 667.5 [$M + H$] $^+$ (LCMS Method - 2).

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Preparation 189: [(3*R*,4*S*)-4-(2,4-Difluoro-5-methyl-phenyl)-1-(5-{[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-methyl-carbamoyl}-pyrimidin-2-yl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester

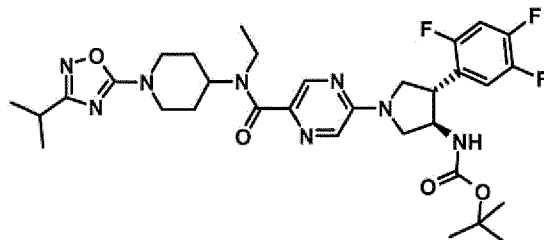
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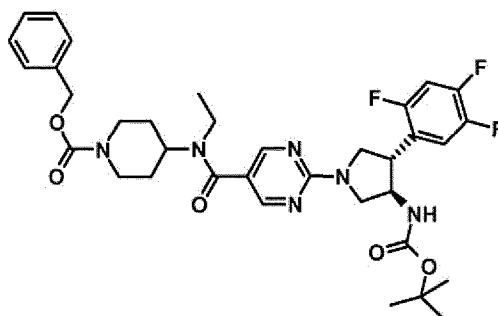
The title compound was synthesised from 2-[(3*R*,4*S*)-3-*tert*-butoxycarbonylamino-4-(2,4-difluoro-5-methyl-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid (**Preparation 96**) and [1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-methyl-amine (**Preparation 35**) employing a procedure similar to that outlined in **Preparation 104**: RT = 1.28 min; m/z (ES^+) = 641.61 [$M + H$] $^+$ (LCMS Method - 2).

Preparation 190: (3*R*,4*S*)-1-(5-{Ethyl-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-carbamoyl}-pyrazin-2-yl)-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester



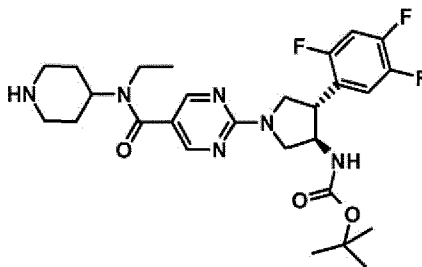
The title compound was synthesised from 5-[(3*R*,4*S*)-3-*tert*-butoxycarbonylamino-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-1-yl]-pyrazine-2-carboxylic acid (**Preparation 94**) and ethyl-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-amine (**Preparation 52**) employing a procedure similar to that outlined in **Preparation 104**: RT = 4.15 min; m/z (ES^+) = 659.19 [$M + H$] $^+$ (LCMS Method - 1).

Preparation 191: 4-({2-[(3*R*,4*S*)-3-*tert*-Butoxycarbonylamino-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carbonyl}-ethyl-amino)-piperidine-1-carboxylic acid benzyl ester



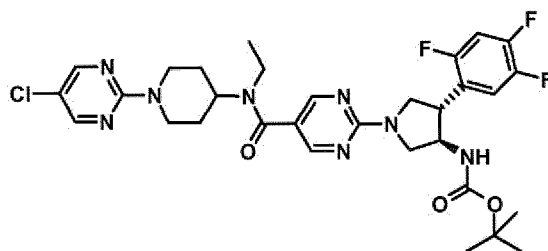
The title compound was prepared by reacting 2-[(3*R*,4*S*)-3-*tert*-butoxycarbonylamino-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid (**Preparation 92**) with 4-ethylamino-piperidine-1-carboxylic acid benzyl ester employing a procedure similar to that outlined in **Preparation 104**: RT = 4.35 min; m/z (ES^+) = 683.13 [$M + H$] $^+$ (LCMS Method - 1).

Preparation 192: [(3*R*,4*S*)-1-[5-(Ethyl-piperidin-4-yl-carbamoyl)-pyrimidin-2-yl]-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester



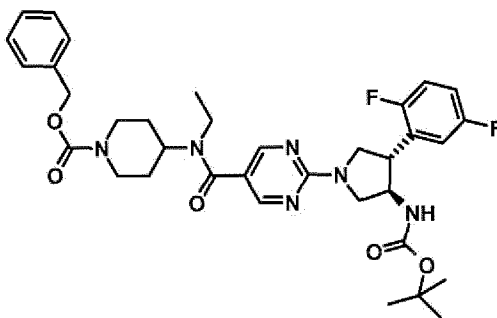
To a solution of 10% Pd/C (24mg, 0.022mmol) in EtOH (15mL) was added 4-({2-[(3*R*,4*S*)-3-*tert*-butoxycarbonylamino-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carbonyl}-ethyl-amino)-piperidine-1-carboxylic acid benzyl ester (**Preparation 191**, 240mg, 0.35mmol) and the mixture placed under hydrogen for 1 h at room temperature. The mixture was then filtered through celite and the filtrate concentrated *in vacuo*, azeotroping with DCM, to afford the title compound: RT = 2.75 min; *m/z* (ES⁺) = 549.16 [*M* + H]⁺ (LCMS Method - 1).

Preparation 193: [(3*R*,4*S*)-1-(5-{[1-(5-Chloro-pyrimidin-2-yl)-piperidin-4-yl]-ethyl-carbamoyl}-pyrimidin-2-yl)-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester



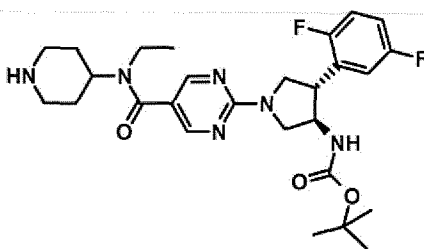
To a solution of [(3*R*,4*S*)-1-(5-(ethyl-piperidin-4-yl-carbamoyl)-pyrimidin-2-yl)-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester (**Preparation 192**, 40mg, 0.07mmol) in DMSO (1mL) was added DIPEA (19μL, 0.11mmol) and 2,5-dichloropyrimidine (16mg, 0.11mmol). The mixture was heated in the microwave at 150 °C for 1 h. The mixture was purified by preparative HPLC and the compound containing fractions concentrated *in vacuo* to afford the title compound: RT = 4.55 min; *m/z* (ES⁺) = 661.13 [*M* + H]⁺ (LCMS Method - 1).

Preparation 194: 4-({2-[(3*R*,4*S*)-3-*tert*-Butoxycarbonylamino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carbonyl}-ethyl-amino)-piperidine-1-carboxylic acid benzyl ester



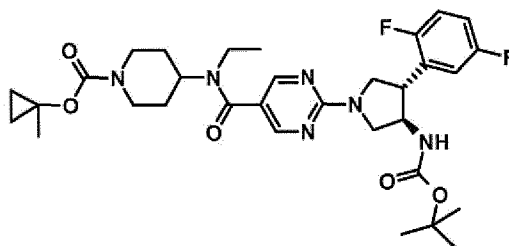
The title compound was prepared by reacting 2-[(3*R*,4*S*)-3-*tert*-butoxycarbonylamino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid (**Preparation 90**) with 4-ethylamino-piperidine-1-carboxylic acid benzyl ester employing a procedure similar to that outlined in **Preparation 105**: RT = 1.33 min; *m/z* (ES⁺) = 665.51 [*M* + H]⁺ (LCMS Method - 2).

Preparation 195: {(3*R*,4*S*)-4-(2,5-Difluoro-phenyl)-1-[5-(ethyl-piperidin-4-yl-carbamoyl)-pyrimidin-2-yl]-pyrrolidin-3-yl}-carbamic acid *tert*-butyl ester



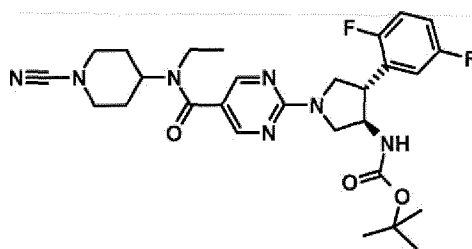
The title compound was prepared from 4-({2-[(3*R*,4*S*)-3-*tert*-butoxycarbonylamino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carbonyl}-ethyl-amino)-piperidine-1-carboxylic acid benzyl ester (**Preparation 194**) employing a procedure similar to that outlined in **Preparation 192**: RT = 0.81 min; m/z (ES^+) = 531.51 [$M + H$] $^+$ (LCMS Method - 2).

Preparation 196: 4-({2-[(3*R*,4*S*)-3-*tert*-Butoxycarbonylamino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carbonyl}-ethyl-amino)-piperidine-1-carboxylic acid 1-methylcyclopropyl ester



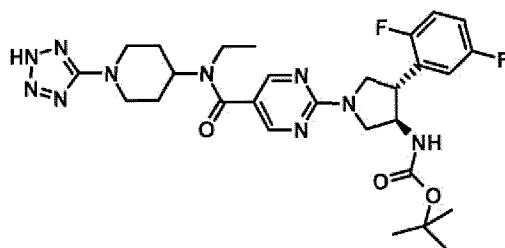
To a stirred solution of {(3*R*,4*S*)-4-(2,5-difluoro-phenyl)-1-[5-(ethyl-piperidin-4-yl-carbamoyl)-pyrimidin-2-yl]-pyrrolidin-3-yl}-carbamic acid *tert*-butyl ester (**Preparation 195**, 200mg, 0.3mmol) and triethylamine (72.5μL, 0.520mmol) in DCM (7mL) was added 1-methylcyclopropyl 4-nitrophenyl carbonate (82.3mg, 0.347mmol) followed by 4-dimethylaminopyridine (4.24mg, 0.0347mmol) and the solution stirred at r.t. for 6 h. The reaction mixture was diluted with EtOAc, washed with saturated aqueous sodium carbonate solution, 1M HCl solution, water and finally brine. The organics were dried (magnesium sulfate), filtered and concentrated *in vacuo*. Purification by column chromatography (97:3 DCM:MeOH) afforded the title compound: RT = 1.25 min; m/z (ES^+) = 629.51 [$M + H$] $^+$ (LCMS Method - 2).

Preparation 197: [(3*R*,4*S*)-1-{5-[(1-Cyano-piperidin-4-yl)-ethyl-carbamoyl]-pyrimidin-2-yl}-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester



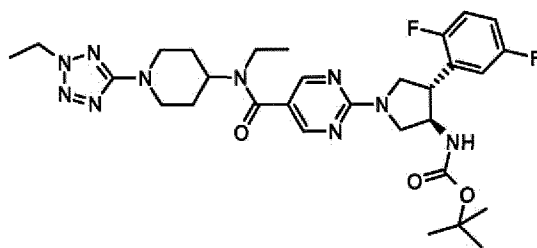
The title compound was prepared from {(3*R*,4*S*)-4-(2,5-difluoro-phenyl)-1-[5-(ethyl-piperidin-4-yl-carbamoyl)-pyrimidin-2-yl]-pyrrolidin-3-yl}-carbamic acid *tert*-butyl ester (**Preparation 195**) employing a procedure similar to that outline in **Preparation 21**: RT = 1.12 min; m/z (ES^+) = 556.49 [$M + H$] $^+$ (LCMS Method - 2).

Preparation 198: [(3*R*,4*S*)-4-(2,5-Difluoro-phenyl)-1-(5-{ethyl-[1-(2*H*-tetrazol-5-yl)-piperidin-4-yl]-carbamoyl}-pyrimidin-2-yl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester



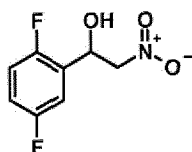
To a solution of [(3*R*,4*S*)-1-{5-[(1-cyano-piperidin-4-yl)-ethyl-carbamoyl]-pyrimidin-2-yl}-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester (**Preparation 197**, 0.180g, 0.324mmol) in DMF (2.5mL) was added ammonium chloride (26mg, 0.486mmol) and sodium azide (31.6mg, 0.486mmol). The mixture was heated at 100 °C for 18 h. The reaction mixture was diluted with water and extracted with EtOAc, then EtOAc:MeOH (95:5). The combined organic extracts were washed with brine, filtered through a hydrophobic frit and concentrated *in vacuo*. Purification by column chromatography (95:5 DCM:MeOH) afforded the title compound: RT = 1.01 min; m/z (ES^+) = 599.46 [$M + H$] $^+$ (LCMS Method - 2).

Preparation 199: [(3*R*,4*S*)-4-(2,5-Difluoro-phenyl)-1-(5-{ethyl-[1-(2-ethyl-2*H*-tetrazol-5-yl)-piperidin-4-yl]-carbamoyl}-pyrimidin-2-yl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester



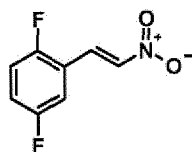
To a solution of [(3*R*,4*S*)-4-(2,5-difluoro-phenyl)-1-(5-{ethyl-[1-(2H-tetrazol-5-yl)-piperidin-4-yl]-carbamoyl}-pyrimidin-2-yl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester (**Preparation 198**, 60mg, 0.10mmol) in acetone (3mL) was added potassium carbonate (42mg, 0.30mmol) followed by the dropwise addition of iodoethane (10μL, 0.13mmol). The mixture was then heated at 45 °C for 2.5 h then concentrated *in vacuo*. The residue was partitioned between EtOAc and water, the organic phase washed with brine, dried (magnesium sulfate), filtered and concentrated *in vacuo*. Purification by preparative HPLC (Standard Method) afforded the title compound: RT = 1.20 min; *m/z* (ES⁺) = 627.54 [*M* + H]⁺ (LCMS Method - 2).

10 **Preparation 200: 1-(2,5-Difluoro-phenyl)-2-nitro-ethanol**



Nitromethane (227mL, 4.22mol) was added in one portion to a solution of 2,5-difluorobenzaldehyde (500g, 3.52mol) in MeOH (5L) in a 10 L jacketed vessel. The solution was cooled to 4 °C (jacket -10 °C) and a solution of NaOH (169g, 4.22mol) in water (500mL) was added over 40 min causing a 6 °C exotherm. The solution was stirred for 60 min (jacket 0 °C) after which time a thick white precipitate formed. Ice water (3L) was added (jacket 5 °C) followed by NH₄Cl (sat. aq., 3.5 L) and the solution extracted with DCM (5 x 2 L). The combined organics were evaporated then taken up into DCM (1L), dried over MgSO₄ and evaporated to dryness to afford the title compound. ¹H NMR δ_H (300MHz, CDCl₃): 7.35 (m, 1H), 7.05 (m, 2H), 5.70 (m, 1H), 4.60 (m, 2H), 3.10 (m, 1H).

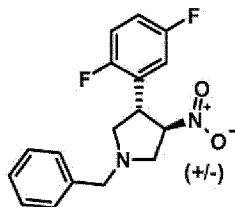
Preparation 201: 1,4-Difluoro-2-((*E*)-2-nitro-vinyl)-benzene



Acetic anhydride (665mL, 7.05mol) was added in one portion to 1-(2,5-difluoro-phenyl)-2-nitro-ethanol (**Preparation 200**, 672g, 3.31mol) at 0 °C under argon. DMAP (28.3g, 0.23mol) was added and the solution darkened in colour. The reaction was warmed to r.t. over 18 h. The reaction mixture was cautiously poured into NaHCO₃ (sat. aq., 3.5L) and stirred to form a yellow solid. The slurry was stirred for 30 min at r.t. before filtering. The solid was washed with NaHCO₃ (sat. aq., 2L) then water (2L). The solid was dissolved in DCM (1.5L) and washed with saturated NaHCO₃ (sat. aq., 4 x 1L), dried over MgSO₄ and evaporated to afford a yellow / orange oil which solidified to give

a yellow solid. This was purified by dry flash chromatography eluting with DCM to afford the title compound. ^1H NMR δ_{H} (300MHz, CDCl_3): 8.05 (d, 1H), 7.70 (d, 1H), 7.20 (m, 3H).

Preparation 202: 1-Benzyl-3-(2,5-difluoro-phenyl)-4-nitro-pyrrolidine

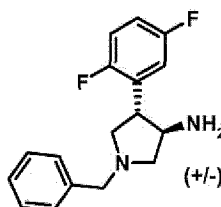


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1,4-Difluoro-2-((*E*)-2-nitro-vinyl)-benzene (**Preparation 201**, 120g, 0.65mol) was dissolved in analytical grade DCM (1.2L) and dried over MgSO_4 . The solution was filtered and split into two portions (60g, 0.32mol). *N*-(Methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine (100mL, 0.39mol) was added to each portion under argon. The yellow solutions were then cooled to -5°C and TFA (2.7mL, 0.04mol) added. After 5 min the temperature rapidly increased to 30°C then cooled back to -5°C . The resulting paler yellow solution was stirred at -10°C for 1 h before quenching cautiously with NaHCO_3 (sat. aq., 1 L). The two batches were combined and the layers partitioned. The DCM layer was washed with water (2L) then brine (2L), dried over MgSO_4 and evaporated to give 209g of an orange oil. The material was purified by dry flash chromatography eluting with DCM to afford the title compound. ^1H NMR δ_{H} (300MHz, CDCl_3): 7.40 – 7.20 (m, 5H), 7.00 (m, 3H), 4.95 (m, 1H), 4.20 (m, 1H), 3.70 (m, 2H), 3.40 (m, 1H), 3.20 (m, 2H), 2.70 (m, 1H).

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Preparation 203: 1-Benzyl-4-(2,5-difluoro-phenyl)-pyrrolidin-3-ylamine

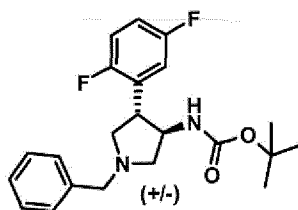


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1-Benzyl-3-(2,5-difluoro-phenyl)-4-nitro-pyrrolidine (**Preparation 202**, 340g, 1.07mol) was dissolved in IMS (5L) and charged into a 7.8L autoclave. RaNi (20g) was added (without washing). The autoclave was sealed and charged with H_2 (50 bar) and stirred at r.t. for 18 h (10°C exotherm). The reaction mixture was filtered through celite, the pad washed with IMS and the filtrate evaporated to dryness. The brown oil was dissolved in DCM (1.5L), extracted with HCl (1M, aq. 2.5L) and washed with DCM (3 x 1L) to remove the colour from the aqueous layer. The aqueous layer was basified to pH 14 with NaOH (2M, aq. 3L) and extracted into DCM (5 x 1L) then the organics were combined, dried over MgSO_4 and evaporated to afford the title compound. ^1H NMR δ_{H} (300MHz, CDCl_3): 7.40 – 7.20 (m, 5H), 7.10 (m, 1H), 6.95 (m, 1H), 6.85 (m, 1H), 3.70 (m, 2H), 3.50 (m, 1H), 3.25 (m, 1H), 3.05 (m, 2H), 2.65 (m, 1H), 2.45 (m, 1H), 1.50 (br s, 2H).

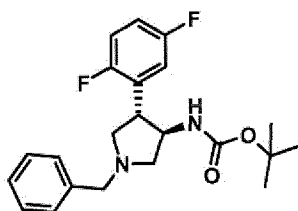
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Preparation 204: 1-Benzyl-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl-carbamic acid *tert*-butyl ester



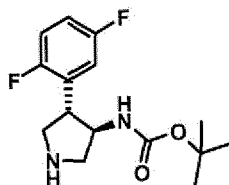
Triethylamine (244mL, 1.75mol) was added to a solution of 1-benzyl-4-(2,5-difluoro-phenyl)-pyrrolidin-3-ylamine (**Preparation 203**, 252g, 0.87mol) in THF (3.8L) and the cloudy light brown solution was cooled to 0 °C. Di-*tert*-butyldicarbonate (229g, 1.05mol) was added in one portion and the suspension warmed to room temperature over 18 h. The THF was removed by evaporation and the off-white slurry taken up into EtOAc (2.5L). The solution was washed with water (3 x 1L), brine (1L), dried over MgSO₄ then evaporated to give a pale yellow oil. Heptane (0.5L) was added and evaporated to give an off white solid, which was triturated with heptane. This was filtered and the solid washed with heptane then dried at 40 °C for 18 h to afford the title compound. ¹H NMR δ_H (300MHz, CDCl₃): 7.40 – 7.20 (m, 5H), 7.05 (m, 1H), 6.95 (m, 1H), 6.85 (m, 1H), 4.95 (m, 1H), 4.20 (m, 1H), 3.60 (s, 2H), 3.30 (m, 1H), 3.10 (m, 1H), 2.95 (m, 1H), 2.65 (m, 1H), 2.45 (m, 1H), 1.40 (s, 9H).

Preparation 205: [(3*R*,4*S*)-1-Benzyl-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester



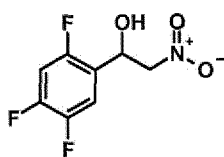
The title compound was afforded via chiral HPLC separation of 1-benzyl-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl-carbamic acid *tert*-butyl ester (**Preparation 204**): IH:IPA:DEA 96:4:0.1, 15ml/min, 270nm, RT = 10.9 min.

Preparation 206: [(3*R*,4*S*)-4-(2,5-Difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester



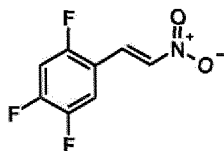
10% Pd/C (20g) was added as a paste in toluene to a solution of [(3*R*,4*S*)-1-benzyl-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester (**Preparation 205**, 212g, 0.55mol) in IMS (6L) in a 7.8L autoclave. The autoclave was sealed, charged with H₂ (50 bar) and heated to 60 °C for 6 h then r.t. for 72 h. The Pd/C was removed by filtration through celite, the pad washed with
5 IMS and the filtrate evaporated to dryness. The reaction was repeated (200g, 0.52mol) and the two batches combined to give 288g of an off-white solid. This was triturated with heptane, filtered, washed with heptane and dried at 40 °C for 18 h to afford the title compound. ¹H NMR δ_H (300MHz, CDCl₃): 7.00 (m, 2H), 6.85 (m, 1H) 4.75 (br s, 1H), 4.15 (m, 1H), 3.45 (m, 2H), 3.25 (m, 1H), 2.90 (m, 2H), 1.90 (s, 1H), 1.35 (s, 9H).

Preparation 207: 2-Nitro-1-(2,4,5-trifluoro-phenyl)-ethanol



Nitromethane (274mL, 5.10mol) was added in one portion to a solution of 2,4,5-trifluorobenzaldehyde (680g, 4.25mol) in MeOH (7.2L) in a 10 L jacketed vessel. The solution was
15 cooled to 0 °C (jacket -10 °C) and a solution of NaOH (204g, 5.10mol) in water (680mL) was added over 30 min. A 5 °C exotherm was observed. The solution was stirred for 30 min (jacket 0 °C) after which time a white precipitate had formed. Half of the material was transferred to a second vessel and both slurries stirred for a further 30 min becoming very thick. Ice water (2L) and NH₄Cl (sat. aq., 2.5L) was added to each to afford a solution. The solutions were extracted with DCM (5 x 1.5L) and
20 the organics from both batches combined and evaporated then dissolved in DCM (1L), dried over MgSO₄ and evaporated to dryness to afford the title compound. ¹H NMR δ_H (300MHz, CDCl₃): 7.45 (m, 1H), 6.95 (m, 1H), 5.70 (m, 1H), 4.55 (m, 2H), 3.10 (d, 1H).

Preparation 208: 1,2,4-Trifluoro-5-((*E*)-2-nitro-vinyl)-benzene

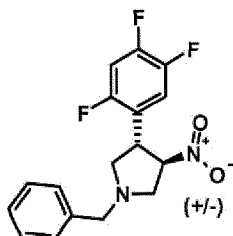


Acetic anhydride (849mL, 8.99mol) was added to 2-nitro-1-(2,4,5-trifluoro-phenyl)-ethanol (**Preparation 207**, 935g, 4.22mol) at 0 °C under argon. DMAP (36g, 0.30mol) was added in one portion and the solution darkened in colour. The temperature reached 50 °C over 20 min before cooling back to 0 °C. The solution was allowed to warm to r.t. over 18 h. The reaction mixture was
30 cautiously poured into NaHCO₃ (sat. aq., 6L) and stirred to form a yellow solid. The slurry was stirred for 30 min at r.t. before filtering and washing with NaHCO₃ (sat. aq., 3L) then water (3L). The

solid was dissolved in DCM (2L) and washed with saturated NaHCO_3 (sat. aq., 2 x 1.5L) then the organics dried over MgSO_4 and evaporated to give 795g of an orange / brown oil which solidified to give an orange solid. Purification by dry flash chromatography eluting with DCM afforded the title compound. $^1\text{H NMR } \delta_{\text{H}}$ (300MHz, CDCl_3): 7.95 (d, 1H), 7.65 (d, 1H), 7.35 (m, 1H), 7.05 (m, 1H).

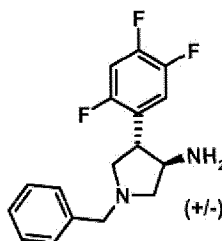
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Preparation 209: 1-Benzyl-3-nitro-4-(2,4,5-trifluoro-phenyl)-pyrrolidine



1,2,4-Trifluoro-5-((*E*)-2-nitro-vinyl)-benzene (**Preparation 208**, 375g, 1.85mol) was dissolved into analytical grade DCM (3.75L) and dried over MgSO_4 . The solution was filtered and split into five batches (75g, 0.37mol). *N*-(Methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine (114mL, 0.44mol) was added to each under argon and the orange solutions were then cooled to -10 °C. TFA (3mL, 40.6mmol) was added to each in one portion and after 5 min the temperature rapidly increased to 30 °C then cooled back to -10 °C. The resulting paler yellow / orange solutions were stirred at -10 °C for 1 h before quenching cautiously with NaHCO_3 (sat. aq., 1L). The layers were partitioned and the DCM layer washed with water (1L), brine (1L), dried over MgSO_4 and evaporated. The crude batches were combined and purified by dry flash chromatography eluting with DCM to afford the title compound. $^1\text{H NMR } \delta_{\text{H}}$ (300MHz, CDCl_3): 7.40 – 7.20 (m, 6H), 6.90 (m, 1H), 4.95 (m, 1H), 4.20 (m, 1H), 3.70 (m, 2H), 3.35 (m, 1H), 3.20 (m, 2H), 2.70 (m, 1H).

Preparation 210: 1-Benzyl-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-3-ylamine

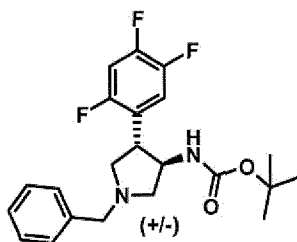


1-Benzyl-3-nitro-4-(2,4,5-trifluoro-phenyl)-pyrrolidine (**Preparation 209**, 621g, 923mol) was run as two batches, each dissolved into IMS (5L) and charged into a 7.8L autoclave. RaNi (20g) was added (without washing) and the autoclave charged with H_2 (50 bar) and stirred at r.t. for 18 h (10 °C exotherm). The mixtures were filtered through celite and both batches combined and evaporated to dryness. The resulting brown oil was dissolved in DCM (1.5L) and extracted with HCl (1M, aq. 2.5L) and washed with DCM (3 x 1L) to remove the colour from the aqueous layer. The aqueous layer was basified to pH 14 with NaOH (2M, aq. 3L) and extracted with DCM (5 x 1L),

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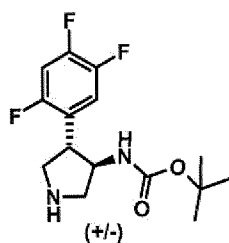
combined, dried over MgSO_4 and evaporated to afford the title compound. ^1H NMR δ_{H} (300MHz, CDCl_3): 7.40 – 7.20 (m, 6H), 6.85 (m, 1H), 3.70 (m, 2H), 3.45 (m, 1H), 3.20 (m, 1H), 3.10 (m, 2H), 2.65 (m, 1H), 2.45 (m, 1H), 2.20 (br s, 2H).

5 **Preparation 211: 1-Benzyl-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-3-yl-carbamic acid *tert*-butyl ester**



Triethylamine (210mL, 1.51mol) was added to 1-benzyl-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-3-ylamine (**Preparation 210**, 231g, 0.75mol) in THF (1.8L) and the light brown cloudy solution was cooled to 0 °C. Di-*tert*-butyldicarbonate (198g, 0.91mol) was added in one portion and the suspension warmed to room temperature over 18 h. The suspension was concentrated and the off-white slurry dissolved into EtOAc (2.5L). The solution was washed with water (3 x 1L) and brine (1L) then dried over MgSO_4 and evaporated to give a pale yellow oil. Heptane (0.5L) was added and evaporated to give an off white solid. This was combined with a second batch (from 218g, 0.71mol starting material) and triturated with heptane, filtered, washed with heptane and dried at 40 °C for 18 h to afford the title compound. ^1H NMR δ_{H} (300MHz, CDCl_3): 7.40 – 7.20 (m, 6H), 6.85 (m, 1H), 4.85 (m, 1H), 4.20 (m, 1H), 3.60 (s, 2H), 3.30 (m, 1H), 3.00 (m, 2H), 2.60 (m, 1H), 2.45 (m, 1H), 1.40 (s, 9H).

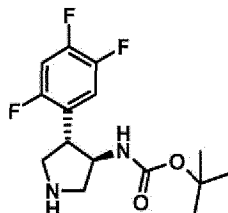
20 **Preparation 212: 4-(2,4,5-Trifluoro-phenyl)-pyrrolidin-3-yl-carbamic acid *tert*-butyl ester**



1-Benzyl-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-3-yl-carbamic acid *tert*-butyl ester (**Preparation 211**, 612g, 1.51mol) was run in two batches each being suspended in EtOAc (0.5L) and IMS (4L) and charged into a 7.8L autoclave. 10% Pd/C (20g) was added to each as a paste in toluene. The autoclave was sealed and charged with H_2 (50 bar) then heated to 55 °C for 6 h, 20 °C for 18 h then 55 °C for 6 h. The reaction mixtures were filtered through celite and the pad washed with IMS before evaporating to dryness. The resulting off-white solids were triturated with heptane, filtered, washed with heptane then dried at 40 °C for 18 h before the two batches were combined to

afford the title compound. ^1H NMR δ_{H} (300MHz, CDCl_3): 7.10 (m, 1H), 6.90 (m, 1H) 4.70 (br s, 1H), 4.15 (m, 1H), 3.45 (m, 2H), 3.20 (m, 1H), 2.85 (m, 2H), 1.75 (br s, 1H), 1.40 (s, 9H).

Preparation 212: [(3*R*,4*S*)-4-(2,4,5-Trifluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester

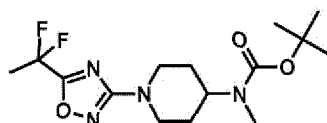


4-(2,4,5-Trifluorophenyl)pyrrolidin-3-yl]carbamic acid *tert*-butyl ester (**Preparation 212**, 30.0g, 95mmol) was suspended in EtOH (100mL) and heated to 70°C. To the suspension was added a warm solution of (*S*)-(+)-naproxen (10.9g, 47mmol) in EtOH (100mL) and the mixture was heated to reflux. The heat was removed and the mixture was slowly allowed to cool to r.t., with stirring, for 16 h. The resulting precipitate was filtered, washing with EtOH, and the solid product was partitioned between DCM (2400mL) and 1M NaOH (600mL). The organic phase was separated, washed with 1M NaOH, brine, then dried (MgSO_4), and the solvent was removed *in vacuo*.

A second portion of [(*trans*)-4-(2,4,5-trifluorophenyl)pyrrolidin-3-yl]carbamic acid *tert*-butyl ester (**Preparation 212**, 29.5g, 93mmol), suspended in EtOH (100mL), was heated to 70°C. Treatment with a warm solution of (*S*)-(+)-naproxen (10.6g, 46mmol) in EtOH (100mL), employing the procedure outlined above, afforded a second batch of the enantiomerically enriched product.

The two products were combined, and suspended in EtOH (200mL) before being treated with a hot solution of (*S*)-(+)-naproxen (16g, 69mmol) in EtOH (150mL). The mixture was heated to reflux, employing the procedure outlined above, and work-up was repeated to afford the title compound: ^1H NMR δ_{H} (400MHz, CD_3OD): 7.38 - 7.25 (m, 1H), 7.14 - 7.01 (m, 1H), 4.20 - 4.09 (m, 1H), 3.30 - 3.21 (m, 3H), 2.90 - 2.81 (m, 1H), 2.77 - 2.68 (m, 1H), 1.34 (br. s., 9H).

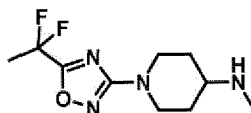
Preparation 213: {1-[5-(1,1-Difluoro-ethyl)-[1,2,4]oxadiazol-3-yl]-piperidin-4-yl}-methyl-carbamic acid *tert*-butyl ester



To a solution of (1-cyano-piperidin-4-yl)-methyl-carbamic acid *tert*-butyl ester (**Preparation 21**, 1.00g, 4.18mmol) in EtOH (10mL) was added 50% hydroxylamine in water (0.26mL, 4.2mmol) and the mixture heated at 70°C for 1 h. The reaction was cooled to r.t. and concentrated under reduced pressure. The resulting solid was dissolved in DMF (6.47mL, 83.6mmol) and HOBt

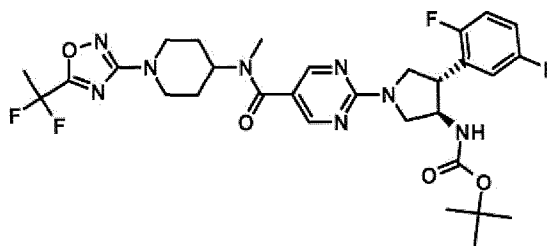
(0.0640g, 0.418mmol), EDCI (0.961g, 5.01mmol) and 2,2-difluoropropionic acid (0.552g, 5.01mmol) added. The reaction mixture was stirred at r.t. over 60 h, after which time it was diluted with EtOAc (150mL) and washed with a saturated solution of sodium bicarbonate (2 x 100mL), 1 M citric acid solution (100mL) then brine (100mL). The organics were concentrated under reduced pressure, and the residue dissolved in toluene (5mL) then heated at reflux for 13 h. The reaction was cooled to r.t. and concentrated under reduced pressure. Purification by column chromatography (7:3 EtOAc:1H) afforded the title compound: RT = 1.33 min; m/z (ES^+) = 347.4 [$M + H$] $^+$ (LCMS Method - 2).

Preparation 214: {1-[5-(1,1-Difluoro-ethyl)-[1,2,4]oxadiazol-3-yl]-piperidin-4-yl}-methyl-amine



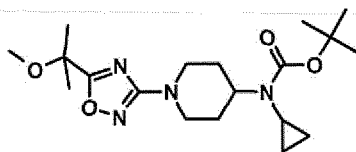
{1-[5-(1,1-Difluoro-ethyl)-[1,2,4]oxadiazol-3-yl]-piperidin-4-yl}-methyl-carbamic acid *tert*-butyl ester (**Preparation 213**, 1.1g, 3.2mmol) was dissolved in DCM (10mL, 200mmol) and TFA (2mL, 20mmol) added. The reaction was stirred at r.t. for 1 h before being loaded directly onto an SCX cartridge. Elution with MeOH followed by 7N ammonia in MeOH solution and concentration *in vacuo* afforded the title compound: RT = 0.52 min, m/z (ES^+) = 247.3 [$M + H$] $^+$ (LCMS Method - 2).

Preparation 215: [(3*R*,4*S*)-1-[5-({1-[5-(1,1-Difluoro-ethyl)-[1,2,4]oxadiazol-3-yl]-piperidin-4-yl}-methyl-carbamoyl)-pyrimidin-2-yl]-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester



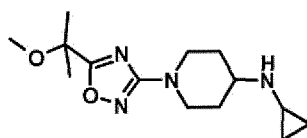
The title compound was synthesized from 2-[(3*R*,4*S*)-3-*tert*-butoxycarbonylamino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid (**Preparation 90**, 430mg, 1.0mmol) and {1-[5-(1,1-difluoro-ethyl)-[1,2,4]oxadiazol-3-yl]-piperidin-4-yl}-methyl-amine (**Preparation 214**, 250mg, 1.015mmol) employing a procedure similar to that outlined in **Preparation 105**: RT = 1.31 min; m/z (ES^+) = 649.6 [$M + H$] $^+$.

Preparation 216: Cyclopropyl-{1-[5-(1-methoxy-1-methyl-ethyl)-[1,2,4]oxadiazol-3-yl]-piperidin-4-yl}-carbamic acid *tert*-butyl ester



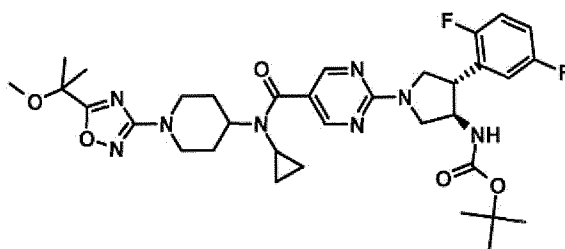
The title compound was synthesized from (1-cyano-piperidin-4-yl)-cyclopropyl-carbamic acid *tert*-butyl ester (**Preparation 26**, 621mg, 2.34mmol) and 2-methoxy-2-methyl-propionic acid (351mL, 2.82mmol) employing a procedure similar to that outlined in **Preparation 213**: RT = 1.34 min; m/z (ES^+) = 381.5 $[M + H]^+$.

Preparation 217: Cyclopropyl-{1-[5-(1-methoxy-1-methyl-ethyl)-[1,2,4]oxadiazol-3-yl]-piperidin-4-yl}-amine



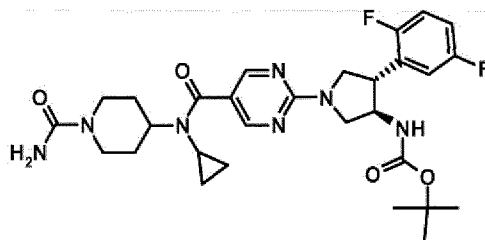
The title compound was synthesized from cyclopropyl-{1-[5-(1-methoxy-1-methyl-ethyl)-[1,2,4]oxadiazol-3-yl]-piperidin-4-yl}-carbamic acid *tert*-butyl ester (**Preparation 216**, 590mg, 1.55mmol) employing a procedure similar to that outlined in **Preparation 214**: RT = 0.51 min; m/z (ES^+) = 281.4 $[M + H]^+$.

Preparation 218: [(3*R*,4*S*)-1-[5-(Cyclopropyl-{1-[5-(1-methoxy-1-methyl-ethyl)-[1,2,4]oxadiazol-3-yl]-piperidin-4-yl}-carbamoyl)-pyrimidin-2-yl]-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester



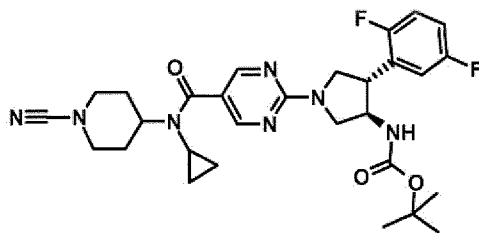
The title compound was synthesized from 2-[(3*R*,4*S*)-3-*tert*-butoxycarbonylamino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid (**Preparation 90**, 277mg, 0.66mmol) and cyclopropyl-{1-[5-(1-methoxy-1-methyl-ethyl)-[1,2,4]oxadiazol-3-yl]-piperidin-4-yl}-amine (**Preparation 217**, 185mg, 0.66mmol) employing a procedure similar to that outlined in **Preparation 105**: RT = 1.33 min; m/z (ES^+) = 683.7 $[M + H]^+$.

Preparation 219: [(3*R*,4*S*)-1-{5-[(1-Carbamoyl-piperidin-4-yl)-cyclopropyl-carbamoyl]-pyrimidin-2-yl}-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester



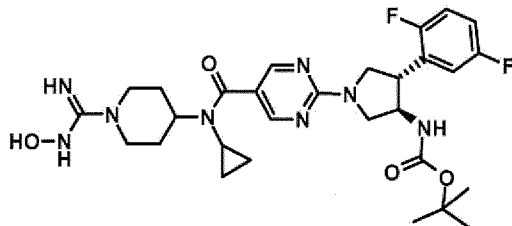
To a stirred solution of (1-cyano-piperidin-4-yl)-cyclopropyl-carbamic acid *tert*-butyl ester
 5 **(Preparation 26**, 1.09g, 4.12mmol) in DCM (20mL) at 0°C was added TFA (4mL, 50mmol). The solution was allowed to warm to r.t. and stirred for 4 h. The reaction mixture was passed through a SCX cartridge and the free base eluted with a 3.5M solution of ammonia in MeOH. The mixture was concentrated *in vacuo* and the residue dissolved in DCM (60mL). To this was added 2-[(3*R*,4*S*)-3-*tert*-butoxycarbonylamino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid
 10 **(Preparation 90**, 1.73g, 4.12mmol), triethylamine (2.29mL, 16.5mmol) and PPA (50% w/w in EtOAc, 4.90mL, 8.23mmol) and the reaction stirred at r.t. for 18 h. The mixture was quenched with MeOH and concentrated under reduced pressure. The residue was dissolved in MeOH and loaded directly onto a SCX cartridge and eluted with MeOH, then 7N ammonia in MeOH solution and concentrated *in vacuo*. Purification of the residue by column chromatography (7:3 EtOAc:IH) afforded the title compound: RT = 0.99 min, *m/z* (ES⁺) = 586.6 [*M* + H]⁺ (LCMS Method - 2).
 15

Preparation 220: [(3*R*,4*S*)-1-{5-[(1-Cyano-piperidin-4-yl)-cyclopropyl-carbamoyl]-pyrimidin-2-yl}-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester



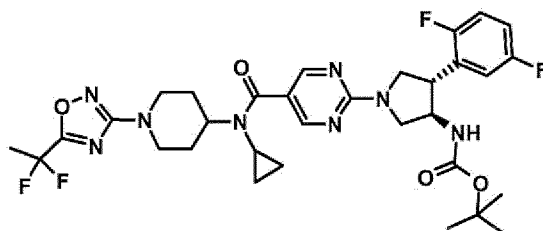
20 [(3*R*,4*S*)-1-{5-[(1-Carbamoyl-piperidin-4-yl)-cyclopropyl-carbamoyl]-pyrimidin-2-yl}-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester **(Preparation 219**, 0.700g, 1.20mmol) and MeCN (20mL) were combined under an argon atmosphere. Methanesulfonyl chloride (0.139mL, 1.79mmol) followed by pyridine (0.242mL, 2.99mmol) were added via syringe. The resulting suspension was stirred for 5 min prior to being heated to 50 °C for 18 h. The solvent was removed under reduced pressure and water (50mL) added to the resulting residue. The mixture was
 25 extracted with EtOAc (3 x 150mL), the organics combined and dried (magnesium sulfate) before concentration under reduced pressure afford the title compound: RT = 1.15 min, *m/z* (ES⁺) = 568.8 [*M* + H]⁺ (LCMS Method -2).

Preparation 221: [(3*R*,4*S*)-1-(5-{Cyclopropyl-[1-(*N*-hydroxycarbamimidoyl)-piperidin-4-yl]-carbamoyl}-pyrimidin-2-yl)-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester



5 [(3*R*,4*S*)-1-{5-[(1-Cyano-piperidin-4-yl)-cyclopropyl-carbamoyl]-pyrimidin-2-yl}-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester (**Preparation 220**, 500mg, 0.881mmol) was dissolved in EtOH (10mL) and 50% hydroxylamine in water (0.11mL, 1.8mmol) added via syringe. The reaction mixture was stirred overnight at r.t. The mixture was then concentrated under reduced pressure and further azeotroped with toluene to afford the title
10 compound: RT = 0.84 min, m/z (ES^+) = 601.6 [$M + H$] $^+$.

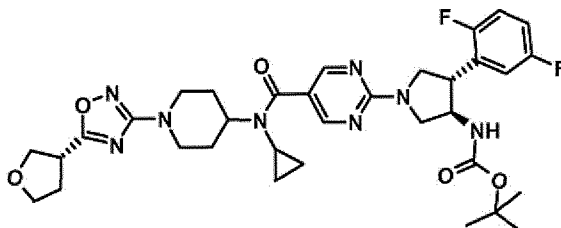
Preparation 222: [(3*R*,4*S*)-1-[5-(Cyclopropyl-{1-[5-(1,1-difluoro-ethyl)-[1,2,4]oxadiazol-3-yl]-piperidin-4-yl}-carbamoyl)-pyrimidin-2-yl]-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester



15 [(3*R*,4*S*)-1-(5-{Cyclopropyl-[1-(*N*-hydroxycarbamimidoyl)-piperidin-4-yl]-carbamoyl}-pyrimidin-2-yl)-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester (**Preparation 221**, 230mg, 0.383mmol), 2,2-difluoropropionic acid (50.6mg, 0.459mmol), EDCI (88.1mg, 0.459mmol) and triethylamine (0.117mL, 0.842mmol) were combined in DCM (20mL) and HOBT
20 (0.8mg, 0.005mmol) added. The reaction was stirred at r.t. for 18 h before quenching with MeOH and concentrating under reduced pressure, azeotroping with toluene. Purification of the residue by preparative HPLC afforded the title compound: RT = 4.32 min, m/z (ES^+) = 675.9 [$M + H$] $^+$ (LCMS Method -1).

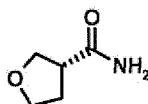
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Preparation 223: [(3*R*,4*S*)-1-[5-(Cyclopropyl-{1-[(*R*)-5-(tetrahydro-furan-3-yl)-[1,2,4]oxadiazol-3-yl]-piperidin-4-yl}-carbamoyl)-pyrimidin-2-yl]-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester



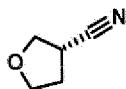
The title compound was synthesized from [(3*R*,4*S*)-1-(5-{cyclopropyl-[1-(*N*-hydroxycarbamimidoyl)-piperidin-4-yl]-carbamoyl}-pyrimidin-2-yl)-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester (**Preparation 221**) and (*R*)-tetrahydro-furan-3-carboxylic acid employing a procedure similar to that outlined in **Preparation 222**: RT = 1.22 min, m/z (ES^+) = 681.6 [$M + H$] $^+$ (LCMS Method - 2).

Preparation 224: (*R*)-Tetrahydro-furan-3-carboxylic acid amide



To a solution of (*R*)-tetrahydro-furan-3-carboxylic acid (500mg, 4.31mmol) in DCM (5mL) at 0 °C under inert atmosphere was added oxalyl chloride (444μL, 5.17mmol) followed by DMF (50μL, 0.65mmol). The reaction mixture was stirred for 1 h then allowed to warm to room temperature and stirred for further 2 h. After cooling to 0 °C, NH_3 in MeOH solution (7*N*, 50mL) was added and the mixture stirred overnight. The solvents were then removed *in vacuo*, azeotroping with DCM to dryness to afford the title compound: 1H NMR δ_H (300MHz, $CDCl_3$): 5.80-5.30 (bs, 2H), 3.90 (m, 4H), 2.90 (m, 1H), 2.20 (m, 2H).

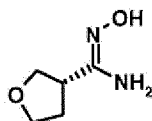
Preparation 225: (*S*)-Tetrahydro-furan-3-carbonitrile



To a solution of (*R*)-tetrahydro-furan-3-carboxylic acid amide (**Preparation 224**, 435mg, 3.78mmol) in THF (10mL) was added pyridine (2.31mL, 28.61mmol) and the reaction cooled to 0 °C. Trifluoroacetic anhydride (2.70mL, 28.61mmol) was added and the mixture stirred for 1 h. The mixture was partitioned between saturated aqueous sodium bicarbonate solution and DCM; the aqueous layer was back-extracted with further DCM. The combined organics were washed with brine and dried with magnesium sulfate before concentrating *in vacuo*. Purification of the residue by

column chromatography (EtOAc) afforded the title compound: ^1H NMR δ_{H} (300MHz, CDCl_3): 4.05 (t, 1H), 3.90 (m, 3H), 3.05 (m, 1H), 2.3 (m, 2H).

Preparation 226: (*S*)-*N*-Hydroxy-tetrahydro-furan-3-carboxamidine

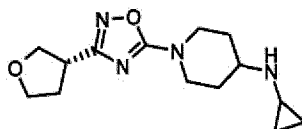


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To a solution of (*S*)-tetrahydrofuran-3-carbonitrile (**Preparation 225**, 280mg, 2.89mmol) in IMS (2mL) was added hydroxylamine (50% in water, 229 μL , 3.46mmol) and the reaction was heated to 70 $^{\circ}\text{C}$ for 18 h. On cooling, the solvent was removed *in vacuo*, azeotroping with toluene. The residue was triturated with toluene then DCM. Purification by column chromatography (DCM:MeOH, 90:10) afforded the title compound: ^1H NMR δ_{H} (300MHz, CDCl_3): 4.70 (bs, 2H), 4.05 (m, 2H), 3.70 (m, 2H), 2.9 (m, 1H), 2.25 (m, 1H), 2.00 (m, 1H).

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Preparation 227: Cyclopropyl-{1-[(*S*)-3-(tetrahydro-furan-3-yl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-amine

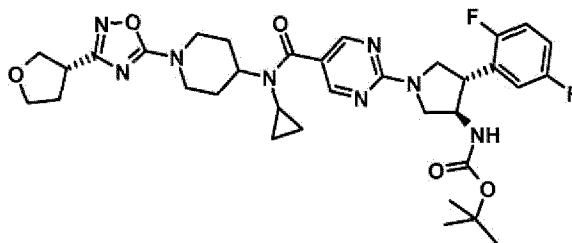


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The title compound was synthesized from (1-cyano-piperidin-4-yl)-cyclopropyl-carbamic acid *tert*-butyl ester (**Preparation 26**) and (*S*)-*N*-hydroxy-tetrahydro-furan-3-carboxamidine (**Preparation 226**) employing a procedure similar to that outlined in **Preparation 35**: RT = 0.46 min; m/z (ES^+) = 279.37 [$M + \text{H}$] $^+$ (LCMS Method - 2).

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Preparation 228: [(3*R*,4*S*)-1-[5-(Cyclopropyl-{1-[(*S*)-3-(tetrahydro-furan-3-yl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-carbonyl)-pyrimidin-2-yl]-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester

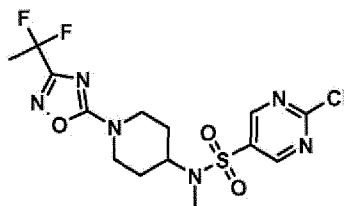


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The title compound was synthesized from 2-[(3*R*,4*S*)-3-*tert*-butoxycarbonylamino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid (**Preparation 90**) and cyclopropyl-{1-[(*S*)-3-(tetrahydro-furan-3-yl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-amine (**Preparation 227**) employing a procedure similar to that outlined in **Preparation 105**: RT = 1.17 min; m/z (ES^+) =

681.56 $[M + H]^+$.

Preparation 229: 2-Chloro-pyrimidine-5-sulfonic acid {1-[3-(1,1-difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-methyl-amide



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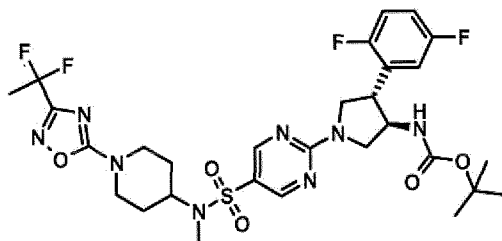
{1-[3-(1,1-Difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-methyl-amine

(**Preparation 44**, 0.150g, 0.609mmol), triethylamine (0.102mL, 0.730mmol) and DCM (4mL) were combined and 2-chloropyrimidine-5-sulfonyl chloride (0.130g, 0.609mmol) added. The reaction was stirred at r.t. for 10 min. Water (20mL) and DCM (50mL) were added and the organic layer separated and washed with 1M HCl solution (50mL) before concentrating under reduced pressure. Purification of the residue by column chromatography (1:1 EtOAc:IH) afforded the title compound: RT = 1.17 min, m/z (ES^+) = 423.4 $[M + H]^+$.

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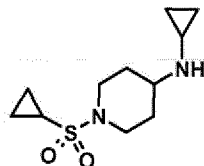
Preparation 230: [(3*R*,4*S*)-1-[5-({1-[3-(1,1-Difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-methyl-sulfamoyl)-pyrimidin-2-yl]-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester



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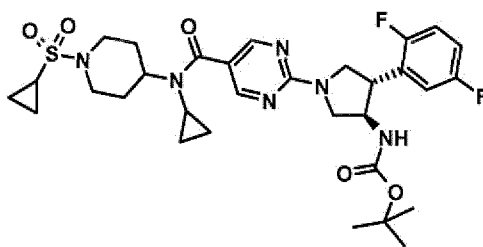
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2-Chloro-pyrimidine-5-sulfonic acid {1-[3-(1,1-difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-methyl-amide (**Preparation 229**, 103mg, 0.244mmol), triethylamine (0.0407mL, 0.292mmol) and THF (5 mL) were combined and [(3*R*,4*S*)-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester (**Preparation 206**, 72.7mg, 0.244mmol) added. The reaction was stirred at 50 °C for 2 h. The reaction was cooled to r.t. and the THF removed under reduced pressure. The residue was dissolved in DCM (50mL) and the organic layer washed with 1M HCl solution (2 x 100mL) and saturated sodium bicarbonate solution (100mL). The organics were dried (magnesium sulfate) before being concentrated under reduced pressure. Purification by column chromatography (3.5:6.5 EtOAc:IH) afforded the title compound: RT = 1.38 min, m/z (ES^+) = 685.6 $[M + H]^+$.

Preparation 231: (1-Cyclopropanesulfonyl-piperidin-4-yl)-cyclopropyl-amine

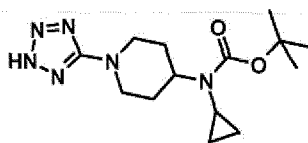
Cyclopropyl-piperidin-4-yl-carbamic acid *tert*-butyl ester (**Preparation 19**, 0.200g, 0.832mmol) was dissolved in DCM (10.0mL, 156mmol) and DIPEA (0.362mL, 2.08mmol) added followed by cyclopropylsulfonylchloride (0.102mL, 0.998mmol). The reaction mixture was stirred at r.t. for 18 h. The mixture was diluted with DCM and washed with water followed by brine, filtered through a hydrophobic frit and then concentrated *in vacuo*. The residue was passed through a SCX cartridge and eluted with MeOH before concentrating *in vacuo*. The residue was dissolved in DCM (10mL) and cooled to 0 °C before the dropwise addition of TFA (1.0mL, 13mmol). The reaction mixture was stirred at room temperature for 1 h. The mixture was then passed through a SCX cartridge and eluted with 10% ammonia in MeOH and concentrated *in vacuo*. Purification by column chromatography (8:92 MeOH:DCM) afforded the title compound: ¹H NMR δ_H (301MHz, CDCl₃): 3.44 - 3.37 (m, 2H), 2.67 - 2.56 (m, 2H), 2.38 - 2.27 (m, 1H), 1.99 - 1.89 (m, 1H), 1.84 - 1.78 (m, 1H), 1.73 - 1.64 (m, 2H), 1.29 - 1.10 (m, 4H), 0.89 - 0.81 (m, 2H), 0.68 - 0.61 (m, 2H), 0.19 - 0.12 (m, 2H), 0.09 - 0.00 (m, 2H).

Preparation 232: [(3*R*,4*S*)-1-{5-[(1-Cyclopropanesulfonyl-piperidin-4-yl)-cyclopropyl-carbamoyl]-pyrimidin-2-yl}-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester



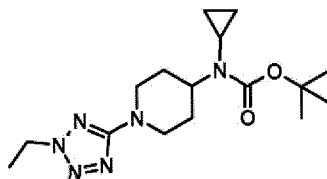
The title compound was synthesized from 2-[(3*R*,4*S*)-3-*tert*-butoxycarbonylamino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid (**Preparation 90**) and (1-cyclopropanesulfonyl-piperidin-4-yl)-cyclopropyl-amine (**Preparation 231**) employing a procedure similar to that outlined in **Preparation 105**: RT = 1.21 min; *m/z* (ES⁺) = 647.61 [*M* + H]⁺ (LCMS Method - 2).

Preparation 233: Cyclopropyl-[1-(2H-tetrazol-5-yl)-piperidin-4-yl]-carbamic acid *tert*-butyl ester



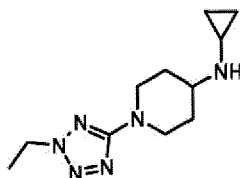
(1-Cyano-piperidin-4-yl)-cyclopropyl-carbamic acid *tert*-butyl ester (**Preparation 26**, 0.514g, 1.94mmol) was dissolved in DMF (1.0mL) and ammonium chloride (0.207g, 3.87mmol) was added followed by sodium azide (0.252g, 3.87mmol). The reaction mixture was heated at 100 °C for 18 h before the addition of water (15mL), then brine. The aqueous layer was extracted with EtOAc (3 x) and the combined organic extracts were filtered through a hydrophobic frit and concentrated *in vacuo*. Purification of the residue by column chromatography (6:94 MeOH:DCM) afforded the title compound: RT = 0.9min; m/z (ES^+) = 309.40 [$M + H$] $^+$ (LCMS Method - 2).

Preparation 234: Cyclopropyl-[1-(2-ethyl-2H-tetrazol-5-yl)-piperidin-4-yl]-carbamic acid *tert*-butyl ester



Cyclopropyl-[1-(2H-tetrazol-5-yl)-piperidin-4-yl]-carbamic acid *tert*-butyl ester (**Preparation 233**, 0.166g, 0.538mmol) was dissolved in acetone (16mL) and potassium carbonate (0.22g, 1.6mmol) added followed by the dropwise addition of iodoethane (0.056mL, 0.70mmol). The reaction mixture was then heated at 45 °C for 5 h before concentrating *in vacuo*. The residue was partitioned between EtOAc (50mL) and water (25mL). The organic phase was separated and washed with brine, filtered through a hydrophobic frit and concentrated *in vacuo*. Purification by column chromatography (3:7 EtOAc:1H) afforded the title compound: RT = 1.22 min; 337.44 m/z (ES^+) = [$M + H$] $^+$ (LCMS Method - 2).

Preparation 235: Cyclopropyl-[1-(2-ethyl-2H-tetrazol-5-yl)-piperidin-4-yl]-amine

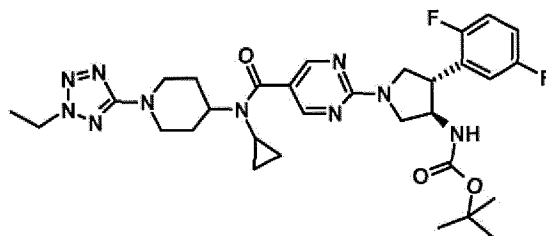


Cyclopropyl-[1-(2-ethyl-2H-tetrazol-5-yl)-piperidin-4-yl]-carbamic acid *tert*-butyl ester (**Preparation 234**, 0.135g, 0.401mmol) was dissolved in DCM (8.0mL) and cooled to 0 °C. TFA

(1.0mL, 13mmol) was added drop wise. Once addition was complete, the reaction was stirred at room temperature for 2 h. The reaction mixture was passed through a SCX cartridge and eluted with 10% ammonia in MeOH solution to obtain the title compound: RT = 0.49min; m/z (ES^+) = 237.35 [$M + H$] $^+$ (LCMS Method - 2).

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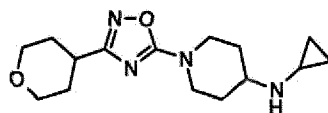
Preparation 236: [(3*R*,4*S*)-1-(5-{Cyclopropyl-[1-(2-ethyl-2*H*-tetrazol-5-yl)-piperidin-4-yl]-carbamoyl}-pyrimidin-2-yl)-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester



The title compound was synthesized from 2-[(3*R*,4*S*)-3-*tert*-butoxycarbonylamino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid (**Preparation 90**) and cyclopropyl-[1-(2-ethyl-2*H*-tetrazol-5-yl)-piperidin-4-yl]-amine (**Preparation 235**) employing a procedure similar to that outlined in **Preparation 105**: RT = 1.24min; m/z (ES^+) = 639.64 [$M + H$] $^+$ (LCMS Method - 2).

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Preparation 237: Cyclopropyl-{1-[3-(tetrahydro-pyran-4-yl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-amine

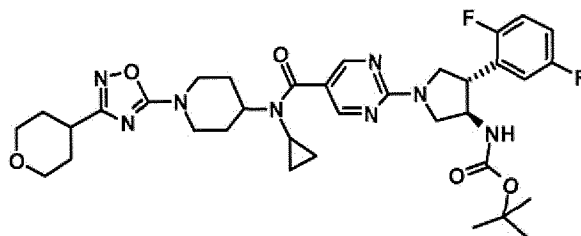


The title compound was synthesized from (1-cyano-piperidin-4-yl)-cyclopropyl-carbamic acid *tert*-butyl ester (**Preparation 26**) and *N*-hydroxy-tetrahydro-pyran-4-carboxamidinium employing a procedure similar to that outlined in **Preparation 35**: RT = 0.50min; m/z (ES^+) = 293.41 [$M + H$] $^+$ (LCMS Method - 2).

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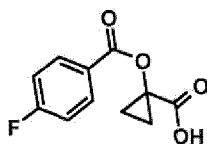
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Preparation 238: [(3*R*,4*S*)-1-[5-(Cyclopropyl-{1-[3-(tetrahydro-pyran-4-yl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-carbamoyl)-pyrimidin-2-yl]-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester



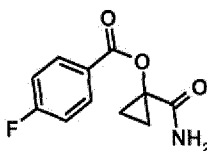
The title compound was synthesized from 2-[(3*R*,4*S*)-3-*tert*-butoxycarbonylamino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid (**Preparation 90**) and cyclopropyl-{1-[3-(tetrahydro-pyran-4-yl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-amine (**Preparation 237**) employing a procedure similar to that outlined in **Preparation 105**: RT = 1.19min; m/z (ES^+) = 695.65 [$M + H$] $^+$ (LCMS Method - 2).

Preparation 239: 4-Fluoro-benzoic acid 1-carboxy-cyclopropyl ester



To a solution of 1-hydroxy-1-cyclopropanecarboxylic acid (0.500g, 4.90mmol) in pyridine (1.25mL) and chloroform (1mL) at 0°C was added 4-fluoro-benzoyl chloride (0.608mL, 5.14mmol) and the resulting reaction mixture was heated at 70°C for 40 min. Upon cooling, the reaction mixture was poured into water (20mL) and extracted with chloroform (3 x 15mL). The combined organic extracts were washed with 2M HCl (20mL) and then extracted into saturated aqueous NaHCO₃ solution (2 x 20mL). The combined NaHCO₃ extracts were adjusted to pH 1 with 12M HCl and then extracted into chloroform (3 x 20mL). The combined organic extracts were passed through a hydrophobic frit and the solvent removed *in vacuo*. Purification by column chromatography (EtOAc:1H; 1:9 to 3:10) afforded the title compound: RT = 0.94 min; m/z (ES^-) = 223.18 [$M - H$] $^+$.

Preparation 240: 4-Fluoro-benzoic acid 1-carbamoyl-cyclopropyl ester

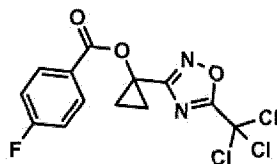


To a solution of 4-fluoro-benzoic acid 1-carboxy-cyclopropyl ester (**Preparation 239**, 0.423g, 1.89mmol) in THF (13mL) was added EDCI (0.434g, 2.26mmol) and HOBt and the resulting reaction mixture was stirred at r.t. for 10 min. NH₃ in 1,4-dioxane (0.5M, 37.74mL, 18.87mmol) was

added and the reaction mixture stirred at r.t. for 72 h. The solvent was removed *in vacuo* and the remainder partitioned between water (100mL) and EtOAc (200mL). The organic layer was separated and washed with saturated aqueous NaHCO₃ solution and brine, dried (MgSO₄), filtered and concentrated *in vacuo*: RT = 0.82 min; *m/z* (ES⁺) = 224.19 [*M* + H]⁺.

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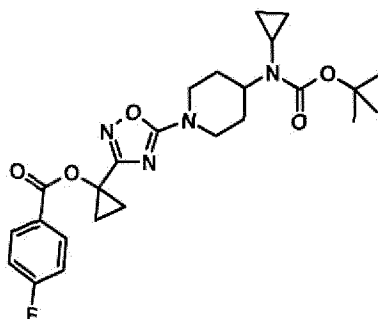
Preparation 241: 4-Fluoro-benzoic acid 1-(5-trichloromethyl-[1,2,4]oxadiazol-3-yl)-cyclopropyl ester



To a solution of 4-fluoro-benzoic acid 1-carbamoyl-cyclopropyl ester (**Preparation 240**, 0.290g, 1.30mmol) in THF (10mL) at 0°C was added triethylamine (0.54mL, 3.9mmol) followed by trifluoroacetic anhydride (0.28mL, 1.9mmol) and the resulting reaction mixture was stirred for 1 h. The reaction was quenched with water (50mL), extracted into DCM (2 x 70mL) and the combined organic extracts were passed through a hydrophobic frit and concentrated *in vacuo*. The remainder was dissolved in EtOH (10mL) and hydroxylamine (50% aqueous solution, 87.6μL, 1.43mmol) was added. The resulting reaction mixture was heated at 60°C for 1.5 h, then the solvent removed *in vacuo*. The remainder was dissolved in toluene (20mL), perchloroacetic anhydride (0.237mL, 1.30mmol) was added and the reaction mixture heated at 90°C for 3 h. The solvent was removed *in vacuo* and the remainder purified by column chromatography (EtOAc:1H; 5:95) to afford the title compound: RT = 1.42 min; *m/z* (ES⁺) = 365.07 [*M* + H]⁺.

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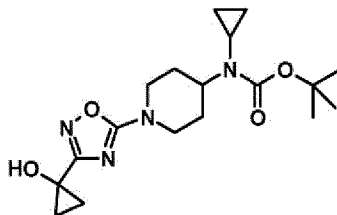
Preparation 242: 4-Fluoro-benzoic acid 1-{5-[4-(*tert*-butoxycarbonyl-cyclopropyl-amino)-piperidin-1-yl]-[1,2,4]oxadiazol-3-yl}-cyclopropyl ester



Cyclopropyl-piperidin-4-yl-carbamic acid *tert*-butyl ester (**Preparation 19**, 0.038g, 0.16mmol) and 4-fluoro-benzoic acid 1-(5-trichloromethyl-[1,2,4]oxadiazol-3-yl)-cyclopropyl ester (**Preparation 241**, 0.034g, 0.093mmol) were combined in dimethyl sulfoxide (0.2mL) and the mixture stirred at room temperature for 16 h. The reaction mixture was diluted with water (15mL) and then extracted with EtOAc (3 x 50mL). The combined organic extracts were washed with brine

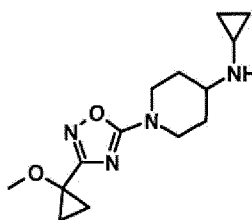
and passed through a hydrophobic frit then concentrated *in vacuo*. Purification by preparative HPLC (standard method) afforded the title compound: RT = 1.45min; m/z (ES^+) = 487.44 [$M + H$] $^+$ (LCMS Method - 2).

5 **Preparation 243: Cyclopropyl-{1-[3-(1-hydroxy-cyclopropyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-carbamic acid *tert*-butyl ester**



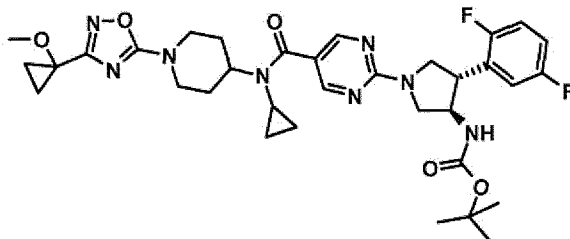
4-Fluoro-benzoic acid 1-{5-[4-(*tert*-butoxycarbonyl-cyclopropyl-amino)-piperidin-1-yl]-[1,2,4]oxadiazol-3-yl}-cyclopropyl ester (**Preparation 242**, 0.034g, 0.070mmol) was dissolved in THF (2.0 mL), MeOH (1.0 mL), water (1.0 mL), lithium hydroxide monohydrate (0.012g, 0.28mmol) added and the mixture stirred at room temperature for 2 h. The reaction mixture was diluted with water and extracted with EtOAc (2 x). The combined organic extracts were filtered through a hydrophobic frit and concentrated *in vacuo* to afford the title compound: RT = 1.04 min ; m/z (ES^+) = 369.39 [$M + H$] $^+$ (LCMS Method - 2).

15 **Preparation 244: Cyclopropyl-{1-[3-(1-methoxy-cyclopropyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-amine**



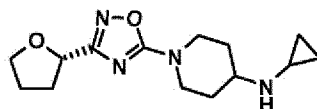
Cyclopropyl-{1-[3-(1-hydroxy-cyclopropyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-carbamic acid *tert*-butyl ester (**Preparation 243**, 0.082g, 0.22mmol) was dissolved in THF (6.0mL) and cooled to 0°C. NaH (60% dispersion in mineral oil, 0.012g, 0.29mmol) was added and the mixture stirred at 0°C for 20 min followed by stirring at room temperature for 10 min. Methyl iodide (0.018mL, 0.29mmol) was added and stirred at r.t. for 2 h. The reaction mixture was diluted with water (30mL) and extracted with EtOAc (3 x 50mL). The combined organic extracts were washed with brine, filtered through a hydrophobic frit and concentrated *in vacuo*. The residue was dissolved in DCM (10mL) and cooled to 0°C. TFA (1.5mL, 19mmol) was added and stirred for 2 h. The mixture was passed through a SCX cartridge eluting with 10% ammonia in MeOH solution to afford the title compound: RT = 0.53 min; m/z (ES^+) = 279.49 [$M + H$] $^+$ (LCMS Method - 2).

Preparation 245: [(3*R*,4*S*)-1-[5-(Cyclopropyl-{1-[3-(1-methoxy-cyclopropyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-carbamoyl)-pyrimidin-2-yl]-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester



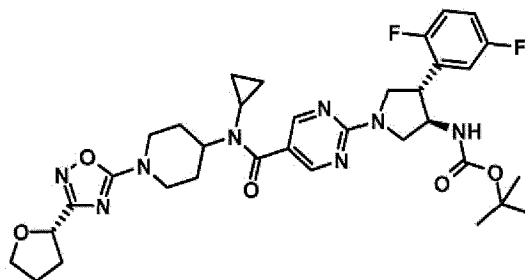
The title compound was synthesized from 2-[(3*R*,4*S*)-3-*tert*-butoxycarbonylamino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid (**Preparation 90**) and cyclopropyl-{1-[3-(1-methoxy-cyclopropyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-amine (**Preparation 244**) employing a procedure similar to that outlined in **Preparation 105**: RT = 1.27 min; m/z (ES^+) = 681.57 [$M + H$] $^+$ (LCMS Method - 2).

Preparation 246: Cyclopropyl-{1-[(*S*)-3-(tetrahydro-furan-2-yl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-amine



The title compound was synthesized from (1-cyano-piperidin-4-yl)-cyclopropyl-carbamic acid *tert*-butyl ester (**Preparation 26**) and (*S*)-*N*-hydroxytetrahydrofuran-2-carboxamidine (**Preparation 34**) employing a procedure similar to that outlined in **Preparation 35**: RT = 0.48min; m/z (ES^+) = 279.35 [$M + H$] $^+$ (LCMS Method - 2).

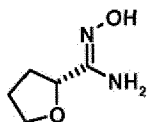
Preparation 247: [(3*R*,4*S*)-1-[5-(Cyclopropyl-{1-[(*S*)-3-(tetrahydro-furan-2-yl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-carbamoyl)-pyrimidin-2-yl]-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester



The title compound was synthesized from 2-[(3*R*,4*S*)-3-*tert*-butoxycarbonylamino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid (**Preparation 90**) and cyclopropyl-{1-[(*S*)-3-(tetrahydro-furan-2-yl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-amine (**Preparation 246**)

employing a procedure similar to that outlined in **Preparation 105**: RT = 1.19 min; m/z (ES^+) = 681.54 [$M + H$] $^+$ (LCMS Method - 2).

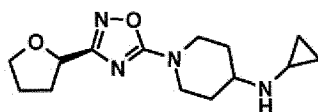
Preparation 248: (*R*)-*N*-Hydroxytetrahydrofuran-2-carboxamidine



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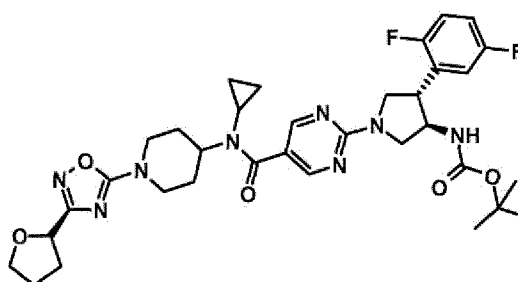
The title compound was synthesized from (*R*)-tetrahydrofuran-2-carbonitrile employing a procedure similar to that outlined in **Preparation 34**: 1H NMR δ_H (300MHz, $CDCl_3$): 4.85 (bs, 2H), 4.44 – 4.32 (m, 1H), 4.00 – 3.74 (m, 2H), 2.20 – 1.80 (m, 4H).

Preparation 249: Cyclopropyl-{1-[(*R*)-3-(tetrahydro-furan-2-yl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-amine



The title compound was synthesized from (1-cyano-piperidin-4-yl)-cyclopropyl-carbamic acid *tert*-butyl ester (**Preparation 26**) and (*R*)-*N*-hydroxytetrahydrofuran-2-carboxamidine (**Preparation 248**) employing a procedure similar to that outlined in **Preparation 35**: RT = 0.48min; m/z (ES^+) = 279.34 [$M + H$] $^+$ (LCMS Method - 2).

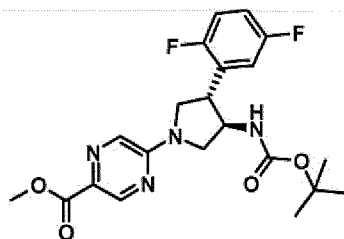
Preparation 250: [(3*R*,4*S*)-1-[5-(Cyclopropyl-{1-[(*R*)-3-(tetrahydro-furan-2-yl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-carbamoyl)-pyrimidin-2-yl]-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester



The title compound was synthesized from 2-[(3*R*,4*S*)-3-*tert*-butoxycarbonylamino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid (**Preparation 90**) and cyclopropyl-{1-[(*R*)-3-(tetrahydro-furan-2-yl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-amine (**Preparation 249**) employing a procedure similar to that outlined in **Preparation 105**: RT = 1.19 min; m/z (ES^+) = 681.54 [$M + H$] $^+$ (LCMS Method - 2).

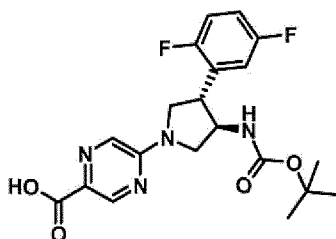
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Preparation 251: 5-[(3*R*,4*S*)-3-*tert*-Butoxycarbonylamino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrazine-2-carboxylic acid methyl ester



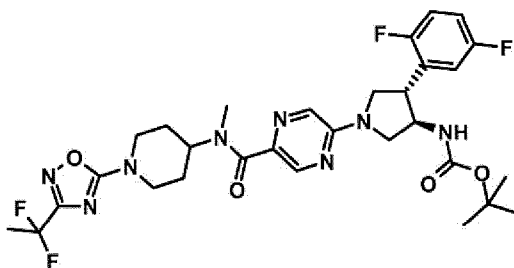
To a solution of 2-chloro-pyrazine-5-carboxylic acid methyl ester (2.55g, 14.75mmol) and triethylamine (4.2ml, 26.82mmol) in anhydrous THF (240mL) was added [(3*R*,4*S*)-4-(2,5-difluorophenyl)pyrrolidin-3-yl]carbamic acid *tert*-butyl ester (**Preparation 206**, 6.6g, 22.12mmol) and the resulting reaction mixture was stirred at 50°C for 4 h. The reaction mixture was concentrated *in vacuo* and the remainder was purified by chromatography on SiO₂ gel using EtOAc first then DCM/MeOH/NH₃ as eluents to afford the title compound: RT = 0.82 min; *m/z* (ES⁺) = 435.12 [*M* + H]⁺.

Preparation 252: 5-[(3*R*,4*S*)-3-*tert*-Butoxycarbonylamino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrazine-2-carboxylic acid



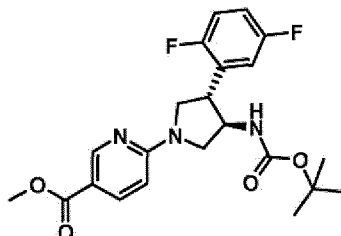
The title compound was synthesized from 5-[(3*R*,4*S*)-3-*tert*-butoxycarbonylamino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrazine-2-carboxylic acid methyl ester (**Preparation 251**) employing a procedure similar to that outlined in **Preparation 90**: RT = 1.54 min; *m/z* (ES⁺) = 421.14 [*M* + H]⁺.

Preparation 253: [(3*R*,4*S*)-1-[5-({1-[3-(1,1-Difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-methyl-carbamoyl)-pyrazin-2-yl]-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester



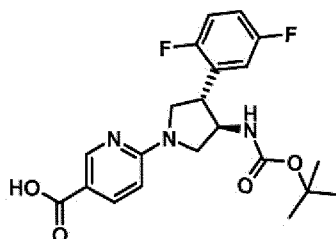
The title compound was synthesized from 5-[(3*R*,4*S*)-3-*tert*-butoxycarbonylamino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrazine-2-carboxylic acid (**Preparation 252**) and {1-[3-(1,1-difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-methyl-amine (**Preparation 44**) employing a procedure similar to that outlined in **Preparation 105**: RT = 1.27min; m/z (ES^+) = 649.65 [$M + H$] $^+$ (LCMS Method - 2).

Preparation 254: 6-[(3*R*,4*S*)-3-*tert*-Butoxycarbonylamino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-nicotinic acid methyl ester



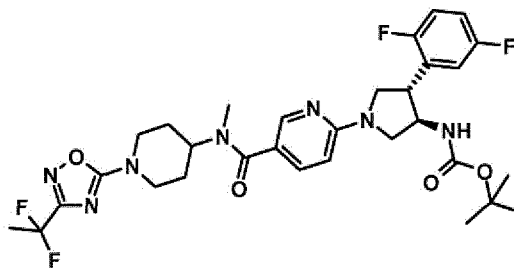
To a solution of 2-chloro-pyridine-5-carboxylic acid methyl ester (0.5g, 2.91mmol) and [(3*R*,4*S*)-4-(2,5-difluorophenyl)pyrrolidin-3-yl]carbamic acid *tert*-butyl ester (**Preparation 206**, 0.96g, 3.21mmol) in DMF (10mL) was added potassium carbonate (0.81g, 5.83mmol) and the resulting reaction mixture was stirred at 50°C for 16 h. The reaction mixture was diluted with DCM (50mL), washed with brine (20mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The remainder was purified by chromatography on SiO_2 gel using EtOAc/hexane as eluents; the resulting product was triturated with Et_2O to afford the title compound: 1H NMR δ_H (300MHz, $CDCl_3$): 8.81 (m, 1H), 8.02 (d, 1H), 7.10-6.90 (m, 3H), 6.35 (d, 1H), 4.46 (m, 1H), 4.10 (m, 2H), 3.85 (s, 3H), 3.60 (m, 2H), 3.35 (t, 1H), 1.40 (s, 9H).

Preparation 255: 6-[(3*R*,4*S*)-3-*tert*-Butoxycarbonylamino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-nicotinic acid



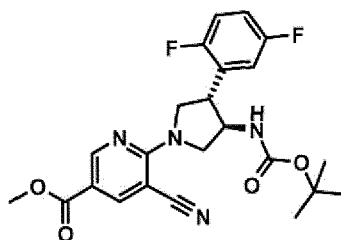
The title compound was synthesized from 6-[(3*R*,4*S*)-3-*tert*-butoxycarbonylamino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-nicotinic acid methyl ester (**Preparation 254**) employing a procedure similar to that outlined in **Preparation 90**: RT = 0.60 min; m/z (ES^+) = 420.48 [$M + H$] $^+$.

Preparation 256: [(3*R*,4*S*)-1-[5-({1-[3-(1,1-Difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-methyl-carbamoyl)-pyridin-2-yl]-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester



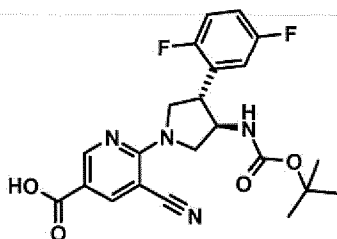
The title compound was synthesized from 6-[(3*R*,4*S*)-3-*tert*-butoxycarbonylamino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-nicotinic acid (**Preparation 255**) and {1-[3-(1,1-difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-methyl-amine (**Preparation 44**) employing a procedure similar to that outlined in **Preparation 105**: RT = 1.11 min; m/z (ES^+) = 648.62 [$M + H$] $^+$ (LCMS Method - 2).

Preparation 257: 6-[(3*R*,4*S*)-3-*tert*-Butoxycarbonylamino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-5-cyano-nicotinic acid methyl ester



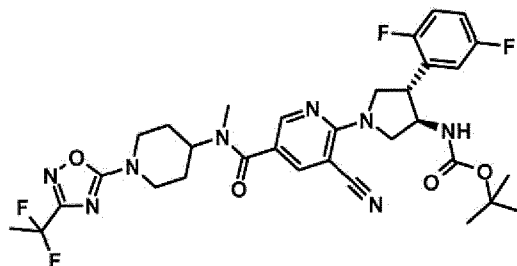
To a solution of 2-hydroxy-3-cyano-pyridine-5-carboxylic acid methyl ester (0.5g, 2.81mmol) and [(3*R*,4*S*)-4-(2,5-difluorophenyl)pyrrolidin-3-yl]carbamic acid *tert*-butyl ester (**Preparation 206**, 1.0g, 3.37mmol) in MeCN (10mL) was added BOP (1.86g, 4.21mmol) and DBU (0.63ml, 4.21mmol); the resulting reaction mixture was stirred at r.t. for 16 h. The reaction mixture was diluted with EtOAc (50mL) and water (20mL); aqueous layer was back-extracted with more EtOAc, then the organics were combined, washed with brine (20mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The remainder was purified by chromatography on SiO_2 gel using EtOAc/Hexane as eluents to afford the title compound: 1H NMR δ_H (300MHz, $CDCl_3$): 8.85 (s, 1H), 8.34 (s, 1H), 7.10-6.90 (m, 3H), 4.44 (m, 1H), 3.90 (s, 3H), 3.75 (t, 1H), 3.65 (m, 1H), 1.40 (s, 9H).

Preparation 258: 6-[(3*R*,4*S*)-3-*tert*-Butoxycarbonylamino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-5-cyano-nicotinic acid



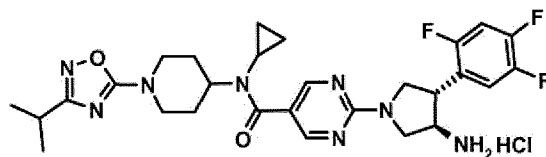
The title compound was synthesized from 6-[(3*R*,4*S*)-3-*tert*-butoxycarbonylamino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-5-cyano-nicotinic acid methyl ester (**Preparation 257**) employing a procedure similar to that outlined in **Preparation 90**: RT = 0.63 min; m/z (ES^+) = 445.20 [$M + H$] $^+$.

Preparation 259: [(3*R*,4*S*)-1-[3-Cyano-5-{1-[3-(1,1-difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-methyl-carbamoyl]-pyridin-2-yl]-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester



The title compound was synthesized from 6-[(3*R*,4*S*)-3-*tert*-butoxycarbonylamino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-5-cyano-nicotinic acid (**Preparation 258**) and {1-[3-(1,1-difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-methyl-amine (**Preparation 44**) employing a procedure similar to that outlined in **Preparation 105**: RT = 1.32 min; m/z (ES^+) = 673.56 [$M + H$] $^+$ (LCMS Method - 2).

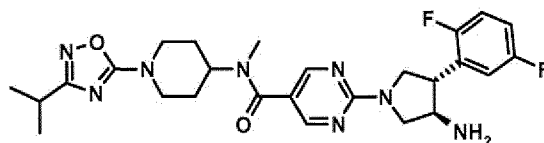
Example 1: 2-[(3*R*,4*S*)-3-Amino-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid cyclopropyl-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-amide hydrochloride



To a solution of [(3*R*,4*S*)-1-{5-[(1-cyano-piperidin-4-yl)-cyclopropyl-carbamoyl]-pyrimidin-2-yl}-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester (**Preparation 103**, 61mg, 100 μ mol) and *N*-hydroxy-isobutyramidine (13mg, 120 μ mol) in EtOH (4mL) was added dropwise zinc dichloride in Et₂O (1M, 120 μ L, 120mmol) and the resulting reaction mixture was

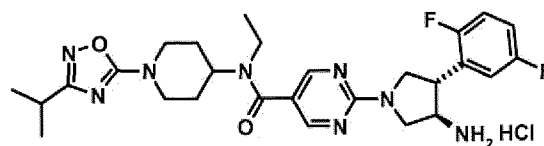
stirred at r.t. for 80 min. HCl in 1,4-dioxane (4M, 130 μ L, 521 μ mol) was added and the reaction mixture was heated at 60 °C for 16 h. Upon cooling, the reaction mixture was diluted with MeOH and loaded onto an SCX cartridge eluting with MeOH followed by NH₃ in MeOH (7M). The basic fraction was concentrated *in vacuo* and purified by preparative HPLC. The product containing fractions were concentrated *in vacuo* and the remainder dissolved in MeOH, added to an SCX cartridge and eluted with MeOH followed by NH₃ in MeOH (7M). The basic fraction was concentrated *in vacuo*, dissolved in MeCN:MeOH (1:2) and HCl in 1,4-dioxane (4M, 19 μ L) was added. The resulting mixture was stirred at r.t. for 10 min and the solvent removed *in vacuo* to afford the title compound: RT = 0.81 min; *m/z* (ES⁺) = 571.52 [M + H]⁺ (LCMS Method - 2).

Example 2: 2-[(3*R*,4*S*)-3-Amino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid [1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-methyl-amide



To a solution of [(3*R*,4*S*)-4-(2,5-difluoro-phenyl)-1-(5-{[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-methyl-carbamoyl}-pyrimidin-2-yl)-pyrrolidin-3-yl]-carbamic ester *tert*-butyl ester (**Preparation 104**, 143mg, 228 μ mol) in DCM (2.9mL) was added TFA (352 μ L, 4.56mmol) and the resulting reaction mixture was stirred at r.t. for 1 h. Further TFA (320 μ L, 4.15mmol) was added and the reaction mixture stirred at r.t. for 1.5 h. The reaction mixture was added to an SCX cartridge and eluted with MeOH followed by NH₃ in MeOH (7M). The basic fraction was concentrated *in vacuo* to afford the title compound: RT = 2.50 min; *m/z* (ES⁺) = 527.29 [M + H]⁺.

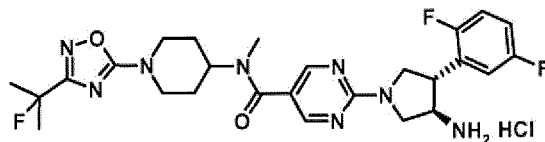
Example 3: 2-[(3*R*,4*S*)-3-Amino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid ethyl-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-amide hydrochloride



To a solution of [(3*R*,4*S*)-4-(2,5-difluoro-phenyl)-1-(5-{ethyl-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-carbamoyl}-pyrimidin-2-yl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester (**Preparation 106**, 95mg, 150 μ mol) in DCM (2.3mL) was added TFA (485 μ L, 6.30mmol) and the resulting reaction mixture stirred at r.t. for 1.5 h. The reaction mixture was added to an SCX cartridge and eluted with MeOH followed by NH₃ in MeOH (7M). The basic fraction was concentrated *in vacuo*, dissolved in MeOH (5mL) and HCl in Et₂O (2M, 380 μ L) was added. The mixture was stirred at r.t. for 15 min, then concentrated *in vacuo* to afford the title compound: RT =

0.78 min; m/z (ES^+) = 541.52 [$M + H$] $^+$ (LCMS Method - 2).

Example 4: 2-[(3*R*,4*S*)-3-Amino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid {1-[3-(1-fluoro-1-methyl-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-methyl-amide hydrochloride



To a solution of {(3*R*,4*S*)-4-(2,5-difluoro-phenyl)-1-[5-({1-[3-(1-fluoro-1-methyl-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-methyl-carbamoyl)-pyrimidin-2-yl]-pyrrolidin-3-yl} carbamic acid *tert*-butyl ester (**Preparation 105**, 85mg, 130μmol) in MeOH (3mL) under argon was added HCl in Et₂O (2M, 660μL) at 0°C. The reaction mixture was allowed to warm to r.t. and stirred for 18 h. The mixture was concentrated *in vacuo* to afford the title compound: RT = 0.77 min; m/z (ES^+) = 545.42 [$M + H$] $^+$ (LCMS Method - 2).

The following compounds were prepared from the appropriate *tert*-butoxy carbonyl protected amino intermediate employing a procedure similar to that outlined in **Example 2**:

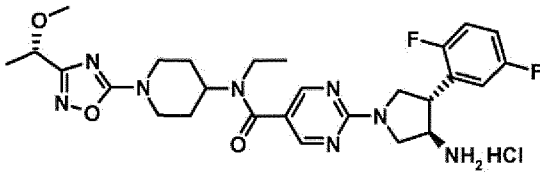
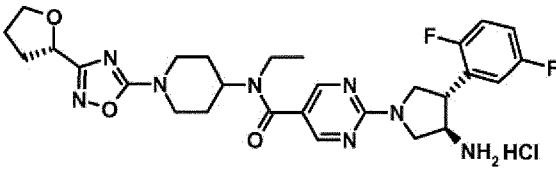
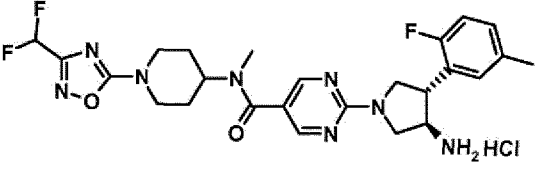
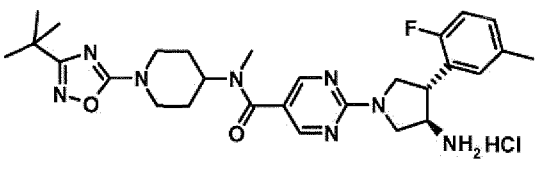
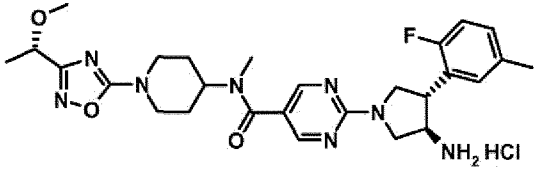
Ex.	Structure	Name	LCMS Data
5		2-[(3 <i>R</i> ,4 <i>S</i>)-3-Amino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid (1-benzyl-piperidin-4-yl)-methyl-amide	RT = 1.93 min; m/z (ES^+) = 507.25 [$M + H$] $^+$.
6		2-[(3 <i>R</i> ,4 <i>S</i>)-3-Amino-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid [1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-methyl-amide	RT = 0.77 min; m/z (ES^+) = 545.5 [$M + H$] $^+$ (LCMS Method - 2).
7		2-[(3 <i>R</i> ,4 <i>S</i>)-3-Amino-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid ethyl-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-amide	RT = 0.79 min; m/z (ES^+) = 559.53 [$M + H$] $^+$ (LCMS Method - 2).

Ex.	Structure	Name	LCMS Data
8		5-[(3 <i>R</i> ,4 <i>S</i>)-3-Amino-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-1-yl]-pyrazine-2-carboxylic acid ethyl-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-amide	RT = 2.96 min; <i>m/z</i> (ES ⁺) = 559.29 [<i>M</i> + H] ⁺ (LCMS Method - 1).

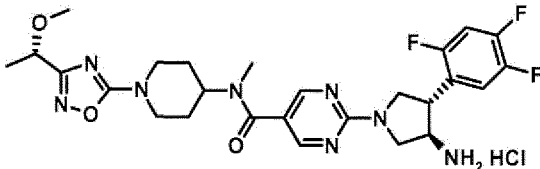
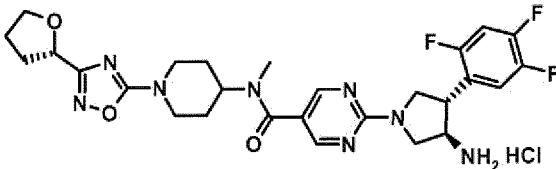
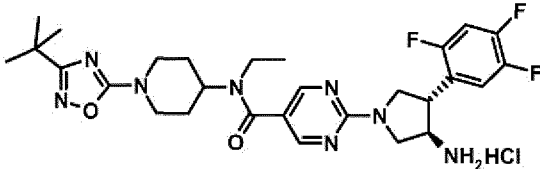
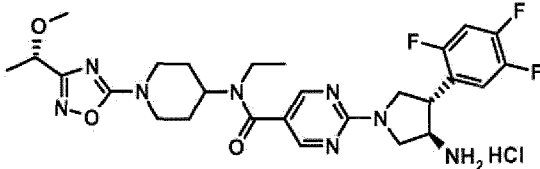
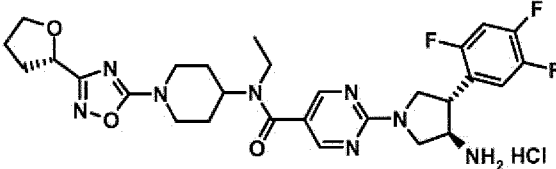
The following compounds were prepared from the appropriate *tert*-butoxy carbonyl protected amino intermediate employing a procedure similar to that outlined in **Example 3**:

Ex.	Structure	Name	LCMS Data
9		2-[(3 <i>R</i> ,4 <i>S</i>)-3-Amino-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid [1-(3-difluoromethyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-methy-amide hydrochloride	RT = 2.50 min; <i>m/z</i> (ES ⁺) = 553.10 [<i>M</i> + H] ⁺ . (LCMS Method - 2).
10		2-[(3 <i>R</i> ,4 <i>S</i>)-3-Amino-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid [1-(3- <i>tert</i> -butyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-methyl-amide hydrochloride	RT = 0.81 min; <i>m/z</i> (ES ⁺) = 559.54 [<i>M</i> + H] ⁺ (LCMS Method - 2).
11		2-[(3 <i>R</i> ,4 <i>S</i>)-3-Amino-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid [1-(3-difluoromethyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-ethyl-amide hydrochloride	RT = 0.80 min; <i>m/z</i> (ES ⁺) = 567.50 [<i>M</i> + H] ⁺ (LCMS Method - 2).
12		2-[(3 <i>R</i> ,4 <i>S</i>)-3-Amino-4-(2,4-difluoro-5-methyl-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid [1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-methyl-amide hydrochloride	RT = 0.79 min; <i>m/z</i> (ES ⁺) = 541.55 [<i>M</i> + H] ⁺ (LCMS Method - 2).

Ex.	Structure	Name	LCMS Data
13		2-[(3R,4S)-3-Amino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid [1-(3-difluoromethyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-methyl-amide hydrochloride	RT = 2.50 min; m/z (ES ⁺) = 535.11 [$M + H$] ⁺ (LCMS Method - 1).
14		2-[(3R,4S)-3-Amino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid [1-(3-tert-butyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-methyl-amide hydrochloride	RT = 2.63 min; m/z (ES ⁺) = 541.17 [$M + H$] ⁺ (LCMS Method - 1).
15		2-[(3R,4S)-3-Amino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid {1-[3-((S)-1-methoxy-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-methyl-amide hydrochloride	RT = 2.35 min; m/z (ES ⁺) = 543.16 [$M + H$] ⁺ (LCMS Method - 1).
16		2-[(3R,4S)-3-Amino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid methyl-{1-[(S)-3-(tetrahydro-furan-2-yl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-amide hydrochloride	RT = 2.34 min; m/z (ES ⁺) = 555.14 [$M + H$] ⁺ (LCMS Method - 1).
17		2-[(3R,4S)-3-Amino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid [1-(3-difluoromethyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-ethyl-amide hydrochloride	RT = 2.56 min; m/z (ES ⁺) = 549.12 [$M + H$] ⁺ (LCMS Method - 1).
18		2-[(3R,4S)-3-Amino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid [1-(3-tert-butyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-ethyl-amide hydrochloride	RT = 2.72 min; m/z (ES ⁺) = 555.18 [$M + H$] ⁺ (LCMS Method - 1).

Ex.	Structure	Name	LCMS Data
19		2-[(3 <i>R</i> ,4 <i>S</i>)-3-Amino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid ethyl-{1-[3-((<i>S</i>)-1-methoxy-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-amide hydrochloride	RT = 2.48 min; <i>m/z</i> (ES^+) = 557.16 [$M + H$] ⁺ (LCMS Method - 1).
20		2-[(3 <i>R</i> ,4 <i>S</i>)-3-Amino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid ethyl-{1-[(<i>S</i>)-3-(tetrahydro-furan-2-yl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-amide hydrochloride	RT = 2.50 min; <i>m/z</i> (ES^+) = 569.16 [$M + H$] ⁺ (LCMS Method - 1).
21		2-[(3 <i>R</i> ,4 <i>S</i>)-3-Amino-4-(2-fluoro-5-methyl-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid [1-(3-difluoromethyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-methyl-amide hydrochloride	RT = 2.59 min; <i>m/z</i> (ES^+) = 531.14 [$M + H$] ⁺ (LCMS Method - 1).
22		2-[(3 <i>R</i> ,4 <i>S</i>)-3-Amino-4-(2-fluoro-5-methyl-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid [1-(3- <i>tert</i> -butyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-methyl-amide hydrochloride	RT = 2.72 min; <i>m/z</i> (ES^+) = 537.19 [$M + H$] ⁺ (LCMS Method - 1).
23		2-[(3 <i>R</i> ,4 <i>S</i>)-3-Amino-4-(2-fluoro-5-methyl-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid {1-[3-((<i>S</i>)-1-methoxy-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-methyl-amide hydrochloride	RT = 2.45 min; <i>m/z</i> (ES^+) = 539.18 [$M + H$] ⁺ (LCMS Method - 1).

Ex.	Structure	Name	LCMS Data
24		2-[(3 <i>R</i> ,4 <i>S</i>)-3-Amino-4-(2-fluoro-5-methyl-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid methyl-{1-[(<i>S</i>)-3-(tetrahydro-furan-2-yl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-amide hydrochloride	RT = 2.47 min; <i>m/z</i> (ES ⁺) = 551.18 [<i>M</i> + H] ⁺ (LCMS Method - 1).
25		2-[(3 <i>R</i> ,4 <i>S</i>)-3-Amino-4-(2-fluoro-5-methyl-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid [1-(3-difluoromethyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-ethyl-amide hydrochloride	RT = 2.60 min; <i>m/z</i> (ES ⁺) = 545.15 [<i>M</i> + H] ⁺ (LCMS Method - 1).
26		2-[(3 <i>R</i> ,4 <i>S</i>)-3-Amino-4-(2-fluoro-5-methyl-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid [1-(3- <i>tert</i> -butyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-ethyl-amide hydrochloride	RT = 2.79 min; <i>m/z</i> (ES ⁺) = 551.21 [<i>M</i> + H] ⁺ (LCMS Method - 1).
27		2-[(3 <i>R</i> ,4 <i>S</i>)-3-Amino-4-(2-fluoro-5-methyl-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid ethyl-{1-[3-((<i>S</i>)-1-methoxy-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-amide hydrochloride	RT = 2.54 min; <i>m/z</i> (ES ⁺) = 553.20 [<i>M</i> + H] ⁺ (LCMS Method - 1).
28		2-[(3 <i>R</i> ,4 <i>S</i>)-3-Amino-4-(2-fluoro-5-methyl-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid ethyl-{1-[(<i>S</i>)-3-(tetrahydro-furan-2-yl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-amide hydrochloride	RT = 2.48 min; <i>m/z</i> (ES ⁺) = 565.19 [<i>M</i> + H] ⁺ (LCMS Method - 1).

Ex.	Structure	Name	LCMS Data
29		2-[(3 <i>R</i> ,4 <i>S</i>)-3-Amino-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid {1-[3-((<i>S</i>)-1-methoxy-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-methyl-amide hydrochloride	RT = 2.43 min; <i>m/z</i> (<i>ES</i> ⁺) = 561.09 [<i>M</i> + <i>H</i>] ⁺ (LCMS Method - 1).
30		2-[(3 <i>R</i> ,4 <i>S</i>)-3-Amino-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid methyl-{1-[(<i>S</i>)-3-(tetrahydro-furan-2-yl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-amide hydrochloride	RT = 2.48 min; <i>m/z</i> (<i>ES</i> ⁺) = 573.12 [<i>M</i> + <i>H</i>] ⁺ (LCMS Method - 1).
31		2-[(3 <i>R</i> ,4 <i>S</i>)-3-Amino-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid [1-(3- <i>tert</i> -butyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-ethyl-amide hydrochloride	RT = 2.82 min; <i>m/z</i> (<i>ES</i> ⁺) = 573.18 [<i>M</i> + <i>H</i>] ⁺ (LCMS Method - 1).
32		2-[(3 <i>R</i> ,4 <i>S</i>)-3-Amino-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid ethyl-{1-[3-((<i>S</i>)-1-methoxy-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-amide hydrochloride	RT = 2.54 min; <i>m/z</i> (<i>ES</i> ⁺) = 575.15 [<i>M</i> + <i>H</i>] ⁺ (LCMS Method - 1).
33		2-[(3 <i>R</i> ,4 <i>S</i>)-3-Amino-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid ethyl-{1-[(<i>S</i>)-3-(tetrahydro-furan-2-yl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-amide hydrochloride	RT = 2.47 min; <i>m/z</i> (<i>ES</i> ⁺) = 587.15 [<i>M</i> + <i>H</i>] ⁺ (LCMS Method - 1).

Ex.	Structure	Name	LCMS Data
34		2-[(3 <i>R</i> ,4 <i>S</i>)-3-Amino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid {1-[3-(1,1-difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-ethyl-amide hydrochloride	RT = 2.70 min; <i>m/z</i> (ES ⁺) = 563.09 [<i>M</i> + H] ⁺ (LCMS Method - 1).
35		2-[(3 <i>R</i> ,4 <i>S</i>)-3-Amino-4-(2,4-difluoro-5-methyl-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid [1-(3-difluoromethyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-methyl-amide hydrochloride	RT = 2.62 min; <i>m/z</i> (ES ⁺) = 549.05 [<i>M</i> + H] ⁺ (LCMS Method - 1).
36		2-[(3 <i>R</i> ,4 <i>S</i>)-3-Amino-4-(2,4-difluoro-5-methyl-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid {1-[3-(1,1-difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-methyl-amide hydrochloride	RT = 2.75 min; <i>m/z</i> (ES ⁺) = 563.05 [<i>M</i> + H] ⁺ (LCMS Method - 1).
37		2-[(3 <i>R</i> ,4 <i>S</i>)-3-Amino-4-(2,4-difluoro-5-methyl-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid [1-(3-cyclopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-methyl-amide hydrochloride	RT = 2.62 min; <i>m/z</i> (ES ⁺) = 539.10 [<i>M</i> + H] ⁺ (LCMS Method - 1).
38		2-[(3 <i>R</i> ,4 <i>S</i>)-3-Amino-4-(2,4-difluoro-5-methyl-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid [1-(3- <i>tert</i> -butyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-methyl-amide hydrochloride	RT = 2.72 min; <i>m/z</i> (ES ⁺) = 555.12 [<i>M</i> + H] ⁺ (LCMS Method - 1).

Ex.	Structure	Name	LCMS Data
39		2-[(3R,4S)-3-Amino-4-(2,4-difluoro-5-methyl-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid {1-[3-((S)-1-methoxy-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-methyl-amide hydrochloride	RT = 2.47 min; m/z (ES ⁺) = 557.11 [$M + H$] ⁺ (LCMS Method - 1).
40		2-[(3R,4S)-3-Amino-4-(2,4-difluoro-5-methyl-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid methyl-{1-[(S)-3-(tetrahydro-furan-2-yl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-amide hydrochloride	RT = 2.52 min; m/z (ES ⁺) = 569.10 [$M + H$] ⁺ (LCMS Method - 1).
41		2-[(3R,4S)-3-Amino-4-(2,4-difluoro-5-methyl-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid [1-(3-difluoromethyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-ethyl-amide hydrochloride	RT = 2.70 min; m/z (ES ⁺) = 563.09 [$M + H$] ⁺ (LCMS Method - 1).
42		2-[(3R,4S)-3-Amino-4-(2,4-difluoro-5-methyl-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid {1-[3-(1,1-difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-ethyl-amide hydrochloride	RT = 2.70 min; m/z (ES ⁺) = 577.08 [$M + H$] ⁺ (LCMS Method - 1).
43		2-[(3R,4S)-3-Amino-4-(2,4-difluoro-5-methyl-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid [1-(3- <i>tert</i> -butyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-ethyl-amide hydrochloride	RT = 2.88 min; m/z (ES ⁺) = 569.15 [$M + H$] ⁺ (LCMS Method - 1).

Ex.	Structure	Name	LCMS Data
44		2-[(3 <i>R</i> ,4 <i>S</i>)-3-Amino-4-(2,4-difluoro-5-methyl-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid ethyl-{1-[3-((<i>S</i>)-1-methoxy-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-amide hydrochloride	RT = 2.62 min; m/z (ES^+) = 571.12 [$M + H$] ⁺ (LCMS Method - 1).
45		2-[(3 <i>R</i> ,4 <i>S</i>)-3-Amino-4-(2,4-difluoro-5-methyl-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid ethyl-{1-[(<i>S</i>)-3-(tetrahydro-furan-2-yl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-amide hydrochloride	RT = 2.68 min; m/z (ES^+) = 583.12 [$M + H$] ⁺ (LCMS Method - 1).
46		2-[(3 <i>R</i> ,4 <i>S</i>)-3-Amino-4-(2,4-difluoro-5-methyl-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid ethyl-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-amide hydrochloride	RT = 2.72 min; m/z (ES^+) = 555.13 [$M + H$] ⁺ (LCMS Method - 1).
47		2-[(3 <i>R</i> ,4 <i>S</i>)-3-Amino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid [1-(3-cyclopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-methyl-amide hydrochloride	RT = 2.55 min; m/z (ES^+) = 525.10 [$M + H$] ⁺ (LCMS Method - 1).
48		2-[(3 <i>R</i> ,4 <i>S</i>)-3-Amino-4-(2-fluoro-5-methyl-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid [1-(3-cyclopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-methyl-amide hydrochloride	RT = 2.57 min; m/z (ES^+) = 521.18 [$M + H$] ⁺ (LCMS Method - 1).

Ex.	Structure	Name	LCMS Data
49		2-[(3 <i>R</i> ,4 <i>S</i>)-3-Amino-4-(2-fluoro-5-methyl-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid {1-[3-(1,1-difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-methyl-amide hydrochloride	RT = 2.75 min; <i>m/z</i> (ES ⁺) = 545.15 [<i>M</i> + H] ⁺ (LCMS Method - 1).
50		2-[(3 <i>R</i> ,4 <i>S</i>)-3-Amino-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid [1-(3-cyclopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-ethyl-amide hydrochloride	RT = 2.63 min; <i>m/z</i> (ES ⁺) = 557.15 [<i>M</i> + H] ⁺ (LCMS Method - 1).
51		2-[(3 <i>R</i> ,4 <i>S</i>)-3-Amino-4-(2-fluoro-5-methyl-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid {1-[3-(1,1-difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-ethyl-amide hydrochloride	RT = 2.67 min; <i>m/z</i> (ES ⁺) = 559.17 [<i>M</i> + H] ⁺ (LCMS Method - 1).
52		2-[(3 <i>R</i> ,4 <i>S</i>)-3-Amino-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid [1-(5-chloro-pyrimidin-2-yl)-piperidin-4-yl]-ethyl-amide hydrochloride	RT = 2.85 min; <i>m/z</i> (ES ⁺) = 561.06 [<i>M</i> + H] ⁺ (LCMS Method - 1).

The following compounds were prepared from the appropriate *tert*-butoxy carbonyl protected amino intermediate employing a procedure similar to that outlined in **Example 4**:

Ex.	Structure	Name	LCMS Data
53		2-[(3 <i>R</i> ,4 <i>S</i>)-3-Amino-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid {1-[3-(1,1-difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-ethyl-amide hydrochloride	RT = 0.81 min; <i>m/z</i> (ES ⁺) = 581.47 [<i>M</i> + H] ⁺ (LCMS Method - 2).

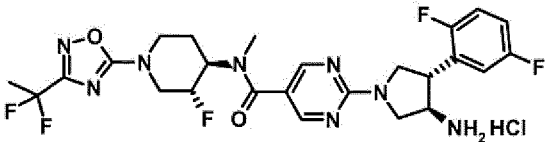
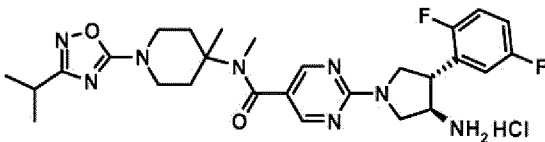
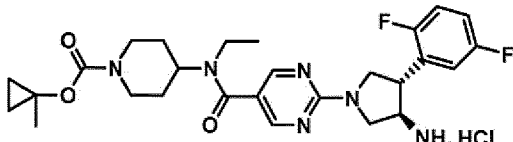
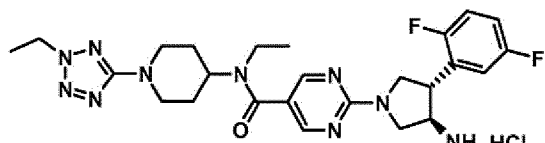
Ex.	Structure	Name	LCMS Data
54		2-[(3R,4S)-3-Amino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid {1-[3-(1,1-difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-methyl-amide hydrochloride	RT = 0.79 min; m/z (ES ⁺) = 549.43 [$M + H$] ⁺ (LCMS Method - 2).
55		2-[(3R,4S)-3-Amino-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid {1-[3-(1,1-difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-methyl-amide hydrochloride	RT = 0.83 min; m/z (ES ⁺) = 567.37 [$M + H$] ⁺ (LCMS Method - 2).
56		2-[(3R,4S)-3-Amino-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid methyl-[1-(3-trifluoromethyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-amide hydrochloride	RT = 0.84 min; m/z (ES ⁺) = 553.37 [$M + H$] ⁺ (LCMS Method - 2).
57		2-[(3R,4S)-3-Amino-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid [1-(3-cyclopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-methyl-amide hydrochloride	RT = 0.77 min; m/z (ES ⁺) = 543.43 [$M + H$] ⁺ (LCMS Method - 2).
58		2-[(3R,4S)-3-Amino-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid [1-(3-cyclopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-ethyl-amide hydrochloride	RT = 0.78 min; m/z (ES ⁺) = 557.4 [$M + H$] ⁺ (LCMS Method - 2).
59		2-[(3R,4S)-3-Amino-4-(2-fluoro-5-methyl-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid [1-(3-cyclopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-ethyl-amide hydrochloride	RT = 0.75 min; m/z (ES ⁺) = 535.5 [$M + H$] ⁺ (LCMS Method - 2).

Ex.	Structure	Name	LCMS Data
60		2-[(3R,4S)-3-Amino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid cyclopropyl-{1-[3-(1-hydroxy-1-methyl-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-amide hydrochloride	RT = 0.70 min; m/z (ES^+) = 569.44 [$M + H$] ⁺ (LCMS Method - 2).
61		2-[(3R,4S)-3-Amino-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid cyclopropyl-{1-[3-(1-hydroxy-1-methyl-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-amide hydrochloride	RT = 0.73 min; m/z (ES^+) = 587.42 [$M + H$] ⁺ (LCMS Method - 2).
62		2-[(3R,4S)-3-Amino-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid {1-[3-(1,1-difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-(2-methoxy-ethyl)-amide hydrochloride	RT = 0.83 min; m/z (ES^+) = 611.38 [$M + H$] ⁺ (LCMS Method - 2).
63		2-[(3R,4S)-3-Amino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid {1-[3-(1,1-difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-(2-methoxy-ethyl)-amide hydrochloride	RT = 0.81 min; m/z (ES^+) = 593.39 [$M + H$] ⁺ (LCMS Method - 2).
64		2-[(3R,4S)-3-Amino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid {1-[3-(1,1-difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-(2,2,2-trifluoro-ethyl)-amide hydrochloride	RT = 0.88 min; m/z (ES^+) = 617.39 [$M + H$] ⁺ (LCMS Method - 2).
65		2-[(3R,4S)-3-Amino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid cyclopropyl-{1-[3-((S)-1-methoxy-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-amide hydrochloride	RT = 0.75 min; m/z (ES^+) = 569.42 [$M + H$] ⁺ (LCMS Method - 2).

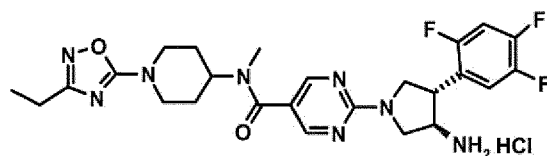
Ex.	Structure	Name	LCMS Data
66		2-[(3R,4S)-3-Amino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid {1-[3-(1,1-difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-isopropyl-amide hydrochloride	RT = 0.85 min; m/z (ES ⁺) = 577.44 [$M + H$] ⁺ (LCMS Method - 2).
67		2-[(3R,4S)-3-Amino-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid {1-[3-(1,1-difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-isopropyl-amide hydrochloride	RT = 0.86 min; m/z (ES ⁺) = 595.44 [$M + H$] ⁺ (LCMS Method - 2).
68		2-[(3R,4S)-3-Amino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid {1-[3-(1,1-difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-propyl-amide hydrochloride	RT = 0.85 min; m/z (ES ⁺) = 577.44 [$M + H$] ⁺ (LCMS Method - 2).
69		2-[(3R,4S)-3-Amino-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid {1-[3-(1,1-difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-propyl-amide hydrochloride	RT = 0.86 min; m/z (ES ⁺) = 595.43 [$M + H$] ⁺ (LCMS Method - 2).
70		2-[(3R,4S)-3-Amino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid cyclopropyl-{1-[3-(1,1-difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-amide hydrochloride	RT = 0.82 min; m/z (ES ⁺) = 575.43 [$M + H$] ⁺ (LCMS Method - 2).
71		2-[(3R,4S)-3-Amino-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid cyclopropyl-{1-[3-(1,1-difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-amide hydrochloride	RT = 0.83 min; m/z (ES ⁺) = 593.42 [$M + H$] ⁺ (LCMS Method - 2).

Ex.	Structure	Name	LCMS Data
		piperidin-4-yl}-amide hydrochloride	
72		2-[(3 <i>R</i> ,4 <i>S</i>)-3-Amino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid [1-(3-cyclopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-ethyl-amide hydrochloride	RT = 0.77 min; <i>m/z</i> (ES ⁺) = 539.4 [<i>M</i> + H] ⁺ (LCMS Method - 2).
73		2-[(3 <i>R</i> ,4 <i>S</i>)-3-Amino-4-(2-fluoro-5-methyl-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid cyclopropyl-{1-[3-((<i>S</i>)-1-methoxy-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-amide hydrochloride	RT = 0.77 min; <i>m/z</i> (ES ⁺) = 565.48 [<i>M</i> + H] ⁺ (LCMS Method - 2).
74		2-[(3 <i>R</i> ,4 <i>S</i>)-3-Amino-4-(2-fluoro-5-methyl-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid cyclopropyl-{1-[3-(1,1-difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-amide hydrochloride	RT = 0.85 min; <i>m/z</i> (ES ⁺) = 571.48 [<i>M</i> + H] ⁺ (LCMS Method - 2).
75		2-[(3 <i>R</i> ,4 <i>S</i>)-3-Amino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid cyclopropyl-[1-(3-methoxymethyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-amide hydrochloride	RT = 0.73 min; <i>m/z</i> (ES ⁺) = 555.46 [<i>M</i> + H] ⁺ (LCMS Method - 2).
76		2-[(3 <i>R</i> ,4 <i>S</i>)-3-Amino-4-(2-fluoro-5-methyl-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid cyclopropyl-[1-(3-methoxymethyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-amide hydrochloride	RT = 0.76 min; <i>m/z</i> (ES ⁺) = 551.48 [<i>M</i> + H] ⁺ (LCMS Method - 2).

Ex.	Structure	Name	LCMS Data
77		2-[(3R,4S)-3-Amino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid [8-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-8-aza-bicyclo[3.2.1]oct-3-yl]-methyl-amide hydrochloride	RT = 0.78 min; m/z (ES ⁺) = 553.44 [$M + H$] ⁺ (LCMS Method - 2).
78		2-[(3R,4S)-3-Amino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid [3-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-3-aza-bicyclo[3.2.1]oct-8-yl]-methyl-amide hydrochloride	RT = 0.80 min; m/z (ES ⁺) = 553.42 [$M + H$] ⁺ (LCMS Method - 2).
79		2-[(3R,4S)-3-Amino-4-(2-fluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid ethyl-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-amide hydrochloride	RT = 0.76 min; m/z (ES ⁺) = 523.45 [$M + H$] ⁺ (LCMS Method - 2).
80		2-[(3R,4S)-3-Amino-4-(2-fluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid cyclopropyl-{1-[3-(1,1-difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-amide hydrochloride	RT = 0.80 min; m/z (ES ⁺) = 557.44 [$M + H$] ⁺ (LCMS Method - 2).
81		2-[(3R,4S)-3-Amino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid {(3S,4R)-1-[3-(1,1-difluoro-ethyl)[1,2,4]oxadiazol-5-yl]-3-fluoro-piperidin-4-yl}-methyl-amide hydrochloride	RT = 0.82 min; m/z (ES ⁺) = 567.4 [$M + H$] ⁺ (LCMS Method - 2).
82		2-[(3R,4S)-3-Amino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid {(3R,4S)-1-[3-(1,1-difluoro-ethyl)[1,2,4]oxadiazol-5-yl]-3-fluoro-piperidin-4-yl}-methyl-amide hydrochloride	RT = 0.82 min; m/z (ES ⁺) = 567.4 [$M + H$] ⁺ (LCMS Method - 2).

Ex.	Structure	Name	LCMS Data
83		2-[(3R,4S)-3-Amino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid {(3R,4R)-1-[3-(1,1-difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-3-fluoro-piperidin-4-yl}-methyl-amide hydrochloride	RT = 0.79 min; m/z (ES ⁺) = 567.4 [M + H] ⁺ (LCMS Method - 2).
84		2-[(3R,4S)-3-Amino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid [1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-4-methyl-piperidin-4-yl]-methyl-amide hydrochloride	RT = 0.82 min; m/z (ES ⁺) = 541.44 [M + H] ⁺ (LCMS Method - 2).
85		4-({2-[(3R,4S)-3-Amino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxyl}-ethyl-amino)-piperidine-1-carboxylic acid 1-methyl-cyclopropyl ester hydrochloride	RT = 0.75 min; m/z (ES ⁺) = 529.49 [M + H] ⁺ (LCMS Method - 2).
86		2-[(3R,4S)-3-Amino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid ethyl-[1-(2-ethyl-2H-tetrazol-5-yl)-piperidin-4-yl]-amide hydrochloride	RT = 0.74 min; m/z (ES ⁺) = 527.53 [M + H] ⁺ (LCMS Method - 2).

Example 87: 2-[(3R,4S)-3-Amino-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid [1-(3-ethyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-methyl-amide hydrochloride



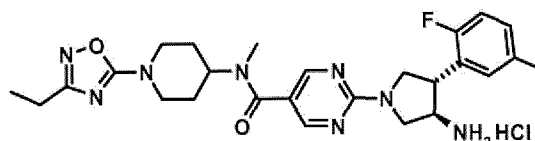
5 To a solution of [(3R,4S)-1-(5-{[1-(3-ethyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-methyl-carbamoyl}-pyrimidin-2-yl)-4-(2,4,5-trifluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester (**Preparation 131**, 115mg, 182μmol) in 1,4-dioxane (5mL) was added HCl in 1,4-dioxane (4M, 182μL, 729μmol) and the resulting reaction mixture was stirred at r.t. for 75 min. Further HCl in 1,4-dioxane (4M, 1.5mL, 6mmol) was added and stirring at r.t. continued for 16 h. The solvent was removed *in vacuo* and the remainder purified by preparative HPLC. The product containing fractions were loaded onto an SCX cartridge and eluted with MeOH followed by NH₃ in MeOH (7M). The

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basic fraction was concentrated *in vacuo*, then the remainder was dissolved in 1,4-dioxane and HCl in 1,4-dioxane (4M, 0.2mL) was added. The resulting mixture was stirred at r.t. for 1 h and concentrated *in vacuo* to afford the title compound: RT = 0.71 min; m/z (ES^+) = 531.5 [$M + H$] $^+$ (LCMS Method - 2).

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Example 88: 2-[(3*R*,4*S*)-3-Amino-4-(2-fluoro-5-methyl-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid [1-(3-ethyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-methyl-amide hydrochloride

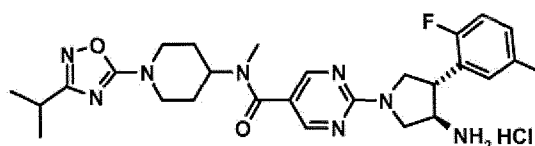


To a solution of [(3*R*,4*S*)-1-(5-{[1-(3-ethyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-methyl-carbamoyl}-pyrimidin-2-yl)-4-(2-fluoro-5-methyl-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester (**Preparation 154**, 109mg, 179μmol) in Et₂O (5mL) at 0°C was added HCl in 1,4-dioxane (4M, 1mL, 4mmol) and the resulting reaction mixture was stirred at r.t. for 4 h. The solvent was removed *in vacuo* and the remainder was dissolved in the minimum amount of hot EtOH and allowed to cool to r.t. Et₂O was added dropwise until a white precipitate formed, then the yellow solution was decanted off and the solid dried *in vacuo* to afford the title compound: RT = 2.48 min; m/z (ES^+) = 509.18 [$M + H$] $^+$.

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Example 89: 2-[(3*R*,4*S*)-3-Amino-4-(2-fluoro-5-methyl-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid [1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-methyl-amide hydrochloride

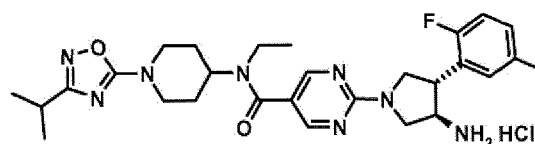
20



The title compound was synthesized from [(3*R*,4*S*)-4-(2-fluoro-5-methyl-phenyl)-1-(5-{[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-methyl-carbamoyl}-pyrimidin-2-yl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester (**Preparation 152**, 180mg, 290μmol) employing a procedure similar to that outlined in **Example 88**: RT = 2.70 min; m/z (ES^+) = 523.19 [$M + H$] $^+$.

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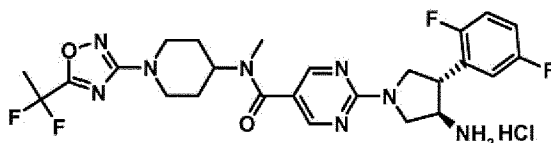
Example 90: 2-[(3*R*,4*S*)-3-Amino-4-(2-fluoro-5-methyl-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid ethyl-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-amide hydrochloride



To a solution of [(3*R*,4*S*)-1-(5-{ethyl-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-carbamoyl}-pyrimidin-2-yl)-4-(2-fluoro-5-methyl-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester (**Preparation 153**, 210mg, 330μmol) in Et₂O (5mL) and DCM (2.5mL) at 0°C was added HCl in 1,4-dioxane (4M, 2.0mL, 8.0mmol) and the resulting reaction mixture was stirred at r.t. for 16 h.

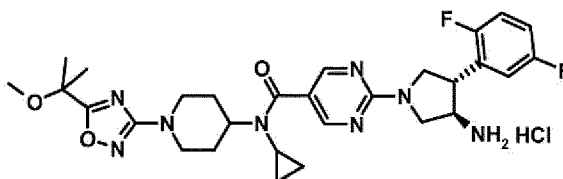
The solvent was removed *in vacuo*, then the remainder dissolved in EtOAc, washed with aqueous NaOH solution (2M), dried (MgSO₄), filtered and concentrated *in vacuo*. The remainder was purified by preparative HPLC (basic method) and the product dissolved in MeOH prior to the addition of HCl in Et₂O (2M, 2.0mL). The solvents were removed *in vacuo* to afford the title compound: RT = 2.72 min; *m/z* (ES⁺) = 537.25 [*M* + H]⁺.

Example 91: 2-[(3*R*,4*S*)-3-Amino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid {1-[5-(1,1-difluoro-ethyl)-[1,2,4]oxadiazol-3-yl]-piperidin-4-yl}-methyl-amide hydrochloride



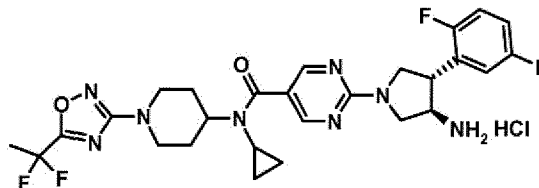
The title compound was synthesized from [(3*R*,4*S*)-1-[5-({1-[5-(1,1-difluoro-ethyl)-[1,2,4]oxadiazol-3-yl]-piperidin-4-yl}-methyl-carbamoyl)-pyrimidin-2-yl]-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester (**Preparation 215**, 357mg, 0.55mmol) employing a procedure similar to that outlined in **Example 4**: RT = 0.81 min; *m/z* (ES⁺) = 549.51 [*M* + H]⁺.

Example 92: 2-[(3*R*,4*S*)-3-Amino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid cyclopropyl-{1-[5-(1-methoxy-1-methyl-ethyl)-[1,2,4]oxadiazol-3-yl]-piperidin-4-yl}-amide hydrochloride



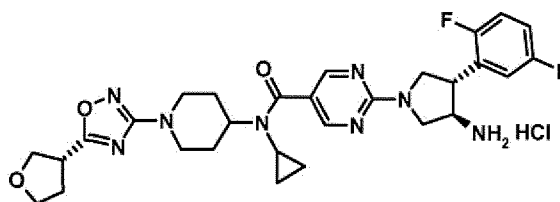
The title compound was synthesized from [(3*R*,4*S*)-1-[5-(cyclopropyl-{1-[5-(1-methoxy-1-methyl-ethyl)-[1,2,4]oxadiazol-3-yl]-piperidin-4-yl}-carbamoyl)-pyrimidin-2-yl]-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester (**Preparation 218**, 91mg, 0.13mmol) employing a procedure similar to that outlined in **Example 3**: RT = 0.81 min; *m/z* (ES⁺) = 583.6 [*M* + H]⁺.

Example 93: 2-[(3*R*,4*S*)-3-Amino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid cyclopropyl-{1-[5-(1,1-difluoro-ethyl)-[1,2,4]oxadiazol-3-yl]-piperidin-4-yl}-amide hydrochloride



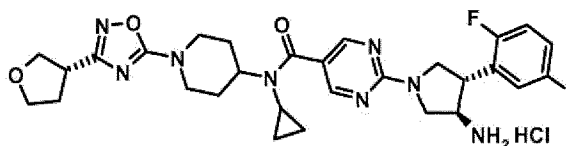
The title compound was synthesized from [(3*R*,4*S*)-1-[5-(cyclopropyl-{1-[5-(1,1-difluoro-ethyl)-[1,2,4]oxadiazol-3-yl]-piperidin-4-yl}-carbamoyl)-pyrimidin-2-yl]-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester (**Preparation 222**, 31mg, 0.046mmol) employing a procedure similar to that outlined in **Example 4**: RT = 0.81 min; m/z (ES^+) = 583.6 [$M + H$] $^+$.

Example 94: 2-[(3*R*,4*S*)-3-Amino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid cyclopropyl-{1-[(*R*)-5-(tetrahydro-furan-3-yl)-[1,2,4]oxadiazol-3-yl]-piperidin-4-yl}-amide hydrochloride



The title compound was synthesized from [(3*R*,4*S*)-1-[5-(cyclopropyl-{1-[(*R*)-5-(tetrahydro-furan-3-yl)-[1,2,4]oxadiazol-3-yl]-piperidin-4-yl}-carbamoyl)-pyrimidin-2-yl]-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester (**Preparation 223**, 36mg, 0.053mmol) employing a procedure similar to that outlined in **Example 4**: RT = 0.72 min; m/z (ES^+) = 581.6 [$M + H$] $^+$ (LCMS Method - 2).

Example 95: 2-[(3*R*,4*S*)-3-Amino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid cyclopropyl-{1-[(*S*)-3-(tetrahydro-furan-3-yl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-amide hydrochloride

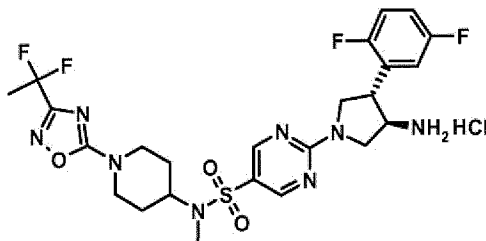


The title compound was synthesized from [(3*R*,4*S*)-1-[5-(cyclopropyl-{1-[(*S*)-3-(tetrahydro-furan-3-yl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-carbamoyl)-pyrimidin-2-yl]-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester (**Preparation 228**) employing a procedure similar to that outlined in **Example 4**: RT = 0.74 min; m/z (ES^+) = 581.46 [$M + H$] $^+$ (LCMS Method -

2).

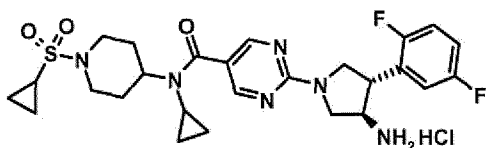
Example 96: 2-[(3*R*,4*S*)-3-Amino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-sulfonic acid {1-[3-(1,1-difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-methyl-amide

5 hydrochloride



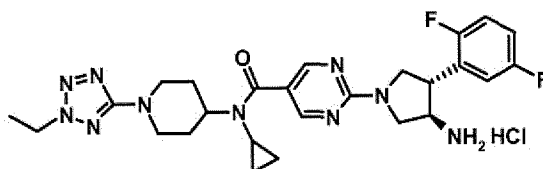
The title compound was synthesized from [(3*R*,4*S*)-1-[5-({1-[3-(1,1-difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-methyl-sulfamoyl)-pyrimidin-2-yl]-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester (**Preparation 230**) employing a procedure similar to that outlined in **Example 3**: LCMS: RT = 0.84 min, m/z (ES^+) = 585.5 [$M + H$] $^+$.

Example 97: 2-[(3*R*,4*S*)-3-Amino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid (1-cyclopropanesulfonyl-piperidin-4-yl)-cyclopropyl-amide hydrochloride



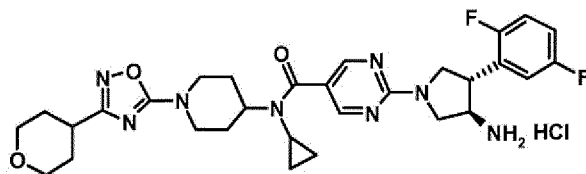
The title compound was synthesized from [(3*R*,4*S*)-1-{5-[(1-cyclopropanesulfonyl-piperidin-4-yl)-cyclopropyl-carbamoyl]-pyrimidin-2-yl}-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester (**Preparation 232**) employing a procedure similar to that outlined in **Example 3**: RT = 0.73 min; m/z (ES^+) = 547.51 [$M + H$] $^+$ (LCMS Method - 2).

Example 98: 2-[(3*R*,4*S*)-3-Amino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid cyclopropyl-[1-(2-ethyl-2H-tetrazol-5-yl)-piperidin-4-yl]-amide hydrochloride



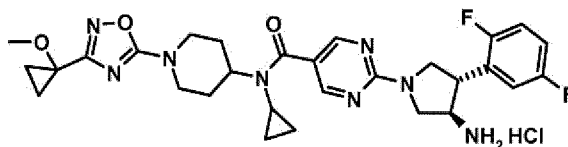
The title compound was synthesized from [(3*R*,4*S*)-1-(5-{cyclopropyl-[1-(2-ethyl-2H-tetrazol-5-yl)-piperidin-4-yl]-carbamoyl}-pyrimidin-2-yl)-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester (**Preparation 236**) employing a procedure similar to that outlined in **Example 4**: RT = 0.75min; m/z (ES^+) = 539.57 [$M + H$] $^+$ (LCMS Method - 2).

Example 99: 2-[(3*R*,4*S*)-3-Amino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid cyclopropyl-{1-[3-(tetrahydro-pyran-4-yl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-amide hydrochloride



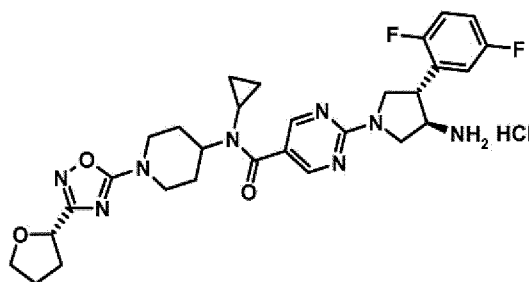
The title compound was synthesized from [(3*R*,4*S*)-1-[5-(cyclopropyl-{1-[3-(tetrahydro-pyran-4-yl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-carbamoyl)-pyrimidin-2-yl]-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester (**Preparation 238**) employing a procedure similar to that outlined in **Example 3**: RT = 0.73min; m/z (ES^+) = 595.62 [$M + H$] $^+$ (LCMS Method - 2).

Example 100: 2-[(3*R*,4*S*)-3-Amino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid cyclopropyl-{1-[3-(1-methoxy-cyclopropyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-amide hydrochloride



The title compound was synthesized from [(3*R*,4*S*)-1-[5-(cyclopropyl-{1-[3-(1-methoxy-cyclopropyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-carbamoyl)-pyrimidin-2-yl]-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester (**Preparation 245**) employing a procedure similar to that outlined in **Example 3**: RT = 0.76min; m/z (ES^+) = 581.57 [$M + H$] $^+$ (LCMS Method - 2).

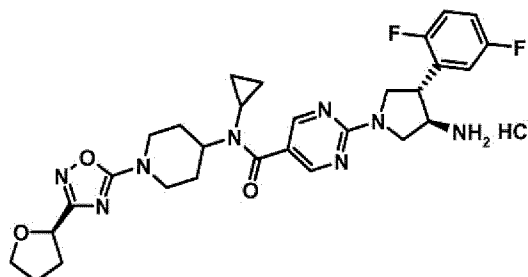
Example 101: 2-[(3*R*,4*S*)-3-Amino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid cyclopropyl-{1-[3-(*S*)-3-(tetrahydro-furan-2-yl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-amide hydrochloride



The title compound was synthesized from [(3*R*,4*S*)-1-[5-(cyclopropyl-{1-[3-(*S*)-3-(tetrahydro-furan-2-yl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-carbamoyl)-pyrimidin-2-yl]-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester (**Preparation 247**) employing a procedure

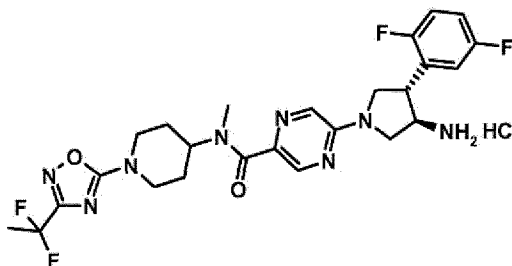
similar to that outlined in **Example 3**: RT = 0.75min; m/z (ES^+) = 581.51 [$M + H$] $^+$ (LCMS Method - 2).

Example 102: 2-[(3*R*,4*S*)-3-Amino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrimidine-5-carboxylic acid cyclopropyl-{1-[(*R*)-3-(tetrahydro-furan-2-yl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-amide hydrochloride



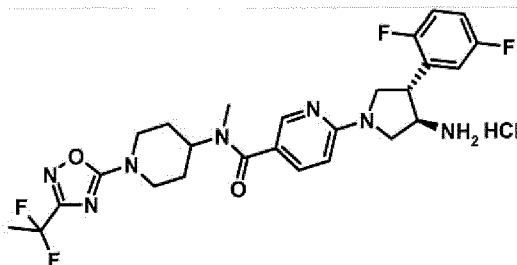
The title compound was synthesized from [(3*R*,4*S*)-1-[5-(cyclopropyl-{1-[(*R*)-3-(tetrahydro-furan-2-yl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-carbamoyl)-pyrimidin-2-yl]-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester (**Preparation 250**) employing a procedure similar to that outlined in **Example 3**: RT = 0.75 min; m/z (ES^+) = 581.46 [$M + H$] $^+$ (LCMS Method - 2).

Example 103: 5-[(3*R*,4*S*)-3-Amino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-pyrazine-2-carboxylic acid {1-[3-(1,1-difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-methyl-amide hydrochloride



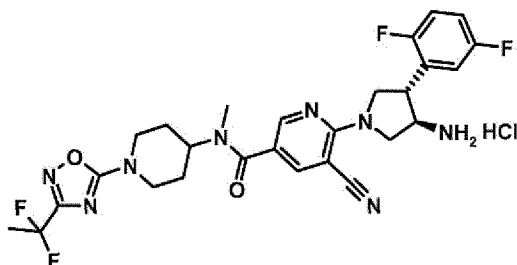
The title compound was synthesized from [(3*R*,4*S*)-1-[5-({1-[3-(1,1-difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-methyl-carbamoyl)-pyrazin-2-yl]-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester (**Preparation 253**) employing a procedure similar to that outlined in **Example 4**: RT = 0.79min; m/z (ES^+) = 549.55 [$M + H$] $^+$ (LCMS Method - 2).

Example 104: 6-[(3*R*,4*S*)-3-Amino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-*N*-{1-[3-(1,1-difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-*N*-methyl-nicotinamide hydrochloride



The title compound was synthesized from [(3*R*,4*S*)-1-[5-(1-[3-(1,1-difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl)-methyl-carbamoyl]-pyridin-2-yl]-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester (**Preparation 256**) employing a procedure similar to that outlined in **Example 3**: RT = 0.74min; m/z (ES^+) = 548.60 [$M + H$] $^+$ (LCMS Method - 2).

Example 105: 6-[(3*R*,4*S*)-3-Amino-4-(2,5-difluoro-phenyl)-pyrrolidin-1-yl]-5-cyano-*N*-{1-[3-(1,1-difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl}-*N*-methyl-nicotinamide hydrochloride



The title compound was synthesized from [(3*R*,4*S*)-1-[3-cyano-5-(1-[3-(1,1-difluoro-ethyl)-[1,2,4]oxadiazol-5-yl]-piperidin-4-yl)-methyl-carbamoyl]-pyridin-2-yl]-4-(2,5-difluoro-phenyl)-pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester (**Preparation 259**) employing a procedure similar to that outlined in **Example 3**: RT = 0.79min; m/z (ES^+) = 573.54 [$M + H$] $^+$ (LCMS Method - 2).

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 AlphaScreenTM (Amplified Luminescent Proximity Homogeneous Assay) cAMP kit. Buffers and assay conditions were as described in the manufacturer's protocol.

A number of representative examples of compounds of the invention were tested and found to produce a concentration-dependent increase in intracellular cAMP levels and generally had an EC₅₀ of <10 μ M; some of the examples showed an EC₅₀ of less than 1 μ M in the cAMP assay.

5 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 μ L per well consisting of 50 mM Tris pH 7.6, 100 μ M GP-AMC, 10-25 μ U 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 105 above were tested and found to show activity in this assay having an IC₅₀ of <20 μ M. Some of the examples were found to have a DPP-IV EC₅₀ value of less than 1 μ M; others an EC₅₀ value of less than 20 μ M.

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 <1 μ M	cAMP EC ₅₀ between 1 μ M and 10 μ M	DPP-IV IC ₅₀ <1 μ M	DPP-IV IC ₅₀ between 1 μ M and 20 μ M
3	+			+
8	+			+
11	+		+	
52	+		+	
66	+			+
72	+		+	

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).

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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, 10 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 15 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 20 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 EC₅₀ of less than 10 µM. Compounds showing an EC₅₀ of less than 1 µM in the cAMP assay may be preferred.

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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 CaCl₂, 1.19 mM MgSO₄, 1.19 mM KH₂PO₄, 25 mM NaHCO₃, 10 mM HEPES at pH 7.4 and 0.1% bovine serum 30 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 35 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 μ M.

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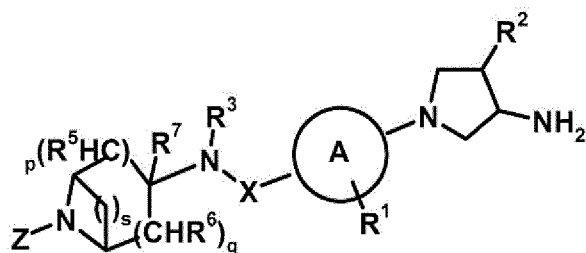
Oral Glucose Tolerance Tests

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® Ultra™ 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 were evaluated in male C57Bl/6 or male *ob/ob* mice. Food was withdrawn 5 h before administration of Glc and remained withdrawn throughout the study. Mice had free access to water during the study. A cut was made to the animals' tails, then blood (20 μ L) was removed for measurement of basal Glc levels 45 min before administration of the Glc load. Then, the mice were weighed and dosed orally with test compound or vehicle (20% aqueous hydroxypropyl- β -cyclodextrin or 25% aqueous Gelucire 44/14) 30 min before the removal of an additional blood sample (20 μ L) and treatment with the Glc load (2-5 g kg^{-1} p.o.). Blood samples (20 μ L) were then taken 25, 50, 80, 120, and 180 min after Glc administration. The 20 μ L blood samples for measurement of Glc levels were taken from the cut tip of the tail into disposable micro-pipettes (Dade Diagnostics Inc., Puerto Rico) and the sample added to 480 μ L of haemolysis reagent. Duplicate 20 μ L aliquots of the diluted haemolysed blood were then added to 180 μ L of Trinders glucose reagent (Sigma enzymatic (Trinder) colorimetric method) in a 96-well assay plate. After mixing, the samples were left at room temperature for 30 min before being read against Glc standards (Sigma glucose/urea nitrogen combined standard set). Compounds of the invention statistically reduced the Glc excursion at doses ≤ 100 mg kg^{-1} , for example at a dose of 30 mg kg^{-1} the compound of Example 7 showed a $> 40\%$ reduction in the Glc excursion

CLAIMS

1.



wherein A is a para-linked phenyl, pyridinyl, pyrimidinyl, pyrazinyl or triazinyl;

R^1 is hydrogen, halo, cyano, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy or C_{2-6} alkoxyalkyl;

R^2 is selected from the group consisting of:

- (a) phenyl optionally substituted by one or more halo, methyl or halomethyl groups,
- (b) pyridyl optionally substituted by one or more halo, methyl or halomethyl groups
- and (c) N-pyridonyl optionally substituted by one or more halo, methyl or halomethyl

groups

R^3 is methyl, C_{3-6} cycloalkyl, 4 to 6 membered saturated heterocyclyl (comprising 1 or 2 ring heteroatoms selected from N, O and S) or C_{2-4} alkyl wherein the C_{3-6} cycloalkyl and C_{2-4} alkyl are optionally substituted by fluoro, cyano, hydroxy or C_{1-2} alkyloxy;

p and q are each 0, 1 or 2, provided that $0 \leq p+q \leq 2$;

Z is selected from the group consisting of:

- (a) $C(O)OR^4$,
- (b) $C(O)R^4$,
- (c) $S(O)_2R^4$,
- (d) 5- or 6-membered N-containing heteroaryl ring optionally

containing 1 to 3 additional heteroatoms selected from N, O and S, or a 8 to 10 membered fused bicyclic system optionally containing 1 to 3 heteroatoms selected from N, O and S, wherein the heteroaryl ring or fused bicyclic system is optionally substituted by one or two groups independently selected from halo, cyano, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{2-4} alkoxyalkyl, heterocyclyl (a 4 to 6 membered saturated heterocycle comprising 1 or 2 ring heteroatoms selected from N, O and S), heterocyclyl C_{1-4} alkyl (wherein the heterocyclyl is a 4 to 6 membered saturated heterocycle comprising 1 or 2 ring heteroatoms selected from N, O and S) and C_{3-6} cycloalkyl optionally substituted by C_{1-4} alkyl, C_{1-4} alkoxy or halo;

and (e) $-\text{CH}_2\text{-phenyl}$, wherein the phenyl is optionally substituted by one or two groups independently selected from C_{1-4} alkyl, C_{1-4} haloalkyl and halo;

and when Z is optionally substituted $-\text{CH}_2\text{-phenyl}$ then p and q are both 0 or 1;

R^4 is selected from the group consisting of:

- a) C_{1-6} alkyl,
- b) phenyl,
- c) C_{2-6} alkoxyalkyl,
- d) C_{3-6} cycloalkyl optionally substituted by C_{1-4} alkyl,
- e) C_{3-6} cycloalkyl C_{1-4} alkyl optionally substituted by C_{1-4} alkyl,
- f) 4 to 6 membered saturated heterocycle comprising 1 or 2 ring heteroatoms selected from N, O and S, and

g) 5 or 6 membered heteroaryl ring containing 1 to 4 heteroatoms selected from N, O and S optionally substituted by one or two groups selected from halo, cyano, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{2-4} alkoxyalkyl, a 4 to 6 membered saturated heterocycle comprising 1 or 2 ring heteroatoms selected from N, O and S and C_{3-6} cycloalkyl wherein the cycloalkyl is optionally substituted by C_{1-4} alkyl or halo;

X is selected from $\text{C}(\text{O})$ or $\text{S}(\text{O})_2$ with the proviso that when X is $\text{S}(\text{O})_2$ then R^3 is methyl, p and q are both 1 and Z is a 5 to 6 membered heteroaryl ring;

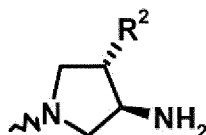
each of R^5 and R^6 is independently hydrogen, halo, C_{1-2} alkyl, C_{1-2} haloalkyl or C_{1-3} alkoxy; alternatively R^5 and R^6 can be joined to form an azabicyclo[3.3.1]nonane, a 3-oxa-7-azabicyclo[3.3.1]nonane or an azabicyclo[3.2.1]octane;

R^7 is hydrogen, halo, C_{1-2} alkyl, C_{1-2} haloalkyl or C_{1-3} alkoxy;
s is 0, 2 or 3

and when R^5 and R^6 are both hydrogen then s is 0, 2 or 3.

and when at least one of R^5 and R^6 is halo, C_{1-2} alkyl, C_{1-4} haloalkyl or C_{1-4} alkoxy then s is 0 and pharmaceutically acceptable salts thereof.

2. A compound as claimed in Claim 1 wherein said compound has the stereochemistry:



wherein R^2 is as defined in claim 1.

3. A compound as claim 1 or claim 2 wherein X is C(O).
4. A compound as claimed in Claim 1 or Claim 2 wherein R^1 is hydrogen.
5. A compound as claimed in any one of Claims 1 to 4 wherein R^3 is methyl, C_{3-6} cycloalkyl or C_{2-4} alkyl, wherein the C_{3-6} cycloalkyl and C_{2-4} alkyl are optionally substituted by fluoro, cyano, hydroxy or C_{1-2} alkyloxy.
6. A compound as claimed in any one of claims 1 to 5 wherein p and q are the same.
7. A compound as claimed in any one of claims 1 to 6 wherein A is pyridine, pyrimidine or pyrazine.
8. A compound as claimed in any of claims 1 to 7 wherein Z is a heteroaryl group optionally be substituted by one or two groups selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{2-4} alkoxyalkyl, heterocyclyl, heterocyclyl C_{1-4} alkyl and C_{3-6} cycloalkyl, wherein the cycloalkyl is optionally substituted by C_{1-4} alkyl, C_{1-4} alkoxy or halo.
9. A compound as claimed in claim 8 wherein the heteroaryl group is oxadiazole, pyrimidine, pyridazine, thiazole, tetrazole, benzothiazole or thiadiazole.
10. A compound as claimed in claim 9 wherein Z comprises optionally substituted 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl or pyrimidin-2-yl.
11. A compound as claimed in any preceding claim wherein Z is -C(O)OR₄.
12. A compound as claimed in any preceding claim wherein R^4 is alkyl, C_{4-5} alkoxyalkyl, cycloalkyl or cycloalkylalkyl, wherein the cycloalkylalkyl is optionally substituted by C_{1-4} alkyl.
13. A compound as claimed in claim 11 wherein R^4 is propyl, preferably isopropyl.
14. A compound as claimed in any preceding claim wherein R^2 is substituted phenyl or pyridyl.
15. A compound as claimed in any preceding claim, wherein R^2 is phenyl substituted by one, two or three halo or methyl groups.
16. A compound as claimed in any preceding claim, wherein R^2 is phenyl substituted by two or three halo groups.
17. A compound according to any of Examples 1 to 105 or a pharmaceutically acceptable salt thereof.
18. A compound as claimed in any preceding claim for use in a method of treatment of a metabolic disorder, including type II diabetes.

19. A pharmaceutical formulation or composition comprising a compound as claimed in any of claims 1 to 19 and a pharmaceutically acceptable carrier therefor.
20. A method for the treatment or prevention of diabetes, including type II diabetes, or 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 human or non-human animal in need thereof an effective amount of a compound according to any one of claims 1 to 18 or a pharmaceutically acceptable salt thereof, or a pharmaceutical formulation or composition as claimed in claim 19.

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2011/070346

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D413/14 C07D401/14 A61K31/506 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)

C07D

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, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2010/103334 A1 (PROSIDION LTD [GB]; BARBA OSCAR [GB]; DUPREE TOM BANKSIA [GB]; FRY PET) 16 September 2010 (2010-09-16) cited in the application page 1, line 5 - page 2, line 18 page 61 - page 84; examples 1-53 claim 1	1-20
A	WO 2010/103335 A1 (PROSIDION LTD [GB]; BARBA OSCAR [GB]; DAVIS SUSAN HELEN [GB]; FYFE MAT) 16 September 2010 (2010-09-16) cited in the application page 1, line 5 - page 2, line 18 page 41 - page 29; examples 1-29 claim 1	1-20



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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"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

4 January 2012

Date of mailing of the international search report

30/01/2012

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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2011/070346

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WRIGHT ET AL: "(3R,4S)-4-(2,4,5-Trifluorophenyl)-pyrroli din-3-ylamine inhibitors of dipeptidyl peptidase IV: Synthesis, in vitro, in vivo, and X-ray crystallographic characterization", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, ELSEVIER SCIENCE, GB, vol. 17, no. 20, 14 September 2007 (2007-09-14), pages 5638-5642, XP022249683, ISSN: 0960-894X, DOI: 10.1016/J.BMCL.2007.07.081 the whole document -----	1-20

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2011/070346

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010103334 A1	16-09-2010	CA 2754791 A1	16-09-2010
		EP 2406251 A1	18-01-2012
		WO 2010103334 A1	16-09-2010

WO 2010103335 A1	16-09-2010	CA 2754794 A1	16-09-2010
		EP 2406256 A1	18-01-2012
		WO 2010103335 A1	16-09-2010
