

DPP-IV inhibitors

5 The present invention relates to a novel class of dipeptidyl peptidase inhibitors, including pharmaceutically acceptable salts and prodrugs thereof, which are useful as therapeutic compounds, particularly in the treatment of Type 2 diabetes mellitus, often referred to as non-insulin dependent diabetes mellitus (NIDDM), and of conditions that are often associated with this disease, such as obesity and lipid disorders.

10

Diabetes refers to a disease process derived from multiple causative factors and characterized by elevated levels of plasma glucose or hyperglycemia in the fasting state or after administration of glucose during an oral glucose tolerance test. Persistent or uncontrolled hyperglycemia is associated with increased and premature morbidity and mortality. Often abnormal glucose homeostasis is associated both directly and
15 indirectly with alterations of the lipid, lipoprotein and apolipoprotein metabolism and other metabolic and hemodynamic disease. Therefore patients with Type 2 diabetes mellitus are at an increased risk of macrovascular and microvascular complications, including coronary heart disease, stroke, peripheral vascular disease, hypertension, nephropathy, neuropathy, and retinopathy. Therefore, therapeutic control of glucose
20 homeostasis, lipid metabolism and hypertension are critically important in the clinical management and treatment of diabetes mellitus.

There are two generally recognized forms of diabetes. In Type 1, or insulin-dependent, diabetes mellitus (IDDM), patients produce little or no insulin, which is the hormone
25 regulating glucose utilization. In Type 2, or noninsulin dependent, diabetes mellitus (NIDDM), patients often have plasma insulin levels that are the same or elevated compared to nondiabetic subjects. These patients develop a resistance to the insulin stimulating effect on glucose and lipid metabolism in the main insulin-sensitive tissues, namely the muscle, liver and adipose tissues. Further, the plasma insulin levels, while
30 elevated, are insufficient to overcome the pronounced insulin resistance.

Insulin resistance is not primarily due to a diminished number of insulin receptors but to a post-insulin receptor binding defect that is not yet understood. This resistance to
35 insulin responsiveness results in insufficient insulin activation of glucose uptake,

oxidation and storage in muscle, and inadequate insulin repression of lipolysis in adipose tissue and of glucose production and secretion in the liver.

The available treatments for Type 2 diabetes, which have not changed substantially in many years, have recognized limitations. While physical exercise and reductions in dietary intake of calories will dramatically improve the diabetic condition, compliance with this treatment is very poor because of well-entrenched sedentary lifestyles and excess food consumption, especially of foods containing high amounts of saturated fat. Increasing the plasma level of insulin by administration of sulfonylureas (e.g., tolbutamide and glipizide) or meglitinide, which stimulate the pancreatic β -cells to secrete more insulin, and/or by injection of insulin when sulfonylureas or meglitinide become ineffective, can result in insulin concentrations high enough to stimulate the very insulin-resistant tissues. However, dangerously low levels of plasma glucose can result from administration of insulin or insulin secretagogues (sulfonylureas or meglitinide), and an increased level of insulin resistance, due to the even higher plasma insulin levels, can occur. The biguanides increase insulin sensitivity resulting in some correction of hyperglycemia. However, the two biguanides, phenformin and metformin, can induce lactic acidosis and nausea/diarrhoea. Metformin has fewer side effects than phenformin and is often prescribed for the treatment of Type 2 diabetes.

The glitazones (*i.e.*, 5-benzylthiazolidine-2,4-diones) are a recently described class of compounds with potential for ameliorating many symptoms of Type 2 diabetes. These agents substantially increase insulin sensitivity in muscle, liver and adipose tissue in several animal models of Type 2 diabetes, resulting in partial or complete correction of the elevated plasma levels of glucose without occurrence of hypoglycemia. The glitazones that are currently marketed are agonists of the peroxisome proliferator activated receptor (PPAR), primarily the PPAR-gamma subtype. PPAR-gamma agonism is generally believed to be responsible for the improved insulin sensitization that is observed with the glitazones. Newer PPAR agonists that are being tested for treatment of Type 2 diabetes are agonists of the alpha, gamma or delta subtype, or a combination of these, and in many cases are chemically different from the glitazones (*i.e.*, they are not thiazolidinediones). Serious side effects (e.g., liver toxicity) have occurred with some of the glitazones, such as troglitazone.

Additional methods of treating the disease are still under investigation. New biochemical approaches that have been recently introduced or are still under

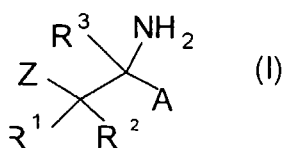
development include treatment with alpha-glucosidase inhibitors (e.g., acarbose) and protein tyrosine phosphatase-1B (PTP-1B) inhibitors.

Compounds that are inhibitors of the dipeptidyl peptidase-IV (DPP-IV) enzyme are also under investigation as drugs that may be useful in the treatment of diabetes, and particularly Type 2 diabetes. See for example WO-A-97/40832, WO-A-98/19998, WO-A-03/180, WO-A-03/181 and WO-A-2004/007468. The usefulness of DPP-IV inhibitors in the treatment of Type 2 diabetes is based on the fact that DPP-IV *in vivo* readily inactivates glucagon like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP). GLP-1 and GIP are incretins and are produced when food is consumed. The incretins stimulate production of insulin. Inhibition of DPP-IV leads to decreased inactivation of the incretins, and this in turn results in increased effectiveness of the incretins in stimulating production of insulin by the pancreas. DPP-IV inhibition therefore results in an increased level of serum insulin. Advantageously, since the incretins are produced by the body only when food is consumed, DPP-IV inhibition is not expected to increase the level of insulin at inappropriate times, such as between meals, which can lead to excessively low blood sugar (hypoglycemia). Inhibition of DPP-IV is therefore expected to increase insulin without increasing the risk of hypoglycemia, which is a dangerous side effect associated with the use of insulin secretagogues.

DPP-IV inhibitors may also have other therapeutic utilities, as discussed elsewhere in this application. DPP-IV inhibitors have not been studied extensively to date, especially for utilities other than diabetes. New compounds are needed so that improved DPP-IV inhibitors can be found for the treatment of diabetes and potentially other diseases and conditions.

Thus, the object of the present invention is to provide a new class of DPP-IV inhibitors which may be effective in the treatment of Type 2 diabetes and other DPP-IV modulated diseases.

Accordingly, the present invention provides novel compounds of formula (I):



or a pharmaceutically acceptable salt thereof, wherein

5 Z is selected from the group consisting of phenyl; naphthyl; indenyl; C₃₋₇ cycloalkyl; indanyl; tetralinyl; decalinyl; heterocycle; and heterobicycle, wherein Z is optionally substituted with one or more R⁴, wherein R⁴ is independently selected from the group consisting of halogen; CN; OH; NH₂; oxo (=O), where the ring is at least partially saturated; R⁵; and R⁶;

10 R⁵ is selected from the group consisting of C₁₋₆ alkyl; O-C₁₋₆ alkyl; and S-C₁₋₆ alkyl, wherein R⁵ is optionally interrupted by oxygen and wherein R⁵ is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

15 R⁶ is selected from the group consisting of phenyl; heterocycle; and C₃₋₇ cycloalkyl, wherein R⁶ is optionally substituted with one or more R⁷, wherein R⁷ is independently selected from the group consisting of halogen; CN; OH; NH₂; oxo (=O), where the ring is at least partially saturated; C₁₋₆ alkyl; O-C₁₋₆ alkyl; and S-C₁₋₆ alkyl;

20 R¹ is selected from the group consisting of H; F; OH; and R⁸;

R² is selected from the group consisting of H; F; and R⁹;

25 R⁸ is independently selected from the group consisting of C₁₋₆ alkyl; O-C₁₋₆ alkyl; N(R^{8a})-C₁₋₆ alkyl; S-C₁₋₆ alkyl; C₃₋₇ cycloalkyl; O-C₃₋₇ cycloalkyl; N(R^{8a})-C₃₋₇ cycloalkyl; S-C₃₋₇ cycloalkyl; -C₁₋₆ alkyl-C₃₋₇ cycloalkyl; O-C₁₋₆ alkyl-C₃₋₇ cycloalkyl; N(R^{8a})-C₁₋₆ alkyl-C₃₋₇ cycloalkyl; S-C₁₋₆ alkyl-C₃₋₇ cycloalkyl; heterocycle; O-heterocycle; N(R^{8a})-heterocycle; S-heterocycle; C₁₋₆ alkyl-heterocycle; O-C₁₋₆ alkyl-heterocycle; N(R^{8a})-C₁₋₆ alkyl-heterocycle; S-C₁₋₆ alkyl-heterocycle; wherein R⁸ is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

30 R^{8a} is selected from the group consisting of H; and C₁₋₆ alkyl;

35 R⁹ is independently selected from the group consisting of C₁₋₆ alkyl; C₃₋₇ cycloalkyl; and -C₁₋₆ alkyl-C₃₋₇ cycloalkyl, wherein R⁹ is optionally substituted with one or more R^{9a}, wherein R^{9a} is independently selected from the group consisting of F; Cl; and OH;

R^3 is selected from the group consisting of H; and C_{1-6} alkyl;

Optionally one or more pairs of R^1 , R^2 , R^3 independently selected from the group consisting of R^1/R^2 ; and R^2/R^3 , form a C_{3-7} cycloalkyl ring, which is optionally substituted with one or more of R^{9b} , wherein R^{9b} is independently selected from the group consisting of F; Cl; and OH;

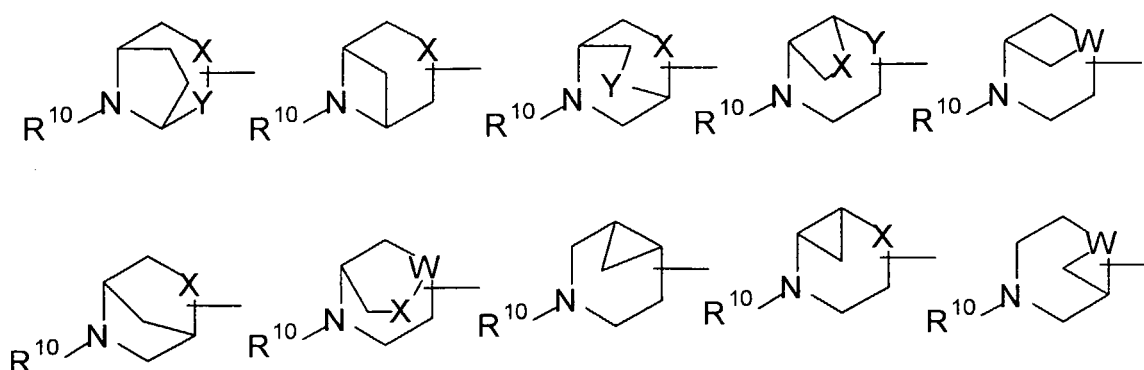
A is selected from the group consisting of A^0 ; and A^1 ;

- 10 A^0 is selected from the group consisting of C_{3-7} cycloalkyl; and a saturated heterocycle with at least one nitrogen as ring atom; wherein A^0 is substituted with one or more R^{10a} , wherein R^{10a} is independently selected from the group consisting of $NR^{10}R^{10b}$; $NR^{10}S(O)_2R^{10b}$; $NR^{10}S(O)R^{10b}$; $S(O)_2NR^{10}R^{10b}$; $C(O)NR^{10}R^{10b}$; R^{10} , provided that R^{10} is bound to a nitrogen, which is a ring atom of the saturated heterocycle; and
- 15 C_{1-3} alkyl, which is optionally substituted with one or more R^{10c} , wherein R^{10c} is independently selected from the group consisting of F; C_{1-3} alkyl; and C_{3-4} cycloalkyl, wherein C_{1-3} alkyl and C_{3-4} cycloalkyl are optionally substituted with one or more F;

Optionally R^{10a} is independently selected from group consisting of F; Cl, and oxo (=O);

20

A^1 is selected from the group consisting of



25

X; Y are independently selected from the group consisting of $-CH_2-$; $-NR^{10b}-$; $-O-$; and $-S-$;

W is selected from the group consisting of $-\overset{|}{\underset{|}{C}}H-$; and $-\overset{|}{\underset{|}{N}}-$;

R^{10} , R^{10b} are independently selected from the group consisting of T^1 - T^2 ; and T^2 ;

T^1 is selected from the group consisting of $-C_{1-6}$ alkyl-; $-C_{1-6}$ alkyl-O-; $-C_{1-6}$ alkyl-S-; $-C_{1-6}$ alkyl-N(R^{11})-; $-C(O)-$; $-C(O)-C_{1-6}$ alkyl-; $-C(O)-C_{1-6}$ alkyl-O-; $-C(O)-C_{1-6}$ alkyl-S-; $-C(O)-C_{1-6}$ alkyl-N(R^{11})-; $-C(O)O-$; $-C(O)O-C_{1-6}$ alkyl-; $-C(O)O-C_{1-6}$ alkyl-O-; $-C(O)O-C_{1-6}$ alkyl-S-; $-C(O)O-C_{1-6}$ alkyl-N(R^{11})-; $-C(O)N(R^{11})-$; $-C(O)N(R^{11})-C_{1-6}$ alkyl-; $-C(O)N(R^{11})-C_{1-6}$ alkyl-O-; $-C(O)N(R^{11})-C_{1-6}$ alkyl-S-; $-C(O)N(R^{11})-C_{1-6}$ alkyl-N(R^{11a})-; $-S(O)_2-$; $-S(O)_2-C_{1-6}$ alkyl-; $-S(O)_2-C_{1-6}$ alkyl-O-; $-S(O)_2-C_{1-6}$ alkyl-S-; $-S(O)_2-C_{1-6}$ alkyl-N(R^{11})-; $-S(O)-$; $-S(O)-C_{1-6}$ alkyl-; $-S(O)-C_{1-6}$ alkyl-O-; $-S(O)-C_{1-6}$ alkyl-S-; and $-S(O)-C_{1-6}$ alkyl-N(R^{11})-; wherein each C_{1-6} alkyl is optionally substituted with one or more halogen selected from the group consisting of F; and Cl;

R^{11} , R^{11a} are independently selected from the group consisting of H; C_{1-6} alkyl; C_{3-7} cycloalkyl; and $-C_{1-6}$ alkyl- C_{3-7} cycloalkyl;

T^2 is selected from the group consisting of H; T^3 ; and T^4 ;

T^3 is selected from the group consisting of phenyl; naphthyl; and indenyl; wherein T^3 is optionally substituted with one or more R^{12} ; wherein R^{12} is independently selected from the group consisting of halogen; CN; $COOR^{13}$; $OC(O)R^{13}$; OR^{13} ; $-C_{1-6}alkyl-OR^{13}$; SR^{13} ; $S(O)R^{13}$; $S(O)_2R^{13}$; $C(O)N(R^{13}R^{14})$; $S(O)_2N(R^{13}R^{14})$; $S(O)N(R^{13}R^{14})$; C_{1-6} alkyl; $N(R^{13})S(O)_2R^{14}$; and $N(R^{13})S(O)R^{14}$; wherein each C_{1-6} alkyl is optionally substituted with one more halogen selected from the group consisting of F; and Cl;

T^4 is selected from the group consisting of C_{3-7} cycloalkyl; indanyl; tetralinyl; decalinyl; heterocycle; and heterobicycle; wherein T^4 is optionally substituted with one or more R^{15} , wherein R^{15} is independently selected from the group consisting of halogen; CN; OR^{13} ; $-C_{1-6}alkyl-OR^{13}$; SR^{13} ; oxo ($=O$), where the ring is at least partially saturated; $N(R^{13}R^{14})$; $COOR^{13}$; $OC(O)R^{13}$; $C(O)N(R^{13}R^{14})$; $S(O)_2N(R^{13}R^{14})$; $S(O)N(R^{13}R^{14})$; C_{1-6} alkyl; $N(R^{13})C(O)R^{14}$; $S(O)_2R^{13}$; $S(O)R^{13}$; $N(R^{13})S(O)_2R^{14}$; and $N(R^{13})S(O)R^{14}$; wherein each C_{1-6} alkyl is optionally substituted with one or more halogen selected from the group consisting of F; and Cl;

Optionally R^{15} is $C(O)R^{13}$, provided that $C(O)R^{13}$ is bound to a nitrogen, which is a ring atom of a heterocycle or heterobicycle;

R^{13} , R^{14} are independently selected from the group consisting of H; C_{1-6} alkyl; C_{3-7} cycloalkyl; and $-C_{1-6}$ alkyl- C_{3-7} cycloalkyl; wherein each C_{1-6} alkyl is optionally substituted with one more halogen selected from the group consisting of F; and Cl.

5 Within the meaning of the present invention the terms are used as follows:

In case a variable or substituent can be selected from a group of different variants and such variable or substituent occurs more than once the respective variants can be the same or different.

10

"Alkyl" means a straight-chain or branched carbon chain that may contain double or triple bonds. It is generally preferred that alkyl doesn't contain double or triple bonds.

" C_{1-3} alkyl" means an alkyl chain having 1 - 3 carbon atoms, e.g. at the end of a molecule methyl, ethyl, $-\text{CH}=\text{CH}_2$, $-\text{C}\equiv\text{CH}$, n-propyl, isopropyl, $-\text{CH}=\text{CH}-\text{CH}_3$,

15 $-\text{CH}_2-\text{CH}=\text{CH}_2$.

" C_{1-4} alkyl" means an alkyl chain having 1 - 4 carbon atoms, e.g. at the end of a molecule methyl, ethyl, $-\text{CH}=\text{CH}_2$, $-\text{C}\equiv\text{CH}$, n-propyl, isopropyl, $-\text{CH}=\text{CH}-\text{CH}_3$, $-\text{CH}_2-\text{CH}=\text{CH}_2$, n-butyl, isobutyl, $-\text{CH}=\text{CH}-\text{CH}_2-\text{CH}_3$, $-\text{CH}=\text{CH}-\text{CH}=\text{CH}_2$, sec-butyl tert-butyl or
20 amid, e.g. $-\text{CH}_2-$, $-\text{CH}_2-\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{CH}(\text{CH}_3)-$, $-\text{C}(\text{CH}_2)-$, $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$, $-\text{CH}(\text{C}_2\text{H}_5)-$, $-\text{CH}(\text{CH}_3)_2-$.

" C_{1-6} alkyl" means an alkyl chain having 1 - 6 carbon atoms, e.g. C_{1-4} alkyl, methyl, ethyl, $-\text{CH}=\text{CH}_2$, $-\text{C}\equiv\text{CH}$, n-propyl, isopropyl, $-\text{CH}=\text{CH}-\text{CH}_3$, $-\text{CH}_2-\text{CH}=\text{CH}_2$, n-butyl, isobutyl, $-\text{CH}=\text{CH}-\text{CH}_2-\text{CH}_3$, $-\text{CH}=\text{CH}-\text{CH}=\text{CH}_2$, sec-butyl tert-butyl, n-pentane,
25 n-hexane, or amid, e.g. $-\text{CH}_2-$, $-\text{CH}_2-\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{CH}(\text{CH}_3)-$, $-\text{C}(\text{CH}_2)-$, $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$, $-\text{CH}(\text{C}_2\text{H}_5)-$, $-\text{CH}(\text{CH}_3)_2-$. Each hydrogen of a C_{1-6} alkyl carbon may be replaced by a substituent.

" C_{3-7} Cycloalkyl" or " C_{3-7} Cycloalkyl ring" means a cyclic alkyl chain having 3 - 7 carbon
30 atoms, e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl. Each hydrogen of a cycloalkyl carbon may be replaced by a substituent.

" C_{3-4} Cycloalkyl" or " C_{3-4} Cycloalkyl ring" means a cyclic alkyl chain having 3 - 4 carbon atoms, e.g. cyclopropyl, cyclobutyl.

35 "Halogen" means fluoro, chloro, bromo or iodo. It is generally preferred that halogen is fluoro or chloro.

"Heterocycle" means a cyclopentane, cyclohexane or cycloheptane ring that may contain up to the maximum number of double bonds (aromatic or non-aromatic ring which is fully, partially or un-saturated) wherein at least one carbon atom up to 4 carbon atoms are replaced by a heteroatom selected from the group consisting of sulfur (including -S(O)-, -S(O)₂-), oxygen and nitrogen (including =N(O)-) and wherein the ring is linked to the rest of the molecule via a carbon or nitrogen atom. Examples for a heterocycle are furan, thiophene, pyrrole, pyrroline, imidazole, imidazoline, pyrazole, pyrazoline, oxazole, oxazoline, isoxazole, isoxazoline, thiazole, thiazoline, isothiazole, isothiazoline, thiadiazole, thiadiazoline, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, imidazolidine, pyrazolidine, oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, thiadiazolidine, sulfolane, pyran, dihydropyran, tetrahydropyran, imidazolidine, pyridine, pyridazine, pyrazine, pyrimidine, piperazine, piperidine, morpholine, tetrazole, triazole, triazolidine, tetrazolidine, azepine or homopiperazine. "Heterocycle" means also azetidine.

"Saturated heterocycle" means a fully saturated heterocycle as defined above.

"Heterobicycle" means a heterocycle which is condensed with phenyl or an additional heterocycle to form a bicyclic ring system. "Condensed" to form a bicyclic ring means that two rings are attached to each other by sharing two ring atoms. Examples for a heterobicycle are indole, indoline, benzofuran, benzothiophene, benzoxazole, benzisoxazole, benzothiazole, benzisothiazole, benzimidazole, benzimidazoline, quinoline, quinazoline, dihydroquinazoline, dihydroquinoline, isoquinoline, tetrahydroisoquinoline, dihydroisoquinoline, benzazepine, purine or pteridine.

Preferred compounds of formula (I) are those compounds in which one or more of the residues contained therein have the meanings given below, with all combinations of preferred substituent definitions being a subject of the present invention. With respect to all preferred compounds of the formulas (I) the present invention also includes all tautomeric and stereoisomeric forms and mixtures thereof in all ratios, and their pharmaceutically acceptable salts.

In preferred embodiments of the present invention, the substituents Z, R¹⁻³ and A of the formula (I) independently have the following meaning. Hence, one or more of the substituents Z, R¹⁻³ and A can have the preferred or more preferred meanings given below.

Preferably, Z is selected from the group consisting of phenyl; and heterocycle; and optionally substituted with up to 3 R⁴, which are the same or different.

Preferably, R⁴ is selected from the group consisting of F; Cl; CN; and C₁₋₆ alkyl.

5

Preferably, R¹, R² are independently selected from the group consisting of H; F; and C₁₋₆ alkyl, optionally substituted with one or more F.

Preferably, R³ is H.

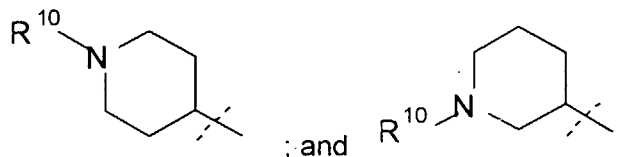
10

Preferably, A is A⁰.

Preferably, A⁰ is a saturated heterocycle with at least one nitrogen as ring atom, preferably piperidine.

15

More preferred, A⁰ is selected from the group consisting of



20 Preferably, R¹⁰ is selected from the group consisting of H; and -C(O)O-C₁₋₆ alkyl.

In a further preferred embodiment, R¹⁰ is selected from the group consisting of T¹-T² and T², where T¹ is selected from -C(O)-; -C(O)-C₁₋₆ alkyl-; -S(O)₂-; and -S(O)₂-C₁₋₆ alkyl-, and T² is selected from H; T³; and T⁴.

25

T³ is preferably selected from the group consisting of phenyl; and N(R¹³)S(O)₂R¹⁴.

R¹³ and R¹⁴ are preferably selected from the group consisting of H; and C₁₋₆ alkyl.

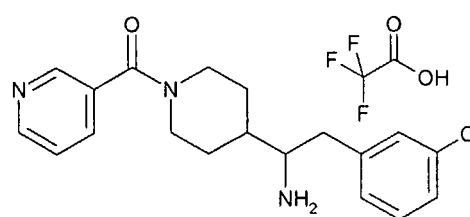
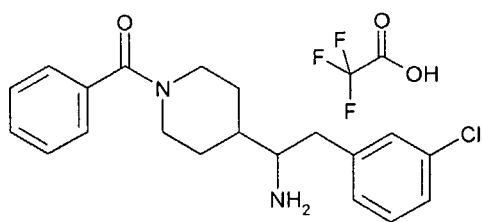
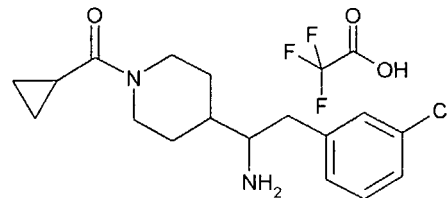
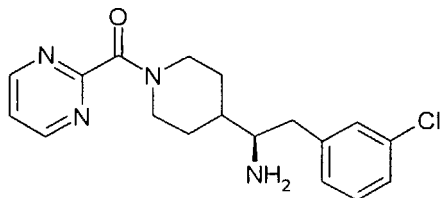
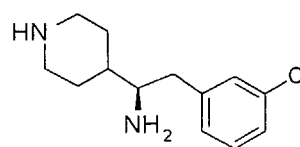
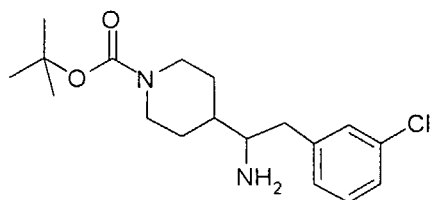
30 Preferably, T⁴ is selected from the group consisting of C₃₋₇ cycloalkyl; and heterocycle, wherein T⁴ is optionally substituted with one or more R¹⁵.

R¹⁵ is preferably selected from the group consisting of halogen; and C₁₋₆ alkyl, wherein the C₁₋₆ alkyl is optionally substituted with one or more halogen selected from the group consisting of F; and Cl.

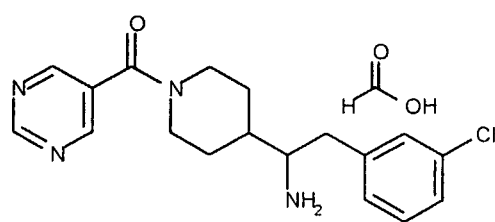
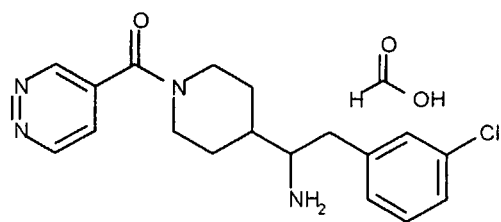
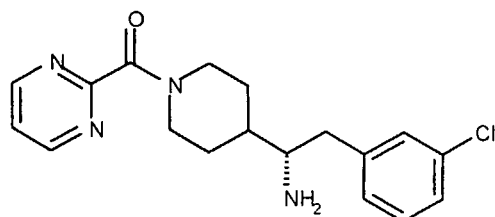
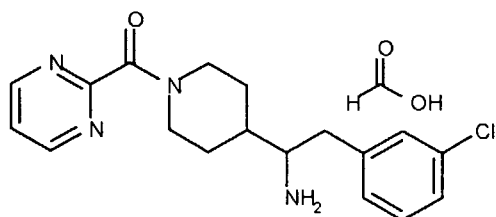
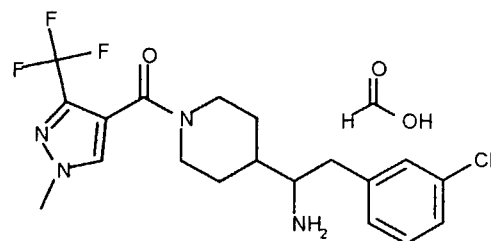
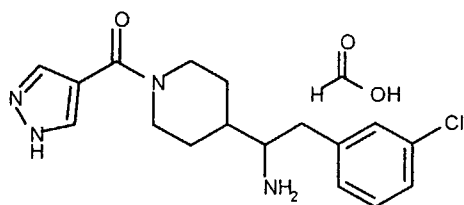
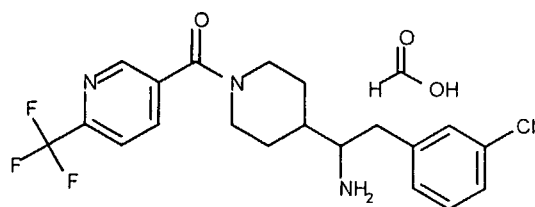
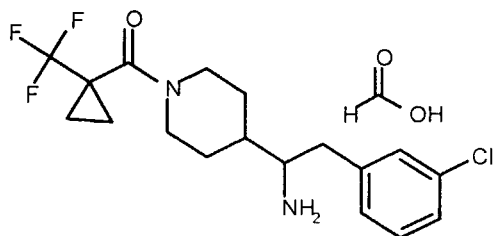
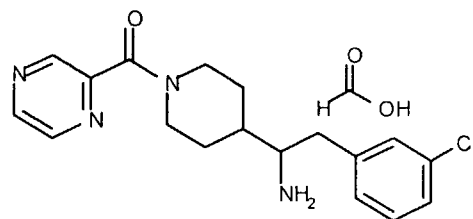
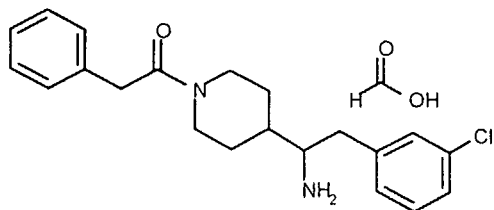
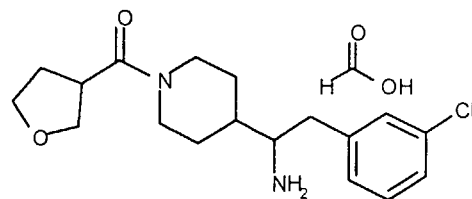
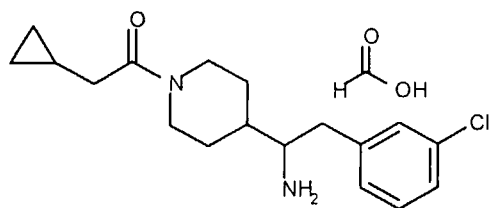
- 5 Compounds of the formula (I) in which some or all of the above-mentioned groups have the preferred or more preferred meanings are also an object of the present invention.

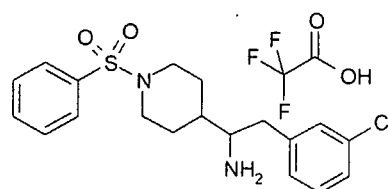
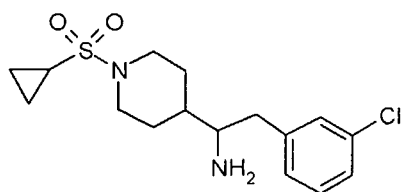
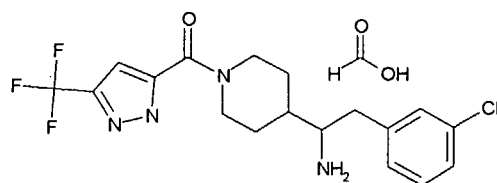
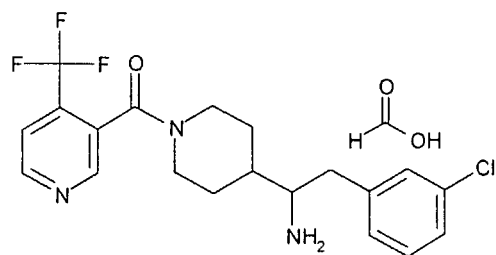
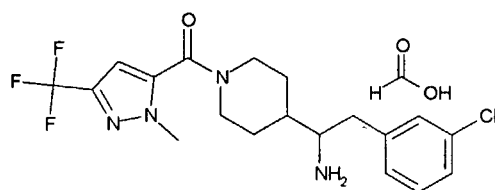
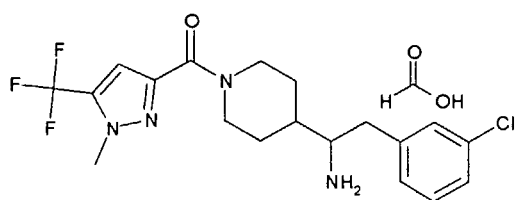
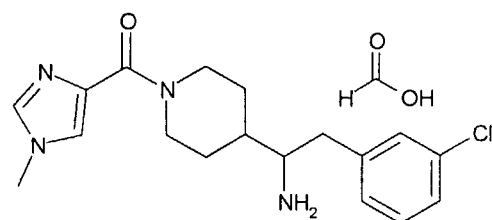
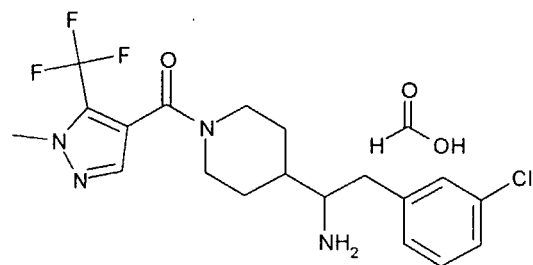
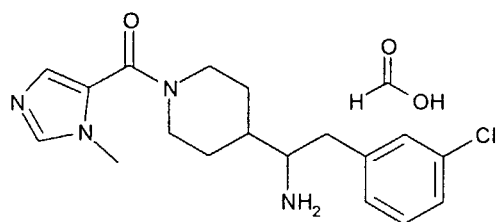
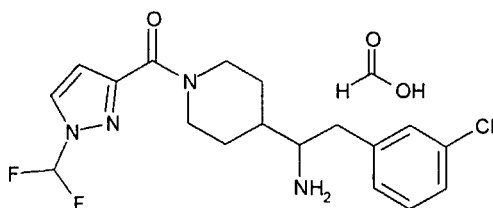
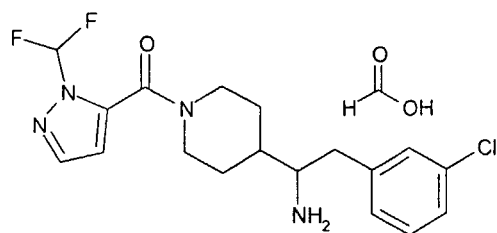
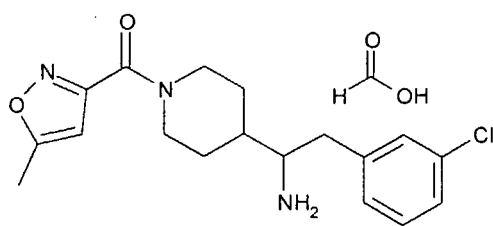
Preferred embodiments of the compounds according to present invention are:

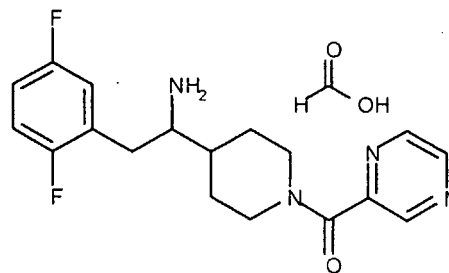
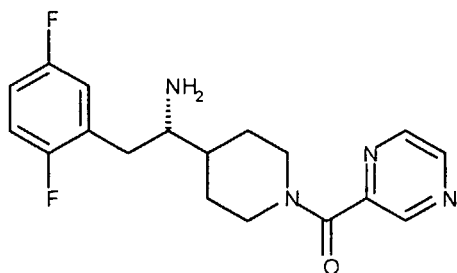
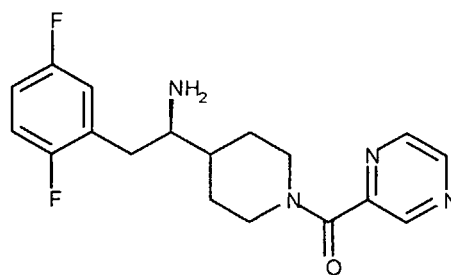
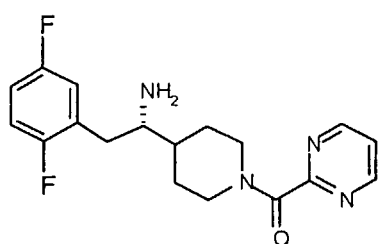
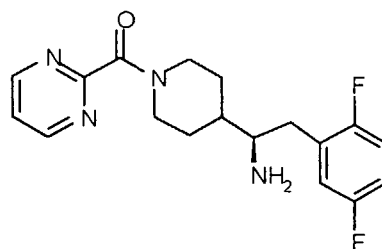
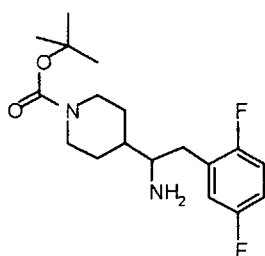
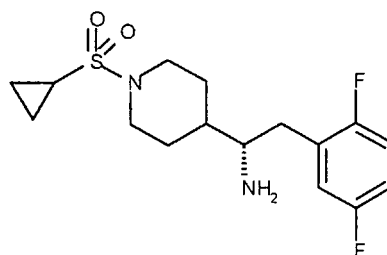
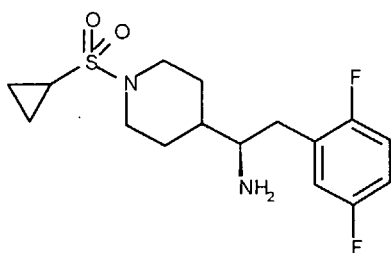
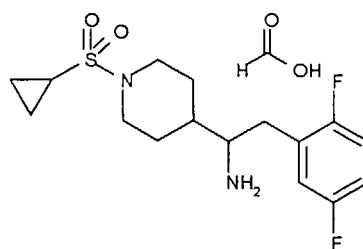
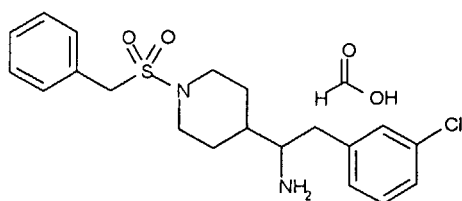
10

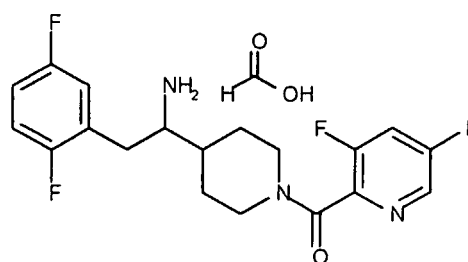
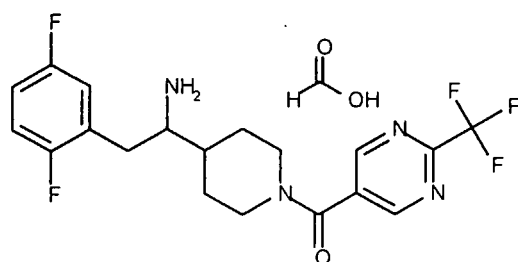
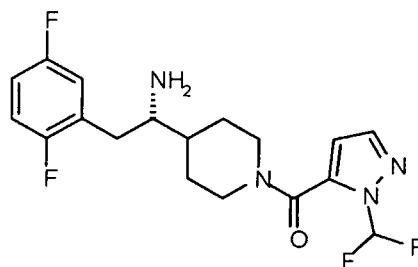
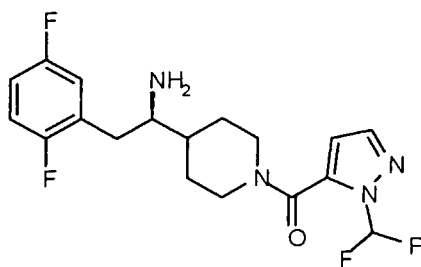
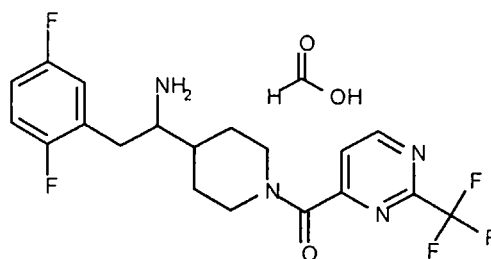
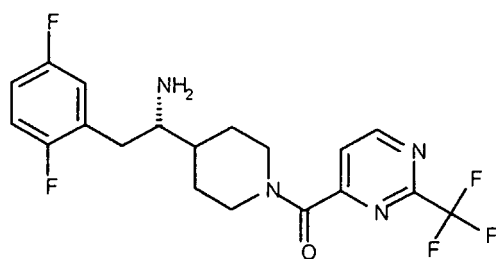
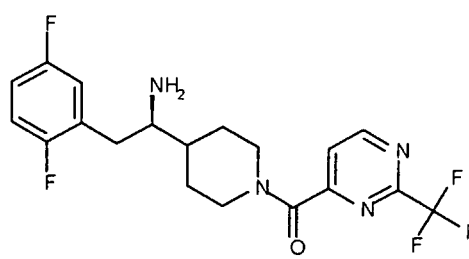
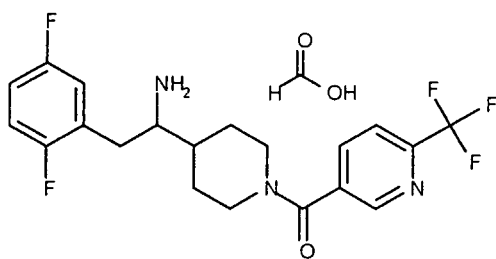
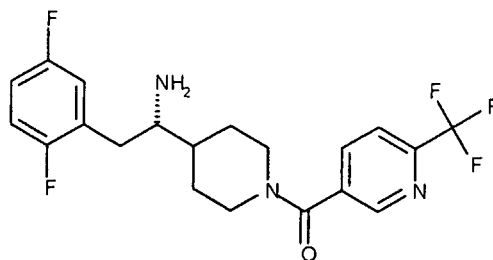
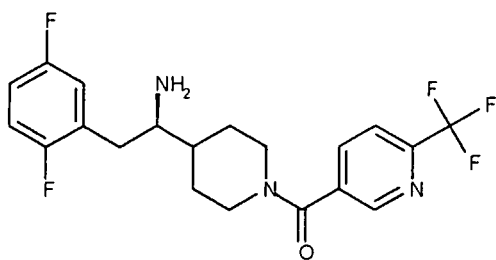


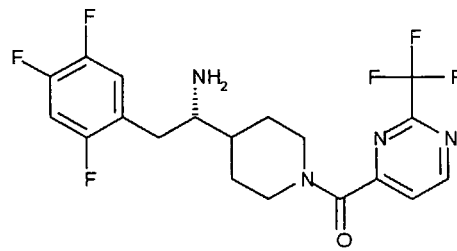
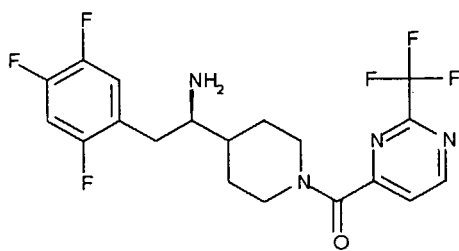
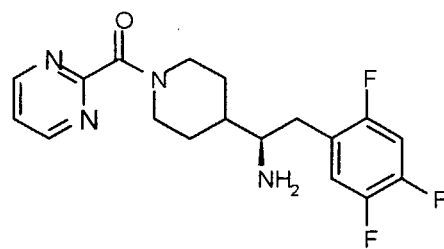
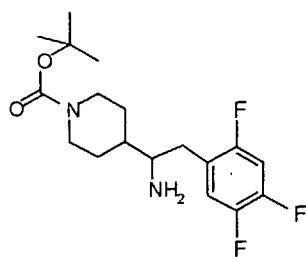
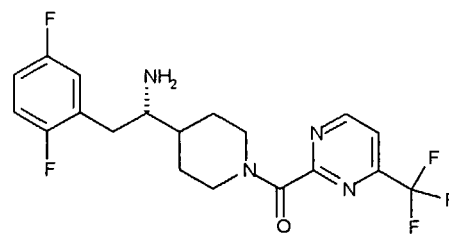
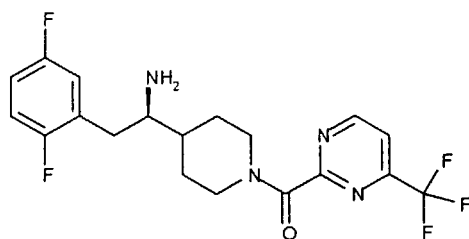
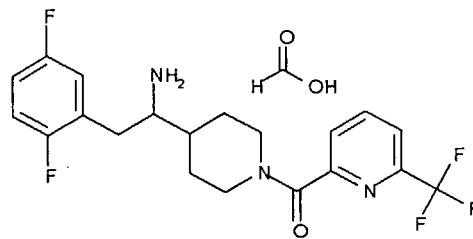
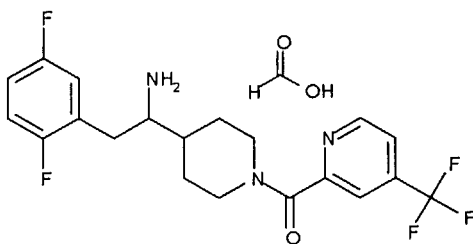
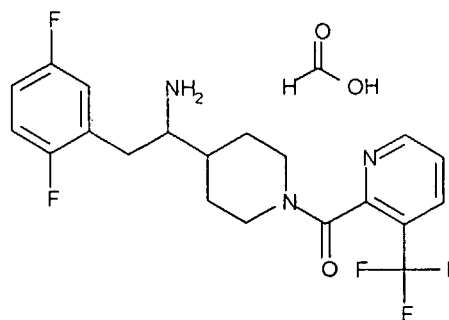
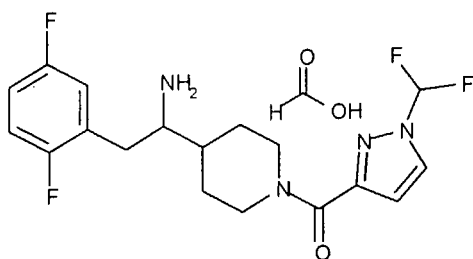
15

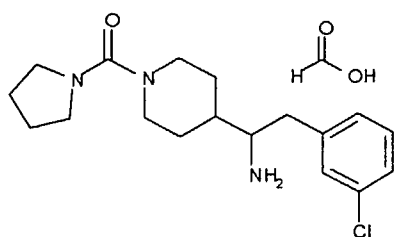
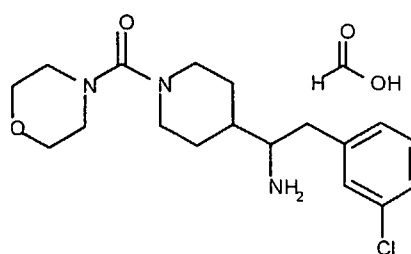
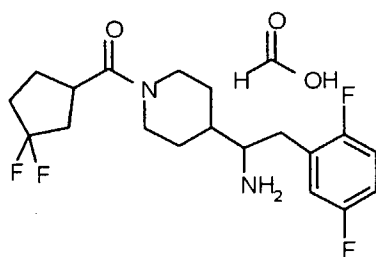
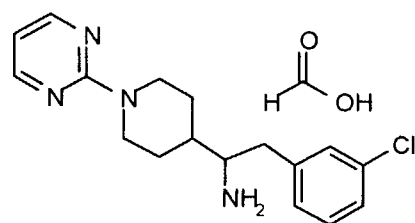
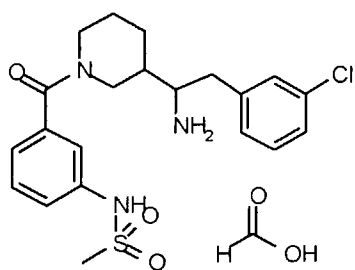
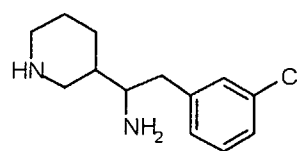
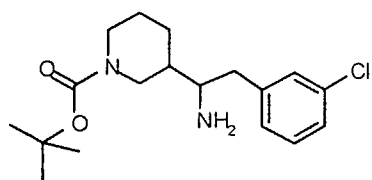
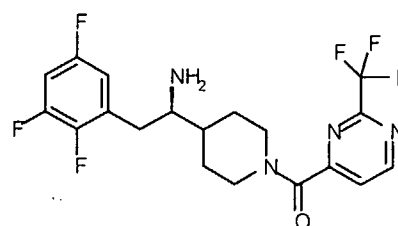
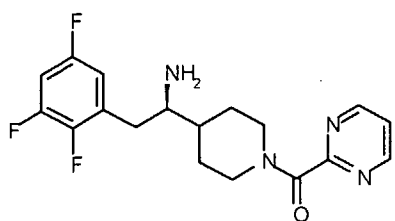
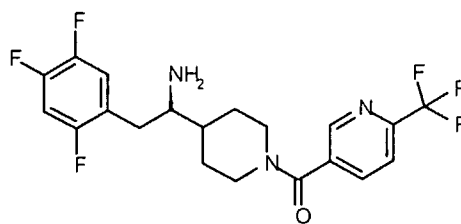
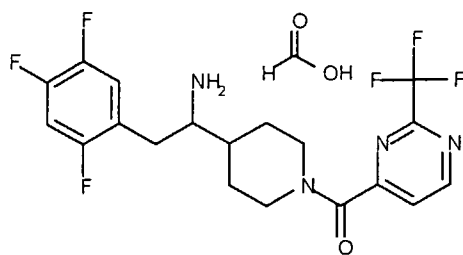












Furthermore, the present invention provides prodrug compounds of the compounds of the invention as described above.

"Prodrug compound" means a derivative that is converted into a compound according to the present invention by a reaction with an enzyme, gastric acid or the like under a physiological condition in the living body, e.g. by oxidation, reduction, hydrolysis or the like, each of which is carried out enzymatically. Examples of the prodrug are compounds, wherein the amino group in a compound of the present invention is acylated, alkylated or phosphorylated to form, e.g., eicosanoylamino, alanyl amino, pivaloyloxymethylamino or wherein the hydroxyl group is acylated, alkylated, phosphorylated or converted into the borate, e.g. acetyloxy, palmitoyloxy, pivaloyloxy, succinyloxy, fumaryloxy, alanyloxy or wherein the carboxyl group is esterified or amidated. These compounds can be produced from compounds of the present invention according to well-known methods.

Metabolites of compounds of formula (I) are also within the scope of the present invention.

Where tautomerism, like e.g. keto-enol tautomerism, of compounds of general formula (I) or their prodrugs may occur, the individual forms, like e.g. the keto and enol form, are claimed separately and together as mixtures in any ratio. Same applies for stereoisomers, like e.g. enantiomers, cis/trans isomers, conformers and the like.

If desired, isomers can be separated by methods well known in the art, e.g. by liquid chromatography. Same applies for enantiomers by using e.g. chiral stationary phases. Additionally, enantiomers may be isolated by converting them into diastereomers, i.e. coupling with an enantiomerically pure auxiliary compound, subsequent separation of the resulting diastereomers and cleavage of the auxiliary residue. Alternatively, any enantiomer of a compound of formula (I) may be obtained from stereoselective synthesis using optically pure starting materials.

In case the compounds according to formula (I) contain one or more acidic or basic groups, the invention also comprises their corresponding pharmaceutically or toxicologically acceptable salts, in particular their pharmaceutically utilizable salts. Thus, the compounds of the formula (I) which contain acidic groups can be present on these groups and can be used according to the invention, for example, as alkali metal salts, alkaline earth metal salts or as ammonium salts. More precise examples of such salts include sodium salts, potassium salts, calcium salts, magnesium salts or salts

with ammonia or organic amines such as, for example, ethylamine, ethanolamine, triethanolamine or amino acids. Compounds of the formula (I) which contain one or more basic groups, i.e. groups which can be protonated, can be present and can be used according to the invention in the form of their addition salts with inorganic or organic acids. Examples for suitable acids include hydrogen chloride, hydrogen bromide, phosphoric acid, sulfuric acid, nitric acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acids, oxalic acid, acetic acid, tartaric acid, lactic acid, salicylic acid, benzoic acid, formic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, malic acid, sulfaminic acid, phenylpropionic acid, gluconic acid, ascorbic acid, isonicotinic acid, citric acid, adipic acid, and other acids known to the person skilled in the art. If the compounds of the formula (I) simultaneously contain acidic and basic groups in the molecule, the invention also includes, in addition to the salt forms mentioned, inner salts or betaines (zwitterions). The respective salts according to the formula (I) can be obtained by customary methods which are known to the person skilled in the art like, for example by contacting these with an organic or inorganic acid or base in a solvent or dispersant, or by anion exchange or cation exchange with other salts. The present invention also includes all salts of the compounds of the formula (I) which, owing to low physiological compatibility, are not directly suitable for use in pharmaceuticals but which can be used, for example, as intermediates for chemical reactions or for the preparation of pharmaceutically acceptable salts.

The present invention provides compounds of general formula (I) or their prodrugs as DPP-IV inhibitors. DPP-IV is a cell surface protein that has been implicated in a wide range of biological functions. It has a broad tissue distribution (intestine, kidney, liver, pancreas, placenta, thymus, spleen, epithelial cells, vascular endothelium, lymphoid and myeloid cells, serum), and distinct tissue and cell-type expression levels. DPP-IV is identical to the T cell activation marker CD26, and it can cleave a number of immunoregulatory, endocrine, and neurological peptides *in vitro*. This has suggested a potential role for this peptidase in a variety of disease processes.

DPP-IV related diseases are described in more detail in WO-A-03/181 under the paragraph "Utilities" which is herewith incorporated by reference.

Accordingly, the present invention provides compounds of formula (I) or their prodrugs or pharmaceutically acceptable salt thereof for use as a medicament.

Furthermore, the present invention provides the use of compounds of formula (I) or their prodrugs or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment or prophylaxis of non-insulin dependent (Type II) diabetes mellitus; hyperglycemia; obesity; insulin resistance; lipid disorders; dyslipidemia; hyperlipidemia; hypertriglyceridemia; hypercholesterolemia; low HDL; high LDL; atherosclerosis; growth hormone deficiency; diseases related to the immune response; HIV infection; neutropenia; neuronal disorders; tumor metastasis; benign prostatic hypertrophy; gingivitis; hypertension; osteoporosis; diseases related to sperm motility; low glucose tolerance; insulin resistance; its sequelae; vascular restenosis; irritable bowel syndrome; inflammatory bowel disease; including Crohn's disease and ulcerative colitis; other inflammatory conditions; pancreatitis; abdominal obesity; neurodegenerative disease; retinopathy; nephropathy; neuropathy; Syndrome X; ovarian hyperandrogenism (polycystic ovarian syndrome; Type II diabetes; or growth hormone deficiency. Preferred is non-insulin dependent (Type II) diabetes mellitus and obesity.

The present invention provides pharmaceutical compositions comprising a compound of formula (I), or a prodrug compound thereof, or a pharmaceutically acceptable salt thereof as active ingredient together with a pharmaceutically acceptable carrier.

"Pharmaceutical composition" means one or more active ingredients, and one or more inert ingredients that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier.

A pharmaceutical composition of the present invention may additionally comprise one or more other compounds as active ingredients like one or more additional compounds of formula (I), or a prodrug compound or other DPP-IV inhibitors.

Other active ingredients are disclosed in WO-A-03/181 under the paragraph "Combination Therapy" which is herewith incorporated by reference.

Accordingly, other active ingredients may be insulin sensitizers; PPAR agonists; biguanides; protein tyrosinephosphatase-1B (PTP-1B) inhibitors; insulin and insulin mimetics; sulfonylureas and other insulin secretagogues; α -glucosidase inhibitors; glucagon receptor antagonists; GLP-1, GLP-1 mimetics, and GLP-1 receptor agonists; GIP, GIP mimetics, and GIP receptor agonists; PACAP, PACAP mimetics, and PACAP receptor 3 agonists; cholesterol lowering agents; HMG-CoA reductase inhibitors; sequestrants; nicotinyl alcohol; nicotinic acid or a salt thereof; PPAR α agonists; PPAR α / γ dual agonists; inhibitors of cholesterol absorption; acyl CoA : cholesterol acyltransferase inhibitors; anti-oxidants; PPAR α agonists; antiobesity compounds; an ileal bile acid transporter inhibitor; or anti-inflammatory agents or pharmaceutically acceptable salts of these active compounds.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids, including inorganic bases or acids and organic bases or acids.

The compositions include compositions suitable for oral, rectal, topical, parenteral (including subcutaneous, intramuscular, and intravenous), ocular (ophthalmic), pulmonary (nasal or buccal inhalation), or nasal administration, although the most suitable route in any given case will depend on the nature and severity of the conditions being treated and on the nature of the active ingredient. They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

In practical use, the compounds of formula (I) 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). In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid preparations, such as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations such as, for example, powders, hard and soft capsules and tablets, with the solid oral preparations being preferred over the liquid preparations.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques. Such compositions and preparations should contain at least
5 0.1 percent of active compound. The percentage of active compound in these compositions may, of course, be varied and may conveniently be between about 2 percent to about 60 percent of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that an effective dosage will be obtained. The active compounds can also be administered intranasally as, for example,
10 liquid drops or spray.

The tablets, pills, capsules, and the like may also contain a binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid; a lubricant such as
15 magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin. When a dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

Various other materials may be present as coatings or to modify the physical form of
20 the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

25 Compounds of formula (I) may also be administered parenterally. Solutions or suspensions of these active compounds can be prepared in water suitably mixed with a surfactant such as hydroxy-propylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the
30 growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be
35 fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must 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), suitable mixtures thereof, and vegetable oils.

Any suitable route of administration may be employed for providing a mammal, especially a human, with an effective dose of a compound of the present invention. For example, oral, rectal, topical, parenteral, ocular, pulmonary, nasal, and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments, aerosols, and the like. Preferably compounds of formula (I) or are administered orally.

The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration, the condition being treated and the severity of the condition being treated. Such dosage may be ascertained readily by a person skilled in the art.

When treating or preventing diabetes mellitus and/or hyperglycemia or hypertriglyceridemia or other diseases for which compounds of formula (I) are indicated, generally satisfactory results are obtained when the compounds of the present invention are administered at a daily dosage of from about 0.1 milligram to about 100 milligram per kilogram of animal body weight, preferably given as a single daily dose or in divided doses two to six times a day, or in sustained release form. For most large mammals, the total daily dosage is from about 1.0 milligrams to about 1000 milligrams, preferably from about 1 milligrams to about 50 milligrams. In the case of a 70 kg adult human, the total daily dose will generally be from about 7 milligrams to about 350 milligrams. This dosage regimen may be adjusted to provide the optimal therapeutic response.

Some abbreviations that may appear in this application are as follows.

ABBREVIATIONS

Designation

Ar	Argon
bs	Broad singlet
Boc (or BOC)	<i>tert.</i> -Butoxycarbonyl
d	Doublet
DCM	Dichloromethane

DEA	Diethylamine
Fmoc	9-Fluorenylmethoxycarbonyl
Fmoc-OSu	N-(9-Fluorenylmethoxycarbonyloxy)succinimide
h	Hour
Hal	Halogen
HPLC	High pressure liquid chromatography
LCMS	Liquid chromatography mass spectrometry
LHMDS	Lithium hexamethyldisilazide
m	Multiplet
Mg	Magnesium
min	Minute
MsCl	Methanesulphonyl chloride
MW	Molecular weight
NH ₄ Cl	Ammonium chloride
NH ₄ OH	Ammonium hydroxide
PG	Protecting group
Prep.	Preparative
rt	Retention time
s	Singlet
t	Triplet
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran

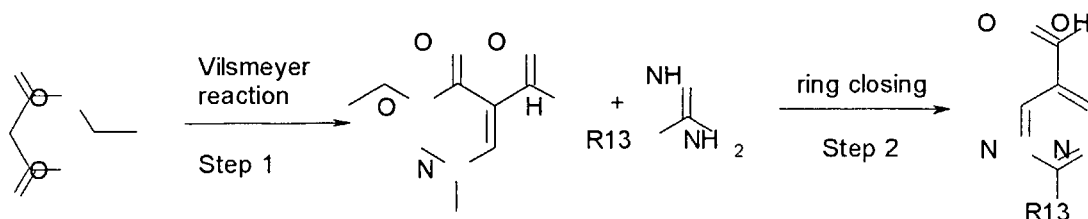
Available starting materials may be carboxylic acids having the formula R¹⁰COOH, which may be purchased from commercially available sources such as ABCR, Array, Astatech, Sigma-Aldrich, Fluka, Kalexsyn, or be synthesized by one skilled in the art.

- 5 Common nucleophilic substitution reactions between compounds containing a suitable leaving group (e.g. halogenides) and nucleophiles (e.g. amines) may be employed. The conversion of diverse functional groups may allow the synthesis of various carboxylic acids, e.g. conversion of esters into acids, or amides intermediates; also novel carbon-nitrogen palladium-catalyzed coupling reactions with suitable functionalized starting
- 10 materials. For the introduction of changes in the carbon chain attached to the nitrogen atom or for the synthesis of diverse (hetero)aryl derivatives, it may be possible to make use of diverse carbon-carbon coupling reactions, e.g. transition-metal catalyzed reactions, conventional techniques for ring closure, formylation of (hetero)aryls.

Schemes A and B outline general procedures for the synthesis of some compounds ($R^{10}COOH$) described below. Unless otherwise indicated in the schemes, the variables have the same meaning as described above.

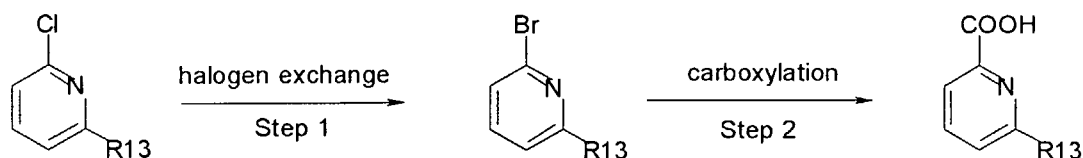
5

Scheme A



10

Scheme B



Unless otherwise noted, all nonaqueous reactions were carried out under an argon atmosphere with commercial dry solvents. Compounds were purified using flash column chromatography using Merck silica gel 60 (230-400 mesh) or reverse phase preparative HPLC using a XTerra MS C18, 3.5 μ m, 2.1 x 100 mm with Shimadzu LC8A-Pump and SPD-10Avp UV/Vis diode array detector. The 1H -NMR spectra were recorded on a Varian VXR-S (400 MHz for 1H -NMR) using d_6 -dimethylsulphoxide as solvent; chemical shifts are reported in ppm relative to tetramethylsilane. Analytical LCMS was performed using: XTerra MS C18, 3.5 μ m, 2.1 * 100 mm, linear gradient with acetonitrile in water (0.1% HCOOH or TFA) at a flow rate of 250 μ L/min; retention times are given in minutes. Methods are:

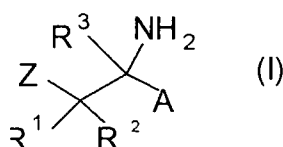
- (I) linear gradient from 5% to 70% acetonitrile in water (0.1% HCOOH or TFA);
 (II) idem but 10 min linear gradient; (III) linear gradient from 5% to 90% acetonitrile in water (0.1% HCOOH or TFA), 5 min linear gradient; (IV) idem but 10 min linear gradient; (V) linear gradient from 1% to 30% acetonitrile in water (0.1% HCOOH or TFA), 10 min linear gradient; (VI) from 1% to 60% acetonitrile in water (0.1%

HCOOH or TFA), 10 min linear gradient; (VII) negative mode, acetonitrile in water (0.1% DEA), linear gradient; (VIII) chiral separation using; Daicel Chiralpak AD-H column, 5 μ m, 20 * 250 prep, 4.6 * 250 analytic), isocratic gradient (0.1% DEA).

5

General procedure for making compounds of the invention

In general, compounds having the structure (I)



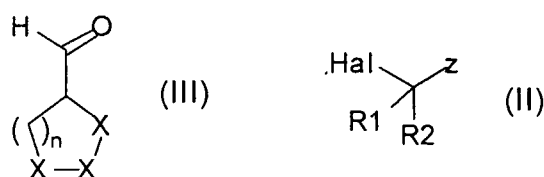
10

wherein the variables have the above described meanings, may be prepared using organolithium or organomagnesium reagents. For example, it may be possible to use 1-bromomethyl-3-chloro-benzene in combination with lithium for the addition of this organolithium reagent to N-(trimethylsilyl)imines, in solvents such as diethyl ether or tetrahydrofuran as described in F. Gyenes, K.E. Bergmann, J. T. Welch, *J. Org. Chem.* **1998**, 63, 2824-2828.

15

Available starting materials may be aldehydes having the formula (III) and benzylhalogenides having the formula (II)

20



X = N_{boc}, CH₂, CH-R¹⁰
n = 0, 1, 2

They may be purchased from commercially available sources such as Array, Sigma-Aldrich, Fluka, ABCR or be synthesized by one skilled in the art. Common reactions between compounds containing amino groups and carboxyl or sulphonyl functionalities may be employed for their synthesis with suitable functionalized starting materials. Nucleophilic substitution reactions between compounds containing a suitable leaving group (e.g., halogenide, mesylate, tosylate) and nucleophiles (e.g., amines) may be also employed. The conversion of diverse functional groups (such as esters, alcohols,

25

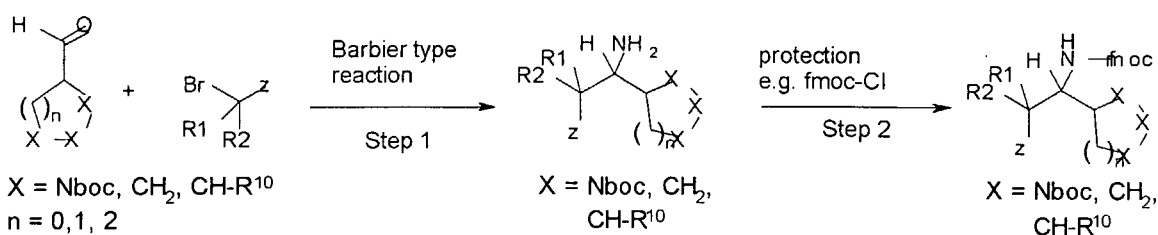
30

amides, nitriles, azides) may allow the synthesis of some intermediates or final compounds.

Schemes C through G outline general procedures for the synthesis of some compounds described below. Unless otherwise indicated in the schemes, the variables

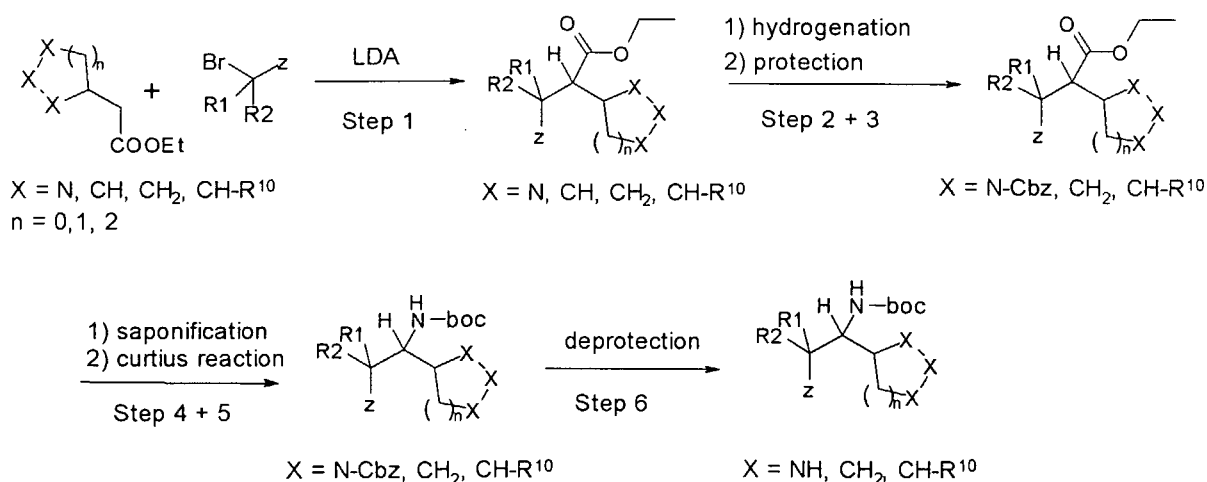
5 have the same meaning as described above.

Scheme C



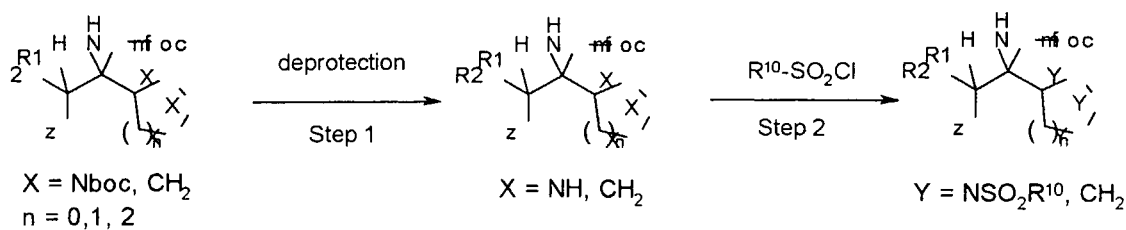
10

Scheme D



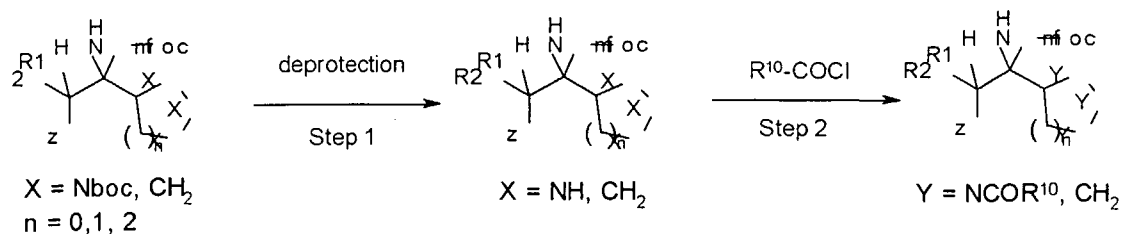
15

Scheme E



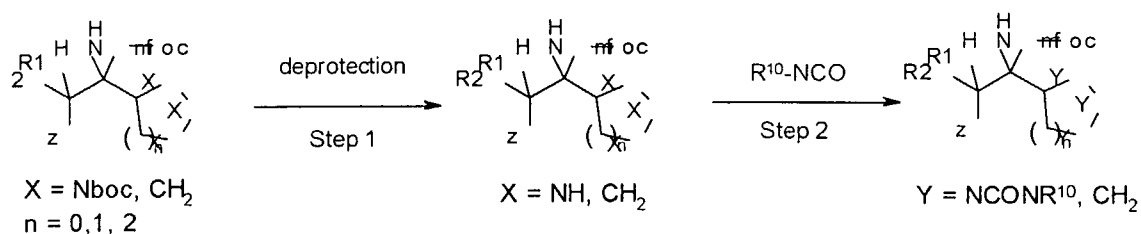
20

Scheme F



5

Scheme G



10

The protecting group may be removed with, for example, diethylamine in dichloromethane in the case of 9-fluorenylmethoxycarbonyl, palladium on charcoal/hydrogen in case of the benzyloxycarbonyl or using acidic conditions (such as trifluoroacetic acid in dichloromethane or hydrochloric acid in dioxane) in the case of *tert*.-butoxycarbonyl, as described in *Protective Groups in Organic Synthesis* 3rd ed., Ed. Wiley-VCH, New York; 1999.

15

For the purification of intermediates or end products, flash chromatography on silica gel may be suitable for the free amines whereas the use of preparative HPLC leads to the isolation of the corresponding trifluoroacetic acid or formate salts. Chiral separation on preparative HPLC gives rise to the free amines.

20

Compounds may be prepared by other means however, and the suggested starting materials and procedures described below are exemplary only and should not be considered as limiting the scope of the invention.

25

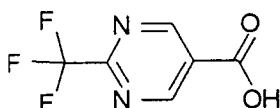
EXAMPLES

The following examples are provided so that the invention might be more fully

understood. These examples are illustrative only and should not be construed as limiting the invention in any way.

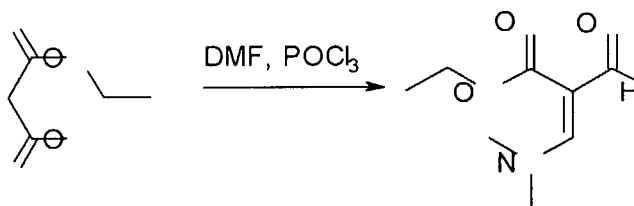
PREPARATIONS

Example 1



Procedure for making an intermediate according to Scheme A.

Step 1

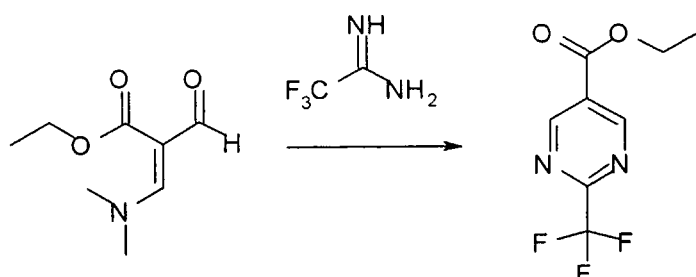


(Z)-3-Dimethylamino-2-formyl-acrylic acid ethyl ester

1000 mg (5.87 mmol) of ethyl potassium malonate and 2702 mg (17.63 mmol) phosphorous oxychloride are dissolved in 7 mL of dry *N,N*-dimethylformamide under an argon atmosphere. The solution is stirred under reflux for 4 hours. Afterwards the solvent is removed under reduced pressure and the residue is dissolved in ice water. By the addition of 25 mL of saturated potassium carbonate the mixture is neutralized. 20 mL of toluene/ethanol (1:1) are added and the precipitated salts are filtered off. The aqueous phase is further extracted with 3 x 20 mL of toluene/ethanol. The combined organic layers are washed with brine and dried over sodium sulphate. The solvent is removed under reduced pressure and the residue is used further without purification in the next step

LCMS (I): rt 2.48 min, m/z 172 ($M+H$)⁺.

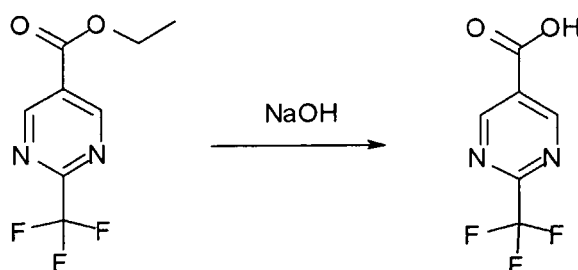
Step 2

5 2-Trifluoromethyl-pyrimidine-5-carboxylic acid ethyl ester

To 160 mg (0.94 mmol) of the product from step 1 ((Z)-3-dimethylamino-2-formylacrylic acid ethyl ester) dissolved in 3 mL of ethanol are added 314 mg (2.80 mmol) of trifluoroacetamidine. The solution is stirred for 3 hours under reflux, then the solvent is removed under reduced pressure and the residue is purified by flash chromatography (hexane/ethyl acetate 4:1) to yield the title compound.

HPLC (I): rt 4.58 min.

Step 3



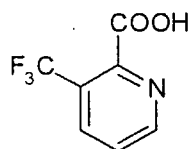
15

2-Trifluoromethyl-pyrimidine-5-carboxylic acid

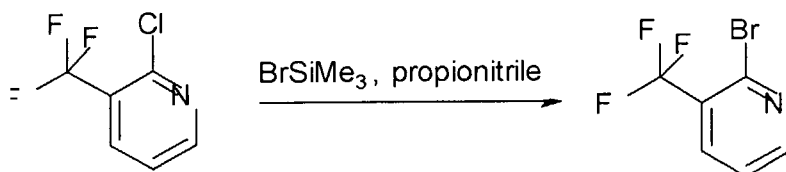
To 140 mg (0.64 mmol) of the product from step 2 2-trifluoromethyl-pyrimidine-5-carboxylic acid ethyl ester dissolved in 8 mL tetrahydrofuran and 2 mL of water are added 38 mg (0.95 mmol) of sodium hydroxide. The solution is stirred for 2 hours at room temperature, then the reaction mixture is quenched with 20 mL of 1M hydrochloric acid. The aqueous phase is extracted with 3x15 mL of ethyl acetate and the combined organic layers are dried over sodium sulphate. The solvent is removed under reduced pressure to yield the title compound.

25 HPLC (I): rt 2.91 min.

LCMS (VII, 1-30%, 10 min): rt 3.89 min, m/z 191 (M-H)⁻.

Example 2

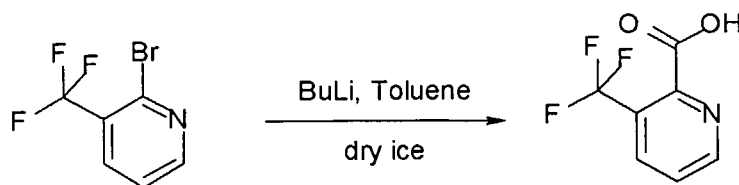
Procedure for making an intermediate according to Scheme B.

Step 1**2-Bromo-3-trifluoromethyl-pyridine**

1000 mg (5.53 mmol) of 2-chloro-3-trifluoropyridine are dissolved in 2.5 mL of propionitrile under an argon atmosphere. 2.10 mL (19.5 mmol) of bromotrimethylsilane are added and the reaction mixture is stirred for 24 h at 100°C. Afterwards the mixture is filtered, the solvent is removed under reduced pressure and the residue is used further without purification in the next step.

LCMS (III): rt 3.73 min, m/z 267; 269 (M+MeCN)⁺.

¹H-NMR (400 MHz, DMSO-d₆) δ = 7.66-7.69 (m, 1H), 8.28 (d, J = 8.0 Hz, 1H), 8.66 (d, J = 4.4 Hz, 1H).

Step 2**3-Trifluoromethyl-pyridine-2-carboxylic acid**

200 mg (0.88 mmol) of 2-bromo-3-trifluoromethyl-pyridine are dissolved in 1.5 mL of dry toluene under an argon atmosphere. The mixture is cooled to -75°C and 500 μL (1.10 mmol) of *n*-butyllithium (2.2M in hexane) is added. The reaction mixture is stirred for 2 h at -75°C and afterwards poured on dry ice. Then 10 mL of 6 M hydrochloric acid are added and the aqueous phase is extracted with 3x10 mL of diethyl ether. The

combined organic layers are dried over sodium sulphate and the solvent is removed under reduced pressure. The residue is recrystallized from ethyl acetate/hexane to yield the title compound.

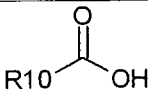
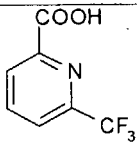
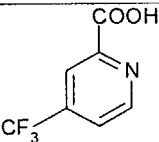
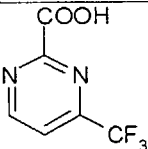
LCMS(III): rt 1.75 min, m/z 192 (M+H)⁺.

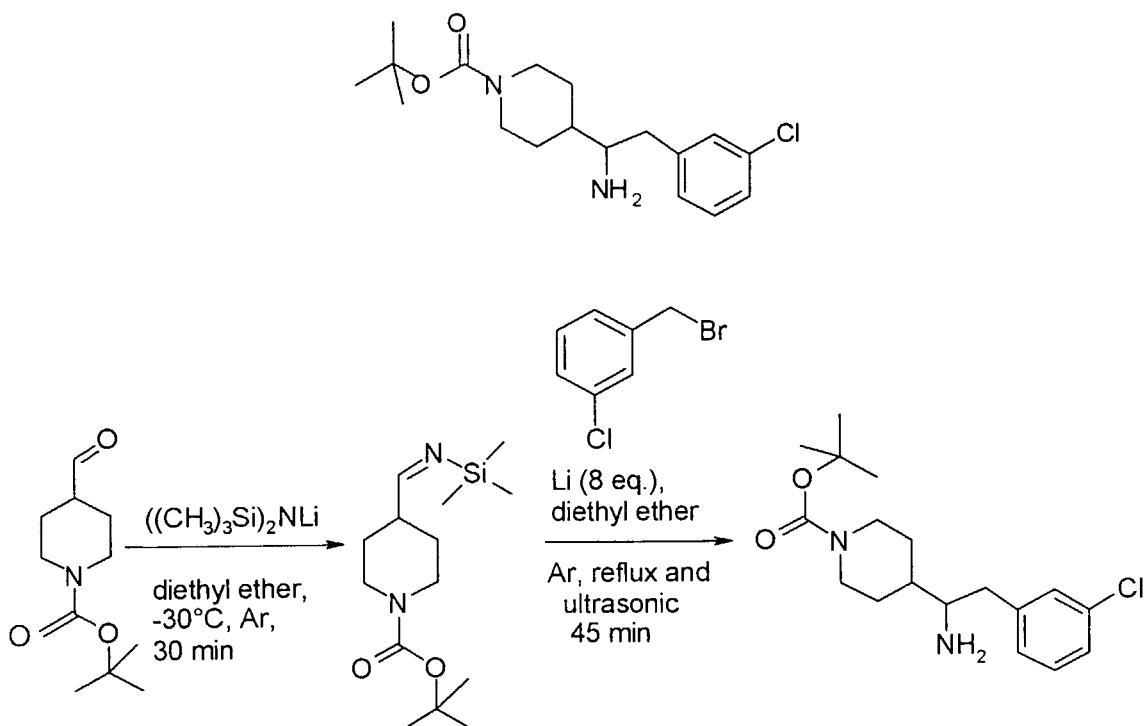
5 LCMS(VII, 5-95%, 5min): rt 1.75 min, m/z 190 (M-H)⁻.

¹H-NMR (400 MHz, DMSO-d₆) δ = 7.73-7.76 (m, 1H), 8.31 (d, J = 8.4 Hz, 1H), 8.58 (d, J = 5.6 Hz, 1H), 14.1 (s, 1H).

10 The compounds in Table 1 are synthesized according to the procedure shown for example 2.

Table 1

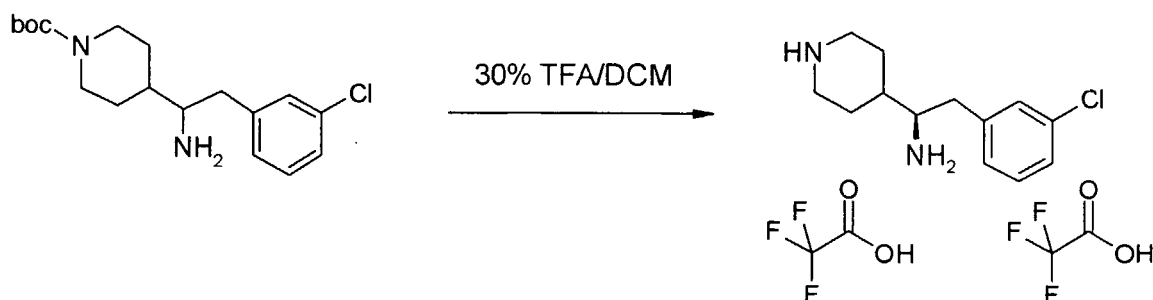
Ex.		LCMS
3		LCMS (VII, 5-70%, 5 min) rt 3.47, m/z 190 [M-H] ⁻ .
4		LCMS (III) rt 2.50, m/z 192 [M+H] ⁺ . LCMS (VII, 5-70%, 5 min) rt 3.32, m/z 190 [M-H] ⁻ .
5		LCMS (III) rt 2.14, m/z 192 [M+H] ⁺ . LCMS (VII, 5-70%, 5 min) rt 2.26, m/z 190 [M-H] ⁻ .

Example 6**4-[1-Amino-2-(3-chloro-phenyl)-ethyl]-piperidine-1-carboxylic acid *tert.*-butyl ester**

- 10 516 μL (0.516 mmol) of lithium hexamethyldisilazide (LHMDS; 1M solution in diethyl ether) are dissolved in 2 mL of dry diethyl ether under an argon atmosphere. The solution is cooled to -30°C , then 100 mg (0.469 mmol) 4-formyl-piperidine-1-carboxylic acid *tert.*-butyl ester dissolved in 1 mL of dry diethyl ether is slowly added and the mixture is stirred at -30°C for 45 min. Afterwards 123 μL (0.938 mmol) of 1-bromomethyl-3-chlorobenzene are added. This reaction mixture is transferred via a syringe in another flask, which is equipped with 26 mg (3.752 mmol) lithium and 10 mL of dry diethyl ether under an argon atmosphere. This flask is placed in an ultrasonic bath and the slow addition of the reaction mixture starts when the diethyl ether is refluxing. The reaction is kept under reflux and ultrasound for 45 min. By the addition of
- 15 5 mL of saturated ammonium chloride solution the reaction is quenched and the aqueous layer is extracted with ethyl acetate. The combined organic layers are extracted with 5 x 10 mL of 5% citric acid. The pH value of the combined acid layers is then adjusted with ammonium hydroxide to pH 12 and this aqueous layer is extracted with 3 x 10 mL of ethyl acetate. The organic layer is washed with brine and dried over
- 20 sodium sulphate. The solvent is removed under reduced pressure and the residue is purified by prep. HPLC to yield the title compound.
- LCMS: rt 3.7 min, m/z 339 ($\text{M}+\text{H}$) $^+$.

$^1\text{H-NMR}$ (300 MHz, DMSO-d_6) δ = 1.10-1.32 (m, 2H), 1.43 (s, 9H), 1.59-1.71 (m, 3H), 2.60-2.64 (m, 2H), 2.75-2.96 (m, 2H), 3.36 (m, 1H), 3.97 (d, J = 12.6 Hz, 2H), 7.20-7.351 (m, 4H), 7.85 (s, 2H).

5 Example 7



10 2-(3-Chloro-phenyl)-1-piperidin-4-yl-ethylamine

20 mg (0.06 mmol) of example 6 [(4-[1-amino-2-(3-chloro-phenyl)-ethyl]-piperidine-1-carboxylic acid *tert*-butyl ester)] dissolved in 1 mL of dichloromethane are diluted with 0.5 mL of trifluoroacetic acid. The solution is stirred for 30 min at ambient temperature, then the solvent is removed under reduced pressure. The residue is purified by prep.

15 HPLC to yield the title compound.

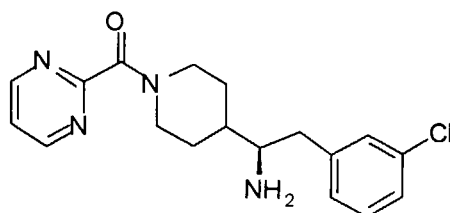
LCMS(I): rt 1.9 min, m/z 239 ($M+H$) $^+$.

$^1\text{H-NMR}$ (300 MHz, MeOD) δ = 1.63-1.79 (m, 2H), 2.02 (m, 3H), 2.80-2.87 (m, 1H), 2.96-3.13 (m, 3H), 3.46-3.51 (m, 3H), 7.22-7.35 (m, 4H).

LCMS (chiral, AD-H, heptane/ethanol 20:80): rt 17.4 min; 26.1 min, m/z 239 ($M+H$) $^+$.

20

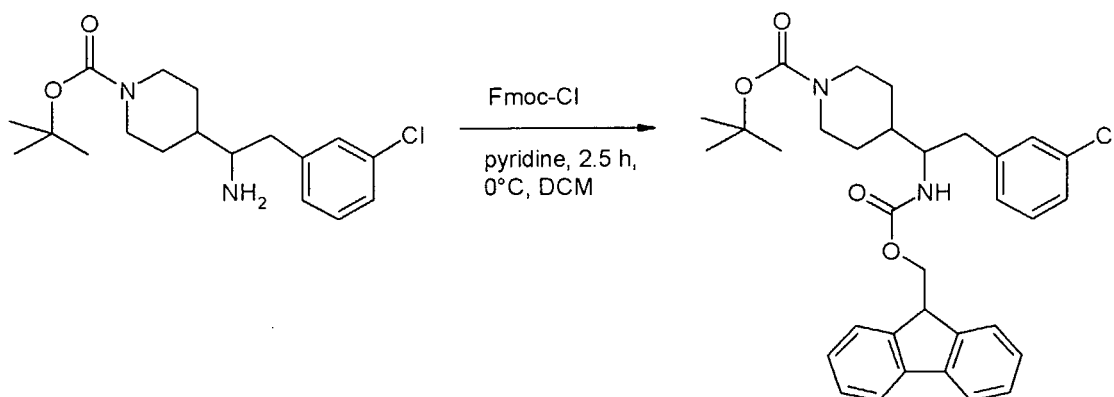
Example 8



25

30

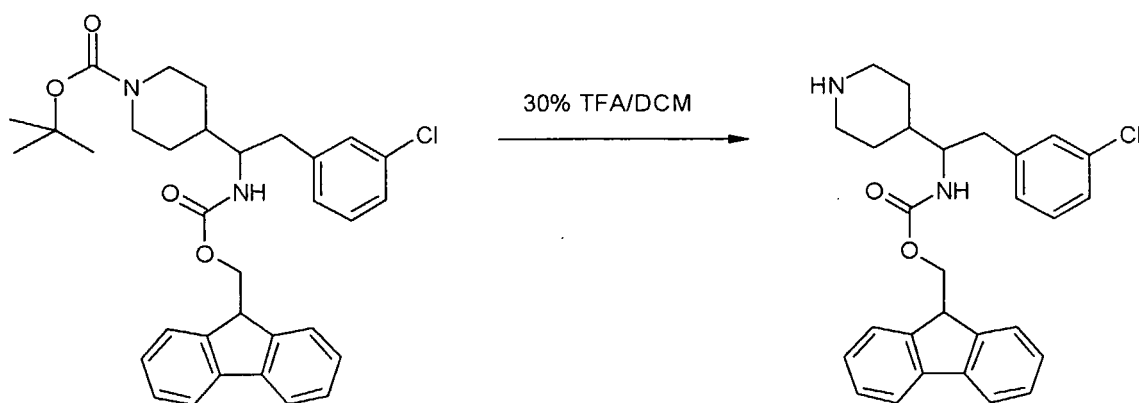
Step 1



5 4-[2-(3-Chloro-phenyl)-1-(9H-fluoren-9-ylmethoxycarbonylamino)-ethyl]-piperidine-1-
carboxylic acid *tert*.-butyl ester

- To a solution of 437 mg (1.29 mmol) of [4-[1-amino-2-(3-chloro-phenyl)-ethyl]-piperidine-1-carboxylic acid *tert*.-butyl ester] example 6 dissolved in 4 mL of dichloromethane are added 842 μ L (10.34 mmol) of pyridine and 368 mg (1.42 mmol)
- 10 of N-(9-fluorenylmethoxycarbonyl-oxy)-chloride at 0°C. The mixture is stirred for 2.5 h, then diluted with 20 mL of 5% citric acid solution. The aqueous layer is extracted with 3 x 15 mL of ethyl acetate, the combined organic layers are washed with water and brine, and dried over sodium sulphate. Removal of the solvent under reduced pressure afforded a residue, which is purified by prep. HPLC to yield the title compound.
- 15 LCMS(II): rt 5.94 min, m/z 583 ($M+Na$)⁺.

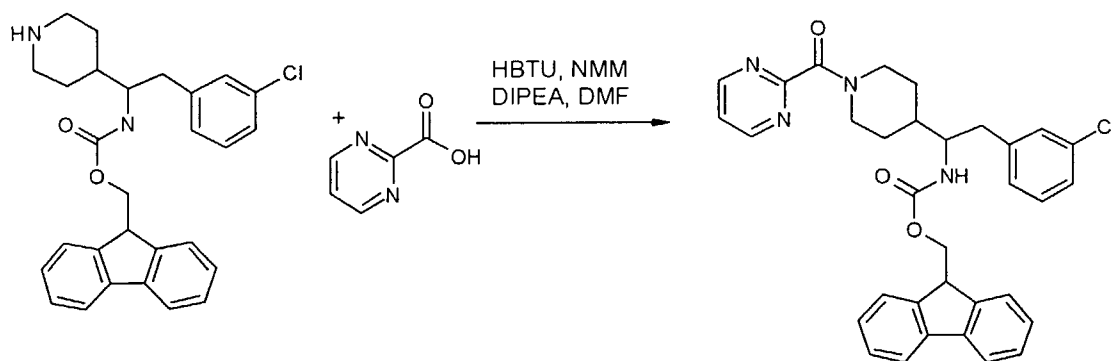
Step 2



[2-(3-Chloro-phenyl)-1-piperidin-4-yl-ethyl]-carbamic acid 9H-fluoren-9-ylmethyl ester

300 mg (0.53 mmol) of the product from step 2 [4-[2-(3-chloro-phenyl)-1-(9H-fluoren-9-ylmethoxycarbonylamino)-ethyl]-piperidine-1-carboxylic acid *tert.*-butyl ester] are dissolved in 1.0 mL of dichloromethane and 1.0 mL of trifluoroacetic acid. The solution is stirred for 30 min at ambient temperature, then the solvent is removed under reduced pressure and the residue is used further without purification in the next step.

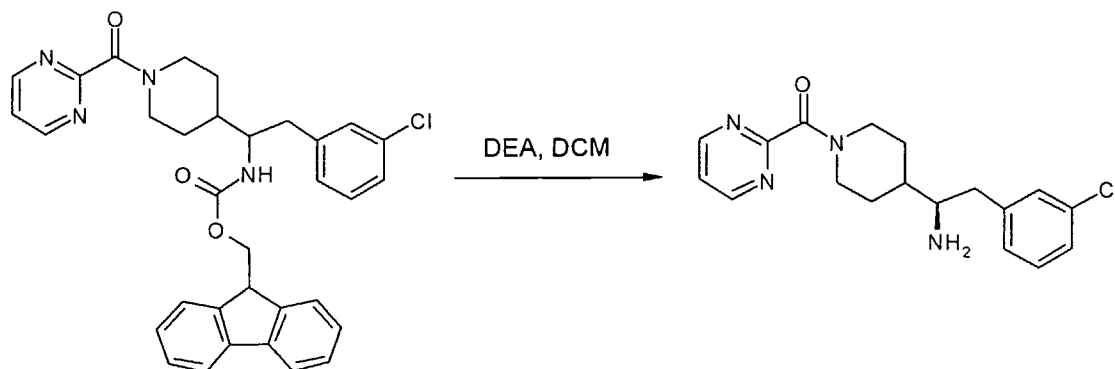
LCMS(I): rt 3.54 min, m/z 461 (M+H)⁺.

Step 3[2-(3-Chloro-phenyl)-1-[1-(pyrimidine-2-carbonyl)-piperidine-4-yl]-ethyl]-carbamic acid 9H-fluoren-9-ylmethyl ester

To a solution of 247 mg (0.535 mmol) of [2-(3-chloro-phenyl)-1-piperidin-4-yl-ethyl]-carbamic acid 9H-fluoren-9-ylmethyl ester in 2 mL of *N,N*-dimethylformamide, 112 μ L diisopropylethyl amine are added. A 15 min preactivated solution of 79.0 mg (0.642 mmol) pyrimidine-2-carboxylic acid, 243 mg (0.642 mmol) of *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyl-uronium hexafluorophosphate (HBTU) and 70.6 μ L (0.642 mmol) of *N*-methylmorpholine dissolved in 2 mL of *N,N*-dimethylformamide are added to the reaction mixture. The mixture is stirred overnight at 50°C. After removal of the solvents under reduced pressure 20 mL of ethyl acetate are added. The organic layer is extracted with 2 x 20 mL of 5% citric acid and saturated sodium hydrogen carbonate solution. The organic layer is washed with brine and dried over sodium sulphate. The solvent is removed under reduced pressure and the residue is purified by flash chromatography (dichloromethane/methanol 95:5) to yield the title compound.

LCMS(I): rt 5.10 min, m/z 567 (M+H)⁺.

Step 4



5 {4-[(R)-1-Amino-2-(3-chloro-phenyl)-ethyl]-piperidin-1-yl}-pyrimidin-2-yl-methanone

To a solution of 253 mg (0.446 mmol) of the product from step 3 ({2-(3-Chloro-phenyl)-1-[1-(pyrimidine-2-carbonyl)-piperidin-4-yl]-ethyl}-carbamic acid 9H-fluoren-9-ylmethyl ester) in 5 mL of dichloromethane are added 2.00 mL of diethylamine at 0°C. The mixture is stirred for 30 min. Removal of the solvent under reduced pressure afforded the title compound, which was purified by prep. reverse phase HPLC and prep. chiral HPLC to yield the enantiomers.

LCMS(I): rt 5.19 min, m/z 345 (M+H)⁺.

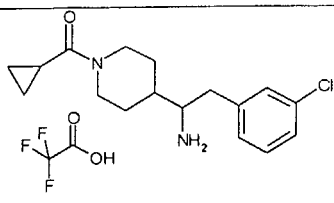
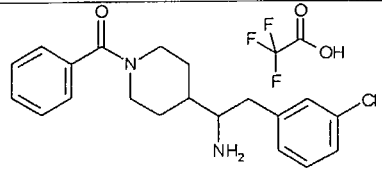
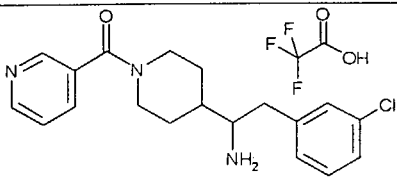
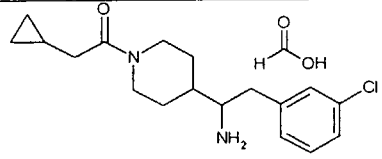
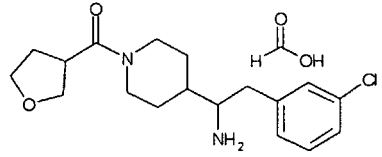
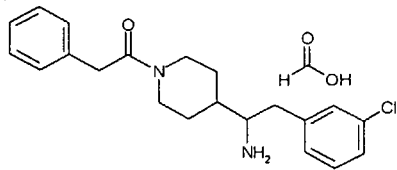
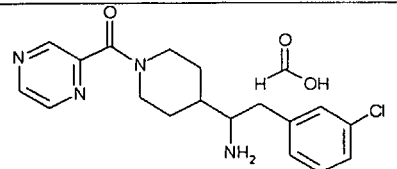
LCMS (AD-H, ethanol 100%): 10.56 min, m/z 345 (M+H)⁺.

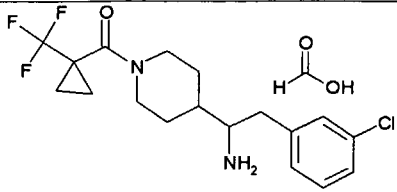
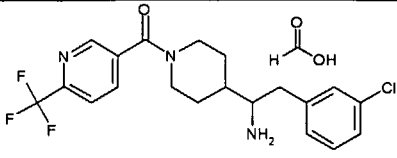
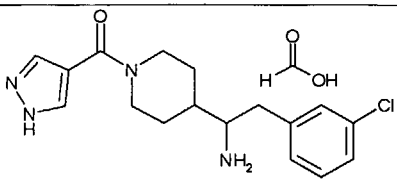
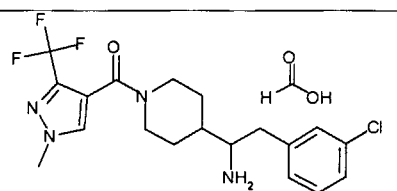
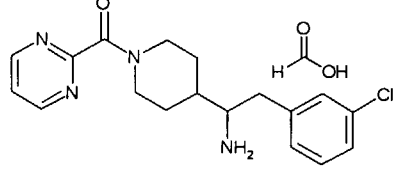
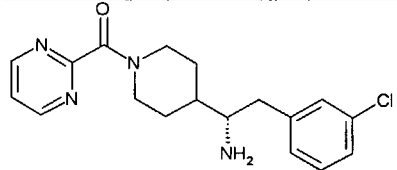
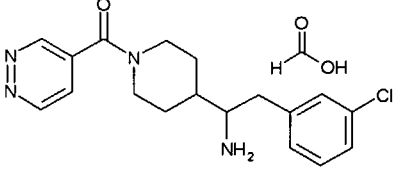
¹H-NMR (500 MHz, DMSO-d₆) δ = 1.23-1.41 (m, 2H), 1.55 (m, 1H), 1.63-1.88 (m, 2H), 2.53 (m, 1H), 2.71-2.81 (m, 3H), 2.90-3.00 (m, 1H), 3.22 (t, J = 15.0 Hz, 1H), 4.54 (t, J = 15.0 Hz, 1H), 7.20-7.22 (m, 2H), 7.25-7.34 (m, 2H), 7.58 (dt, J = 6.0 Hz, J = 2.5 Hz, 1H), 8.27 (s, 2H, NH₂), 8.88 (dd, J = 6.0 Hz, J = 1.5 Hz, 2H).

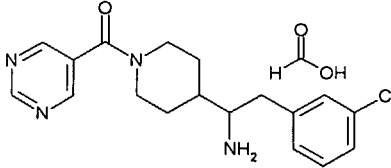
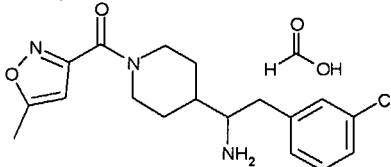
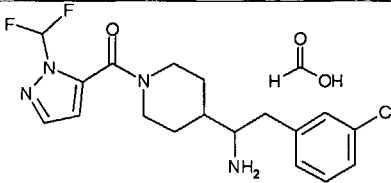
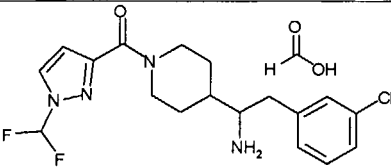
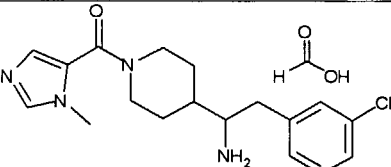
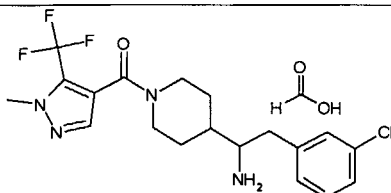
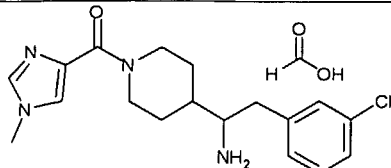
¹³C-NMR (125 MHz, DMSO-d₆) δ = 26.6; 27.4 (CH₂, boot/chair), 28.4; 29.2 (CH₂, boot, chair), 39.1; 39.2 (CH₂, boot, chair), 41.0 (CH₂), 41.1 (CH), 46.6 (CH₂), 56.3 (CH), 122.0 (CH), 126.0 (CH), 128.0 (CH), 129.5 (CH), 130.5 (Cq), 133.3 (Cq), 142.4 (Cq), 158.1 (2CH), 162.6 (Cq), 164.5 (Cq).

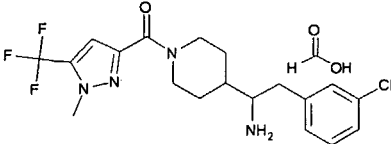
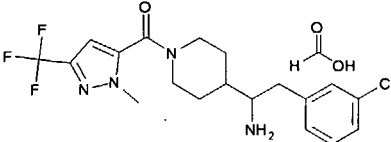
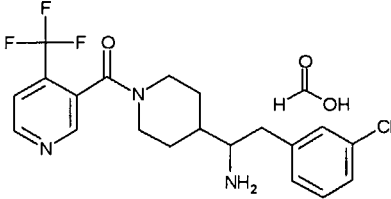
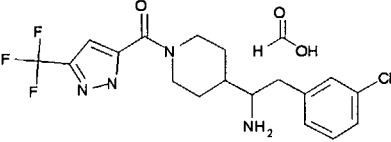
The compounds in Table 2 are synthesized according to the procedure shown for example 8

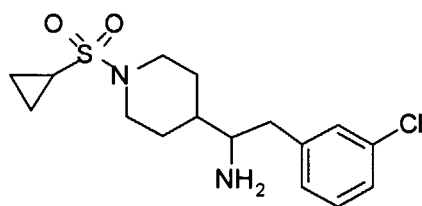
Table 2

Ex.		LCMS	NMR
9		LCMS (IV) rt 2.66, m/z 307 [M+H] ⁺ .	
10		LCMS (II) rt 7.58, m/z 343 [M+H] ⁺ .	
11		LCMS (II) rt 6.39, m/z 344 [M+H] ⁺ .	
12		LCMS (IV) rt 2.73, m/z 321 [M+H] ⁺ .	
13		LCMS (II) rt 5.71, m/z 337 [M+H] ⁺ .	
14		LCMS (II) rt 7.42, m/z 357 [M+H] ⁺ .	
15		LCMS (II) rt 5.35, m/z 345 [M+H] ⁺ .	

16		LCMS (II) rt 7.71, m/z 375 [M+H] ⁺ .	
17		LCMS (IV) rt 3.55, m/z 412 [M+H] ⁺ .	
18		LCMS (II) rt 5.43, m/z 333 [M+H] ⁺ .	
19		LCMS (II) rt 7.20, m/z 415 [M+H] ⁺ .	
20		LCMS (II) rt 5.80, m/z 345 [M+H] ⁺ .	
21		LCMS (II) rt 5.80, m/z 345 [M+H] ⁺ . LCMS (AD-H, ethanol 100%, isocratic): 9.46 min, m/z 345 (M+H) ⁺ .	
22		LCMS (II) rt 5.35, m/z 345 [M+H] ⁺ .	

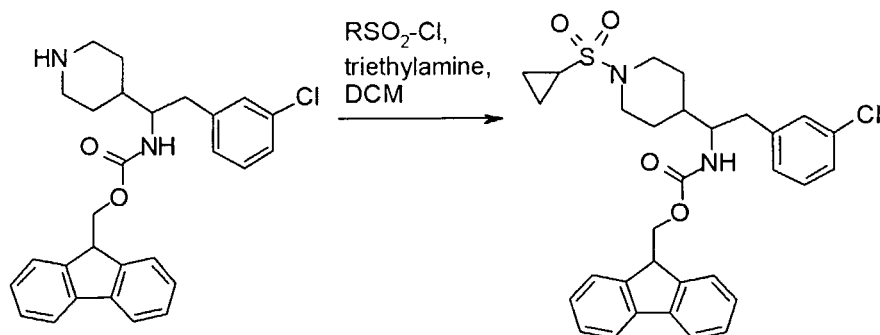
23		LCMS (II) rt 5.77, m/z 345 [M+H] ⁺ .	
24		LCMS (IV) rt 3.90, m/z 348 [M+H] ⁺ .	
25		LCMS (IV) rt 3.82, m/z 383 [M+H] ⁺ .	¹ H-NMR (400 MHz, DMSO-d ₆) δ = 1.22-1.41 (m, 2H), 1.55-1.88 (m, 3H), 2.33 (m, 1H), 2.59-2.78 (m, 3H), 2.85-2.90 (m, 1H), 3.75 (m, 1H), 4.53 (m, 1H), 6.71 (m, 1H), 7.23-7.25 (m, 1H), 7.32-7.37 (m, 3H), 7.77 (t, 1H), 7.87 (m, 1H), 8.17 (s, 2H, NH ₂).
26		LCMS (IV) rt 4.07, m/z 383 [M+H] ⁺ .	
27		LCMS (II) rt 3.64, m/z 347 [M+H] ⁺ .	
28		LCMS (IV) rt 4.87, m/z 415 [M+H] ⁺ .	
29		LCMS (IV) rt 2.61, m/z 347 [M+H] ⁺ .	

30		LCMS (IV) rt 5.02, m/z 415 [M+H] ⁺ .	
31		LCMS (IV) rt 5.22, m/z 415 [M+H] ⁺ .	
32		LCMS (IV) rt 4.30, m/z 412 [M+H] ⁺ .	
33		LCMS (IV) rt 4.76, m/z 401 [M+H] ⁺ .	

Example 34

The intermediate [2-(3-Chloro-phenyl)-1-piperidin-4-yl-ethyl]-carbamic acid 9H-fluoren-9-ylmethyl ester is synthesized according to the procedure described for example 8 (step 1 – step 2).

Step 1

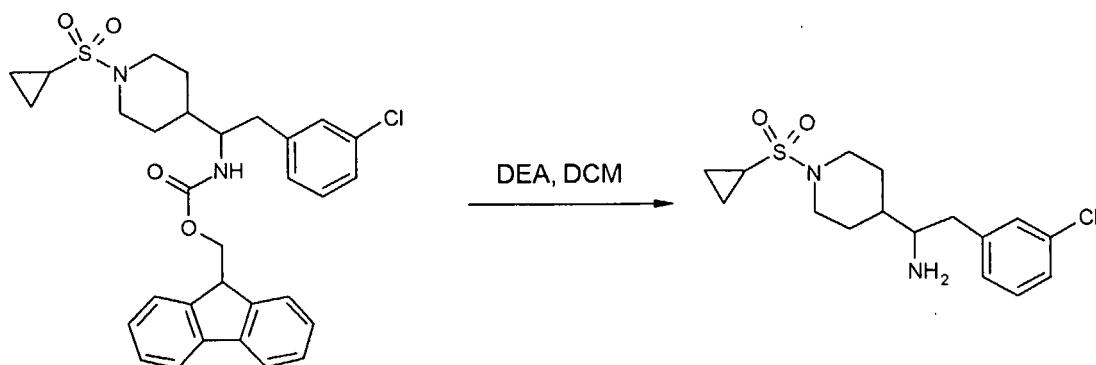
5 2-(3-Chloro-phenyl)-1-(1-cyclopropanesulphonyl-piperidin-4-yl)-ethylamine

To a solution of 30 mg (0.06 mmol) [2-(3-chloro-phenyl)-1-piperidin-4-yl-ethyl]-carbamic acid 9H-fluoren-9-ylmethyl ester (product of example 8 step 2) in dichloromethane are added at 0°C 5.4 μL (0.07 mmol) of methanesulphonyl chloride and 10 μL (0.08 mmol) of triethylamine. The mixture is stirred for 2 h at 0°C, then diluted with 20 mL of dichloromethane and washed with 10 mL of 5% citric acid solution, saturated sodium bicarbonate solution and brine, and dried over sodium sulphate. Removal of the solvent under reduced pressure afforded the title compound which was used in the next step without further purification.

LCMS(IV): rt 6.49 min, m/z 565 ($\text{M}+\text{H}$)⁺.

15

Step 2

20 2-(3-Chloro-phenyl)-1-(1-cyclopropanesulphonyl-piperidin-4-yl)-ethylamine

To a solution of 10 mg (0.03 mmol) of the product from step 1 (2-(3-chloro-phenyl)-1-(1-cyclopropanesulphonyl-piperidin-4-yl)-ethylamine) in 5 mL of dichloromethane is added at 0°C 1.00 mL of diethylamine. The mixture is stirred for 30 min, then diluted

with 20 mL of dichloromethane and washed with 10 mL of 5% citric acid solution, brine and dried over sodium sulphate. Removal of the solvent under reduced pressure afforded the title compound, which was purified by prep. HPLC.

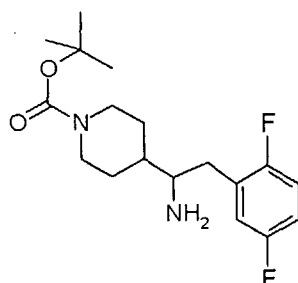
LCMS (II): rt 7.34 min, m/z 343 (M+H)⁺.

- 5 ¹H-NMR (400 MHz, DMSO-d₆) δ = 0.90-0.97 (m, 4H), 1.23-1.47 (m, 3H), 1.69-1.83 (m, 2H), 2.53 (m, 2H), 2.63-2.84 (m, 3H), 2.94 (m, 1H), 3.47 (m, 1H), 3.64 (m, 1H), 6.71-7.35 (m, 4H), 8.26 (s, 2H, NH₂).

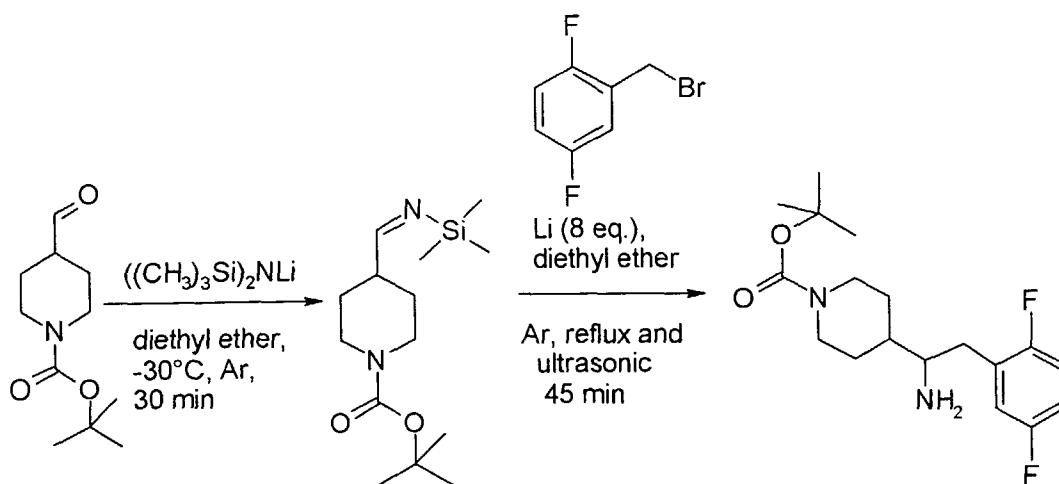
The compounds in Table 3 are synthesized according to the procedure shown for example 34.

Table 3

Ex.		LCMS	NMR
35		LCMS (II) rt 9.04, m/z 379 [M+H] ⁺ .	
36		LCMS (II) rt 7.83, m/z 393 [M+H] ⁺ .	
37		LCMS (IV) rt 2.38, m/z 345 [M+H] ⁺ .	
38		LCMS (IV) rt 2.38, m/z 345 [M+H] ⁺ . LCMS (chiral, ethanol) rt 67 min.	¹ H-NMR (400 MHz, DMSO-d ₆) δ = 0.91-0.97 (m, 4H), 1.23-1.46 (m, 3H), 1.69-1.82 (m, 2H), 2.53 (m, 2H), 2.75-2.79 (m, 4H), 3.64 (m, 2H), 7.04-7.23 (m, 3H), 8.26 (s, 2H, NH ₂).
39		LCMS (IV) rt 2.38, m/z 345 [M+H] ⁺ . LCMS (chiral, ethanol) rt 109 min.	

Example 40

5

Step 1

10

4-[1-Amino-2-(2,5-difluoro-phenyl)-ethyl]-piperidine-1-carboxylic acid tert-butyl ester

1540 μ L (1.54 mmol) of lithium hexamethyldisilazide (LHMDS; 1 M solution in diethyl ether) are dissolved in 2 mL of dry diethyl ether under an argon atmosphere. The solution is cooled to -30°C , then 300 mg (1.40 mmol) 4-formyl-piperidine-1-carboxylic acid *tert.*-butyl ester dissolved in 1 mL of dry diethyl ether are slowly added and the mixture is stirred at -30°C for 45 min. Afterwards 367 μ L (2.80 mmol) of 1-bromomethyl-2,5-difluoro-benzene are added. This reaction mixture is transferred via a syringe in another flask, which is equipped with 78 mg (11.20 mmol) lithium and 10 mL of dry diethyl ether under an argon atmosphere. This flask is placed in an ultrasonic bath and the slow addition of the reaction mixture starts when the diethyl ether is refluxing. The reaction is kept under reflux and ultrasound for 45 min. By the addition of 15 mL of saturated ammonium chloride solution the reaction is quenched and the aqueous layer is extracted with 3 x 20 mL of ethyl acetate. The combined organic

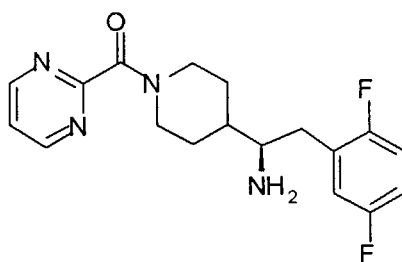
25

layers are extracted with 5 x 10 mL of 5% citric acid. The pH value of the combined acid layers is then adjusted with ammonium hydroxide to pH 12 and this aqueous layer is extracted with 3 x 10 mL of ethyl acetate. The organic layer is washed with brine and dried over sodium sulphate. The solvent is removed under reduced pressure and the residue is used further without purification in the next step.

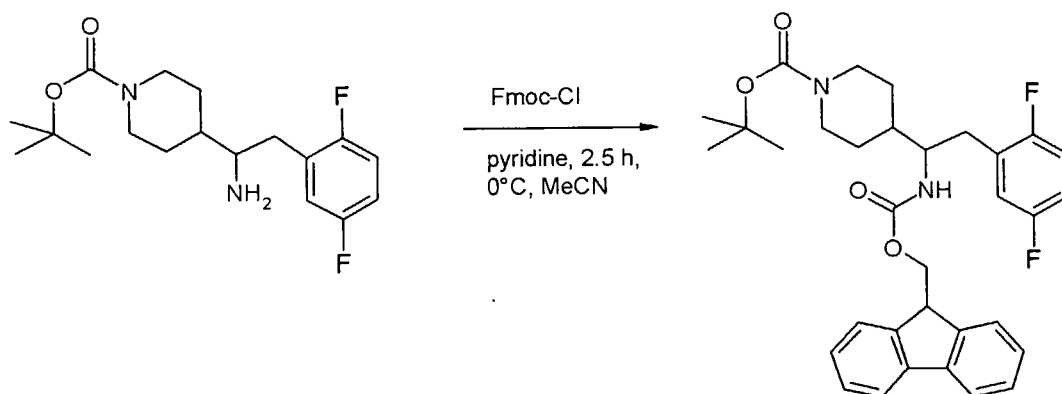
LCMS: rt 2.68 min, m/z 341 (M+H)⁺.

¹H-NMR (400 MHz, MeOD) δ = 1.25-1.43 (m, 2H), 1.44 (s, 9H), 1.59-1.79 (m, 3H), 2.63-2.71 (m, 3H), 2.96-3.02 (m, 1H), 3.09-3.15 (m, 1H), 4.11-4.16 (m, 2H), 6.95-7.11 (m, 3H), 8.48 (s, 2H, NH₂).

Example 41



Step 1



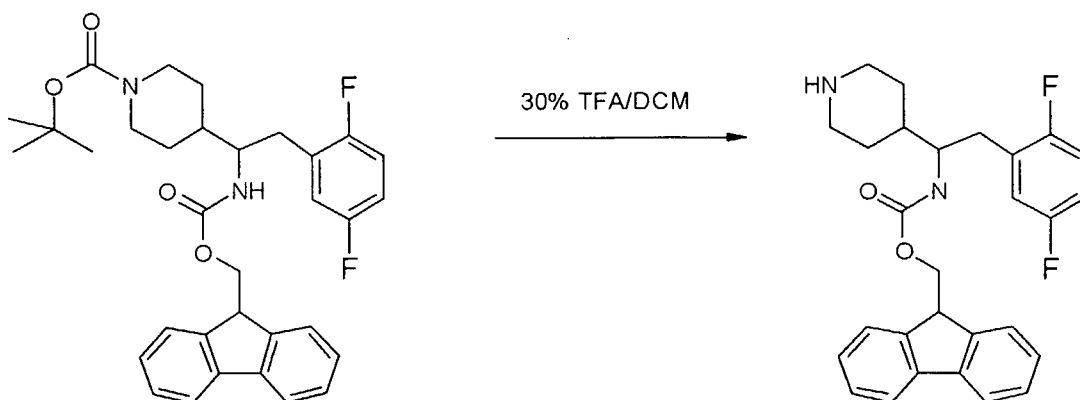
4-[2-(2,5-Difluoro-phenyl)-1-(9H-fluoren-9-ylmethoxycarbonylamino)-ethyl]-piperidine-1-carboxylic acid *tert*-butyl ester

To a solution of 278 mg (0.80 mmol) [4-[1-amino-2-(2,5-difluoro-phenyl)-ethyl]-piperidine-1-carboxylic acid *tert*-butyl ester] (example 40 step 1) in 4 mL of

dichloromethane are added 521 μ L (6.40 mmol) of pyridine and 227 mg (0.88 mmol) of N-(9-fluorenylmethoxycarbonyloxy)-chloride at 0°C. The mixture is stirred for 2.5 h and then diluted with 20 mL of 5% citric acid solution. The aqueous layer is extracted with 3 x 15 mL of ethyl acetate and the combined organic layers are washed with water, brine and dried over sodium sulphate. Removal of the solvent under reduced pressure afforded a residue, which is purified by prep. HPLC to the title compound.

LCMS (IV): rt 6.99 min, m/z 585 (M+Na)⁺.

Step 2

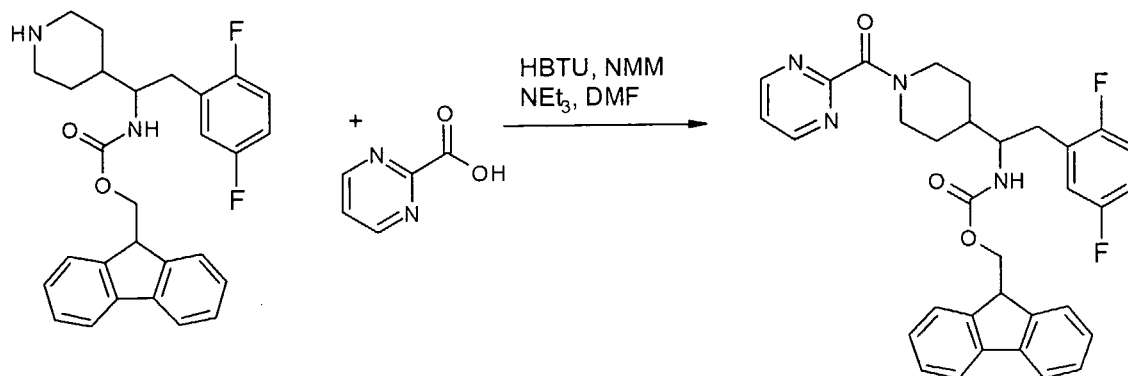


[2-(2,5-Difluoro-phenyl)-1-piperidin-4-yl-ethyl]-carbamic acid 9H-fluoren-9-ylmethyl ester

20 mg (0.06 mmol) of the product from Step 2 (4-[2-(2,5-Difluoro-phenyl)-1-(9H-fluoren-9-ylmethoxycarbonylamino)-ethyl]-piperidine-1-carboxylic acid *tert*-butyl ester) are dissolved in 1 mL of dichloromethane and 0.5 mL of trifluoroacetic. The solution is stirred for 30 min at ambient temperature, then the solvent is removed under reduced pressure and the residue is used further without purification in the next step.

LCMS (IV): rt 3.87 min, m/z 463 (M+H)⁺.

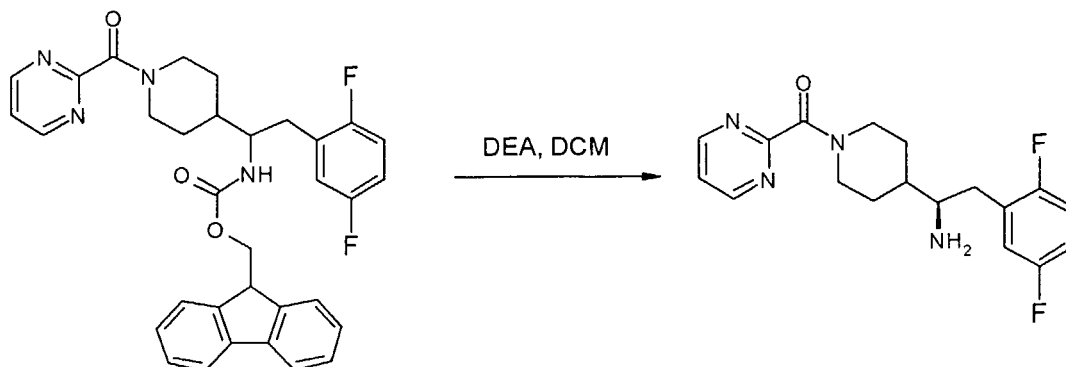
Step 3



5 [2-(2,5-Difluoro-phenyl)-1-[1-(pyrimidine-2-carbonyl)-piperidin-4-yl]-ethyl]-carbamic acid
9H-fluoren-9-ylmethyl ester

To a solution of 247 mg (0.535 mmol) [2-(2,5-difluoro-phenyl)-1-piperidin-4-yl-ethyl]-carbamic acid 9H-fluoren-9-ylmethyl ester (product of step 2) dissolved in 2 mL of *N,N*-dimethylformamide, 112 μ L (0.642 mmol) diisopropylethylamine are added. A solution
 10 of 79.0 mg (0.642 mmol) pyrimidine-2-carboxylic acid, 243 mg (0.642 mmol) of *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU) and 70.6 μ L (0.642 mmol) of *N*-methylmorpholine dissolved in 2 mL of *N,N*-dimethylformamide, which was preactivated for 15 min, is added to the reaction
 15 mixture. The mixture is stirred overnight at 50°C. After removal of the solvents under reduced pressure, 20 mL of ethyl acetate are added. The organic layer is extracted with 2 x 20 mL of 5% citric acid and saturated sodium hydrogen carbonate. The organic layer is washed with brine and dried over sodium sulphate. The solvent is removed under reduced pressure and the residue is purified by flash chromatography (dichloromethane/methanol 95:5) to yield the title compound.
 20 LCMS (I): rt 5.49 min, m/z 569 ($M+H$)⁺.

Step 4



5 {2-(2,5-Difluoro-phenyl)-1-[1-(pyrimidine-2-carbonyl)-piperidin-4-yl]-ethyl}-carbamic acid 9H-fluoren-9-ylmethyl ester

To a solution of 183 mg (0.322 mmol) {2-(2,5-difluoro-phenyl)-1-[1-(pyrimidine-2-carbonyl)-piperidin-4-yl]-ethyl}-carbamic acid 9H-fluoren-9-ylmethyl ester (product of step 3) dissolved in 5 mL of dichloromethane are added 1.00 mL of diethylamine at
 10 0°C. The mixture is stirred for 30 min. Removal of the solvent under reduced pressure afforded the title compound, which was purified by prep. HPLC and prep. chiral HPLC to yield the single enantiomers.

LCMS (II): rt 4.45 min, m/z 347 (M+H)⁺.

LCMS (heptane/ethanol 20:80, isocratic): 52.2 min, m/z 347 (M+H)⁺.

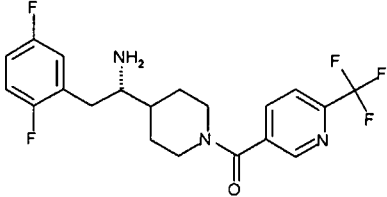
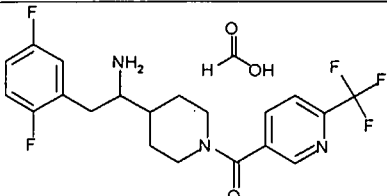
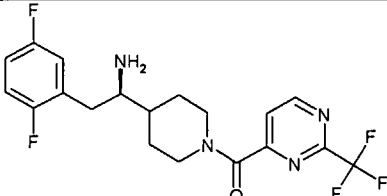
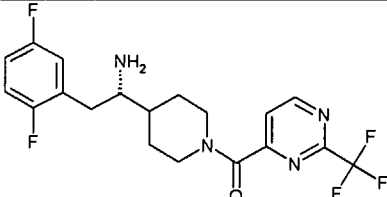
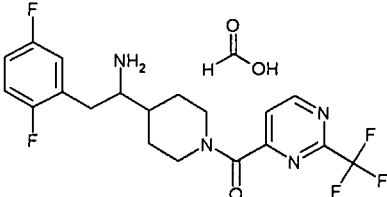
15 ¹H-NMR (500 MHz, DMSO-d₆) δ = 1.23-1.43 (m, 2H), 1.51 (m, 1H), 1.63-1.87 (m, 2H), 2.42 (m, 1H), 2.71-2.81 (m, 3H), 2.93-3.01 (m, 1H), 3.21 (t, J = 15.0 Hz, 1H), 4.51 (t, J = 15.0 Hz, 1H), 7.04-7.09 (m, 1H), 7.16-7.24 (m, 2H), 7.58 (dt, J = 6.0 Hz, J = 2.5 Hz, 1H), 8.31 (s, 2H, NH₂), 8.88 (dd, J = 6.0 Hz, J = 1.5 Hz, 2H).

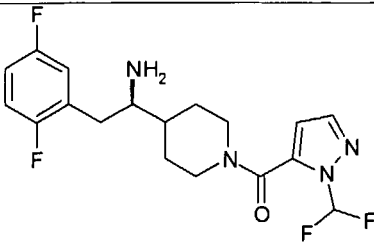
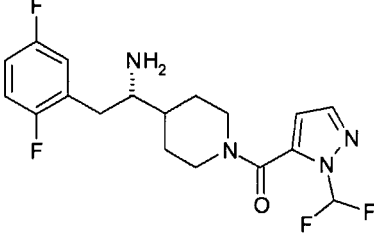
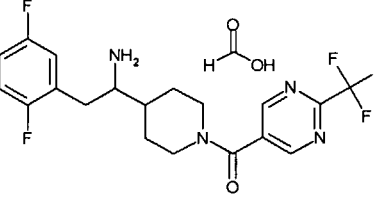
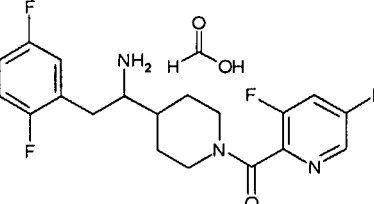
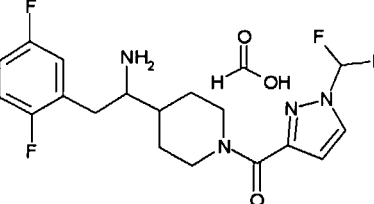
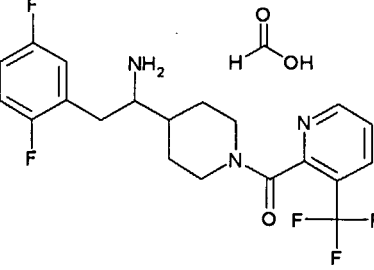
¹³C-NMR (125 MHz, DMSO-d₆) δ = 26.0; 26.9 (CH₂, boot/chair), 28.2; 29.0 (CH₂, boot, chair), 33.3; 33.5 (CH₂, boot, chair), 41.0 (CH₂), 41.1 (CH), 46.3 (CH₂), 55.1 (CH), 114.0 (dd, J = 24.0 Hz, J = 8.75 Hz, CH), 116.0 (dd, J = 25.3 Hz, J = 9.0 Hz, CH), 118.0 (CH), 121.5 (CH), 156.0 (d, J = 128.3 Hz, Cq), 157.7 (2CH), 158.1 (d, J = 129.3 Hz, Cq), 162.3 (Cq), 164.3 (Cq), 164.5 (Cq).

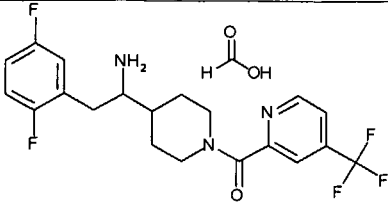
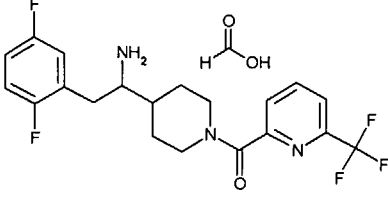
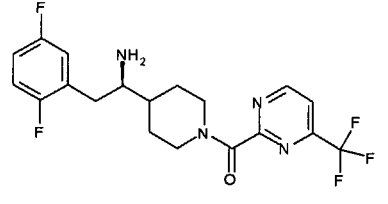
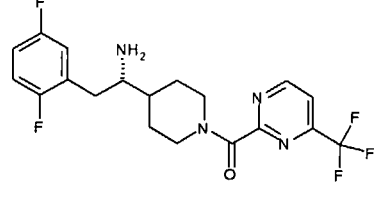
25 The compounds in Table 4 are synthesized according to the procedure shown for example 41.

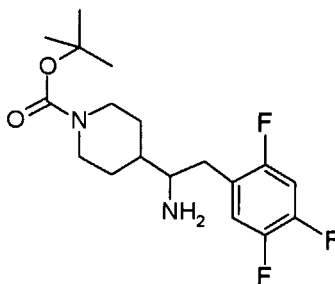
Table 4

Ex.		LCMS	NMR
42		LCMS (II) rt 4.45, m/z 347 [M+H] ⁺ . LCMS (AD-H, heptane/ethanol 20:80, isocratic): 60.0 min, m/z 347 (M+H) ⁺ .	
43		LCMS (II) rt 4.95, m/z 347 [M+H] ⁺ . LCMS (AD-H, ethanol 100%, isocratic): 37.9 min, m/z 347 (M+H) ⁺ .	
44		LCMS (II) rt 4.95, m/z 347 [M+H] ⁺ . LCMS (AD-H, ethanol 100%, isocratic): 48.2 min, m/z 347 (M+H) ⁺ .	¹ H-NMR (400 MHz, DMSO-d ₆) δ = 1.23-1.47 (m, 3H), 1.57-1.88 (m, 2H), 2.42 (m, 1H), 2.70-2.78 (m, 3H), 2.93-3.01 (m, 1H), 3.68 (t, J = 12.8 Hz, 1H), 4.57 (t, J = 12.0 Hz, 1H), 7.04-7.09 (m, 1H), 7.16-7.24 (m, 2H), 8.67 (m, 1H), 8.73 (m, 1H), 8.81 (s, NH ₂ , 2H).
45		LCMS (II) rt 4.95, m/z 347 [M+H] ⁺ .	
46		LCMS (II) rt 7.38, m/z 190 [M+H] ⁺ . LCMS (AD-H, methanol 100%, isocratic): 90.0 min, m/z 414 (M+H) ⁺ .	

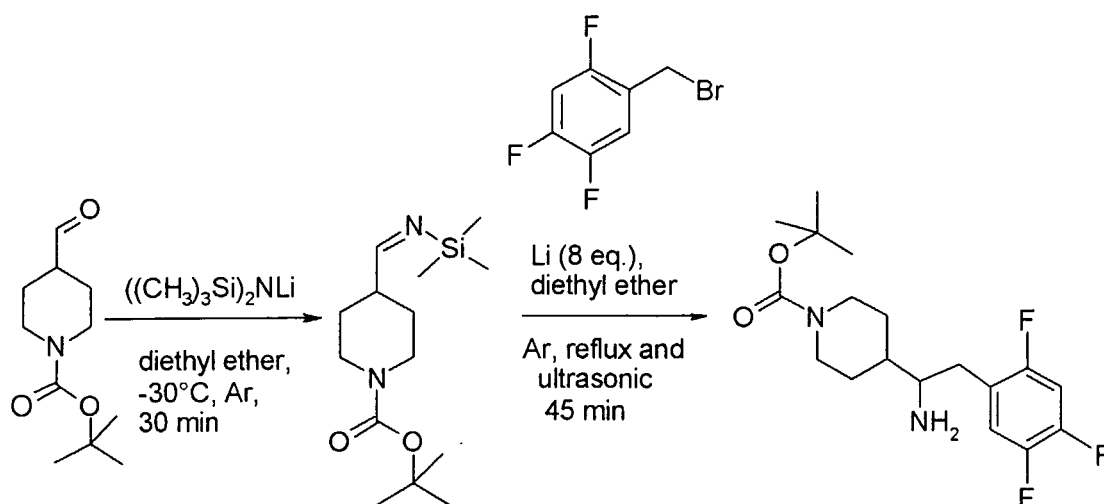
47		LCMS (II) rt 7.38, m/z 190 [M+H]⁺. LCMS (AD-H, methanol 100%, isocratic): 62.0 min, m/z 414 (M+H)⁺.	
48		LCMS (II) rt 7.38, m/z 414 [M+H]⁺.	
49		LCMS (IV) rt 4.35, m/z 415 [M+H]⁺. LCMS (AD-H, heptane/ethanol 40:60, isocratic): 19.0 min, m/z 415 (M+H)⁺.	
50		LCMS (IV) rt 4.20, m/z 415 [M+H]⁺. LCMS (AD-H, heptane/ethanol 40:60, isocratic): 26.0 min, m/z 415 (M+H)⁺.	
51		LCMS (IV) rt 3.86, m/z 415 [M+H]⁺.	¹H-NMR (400 MHz, DMSO-d₆) δ = 1.23-1.42 (m, 2H), 1.57-1.88 (m, 3H), 2.54 (m, 1H), 2.73-2.90 (m, 3H), 2.98-3.01 (m, 1H), 3.58 (t, J = 12.0 Hz, 1H), 4.53 (t, J = 10.8 Hz, 1H), 7.07-7.11 (m, 1H), 7.17-7.23 (m, 2H), 7.97 (d, J = 5.2 Hz, 1H), 8.81 (s, NH₂, 2H), 9.21 (m, 1H).

52		LCMS (IV) rt 3.21, m/z 385 [M+H]⁺. LCMS (AD-H, ethanol 100%, isocratic): 33.5 min, m/z 407 (M+Na)⁺.	
53		LCMS (IV) rt 3.34, m/z 385 [M+H]⁺. LCMS (AD-H, ethanol 100%, isocratic): 66.0 min, m/z 407 (M+Na)⁺.	
54		LCMS (II) rt 7.17, m/z 415 [M+H]⁺.	
55		LCMS (II) rt 6.12, m/z 382 [M+H]⁺.	
56		LCMS (II) rt 6.29, m/z 385 [M+H]⁺.	
57		LCMS (IV) rt 3.65, m/z 414 [M+H]⁺.	¹H-NMR (500 MHz, DMSO-d₆) δ = 1.18-1.36 (m, 2H), 1.50-1.63 (m, 2H), 1.72-1.86 (m, 1H), 2.53-2.57 (m, 1H), 2.65-3.00 (m, 3H), 3.11-3.22 (m, 2H), 4.54 (m, 1H), 7.13-7.18 (m, 1H), 7.18- 7.24 (m, 2H), 7.67-7.70 (m, 1H), 8.21 (s, 2H, NH₂), 8.30 (d, J = 8.0 Hz, 1H), 8.45 (d, J = 8.0 Hz, 1H).

58		LCMS (II) rt 7.57, m/z 414 [M+H] ⁺ .	
59		LCMS (IV) rt 4.30, m/z 414 [M+H] ⁺ .	¹ H-NMR (500 MHz, DMSO-d ₆) δ = 1.20-1.46 (m, 2H), 1.54 (m, 1H), 1.59-1.86 (m, 2H), 2.53 (m, 1H), 2.69-2.91 (m, 3H), 2.97-3.03 (m, 1H), 3.57 (t, J = 13.6 Hz, 1H), 4.54 (t, J = 10.4 Hz, 1H), 7.04-7.10 (m, 1H), 7.15-7.23 (m, 2H), 7.84 (d, J = 8.0 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 8.21 (s, 2H, NH ₂), 8.19-8.23 (m, 1H).
60		LCMS (IV) rt 3.90, m/z 415 [M+H] ⁺ . LCMS (AD-H, ethanol 100%, isocratic): 10.5 min, m/z 437 (M+Na) ⁺ .	
61		LCMS (IV) rt 3.87, m/z 190 [M+H] ⁺ . LCMS (AD-H, ethanol 100%, isocratic): 13.5 min, m/z 437 (M+Na) ⁺ .	

Example 62

Step 1



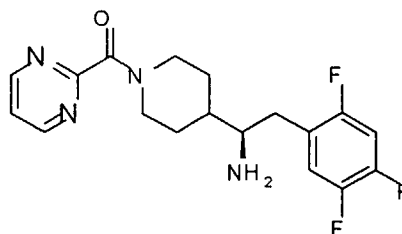
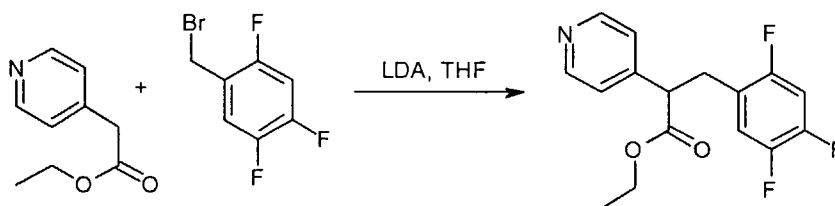
5

4-[1-Amino-2-(2,4,5-trifluoro-phenyl)-ethyl]-piperidine-1-carboxylic acid tert-butyl ester

3010 μL (3.01 mmol) of lithium hexamethyldisilazide (LHMDS; 1M solution in diethyl ether) are dissolved in 4 mL of dry diethyl ether under an argon atmosphere. The solution is cooled to -30°C , then 600 mg (2.80 mmol) 4-formyl-piperidine-1-carboxylic acid *tert.*-butyl ester dissolved in 2 mL of dry diethyl ether are slowly added and the mixture is stirred at -30°C for 45 min. Afterwards 740 μL (5.63 mmol) of 1-bromomethyl-2,4,5-trifluoro-benzene are added. This reaction mixture is transferred via a syringe in another flask, which is equipped with 157 mg (22.5 mmol) lithium and 10 mL of dry diethyl ether under an argon atmosphere. This flask is placed in an ultrasonic bath and the slow addition of the reaction mixture starts when the diethyl ether is refluxing. The reaction is kept under reflux and ultrasound for 45 min. By the addition of 15 mL of saturated ammonium chloride solution the reaction is quenched and the aqueous layer is extracted with 3 x 20 mL ethyl acetate. The combined organic layers are extracted with 5 x 10 mL of 5% citric acid. The pH value of the combined acid layers is then adjusted with ammonium hydroxide to pH 12 and this aqueous layer is extracted with 3 x 10 mL ethyl acetate. The organic layer is washed with brine and dried over sodium sulphate. The solvent is removed under reduced pressure and the residue is purified by prep. HPLC.

LCMS (VI): rt 4.95 min, m/z 358 ($M+H$) $^+$.

$^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ = 1.21-1.37 (m, 2H), 1.44 (m, 9H), 1.64-1.78 (m, 3H), 2.69-2.88 (m, 3H), 2.93-3.01 (m, 1H), 3.23 (t, J = 15.0 Hz, 1H), 4.55 (t, J = 15.0 Hz, 1H), 7.45-7.52 (m, 2H), 7.58 (dt, J = 6.0 Hz, J = 2.5 Hz, 1H), 8.25 (s, 2H, NH_2), 8.88 (dd, J = 6.0 Hz, J = 1.5 Hz, 2H).

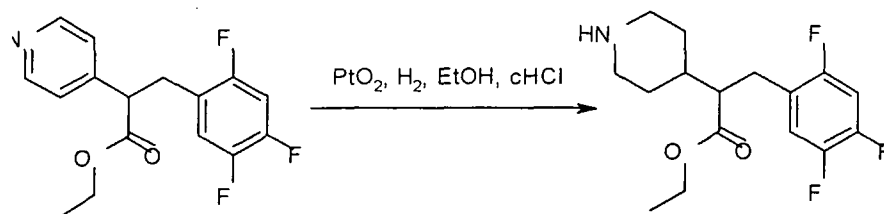
Example 63**Step 1****2-pyridine-4-yl-3-(2,4,5-trifluoro-phenyl)-propionic acid ethyl ester**

1.02 mL (7.50 mmol, 1.00 eq) of diisopropylamine are dissolved in 25 mL of tetrahydrofuran. The solution is cooled to -15°C and 3.75 mL (7.50 mmol, 1.00 eq) of a 2 M solution of *n*-butyllithium in cyclohexane are added. The reaction mixture is stirred for 15 min and cooled to -60°C . To the reaction mixture, 1.15 mL (7.50 eq) of pyridin-4-yl-acetic acid ethyl ester are added and the solution was stirred for 30 min, while the temperature is allowed to rise to -30°C . The solution is then cooled to -50°C and 1 mL (7.50 mmol, 1.00 eq) of 1-bromomethyl-2,4,5-trifluoro-benzene is added. After the stirring is continued for 3 h, the reaction mixture is diluted with water and ethyl acetate. The aqueous layer is extracted three times with ethyl acetate and the combined organic layers are washed with brine, dried with sodium sulphate, filtered and evaporated under reduced pressure. The crude product is purified by flash chromatography on silica gel with cyclohexane:ethyl acetate (1:0 to 0:1) as eluent.

LCMS (I) rt 3.40 min; m/z 310 $[\text{M}+\text{H}]^{+}$, 341 $[\text{M}+\text{ACN}]^{+}$.

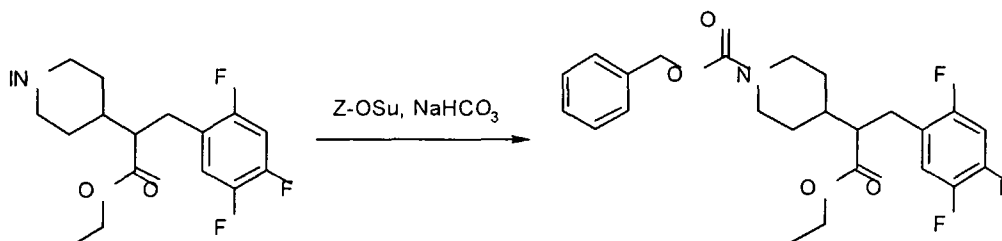
$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ = 8.56-8.55 (m, 2H, aryl-H), 7.21-7.20 (m, 2H, aryl-H), 6.93-6.84 (m, 2H, aryl-H), 4.13-4.07 (m, 2H, CH_2), 3.83 (t, 1H, CH), 3.30 (dd, 1H, CH_2), 3.03 (dd, 1H, CH_2), 1.85 (t, 3H, CH_3).

Step 2

2-piperidine-4-yl-3-(2,4,5-trifluoro-phenyl)-propionic acid ethyl ester

- 5 1.9 g (5.96 mmol, 1.00 eq) of 2-pyridine-4-yl-3-(2,4,5-trifluoro-phenyl)-propionic acid ethyl ester (product of step 1) are dissolved in 76 mL of ethanol. 11 mL of concentrated hydrochloric acid and 250 mg of platinum oxide are added and the reaction mixture is stirred under hydrogen atmosphere at room temperature for 15 h. The mixture is filtered through celite and the filtrate is evaporated under reduced pressure and used
- 10 without further purification in the next step.
- LCMS (I) rt 2.92 min; m/z 316 $[\text{M}+\text{H}]^+$, 357 $[\text{M}+\text{ACN}]^+$.

Step 3

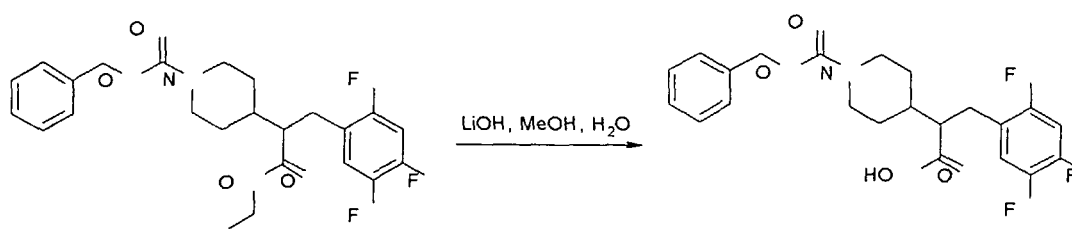


- 15 4-[1-ethoxycarbonyl-2-(2,4,5-trifluoro-phenyl)-ethyl]-piperidine-1-carboxylic acid benzyl ester
- 2.23 g (7.07 mmol, 1.00 eq) of crude 2-piperidine-4-yl-3-(2,4,5-trifluoro-phenyl)-propionic acid ethyl ester from step 2 are dissolved in 200 mL of tetrahydrofuran. Then
- 20 100 mL of saturated sodium bicarbonate solution and 2.10 g (8.49 mmol, 1.20 eq) of N-(benzyl-oxycarbonyloxy)succinimide are added. The reaction mixture is stirred for 3 h at room temperature, and diluted with ethyl acetate. The organic layer is washed with 20 mL of 1 M hydrochloric acid and brine, dried with sodium sulphate and evaporated under reduced pressure. The crude product is purified by column chromatography on
- 25 silica gel with cyclohexane:ethyl acetate (1:0 to 3:1) as eluent to yield the title compound.

LCMS (I) rt 5.29 min; m/z 450 $[M+H]^+$.

1H -NMR (400 MHz, $CDCl_3$) δ = 7.38-7.30 (m, 5H, aryl-H), 7.00-6.84 (m, 2H, aryl-H), 5.12 (s, 2H, CH_2), 4.27-4.17 (m, 2H, CH_2), 4.02 (q, 2H, CH_2), 2.92 (dd, 1H, CH_2), 2.80-2.70 (m, 3H), 2.53-2.49 (m, 1H), 1.82-1.74 (m, 2H), 1.64-1.55 (m, 1H), 1.32-1.25 (m, 2H), 1.11 (t, 3H, CH_3).

Step 4

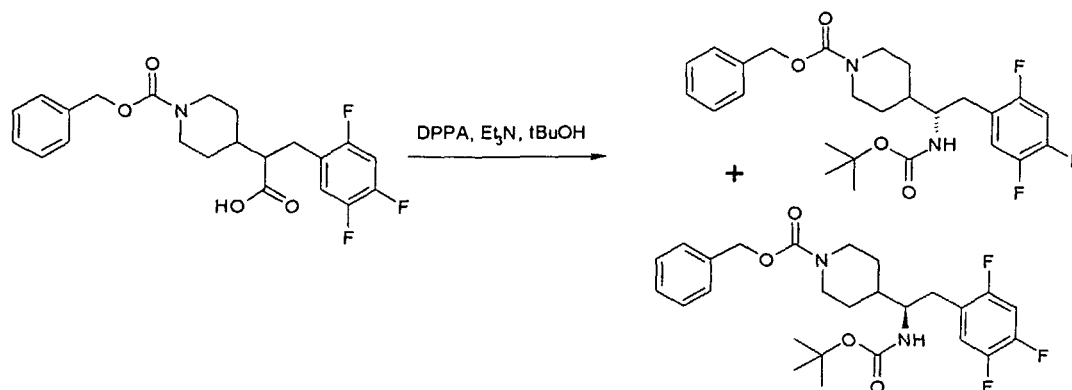


4-[1-carboxy-2-(2,4,5-trifluoro-phenyl)-ethyl]-piperidine-1-carboxylic acid benzyl ester

2.05 g (4.45 mmol, 1.00 eq) of 4-[1-ethoxycarbonyl-2-(2,4,5-trifluoro-phenyl)-ethyl]-piperidine-1-carboxylic acid benzyl ester (product of step 3) is dissolved in 60 mL of methanol and 20 mL of water. After the addition of 240 mg (10 mmol, 2.25 eq) of lithium hydroxide, the reaction mixture is stirred at 95°C for 7h and then concentrated to one third of its volume under reduced pressure. The remaining solution is diluted with dichloromethane, washed with 1 M hydrochloric acid solution, dried with sodium sulphate, filtered and evaporated to dryness. The crude product is used in the next step without further purification.

LCMS (I) rt 4.43 min; m/z 422 $[M+H]^+$, 463 $[M+ACN]^+$.

Step 5



4-[(R)-1-*tert*-butoxycarbonylamino-2-(2,4,5-trifluoro-phenyl)-ethyl]-piperidine-1-carboxylic acid benzyl ester and 4-[(S)-1-*tert*-butoxycarbonylamino-2-(2,4,5-trifluoro-phenyl)-ethyl]-piperidine-1-carboxylic acid benzyl ester

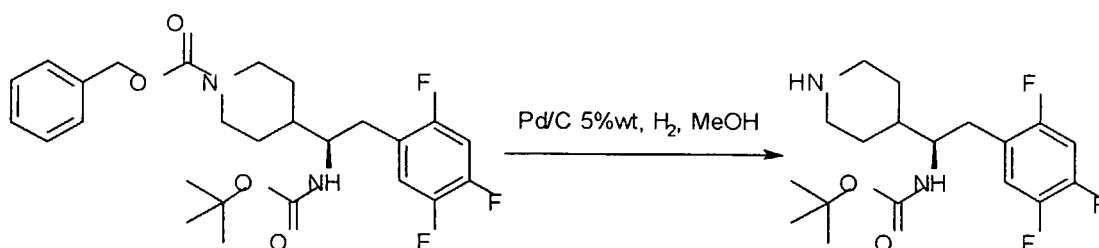
920 mg (2.18 mmol, 1.00 eq) of 4-[1-carboxy-2-(2,4,5-trifluoro-phenyl)-ethyl]-piperidine-1-carboxylic acid benzyl ester (product of step 4) are dissolved in 45 mL of *tert*-butylalcohol, and 321 μ L (2.29 mmol, 1.05 eq) of diphenylphosphoric azide followed by 495 μ L (2.29 mmol, 1.05 eq) of triethylamine are added. The reaction mixture is stirred overnight at 70°C, diluted with ethyl acetate and washed with saturated sodium bicarbonate solution and brine. The organic layer is dried with sodium sulphate, filtered and evaporated under reduced pressure. The crude product is purified by preparative HPLC to yield a racemic mixture of the title compound. The enantiomers were separated by preparative chiral HPLC.

LCMS (IV) rt 5.25 min; m/z 493 $[M+H]^+$, 515 $[M+Na]^+$.

LCMS (chiral, AD-H, ethanol 100%) rt 7.3 / 9.8 min.

1H -NMR (400 MHz, $CDCl_3$) δ = 7.38-7.28 (m, 5H, aryl-H), 7.05-6.85 (m, 2H, aryl-H), 5.12 (s, 2H, CH_2), 4.33-4.22 (m, 3H, NH, CH_2), 3.73-3.66 (m, 1H, CH), 2.85-2.53 (m, 4H, CH_2), 1.80-1.55 (m, 3H, CH, CH_2), 1.35-1.22 (m, 2H, CH_2).

Step 6

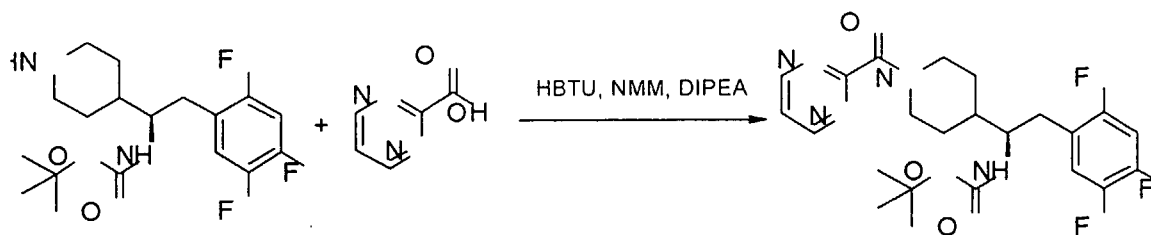


[(R)-1-piperidine-4-yl-2-(2,4,5-trifluoro-phenyl)-ethyl]-carbamic acid *tert*-butyl ester

80 mg (0.16 mmol, 1.00 eq) of 4-[(R)-1-*tert*-butoxycarbonylamino-2-(2,4,5-trifluoro-phenyl)-ethyl]-piperidine-1-carboxylic acid benzyl ester (product of step 5) are dissolved in 4 mL of methanol. 9 mg of 5wt% palladium on charcoal (Degussa type E101) is added and the reaction mixture is stirred under hydrogen atmosphere at room temperature for 1h. The mixture is filtered through celite and the filtrate is evaporated under reduced pressure and used without further purification in the next step.

LCMS (IV) rt 2.66 min; m/z 359 $[M+H]^+$, 400 $[M+ACN]^+$.

Step 7

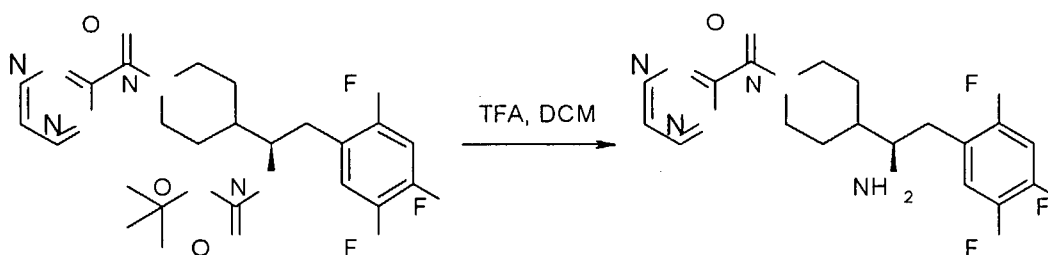


[(R)-1-[pyrimidine-2-carbonyl]-piperidine-4-yl-2-(2,4,5-trifluoro-phenyl)-ethyl]-carbamic acid tert-butyl ester

24 mg (0.195 mmol, 1.20 eq) of pyrimidin-2-carboxylic acid and 74 mg (0.195 mmol, 1.20 eq) of *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium-hexa-fluorophosphate are dissolved in 1 mL of *N,N*-dimethylformamide. The solution is cooled to 0°C and 21.5 μ l (0.195 mmol, 1.20 eq) of 4-methyl-morpholine are added. The mixture is stirred for 10 min and a solution of the crude product of step 6 and 35 μ l (0.195 mmol, 1.20 eq) of di-*iso*-propylethylamine in 1 mL of *N,N*-dimethylformamide are added. The reaction mixture is stirred for 2 h at room temperature and the solvent is evaporated. The residue is purified by flash chromatography (dichloromethane:methanol 9:1) to afford the title compound.

LCMS (IV) rt 3.87 min; m/z 365, 409, 465 $[M+H]^+$, 487 $[M+Na]^+$.

Step 8



{4-[(R)-1-amino-2-(2,4,5-trifluoro-phenyl)-ethyl]-piperidine-1-yl}-pyrimidine-2-yl-methanone

The product of step 7 is dissolved in 2.5 mL of dichloromethane and 800 μ l of trifluoroacetic acid are added. The mixture is stirred for 1 h and the solvent is evaporated under reduced pressure. The crude product is purified by preparative HPLC to afford the title compound.

LCMS (II) rt 1.86 min; m/z 365 [M+H]⁺.

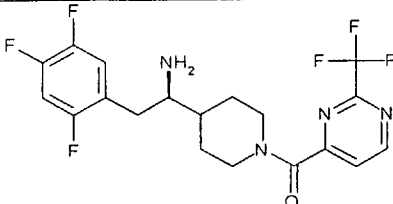
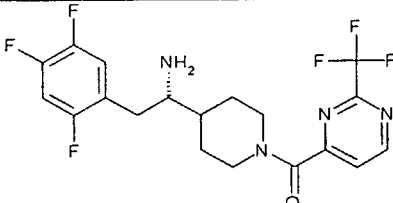
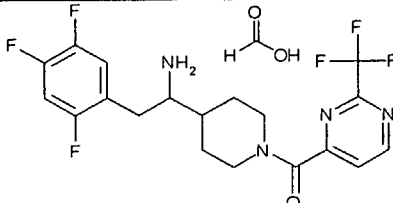
LCMS (chiral, AD-H, ethanol 100%): 9.04 min, m/z 365 (M+H)⁺.

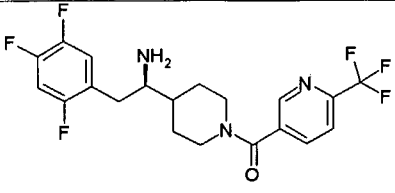
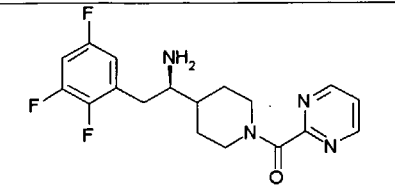
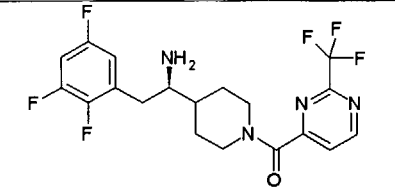
¹H-NMR (500 MHz, DMSO-d₆) δ = 1.20-1.43 (m, 2H), 1.52 (m, 1H), 1.55-1.87 (m, 2H), 2.52 (m, 1H), 2.69-2.88 (m, 3H), 2.93-3.01 (m, 1H), 3.23 (t, J = 15.0 Hz, 1H), 4.55 (t, J = 15.0 Hz, 1H), 7.45-7.52 (m, 2H), 7.58 (dt, J = 6.0 Hz, J = 2.5 Hz, 1H), 8.25 (s, 2H, NH₂), 8.88 (dd, J = 6.0 Hz, J = 1.5 Hz, 2H).

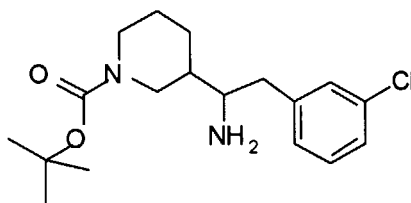
The compounds in Table 5 are synthesized according to the procedure shown for example 63.

10

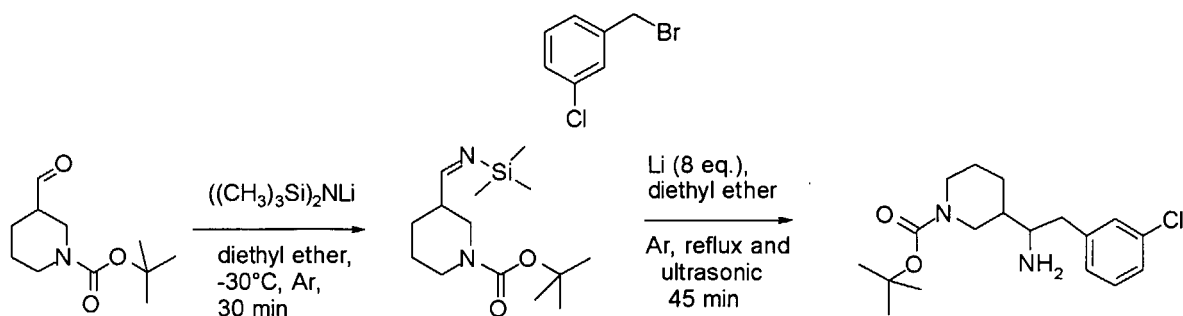
Table 5

Ex.		LCMS	NMR
64		LCMS (IV) rt 4.58, m/z 433 [M+H] ⁺ . LCMS (AD-H, heptane/ethanol 20:80, isocratic): 7.84 min, m/z 455 (M+Na) ⁺ .	¹ H-NMR (400 MHz, DMSO-d ₆) δ = 1.21-1.41 (m, 2H), 1.52 (m, 1H), 1.65-1.87 (m, 2H), 2.44 (m, 1H), 2.69-2.81 (m, 3H), 2.97-3.06 (m, 1H), 3.56 (t, J = 11.2 Hz, 1H), 4.51 (t, J = 10.4 Hz, 1H), 7.07-7.09 (m, 1H), 7.29-7.36 (m, 1H), 7.96 (d, J = 5.20 Hz, 1H), 8.28 (s, 2H, NH ₂), 9.2 (dd, J = 6.0 Hz, J = 1.5 Hz, 1H).
65		LCMS (IV) rt 4.58, m/z 433 [M+H] ⁺ . LCMS (AD-H, heptane/ethanol 20:80, isocratic): 10.56 min, m/z 455 (M+Na) ⁺ .	
66		LCMS (IV) rt 4.58, m/z 433 [M+H] ⁺ .	

67		LCMS (IV) rt 4.29, m/z 432 [M+H] ⁺ .	
68		LCMS (IV) rt 2.10, m/z 365 [M+H] ⁺ . LCMS (AD-H, ethanol 100%, isocratic): 17.4 min, m/z 387 (M+Na) ⁺ .	¹ H-NMR (400 MHz, DMSO-d ₆) δ = 1.21-1.39 (m, 2H), 1.52 (m, 1H), 1.57-1.86 (m, 2H), 2.53 (m, 1H), 2.69-2.83 (m, 3H), 2.92- 3.00 (m, 1H), 3.20 (m, 1H), 4.52 (m, 1H), 7.07 (m, 1H), 7.30-7.37 (m, 1H), 7.57 (dt, J = 4.8 Hz, J = 2.0 Hz, 1H), 8.19 (s, 2H, NH ₂), 8.7 (d, J = 4.8 Hz, 2H).
69		LCMS (IV) rt 3.12, m/z 433 [M+H] ⁺ .	

Example 70

5



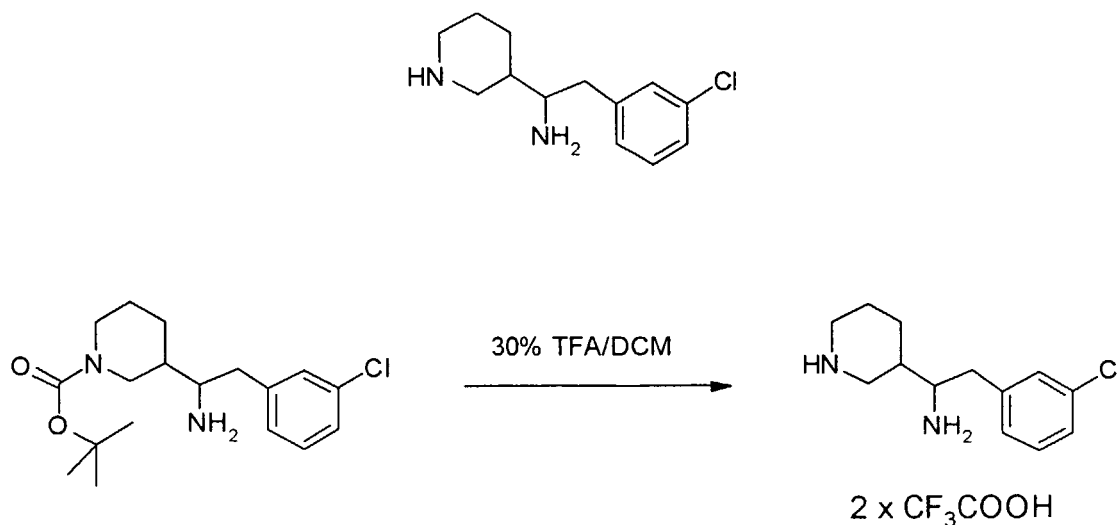
10

3-[1-Amino-2-(3-chloro-phenyl)-ethyl]-piperidine-1-carboxylic acid *tert.*-butyl ester

1.55 mL (0.516 mmol) of lithium hexamethyldisilazide (LHMDS; 1M solution in diethyl ether) are dissolved in 5 mL of dry diethyl ether under an argon atmosphere. The solution is cooled to -30°C , then 800 mg (3.75 mmol) 3-formyl-piperidine-1-carboxylic acid *tert.*-butyl ester dissolved in 5 mL of dry diethyl ether are slowly added and the mixture is stirred at -30°C for 45 min. Afterwards 986 μL (7.50 mmol) of 1-bromomethyl-3-chloro-benzene are added. This reaction mixture is transferred via a syringe in another flask, which is equipped with 210 mg (30.0 mmol) lithium and 40 mL of dry diethyl ether under an argon atmosphere. This flask is placed in an ultrasonic bath and the slow addition of the reaction mixture starts when the diethyl ether is refluxing. The reaction is kept under reflux and ultrasound for 45 min. By the addition of 20 mL of saturated ammonium chloride solution the reaction is quenched and the aqueous layer is extracted with 3 x 20 mL of ethyl acetate. The combined organic layers are extracted with 5 x 20 mL of 5% citric acid. The pH value of the combined acid layers is then adjusted to pH 12 with ammonium hydroxide and this aqueous layer is extracted with 3 x 20 mL of ethyl acetate. The organic layer is washed with brine and dried over sodium sulphate. The solvent is removed under reduced pressure and the residue is purified by prep. HPLC to yield the title compound.

LCMS: rt 3.7 min, m/z 339 ($M+H$) $^{+}$.

$^1\text{H-NMR}$ (300 MHz, DMSO-d_6) δ = 1.19-1.35 (m, 2H), 1.37 (s, 9H), 1.59-1.70 (m, 3H), 2.55-2.59 (m, 1H), 2.75-2.96 (m, 2H), 3.36 (m, 2H), 3.95 (dd, J = 13.0 Hz, 2H), 7.22-7.37 (m, 4H), 7.91 (bs, 2H).

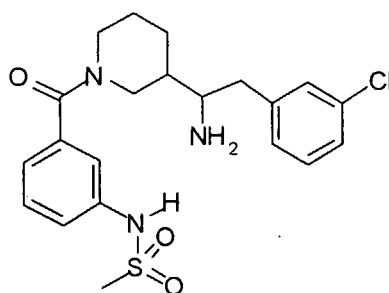
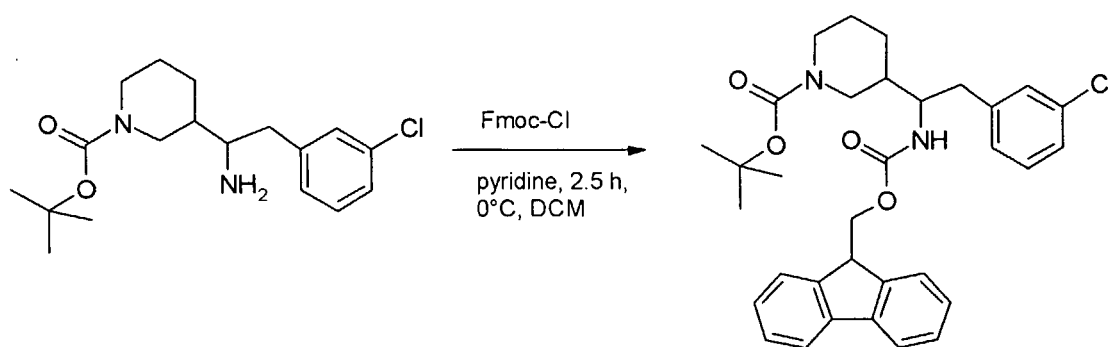
Example 71

2-(3-Chloro-phenyl)-1-piperidin-3-yl-ethylamine

20 mg (0.06 mmol) of example 70 [(3-[1-amino-2-(3-chloro-phenyl)-ethyl]-piperidine-1-carboxylic acid *tert.*-butyl ester)] dissolved in 1 mL of dichloromethane are diluted with 0.5 mL of trifluoroacetic acid. The solution is stirred for 30 min at ambient temperature and then the solvent is removed under reduced pressure. The residue is purified by prep. HPLC to yield the title compound.

LCMS: rt 2.21 min, m/z 239 ($M+H$)⁺.

¹H-NMR (300 MHz, DMSO- d_6) δ = 1.45-1.61 (m, 2H), 1.79-1.88 (m, 2H), 2.04-2.10 (m, 1H), 2.70-2.98 (m, 4H), 3.23 (d, J = 11.0 Hz, 1 H), 3.39 (d, J = 13.2 Hz, 1H) , 3.51 (brs, 1H), 7.25-7.41 (m, 4H), 8.03 (brs, 3 H), 8.66 (brs, 1 H), 9.00 (brs, 1H).

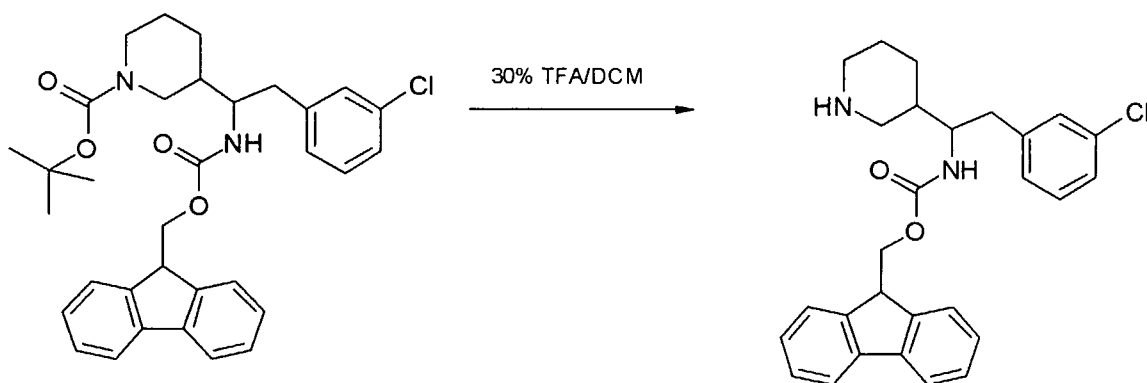
Example 72Step 13-[2-(3-Chloro-phenyl)-1-(9H-fluoren-9-ylmethoxycarbonylamino)-ethyl]-piperidine-1-carboxylic acid *tert.*-butyl ester

To a solution of 69 mg (0.20 mmol) of [4-[1-amino-2-(3-chloro-phenyl)-ethyl]-piperidine-1-carboxylic acid *tert.*-butyl ester] (example 70) dissolved in 5 mL of dichloromethane are added 132 μ L (1.63 mmol) of pyridine and 58 mg (0.224 mmol) of N-(9-fluorenylmethoxycarbonyloxy)-chloride at 0°C. The mixture is stirred for 2.5 h and then diluted

with 20 mL of 5% citric acid solution. The aqueous layer is extracted with 3 x 15 mL of ethyl acetate and the combined organic layers are washed with water and brine and dried over sodium sulphate. Removal of the solvent under reduced pressure afforded a residue, which is purified by prep. HPLC to yield the title compound.

5 LCMS(I): rt 3.74 min, m/z 562 (M+H)⁺.

Step 2



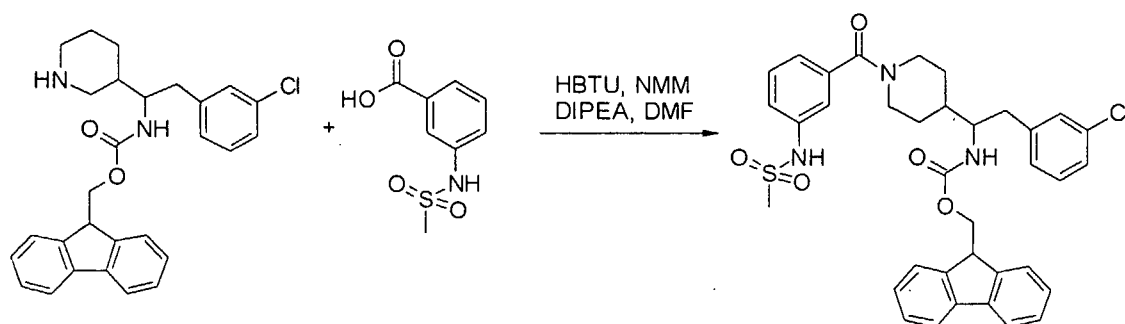
10

[2-(3-Chloro-phenyl)-1-piperidin-3-yl-ethyl]-carbamic acid 9H-fluoren-9-ylmethyl ester

19 mg (0.03 mmol) of the product from Step 1 ([2-(3-Chloro-phenyl)-1-(9H-fluoren-9-ylmethoxycarbonylamino)-ethyl]-piperidine-1-carboxylic acid tert-butyl ester) are dissolved in 1.0 mL of dichloromethane and 1.0 mL of trifluoroacetic acid. The solution is stirred for 30 min at ambient temperature, then the solvent is removed under reduced pressure. The crude product is used in the next step without further purification.

LCMS(III): rt 2.42 min, m/z 462 (M+H)⁺.

20 Step 3

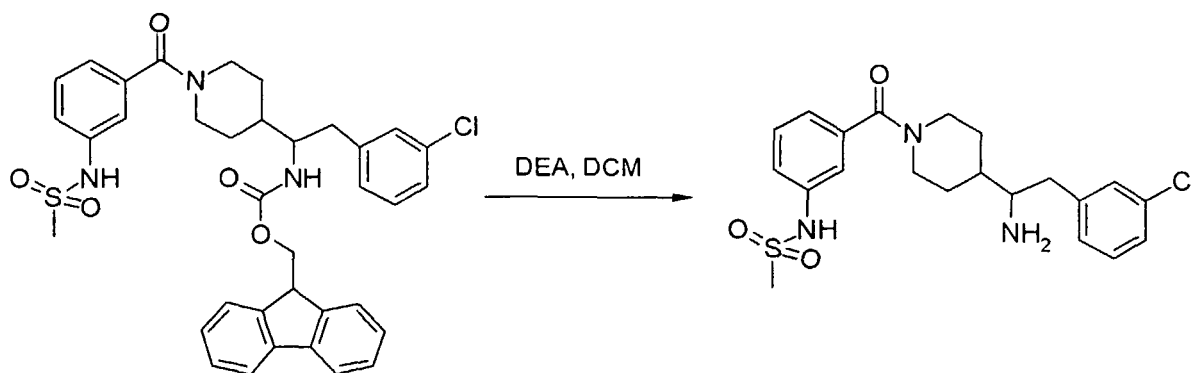


{2-(3-Chloro-phenyl)-1-[1-(3-methanesulphonylamino-benzoyl)-piperidine-4-yl]-ethyl}-
carbamic acid 9H-fluoren-9-ylmethyl ester

To a solution of 16 mg (0.03 mmol) [2-(3-chloro-phenyl)-1-piperidine-3-yl-ethyl]-carbamic acid 9H-fluoren-9-ylmethyl ester (product of step 2) in 2 mL of *N,N*-dimethylformamide, 7.10 μ L (0.04 mmol) diisopropylethyl amine are added. A solution of 8.75 mg (0.04 mmol) 3-ethanesulphonylamino-benzoic acid, 15.4 mg (0.04 mmol) of *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU) and 4.50 μ L (0.04 mmol) of *N*-methylmorpholine dissolved in 1 mL of *N,N*-dimethylformamide, preactivated for 15 min, are added to the reaction mixture. The mixture is stirred overnight at 50°C. After removal of the solvents under reduced pressure 20 mL of ethyl acetate are added. The organic layer is extracted with 2 x 20 mL of 5% citric acid and saturated sodium hydrogen carbonate solution. Then the organic layer is washed with brine and dried over sodium sulphate. The solvent is removed under reduced pressure and the residue is used further without purification in the next step.

LCMS(I): rt 4.35 min, m/z 658 ($M+H$)⁺.

Step 4



N-(3-{4-[1-Amino-2-(3-chloro-phenyl)-ethyl]-piperidine-1-carbonyl}-phenyl)-methane-
sulphonamide

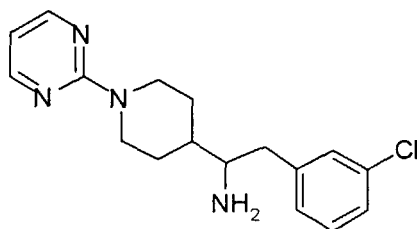
The residue from step 3 ({2-(3-Chloro-phenyl)-1-[1-(3-methanesulphonylamino-benzoyl)-piperidin-4-yl]-ethyl}-carbamic acid 9H-fluoren-9-ylmethyl ester) is dissolved in 1.0 mL of dichloromethane and 0.8 mL of diethylamine are added at 0°C. The mixture is stirred for 30 min. Removal of the solvent under reduced pressure afforded the title

compound, which was purified by prep. reverse phase HPLC to yield the title compound.

LCMS (IV): rt 3.16 min, m/z 436 (M+H)⁺.

5

Example 73



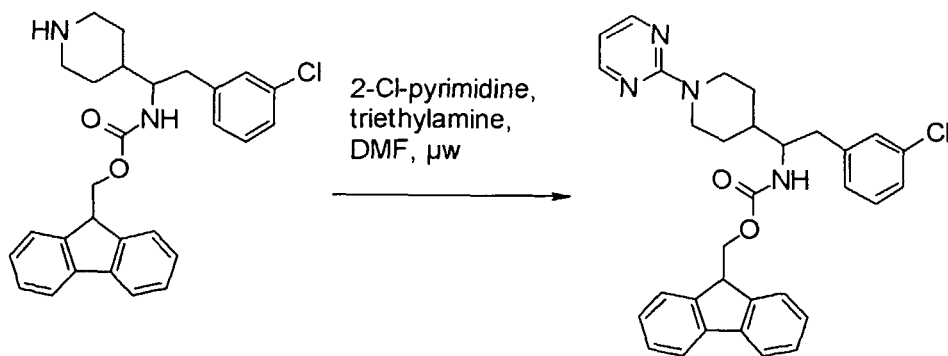
10

The intermediate [2-(3-chloro-phenyl)-1-piperidine-4-yl-ethyl]-carbamic acid 9H-fluoren-9-ylmethyl ester is synthesized according to the procedure described for example 8 (step 1 – step 2).

15

Step 1

20



[2-(3-Chloro-phenyl)-1-(1-pyrimidin-2-yl-piperidin-4-yl)-ethyl]-carbamic acid 9H-fluoren-9-ylmethyl ester

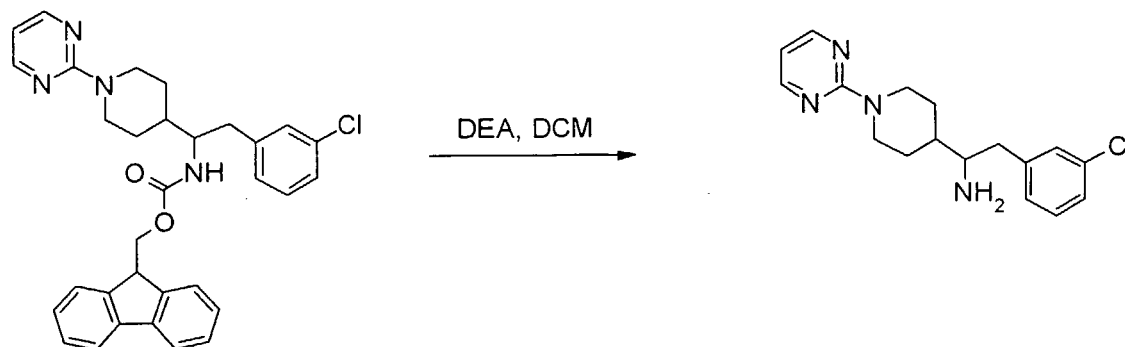
To a solution of 20 mg (0.04 mmol) of [2-(3-chloro-phenyl)-1-piperidin-4-yl-ethyl]-carbamic acid 9H-fluoren-9-ylmethyl ester (example 8, step 2) dissolved in 0.50 mL of *N,N*-dimethylformamide are added at 0°C 6.0 mg (0.054 mmol) of 2-chloropyrimidine and 6.5 μL (0.05 mmol) of triethylamine. The mixture is stirred for 5 min at 180°C in the

25

microwave. Afterwards the solvent is removed under reduced pressure and the residue is used in the next step without purification.

LCMS (IV): rt 6.64 min, m/z 539 (M+H)⁺.

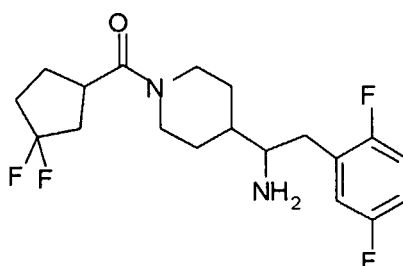
5 Step 2



2-(3-Chloro-phenyl)-1-(1-cyclopropanesulphonyl-piperidin-4-yl)-ethylamine

- 10 To a solution of 19 mg (0.03 mmol) of the product from Step 1 ([2-(3-chloro-phenyl)-1-(1-pyrimidin-2-yl-piperidin-4-yl)-ethyl]-carbamic acid 9H-fluorene-9-ylmethyl ester) in 1 mL of dichloromethane are added at 0°C 0.40 mL of diethylamine. The mixture is stirred for 30 min, then diluted with 10 mL of dichloromethane and washed with 5% citric acid solution, brine and dried over sodium sulphate. Removal of the solvent under
- 15 reduced pressure afforded the title compound, which was purified by prep. HPLC.
LCMS (IV): rt 3.20 min, m/z 317 (M+H)⁺.

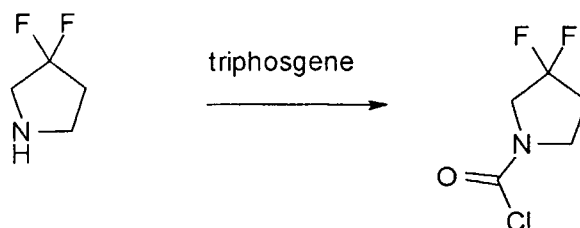
20 Example 74



The intermediate [2-(2,5-difluoro-phenyl)-1-piperidin-4-yl-ethyl]-carbamic acid 9H-fluoren-9-ylmethyl ester is synthesized according to the procedure described for example 41 (step1 – step 2).

5

Step 1



10 3,3-Difluoro-pyrrolidine-1-carbonyl chloride

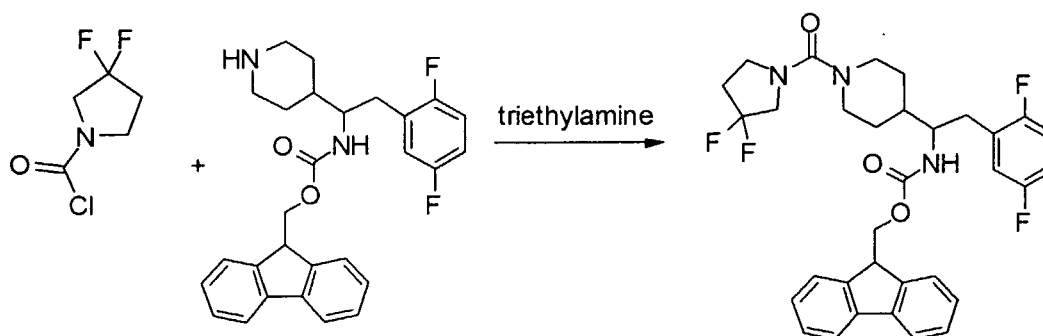
To a solution of 153 mg (0.52 mmol) triphosgene and 250 μ L (3.07 mmol) pyridine dissolved in 3.0 mL of dichloromethane are added dropwise at -78°C a solution of 200 mg (1.40 mmol) 3,3-difluoropyrrolidine and 113 μ L (1.40 mmol) of pyridine dissolved in 3 mL of dichloromethane. The mixture is stirred for 3 h at room temperature, then

15 diluted with 20 mL of 1M hydrochloric acid and the aqueous phase is extracted with 2 x 15 mL of dichloromethane. The combined organic layers are washed with brine and dried over sodium sulphate. Removal of the solvent under reduced pressure afforded a residue, which is used further for the next step without purification.

LCMS (I): rt 3.75 min.

20 $^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ = 2.92 (m, 2H), 4.05 (t, J = 7.2 Hz, 1H), 4.20 (t, J = 7.2 Hz, 1H), 4.28 (t, J = 12.8 Hz, 1H), 4.43 (t, J = 12.8 Hz, 1H).

Step 2



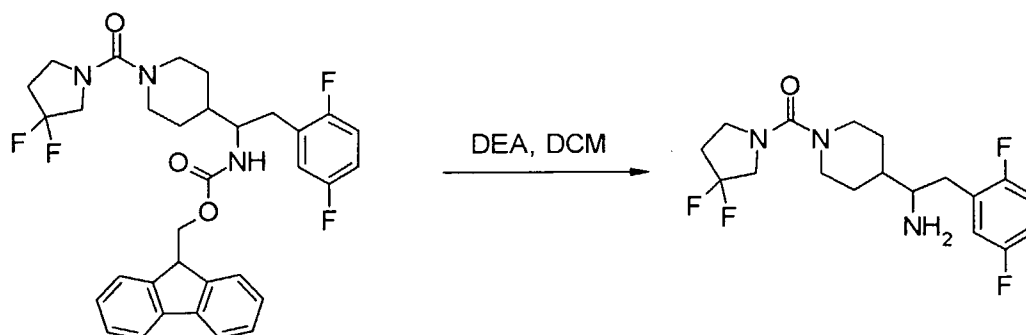
25

{2-(2,5-Difluoro-phenyl)-1-[1-(3,3-difluoro-pyrrolidine-1-carbonyl)-piperidin-4-yl]-ethyl}-carbamic acid 9H-fluoren-9-ylmethyl ester

To a solution of 42.4 mg (0.25 mmol) of the product from Step 1 (3,3-difluoro-pyrrolidine-1-carbonyl chloride) and 40 mg (0.17 mmol) [2-(2,5-difluoro-phenyl)-1-piperidin-4-yl-ethyl]-carbamic acid 9H-fluoren-9-ylmethyl ester (example 41, step 2) dissolved in 2.0 mL of dichloromethane are added at 0°C 49 μ L (0.35 mmol) triethylamine. The mixture is stirred for overnight, then diluted with 20 mL of saturated sodium hydrogen carbonate solution. The aqueous phase is extracted with 2 x 15 mL of dichloromethane, washed with brine and dried over sodium sulphate. Removal of the solvent under reduced pressure afforded the title compound.

LCMS (I): rt 5.93min, m/z 374 (M+H)⁺.

Step 3



{4-[1-Amino-2-(2,5-difluoro-phenyl)-ethyl]-piperidin-1-yl}-(3,3-difluoro-pyrrolidin-1-yl)-methanone

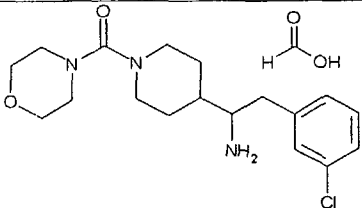
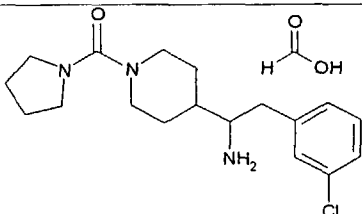
The residue from Step 2 ({2-(2,5-difluoro-phenyl)-1-[1-(3,3-difluoro-pyrrolidine-1-carbonyl)-piperidin-4-yl]-ethyl}-carbamic acid 9H-fluoren-9-ylmethyl ester) is dissolved in 1 mL of dichloromethane and 0.40 mL of diethylamine are added at 0°C. The mixture is stirred for 2 h, then diluted with dichloromethane and washed with 5% citric acid solution, brine and dried over sodium sulphate. Removal of the solvent under reduced pressure afforded the title compound, which was purified by prep. HPLC.

LCMS (IV): rt 3.93 min, m/z 374 (M+H)⁺.

¹H-NMR (500 MHz, DMSO-d₆) δ = 1.97-1.42 (m, 2H), 1.50 (m, 1H), 1.57-1.71 (m, 2H), 2.33 (m, 2H), 2.53 (m, 1H), 2.59-2.67 (m, 2H), 2.79-2.90 (m, 2H), 3.49 (t, 2H), 3.63-3.73 (m, 4H), 7.04-7.09 (m, 1H), 7.12-7.22 (m, 2H), 8.21 (s, 2H, NH₂).

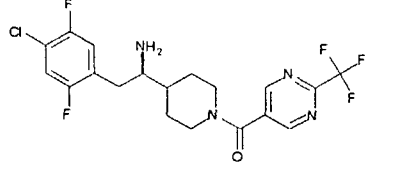
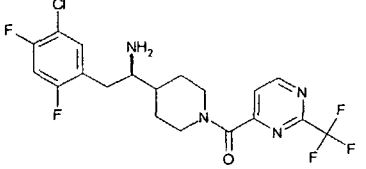
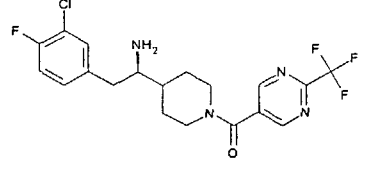
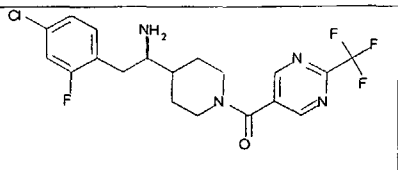
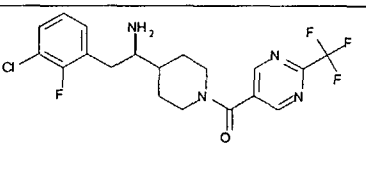
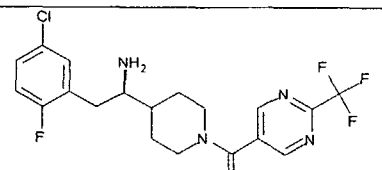
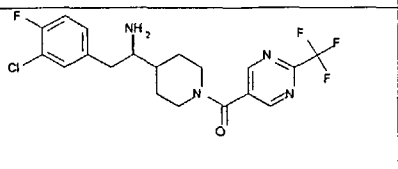
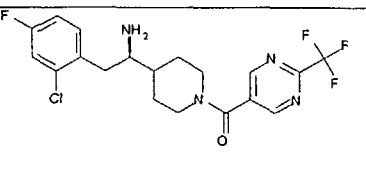
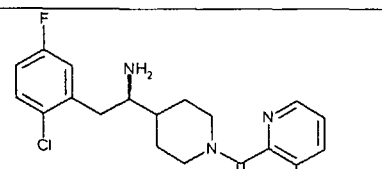
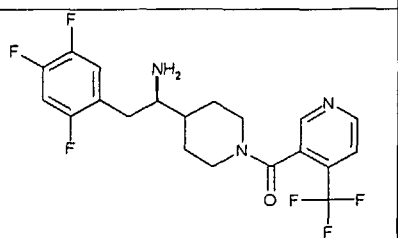
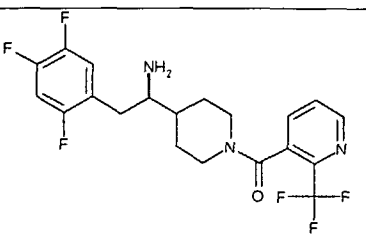
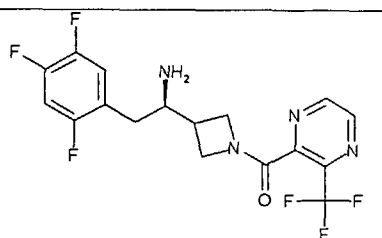
The compounds in Table 6 are synthesized according to the procedure shown for example 74.

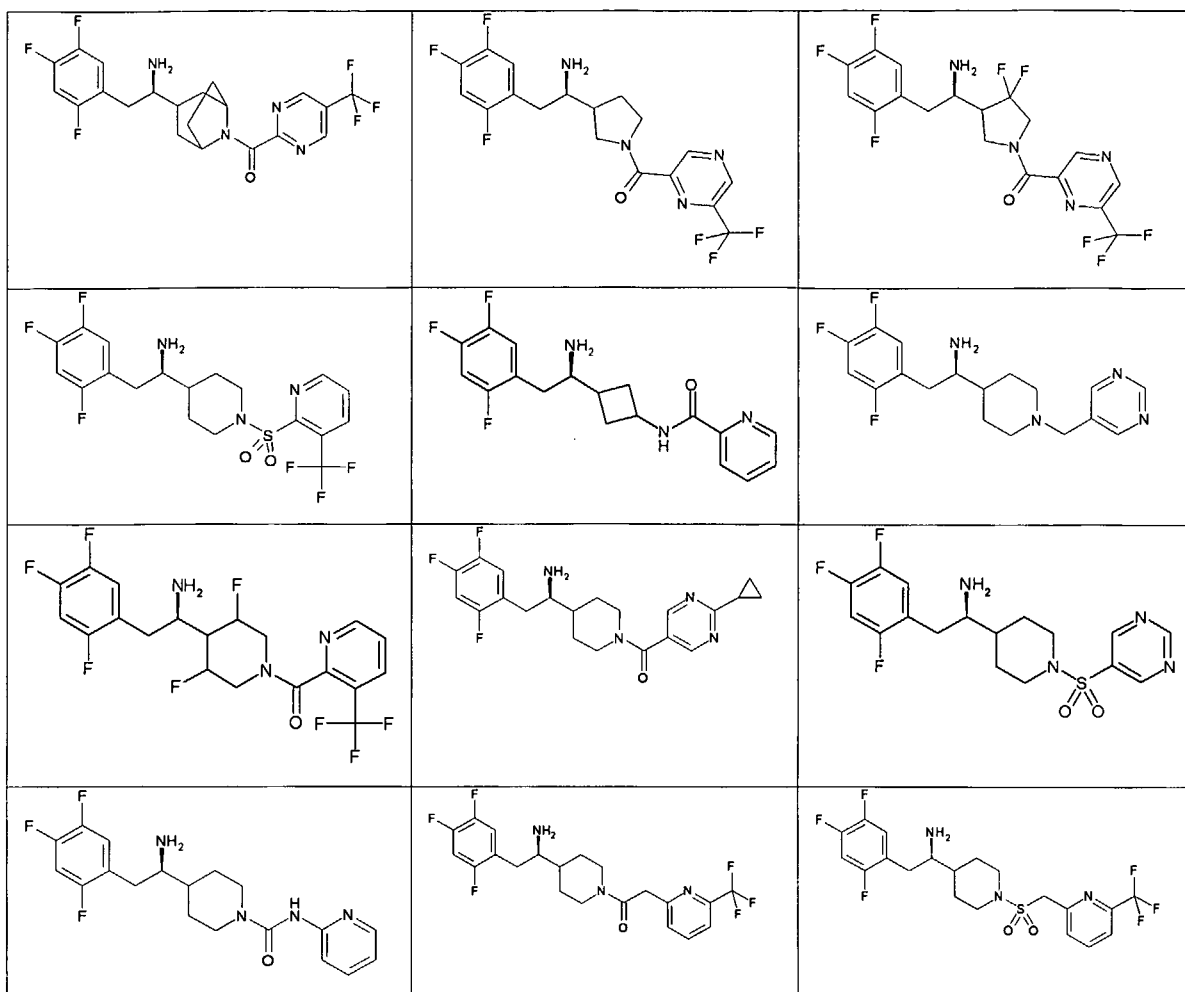
Table 6

Ex.		LCMS	NMR
75		LCMS (IV) rt 2.44, m/z 352 [M+H] ⁺ .	
76		LCMS (II) rt 6.98, m/z 336 [M+H] ⁺ .	

5

Further examples from this series are exemplified below:



ASSAYS

5

Inhibition of DPP-IV peptidase activity was monitored with a continuous fluorimetric assay. This assay is based on the cleavage of the substrate Gly-Pro-AMC (Bachem) by DPP-IV, releasing free AMC. The assay is carried out in 96-well microtiterplates. In a total volume of 100 μ L, compounds are preincubated with 50 pM DPP-IV employing a buffer containing 10mM Hepes, 150mM NaCl, 0.005% Tween 20 (pH 7.4). The reaction is started by the addition of 16 μ M substrate and the fluorescence of liberated AMC is detected for 10 minutes at 25 $^{\circ}$ C with a fluorescence reader (BMG-Fluostar; BMG-Technologies) using an excitation wavelength of 370 nm and an emission wavelength of 450 nm. The final concentration of DMSO is 1 %. The inhibitory potential of the compounds were determined. DPP-IV activity assays were carried out with human and porcine DPP-IV (see below); both enzymes showed comparable activities.

10

15

Soluble human DPP-IV lacking the transmembrane anchor (Gly31-Pro766) was expressed in a recombinant YEAST-strain as Pre-Pro-alpha-mating fusion. The secreted product (rhuDPP-IV-Gly31-Pro766) was purified from fermentation broth (>90% purity).

5

In table 7 are listed the IC₅₀ values for inhibition of DPP-IV peptidase activity determined in assays as described above. The IC₅₀ values were grouped in 3 classes: a ≤ 100 nM; b ≥101 nM and ≤ 1000 nM ; c ≥1001 nM ≤ 2000 nM.

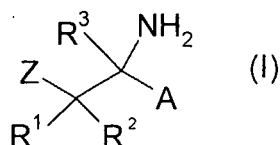
10 **Table 7**

Example	IC ₅₀	Example	IC ₅₀	Example	IC ₅₀
6	b	30	a	54	a
7	b	31	b	55	a
8	a	32	a	56	a
9	b	33	b	57	a
10	a	34	a	58	a
11	a	35	a	59	a
12	b	36	a	60	a
13	b	37	a	61	b
14	b	38	a	62	a
15	a	39	b	63	a
16	b	40	a	64	a
17	a	41	a	65	c
18	b	42	c	66	a
19	a	43	a	67	a
20	a	44	b	68	b
21	c	45	a	69	a
22	a	46	a	70	b

23	a	47	c	71	c
24	a	48	a	72	a
25	a	49	a	73	b
26	a	50	b	74	a
27	a	51	a	75	a
28	a	52	a	76	a
29	b	53	c		

Claims

1. A compound of the formula (I)



or a pharmaceutically acceptable salt thereof, wherein

10 Z is selected from the group consisting of phenyl; naphthyl; indenyl; C₃₋₇ cycloalkyl; indanyl; tetralinyl; decalinyl; heterocycle; and heterobicycle, wherein Z is optionally substituted with one or more R⁴, wherein R⁴ is independently selected from the group consisting of halogen; CN; OH; NH₂; oxo (=O), where the ring is at least partially saturated; R⁵; and R⁶;

15 R⁵ is selected from the group consisting of C₁₋₆ alkyl; O-C₁₋₆ alkyl; and S-C₁₋₆ alkyl, wherein R⁵ is optionally interrupted by oxygen and wherein R⁵ is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

20 R⁶ is selected from the group consisting of phenyl; heterocycle; and C₃₋₇ cycloalkyl, wherein R⁶ is optionally substituted with one or more R⁷, wherein R⁷ is independently selected from the group consisting of halogen; CN; OH; NH₂; oxo (=O), where the ring is at least partially saturated; C₁₋₆ alkyl; O-C₁₋₆ alkyl; and S-C₁₋₆ alkyl;

25 R¹ is selected from the group consisting of H; F; OH; and R⁸;

R² is selected from the group consisting of H; F; and R⁹;

30 R⁸ is independently selected from the group consisting of C₁₋₆ alkyl; O-C₁₋₆ alkyl; N(R^{8a})-C₁₋₆ alkyl; S-C₁₋₆ alkyl; C₃₋₇ cycloalkyl; O-C₃₋₇ cycloalkyl; N(R^{8a})-C₃₋₇ cycloalkyl; S-C₃₋₇ cycloalkyl; -C₁₋₆ alkyl-C₃₋₇ cycloalkyl; O-C₁₋₆ alkyl-C₃₋₇ cycloalkyl; N(R^{8a})-C₁₋₆ alkyl-C₃₋₇ cycloalkyl; S-C₁₋₆ alkyl-C₃₋₇ cycloalkyl; heterocycle; O-heterocycle; N(R^{8a})-heterocycle; S-heterocycle; C₁₋₆ alkyl-heterocycle; O-C₁₋₆ alkyl-heterocycle; N(R^{8a})-C₁₋₆ alkyl-heterocycle; S-C₁₋₆ alkyl-heterocycle; wherein

R⁸ is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

R^{8a} is selected from the group consisting of H; and C₁₋₆ alkyl;

5

R⁹ is independently selected from the group consisting of C₁₋₆ alkyl; C₃₋₇ cycloalkyl; and -C₁₋₆ alkyl-C₃₋₇ cycloalkyl, wherein R⁹ is optionally substituted with one or more R^{9a}, wherein R^{9a} is independently selected from the group consisting of F; Cl; and OH;

10 R³ is selected from the group consisting of H; and C₁₋₆ alkyl;

Optionally one or more pairs of R¹, R², R³ independently selected from the group consisting of R¹/R²; and R²/R³; form a C₃₋₇ cycloalkyl ring, which is optionally substituted with one or more of R^{9b}, wherein R^{9b} is independently selected from the

15 group consisting of F; Cl; and OH;

A is selected from the group consisting of A⁰; and A¹;

A⁰ is selected from the group consisting of C₃₋₇ cycloalkyl; and a saturated heterocycle with at least one nitrogen as ring atom; wherein A⁰ is substituted with one or more R^{10a}, wherein R^{10a} is independently selected from the group consisting of NR¹⁰R^{10b}; NR¹⁰S(O)₂R^{10b}; NR¹⁰S(O)R^{10b}; S(O)₂NR¹⁰R^{10b}; C(O)NR¹⁰R^{10b}; R¹⁰, provided that R¹⁰ is bound to a nitrogen, which is a ring atom of the saturated heterocycle; and

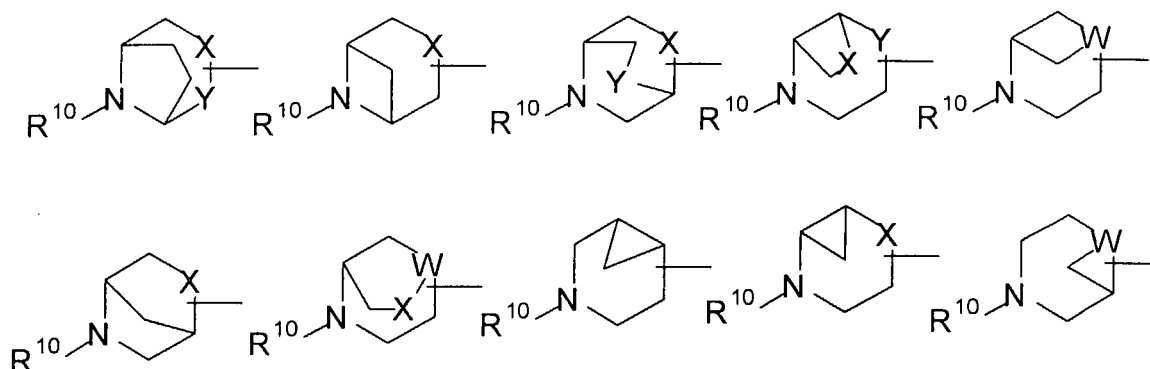
20

C₁₋₃ alkyl, which is optionally substituted with one or more R^{10c}, wherein R^{10c} is independently selected from the group consisting of F; C₁₋₃ alkyl; and C₃₋₄ cycloalkyl, wherein C₁₋₃ alkyl and C₃₋₄ cycloalkyl are optionally substituted with one or more F;

25

Optionally R^{10a} is independently selected from group consisting of F; Cl, and oxo (=O);

30 A¹ is selected from the group consisting of



X; Y are independently selected from the group consisting of $-\text{CH}_2-$; $-\text{NR}^{10\text{b}}-$; $-\text{O}-$; and $-\text{S}-$;

W is selected from the group consisting of $-\text{CH}-$; and $-\text{N}-$;

R^{10} , $\text{R}^{10\text{b}}$ are independently selected from the group consisting of T^1 - T^2 ; and T^2 ;

T^1 is selected from the group consisting of $-\text{C}_{1-6}$ alkyl-; $-\text{C}_{1-6}$ alkyl- $\text{O}-$; $-\text{C}_{1-6}$ alkyl- $\text{S}-$; $-\text{C}_{1-6}$ alkyl- $\text{N}(\text{R}^{11})-$; $-\text{C}(\text{O})-$; $-\text{C}(\text{O})-\text{C}_{1-6}$ alkyl-; $-\text{C}(\text{O})-\text{C}_{1-6}$ alkyl- $\text{O}-$; $-\text{C}(\text{O})-\text{C}_{1-6}$ alkyl- $\text{S}-$; $-\text{C}(\text{O})-\text{C}_{1-6}$ alkyl- $\text{N}(\text{R}^{11})-$; $-\text{C}(\text{O})\text{O}-$; $-\text{C}(\text{O})\text{O}-\text{C}_{1-6}$ alkyl-; $-\text{C}(\text{O})\text{O}-\text{C}_{1-6}$ alkyl- $\text{O}-$; $-\text{C}(\text{O})\text{O}-\text{C}_{1-6}$ alkyl- $\text{S}-$; $-\text{C}(\text{O})\text{O}-\text{C}_{1-6}$ alkyl- $\text{N}(\text{R}^{11})-$; $-\text{C}(\text{O})\text{N}(\text{R}^{11})-$; $-\text{C}(\text{O})\text{N}(\text{R}^{11})-\text{C}_{1-6}$ alkyl-; $-\text{C}(\text{O})\text{N}(\text{R}^{11})-\text{C}_{1-6}$ alkyl- $\text{O}-$; $-\text{C}(\text{O})\text{N}(\text{R}^{11})-\text{C}_{1-6}$ alkyl- $\text{S}-$; $-\text{C}(\text{O})\text{N}(\text{R}^{11})-\text{C}_{1-6}$ alkyl- $\text{N}(\text{R}^{11\text{a}})-$; $-\text{S}(\text{O})_2-$; $-\text{S}(\text{O})_2-\text{C}_{1-6}$ alkyl-; $-\text{S}(\text{O})_2-\text{C}_{1-6}$ alkyl- $\text{O}-$; $-\text{S}(\text{O})_2-\text{C}_{1-6}$ alkyl- $\text{S}-$; $-\text{S}(\text{O})_2-\text{C}_{1-6}$ alkyl- $\text{N}(\text{R}^{11})-$; $-\text{S}(\text{O})-$; $-\text{S}(\text{O})-\text{C}_{1-6}$ alkyl-; $-\text{S}(\text{O})-\text{C}_{1-6}$ alkyl- $\text{O}-$; $-\text{S}(\text{O})-\text{C}_{1-6}$ alkyl- $\text{S}-$; and $-\text{S}(\text{O})-\text{C}_{1-6}$ alkyl- $\text{N}(\text{R}^{11})-$; wherein each C_{1-6} alkyl is optionally substituted with one or more halogen selected from the group consisting of F; and Cl;

R^{11} , $\text{R}^{11\text{a}}$ are independently selected from the group consisting of H; C_{1-6} alkyl; C_{3-7} cycloalkyl; and $-\text{C}_{1-6}$ alkyl- C_{3-7} cycloalkyl;

T^2 is selected from the group consisting of H; T^3 ; and T^4 ;

T^3 is selected from the group consisting of phenyl; naphthyl; and indenyl; wherein T^3 is optionally substituted with one or more R^{12} ; wherein R^{12} is independently selected from the group consisting of halogen; CN; COOR^{13} ; $\text{OC}(\text{O})\text{R}^{13}$; OR^{13} ; $-\text{C}_{1-6}\text{alkyl}-\text{OR}^{13}$; SR^{13} ; $\text{S}(\text{O})\text{R}^{13}$; $\text{S}(\text{O})_2\text{R}^{13}$; $\text{C}(\text{O})\text{N}(\text{R}^{13}\text{R}^{14})$; $\text{S}(\text{O})_2\text{N}(\text{R}^{13}\text{R}^{14})$; $\text{S}(\text{O})\text{N}(\text{R}^{13}\text{R}^{14})$; C_{1-6} alkyl;

$N(R^{13})S(O)_2R^{14}$; and $N(R^{13})S(O)R^{14}$; wherein each C_{1-6} alkyl is optionally substituted with one or more halogen selected from the group consisting of F; and Cl;

T^4 is selected from the group consisting of C_{3-7} cycloalkyl; indanyl; tetralinyl; decalanyl; heterocycle; and heterobicycle; wherein T^4 is optionally substituted with one or more R^{15} , wherein R^{15} is independently selected from the group consisting of halogen; CN; OR^{13} ; $-C_{1-6}alkyl-OR^{13}$ SR^{13} ; oxo ($=O$), where the ring is at least partially saturated; $N(R^{13}R^{14})$; $COOR^{13}$; $OC(O)R^{13}$; $C(O)N(R^{13}R^{14})$; $S(O)_2N(R^{13}R^{14})$; $S(O)N(R^{13}R^{14})$; C_{1-6} alkyl; $N(R^{13})C(O)R^{14}$; $S(O)_2R^{13}$; $S(O)R^{13}$; $N(R^{13})S(O)_2R^{14}$; and $N(R^{13})S(O)R^{14}$; wherein each C_{1-6} alkyl is optionally substituted with one or more halogen selected from the group consisting of F; and Cl;

Optionally R^{15} is $C(O)R^{13}$, provided that $C(O)R^{13}$ is bound to a nitrogen, which is a ring atom of a heterocycle or heterobicycle;

R^{13} , R^{14} are independently selected from the group consisting of H; C_{1-6} alkyl; C_{3-7} cycloalkyl; and $-C_{1-6}$ alkyl- C_{3-7} cycloalkyl; wherein each C_{1-6} alkyl is optionally substituted with one more halogen selected from the group consisting of F; and Cl.

2. A compound according to claim 1, wherein Z is selected from the group consisting of phenyl; and heterocycle; and wherein Z is optionally substituted with up to 2 R^4 , which are the same or different.

3. A compound according to any one of the preceding claims, wherein R^4 is selected from the group consisting of F; Cl; CN; and C_{1-6} alkyl.

4. A compound according to any one of the preceding claims, wherein R^1 , R^2 are independently selected from the group consisting of H; F; and C_{1-6} alkyl, optionally substituted with one or more F.

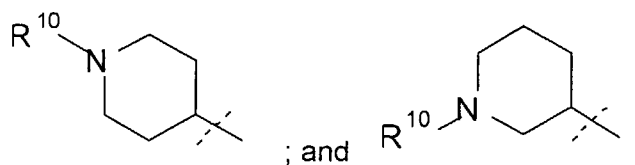
5. A compound according to any one of the preceding claims, wherein R^3 is H.

6. A compound according to any of the preceding claims, wherein A is A^0 .

7. A compound according to any of the preceding claims, wherein A^0 is a saturated heterocycle with at least one nitrogen as ring atom.

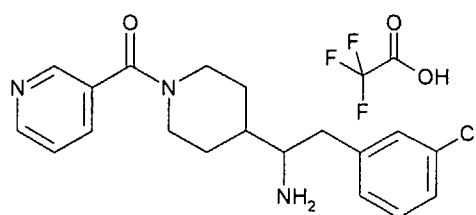
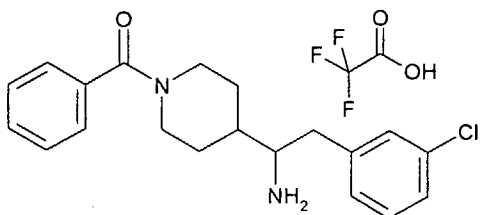
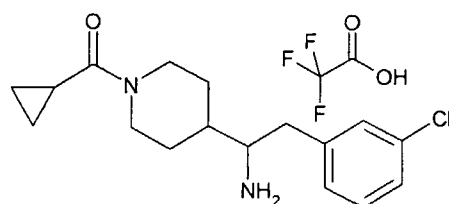
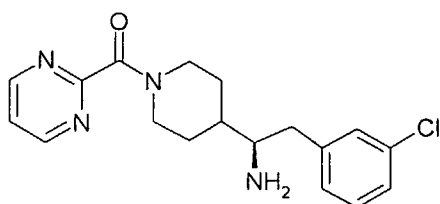
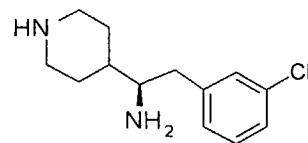
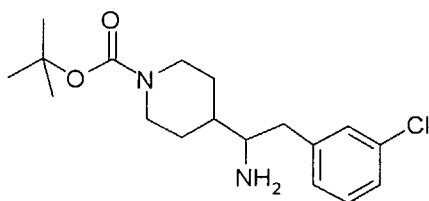
8. A compound according to any of the preceding claims, wherein A⁰ is piperidine.

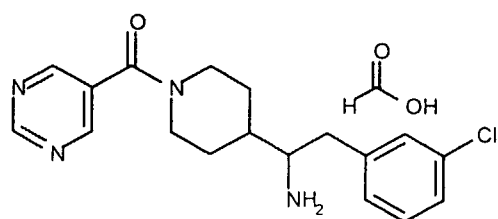
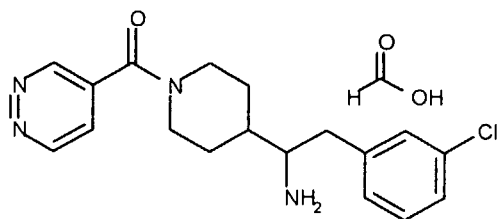
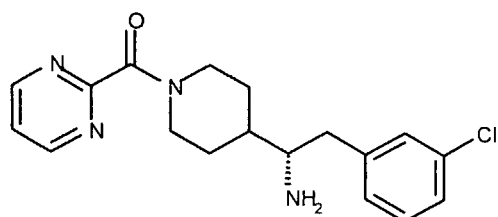
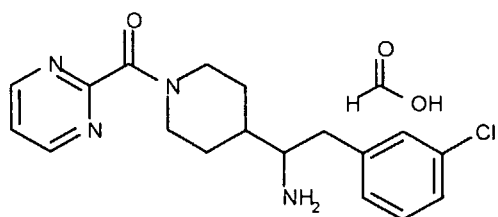
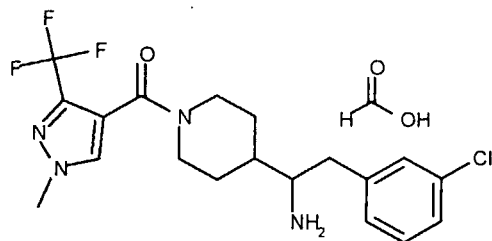
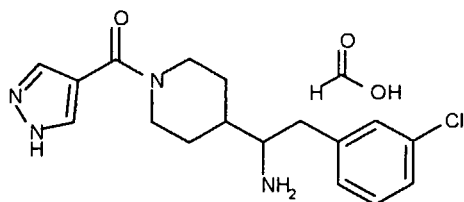
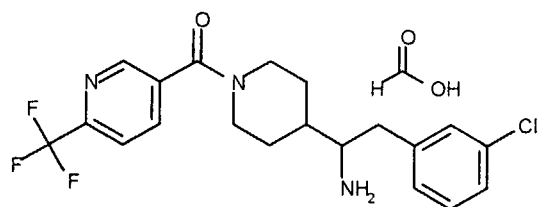
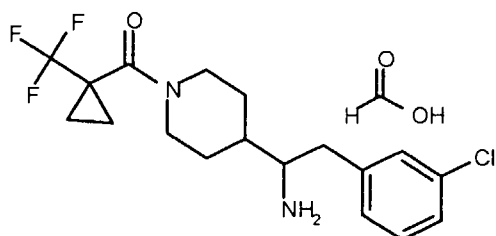
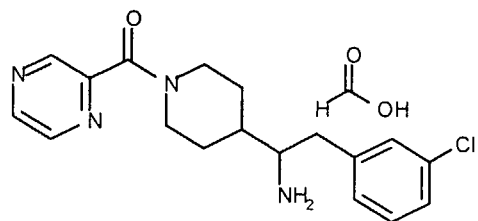
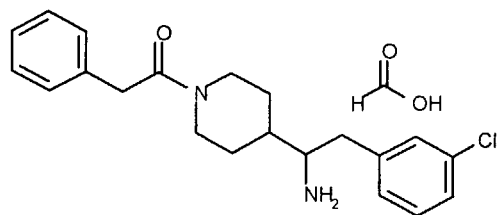
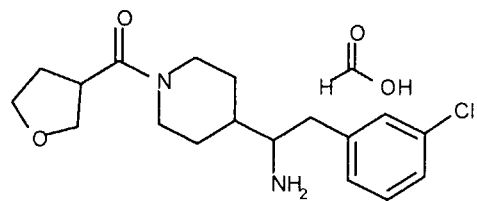
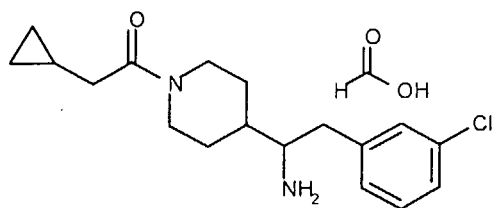
9. A compound according to claim 8, wherein A⁰ is selected from the group consisting of

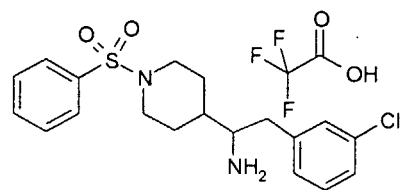
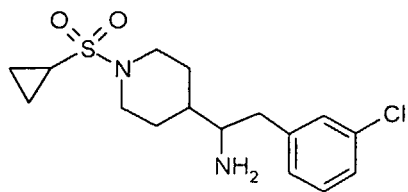
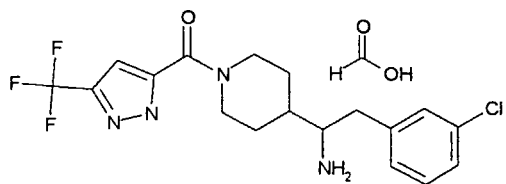
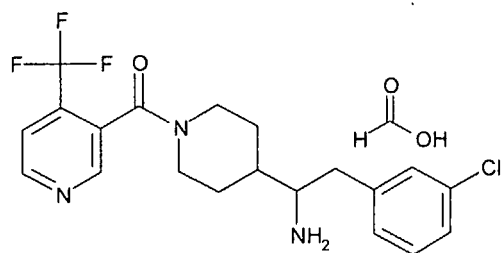
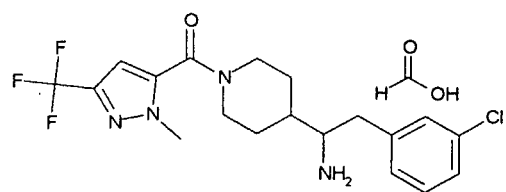
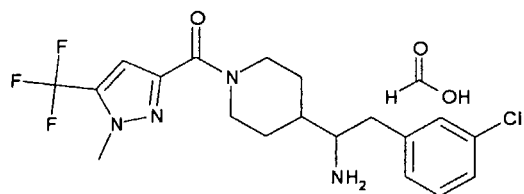
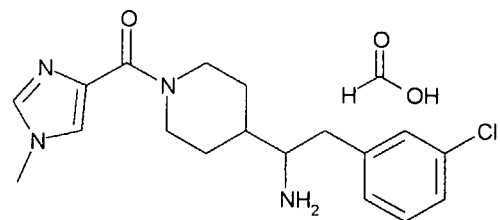
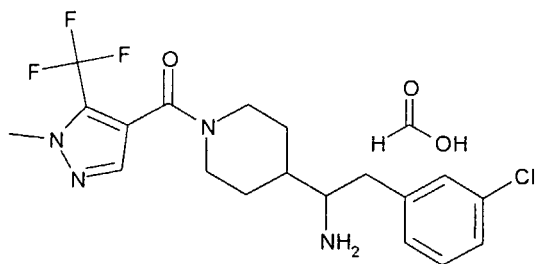
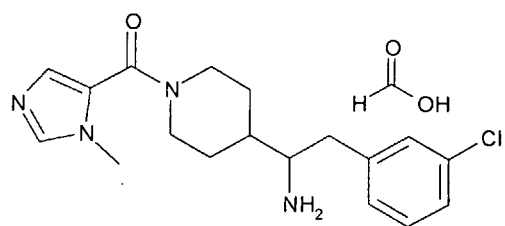
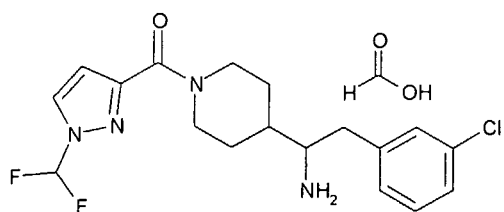
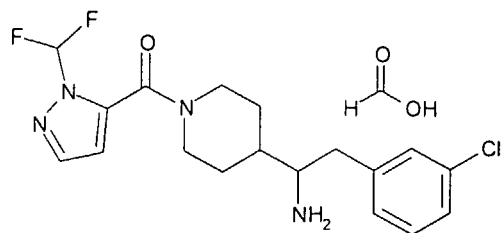
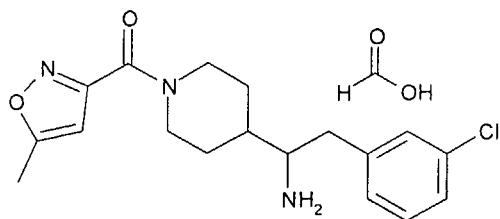


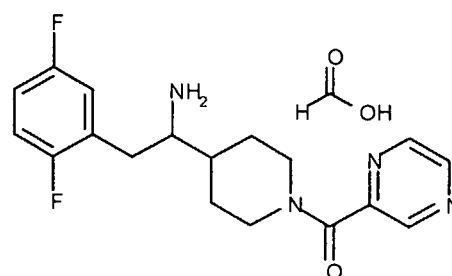
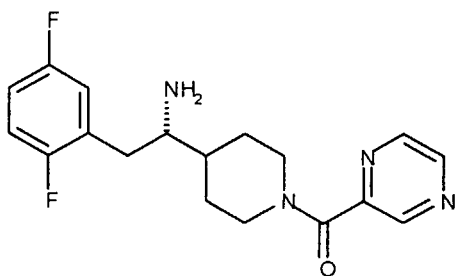
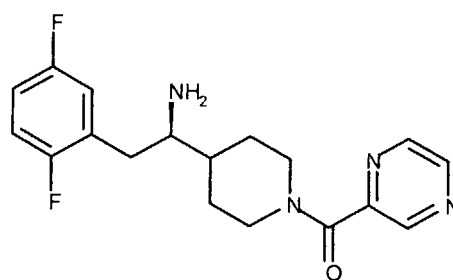
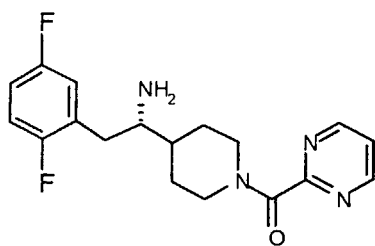
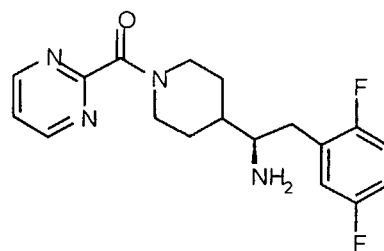
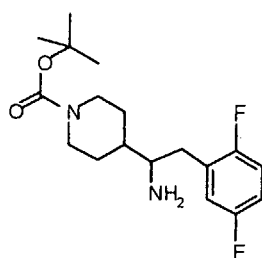
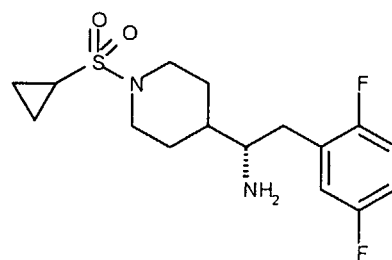
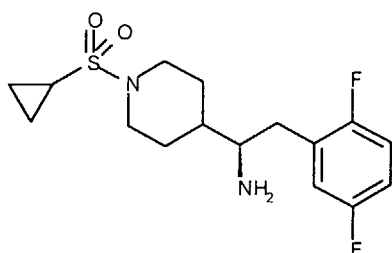
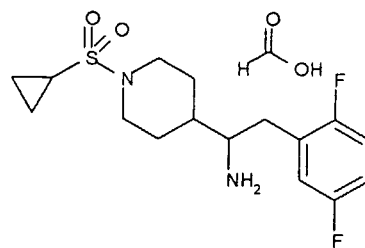
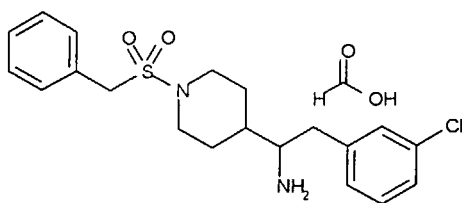
10. A compound according to any of the preceding claims, wherein R¹⁰ is selected from the group consisting of H; and -C(O)O-C₁₋₆ alkyl.

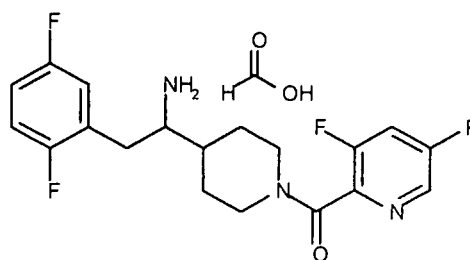
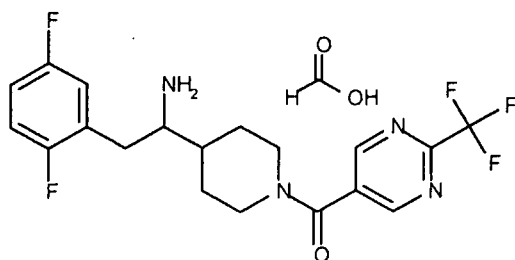
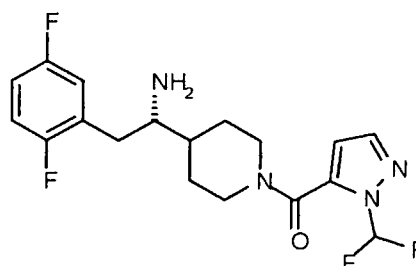
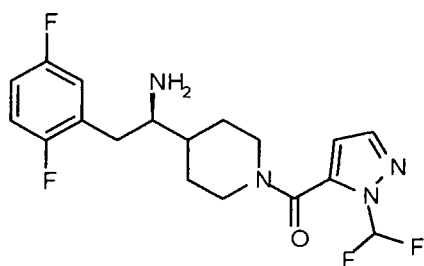
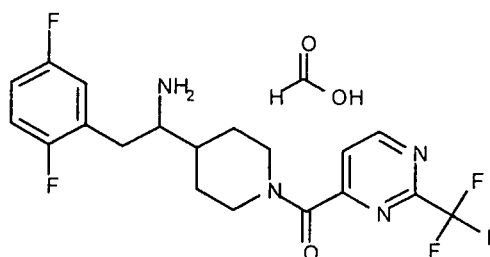
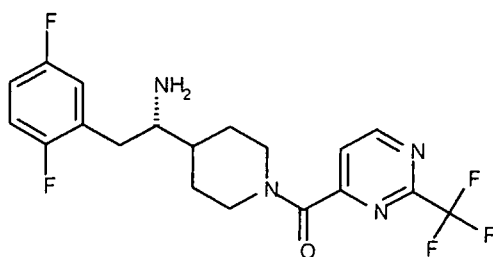
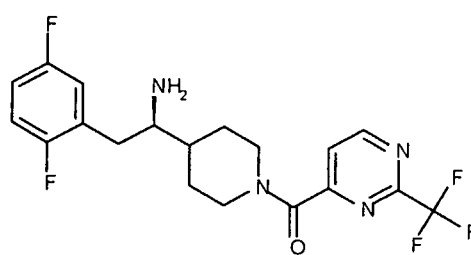
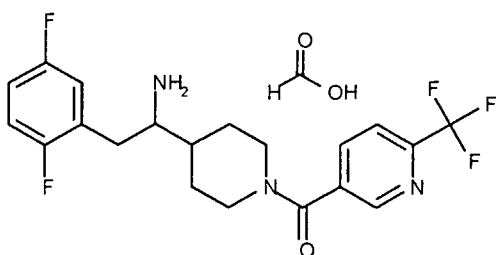
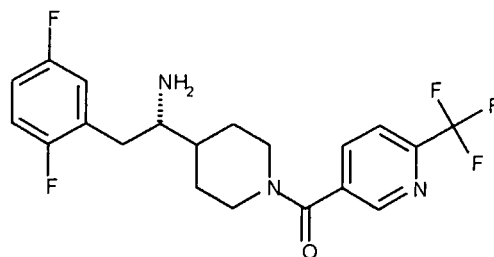
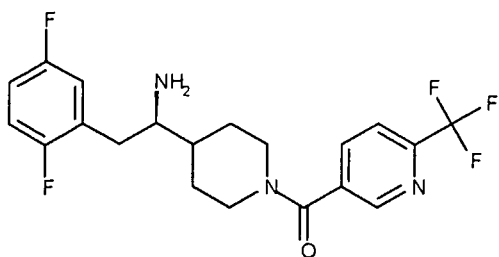
11. A compound according to claim 1 selected from the group consisting of

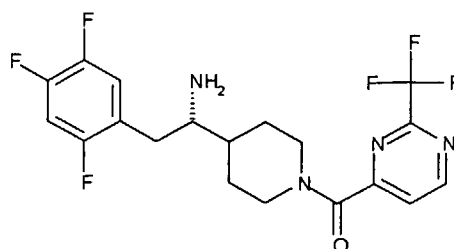
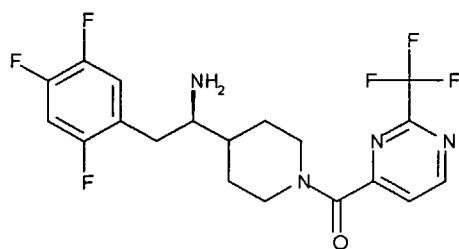
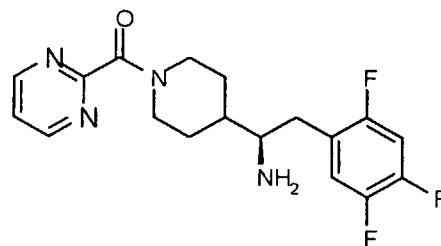
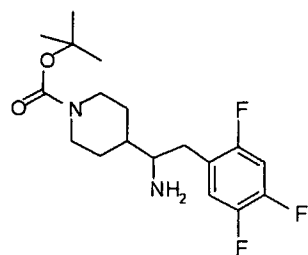
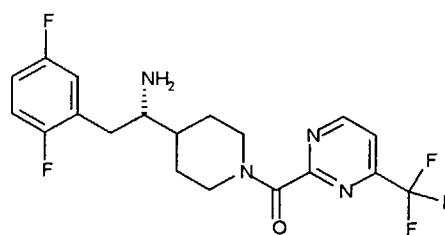
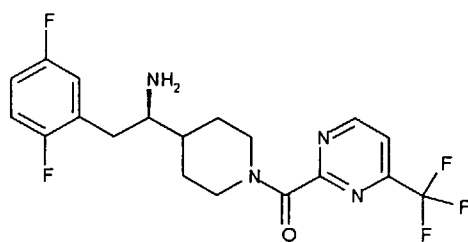
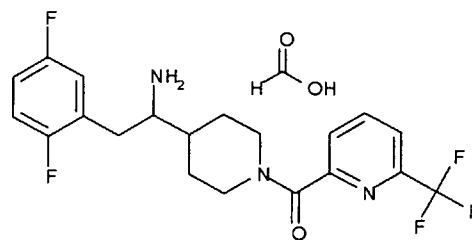
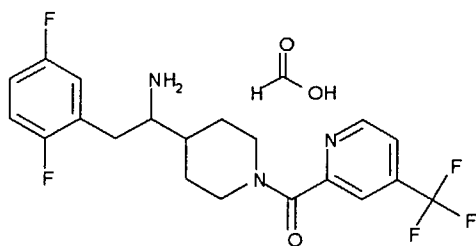
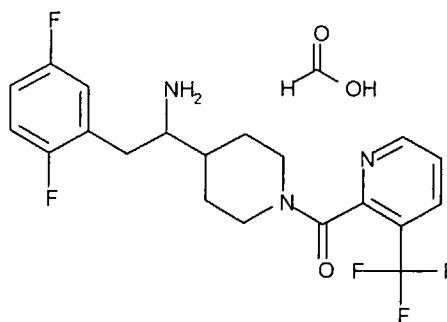
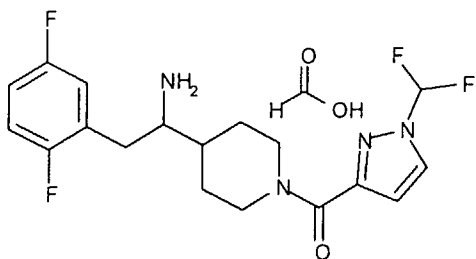


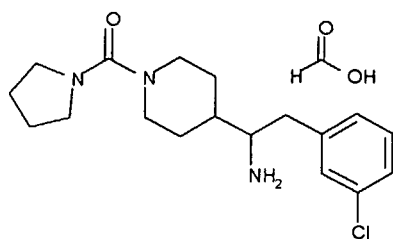
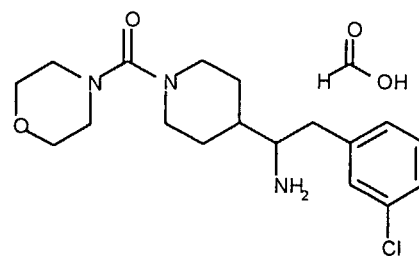
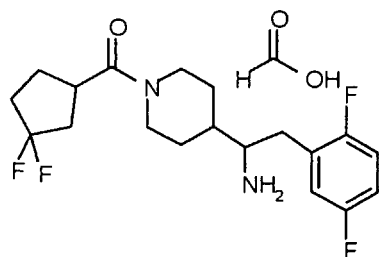
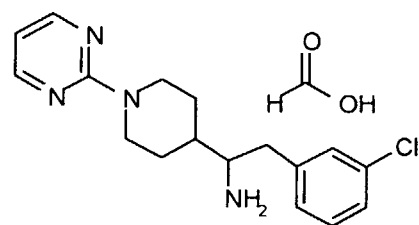
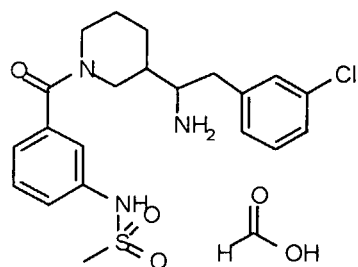
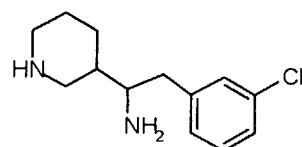
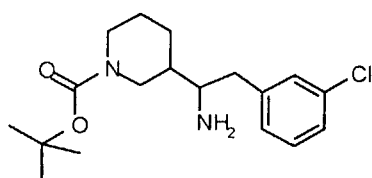
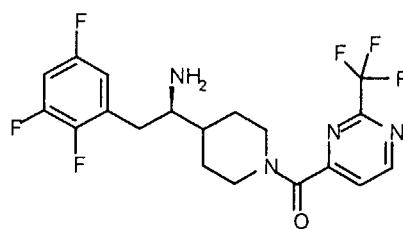
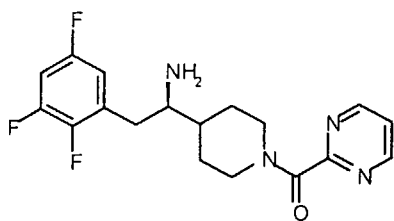
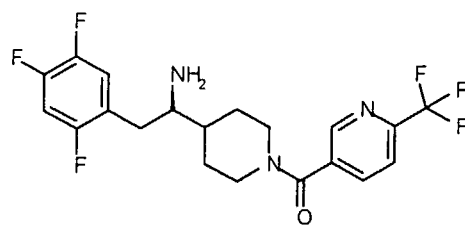
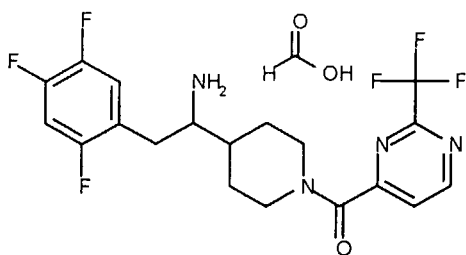












12. A prodrug compound of a compound according to any one of the claims 1 to 11.

13. A pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt thereof according to any one of the claims 1 to 12 together with a pharmaceutically acceptable carrier.

14. A pharmaceutical composition according to claim 13, comprising one or more additional compounds or pharmaceutically acceptable salts thereof selected from the group consisting of another compound according to any one of the claims 1 to 12; another DPP-IV inhibitor; insulin sensitizers; PPAR agonists; biguanides; protein tyrosinephosphatase-1B (PTP-1B) inhibitors; insulin and insulin mimetics; sulfonylureas and other insulin secretagogues; α -glucosidase inhibitors; glucagon receptor antagonists; GLP-1, GLP-1 mimetics, and GLP-1 receptor agonists; GIP, GIP mimetics, and GIP receptor agonists; PACAP, PACAP mimetics, and PACAP receptor 3 agonists; cholesterol lowering agents; HMG-CoA reductase inhibitors; sequestrants; nicotinic alcohol; nicotinic acid or a salt thereof; PPAR α agonists; PPAR γ dual agonists; inhibitors of cholesterol absorption; acyl CoA : cholesterol acyltransferase inhibitors; anti-oxidants; PPAR α agonists; antiobesity compounds; an ileal bile acid transporter inhibitor; and anti-inflammatory agents.

15. A compound or a pharmaceutically acceptable salt thereof of any one of the claims 1 to 12 for use as a medicament.

16. Use of a compound or a pharmaceutically acceptable salt thereof of any of the claims 1 to 12 for the manufacture of a medicament for the treatment or prophylaxis of non-insulin dependent (Type II) diabetes mellitus; hyperglycemia; obesity; insulin resistance; lipid disorders; dyslipidemia; hyperlipidemia; hypertriglyceridemia; hypercholesterolemia; low HDL; high LDL; atherosclerosis; growth hormone deficiency; diseases related to the immune response; HIV infection; neutropenia; neuronal disorders; tumor metastasis; benign prostatic hypertrophy; gingivitis; hypertension; osteoporosis; diseases related to sperm motility; low glucose tolerance; insulin resistance; its sequelae; vascular restenosis; irritable bowel syndrome; inflammatory bowel disease; including Crohn's disease and ulcerative colitis; other inflammatory conditions; pancreatitis; abdominal obesity; neurodegenerative disease; retinopathy; nephropathy; neuropathy; Syndrome X;

ovarian hyperandrogenism (polycystic ovarian syndrome; Type n diabetes; or growth hormone deficiency.

17. Use of a compound according to any one of the claims 1 to 12 as a DPP-IV
5 inhibitor.